Ibuprofen: Pharmacology, Therapeutics and Side Effects

K.D. Rainsford

Ibuprofen: Pharmacology, Therapeutics and Side Effects

Springer

K.D. Rainsford
Biomedical Research Centre
Sheffield Hallam University
Sheffield
United Kingdom

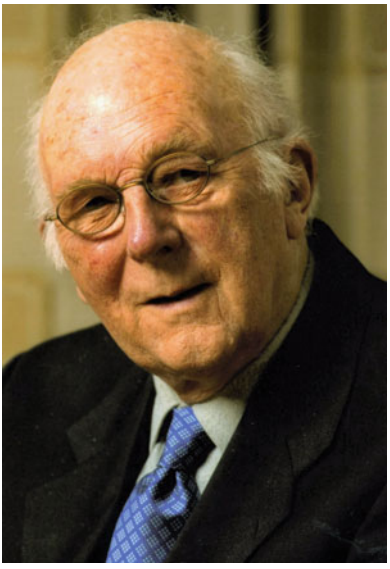
ISBN 978 3 0348 0495 0 ISBN 978 3 0348 0496 7 (eBook)
DOI 10.1007/978 3 0348 0496 7
Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2012951702

Printed on acid free paper

Springer is part of Springer Science+Business Media (www.springer.com)

This book is respectfully dedicated to ***Professor Stewart Adams OBE*** *and his colleagues for their discovery of ibuprofen 50 years ago and its implementation in the therapy of pain and inflammatory conditions.*



Professor Stewart Adams, BPharm, PhD, DSc(hc), OBE

Foreword

I am very pleased to write the foreword to this book, since Professor Rainsford over the years has written extensively and expertly on ibuprofen. It is difficult now to look back to 1953 when I first began to think about the possibility of finding a non-corticosteroid drug for the treatment of rheumatoid arthritis (RA). It was a forbidding prospect, for little was known about the disease process and nothing about the mode of action of aspirin (aspirin being effective in very high doses in RA).

After several disappointing and non-productive years we finally discovered the "propionics", and selected ibuprofen, which we estimated would potentially be the best tolerated. In 1969 as a prescription drug, ibuprofen started slowly because the recommended dose of 600 800 mg/day was too low for the effective treatment of the rheumatic diseases and well below the now usual doses of 1,200 1,800 mg/day. Later studies showed ibuprofen was an effective analgesic in many painful conditions in doses up to 1,200 mg/day, and in 1983 it was approved as a non-prescriptive (OTC) analgesic. It is perhaps these differences between the prescription and non-prescription doses which have led to the mistaken view that at the lower doses ibuprofen is only an analgesic.

A most satisfying aspect of ibuprofen has been its good tolerance, always a major aim of our research, and one of the reasons for its ever increasing world-wide use since 1969.

Nottingham, UK
October 2011

Stewart Adams

Preface

Ibuprofen is probably one of the most successful drugs used worldwide for the treatment of mild to moderate pain and various inflammatory conditions. Since its initial discovery half a century ago in December 1961 by Dr. (now Professor) Stewart Adams, the late Dr. John Nicholson and Mr. Colin Burrows of the Boots Co. Nottingham (UK) (see photo), ibuprofen has been developed in a wide variety of oral and parenteral formulations for use in an amazing variety of indications. My chapter on the "History and Development of Ibuprofen" written in the first monograph (which I also edited) on this drug details the twists and turns that took place in the discovery and development of ibuprofen from initial humble beginnings. It is a great tribute to Stewart Adams and his colleagues that their insight and persistence enabled the pharmacological activities of ibuprofen to be discovered and clinical potential to be realized at a time when little was known about inflammatory processes, let alone the techniques for quantifying clinical responses in arthritic and other painful inflammatory conditions. Indeed, it was only through screening several thousand compounds for anti-inflammatory, analgesic, and antipyretic activity in what were then relatively newly established animal models in guinea pigs and rats that the pharmacological activity of ibuprofen was identified, and found to be uniquely active compared with other compounds including that of aspirin, a reference standard employed at the time. These discoveries were essentially made on an empirical basis. It was a decade or so later before the discovery of prostaglandins and their actions in regulating inflammation. Also, it took longer before assays for detecting anti-inflammatory activity based on prostaglandin synthesis inhibition were developed, conditions understood and then refined as well as validated for screening potential therapeutic agents.

In the process of the early clinical trials with ibuprofen, initially in patients with rheumatoid arthritis, using the approach of cautious introduction using relatively low doses of the drug, that its efficacy and safety were appreciated. Later on, higher doses were found necessary for optimal effects, and proved relatively safe after long-term usage. This, and evidence from toxicological studies and extensive clinical investigations, showed that ibuprofen was safer as or more effective than

the established non-steroidal anti-inflammatory drugs (NSAIDs) (aspirin, indomethacin, and phenylbutazone).

As detailed in this book, ibuprofen has since been proven to be one of the safer NSAIDs. This is such that it has been used extensively as a standard for comparison in the large number of clinical trials of newly developed agents. These trials are reviewed here, and although some newer drugs (e.g., coxibs) have been found to have fewer gastrointestinal (GI) adverse effects, their margin of improved GI safety is relatively small, and this improvement has not come without other safety issues (e.g,. cardiovascular reactions) or added costs to healthcare budgets or the individual.

One of the great successes with ibuprofen was its introduction in a low dose ($\leq$1,200 mg/day) form for over-the-counter (OTC), non-prescription sale in the UK (in 1983), USA (in 1984) and now in 82 countries worldwide. Large-scale clinical and epidemiological studies have shown that this OTC form of the drug is relatively safe in the GI tract compared with aspirin and other NSAIDs, and is comparable in GI safety with paracetamol (acetaminophen), yet without the risks of liver toxicity seen with the latter. This is not to say that OTC ibuprofen is without adverse effects. As reviewed in this book, development of these untoward actions is now well-understood, and most reactions, though discomforting to some degree, are minor and preventable, or at least are reversible upon with drawing the drug (indicating reversibility of toxic mechanisms).

This book also reviews the disposition and unique modes of action of ibuprofen. Studies on the pharmacological properties of ibuprofen have advanced in parallel with understanding of the cell and molecular biology of inflammatory processes, especially those underlying neuro-pathological reactions in pain and neurodegenerative diseases and cancer-related inflammatory reactions. Consequently, much interest has been shown in the past two decades or so in the potential for ibuprofen to prevent conditions such as Alzheimer's and atherosclerotic dementias, Parkinson's disease and neural injuries, as well as colo-rectal, mammary, and some other cancers. While these developments are undoubtedly exciting, there are, however, extensive investigations which will have to be performed to understand when ibuprofen should be employed in the various stages of these chronic and complex conditions, and at what dose(s). Indeed, special formulations of ibuprofen may need to be developed to ensure optimal biodisposition of the drug (e.g., localized delivery in the colon in colo-rectal cancer) or prolonged pharmacokinetics for specific applications in different chronic diseases (e.g., in cystic fibrosis) or special patient groups (young and the elderly) in which long-term safe use is required.

Recently, there has been much commercial and clinical interest in developing and use of combinations of ibuprofen with other drugs (e.g., paracetamol, codeine, caffeine) and some natural products. The objective of many drug combinations has been to raise the "analgesic ceiling" to achieve greater or more sustained acute pain relief. While in many cases the "jury may still be out" on most of these claims, there are already some indications of potential therapeutic benefits of the drug combinations in certain painful conditions, while still retaining the relative safety benefits of ibuprofen (at least at OTC dosages). Further investigations will be

required with some of these ibuprofen drug mixtures to establish optimal conditions for their application and use in specific indications.

This book is intended for a broad readership for anyone interested in the properties, actions, and uses of ibuprofen. It is intended that this book be written in a more general style to reflect interest in it by a broad readership. There are several concepts that are presented diagrammatically but with sufficient detail such that key points are emphasized. For more in-depth information, the reader is referred to the specialist book "Ibuprofen: A Critical Bibliographic Review" (1999; 2nd edition in preparation), edited by myself.

This book would not have been possible without the privileged collaboration and valuable advice of my long standing research colleagues, among them Dr. Brian Callingham (University of Cambridge, UK), Professor Michael Whitehouse (University of Queensland & Griffiths University, Queensland, Australia), Professors Walter Kean and Richard Hunt and the late Watson Buchanan (McMaster University, Hamilton, Ontario, Canada).

I would also like to record my appreciation of advice of research colleagues in pharmaceutical companies that produce and market ibuprofen who have often given me valuable information on this drug, and access to their drug safety databases without prejudice. Among these, I have been privileged to have advice and receive important historical information from the discoverer of ibuprofen, Professor Stuart Adams, OBE, to whom this book is dedicated.

My thanks to Dr. Hans-Detlef Klüber of Springer Basel AG (formerly Birkhäuser Verlag), Basel, Switzerland for his idea that has led to this book based on a review I published (Inflammopharmacology, 2009;17:275 342), and his long-standing and valuable help and collaborations.

I would like to record my appreciation for invaluable secretarial support to Veronica Rainsford-Koechli and to Alexander and William Rainsford for their expert preparation of the figures and tables in this book.

Sheffield, UK K. D. Rainsford
10 December 2012

Contents

Abbreviations and Explanations

5-HT	5-Hydroxytryptamine (serotonin)
Acetaminophen	Paracetamol [synonym]
ADR	Adverse drug reaction
AE	Adverse event
AIA	Aspirin intolerant asthma
ALT	Alanine amino transferase (*syn* SGPT)
ASA	Acetyl-salicylic acid (= aspirin)
AST	Aspartate amino transferase (*syn* SGOT)
ATP	Adenosine monophosphate
AUC	Area under the curve
b.d.	*bis die* (twice a day)
B-cell	Bursar-derived or -like lymphocyte
BK	Bradykinin
cAMP	Cyclic adenosine monophosphate
CB	Cannabinoid (receptor)
CGRP	Calcitonin gene-related peptide
CHD	Coronary heart disease
CI	Confidence interval
Cl	Clearance
Cl/F	Fractional clearance
CLASS	Celecoxib Long-term Arthritis Safety Study (clinical trial)
C_{max}	Maximal concentration
CNS	Central nervous system
COSTART	Coding symbols for a thesaurus of adverse reaction terms
COX	Cyclo-oxygenase
COX-1	Cyclo-oxygenase-1 [isoform]
COX-2	Cyclo-oxygenase-2 [isoform]
Cp	Plasma concentration
CSM	UK Committee on the Safety of Medicines (now MHRA)
CTM	Chinese traditional medicines
CV	Cardio-vascular

CYP-2C19	2C19 isoform of Cytochrome P_{450}
CYP-2C8	2C8 isoform of Cytochrome P_{450}
CYP-2C9	2C9 isoform of Cytochrome P_{450}
CYP-2C9*1, *2 or *3	2C9 Genetic variants 1, 2 or 3 of the isoform of Cytochrome P_{450}
CYP_{450}	Cytochrome P_{450}
DDD	Defined daily dose
DRG	Dorsal root ganglion
EC_{50}	Concentration for half-maximal effect
EEG	Electro-encephalograph(y)
EMA (EMEA)	European Medicines (Evaluation) Agency
eNOS	Endothelial nitric oxide synthase
EP (receptor)	E-Prostaglandin receptor(s)
EP	Evoked potential(s)
ER	Extended release
FDA	US Food and Drug Administration
FP (receptor)	F-Prostaglandin receptor(s)
GCP	Good clinical practice
GI	Gastrointestinal
GI	Gastro-intestinal
GLU	Glutamate
GSL	General sales list [direct to public sale]
GU	Gastric ulcer
HAQ	Health assessment questionnaire
HR	Hazard rate
i.p.	intra-peritoneal
i.r.	intra-rectal
IBU	Ibuprofen
ICH	International Committee for Harmonization of clinical trials
IE	Intensity estimates (of pain responses)
IκB	Inhibitor of nuclear factor kappa B
IL	Interleukin
IL-1, -6, -8	Interleukins 1, 6 or 8
iNOS	Inducible nitric oxide synthase
IP (receptor)	I-Prostaglandin, or prostacyclin receptor(s)
JIA	Juvenile inflammatory arthritis, or juvenile rheumatoid arthritis (JRA)
K_a	Absorption rate constant
k_{el} or K_e	Elimination rate constant
LC-MS	Liquid chromatography mass spectrometry
LFT	Liver function tests
LT	Leukotriene
MHRA	UK Medicine and Healthcare Products Regulatory Agency

MI	Myocardial Infarction
MMP	Matrix metalloproteinase(s)
MRT	Mean (or median) residence time
MTT	Mean transit time
N	Number of subjects or patients
NA	Noradrenaline (norepinephrine)
NFκB	Nuclear factor kappa B
NGF	Nerve growth factor
NMDA	*N*-methyl-D-aspartate (glutamate receptor)
NN	Non-narcotic
nNOS	Neuronal nitric oxide synthase
NNT	Number needed to treat
NO	Nitric oxide
NOS	Nitric oxide synthase
NP	Non-prescription
NS (NSAID)	Non-selective (COX-inhibitory) NSAID
NSAIDs	Non-steroidal anti-inflammatory drugs
OA	Osteoarthritis
$OH^{\bullet}$	Hydroxyl radical(s)
$ONOO^{\bullet}$	Peroxy-radical(s)
OR	Odds ratio
OTC	Over-the-counter (sale) or non-prescription
P- or P-only	Prescription
p.r.n.	*pro re nata* (as required)
PAR	Pain relief (score(s))
PD	Pharmacodynamic(s)
PDA	Patient ductus arteriosus
PG	Prostaglandin
PGD_2	Prostaglandin D_2
PGE_2	Prostaglandin E_2
$PGF_{2\alpha}$	Prostaglandin $F_{2\alpha}$
PGH_2	Prostaglandin G/H synthase
PGI_2	Prostaglandin I_2 or prostacyclin
PID	Pain intensity difference
PK	Pharmacokinetic(s)
pKa	negative logarithm of the dissociation constant
Plasma or serum	Refers to the medium in which drug concentrations are measured
PMN	Polymorphonuclear leucocytes (neutrophils)
PPIs	Proton pump inhibitors
q.i.d.	*quarter in die* (4 times a day)
R(-)	R enantiomer
RA	Rheumatoid arthritis
rac	Racemic (mixture) or racemate

RR	Relative risk
S(+)	S (+) enantiomer (*syn*. dexibuprofen)
SD	Standard deviation
SEM	Standard error of the mean
Serotonin	5-Hydroxytryptamine
SGOT	Serum glutamate oxaloacetate transaminase (*syn* AST)
SGPT	Serum glutamate pyruvate transaminases (*syn* ALT)
SP	Substance P
SPID	Sum of pain intensity difference(s)
SR	Sustained release
t.i.d.	*ter in die* (3 times a day)
$t_{1/2}$	Half-life of elimination
T-cell or Th	Thymus-derived lymphocyte
TIA	Transient ischaemic attack
t_{max}	Time at peak maximal concentration
TNFα	Tumour necrosis factor-α
TOTPAR	Total pain relief
TRIAD	Tri-organ (gastro-intestinal, liver and caradiovascular) toxicity
TRPC	Therapeutically relevant plasma concentrations
TxA_2	Thromboxane A_2
TxB_2	Thromboxane B_2
VAS	Visual analogue scale
V_D	Volume of distribution
V_D/F	Fractional volume of distribution
VIGOR	Vioxx Gastrointestinal Outcomes Research Study (clinical trial)
WOMAC	Western Ontario McMaster University Assessment

Chapter 1
Introduction

It is now half a century since ibuprofen was discovered to have anti-inflammatory properties by Dr (now Professor) Stewart Adams at the Boots Company in Nottingham (UK) (Rainsford 2011). Since then, ibuprofen has evolved to be amongst the most widely-used analgesic antipyretic anti-inflammatory drugs today. It is available in nearly all countries in the world as both a prescription and over-the-counter sale drug for treating a wide variety of painful and inflammatory conditions, although its principal approved application is the for the treatment of mild moderate pain, including musculo-skeletal conditions, headache/migraine, fever, and accidental injuries. As an over-the-counter sale remedy it is registered for sale in 82 countries worldwide. It probably ranks after aspirin and paracetamol in non-prescription over-the-counter (OTC) use for the relief of symptoms of acute pain, inflammation, and fever, although the patterns of use of these analgesics vary considerably from country to country worldwide. Of these three analgesics, OTC ibuprofen is probably the least toxic, being rarely associated with deaths from accidental or deliberate misuse, or with serious adverse reactions. Indeed, it has been described as "the mildest NSAID with the fewest side-effects, and has been in clinical use for a long time" (General Practice Notebook; http://www.gpntebook.co.uk, accessed 1/12/2011).

1.1 Background

Ibuprofen was initially introduced in the UK in 1969, and afterwards during the 1970s worldwide, as a prescription-only medication, where it was recommended to be prescribed at up to 2,400 mg per day (and even at a higher dose in the USA) for the treatment of musculo-skeletal pain and inflammation as well as other painful conditions (Rainsford 1999a). During the 1970s, it was the most frequently prescribed drug for use either as a first-line NSAID or in place of aspirin, indomethacin, or phenylbutazone for treatment of arthritic conditions. The experience during and after this period showed it had a reputation for good efficacy and lower

K.D. Rainsford, *Ibuprofen: Pharmacology, Therapeutics and Side Effects*,
DOI 10.1007/978 3 0348 0496 7 1, © Springer Basel 2012

gastrointestinal adverse effects. Initially, the drug was used in low doses ranging from 400 to 1,200 mg per day and, with latitude and experience, by physicians' cautious dose-escalation proceeded to the current recommended dosage of 2,400 mg per day (Rainsford 1999a, 2009; Kean et al. 1999).

1.2 Introduction of Ibuprofen for Non-Prescription (OTC) Use

The emphasis on the initial cautious use of ibuprofen was one of the hallmarks of its early success and the development of confidence in its safe use (Rainsford 1999a). It was following a long period of safety evaluation of prescription-level dosage of ibuprofen for treating rheumatic conditions that the Boots Company Ltd. (Nottingham, UK) applied for and was granted a licence in 1983 to market ibuprofen as a non-prescription (NP) drug for over-the-counter (OTC) sale (or General Sales Listing, GSL) at a daily dose of up to 1,200 mg. In the following year, the Upjohn Company in collaboration with the Boots Company was granted a licence by the US Food and Drug Administration (FDA) to market ibuprofen as an OTC drug in the USA. The decision by the FDA was predicated on the basis of the drug having a proven record of safety, for at that stage it was given that the drug was efficacious in the treatment of pain and associated inflammatory conditions (Paulus 1990).

Following these two successful introductions of ibuprofen for NP-OTC use, there followed approvals in a large number of countries worldwide. Overall, the drug is licensed for OTC use in 27 European and 55 non-European countries, making a total of 82 countries worldwide. In contrast to some other NSAIDs, ibuprofen has never had its licence revoked or suspended for reasons relating to safety or other factors concerned with the use of this drug.

A major competitor to ibuprofen has been paracetamol (acetaminophen), especially in the OTC field but also, as discussed later, in therapy of osteoarthritis. In non-prescription OTC use for paediatric use, both ibuprofen and paracetamol are equally effective in controlling fever, but there are recent data to suggest that combination of these two drugs may be particularly useful in severe febrile or painful conditions. It appears that ibuprofen and paracetamol have differing modes of action, and ibuprofen is the more potent of the two for anti-inflammatory activities. It is possible that they may have additive or synergistic analgesic effects.

Claims by those advocating paracetamol are that this drug is associated with lower gastrointestinal (GI) and renal adverse reactions than observed with ibuprofen. For OTC use, these differences are minimal or nonexistent (Rainsford et al. 1997, Rainsford 2009). At higher prescription doses as used in arthritis therapy, the consensus is that the differences in GI adverse reactions are relatively low, while renal adverse reactions may be more prevalent in patients taking ibuprofen. A major issue with paracetamol is hepatotoxicity especially when taken in the range of 3 4 g daily long-term and with alcohol. The situation with regard to consumption of alcohol and the use of paracetamol in patients with alcoholic liver disease or signs

of alcohol abuse is quite serious. Mild to moderate hepatic reactions have been observed infrequently with high prescription doses of ibuprofen, but rarely with NP-OTC doses of this drug.

In some countries (e.g., USA, UK, Australia) where naproxen and ketoprofen are marketed for OTC use, these have been competitors for ibuprofen. Both these drugs are more potent as anti-inflammatory agents and prostaglandin inhibitors than ibuprofen, and are associated with higher risk of upper GI adverse reactions at prescription doses. Naproxen tends to be used as a second-line drug for treatment of primary dysmenorrhoea where aspirin, ibuprofen, and paracetamol are found to be less effective. Ketoprofen is favoured by some for more severe joint pain in arthritic disease.

Overall, ibuprofen has withstood competition and challenges over the four decades since its introduction as a prescription drug, and in the period of over two decades since it was introduced for over-the-counter sale.

1.3 Experience at Prescription Level Dosage

Over the years, there have been many challenges to ibuprofen, some from concerns about safety including the occurrence of some very rare serious adverse reactions [e.g., Stevens-Johnson and Lyell's (toxic epidermal necrolysis) syndromes, renal or cardiovascular failure, necrotising fasciitis] as well as some that are more common to the class of NSAIDs. Most recent of these have been cardiovascular (CV) conditions that were highlighted by the occurrence of fatal and non-fatal myocardial infarction and cardio-renal symptoms in patients receiving the newer class of NSAIDs, the coxibs (rofecoxib, valdecoxib and to some extent celecoxib (Östör and Hazleman 2005; Rainsford 2005a). This had the effect of regulatory agencies worldwide examining the potential of all NSAIDs to cause CV and cardio-renal symptoms, an aspect that is still of concern for some of the coxibs and some NSAIDs.

There have also been many challenges from newer NSAIDs, particularly the wave of some 20 30 new NSAIDs introduced in the period of 1970s 1980s and the much celebrated introduction of the selective cyclooxygenase-2 (COX-2) inhibitors ("coxibs") that appeared in 1999 following the discovery of COX-2 as the main prostaglandin synthesising enzyme expressed in inflammation and pain pathways (Rainsford 2007). Surprisingly, one-half to two thirds of the NSAIDs introduced to the clinic since the 1970s have been withdrawn from the market, mostly due to unacceptable and unpredictable toxicities (Rainsford 1987). So in a sense, ibuprofen has survived these challenges both from the point of view of competition from the newer drugs and the inevitable negative impact of the failures or associations with other drugs that have raised safety issues (e.g., the CV risks raised by the coxibs). Mostly, these issues have concerned prescription-only NSAIDs, although those sold OTC like ibuprofen may also have been affected by these issues.

1.4 Scope and Objectives

This book aims to bring together key salient and clinically important published data and information on the safety and efficacy of ibuprofen at *both* prescription (up to 2,400 mg per day) and non-prescription or OTC ($\leq$1,200 mg per day) doses. While the focus of attention is on consideration of the application of the lower OTC doses of the drug for wider use in the population, the data on prescription-level dosage is useful for showing the safety potential of the drug and the important issues of what happens when OTC doses might be exceeded.

The main emphasis in this review is on the scientific evidence for safety of ibuprofen at OTC dosage ($\leq$1,200 mg per day), since this is the central issue that is recognised in the evaluation of the drug for OTC sale. The safety profile of ibuprofen at prescription-level (P-level) doses (>1,200 mg per day; usually 1,800 2,400 mg per day) is reviewed and evaluated as an indication of what can be considered the upper limits of toxic actions of the drug. It is not expected that the public taking the drug at the recommended OTC doses would experience adverse reactions observed at prescription level, but this may be considered as an indicator of safety *at the upper limit or extreme of dosage*. Based on this evidence and that for the efficacy of the drug, including that in relation to its competitors, an assessment of the benefit/risk profile of ibuprofen is considered and the risks are presented.

This review also focuses on the modes of action of ibuprofen especially in relation to its pharmacokinetics, recent concepts of inflammatory processes, and clinical indications.

Chapter 2
Biodisposition in Relation to Actions

Like most NSAIDs, ibuprofen has multiple actions including the inhibition of prostaglandin (PG) production, and these activities underlie the clinical effects that are linked to its pharmacokinetic (PK) properties (Rainsford 1996, 1999b, 2009). In this chapter, the principal PK and pharmacodynamic (PD) properties that are relevant to the analgesic and anti-inflammatory activities of ibuprofen are considered.

2.1 Key Aspects of the Pharmacokinetics and Biodisposition of Ibuprofen

The form of ibuprofen sold OTC has a racemic chemical structure. This arises from the position of the methyl moiety that is attached to the 2-carbon atom (i.e., adjacent to the carboxyl group) (Fig. 2.1).

The commercially available drug is composed of a 50:50 mixture of the R(−)- and S(+)- enantiomers (or isomers) (Fig. 2.1).

The existence of the racemic mixture was not appreciated in the early chemical development of the drug, but studies on the metabolism and identification of the prostaglandin synthesis (PG) inhibitory activities (Adams et al. 1976; Rainsford 1999a, b) showed that S(+)-ibuprofen was a potent inhibitor and R(−)-ibuprofen was a relatively weak inhibitor of PGs. Since the original observations concerning the selectivity of the two enantiomers on the production of PGs (Adams et al. 1976), it is now known that this effect is achieved by the selective actions on different components of inflammatory pathways. The major pathways of metabolism of racemic [i.e., R(−)- and S(+)]-ibuprofen involved (a) conversion of about 40 60 % or the R(−) form to the S(+) antipode, (b) oxidative conversion catalysed by cytochromes P_{450} of the *tert*-butyl side chain to hydroxyl or carboxyl moieties, and (c) conjugation with glucuronic acid catalysed by glucuronyl transferases or with taurine by aminoacyl transferases (Fig. 2.2). Relatively small quantities

K.D. Rainsford, *Ibuprofen: Pharmacology, Therapeutics and Side Effects*,
DOI 10.1007/978 3 0348 0496 7 2, © Springer Basel 2012

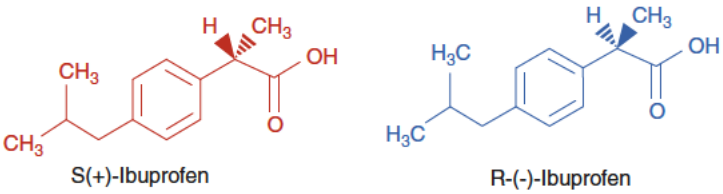


Fig. 2.1 Chemical structures of the R( ) and S(+) isomers of ibuprofen (Nichol 1999). The ibuprofen molecule has a chiral centre at carbon 2 of the propionic acid group. This leads to the formation of two optical isomers or enantiomers. The (+) form (originally described as *d* or *dextro*) has the S configuration. The ( ) form (comprising the *l* or *leavo*) has the R configura tion (Ghislandi et al. 1982).

(circa 4 %) of ibuprofen glucuronides are formed in isolated cell systems (Koga et al. 2011; Buchheit et al. 2011) and in subjects who have taken repeated oral doses of ibuprofen (Castillo et al. 1995), which are excreted in urine (Ikegawa et al. 1998). The half-lives of the S(+)-ibuprofen, 2-hydroxylated or carboxylated glucuronides are approximately 3.7 h, while the R(−)-ibuprofen acyl glucuronides are about 1.7 h (Johnson et al. 2007). The *S*-acyl-glutathione, but not the glucuronides, appears to have the capacity to be reactive in transacylation reactions in vitro (Grillo and Hua 2008). The acylation of plasma and other proteins from ibuprofenyl glucuronide occurs to a limited extent, but is not appreciable and appears short-lived (Vanderhoeven et al. 2006).

Ibuprofen is rapidly, and almost completely, absorbed from the upper gastrointestinal tract. As shown in Fig. 2.3 (Dewland et al. 2009), the plasma concentration profiles of ibuprofen can vary according to the drug formulation (Ceppi Monti et al. 1992; Brocks and Jamali 1999; Lötsch et al. 2001; Dewland et al. 2009; Cattaneo and Clementi 2010). Thus, sodium salt or solubilised (poloxamer) formulations of ibuprofen are more rapidly absorbed than the acid (Dewland et al. 2009). Most other formulations of ibuprofen, including extended- or sustained-release types, show similar and near complete bioavailability compared with the immediate-release forms (Brocks and Jamali 1999).

Comparing the plasma profiles of the R(−)- and S(+)-enantiomers of ibuprofen (Figs. 2.3 and 2.4) shows that following the plasma profile of the S(+)-ibuprofen lags behind that of the R(−)-isomer, whether the drug is taken as the racemic mixture (a) or and the separate R(−) isomer (c) compared with the S(+) isomer (b). This lag of the S(+)- form is considered to be a consequence of the metabolic conversion of the R(−)- to S(+) forms (Rudy et al. 1992; Brocks and Jamali 1999; Graham and Williams 2004; Fig. 2.4; Table 2.1).

A typical set of quantitative pharmacokinetic parameters for the R(−)- and S(+)-isomers of racemic ibuprofen taken orally by healthy human volunteers at an OTC dose of 400 mg is shown in Table 2.1. Here, it is evident that the rate of elimination k_{el}, of S(+) ibuprofen is lower than that of the R(−)-enantiomer and this may reflect the combination of longer $t_{1/2}$, and lower clearance of the S(+) enantiomer compared with that of the R(−) antipode. The C_{max}, AUC and mean residence time (MRT) for S(+) ibuprofen are all greater than that of the R(−) enantiomers,

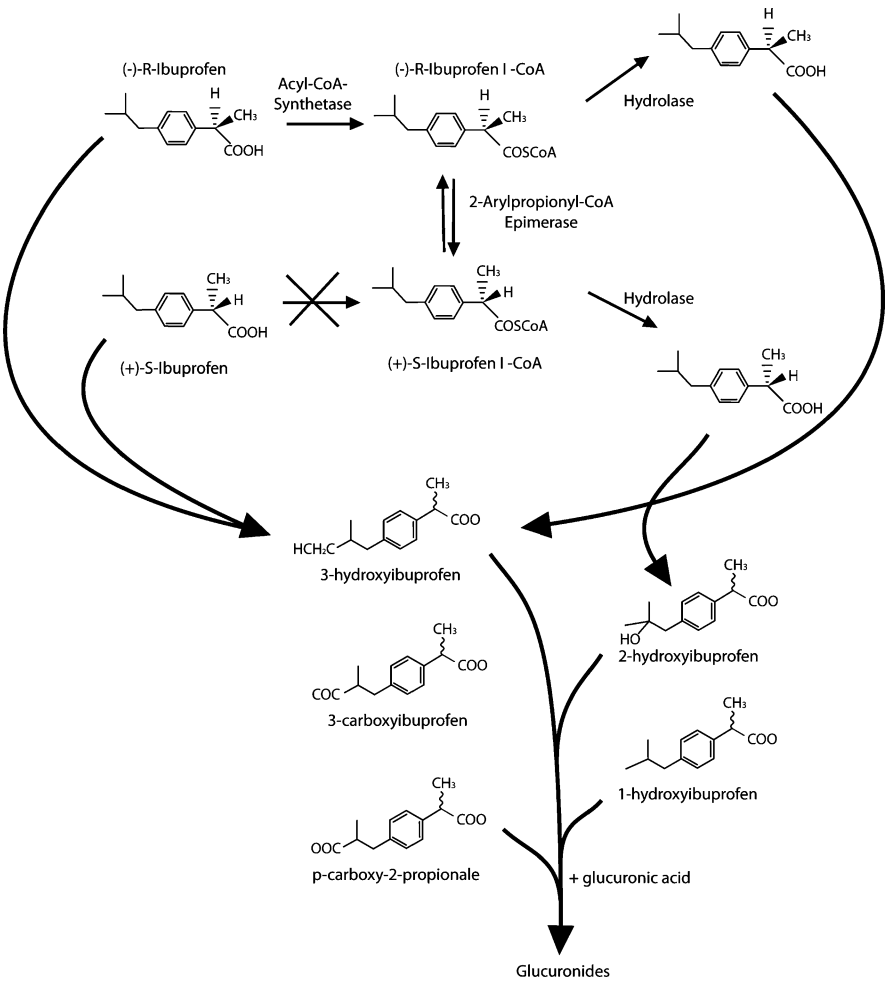


Fig. 2.2 Metabolism of the PG (COX) inactive R( ) ibuprofen to the COX inhibitory or active S(+) antipode catalysed by 2 aryl proprionyl coenzyme A epimerase (Reichel et al. 1997) and subsequent oxidative reactions and glucuronidation. About 40 60 % of the R( ) ibuprofen is converted to the S(+), whereupon there may be addition of glucuronic acid to form acyl (i.e. carboxyl) glucuronides and hydroxylation of the *tert* butyl side chain to form 1 , 2 or 3 hydroxyl ibuprofen metabolites, and subsequently 3 carboxy ibuprofen from 3 hydroxy ibuprofen (Brocks and Jamali 1999; Graham and Williams 2004). The formation of the hydroxyl and carboxy metabolites is catalysed by cytochromes P 450. The carboxy metabolite may be subsequently glucuronidated to form the acyl glucuronides Holmes et al. (2007). All these metabolites appear to be pharmacologically inactive, and these metabolic pathways constitute detoxification of the drug. Additionally, a disopyramide metabolite has been identified in human urine by NMR and MS hyperspectroscopy (Crockford et al. 2008), but the metabolic origins and fate of this are unknown. Mixed triglyceride derivatives (termed hybrid lipids) of ibuprofen have been identified (Williams et al. 1986), and are synthesised following the formation of the ibuprofen thioester of coenzyme A through a corruption of the short medium fatty acyl coenzyme A synthetic pathway. These metabolites are present in small quantities relative to other triglycerides in liver cells, adipose tissue, and plasma, and they have slow turnover (Brocks and Jamali 1999; Graham and Williams 2004). Little is known about the pharmacological activity of these hybrid triglycerides

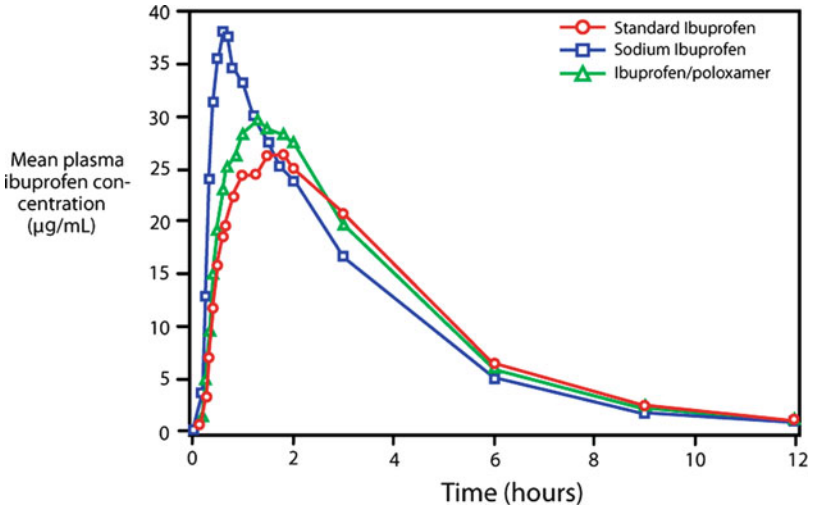


Fig. 2.3 Mean plasma concentration profiles of racemic ibuprofen (determined by LC MS) following oral ingestion of a single dose of: (a) 2 × 200 mg tablets of ibuprofen acid ["standard ibuprofen" in the figure, i.e., Nurofen®], (b) 2 × 256 mg tablets of sodium dihydrate ibuprofen ["sodium ibuprofen", with the equivalent mass of ibuprofen to that in (a)], and (c) 2 × 200 mg ibuprofen acid in which is incorporated 60 mg poloxamer as a solubilising excipient ["ibuprofen/poloxamer"]. The sodium ibuprofen achieved the shortest t_{max} of 35 min and higher C_{max} of 41.47 µg/mL, compared with that of standard ibuprofen (acid) with a t_{max} of 90 min and C_{max} of 31.88 µg/mL, while the ibuprofen/poloxamer had a t_{max} of 75 min and a C_{max} of 35.22 µg/mL, which was a shorter time interval but little difference in C_{max} compared with the latter. The bioavailability of ibuprofen from all these formulations was similar [expressed as $AUC_{0\ inf}$ (range 117 122 µg/h/mL) and $AUC_{0\ 4}$ (range 115 120 µg/h/mL)], and amounted to approximately 100 %. Redrawn and reproduced with permission from Dewland et al. (2009) under the terms of BMC Open Access

reflecting the increase in formation of the S(+) over the R(−) antipode. Overall, these data confirm the dynamic formation of the S(+) enantiomer from R(−) ibuprofen in accordance with the mechanism of inversion as shown in Fig. 2.4. This emphasises the importance of the enantiomeric conversion of ibuprofen for the actions of this drug on prostaglandin-related inflammation.

Ibuprofen is extensively metabolised in humans to hydroxyl, carboxyl, and glucuronyl metabolites which are pharmacologically inactive (Brocks and Jamali 1999; Graham and Williams 2004; Holmes et al. 2007). Ibuprofen glucuronide can also form irreversibly bound drug protein adducts in vitro, including those to albumin (Castillo et al. 1995). The stability and reactivity of these different adducts is not known.

Like that of other NSAIDs, ibuprofen displays extensive (~99 %) binding to plasma proteins (Brocks and Jamali 1999; Graham and Williams 2004). Thus, there is a relatively low volume of distribution of the drug of approximately 10 20 l in adult volunteers (Table 2.1) as well as in patients. The non-linear PKs of ibuprofen at high doses are due to saturation of plasma protein binding.

Simulations of the rate of absorption on the relative t_{max} of the enantiomers of ibuprofen in the presence and absence of pre-systemic inversion support the view

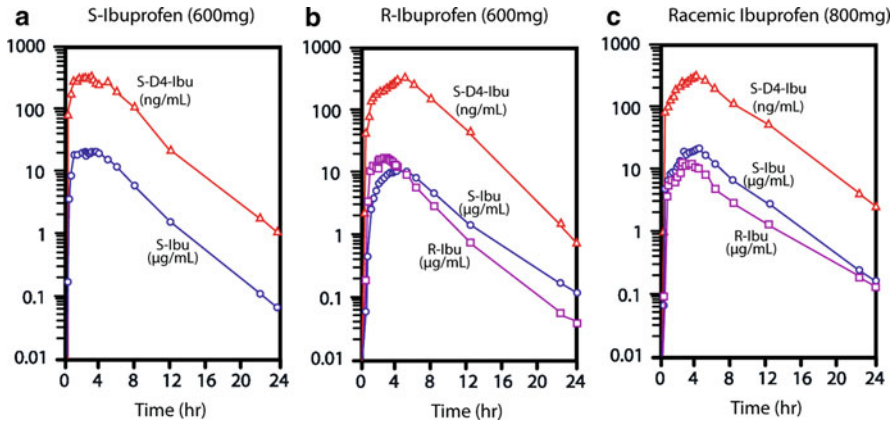


Fig. 2.4 Mean serum concentrations of S(+) ibuprofen (*open circles*) or R( ) ibuprofen (*open squares*) with time after oral intake by healthy human volunteers of 600 mg S(+) ibuprofen (**a**), 600 mg of R( ) ibuprofen (**b**), or 800 mg of the racemate (**c**). Note the appearance of S(+) ibuprofen following that of the R( ) isomer both after intake of R( ) ibuprofen (**b**) and the racemic mixture (**c**). The studies were undertaken using a stable deuterium isotope methodology (Rudy et al. 1992). Modified from Rudy et al. (1992) with the tracing of the internal standard of S D_4 ibuprofen shown in *red*. Reproduced according to the proprietary rights and permission of The Journal of Pharmacology and Experimental Therapeutics

Table 2.1 Pharmacokinetic parameters for oral ibuprofen (400 mg)

Data analysis	S ibuprofen	R ibuprofen
Non compartmental analysis		
K_e (h^{-1})	0.359 ± 0.128	0.538 ± 0.087*
$t_{1/2}$ (h)	2.18 ± 0.83	1.33 ± 0.25
t_{max} (h)	1.64 ± 0.71	1.59 ± 0.77
C_{max} (µg/mL)	19.0 ± 4.7	17.8 ± 3.3
AUC (µg/h/mL)	75.0 ± 27.1	52.2 ± 11.5*
AUMC (µg/h/mL)	328 ± 229	155 ± 72*
MRT (h)	4.08 ± 1.52	2.86 ± 0.79*
Cl/*F* (L/h)	2.90 ± 0.73	4.00 ± 0.85*
V_d/F (L)	8.61 ± 2.63	7.46 ± 1.22
Compartmental analysis		
V_d/F (L)	6.28 ± 2.2	
K_a (h^{-1})	1.08 ± 0.95	
K_e (h^{-1})	0.50 ± 0.22	

*Indicates statistically significant difference at $P < 0.05$. Values are means + SD. From Suri et al. (1997a)

that a pre-systemic process predominates in the chiral inversion of ibuprofen. This pre-systemic inversion of ibuprofen takes place in the GI tract.

As shown in Fig. 2.5, there is approximate linearity in the values of C_{max} and AUC with dosage of ibuprofen.

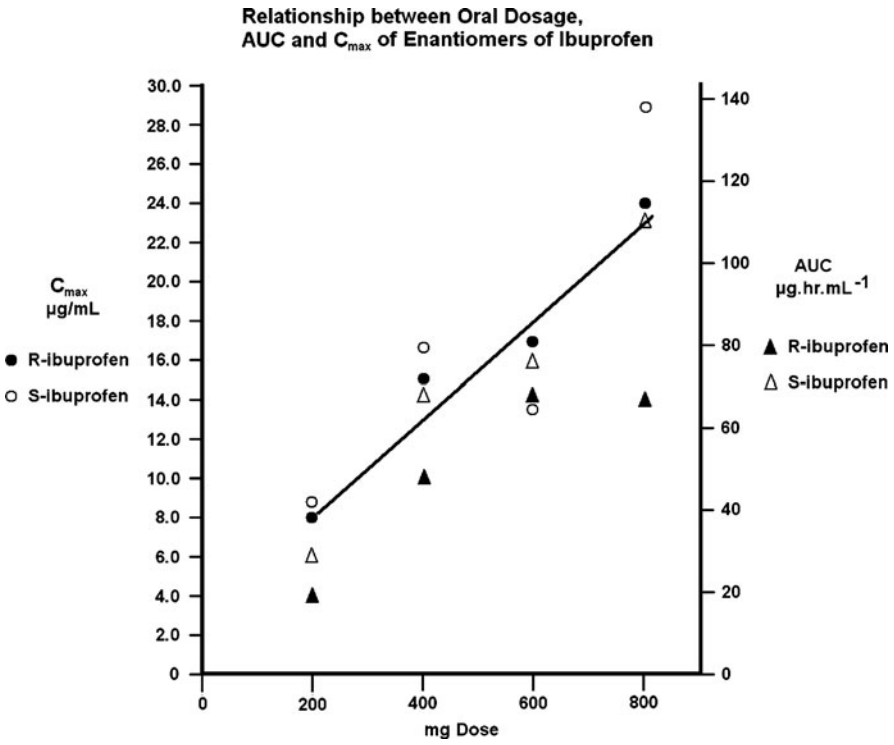


Fig. 2.5 Relationships between dose of ibuprofen and the C_{max} and AUC of the R( ) and S(+) enantiomers

The synovial compartment is considered a site of action, and several studies have shown the accumulation of either racemic ibuprofen or its enantiomers in the synovial fluid of arthritic patients requiring aspiration of synovial effusions of the knee (Whitlam et al. 1981; Gallo et al. 1986; Day et al. 1988; Cox et al. 1991; Seideman et al. 1994; Elmquist et al. 1994; Dominkus et al. 1996). The accumulation of ibuprofen occurs to about 40 60 % of the concentration of the drug in plasma or serum. The t_{max} in synovial fluid of both enantiomers lags approximately 2 h behind that in serum or plasma. The mean rate constants for ibuprofen transfer into and out of the synovial fluid are 0.91 and 0.34 h^{-1} respectively (Seideman et al. 1994). The mean S:R ratio of AUC in synovial fluid is 2.1 compared with 1.6 in plasma, with a linear relationship between the two (Day et al. 1988). The protein content (mostly albumin) is a major contribution to ibuprofen kinetics into synovial fluid as the drug is strongly bound to synovial fluid, though not to the extent of that in plasma (Whitlam et al. 1981; Gallo et al. 1986; Cox et al. 1991).

Since the pathways in the CNS underlie the antipyretic and analgesic properties of NSAIDs, including ibuprofen, the potential for uptake of ibuprofen enantiomers into the CSF was studied by Bannwarth et al. (1995). They found that the $AUC_{0–8h}$ of the R and S enantiomers in CSF were 0.9 % and 1.5 % respectively of those in plasma, which reflects the higher unbound fraction of the S enantiomer in plasma.

As in the synovial fluid compartment, the peak ibuprofen enantiomer concentrations are present in CSF later than in plasma, and are attributed to passive transport of drug into the CSF. Higher concentrations of ibuprofen enantiomers were present in the CSF than could be accounted for on the basis of the unbound concentration in plasma. The S:R ratios of ibuprofen enantiomers in CSF was found to be 2:1, similar to that of unbound drug in plasma but higher than in the synovial fluids suggesting that the outward kinetics of the enantiomers determines the ratio of R:S in the CSF compartment.

These studies on the kinetics and disposition of ibuprofen and its enantiomers in synovial fluids and the CNS form an important basis for understanding the analgesic actions of the drug in these compartments.

2.1.1 Impact of Variability in Pharmacokinetics

The pharmacokinetic (PK) variations with individual NSAIDs may constitute an important reason for their differing toxicities and occurrence of ADRs in different organ systems. A concept of the TRIAD toxicity may be postulated to show these inter-relationships between PK and PD or relatively toxicity of NSAIDs, as shown in Fig. 2.6.

The pathways of oxidative metabolism of ibuprofen are shown in Fig. 2.1. These principally involve the cytochromes P_{450} 2C9 (CYP-2C9), CYP-2C8 and 2C19 participating in the oxidation of the alkyl side chain to hydroxyl and carboxyl derivatives. These cytochromes are coded by a gene cluster on chromosome 10q24 (Mo et al. 2009). CYP-2C9 is probably the most abundant of these three cytochromes, and metabolises about 20 % of clinically used drugs of a wide variety of pharmacological classes (amounting to some 120 in all) (Mo et al. 2009). With such wide substrate specificity, it is not surprising that there are extensive drug interactions at the level of CYP-2C9 as well as CYP-2C19. The S(+) and R(−) isomers have approximately the same kinetic constants for hydroxylation at their 2-or 3-position (Hamman et al. 1997).

Differential metabolism of S(+) and R(−) ibuprofen occurs as a result of CYP-2C9, CYP-2C19 and CYP-2C8, with these being referred to as S(+) ibuprofen and R(−)-ibuprofen hydroxylase activities respectively (Kirchheiner et al. 2002). Of the allelic frequencies of these CYP isoenzymes, the three ascribed to CYP-2C9 comprise the wild type CYP-2C9*1 which is characterised by an arginine at codon 359 on the gene. In the variant CYP-2C9*2, this arginine is replaced by cysteine, and in the variant CYP-2C9*3 the isoleucine-359 is replaced by leucine. In vitro studies and human PK studies have shown that CYP-2C9*2 has only slightly less activity than that of the wild type CYP2C9*1, whereas that of CYP-2C9*3 is 10 30 % less so (Kirchheiner et al. 2002). In comparisons of the pharmacokinetics of the S(+) enantiomer, the rates of clearance were found to

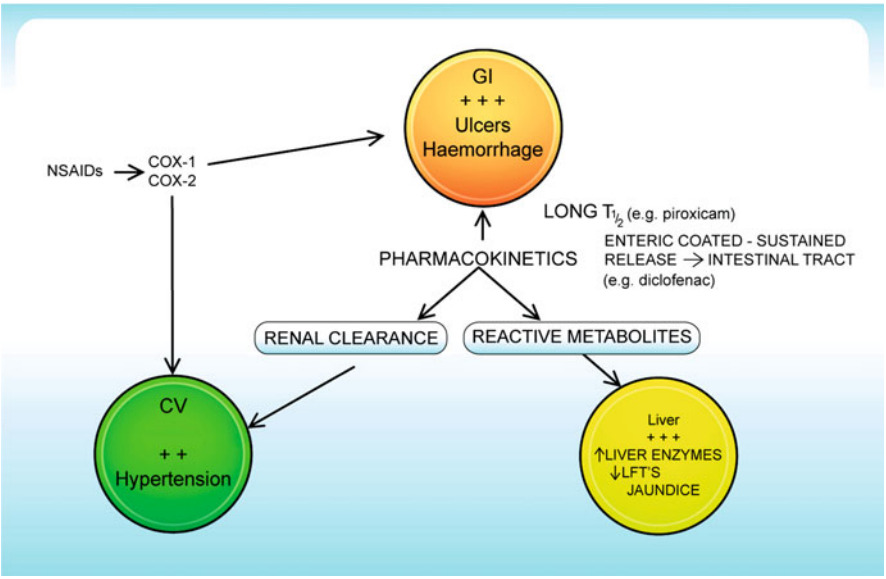


Fig. 2.6 Postulated inter relationships between differences in PK of NSAIDs and their propensity to develop toxicity or ADRs. Based on Rainsford et al. (2008a, b)

parallel the enzymic activity, with subjects having the CYP-2C9*1/*2 and *3/*3 variants having 27 % and 53 % less clearance than those with the wild type *1/*1 genotype (Kirchheiner et al. 2002). For other NSAIDs (e.g., celecoxib, diclofenac) there is either increased or decreased clearance in individuals with these isoforms. These aspects are discussed in Sect. 6.3 on "Pharmacokinetic Variations". Thus, overall it can be stated that there is marked variation in the PK of ibuprofen and other NSAIDs according to the CYP-2C9 status.

Single nucleotide polymorphism studies in 45 populations worldwide have highlighted the global variation that occurs in different populations in the CYP2C8 and CYP2C9 functional haplotypes (Speed et al. 2009). It has been suggested from these studies that global variation in these cytochromes may account for the substantial variations in drug metabolism, response, and toxicity. One such example of the functional impact shows that increased risks of international normalisation ratio (INR) may be seen in patients receiving warfarin who have the *2 and *3 variants of CYP2C9 system (Lindh et al. 2005).

As far as other indications of the significance of CYP polymorphisms, studies by Pachkoria et al. (2007a, b) have examined the role of CYP-2C9 and CYP-2C19 polymorphisms for associations with drug-induced idiosyncratic reactions. While arguably liver reactions from NSAIDs have been associated with abnormalities of phase 1 and phase 2 metabolism, the studies by Pachkoria et al. (2007a, b) have failed to establish if polymorphisms of CYP-2C9 or CYP-2C19 are associated with liver disease.

In summary, the key pharmacokinetic properties of ibuprofen (Rainsford 2009) include:

1. Depending on the particular formulation there are relatively fast rates of absorption of the drug, with subsequent "first pass" liver phase 1 and phase 2 metabolism to well-characterised (a) phenolic and carboxylic acid derivatives via CYP-2C8, CYP-2C9 and CYP-2C19 activities, and (b) subsequent conjugation with glucuronic acid and taurine (a minor metabolite).
2. The overall biodisposition of ibuprofen is a consequence of high plasma protein binding and low volume of distribution, but with the capacity to be accumulated in appreciable quantities in inflamed compartments where there is need for anti-inflammatory/analgesic activity (synovial fluids, CSF), but not in those sites in which side-effects occur (Brune 2007).
3. Ibuprofen has a relatively short plasma elimination half-life, and although prolonged in liver and renal diseases this is not so appreciable as to be a factor accounting for a high frequency of adverse events. Indeed, the longer $t_{½}$ has been suggested as a factor accounting for low incidence of serious GI events (bleeding, peptic ulcers) (Henry et al. 1996, 1998; see Chap. 7).
4. Ibuprofen exhibits approximately linear kinetics to within 1,200 mg dosage, or near compliance with predictable kinetics.
5. Chronic disease states (arthritis) have relatively little impact on the overall kinetics of ibuprofen. However, acute surgical pain reduces the plasma concentrations of R(−) and S(+)-ibuprofen, which may arise from the stressful conditions of the surgery (Jamali and Kunz-Dober 1999). This has been suggested as evidence for considering dosage adjustment in the therapy of acute surgical pain on the basis of allowance for increasing dosage to meet adequate pain control. However, other studies reviewed in the next section suggest that 400 600 mg ibuprofen produces adequate pain control in dental surgery, with in some reports evidence of superiority over paracetamol (1,000 mg) (see Chap. 4).
6. The $t_{½}$, AUC, V_d, and clearance kinetics of conventional ibuprofen tablets are consistent with the usual dosage regime of either 400 mg t.i.d. for OTC use or 400 800 mg t.i.d. or q.i.d. as appropriate for prescription use to 2,400 mg daily. Extended release formulations that have been developed could enable twice daily dosage to limits of 1,200 mg/day OTC or 2,400 mg/day prescription requirements.

2.2 Plasma/Serum Concentrations Relevant to Onset of Analgesia

One of the basic tenets of pharmacology is that drug molecules exert influence on cells or molecules in order to produce a pharmacological response (Rang et al. 2003; Brunton et al. 2008). To achieve this, drugs must penetrate or be present in

defined concentrations adjacent to cells to enable them to interact with specific receptors (Rang et al. 2003). The properties governing the concentration of drugs at their receptors depend on the physicochemical properties that underlie their properties of absorption, distribution, metabolism, and elimination (ADME) their pharmacokinetics (PK). Thus, it is axiomatic that for understanding the therapeutic actions of drugs it is necessary to be able to quantify the amount of drug (or metabolite[s]) in the circulation, i.e., in blood or plasma/serum, and to determine their "free" (i.e., unbound form) or active concentration (Brunton et al. 2008). The situation for the non-steroidal anti-inflammatory drugs (NSAIDs) and non-narcotic analgesics (NN analgesics) is complicated, because these drugs have multiple modes of action and varying potencies as anti-inflammatories, and specifically, as pain-relieving agents (Rainsford 1996). Thus, differentiating the quantitative actions or potencies of these agents depends on knowledge of the amounts of drugs that are in the circulation, and thence how much of the drugs will penetrate to their sites of action (Orme 1990). Plasma concentrations of NSAIDs can be correlated to their clinical effects when certain criteria (analytical methodology, principles of distribution equilibrium, and other PK properties and specific mechanisms of their actions) are known (Orme 1990). Ranges of plasma concentrations for their therapeutic and toxic effects are well-established for many drugs, and particularly for NSAIDs and NN analgesics that are used in the relief of acute and chronic pain (Orme 1990; Rainsford 1996; Suri et al. 1997a; Graham and Scott 2003).

In order to derive values of the therapeutically relevant plasma concentrations (TRPC) of ibuprofen, information was derived from published studies in various acute and chronic (arthritis) studies and acute experimental pain models in humans, in which plasma concentrations of the racemic or enantiomeric forms of the drug were compared with therapeutic response, comprising the relief of pain symptoms or the pharmacological actions as attributed to the S(+) and R(−) in reducing circulating levels of the cyclo-oxygenase products.

Attempts to model therapeutically-relevant drug concentrations are governed by (a) the respective PK parameters at which pain responses can be directly related, (b) the contribution of the individual enantiomer concentrations to their pharmacodynamic (PD) activity (assuming the fact that the S(+) isomer is the relevant enantiomers for both pain relief and prostaglandin synthesis inhibitory actions), and (c) the impact of different painful conditions on both the PK of ibuprofen and the analgesic responses.

In modelling of the data on PK in relation to PD from published studies it is possible to take two approaches: (1) select data at the earliest period when there is significant increase in plasma concentrations and relate this to the development of the analgesic response, or (2) to select data on the plasma concentrations of the drug, C_p, at the lowest effective dose of the drug (400 mg) and relate this to analgesic activity; the latter occurs mostly after the peak concentrations of the drug. Using data derived from the third molar dental surgery pain model, it has been possible to identify the earliest significant analgesic activity from ibuprofen 400 mg at 0.5 h associated with serum concentrations of 17.5 μg/mL of racemic ibuprofen.

In less severe inflammatory conditions than observed in dental surgery it is established that the lowest dose of 200 mg ibuprofen can be effective in relieving symptoms of mild pain (headache, colds, acute injuries). Under these circumstances, lower TRPC is anticipated. Thus, in considering the TRPC of ibuprofen, it is important to identify the degree of pain and inflammation accompanying the respective painful conditions.

A central question concerning the therapeutics of ibuprofen is: what concentrations of the drug in plasma are required to achieve analgesic and/or anti-inflammatory activity? This question can be divided into several parts:

1. What are the minimal concentrations required to achieve analgesic effects?
2. Do these minimal concentrations and the other pharmacokinetic (PK) parameters of ibuprofen differ in various pain states?
3. What is the relationship between the individual enantiomer concentration and the development of analgesia?
4. What is the relationship between inhibition of ex vivo production of prostaglandins (via COX-1 and COX-2 inhibition) and plasma concentrations of ibuprofen (in racemic or enantiomeric forms), and how does this relate to the analgesic activity of the drug?
5. What are the relevant plasma concentrations of ibuprofen (in racemic or enantiomeric forms) at which pain relief and anti-inflammatory activities are achieved in arthritic pain conditions?

Since ibuprofen is chemically a diastereoisomeric equal mixture of R(−) ibuprofen and S(+) ibuprofen (Brocks and Jamali 1999; Rainsford 2009), it is important to consider the respective contribution of the S(+) enantiomer, since this is considered the "active" form of the drug as it is the more potent inhibitor of the two of prostaglandin synthesis (Rainsford 2009). This effect of ibuprofen is amongst the principal modes of action of the drug in controlling pain, but other activities underlie other anti-inflammatory effects of the drug which contribute to pain reduction (Rainsford 2009). Following absorption, about 40 60 % of the R(−) enantiomer is metabolised principally in the liver to the S(+) form, so that about 80 90 % of the ingested drug is in the active S(+) form.

Thus, from the point of view of estimating the TRPC of ibuprofen, it is possible to consider the amounts in circulation of both the racemic [i.e., R(−) + S(+)] forms as well as the S(+) enantiomer as being therapeutically relevant. Indeed, one estimate (Brocks and Jamali 1999) claims that attainment of the S+R (i.e., racemic) concentration range of 11 30 μg/mL 1 h post-dose was needed for complete pain relief in a study by Laska et al. (1986). However, the procedures used to calculate this and the dose of drug were not specified. In the study by Laska et al. (1986), the conditions for estimating the range of plasma or serum concentrations required for pain relief in various painful conditions have been determined.

The PK and pharmacodynamic (PD; analgesia) data used for the analysis described here were selected from relevant literature, and models for understanding the relationships between ibuprofen concentrations and therapeutic responses have either been discussed or derived from these data. It should be noted that there have

been several reviews published on the general PK/PD properties of ibuprofen in which general aspects of the relationships between PK properties and therapy have been reviewed. These articles do not, however, address the central issues posed by the above question.

Most of the data reviewed in relation to questions (1) to (4) are derived from studies using the acute dental pain model, in which pain responses and analgesic activity of ibuprofen have been determined in double-blind, placebo controlled trials. In many respects, this is about the most satisfactory clinical pain model of acute pain which has a pronounced local inflammatory component. Analgesic activity is usually achieved in this model at the lowest dose of 400 mg ibuprofen (sometimes even 200 mg), and thus pain relief is at doses within those recommended for non-prescription pain relief. It is possible to accurately quantify the analgesic effects in this model using well-established methodology. There have been several studies reported in which plasma or serum concentrations have been related to analgesic activity, using either the third molar dental extraction model or that following induction of acute pain from locally applied stimuli. Comparisons of the analgesic responses in these different acute pain models are useful for discriminating the varying analgesic responses in a quantitative and time-dependent manner.

2.2.1 Dental Pain Model

The third molar extraction model, or variants thereof, has proven the most reliable and sensitive method for determining the acute pain relief afforded by analgesics, whether narcotic or non-narcotic (Dionne 1998; Moore et al. 2011a, b).

Most dental pain studies in which racemic ibuprofen has been administered within 30 min of pain show onset of analgesic activity within 30 min and peak activity at 2 3 h post drug administration (Cooper 1984; Cooper et al. 1989; Dionne and Cooper 1978, 1999; Laska et al. 1986; Jain et al. 1986; Seymour et al. 1991, 1996, 1998, 1999; Walker et al. 1993a; Jones et al. 1997; Averbuch and Katzper 2003; Barden et al. 2004; Malmstrom et al. 2004; Schleier et al. 2007; Daniels et al. 2009, 2011; Figs. 2.7 and 2.8).

The analgesic activity from ibuprofen is usually accompanied by reduction in oedema in the inflamed tissues around the area of extracted tooth (Dionne and Cooper 1999; Bjørnsson et al. 2003). Some studies have compared the time-course of analgesia by ibuprofen with serum/plasma concentrations of the drug (Laska et al. 1986; Jones et al. 1997; Hersh et al. 2000a; Fig. 2.8). In one study, there were no significant correlations between efficacy measures and the PK parameters comprising C_{max}, t_{max} or AUC following a single dose of 400 mg ibuprofen (Jones et al. 1997).

The study by Laska et al. (1986) (Fig. 2.8) was the first study designed to compare serum concentrations with analgesic response following 400, 600 or 800 mg ibuprofen in patients with moderate to severe pain after third molar extraction. The authors found that serum levels correlated with global analgesic response measured by the sum of pain intensity difference (SPID) scores, but the

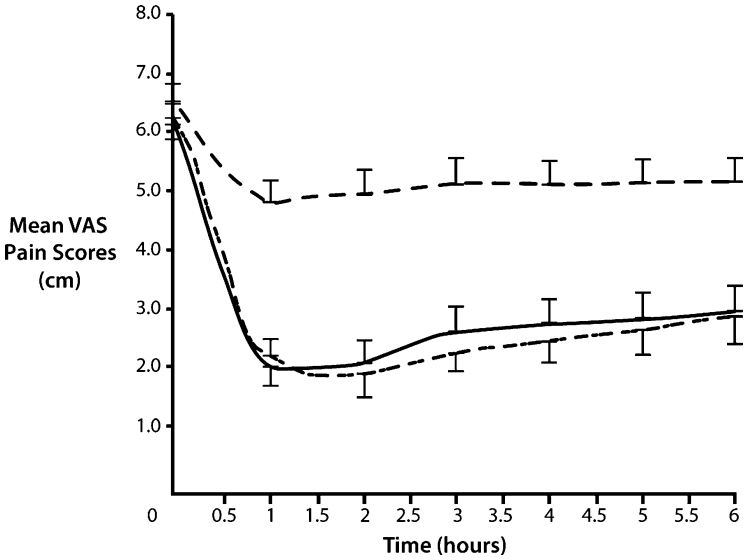


Fig. 2.7 Time courses of the mean pain scores (determined from 100 mm visual analogue scales) (±SEM) in randomised controlled studies in which patients undergoing third molar surgery received treatment with placebo (*small dashed line*) ibuprofen 400 mg as a liquid in soft gelatin capsules (*continuous line*) or ibuprofen 400 mg tablets (*dashed line*) in a double dummy array. Statistically significant differences from 1 to 6 hr between the values for ibuprofen and placebo ($P < 0.05$). Note that these were apparent at, or after, 30 min of treatment. Redrawn from Seymour et al. (1991), reproduced with permission of Wiley Blackwell for the British Journal of Clinical Pharmacology

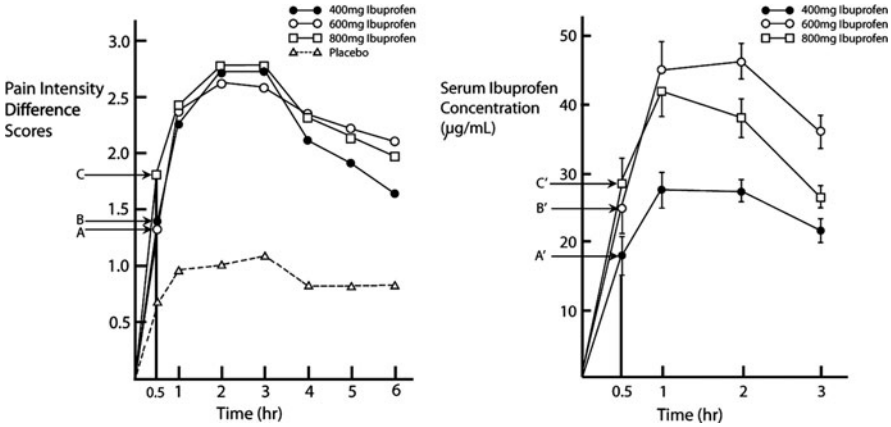


Fig. 2.8 Redrawn from Laska et al. (1986) with modifications showing calculations of effective doses and serum concentrations (i.e., A, $A,'$ B, B', C, and C' respectively) as shown in the figure

correlation coefficients ($r = 0.28$, 0.34, and 0.26 for the three dose levels of 400, 600, or 800 mg) appeared rather low. This was probably due to the doses employed being at the upper limit for near maximal response; the doses of 600 and 800 mg being at the upper limit for response (Fig. 2.8). It is noteworthy that most other

studies on the effects of ibuprofen in the third molar dental pain model have shown that effective doses for analgesia were 400 mg, with a few at 600 mg ibuprofen.

Given these limitations, it is possible to use the information in this study by Laska et al. (1986) to give some estimates of relevant therapeutic concentrations of ibuprofen. There are several approaches which can be employed:

1. Taking data on serum concentrations at the earliest point at which there is a statistically significant difference in analgesic activity (i.e., pain intensity difference scores) (see Fig. 2.8), gives a time of 0.5 h. The right side graph in Fig. 2.8, gives values for the serum concentrations for the 400 mg dose of approximately 17.5 μg/mL, for the 600 mg dose 24.8 μg/mL and the highest dose of 800 mg gives 28.8 μg/mL.
2. Taking the maximal serum concentrations of ibuprofen at 1 h those for the 400 mg dose would approximate to 27 μg/mL; at the 600 mg dose this would be 42 μg/mL and at the 800 mg dose about 45 μg/mL ibuprofen. This would seem at variance with the previously mentioned statement by Brocks and Jamali (1999) that the S + R (i.e., racemic) concentration range is 11 30 μg/mL 1 h post-dose.
3. If data for the onset of analgesia for 15 and 20 min period were available, it might be possible to derive an earlier time estimate of the serum concentrations at this period which might be statistically significant. By visual inspection of the graphs in Fig. 2.8, an approximate estimate of 10 μg/mL of ibuprofen appears to coincide with reduction in pain at about 15 20 min.

The study by Schou et al. (1998), showed that the pain intensity difference (PID) and pain relief (PAR) scores were dose-related, with the peak of these scores at 2 3 h. Compared with PK values for the drug, it is evident that the peaks of pain relief follow those for the peak plasma levels.

Dose response effects of ibuprofen 50 400 mg on pain parameters have been shown in the dental pain model by Schou et al. (1998) (Fig. 2.9). An estimate of the number of patients with at least 50% pain relief from the percent maximum of TOTPAR and SPID values has been derived from meta-analyses by McQuay and Moore (2007). Using a similar approach, Li Wan Po (2006) calculated dose response data from a large study in 258 Danish patients, in which the analgesic effects of 50 400 mg ibuprofen were compared (see Fig. 2.9). The 50% pain responses calculated by Li Wan Po (2006) are shown in Fig. 2.9. These data show there is a linear dose response in the analgesic parameters ranging from 50 to 400 mg ibuprofen. Thus, using doses of 2 × 200 mg or 400 mg ibuprofen in comparisons of PK of ibuprofen with the time-course of analgesia from *rac*-ibuprofen lysinate (Nelson et al. 1994) would appear to show that the earliest significant pain relief is evident at 30 min, at which there is a significant plasma concentration of R(−) and S(+) ibuprofen (Lötsch et al. 2001; Fig. 2.10). This time point may be used to derive the effective therapeutic concentrations required for the earliest onset of effects of the racemic drug. This would appear to be approximately 25 30 μg/mL for the racemate, 15 μg/mL for the S(+) isomer and 14 μg/mL for the R(−) isomer (see Fig. 2.10), based on the extrapolation of the time to reach specific concentrations. At least by 1 h (t_{max}) the C_{max} value can be confidently used for calculations of the therapeutically-relevant concentrations at t_{max}.

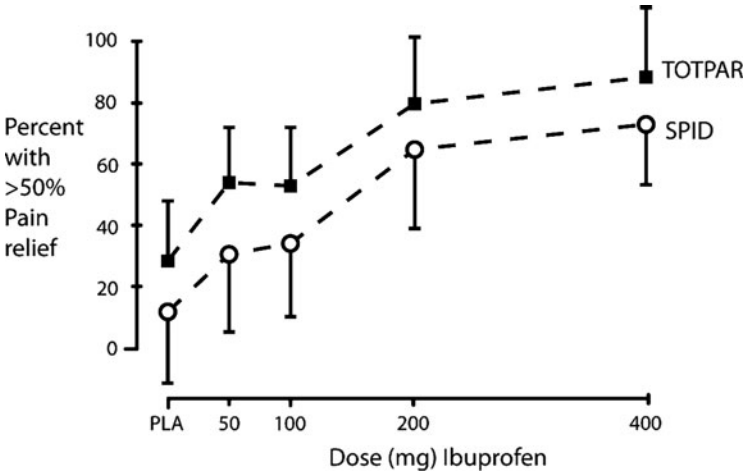


Fig. 2.9 Dose response of ibuprofen in the third molar dental pain model in which the percentage of patients showing greater than 50 % pain relief is shown in relation to data of Schou et al. (1998) on the sum of pain intensity difference (SPID) (*open circle*) and total rain relief (*filled circle*). These data show that doses of 200 mg and 400 mg produce >50 % pain relief. Re drawn from: Li Wan Po (2006). Reproduced with permission of John Wiley and Sons, publishers of the British Journal of Clinical Pharmacology. *PLA* Placebo

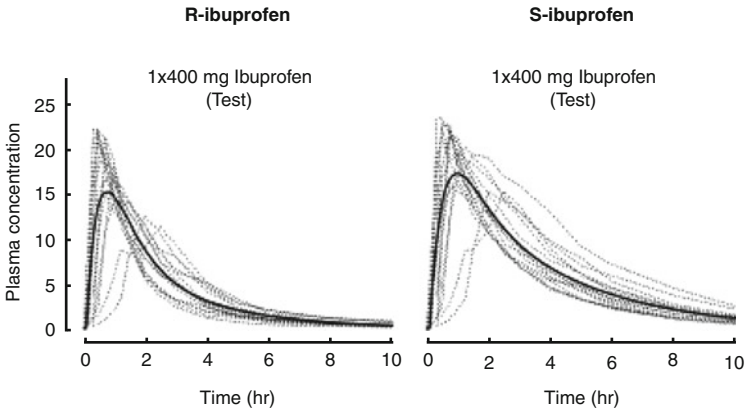


Fig. 2.10 Time course of plasma concentrations of ibuprofen enantiomers following 400 mg ibuprofen lysinate (test) tablets. From Lötsch et al. (2001), reproduced with permission of John Wiley and Sons, publishers of the British Journal of Clinical Pharmacology

A possible confounder of these estimates might be the time of intake of the drug in relation to surgery. This suggestion arises from the observations by Jamali and Kunz-Dober (1999), who showed that when ibuprofen 200 mg or 600 mg was taken following third molar surgery there was about a 2-h delay in the mean time to peak concentrations. The S(+) ibuprofen serum concentrations were more markedly affected than those for the R(−) enantiomers. If the drug was taken prior to surgery, then the t_{max} for both enantiomers was 1 h for both doses, and this is within the range of the t_{max} in normal volunteers.

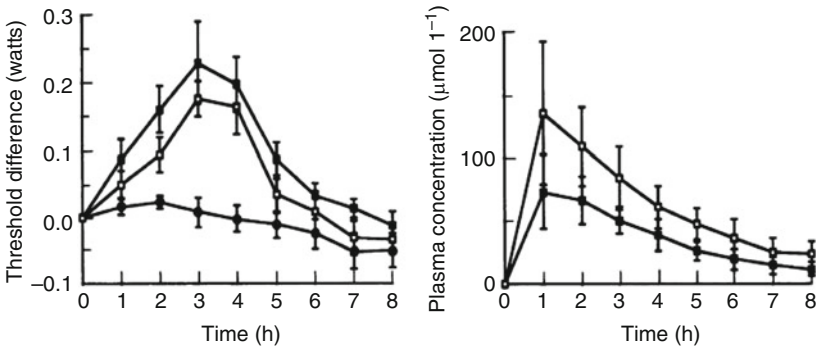


Fig. 2.11 Time course of pain responses from laser induced pain applied to right hand dorsum (*left graph*) compared with the plasma concentrations of the prostaglandin synthesis inhibitory S (+) ibuprofen active enantiomer (*right graph*). The pain threshold differences (mean ± SEM, watts; *left graph*) and plasma concentrations (μmol/L; *right graph*) are shown following intake of 400 mg (*filled square*) or 800 mg (*open square*) ibuprofen, or placebo (*open circle*) in the pain measurements. Reproduced from Nielsen et al. (1990) with permission of John Wiley and Sons, publishers of the British Journal of Clinical Pharmacology

2.2.2 Induced Pain Models

A number of studies have been performed in which the nociceptive responses induced by various peripheral stimuli have been employed to investigate the analgesic responses to ibuprofen but without investigating the time-course of plasma concentrations of ibuprofen (see Walker and Carmody 1998; Walker et al. 1993a; Growcott et al. 2000; Sycha et al. 2003).

Amongst the first studies in which plasma ibuprofen concentrations were compared with the time course of analgesic response was a model of pain from the laser-induced stimulus applied to the dorsum (C7-dermatome) of the right hand, investigated by Nielsen et al. (1990). In a double-blind, placebo-controlled, three-way crossover study, these authors compared the effects of 400 mg and 800 mg racemic ibuprofen tablets. The results of this study (Fig. 2.11) show that the peak plasma concentrations of ibuprofen enantiomers were evident at 1.4 1.5 h, while the peak of analgesia occurred at 3 h. This shows that there is a clear differentiation between the absorption of ibuprofen and the later onset of analgesic effects. The use of the earliest onset of analgesia in relation to drug concentration as applied previously does not appear applicable in this case. However, the relationship between analgesia and peak concentrations of ibuprofen can be established using C_{max} (at t_{max}) of the S(+) and R(−) enantiomers. Unfortunately, values for R(−) ibuprofen were not stated. Thus, the concentrations of S(+) ibuprofen peaked at 1.2 1.5 h, these being 18.2 μg/mL (from a 400 mg dose) and 27.8 μg/mL (from a 800 mg dose) respectively.

Kobal et al. (1994) investigated the effects of ibuprofen 400 mg and 800 mg on the EEG activity over three positions (Fz, Cz, Pz) in response to application of two

pulses of CO_2 applied to the right nostril while the left nostril was stimulated with a stream of dry air. The volunteers recorded the intensity of painful stimuli by visual analogue scales (VAS). This so-called chemo-somatosensory model is in the experience of the author of this report so objectionable that it is difficult to determine whether the responses are due to painful stimuli from cold CO_2 per se or are a result of reflex irritation. The peak plasma concentrations of racemic ibuprofen were obtained at 90 min after intake, and were 28 μg/mL (after a dose of 400 mg) and 41.7 μg/mL (after a dose of 800 mg) respectively. There did not appear to be any time-course data available in this study. The pain intensity estimates did not reach a level of significance, so the experimental design would appear to be somewhat flawed.

Another approach by the same group (Hummel et al. 1997) using a modification of the above CO_2 nasal irritation system in which pulsed stimuli were employed to compare the effects of proprietary tablets of racemic ibuprofen 400 mg and 800 mg with an effervescent formulation of the same doses of the drug in a randomised, double-dummy crossover study. The authors also performed a comprehensive plasma concentration profile of ibuprofen, with both enantiomers being measured.

The plasma concentrations of R(−) and S(+) ibuprofen were greater overall at earlier time intervals in the subjects that received the effervescent ibuprofen preparation than in those that received the tablet formulation. Using measurements of EEG components, there did not appear to be any consistent dose-related changes upon intake of ibuprofen tablets, but there was a more pronounced increase in latencies with the two doses of the effervescent preparation. A reduction in intensity estimates (IE) of pain recorded by the subjects was evident at 15 and 60 min with both doses of the effervescent preparation, while the tablet preparations showed more delayed response. Using data at 15 min intervals on the plasma concentrations of R(−) and S(+) ibuprofen, the means ± SD at 15 min were 25.33 ± 5.65 μg/mL and 22.11 ± 4.57 μg/mL (for 400 mg effervescent ibuprofen), and 40.56 ± 14.64 μg/mL and 35.62 ± 12.62 μg/mL (for the 800 mg effervescent ibuprofen) respectively. By comparison, the plasma concentrations of R(−) and S(+) ibuprofen following intake of tablets were 6.42 ± 6.32 μg/mL and 5.51 ± 5.43 μg/mL (for 400 mg tablets), and 12.54 ± 8.3 μg/mL and 10.85 ± 7.8 μg/mL (800 mg tablets) respectively. This study with an effervescent formulation of ibuprofen raises the possibility that salts of ibuprofen which have fast onset of action (e.g., see Geisslinger et al. 1989; Ceppi Monti et al. 1992; Seibel et al. 2004; Jamali and Aghazadeh-Habashi 2008) may give lower estimates of the TRPC from ibuprofen.

Given that the lowest dose of the effervescent preparation gave significant changes in pain Intensity estimates at 15 min, it is possible to conclude that the effective therapeutic concentrations for analgesia were 25 μg/mL (R(−) ibuprofen) and 22 μg/mL (S(+) ibuprofen). Assuming that the analgesic effect is due to the S(+) enantiomer, then the effective therapeutic concentration of these enantiomer is in the range of 22 μg/mL. By comparison with data (Table 2.2) in the third molar extraction studies (e.g., of Jamali and Kunz-Dober 1999) a lower dose of 200 mg ibuprofen tablets produced effective plasma concentrations which were 1/4 of those in the CO_2-pain model [i.e., ~4 5 μg/mL of the S(+) or R(−) isomer]. Comparing these results suggests that the effective therapeutic concentration varies according

Table 2.2 Plasma serum concentrations of ibuprofen in analgesia models

Author (year)	Pain model	Dose (mg)	Time at earliest sig analgesia (h)	Corresponding conc (μg/mL)	Earliest maximal Cp_{max} (μg/mL)	Earliest time T_{max} (h)	AUC $(0 - t)$ t = h (mg/L/h)
Laska et al. (1986)	Third molar extraction	400	0.5	17.5	27	1	
		600	0.5	24.8	42	1	
		800	0.5	28.8	45	1	
Nelson et al. (1994)	Third molar extraction	400 (lysinate)	0.5				
Lötsch et al. (2001)		400 (different formulations)		25–30(rac)			
				15[S(+)]	~20	1	
				14[R(−)]	~18	1	
Jamali and Kunz-Dober (1999)	Third molar extraction	200	N/A	N/A	6.3	1	[S(+)] 5.6 (0–2)
					3.9	6	Before Surg. 1.6 After Surg.
					6.1	1	[R(−)] 5.5 (0–2)
					5.3	6	Before Surg. 2.1 After Surg.
		600	N/A	N/A	14.5	1	[S(+)] 14.2 (0–2)
					11.1	4	Before Surg. 7.2 After Surg.
					14.8	1	[R(−)] 14.1 (0–2)
					13.4	4	Before Surg. 1.8 After Surg.
Nielsen et al. (1990)	Laser beam applied to right hand dorsum	400	3		18.2[S(+)]	1.4–1.5	
		800	3		27.8[S(+)]	1.2–1.5	

to the type and severity of the painful stimulus, given that the inflammatory pain in the third molar extraction model is appreciably greater than the CO_2-stimulus model.

An elegant quantitative approach to relating the PK of ibuprofen to pain responses in an analgesic model was developed by Suri et al. (1997a). These authors employed the tooth pulp electrical stimulation model, and quantified the pain response by subjective pain ratings (PR) and pain evoked potentials (EP) following electrical pulp stimulation. Racemic ibuprofen 400 mg was administered, and the serum concentrations of the enantiomers were determined. The pharmacokinetic data was modelled to the effects of the drug treatments on the maximal responses, E_{max}, of these two pain parameters. There were clear time-related responses on both pain-related parameters and these coincided, or nearly so, with the development of the peak serum concentrations of S(+) ibuprofen (Fig. 2.12). A model integrating plasma concentrations of S(+) ibuprofen (measured by Lötsch et al. 2001; Fig. 2.12) with PKs for pain ratings (EC_{50} set to 24.37 μg/mL) and evoked potential (EC_{50} set to 8.71 μg/mL) using data from Suri et al. (1997a) was developed by Lötsch et al. (2001), and this is shown in Fig. 2.13. This model shows several important phenomena and details:

1. Plasma concentrations of S(+) ibuprofen peak and are ahead of the peak pain-related parameters. Thus, peak concentrations of S(+) ibuprofen occur at 1 h, while that of the evoked potentials is at 2 h and the subject-assessed pain ratings follow at a peak at 3 h. The latter extends for a longer period, and the AUC for the pain ratings extends over a much longer period that that of the evoked potential.
2. These time-course data suggest that the S(+) ibuprofen requires penetration to brain sites to modify the EEG pain-related responses ahead of the full subjective pain response.
3. Given that the EC_{50} for pain ratings is 24.37 μg/mL then it would be safe to assume this value approximated to 24 μg/mL as the effective therapeutic concentration. The lower value of the EC_{50} being 8.71 μg/mL reflects greater sensitivity of the electrical or EEG responses compared with the corresponding value for pain ratings, as well as in the data from the third molar surgical pain model discussed previously.

In conclusion, the data summarised in Table 2.2 and Figs. 2.12 and 2.13 from third molar and the pain-evoked models show that:

(a) Plasma concentrations of racemic ibuprofen at which pain responses are detected from 400 mg oral dosage form are ~18 27 μg/mL while those of the active S(+) isomer after 200 mg of the racemate are ~14 μg/mL and after 400 mg of this are 25 μg/mL.
(b) There is a clearly a trend for the peak ibuprofen (racemic or S(+) forms) to precede the development of the analgesic pain responses to the drug.
(c) Given that 400 mg ibuprofen is about the lowest effective dose of the drug in the third molar pain model, then the effective therapeutic plasma/serum

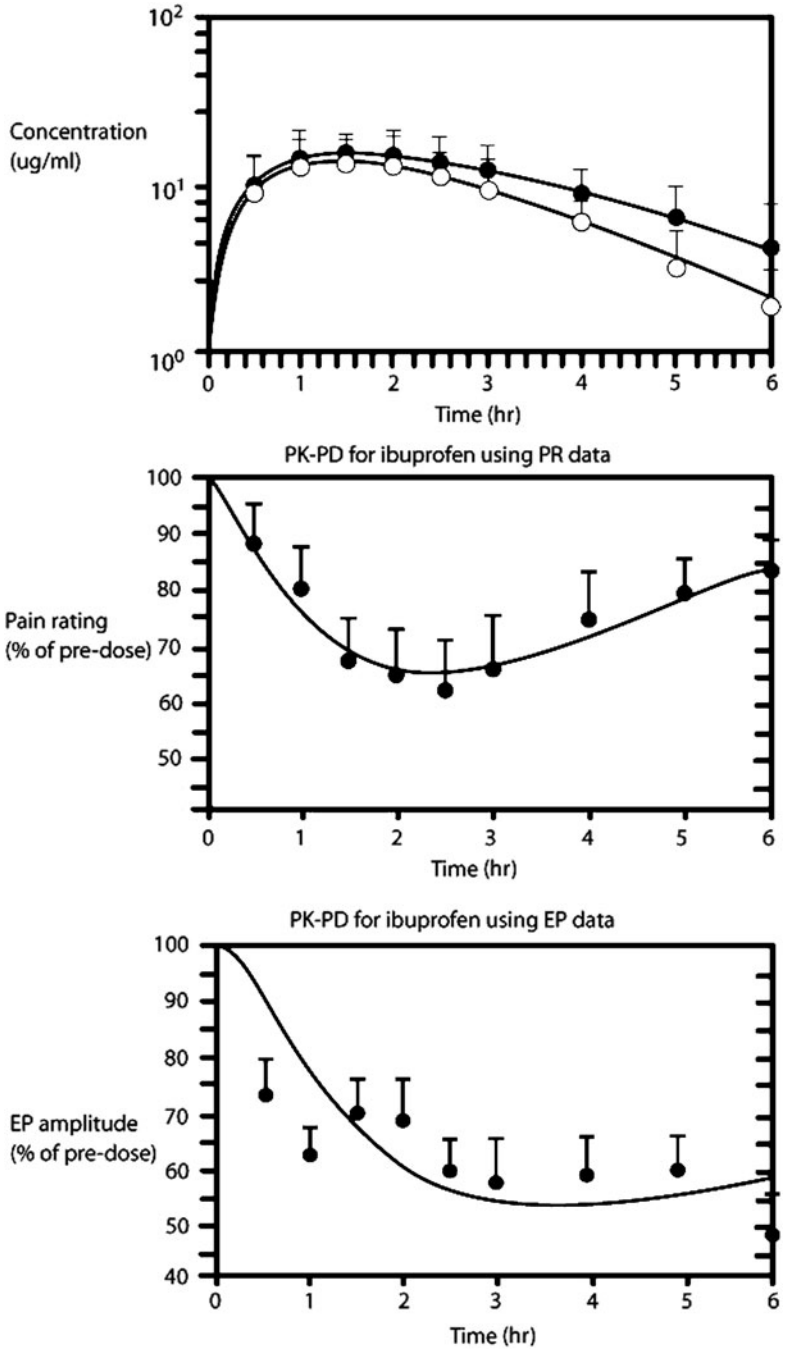


Fig. 2.12 Relationships between objective evoked potentials and subjective pain ratings in subjects who had pain from tooth pulp stimulation and treatment with ibuprofen 400 mg tablets. Comparison of pharmacokinetics of ibuprofen enantiomers (**a**) with pain response (**b**) and (**c**)

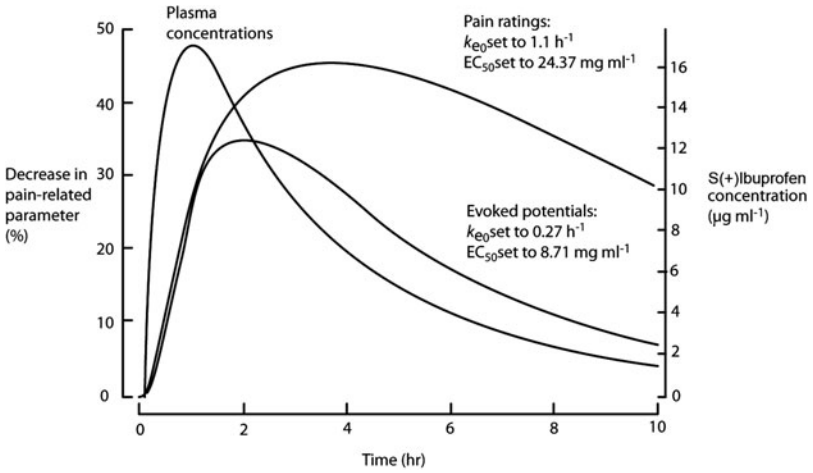


Fig. 2.13 Prediction of time course of plasma concentrations of ibuprofen related to simulated time course of analgesic effects determined from pain ratings and evoked potentials following electrical pulp stimulation and intake of racemic ibuprofen. Data from Suri et al. (1997a); figure reproduced with permission and redrawn from Lötsch et al. (2001)

concentrations may be approximated to about 25 µg/mL. However, the lower dose of 200 mg might also be considered effective in some pain states, giving a lower estimate of the effective therapeutic plasma concentration of the S(+) isomer of ~15 µg/mL (Jamali and Kunz-Dober 1999). Since this parameter has been derived from only one study and does not have corroborating evidence such as provided from data using 400 mg of racemic ibuprofen (Table 2.2), then caution should be employed using this extrapolated value.

2.2.3 Applicability to Other Acute Pain States

There do not appear to be any published studies comparing plasma/serum levels of ibuprofen with development of pain or analgesia. There is a considerable number of studies in which the time-course of analgesic response to ibuprofen has been compared with placebo. Thus, time- and dose-dependent effects of 200 or 400 mg ibuprofen in migraine headache show statistically-significant changes after 1 2 h,

Fig. 2.12 (continued) evoked potentials (*EP*) following tooth pulp stimulation. Integration of ibuprofen concentrations with the percent decrease in pain produces the expected hysteresis loop (figure not shown). **a** Plasma concentrations of S(+) ibuprofen (*filled circle*) and R( ) ibuprofen (*open circle*) after 400 mg *rac* ibuprofen tablets. **b** Effects of ibuprofen on subjective pain responses recorded by subjects after tooth pulp stimulation. **c** Effects of ibuprofen on objective brain recordings of evoked potentials in subjects following tooth pulp stimulation. Redrawn from Suri et al. (1997a). Reproduced with permission of the publishers Dustri Verlag Dr Karl Feistle GmbH & Co KG, Deisenhofen, Germany

depending on the pain parameters that were measured (Codispoti et al. 2001). Similar results have been observed in tension-type or migraine headaches (Lange and Lentz 1995; Schachtel et al. 1996; Sandrini et al. 1998; Packman et al. 2000; Diener et al. 2004), acute sore throat or tonsillitis (Schachtel et al. 1988, 1994, 2007; Boureau 1998), dysmenorrhoea (Zhang and Li Wan Po 1998), and other acute conditions (Kean et al. 1999). Suffice it to say that based on the established PK properties of 200 and 400 mg racemic ibuprofen, it would be expected that the therapeutic concentrations of the drug (*racemic,* or S(+)) required for treating these acute pain states would be of the same order as those mentioned in the previous section.

2.3 Antipyresis

As a component of inflammation, fever is a very good index of systemic as well as central nervous system reactions to inflammogens, even though the mechanisms involved centre around leucocyte activation and the effects of pyrogens (principally interleukins 1 and 6 and tumour necrosis factor α) on hypothalamic pathways leading to PGE_2 production. Thus, a model of antipyretic effects of NSAIDs, including ibuprofen, focuses principally on the direct inhibition of hypothalamic PGE_2, and may with some drugs involve reduction in pyrogens generated from activated leucocytes via, in the case of ibuprofen, inhibition of signalling pathways within these cells (Rainsford 2009).

Trocóniz and co-workers (2000) developed a PK/PD model from studies on two formulations of racemic ibuprofen in healthy adults and febrile children. The population PD model they developed established on EC_{50} [the plasma concentration that elicits half maximal drug effect, or E_{max}] for reduction of temperature at 6.18 μg/mL. Thus, for the purposes of comparison with analgesic effects (e.g., Suri et al. 1997a) this could be employed at the effective therapeutic drug concentration.

Another model for the PK/PD of racemic ibuprofen was developed by Garg and Jusko (1994) based on data of Walson et al. (1989) in febrile children. Using data based on 5 and 10 mg/kg doses, the profiles of plasma concentration of racemic ibuprofen and mean temperature showed that peak levels of the drug were achieved at approximately 1 h and coincided with the decline in temperature, which reached a maximum at 2 6 h. As with the pattern of analgesia, the actions of the drug peak after the maximal drug concentrations. Using a kinetic model in which the change in response with time dR/dt was related to plasma concentrations, C_p, thus:

$$dR/dt = k_m\left\{\left(1 - C_p/\left(C_p + IC_{50}\right)\right\} - k_{out}R$$

Where IC_{50} is the plasma ibuprofen concentration producing 50 % reduction in fever, k_m is the zero order rate of synthesis, and k_{out} the first order degradation, both hypothetical parameters.

Reconstructing this equation after fitting of the data of Walson et al., the IC_{50} was determined to be 10.1 μg/mL. This value is of interest, since it falls within the range of concentrations required for effects in analgesic systems (Table 2.2).

To determine the concentrations of the ibuprofen enantiomers required for antipyretic effects in children following treatment with 6 mg/kg of liquid racemic ibuprofen, Kelley et al. (1992) found that the time for maximal effects of ibuprofen ($t_{max.ef}$) was 183 min, with the time of maximal concentrations of both isomers and the racemate being at approximately 1 h, showing again that the maximal effects occur following the peak concentrations of the drug. The EC_{50} was not specifically calculated by the authors, but the C_{max} for total racemic ibuprofen was 26.67 μg/mL and those for S(+) ibuprofen were 13.8 μg/mL and for R(−) ibuprofen 13.39 μg/mL respectively.

2.4 Therapeutically-Relevant Concentrations in Rheumatic Diseases

Ibuprofen is used extensively for the relief of joint and other painful symptoms in osteoarthritis (OA) or rheumatoid arthritis (RA). Most studies in which the PK of ibuprofen has been investigated in patients with OA and RA show that the PK properties are not appreciably different from normal volunteers (Aarons et al. 1983; Grennan et al. 1983; Bradley et al. 1992; Rudy et al. 1992; Shah et al. 2001; Rainsford 2009). Moreover, as many rheumatic patients are elderly, it is relevant to consider the impact of age on PK of ibuprofen. Studies by Albert et al. (1984) have shown that the PK of ibuprofen is not different from that in younger normal volunteers.

As significant pain relief is evident in RA and OA with even a single low dose of 400 mg or 600 mg of racemic ibuprofen or multiple doses, it is possible to use plasma/serum concentrations of the drug at these doses as a guide to establishing the therapeutically-relevant serum or plasma concentrations of ibuprofen. Variability in PKs and especially enantiomer concentrations is a known problem in patients with RA (Geisslinger et al. 1993) and OA (Rudy et al. 1992). Aarons et al. (1983) found that the values for C_{max} of racemic ibuprofen at the first dose or after 7 or 14 days treatment with 1,600 mg/day ibuprofen were (a) not significantly different from one another, (b) approximately 27 29 μg/mL, and (c) coincided with reduction in VAS estimates of pain and articular indices. There were no differences in the time of C_{max} (approximately 1 h) or other PK parameters with time of drug administration.

Geisslinger et al. (1993) observed that a 600 mg single dose of racemic ibuprofen in RA patients produced plasma concentration values of 20.3 ± 5.3 μg/mL S(+) ibuprofen and 17.7 μg/mL R(−) ibuprofen at 2.4 and 2.3 h respectively. Corresponding doses of ibuprofen 600 mg taken for 3 days by patients with OA produced plasma values of 11.2 μg/mL for S(+) ibuprofen and 8.8 μg/mL for R(−)

ibuprofen, which are about 1/2 those observed by Geisslinger et al. (1993). The lower dose of 300 mg/day ibuprofen produced values of 7.5 μg/mL S(+) ibuprofen and 6.5 μg/mL R(−) ibuprofen. These values are appreciably different from those obtained at the higher 600 mg dose, suggesting that the values at 600 mg ibuprofen may represent the upper concentrations in relation to dosage.

In a study in which OA patients received ibuprofen 600 mg t.i.d./day for 5 days, the plasma C_{max} for racemic ibuprofen was 31.1 35.6 μg/mL and was achieved at t_{max} of 1.2 1.5 h (Shah et al. 2001).

Thus, as a rough approximation the upper limit therapeutically relevant concentration of ibuprofen after administration of 600 mg of racemic drug would appear to be in the range of 30 μg/mL of the racemate and approximately 10 20 μg/mL of the pharmacologically active S (+) isomer.

In summary, this section has highlighted procedures and studies that can be used to derive values of the therapeutically relevant plasma concentrations (TRPC) of ibuprofen. Data have been obtained from various acute and chronic (arthritis) studies and acute experimental pain models in humans where the plasma (or serum) concentrations of the racemic or enantiomeric forms of the drug were compared with therapeutic response, comprising the relief of pain symptoms or the pharmacological actions as attributed to the S(+) and R(−) in reducing circulating levels of the cyclo-oxygenase products. There is some variability in the estimates of TRPC, as would be expected from different pain models and methodologies for determining PK and PD.

It is suggested that the TRPC of racemic ibuprofen are at the upper end in the range of 20 30 μg/mL and 10 15 μg/mL of S (+) ibuprofen following 400 600 mg ibuprofen, these doses being within the optimal for lowest dose of the non-prescription (OTC) use of the drug normally employed for relief of acute pain

It should be emphasised that these data are only first-level approximations derived from diverse models and pain states.

2.4.1 Plasma/Serum Levels in Arthritic Diseases

The PKs of ibuprofen in patients with osteoarthritis (OA) and rheumatoid arthritis (RA) have been investigated by several authors (Brocks and Jamali 1999; Graham and Williams 2004). In general, the main kinetic parameters do not differ appreciably between these patient groups and normal subjects (see Table 2.3 compared with Table 2.1).

Comparing the clinical responses to ibuprofen in patients with OA (Table 2.3), Bradley et al. (1992) showed that the trough serum concentrations of racemic [i.e., R(−) + S(+)] or S(+)-ibuprofen correlated with the Health Assessment Questionnaire (HAQ) or physicians' global assessments of pain relief respectively (Table 2.4).

In patients with RA, there is a relationship between parameters of joint pain and dose above 1,600 mg/day as well as the AUC (Table 2.5; Grennan et al. 1983).

Table 2.3 Pharmacokinetic parameters following administration of 300 or 600 mg of ibuprofen as single or chronic doses to patients with osteoarthritis

	Single		Chronic		Chronic
	300 mg (*n* 8)	600 mg (*n* 7)	300 mg (*n* 21)	600 mg (*n* 24)	overall (*n* 45)
S(+) ibuprofen					
AUCa (mg h/L)	42.9 (21)	74.3 (31)	54.4 (22)	81.4 (33)	
CLS 1 (mL/min)	115.5 (53)	124.3 (45)	87.9 (31)	120.7 (64)	105.4 (53)
C_{max} (mg/L)	11.1 (5.3)	13.8 (8.5)	12.7 (5.4)	18.2 (6.8)	
T_{max} (h)	2.0 (0.89)	1.9 (0.73)	2.1 (0.98)	2.0 (1.2)	
Css.av (mg/L)			7.5 (3.2)	11.2 (4.4)	
$t_{1/2}$ (h)	2.0 (0.83)	3.5 (2.8)	3.1 (1.9)	3.0 (2.3)	3.1 (2.1)
R( ) ibuprofen					
AUCa (mg h/L)	27.7 (8.9)	56.6 (20)	35.9 (14)	55.5 (22)	
CLR 1 (mL/min)	99.0 (32)	96.5 (27)	82.7 (39)	108.4 (55)	96.4 (49)
C_{max} (mg/L)	10.5 (3.8)	16.4 (8.5)	12.0 (4.9)	18.7 (7.4)	
T_{max} (h)	1.9 (1.1)	2.3 (1.2)	1.7 (0.82)	1.6 (1.0)	
Css.av (mg/L)			6.5 (3.1)	8.8 (3.4)	
$t_{1/2}$ (h)	1.7 (0.58)	2.3 (0.82)	2.8 (2.9)	2.9 (3.3)	2.9 (3.1)
Finv (%)	62.5 (9.9)	63.2 (5.8)	66.6 (12)	64.0 (13)	65.2 (12)
AUC S/R ratio	1.5 (0.42)	1.3 (0.30)	1.6 (0.61)	1.5 (0.42)	1.6 (0.51)

AUC area under the serum concentration time curve from zero to infinity, *CLS 1* clearance of S ibuprofen taking into account the inversion of R to S ibuprofen, C_{max} maximum serum concentration, T_{max} time to C_{max}, *Css.av* average steady state serum concentration, $t_{1/2}$ half life, *Finv* fraction of R ibuprofen inverted to S ibuprofen, *n* number of observations. From Bradley et al. (1992)

Table 2.4 Serum concentrations of ibuprofen in patients with osteoarthritis of the hip or knee

Parameter	S(+) Ibuprofen	S(+) Ibuprofen
Dose	1,200 mg/day	2,400 mg/day
Av. Cp (0 6 h) μg/mL	7.5 ± 3.2	11.2 ± 4.4
Trough Cp (6 h) μg/mL	4.6 ± 2.2	6.9 ± 3.7
AUC (0 12 h) μg h/mL	67.2 ± 34.0	98.7 ± 43.6

Patients received *rac* ibuprofen for 4 weeks. The AUC of S(+) ibuprofen correlated with pain at rest, Health Assessment Questionnaire (HAQ), improvement in HAQ disability and physician's global assessment, Trough concentrations of S(+) ibuprofen correlated with HAQ disability and physician's global assessment. Similar associations were observed with R( ) and S(+) ibuprofen, though no data was provided on the serum concentrations of R( ) ibuprofen. Data from Bradley et al. (1992)

The values of C_{max} and t_{max} are not different from one another at doses of 800 24,000 mg/day suggesting that the peak concentrations of ibuprofen are unrelated to joint pain parameters or thermographic index. There is, however, much greater variability in the plasma/serum concentrations of ibuprofen in patients with RA. This is especially evident in the rates of inversion of R(−)- to S(+)-ibuprofen (Geisslinger et al. 1993).

Table 2.5 Relationship between pharmacokinetic parameters for ibuprofen with clinical response in patients with rheumatoid arthritis

		Dose of ibuprofen (1 week)		
		800 mg/day	1,600 mg/day	2,400 mg/day
PK Parameters	Placebo			
C_{max} (μg/mL)		19.4 ± 6.8	18.2 ± 4.0	17.5 ± 3.9
AUC (μg/mL/min)		3,042 ± 966	5,564 ± 1,152	7,962 ± 1,653
t_{max} (min)		61.4 ± 18.1	56.9 ± 12.4	58.3 ± 13.9
Clinical responses	(*vs. placebo)*			
VAS pain		NS	<0.005	≤0.005
Articular index		NS	<0.01	≤0.005
Pain scores		NS	<0.05	≤0.02
Thermographic index	445.4 ± 188.5	429 ± 220.2	443.3 ± 204.6	462 ± 203.9

Arthritis patients (*N* 20 total) took either placebo or iIbuprofen in stated dosages four times daily for 1 week in a double blind, crossover study starting with a 2 day washout period in a Latin square sequence design
From: Grennan et al. (1983)

2.4.2 Accumulation in Synovial Fluids

There is appreciable accumulation of R/S (i.e. both R(−) and S(+))-ibuprofen in synovial fluids, with broad peaks occurring over a period of 2 6 h which follow the peak plasma or serum concentrations (Glass and Swannell 1978; Mäkelä et al. 1981; Whitlam et al. 1981; Albert and Gernaat 1984; Gallo et al. 1986; Walker et al. 1993a; Davies 1998). It is generally agreed that ibuprofen readily partitions into synovial fluid from plasma/serum, and that the total levels (Table 2.6) are about one-half of those in synovial fluids (Whitlam et al. 1981; Graham 1988). The uptake of ibuprofen into synovial fluids of arthritic patients is dependent upon the bound drug in plasma; decrease in protein binding of the drug explains the total drug concentrations in synovial fluids (Wanwimolruk et al. 1983).

The free concentrations in synovial fluids (0.19 μg/mL) do not differ significantly from those in plasma (0.25 μg/mL) when corrected for protein content (Whitlam et al. 1981) which is lower in synovial fluid, these data supporting the concept that the synovial compartment is readily accessible to free plasma/serum concentrations of the drug (Whitlam et al. 1981; Rau et al. 1989).

Gallo et al. (1986) found that the ratios of total ibuprofen concentrations in the synovial fluid to those in plasma is about 1.24 according to time at 7 h following single dose of 600 mg of the drug, and 0.52 1.46 at 3 12 h after three daily doses of ibuprofen 1.8 g/day. The mean free total ibuprofen in synovial fluid ranged from 1.81 to 2.91 %, compared with that in plasma which is 1.54 2.53 %. Thus, there is appreciable total and free R/S-ibuprofen that accumulates in synovial fluids of

Table 2.6 Pharmacological concentrations of ibuprofen and enantiomers in synovial or CSF compartments

Dose	Enantiomer	Compartment	Concentration (μmol)	Rate constant, k^{-1} (h) or MTT (h)	AUC (μg/mL/h)	Author(s)
400–1,200 mg	rac	Syn fluid	4.0–63 [a][0.6–1.6]			Wallis and Simpkin (1983)
		Syn tissue	126–150			
800 mg	rac	Syn fluid	11S(+) 6.4R(−)			Cox et al. (1991)
600 mg	rac	Syn fluid	9.7 S(+)[b] 8.6 R(−)			Geisslinger et al. (1993)
400 mg	S(+)	Syn fluid	10.6(S+)[c]			
40 mg/kg Children JCA[d]	rac	Syn fluid	20	$K = 0.45$; 0.29 sp MTT = 2.22, 3.44		Elmquist et al. (1994)
1,200	rac	Syn fluid	3.3–4.9 S(+)	$K_i = 0.29$ $K_0 = 0.36$[e]	110 ± 28[e]	Seideman et al. (1994)
			2.4–4.4 R(−)	$K_i = 0.19$ $K_0 = 0.34$	56 ± 8	
		Blister fluid	2.4–6.0 S(+)	$K_i = 0.22$ $K_0 = 0.77$	116 ± 43	
			R(−)	$K_i = 0.14$ $K_0 = 0.20$	73 ± 32	
800	rac	Lumbar CSF	1.5			Bannwarth et al. (1995)

[a]Free concentrations from estimates of free fraction ~0.026.
[b]t_{max} ~ 2.4 h.
[c]t_{max} ~ 2.3 h.
[d]*JCA* children with juvenile chronic arthritis; data from Mäkelä et al. (1981).
[e]Rate constants, k^{-1} (h) as K_i = inward, K_0 = outward of synovial fluid or blister fluid values of K_i or K_0 and AUCs of synovial fluids not significantly different from blister fluids.

arthritic patients, and clearly this will have therapeutic significance in relation to the local anti-inflammatory and analgesic effects of the drug in pain control.

Rau et al. (1989) found that the synovial fluid concentrations of ibuprofen 4 h after administration of 400 mg of the drug to patients with a mixture of arthropathies having knee effusions were 9.4 μg/mL (45.6 μM), compared with those in plasma at that time which were 15.45 μg/mL (75 μM), the ratios of synovial fluid to plasma being 0.61. These are lower than those found by Gallo et al. (1986), probably because of the earlier time interval. Most studies of the profiles of ibuprofen (as well as other NSAIDs) in synovial fluids show they are somewhat lower than the peak plasma concentrations, and the synovial fluid profiles follow those of the plasma profiles (Graham 1988). Rau et al. (1989) did not find that the pH of the synovial fluid was different than that of plasma (pH 7.4), and so the view that the synovial fluid is more acidic than the plasma would appear to be challenged by these data. It appears that the efflux of ibuprofen from the plasma into the synovial fluid is by diffusion of plasma protein-bound drug (Day et al. 1988). There is no evidence of time-dependent accumulation of the drug in plasma or synovial fluids following repeated doses compared with single doses (Cox et al. 1991).

Estimates of the synovial exit rates have been determined for a number of NSAIDs, and result in first-order kinetics of drug transport out of the synovial space. The exit rate constants (k_{sp}) are the sum of the rate constants for both diffusion and lymphatic blood flow out of the synovial space (Elmquist et al. 1994). The mean residence times ($MTT_{synovial}$) can be calculated in relation to the exit rate constants. Using partial-areas analysis, Elmquist et al. (1994) calculated the k_{sp} for ibuprofen as 0.29 h^{-1} and the $MTT_{synovial}$ 3.44 h. This indicates that ibuprofen has an appreciable time of retention in synovial fluids. Moreover, this was comparable with four other NSAIDs, i.e. diclofenac, etodolac, indomethacin and tenoxicam, which had $MTT_{synovial}$ values of 1.84 2.04 h, 5.29 h, 4.67 h and 4.03 h respectively.

Stereospecific disposition of ibuprofen enantiomers occurs into the synovial fluids of arthritic patients, many of whom have synovitis or inflammation of their knees (Table 2.6). In the disposition of the individual enantiomers, it has been found that the concentrations of the S(+) isomer as well as values of AUC S(+) always exceed those of the R(−) enantiomer (Day et al. 1988; Cox et al. 1991; Geisslinger et al. 1993; Seideman et al. 1994), with similar selective accumulation being shown in experimentally-induced skin suction blisters (Seideman et al. 1994). The patterns of synovial fluid accumulation of the enantiomers follows that of the peak plasma levels, with broad peaks of R(−) and S(+) ibuprofen at about 2 4 h and extending to about 12 15 h (Seideman et al. 1994), thus showing persistence of the enantiomers in synovial fluids well past those of their peak plasma concentrations (Fig. 2.14; Graham and Williams 2004).

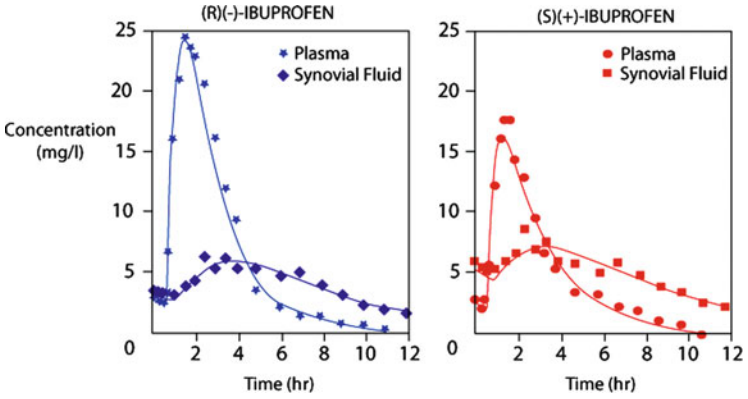


Fig. 2.14 Pharmacokinetics of ibuprofen enantiomers in synovial fluids compared with plasma. Redrawn from Graham and Williams (2004), which was based on data of Day et al. (1988)

2.4.3 Rectal Administration in Adults and Children

Ibuprofen, like other NSAIDs, has been employed in suppository formulations principally for treatment of fever, musculo-skeletal pain, perioperative pain and other painful conditions, principally in children (Viitanen et al. 2003; Yoon et al. 2008; Rainsford 2009). Ibuprofen suppositories are generally well-tolerated in children, with the most common adverse reaction being diarrhoea (Hadas et al. 2011). NSAID suppositories are not widely used in certain parts of the world (e.g., UK, USA) but are popular in some continental European countries. There is considerable potential for their development for treating patients that have dyspeptic or other gastro-duodenal symptoms associated with NSAIDs. The properties of drugs administered by the rectal route using suppositories are related to their being in intimate contact with the rectal mucosa which is normally pH 7.2 7.4, a tissue that has unique fatty acid metabolism with a lipoidal barrier (Florence and Attwood 1998). They present in contact with the mucous membrane of the rectal ampulla, which comprises a layer of epithelial cells without villi (Florence and Attwood 1998). The main blood supply of importance to absorption through the rectal mucosa is in the superior rectal or haemorrhoidal artery, while drug absorption per se takes place through the venous network of the submucous plexus, which then becomes the inferior, middle superior rectal veins, the latter being connected to the portal veins, leading to transport of drugs direct to the liver. In contrast, the inferior veins enter the inferior vena cava and thus bypass the liver. The proportion of drug that is absorbed by these two venous routes depends on the extent to which the suppository migrates in its original or molten form up the intestinal tract (Noro et al. 1982a, b). Thus, this use can be variable and so drugs administered rectally may not bypass the liver (Florence and Attwood 1998).

The factors influencing rectal absorption of drugs include (a) the melting point and liquefaction properties of the suppository, and (b) physico-chemical and solubility properties of the drug that initially influence contact of the drug with the mucosa (Noro et al. 1982a, b; Bergogne-Bérézin and Bryskier, 1999). Aqueous solubility and pK_a of the drug influence absorption from "fat" based or liposoluble drugs. Viscosity of the base and excipients or dispersants added to disperse the fat can influence absorption (Noro et al. 1982b; Toshino et al. 1983). The rate-limiting step in drug absorption for suppositories made from a fatty base is the partitioning of the dissolved drug from the molten base, not the solubilisation of drug in body fluids (Florence and Attwood 1998).

NSAIDs and paracetamol vary considerably in their rates of absorption when administered rectally (van Hoogdalem et al. 1991; Yong et al. 2004). The formulations of these drugs clearly are a major factor in influencing their absorption. For example, addition of increasing amounts of lecithin can delay the rectal absorption of diclofenac (van Hoogdalem et al. 1991). The physico-chemical properties of NSAIDs influence their absorption. Studies in rats have shown that ibuprofen is strongly retained in a lipophilic base, so limiting absorption through rectal mucosal membranes (Kaka and Tekle 1992). The inclusion of polyethylene glycols (PEG) may slightly enhance absorption (Kaka and Tekle 1992), and menthol can also affect properties of suppositories (Yong et al. 2004). It has been suggested that the relatively small pore size in the rectal mucosa compared with that in the small intestinal membrane may limit the rate and extent of absorption of ibuprofen (Kaka and Tekle 1992). Despite this limitation, studies in rabbits by Hermann et al. (1993) have shown that the AUC values for ibuprofen (as the lysine salt) when given rectally are comparable with those when the drug is given intravenously. The ibuprofen acid is absorbed more readily than the lysine salt, though this is dependent on the type of excipient (Hermann et al. 1993).

Of the PK studies performed with rectally-administered ibuprofen, these show that ibuprofen in adults is absorbed at rates that are nearly those of conventional oral formulations of the drug (Aiache 1990; Kyllönen et al. 2005).

Eller et al. (1989) studied the bioavailability of ibuprofen from rectally- or orally-administered sodium or aluminium salts of ibuprofen as solutions (pH 7.8) or suspensions (pH 5.2) in eight normal healthy, non-obese, male subjects using a randomised Latin square design The bioavailability for these forms was compared with that of the orally-administered drug. In essence, the results showed that both rectal formulations showed similar extent of bioavailability being about 60 % of the oral formulation; the C_{max} values being 62 67 %, and the t_{max} was longer. Both the rectally-administered preparations were significantly less bioavailable as shown by the AUC values (Table 2.7), and were relatively high, as were the C_{max} values compared with the oral solutions/suspensions. However, as expected, the t_{max} values were longer for the rectally-administered preparation than for those taken orally (Table 2.7). The serum elimination half-lives ($t_{½}$) were almost identical for the oral and rectal solutions, and about 1/3 lower with the oral suspension compared with the former or the rectally-administered suspension.

Table 2.7 Bioavailability of rectal compared with oral solutions/suspensions of ibuprofen in 8 normal, non obese male human volunteers

	Treatment A	Treatment B	Treatment C	Treatment D
Parameter	Oral solution	Oral suspension	Rectal solution	Rectal suspension
Peak concentration (μg/mL)	80.7 (6)	28.7 (28)	50.3 (36)	19.2 (63)
AUC (μg/mL/h)	2.7			
0 12	197.8 (12)	164.2 (21)	172.5 (36)	97.6 (73)
0 ∞	200.3 (12)	179.1 (30)	175.5 (36)	102.9 (74)
Peak time (h)	0.33 (30)	2.12 (28)	1.14 (36)	2.44 (45)
Mean residence time (h)	2.60 (12)	5.99 (23)	3.19 (6)	4.49 (24)
Terminal elimination rate constant (h^{-1})	0.351 (11)	0.211 (19)	0.344 (6)	0.367 (22)

From Eller et al. (1989). Reproduced with permission of the publishers from Rainsford (2009)

The rectal solution showed greater bioavailability than the suspension and achieved higher serum C_{max} values than the suspension (Table 2.7). In addition, the MRT was shorter for the rectal solution than the suspension.

These results showed that the sodium solution was the preferred salt to be used in any fundamental considerations of suppository formulations. Głowka (2000) studied the enantiomeric pharmacokinetics in rabbits of suppositories of ibuprofen acid and the lysine salt prepared in the lipophilic base Witepsol H-15. They observed there was no pre-systemic inversion of R(−) to the S(+) enantiomers; the S:R ratios only increasing after about 1.5 h following administration of both formulations, and being greater with the lysine salt. The AUCs were greater after administering ibuprofen acid suppositories compared with the lysine salt, even though the latter was more rapidly absorbed.

Kyllönen et al. (2005) investigated the R(−) and S(+) pharmacokinetics of what is now a widely used commercial suppository formulation of ibuprofen, Burana® (Orion Pharma, Espoo, Finland). These investigations are amongst the most extensively investigated, and involved studying the PKs of suppositories of ibuprofen in: (a) nine full-term infants aged 1 7 weeks, (b) eight infants aged 8 to 25 weeks, (c) seven infants aged 26 52 weeks, and (d) seven adults aged 20 40 years after single-dose administration of approximately 19 20 mg/kg ibuprofen suppositories and following induction of anaesthesia for minor general or orthopaedic surgery in infants or lumbar disc surgery in adults.

The results (Table 2.8) show that ibuprofen was rapidly absorbed from the suppository formulation in all age groups. The t_{max} in infants for the ratio of R/S enantiomers of ibuprofen was 1.6 3.3 h, and the $t_{½}$ for absorption was 1.9 2.9 h. In four of the youngest group of infants (1 7 weeks; group 1), the t_{max} was similar to that in those where the suppository was not fully retained in situ, even though the C_{max} values were about 40 % less than in the retained suppository group. The only differences in t_{max} for R/S ibuprofen were observed in the adults (group 4) where this was 3.3 h, and so was greater than in all the other groups (infants), which ranged from 1.6 to 1.9 h.

Table 2.8 Ibuprofen enantiomers after rectal administration. Pharmacokinetic variables of (S) (+) ,(R) ( ) and (R,S) (±) ibuprofen following rectal administration of 20 mg/kg of racemic ibuprofen

	(S) (+) ibuprofen	(R) ( ) ibuprofen	(R,S) (±) ibuprofen	AUC ratio
Group 1 (n 5) suppository retained				
C_{max} (mg/L)	29.3 ± 16.2	23.8 ± 9.4	49.2 ± 20.7	1.7 ± 1.1
T_{max} (h)	2.2 ± 1.0[b]	1.8 ± 1.3[b]	1.9 ± 1.2[b]	
Chronological $t_{1/2}$ (h)	2.9 ± 1.8	3.2 ± 2.7	4.6 ± 5.1	
Physiological $t_{1/2}$ (h)	5.8 ± 3.5[b]	6.6 ± 5.4[b]	8.9 ± 10.1	
AUC (mg/L × h)	159 ± 81[a]	112 ± 54	299 ± 69[a]	
Group 1 (n 4) suppository expelled				
C_{max} (mg/L)	12.4 ± 6.4	13.4 ± 8.1	25.7 ± 14.2	1.6 ± 1.4
T_{max} (h)	1.9 ± 0.9	1.9 ± 0.9	1.9 ± 0.9	
Chronological $t_{1/2}$ (h)	3.8 ± 2.9	3.1 ± 2.4	2.9 ± 2.1	
Physiological $t_{1/2}$ (h)	7.8 ± 5.8	6.3 ± 5.1	6.0 ± 4.4	
AUC (mg/L × h)	66 ± 40	54 ± 48	108 ± 83	
Group 2 (n 8)				
C_{max} (mg/L)	38.5 ± 20.7	40.0 ± 21.8	75.6 ± 44.6	1.1 ± 0.2
T_{max} (h)	1.6 ± 0.7[b]	1.4 ± 0.8[b]	1.6 ± 0.7[b]	
Chronological $t_{1/2}$ (h)	1.7 ± 0.4	2.2 ± 0.7	1.9 ± 0.5	
Physiological $t_{1/2}$ (h)	3.1 ± 0.9	3.9 ± 1.4	3.4 ± 1.0	
AUC (mg/L × h)	131 ± 79	124 ± 67	248 ± 153	
Group 3 (n 7)				
C_{max} (mg/L)	42.7 ± 16.0	49.7 ± 23.3	87.9 ± 36.6	1.1 ± 0.4
T_{max} (h)	1.7 ± 0.3[b]	1.6 ± 0.7[b]	1.6 ± 0.3[b]	
Chronological $t_{1/2}$ (h)	2.8 ± 1.3	1.8 ± 0.4	2.1 ± 0.7	
Physiological $t_{1/2}$ (h)	4.6 ± 2.3	2.9 ± 0.7	3.6 ± 1.3	
AUC (mg/L × h)	180 ± 98	167 ± 56	339 ± 136	
Group 4 (n 7)				
C_{max} (mg/L)	30.1 ± 12.5	30.1 ± 9.9	63.8 ± 20.4	0.9 ± 0.1
T_{max} (h)	3.5 ± 0.8	2.9 ± 1.0	3.3 ± 0.8	
Chronological $t_{1/2}$ (h)	2.1 ± 0.3	2.5 ± 0.7	2.2 ± 0.4	
Physiological $t_{1/2}$ (h)	2.1 ± 0.3	2.5 ± 0.6	2.2 ± 0.4	
AUC (mg/L × h)	160 ± 65	177 ± 59	334 ± 123	

Values are mean ± SD. Only those patients in group 1 in whom the suppository was retained were included in the comparisons between the groups 1 and 4.

[a]Significantly ($P > 0.05$) different from the corresponding value in group 1 where the suppository was expelled.

[b]Significantly ($P < 0.05$) different from the corresponding value in group 4.

AUC ratio is the ratio of (S) (+) ibuprofen AUC to that of (R) ( ) ibuprofen.

Reproduced from Kyllönen et al. (2005) with permission of the publishers of Paediatric Anaesthesiology.

The ratios of the AUC values for the R/S, R(−) and S(+) isomers were similar in all the groups except, as expected, in the youngest infant group who had expelled suppositories.

The values of t_{max} for R(−) ibuprofen ranged from 1.4 to 2.9 h. The highest values of 2.9 h achieved in adults, in contrast to the range of values in infants of

1.4 1.8 h. There were no significant differences in the values of t_{max} between the infant groups. However, there were significant differences between the two older infant groups, as well as with the adult group. Only in adults was the t_{max} of 3.5 h greater for the S(+) isomer than the R(−) enantiomer (1.6 2.2 h).

The ratios of the AUCs for R/S-ibuprofen was greater in the youngest infant group, being 1.7 in those that had retained the suppositories, and 1.6 in the expelled suppository groups, compared with those in all the other groups (0.9 1.1). This indicates that there is a greater rate of conversion of R(−) to S(+) ibuprofen from suppositories, an observation which parallels that observed following oral administration of the drug. The plasma elimination half-life ($t_{½}$) of both the racemic ibuprofen as well as the R(−) and S(+) enantiomers was greater in the youngest of the infant groups compared with those in others and adults, indicating slower rates of elimination in young infants, perhaps as a consequence of ibuprofen-metabolising enzymes not being fully developed in infants.

These studies show that rectal administration of ibuprofen is an easy and effective way of achieving therapeutic plasma concentrations, especially in children or in the perioperative or post-operative surgery. The slightly delayed absorption of ibuprofen in adults may have been due to the stress of the more extensive disc herniation surgery, contrasted with the minor surgery in children where there were higher plasma half-lives in infants aged 1 7 weeks. Otherwise, there do not appear to be any substantial differences in pharmacokinetics between infants and adults from ibuprofen administered as a suppository formulation.

2.5 Pharmacokinetics in Children

Of the limited number of studies on the PKs of ibuprofen in children, the only appreciable changes observed in paediatric populations have been found in young children aged less than 5 years, where the clearance (CL/F) and volume of distribution (V_d/F) may be less than that in adults or older children, and the plasma half-life of elimination ($t_{½}$) prolonged to about twice that in adults or older children (Autret-Leca 2003; Jacqz-Aigrain and Anderson 2006).

There are, however, relatively few studies that have been performed in very young children (Jacqz-Aigrain and Anderson 2006; Rainsford 2009). The limited data suggest that the PK and pharmacodynamic (PD) properties of ibuprofen in 3 4 month to 12-year-old children may be similar to that of young-mid aged adults. Variations in PK in most age groups >1 2 years might be related to differences in growth rates, thus affecting body mass indices, and possibly gender, both of which may influence developmental and hormonal regulation of drug metabolising enzymes.

The PK and PD properties of ibuprofen in children >1 2 years are generally believed to be related to that in adults. The few PK studies have been performed in children in the <1 2 years age group are enough to conclude that, in general, the PK properties are similar to those in adults. While relatively little is known about PD properties in young children, it appears that dose-related pain relief is similar in

Table 2.9 General pharmacokinetic properties of ibuprofen in children

Oral absorption	$t_{½}$: 0.3 0.9 h t_{max}: 1 2 h 10 mg/kg → C_{max}: 44 mg/L
Protein binding	99 %
Active isomer	S(+)
Plasma conc.	S(+) children < S(+) adults
Metabolism	CYP450 2C9 and 2C8
$t_{½}$	0.9 2.3 h

From Autret Leca (2003) and Rainsford (2009)
Reproduced with permission of John Wiley and Sons, publishers of the International Journal of Clinical Practice

young adults to that in younger children (Jacqz-Aigrain and Anderson 2006; Rainsford 2009).

The population PK properties of ibuprofen in children (aged ≥6 months) following oral administration are summarised in Table 2.9 (cf. Table 2.1 in adults), from which it is apparent that these properties are similar to those in adults.

The data in Table 2.9 show that the mean (±SD) values for many of these parameters in children show remarkable consistency from the different studies, and indicate that ibuprofen has, in general, predictable and reliable kinetic properties. Furthermore, there is dose-related increase in plasma concentration C_p and to some extent AUC values, but the kinetic constants reflected by $t_{½}$ (or the inverse, k_{el}) suggest that there is little variation with dosage. There is also little variation of these kinetic parameters with repeated dosage.

The PK properties of various formulations, including those given parenterally as well as orally, are shown in Table 2.10. It is apparent that the $t_{½}$ and V_d of ibuprofen in patients receiving i.v. drugs is about 25-fold higher than from orally-administered ibuprofen; yet there is the same order of elimination and distribution of oral ibuprofen from an early age of about 0.5 year. In older subjects, the $t_{½}$ and V_d are within the range of those in adults. The rates of clearance are, greater in young children up to about 5 years and decline in higher age groups, and are appreciably lower in i.v.-administered infants (Table 2.10). Ibuprofen has a lower rate of glomerular filtration in premature infants, so this may be a factor accounting for higher $t_{½}$ and V_d in this group compared with that in adults.

Some differences in stereospecific PK are apparent in children compared with adults. Thus, in a study in 11 infants (6 18 months) the plasma levels of the S(+) enantiomer of ibuprofen were found to be lower than in adults, while the values for $t_{½}$ for R(−) and S(+) ibuprofen were within the range of those expected in older children or adults (Kauffman and Nelson 1992; see also Jacqz-Aigrain and Anderson 2006). It is possible that the relatively low levels of S(+) ibuprofen would be an argument for advocating higher dosage of ibuprofen in infants. However, it can at least be a reason for erring on the side of caution, especially if the drug is give on a body-weight basis.

Table 2.10 Pharmacokinetic parameter estimates for ibuprofen given by different routes to paediatric patients

Age	Formulation	CL/*F* (mL/h/kg)	*V*/*F* (L/kg)	$t_{1/2}$ (h)
Ibuprofen	i.v.	2.06 (0.33)	0.062 (0.004)	30.5
22 31 weeks[a]	i.v.	9.49 (6.82)	0.357 (0.121)	43.1 (26.1)
28.6 (1.9) weeks[a]	Suspension	110 (40)	0.20 (0.09)	1.6 (0.4)
0.5 1.5 years	Suspension	57.6	0.164	1.97
11 mo 11 years	Suspension	80 (10)[SE]	0.16 (0.02)[SE]	1.44 (0.15)
3 mo 12 years	Suspension	110 (10)[SE]	0.22 (0.02)[SE]	1.37 (0.09)
3 mo 12 years	Suspension	140 (32)	0.27 (0.11)	1.4 (0.5)
5.2 (1.7) years	Tablet	114 (26)	0.26 (0.1)	1.6 (0.4)
5.2 (2.5) years	Suspension/	71 (CV 24 %)	V_c 0.06, V_p 0.1	
4 16 years	granules	(4.05 L/h x 70 kg)$^{-1}$	(CV 65 %)	

Based on Jacqz Aigrain and Anderson (2006).
Variability presented as standard deviation (SD), range (*x y*) or standard error (SE). *CL*/*F* apparent drug plasma clearance, *i.v.* intravenous, $t_{1/2}$ elimination half life, *V*/*F* apparent volume of distri bution, V_{ss} volume of distribution at steady state, V_c initial volume of distribution, V_p apparent volume of distribution of peripheral compartment, *SE* standard error.
[a]Age is gestation age (GA, weeks).
[b]Data reported using allometric model. Estimate presented for a 30kg individual estimated.
Reproduced from Jacqz Aigrain and Anderson (2006) with permission of Elsevier, publishers of Seminars in Fetal and Neonatal Medicine.

A kinetic analysis has shown that there was no effect of age on the pharmacokinetic properties of a suspension of the drug in a group of 38 patients (Kauffman and Nelson 1992). It was found that ibuprofen was rapidly absorbed with a C_{max} of 35.8 ± 16.7 (mean ± SD) at 0.7 ± 0.5 h (mean ± SD). The absorption was faster than that found in earlier studies, and similarly the half-life of absorption was fast ($t_{½abs}$ 0.3 ± 0.3 h). The plasma elimination $t_{½}$ was 1.6 ± 0.7 (mean ± SD) h, which was within the range observed in other studies and in adults.

Brown et al. (1992) investigated the bioavailability of 5 or 10 mg/kg ibuprofen and 12.5 mg/kg paracetamol in 153 febrile children. The C_{max} occurred about 2.5 h earlier than the maximal antipyresis with both drugs, thus being in agreement with the study of Kauffman and Nelson (1992). The plasma $AUC_{0-\infty}$ was lower for the high dose of ibuprofen than the lower, an observation which is at variance with that obtained in other studies.

Kelley et al. (1992) undertook a randomised, open-label parallel PK study of the R(−) and S(+) enantiomers of ibuprofen in febrile children, in which 39 patients (aged 11 months to 11.5 years) received 6 mg/kg ibuprofen suspension or 5 10 mg/kg paracetamol. However, only values of C_{max} being 33.5 ± 14.7 (mean ± SD) μg/mL and t_{max} being 60 ± 19.7 min were recorded, but not the values for the individual enantiomers.

The disposition of ibuprofen enantiomers was studied in 11 infants (6 to 18 months) who were anaesthetised for minor genitor-urinary surgery and given 7.6 ± 0.3 mg/kg ibuprofen suspension post-operatively (Re et al. 1994). The values of racemic S(+) and R(−) were 24.4 ± 6.6, 9.7 ± 2.9 and 11.8 ± 4.4 μg/mL at t_{max} approximately 2 4 h respectively. It was apparent from these studies that the

peak plasma concentrations were much longer than those observed in the previous studies in febrile infants and children, suggesting that either the surgical anaesthetic procedure delayed GI absorption of the drug, or the age of the infants influenced the PK of ibuprofen. The lower S/R ratio obtained is in contrast to that of other investigators in infants where this was higher.

2.5.1 Juvenile Idiopathic (Rheumatoid) Arthritis

Mäkelä et al. (1979, 1981) published two studies on the PK of ibuprofen in juvenile idiopathic arthritis (JIA): these studies determined the concentrations of racemic drug in serum and synovial fluids in 17 patients with JIA (aged 1.5 15 years) who received ~40 mg/kg/day ibuprofen. It was found that the proportion of ibuprofen in the synovial fluids was relatively high compared with that in the serum (Fig. 2.14). The absorption of oral ibuprofen was rapid, and comparable to that in adults (Mäkelä et al. 1979, 1981). In 33 patients (1.5 15 years) that received approximately 40 mg/kg/day t.i.d., peak serum concentrations C_{max} were 31 μg/mL at 1.0 2.0 h while those in the synovial fluid were approximately 1/2 those in serum and peaked at about 5 6 h. The $t_{½}$ in serum was 2.3 h, which is comparable with that in adults.

2.5.2 Cystic Fibrosis

Ibuprofen is not specifically indicated for use in cystic fibrosis (CF), but has been investigated and found efficacious in this disease (Rainsford 2009). Data on the PK of ibuprofen in cystic fibrosis (CF) are both extensive and useful for indicating the disposition of ibuprofen at high dosages, especially where there is considerable pulmonary (often with accompanying *Pseudomonas* or other bacterial infections as well as from the disease) and gastrointestinal inflammation (Rainsford 2009). Konstan et al. (1991, 1995) were amongst those who initiated the application of ibuprofen for treating CF. In a randomised, double-blind, placebo-controlled, dose-escalating study in 19 children (6 12 years) in Ohio (USA), they compared the plasma PK of the enantiomers following 300 mg of the racemic drug for first month, followed by 400 mg in the second month and 600 mg in the third month (Konstan et al. 1991). The dose of ibuprofen was increased if the peak plasma level was $\leq$50 μg/mL.

The PK of ibuprofen was also investigated in 13 children who received 13.4 $\pm$ 4.1 mg/kg (mean $\pm$ SD) compared with that in four normal children who received similar doses of the drug.

In the dose-escalation study, the values of C_{max} were 38, 29 and 65 μg/mL for the three dosages 300, 400 and 600 mg/day respectively. The t_{max} values were 68, 128,

and 109 min, indicating that at the highest dose there was some limitation due to gastric absorption. Indeed, there are indications of drug absorption and a wide scattering of C_{max} data in relation to dose (mg/kg) of ibuprofen, suggesting that some of the GI effects of the disease (excess mucus secretion) may influence absorption of the drug. Compared with PK in normal adults or those with arthritic diseases (Tables 2.1, 2.3, 2.4 and 2.5) the values of C_{max} and t_{max} are higher by a twofold factor or greater. The values of AUC (5.8, 6.3 and 10.8 mg/min/mL) for the three doses also appear higher than in adults with the rates of clearance (1.8, 2.1, 1.9 mL/min/kg) being relatively low. The $t_{½}$ was approximately 68, 128 and 109 min for each dosage level, reflecting extension of residence time of the drug in the body. Thus, these investigations show that there are marked differences in the PK of ibuprofen in CF patients compared with young or mid-aged adults. In the second part of this study, the plasma concentrations and the AUC values in the CF patients (6.1 ± 1.7; mean ± SD mg/min/mL) were significantly lower than in controls (11.3 ± 3.4, mean ± SD, mg/min/mL), with reduction in clearance being about 1/3 accompanied by an increase in V_d. The possible reasons for these substantial alterations in PK include decreased bioavailability (from possible reduced GI absorption), increased metabolic clearance, and increased unbound fraction in plasma (Brocks and Jamali 1999).

Dong et al. (2000) undertook a study of 38 children of both sexes, age range 2 13 years, with CF; the enantiomer PK's were investigated in a single-dose, open-label investigation following 20 mg/kg racemic ibuprofen (Dong et al. 2000). The enantiomeric ratio of the plasma AUC was 2.09:1 (S:R) and the free and conjugated ibuprofen in urine was 13.9:1 (S:R), which indicated there were no differences in these parameters compared with those in normal children. While there were no differences observed in other PK parameters, there was an inverse relationship between the CI/F for R(−) ibuprofen with age in CF patients. There was no significant difference in PK parameters with gender or formulations (suspensions, tablets) of ibuprofen.

The dose of ibuprofen employed by Dong et al. (2000) was 20 mg/kg, and was greater than that in the second PK study by Konstan et al. (1991) (13.4 mg/kg in CF and 13.9 in controls), so the differences in PKs between these studies might be explained, in part, by differences in dosages, even though the actual values for the R(−) and S(+) enantiomers were not clear from the study by Konstan and co-workers.

Arranz and co-workers (2003) investigated the population PK of serum ibuprofen in 59 CF patients (2 18 years) in order to identify the factors accounting for inter-individual variability. Their PK analysis revealed that the inter-individual variability was such that the absorption constant (K_a) could not be estimated accurately. Dose-dependent kinetics were, however, demonstrated, which affected clearance and V_d. The fasting status and formulation (acid or lysine salt) appeared to affect the bioavailability and clearance of ibuprofen, as would be expected. Slower absorption of the free acid was evident compared with that of the lysine salt of ibuprofen.

2.5.3 Patent Ductus Arteriosus

The i.v. lysine or other salts of ibuprofen have been employed for closure of patent ductus arteriosus (PDA) in preterm neonates (Aranda and Thomas 2006; Aranda et al. 2009a). Ibuprofen and indomethacin have both been approved by the FDA and EMEA for use in closure of PDA in the newborn (Aranda et al. 2009a). However, only indomethacin is approved for prevention of intraventricular haemorrhage (Aranda et al. 2009a).

Studies on the safety, efficacy, pharmacokinetics, and pharmacodynamics in patients with PDA have shown the favourable benefits of i.v. ibuprofen, especially the lysine salt (Aranda and Thomas 2006; Aranda et al. 2009a). In comparison with oral ibuprofen, the i.v. administration yields higher plasma concentrations (Sharma et al. 2003; Aranda and Thomas 2006).

Aranda et al. (1997) were the first to report the pharmacokinetics and plasma protein of i.v. lysine salt of ibuprofen 10 mg/kg bolus given within 3 h of birth to 21 premature neonates. Unfortunately, only the racemic drug was analysed. There was a relatively high scatter in plasma concentration profiles, although the values for AUC and V_d (62.1 mL/kg) had reasonable error. The plasma $t_{½}$ was (mean ± SD) 30.5 ± 4.2 h, which was appreciably longer than in infants, children, or adults (approximately 1 2 h). The percentage binding to cord plasma was significantly lower (94.98 ± 0.39 %, mean ± SD) compared with that in adult plasma (98.73 ± 0.31 %, mean ± SD). There was no correlation between gestational age (22 31 weeks) and plasma clearance or half-life, or elimination rate constant, indicating that there was no effect of fetal age on the disposition of ibuprofen. The rate of clearance was low (2.06 ± 0.33 mL/kg/h, mean ± S.D.) compared with that in infants through to adults. It was suggested that the prolonged $t_{½}$ and Cl may reflect immaturity in the formation of cytochrome P_{450} and glucuronyl-transferase enzyme systems. Van Overmeire et al. (2001) studied the PK of lysine ibuprofen in 27 patients with PDA, in 13 of whom there were complete data for PK analysis, and incomplete (although useful) data in the remaining 14. In this study, ibuprofen was administered on days 3, 4 and 5 by 15-min i.v. infusion of 10 and 5 mg/kg respectively.

Chapter 3
Mechanisms of Inflammation and Sites of Action of NSAIDs

Understanding of the mechanisms underlying acute and chronic inflammation is central to the understanding of the actions of NSAIDs and NN analgesics (Rainsford 2004c). Moreover, the site and factors controlling the expression of inflammatory pathways and events underlie the occurrence of inflammatory events at different sites in the body. In relation to inflammatory pain these sites have widespread location in the body, yet the underlying inflammatory reactions are essentially common (Wall and Melzack 1989; Gallin et al. 1992). This is especially so in the peripheral and central nervous system pathways that underlie pain responses.

3.1 Pathways of Inflammation

The sequence of changes in microvascular and cellular events that characterise acute inflammation has been well-defined (Gallin et al. 1992; Rainsford 2004c).

A schematic representation of the sequence of events following a hypothetical injurious event is shown in Fig. 3.1, along with an explanation of the major events underling these reactions. The cellular responses and mediators produced by leucocytes are shown in Fig. 3.2.

To illustrate how these initiating cellular events in acute inflammation, and the transition to chronic, fit in with the pathogenesis of arthritic states, it is necessary to consider the inter-relationships with the immune pathways involved in conditions such as rheumatoid arthritis. Figure 3.3 shows these inter-relationships and how they impact upon the processes of joint destruction. Since ibuprofen affects a limited array of cellular mediators and reactions, but few if any immune pathways (e.g., T- and B-cell functions, it is evident that the drug has limited effects involving local cellular reactions and mediators which underlie soft-tissue inflammation and joint-destructive enzymes. The same is true of the local joint destruction in osteoarthritis.

K.D. Rainsford, *Ibuprofen: Pharmacology, Therapeutics and Side Effects*,
DOI 10.1007/978 3 0348 0496 7 3,

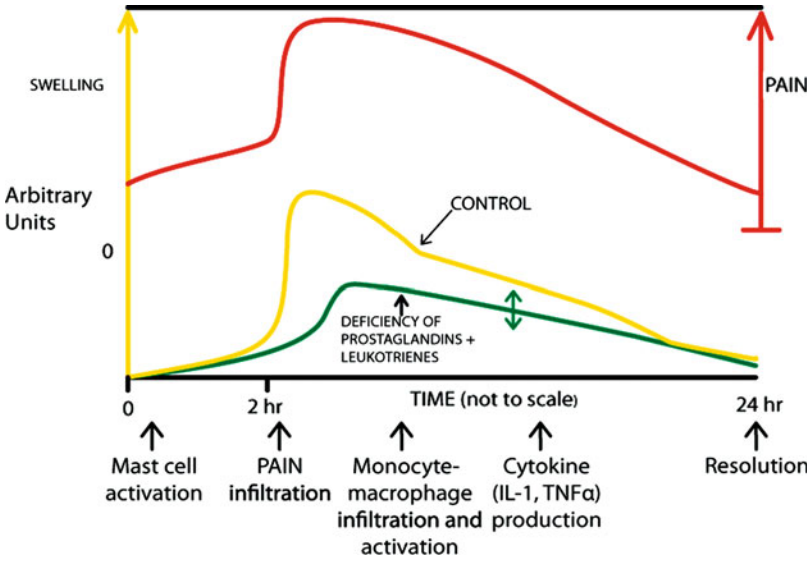


Fig. 3.1 Hypothetical series of vascular and cellular events accompanying the development of swelling (oedema) and associated production of inflammatory mediators with cellular infiltration and activation of leucocytes during *acute* inflammation (based on Rainsford 2004c, Gilroy and Lawrence 2008). The development of pain (*right side scale*) is associated with local tissue swelling (*left side scale*). The sequence of cellular infiltration and activation is shown below the *x* axis. The initial mast cell activation releases amines (5 HT, histamine), which initiate swelling by vascular dilatation in what is termed the "histamine phase". Antihistamines block this reaction, and consequently reduce swelling. After about 1 2 h there is accumulation and activation of comple ment components for the circulation. At about this time there is appreciable generation of prostaglandins and bradykinin activation (from the actions of kinases on kinins in the circulation), which characterises what has been termed the "prostaglandin (PG) phase". The significance of this phase is illustrated by the reduced swelling that occurs in rats that have been rendered deficient in dietary poly unsaturated fatty acids, which are necessary for the formation of the arachidonic acid precursor for the oxidative production of PGs and leukotrienes (Bonta and Parnham 1981). Vasodilatation follows which leads to a cycle of ischaemia reperfusion and extravasation of blood borne proteins and inflammatory mediators, among them superoxide and hydroxyl radicals. During this and later phases there is a progressive vascular adhesion and transcellular migration and activation of polymorphonuclear neutrophil leucocytes (PMN), followed by accumulation of monocytes which adhere to microvessels, which then transgress across the endothelia and are activated to form macrophages. Activation of macrophages and PMNs leads to (a) induction of COX 1 and PLA 2, with subsequent amplified generation of PGs and LTs, (b) production of oxyradicals and nitric oxide, which in turn form peroxynitrite among the most powerful tissue oxidants known with tissue destructive activity, (c) production of pro inflammatory cytokines, and (d) release of lysosomal enzymes which cause autolysis of local tissues. The progress to *resolution* of inflammation is regulated by lipoxins/resolvins and D/J type prostaglandins, and the TGFβ1 regulation of apoptosis and phagocytosis (Gilroy and Lawrence 2008). Should the supervening insult or immunological reactions be so severe as to overcome the development of resolution then this process is deemed to have "failed", and persistent inflammatory reactions ensue, resulting in *chronic* inflammation which may involve abscess formation (from persistent infectious agents), excess scarring and auto immunity from severe immunological reactions

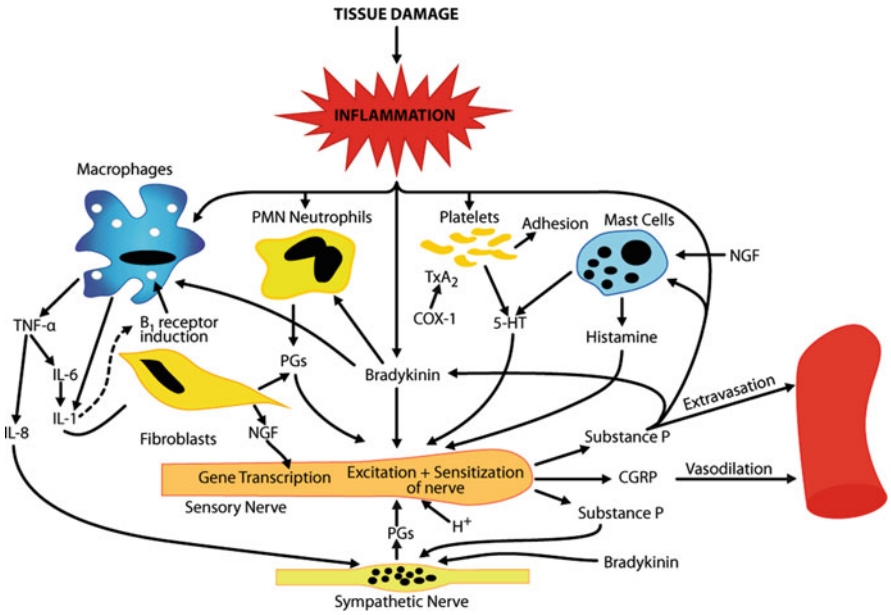


Fig. 3.2 Cells and mediators involved in the expression and development of inflammation and their interaction with peripheral neural systems

3.2 Link of Pharmacokinetics to Pharmacodynamics

Ibuprofen has multiple modes of action through inhibition of the production of inflammatory prostaglandins (PGs) such as PGE_2 which is one of a number of the key components of this multi-factorial property of the drug (Rainsford 1999b). Like many conventional (or traditional) NSAIDs, ibuprofen inhibits both the constitutive cyclo-oxygenase-1 (COX-1) which is responsible for production of prostanoids (PGs and thromboxane A_2, TxA_2) that control a range of physiological or "housekeeping" functions (vascular, blood flow, gastric, and renal functions), and the inducible COX-2 whose synthesis is increased, leading to amplified production of PGE_2 in inflammation and pain (Cryer and Feldman 1998; Rainsford 1999b, 2004a, b; Vane and Botting 2001; Warner et al. 1999; Fig. 3.4).

COX-1 inhibition has been considered a factor underlying the possibility of NSAIDs to cause some adverse effects (GI ulcers, bleeding, renal abnormalities), although there are other biochemical and cellular actions of NSAIDs that contribute to their untoward effects (Rainsford 2004a; Bjarnason et al. 2007; Fig. 3.4). The ratio of inhibition of COX-1 to COX-2 varies considerably among different NSAIDs and the coxibs (Table 3.1), although part of the variability may be due to the experimental conditions under which the inhibitory effects of the drugs has been measured (Warner et al. 1999).

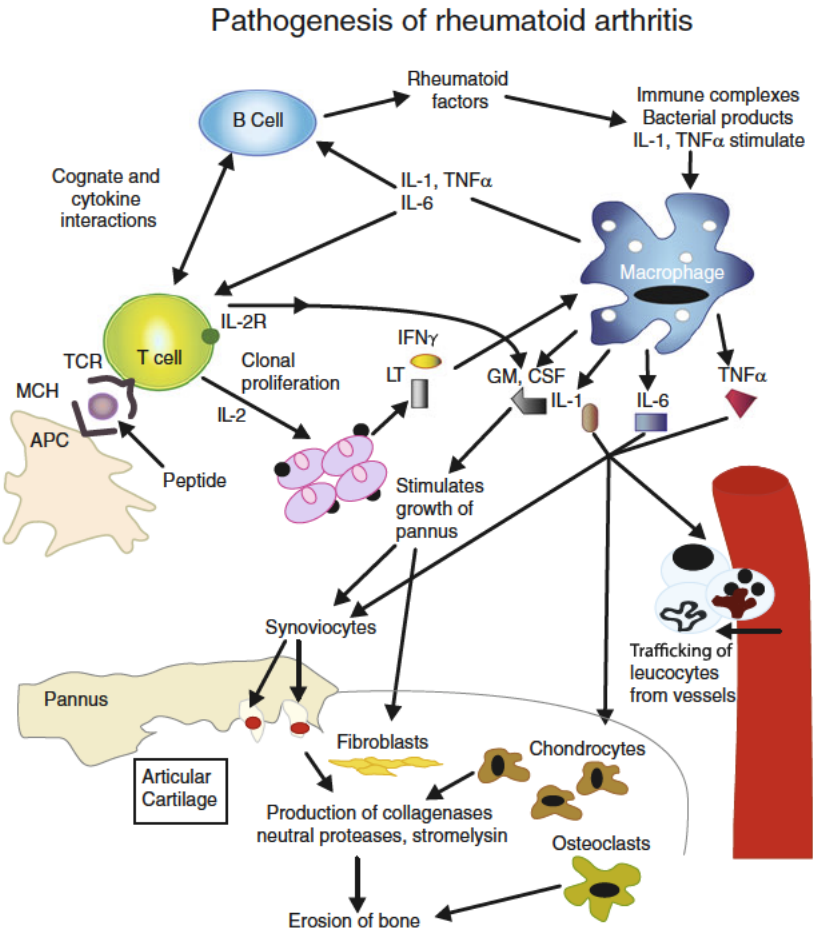


Fig. 3.3 Concepts of the pathogenesis of rheumatoid arthritis showing the range of immuno inflammatory cells and mediators that are involved in the joints of patients with this disease. Ibuprofen, like other NSAIDs, affects the vascular, eicosanoid, IL 1/TNFα, macrophage and synovial/cartilage production of actions of cell and matrix destructive components of joint inflammatory disease. The production and action of B and T cell mediators is unaffected or limited with ibuprofen. From: Patel et al. (2010) with modifications. Reproduced with permission of Cambridge University Press

The relative inhibitory effects of NSAIDs and coxibs on COX-1 and COX-2 have been considered to relate to the likelihood of developing upper GI and possibly renal and other reactions by NSAIDs in relation to their anti-inflammatory activities (Cryer and Feldman 1998; Warner et al. 1999; Vane and Botting 2001; Huntjens et al. 2005). The newer class of highly selective COX-2 inhibitors, the coxibs, were developed in attempts to reduce the risks of serious upper GI and other reactions (Rainsford 2004b).

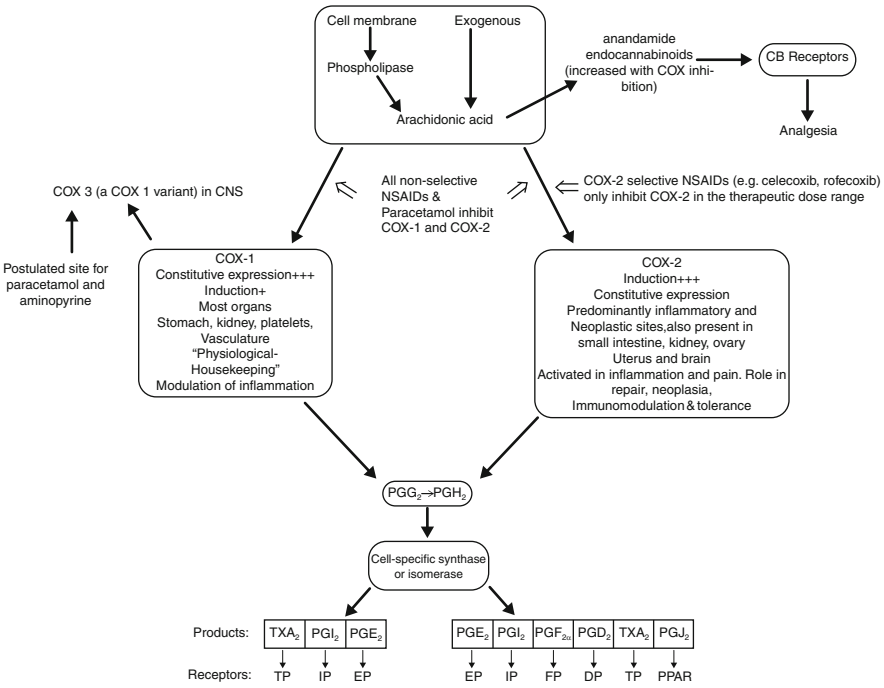


Fig. 3.4 Pathways of arachidonic acid metabolism involving the actions of constitutive cyclo oxygenase 1 (COX 1) and inducible cyclo oxygenase 2 and subsequently the respective synthase or isomerase enzymes, leading to the formation of specific prostaglandins (PG) or thromboxane A_2 (TXA_2). These prostanoids act on their specific receptors. Ibuprofen, like other NSAIDs, inhibits both COXs. Additionally, phospholipid derived anandamide, which is an endogenous cannabi noid, can be stimulated by ibuprofen from the combination of inhibiting anandamide hydrolase, an enzyme that breaks down anandamide, while the net effect of inhibiting COXs may contribute to the increased production of anandamide. Both effects may contribute to the CNS components of analgesia induced by ibuprofen. Modified from Rainsford (2004c)

Ibuprofen, like a number of traditional NSAIDs has been shown in a number of in vitro and some in vivo studies to have inhibitory effects on both COX-1 and COX-2 (Boneberg et al. 1996; Cryer and Feldman 1998; Warner et al. 1999; Rainsford 1999b, 2004; Vane and Botting 2001; Huntjens et al. 2005), which raises issues about why such an non-selective COX-1/2 inhibitor would have low risks of GI and renal effects compared with other NSAIDs. It has been suggested that one of the reasons for the low gastro-ulcerogenicity of ibuprofen may relate to the competition of the COX-1 inactive R(−)-isomer with the active enantiomer for the active site of COX-1, so effectively diminishing the potential for inhibition of PG synthesis by the drug (Rainsford 1999b, 2003). The short plasma elimination half-life of the drug may also be a feature accounting for low risks of upper GI injury from the drug (Henry et al. 1993, 1996, 1998).

Table 3.1 Relative effects of NSAIDs on cyclo-oxygenase activities in different systems

Drug	Therapeutic dose (mg/day)	Therapeutic plasma concentration		Whole blood COX-1 IC_{50} (μM)	Whole blood COX-1 IC_{80} (μM)	Gastric mucosa COX IC_{50} (μM)	Whole blood COX-2 IC_{50} (μM)	Whole blood COX-2 IC_{80} (μM)
		μM	μg/mL					
Aspirin (high dose)	1,200–5,200	111	6 17*	4 45	8	0 03	13 88	>100
Aspirin (low dose)	81–325	15	2 7*	4 45	NA	0 03	13 88	NA
Celecoxib	100–200	0 8	0 29	10 0–20 0	28	NA	0 3	6
Diclofenac	150–200	0 8	0 25	0 26	1	0 23	0 01	0 27
Ibuprofen (high dose)	1,200–3,200	111	22 9	5 9	58	0 7	9 9	67
Ibuprofen (low dose)	800–1,200	38 8	7 8	5 9	NA	0 7	9 9	NA
Indomethacin	75–200	3	1 1	0 16	0 46	0 85	0 5	5
Ketoprofen	100–300	9 4	2 4	0 11	1	0 08	0 88	22
Naproxen	500–1,000	253	58 2	32 01	110	0 52	28 19	260
Piroxicam	20	16 6	5 5	2 68	15	0 87	2 11	31
Rofecoxib	25–50	1 9	0 68	13	>100	NA	0 59	6

Modified from Huntjens et al. (2005), with permission of Oxford University Press publishers of Rheumatology

*Aspirin concentrations relate to its metabolite, salicylate. It is also an irreversible inhibitor of COX-1

3.3 Relation of Analgesic Effects to COX-1 and COX-2 Inhibition

It is well-established that the anti-inflammatory and analgesic effects of ibuprofen are due in a large part to inhibition of the inducible pro-inflammatory cyclo-oxygenase (COX-2), as well as the constitutive, physiologically related COX-1 (Rainsford 2009). To establish what could be regarded as "clinically-significant" effects of NSAIDs/coxibs on COX-1 and COX-2 activities in humans requires use of either ex-vivo whole blood or in-vivo blood or tissue-sampling techniques that are now well-established (Rainsford et al. 1993; Warner et al. 1999; Brooks et al. 1999; Bjarnason and Rainsford 2001).

Among the studies which have addressed the issue of the PK of NSAIDs to their in-vivo activities as COX inhibitors is the study by Blain et al. (2002). Using the whole blood assay, these authors compared the effects of ibuprofen, diclofenac, and meloxicam on in-vitro activities of COX isoenzymes using blood from 24 healthy male volunteers, and the ex-vivo production of COX-1-derived TxB_2 during clotting and COX-2-derived PGE_2 upon stimulation with endotoxin after the same volunteers took single and multiple (3 days for ibuprofen and diclofenac and 5 days for meloxicam) doses of 400 mg ibuprofen (Brufen®), 75 mg diclofenac SR (Voltaren®), or 7.5 mg meloxicam (Mobic®). Plasma concentrations of the drugs and in the case of ibuprofen the R/S enantiomers were determined and used to relate these as free and unbound concentrations to in-vitro inhibition profiles.

These authors then modelled the time-course of plasma concentrations of the drugs to the inhibition of the COX isoenzymes.

The plasma concentration of ibuprofen after a single dose of 400 mg was 24.0 ± 8.0 μg/mL (116 μM) while that after 400 mg t.i.d. for 3 days was 14.8 ± 5.9 μg/mL (70.4 μM). At these concentrations the ex-vivo inhibition of COX-1 and COX-2 was 83 %, while COX-1 was 96 % after single dose of 400 mg and 76 % and 83 % after multiple dosing, respectively.

These data in essence mean that during analgesia with 400 mg ibuprofen, the therapeutic drug concentrations of racemic ibuprofen are 24 μg/mL (single dose) and 14.9 μg/mL (multiple doses). These concentrations are within those required for analgesia (Table 2.1), showing that relevant therapeutic drug concentrations for ibuprofen are in the order of 15 25 μg/mL.

Ibuprofen, taken singly or repeatedly, inhibited production of TxB_2 by COX-1 by 96 % and 90 % respectively. COX-2 production of PGE_2 was inhibited by 84 % and 76 % respectively after single and multiple doses. Almost complete inhibition of both COX-1 and COX-2 was achieved under in-vivo conditions and this was paralleled by the modelling of in-vitro inhibition profiles. Near complete COX-2 inhibition in vitro was achieved at free concentrations of the racemate as well as the S(+) enantiomer, which almost completely inhibited both COX-1 and COX-2 in vitro. When these data were compared with the inhibition ex vivo, it was evident that although there was wide scatter of about 10 % of the latter data most fell within about 80 % inhibition of COX-1 and COX-2 observed in vitro.

In comparison, after oral intake diclofenac inhibited COX-1 by 70 % and COX-2 by 95 % and 97 %. COX-1 inhibition from meloxicam was 30 % and 55 %, and COX-2 was 63 % and 83 % respectively after single and repeated doses.

The time course of inhibition by ibuprofen 400 mg of COX-1 and COX-2 activities ex vivo has been shown by Kerola et al. (2008) to extend from 1 to 6 h, and this is within the time of analgesia with this drug (Table 2.2). Thus, in conclusion, the therapeutically relevant concentrations of ibuprofen after 400 mg dosage are those at which there is appreciable and significant inhibition of COX activities.

The data obtained in these studies gives a clear basis for relating the in-vivo effects of ibuprofen on prostanoids from COX-1 and COX-2 activities with the anti-inflammatory and analgesic effects of the drug in various clinical models and during therapy. Since the doses of ibuprofen used in these studies (1.2 g/day) correspond to those used OTC, and these doses produce effective analgesic activity in various pain models, notably also inflammatory states such as dental pain involving extraction of molars, or throat pain where there is local inflammation, it can be concluded that inhibition of COX-2 as well as COX-1 underlies the therapeutic effects of ibuprofen in these conditions. It could be argued that the studies of Blain et al. (2002) were in normal volunteers, and during inflammatory pain there is likely to be more COX-2 activity. However, the in-vitro inhibition profiles modelled against plasma concentration profiles of R(−) and S(+) ibuprofen determined before and after surgery make it possible to suggest that these concentrations as well as free concentrations of the drug would be sufficient to achieve about 70 80 % inhibition.

Thus, this evidence shows that there is a direct relationship between inhibition of the synthesis of *pro*-inflammatory prostanoids that is within the dose range of ibuprofen which corresponds to that used in OTC conditions for the relief of mild to moderate pain; a central tenet of the therapeutic actions of ibuprofen in the context of the OTC dosage of the drug.

3.4 Multiple Modes of Anti-inflammatory Activities

Another key feature about the mode of action of ibuprofen in inflammation is that it has multiple modes of action (Rainsford 1999b, 2009; Figs. 3.5, 3.6 and 3.7). There are several sites of action of ibuprofen enantiomers, including (a) prevention of the accumulation of activated leucocytes (neutrophil PMNs, monocytes macrophages), (b) reduced expression of leucocyte adhesion molecules which underlies the reduction of leucocyte accumulation in inflamed tissues, (c) inhibition of the production and actions of leucocyte-derived inflammogens (e.g., leukotriene B_4 [LTB_4], nitric oxide [NO]), pro-inflammatory cytokines (e.g., interleukin-1 [IL-1], tumour necrosis factor-α [TNFα]), and (d) reduction in selected neural afferent and efferent pathways mediating pain resulting from inhibition of PGs, NO as well as Na^+ and Ca^{++} fluxes (Malmberg and Yaksh 1992a, 1992b; Björkman 1995a, b; Rainsford 2009). Several studies have emphasised the differentiation of

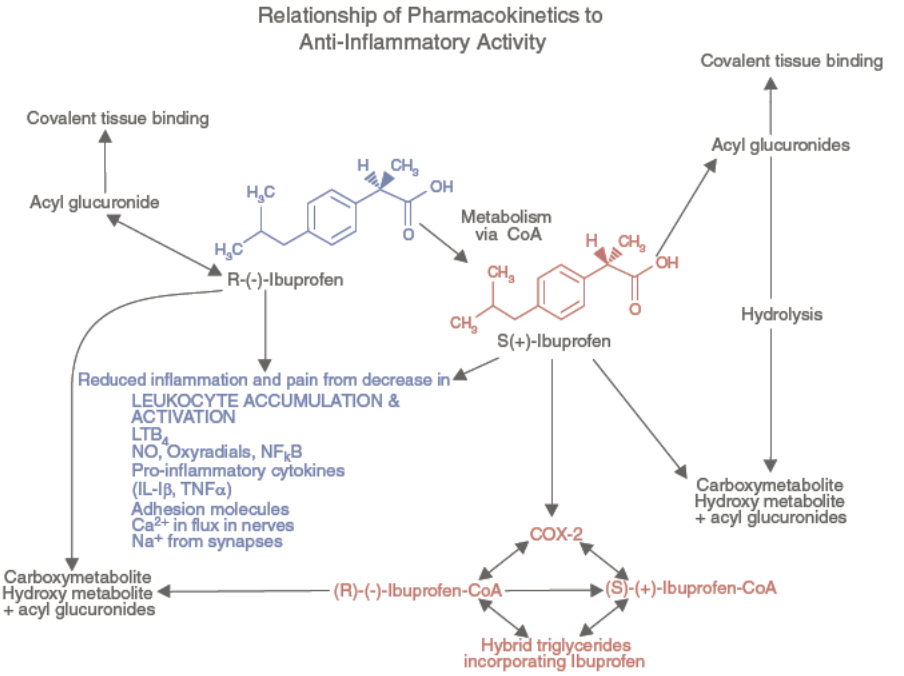


Fig. 3.5 The inter relationships between the actions of R(−) and S(+) ibuprofen and intermediary metabolites on cyclo oxygenases, leukotrienes, and leucocyte derived inflammatory mediators and functions. Modified and redrawn from Rainsford (2009) with permission of Springer, publishers of Inflammopharmacology

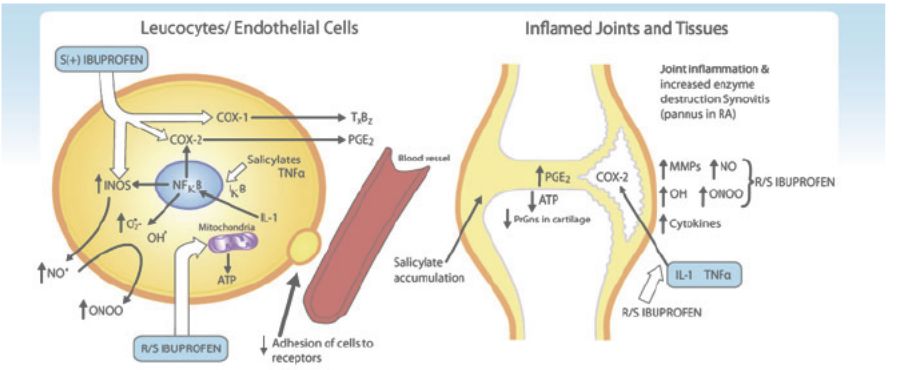


Fig. 3.6 Sites of actions of the enantiomers of ibuprofen on leucocytes, endothelial cells, and postulated localization of effects on inflamed joints of arthritic patients. Modified from Rainsford (2004c, 2009) with permission of Springer, publishers of Inflammopharmacology

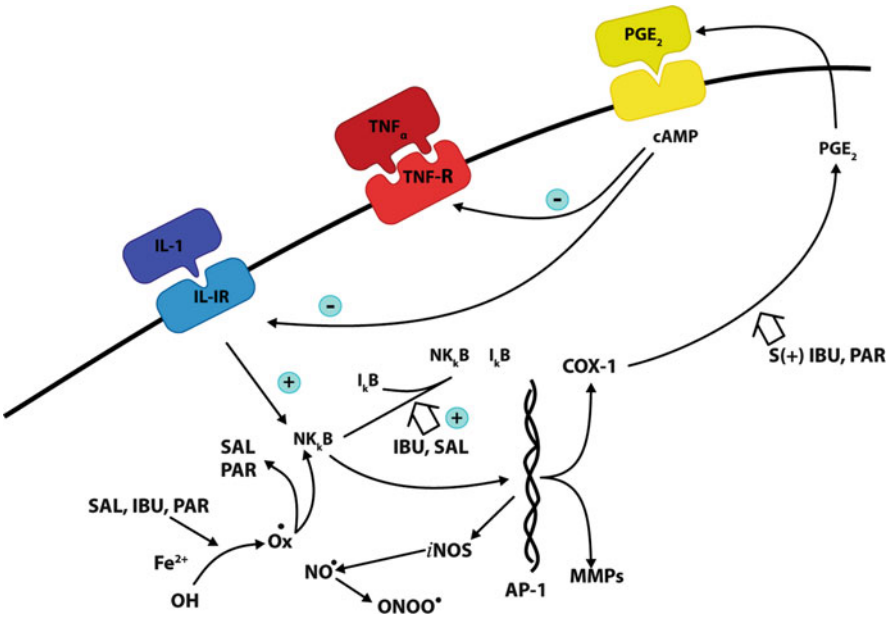


Fig. 3.7 Sites of action of ibuprofen in comparison with those of salicylate and paracetamol (as oxyradical scavengers) on (a) the receptors and receptor signalling and inter relationships between PGE_s and the pro inflammatory cytokines, interleukin 1 (IL 1) and tumour necrosis factor α (TNF α), (b) relative effects on oxyradicals that regulate nuclear factor kappa B (NFκB) activation and nitric oxide production from inflammatory regulated nitric oxide synthesis (iNOS), and (c) control of gene regulated production of COX 1, iNOS, metalloproteinases (MMP) and pro inflammatory cytokines. Based on Rainsford (1999b, 2009) with permission of Springer, publishers of Inflammopharmacology. *IBU* ibuprofen, *PAR* paracetamol, *SAL* salicylate

analgesic from anti-inflammatory mechanisms of NSAIDs (McCormack and Brune 1991) but there is a clear anti-inflammatory component that contributes to the relief of pain, especially that in chronic conditions (Rainsford 1999b, 2009). In addition to the range of actions of ibuprofen on cyclo-oxygenases, leukotrienes, oxyradicals, nitric oxide and leucocyte adhesion and accumulation (Fig. 3.5), there is a range of anti-inflammatory actions of ibuprofen on signalling pathways (e.g. NFκB/IκB dissociation and activation) which underlie the activation of leucocytes and other cells mediating inflammation (Rainsford 2009) (Figs. 3.6 and 3.7).

3.4.1 Pain Control Pathways

Control of pain by NSAIDs, including ibuprofen, involves several different but inter-related mechanisms (Rainsford 1999b, 2004c, 2005b, 2009). The principal components of analgesic activity relate to the anti-inflammatory actions of the drug

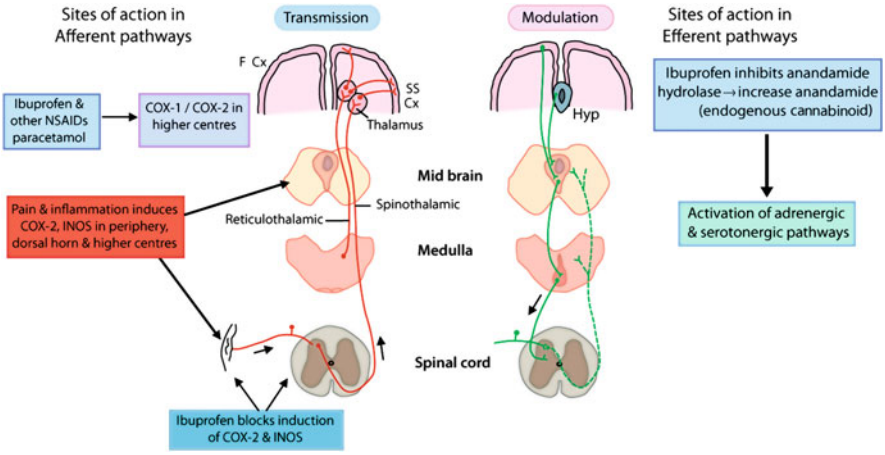


Fig. 3.8 Sites of action of ibuprofen on the peripheral and central neural afferent pathways of pain transmission, as well as the efferent modulating pathways. Main neural pathways based on Fields (1987) and modified from Rainsford (2004c)

and several sites of action in peripheral and central pathways of the nervous system. As shown in Fig. 3.8 (Rainsford 2004c; with modifications based on Rainsford 2009) there are several sites of action of ibuprofen on the afferent transmitting and efferent modulating pain pathways in the nervous system.

Like many other NSAIDs, ibuprofen inhibits the PG and NO components of peripheral and spino-thalamic transmission of afferent pain impulses by the inhibition of the production of these mediators (Fig. 3.8; Rainsford 2009). Moreover, ibuprofen is one of a few NSAIDs that stimulate production in the CNS of the endogenous cannabinoid-like analgesic, anandamide, by inhibiting the enzyme that hydrolyses this to arachidonic acid (Fowler et al. 1997a, b; Tiger et al. 2000; Holt et al. 2007).

The components of peripheral neurotransmission that are affected by ibuprofen and some other NSAIDs are shown in Fig. 3.9. Here, multiple actions of the drug occur on the mediators of the peripheral inflammogenic response, including the unique regulation and facilitation of these pathways by prostaglandin E_2 (PGE_2), which in turn acts in the periphery via its specific receptor subtypes, EP_1 and EP_2 (Rodger 2009). The expression of inflammatory reactions and pain mediators that occurs in a hypothetical arthritic joint, and the actions of ibuprofen are shown in Fig. 3.10.

In the spinal cord (Figs. 3.9 and 3.11), ibuprofen has multiple actions the transmission of pain stimuli at the level of the dorsal horn by affecting the release and actions of the pain mediating peptides, substance P, calcitonin gene-related peptide (CGRP), the excitatory amino acid, glutamate, in part, via PGE_2, whose production is reduced by COX-1 and COX-2 (Fig. 3.10; Rodger 2009).

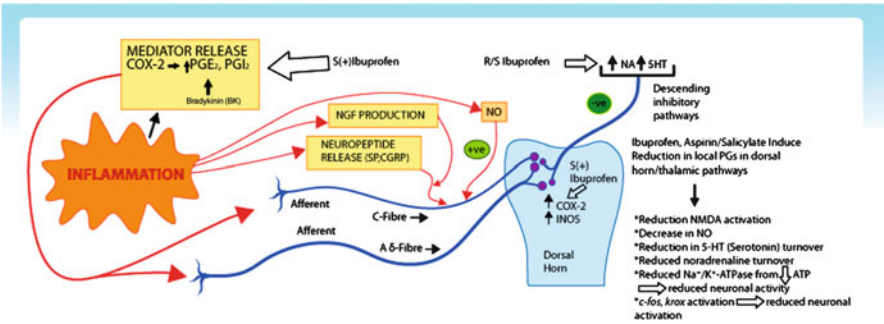


Fig. 3.9 Peripheral pain pathways leading from the sites of inflammation wherein there is (a) production of various pain evoking mediators in the "inflammatory soup", (b) the subsequent actions of these various mediators on their specific receptors on peripheral nerves, and (c) actions at the level of the dorsal horn with activation of local COX 2 and iNOS, so amplifying the pain responses. Regulation of these afferent pathways is achieved at the dorsal horn via negative "gate control" of afferent nerves by downward projecting efferent pathways originating from central activation of serotonergic (5 hydroxytryptamine producing) and noradrenergic pathways. Based on Rainsford (1999b, 2009) and Rodger (2009)

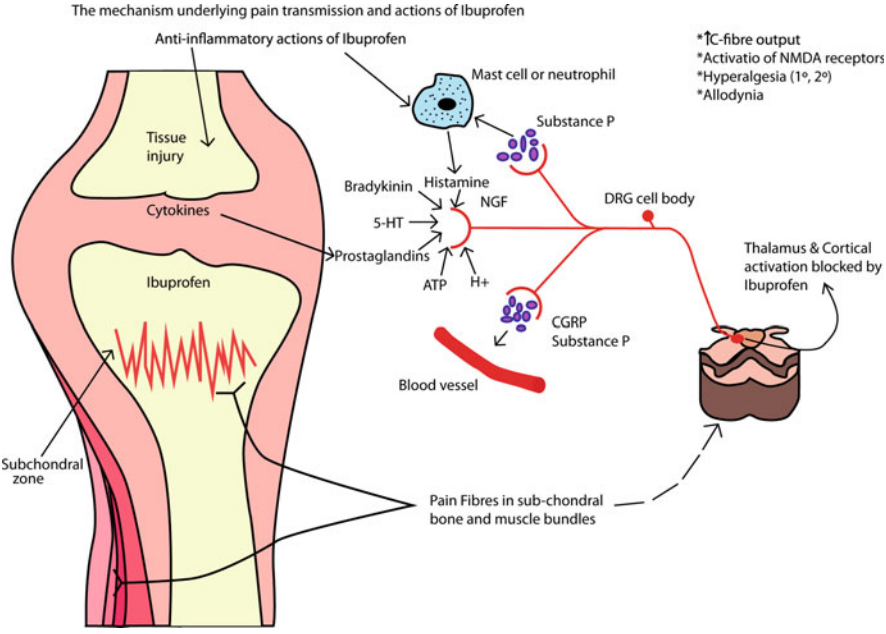


Fig. 3.10 Actions of ibuprofen on peripheral pathways involved in the mediation of pain in a typically inflamed joint, emphasising the variety of inflammatory mediators, including prostaglan din E mediated regulation of pain transmission. *Abbreviations: ATP* adenosine triphosphate; *5 HT* 5 hydroxytryptamine; *CGRP* calcitonin gene related peptide; *DRG* dorsal root ganglion

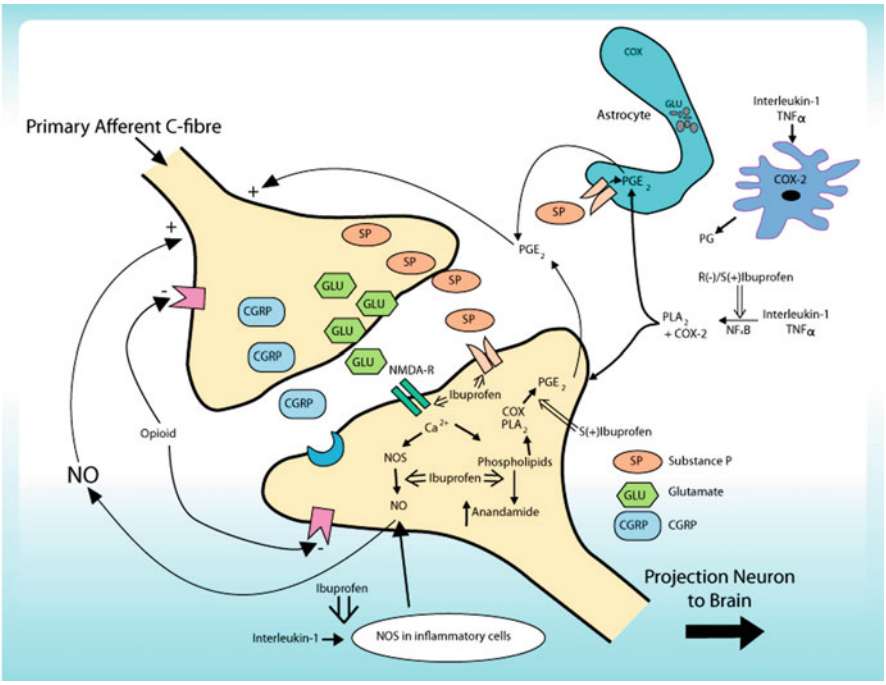


Fig. 3.11 Actions of ibuprofen on pain transmission at the dorsal horn mediated via substance P, calcitonin gene related peptide (CGRP), and glutamate, each of which acts on their own specific receptors. Based on Rodger (2009)

The induction of COX-2 activity is a feature of inflammatory pathways and those in the spinal cord, so that inhibition of this enzymic activity by ibuprofen and other NSAIDs and coxibs has a profound effect on the production of $PGE_{2,}$ since its production is amplified via inflammogenic and pain responses; the impact quantitatively of inhibiting COX-2 is, therefore, greater than that of the inhibition of COX-1, even though the latter enzyme exists in a variety of pathways of pain transmission and modulation in the CNS. Gene-knockout experiments (k/o) in mice have shown that compensation for the absence of COX-1 in the spinal cord may not involve increased expression of COX-2, whereas up-regulation of COX-1 in the spinal cord may compensate for the absence of COX-2 (Ballou et al. 2000). This shows there is evidence of cross-talk in the control of COX-1 and COX-2. These observations are to some extent paralleled by responses to painful stimuli in mice. Thus, in male and female COX-1 +/− mice, the reaction times are increased compared with those in COX-1 and COX-2 k/o or wild type mice in the hot plate test, a model of central or spinal algesia. In contrast in the writhing test, a model of peripheral pain, COX-1 −/+ or k/o mice and female COX-2 −/+ mice had remarkably lower pain response (numbers of writhes) (Ballou et al. 2000). From the point of view of analgesic actions by ibuprofen it is possible that this drug inhibits COX-1 somewhat more than COX-2.

With COX-1/COX-2 ratios being approximately 2.6 (compared with rofecoxib with ratios of ~0.05 0.0049, and celecoxib with ratios of 0.11 0.3; Warner et al. 1999) this would suggest that COX-1 inhibition by ibuprofen might have the effect of decreasing peripheral COX-1, and thus produce peripheral analgesia, whereas in the central analgesia this may be less pronounced.

The pioneering studies by Malmberg and Yaksh (1992a, b) highlighted the central actions of some NSAIDs, including notably S(+), but not R(−)-ibuprofen. Thus, intrathecal administration of S(+) ibuprofen inhibited the 2nd phase of flinching induced by hindpaw administration of formalin in rats. Other NSAIDs and paracetamol also inhibited the nociceptive reactions in approximate order of potency as PG synthesis inhibitors ranging from the more potent, flurbiprofen (IC_{50} 2.1 nmol), S(+) ibuprofen (IC_{50} 16 nmol) to paracetamol (IC_{50} 250 nmol) (Malmberg and Yaksh 1992a). These authors inferred that the central analgesic actions of NSAIDs and paracetamol relate to their effects as PG synthesis inhibitors. Another study by the same group focussing on the role of NMDA and substance P receptors showed that spinal administration of S(+)-ibuprofen (like aspirin or ketorolac) inhibited the hyperalgesia induced in rats by the excitatory amino acid, glutamate, and the pain-mediating peptide, substance P (Malmberg and Yaksh 1992a). Studies by Björkman (1995a, b) showed that the "scratching bitin-g licking" response during thermal hyperalgesia in rats was markedly reduced by spinal administration of S(+) but not by R(−) ibuprofen. This author also showed (Björkman 1995a, b; Björkman et al. 1996) that the analgesic response from the spinal administration to rats of NMDA agonist was observed following S(+)-ibuprofen, but not R(−)-ibuprofen. The pain response was also reduced by L-, but not, D-arginine, suggesting that the nitric oxide (NO) generated from the L-arginine overcame the excitatory effect of NMDA, invoking a NO mechanism in the analgesic actions of ibuprofen. No responses to these NSAIDs were observed to spinal application of substance P (Björkman et al. 1996).

Spinal serotonergic pathways have been shown to be involved in the analgesia induced by NSAIDs (Björkman 1995a, b; Rainsford 2004c).

3.4.2 Antipyretic Activity

Another well-established anti-inflammatory action of ibuprofen and other NSAIDs is the ability to control fever. This antipyretic response to ibuprofen and some other NSAIDs has two components: (a) the control of the production of leucocyte-derived interleukin-1 and other peptide components of endogenous pyrogen, and (b) the direct inhibition of the production of endogenous pyrogens (or IL-1) induced PGE_2 by the hypothalamus (Rainsford 1999b, 2004c, 2005b; Fig. 3.12).

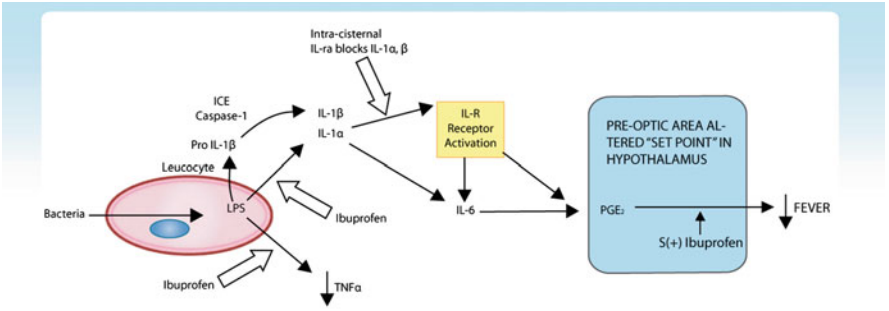


Fig. 3.12 Sites of antipyretic activity of ibuprofen involving the control of leucocyte production of interleukin 1β (IL 1β) and IL 6, their subsequent actions at the level of the hypothalamus on their respective receptors and the principal CNS actions of S(+) ibuprofen on PGE_2 production. With modifications from Rainsford (2004a, b, c) based on Rainsford (1999b, 2004b, c, 2009)

Chapter 4
Clinical Efficacy

It is well-established that ibuprofen at both OTC and prescription level dosages is effective in controlling pain and inflammation in a variety of inflammatory and painful conditions. Among these are rheumatic and other musculo-skeletal conditions, dental pain and surgery, dysmenorrhoea, upper respiratory tract conditions (colds, influenza), headaches, accidental sports injuries, and surgical conditions (Dionne 1998; Nørholt et al. 1998; Kean et al. 1999; Dionne and Cooper 1999; Rainsford 1999c; Hersh et al. 1993, 2000a, b; Steen Law et al. 2000; Doyle et al. 2002; Beaver 2003; Dalton and Schweinle 2006; Sachs 2005; McQuay et al. 1986, 1989, 1992, 1993, 1996; McQuay and Moore 1998, 2006; Eccles 2006; Verhagen et al. 2006; Huber and Terezhalmi 2006; Tables 4.1, 4.2 and 4.3). It is not the purpose of this report to review the evidence in extenso about the clinical efficacy in various painful states, since this is well-established from over 40 years of research and applications of ibuprofen in the treatment of these conditions (Kean et al. 1999; Rainsford 1999c).

4.1 Dental Pain

The dental pain model, involving the measurement of acute pain following extraction of one or more impacted third molars, is probably the most-widely accepted robust and reliable method of determining relief from pain and swelling in humans (Cooper 1984; Dionne and Cooper 1999). As shown in Table 4.1 ibuprofen has comparable analgesic effects to other NSAIDs in the model of dental pain elicited following surgical removal of third molars. Indeed, the relative efficacy of ibuprofen as measured by the Number Needed to Treat (NNT) for determining the efficacy from ibuprofen is either comparable or superior to other NSAIDs or analgesics (Table 4.1). The adverse reactions from ibuprofen are often lower than with other drugs (Table 4.1).

Another significant clinico-experimental fact is that ibuprofen has frequently been used as a comparator drug in clinical trials with other NSAIDs, including those

K.D. Rainsford, *Ibuprofen: Pharmacology, Therapeutics and Side Effects*,
DOI 10.1007/978 3 0348 0496 7 4, © Springer Basel 2012

Table 4.1 Relative efficacy and adverse events from single doses of analgesics or NSAIDs used for relief of pain following dental (third molar extraction) surgery

Drug (dose)	NNT[a] (95 % CI)	No. of patients	Relative[b] efficacy (RR 95 % CI)	Adverse events (%)[c]		
				Active	Placebo	Relative risk (95 %) CI
Ibuprofen (400 mg)	2.4(2.3–2.6)	4,703	6.3(4.2–2.9)	34	41	0.8(0.7–1.0)
Aspirin (600/650 mg)	4.4(4.0–4.9)	5,061				
Celecoxib (200 mg)	4.2(3.4–5.6)	497				
400 mg	2.5(2.2–2.9)	412				
Diclofenac (50 mg)	2.3(2.0–2.7)	734	2.1(1.2–4.2)	60	41	1.2(0.9–1.6)
Morphine (10 mg IM)	2.9(2.6–3.6)	946				
Naproxen (550 mg)	2.1(1.6–2.7)	88	5.7(3.0–1.1)	31	29	1.1(0.7–1.7)
Paracetamol (1,000 mg)	3.8(3.4–4.4)	2,759				
Paracetamol (600/650 mg) + codeine (60 mg)	4.2(3.4–5.3)	1,123		41	39	1.0(0.7–1.4)
Rofecoxib (50 mg)	2.3(2.0–2.7)	738	5.9(3.0–1.1)			

Data compiled from meta-analysis or Cochrane Collaborative review studies undertaken by the Oxford University Pain Research & Nuffield Division of Anaesthesia (Barden et al. 2002, 2004; Derry et al. 2008; Edwards et al. 2004)

[a]*NNT* Number need to treat to obtain 50 % pain relief at 6 h (approx).

[b]Relative efficacy is determined as a relative risk (RR) value.

[c]Adverse events—mostly minor and include nausea, dizziness in about 1–2 % of patients. Some patients had alveolitis from the surgery, but this was mostly unaffected by treatment with the drugs.

Rofecoxib is now discontinued, but data included as this was investigated in original comparative studies

Table 4.2 Effects of ibuprofen compared with placebo or other analgesics in headache/migraine

Author (year)	Treatment drug dosage (mg)	Outcome pain relief	Adverse effects
Tension headache			
Diamond (1983)	Ibu (400), Ibu (800), Asp (650), Pla	All drugs = > Pla	
Noyelle et al (1987)	Ibu (400), Asp (650, 1,000), Par (1,000)		
Nebe et al (1995)	Ibu (200), Asp (500), Pla	Ibu = Asp; both > Pla	
Schachtel et al (1996)	Ibu (400), Par (1,000), Pla	Ibu > Par Both > Pla	1 pt Pla, nausea
Lange and Lentz (1995)	Ibu (200), Ket(12 5, 25), Nab (275)	Ibu = all other drugs	
High-altitude headache			
Broome et al (1994)	Ibu (400), Pla	Ibu > Pla	1 Ibu and 1 Pla pt vomited
Packman et al (2000)	Ibu (400; solubilised), Par (1,000), Pla	Ibu > Par, both > Pla	None
Diamond et al (2000)	Ibu (400), Ibu (400) + Caffeine (200), Caffeine (200), Pla	Ibu + Caffeine > Ibu > Caffeine > Pla (greater effect of Ibu + Caffeine and Ibu at 3–6 h)	Nervousness, nausea and dizziness most frequent in Ibu + Caffeine
Harris et al (2003)	Ibu (400), Par (1,000)	Ibu = Par	Reduced nausea in both, no headache or pulmonary oedema
Kubitzek et al (2003)	Ibu (400), Dic (12 5), Dic (25), Pla	All drugs equivalent effects > Pla	AEs equal, less digestive AEs in Dic group (1 %) than Ibu (3 %)
Migraine			
Havanka-Kanniainen (1989)	Ibu (800), Ibu (1,200), Pla	Ibu (800) Ibu (1,200) > Pla	None
Kloster et al (1992)	Ibu (400), Pla	Ibu > Pla (reduced migraine index)	12 % Ibu had stomach discomfort (non-serious)
Kellstein et al (2000)	Ibu (400, 600 soluble), Pla	Ibu (400 = 600) > Pla	
EMSASI study group Diener et al (2004)	Ibu (400), Asp (1,000), Sumatriptan (50), Pla	All drugs equiactive > Pla	AEs Asp (16 %), Ibu (12 %), Sumatriptan (20 %), Pla (14 %) 1 pt dizziness
Goldstein et al (2006)	Ibu (200), Par (250) + Asp (250) + caffeine (65) (=PAC) Pla	PAC > Ibu; both > Pla	AEs all non serious 9 7 % PAC > 5 1 % Ibu < 5 5 % Pla PAC nervousness (1 9 %) + nausea (1 6 %) > Ibu + Pla dizziness Pla > Ibu

Based on data in Dotzel (2002)

Table 4.3 Comparison of Ibuprofen with other analgesics (given as single doses) in acute post-operative pain in adults

				At least 50 % maximum pain relief over 4–6 h					
		Number of:		Number with outcome/ total		Percent with outcome		Relative benefit	
Drug	Dose (mg)	Studies	Participants	Active	Placebo	Active	Placebo	(95 % CI)	NNT (95 % CI)
A. Painful dental conditions									
Ibuprofen	200	18	2,470	680/1,462	100/1,008	47	10	4.5(3.7–5.4)	2.7(2.5–3.0)
Ibuprofen	400	49	5,428	1,746/3,148	271/2,280	55	12	4.3(3.8–4.9)	2.3(2.2–2.4)
Ibuprofen	200 soluble[a]	7	828	270/478	34/350	56	10	5.7(4.2–7.9)	2.1(1.9–2.4)
Ibuprofen	200 standard[a]	15	1,883	406/984	62/899	41	7	5.9(4.7–7.6)	2.9(2.6–3.2)
Ibuprofen	400 soluble[b]	9	959	361/550	41/409	66	10	6.5(4.8–8.9)	1.8(1.7–2.0)
Ibuprofen	400 standard[b]	46	4,772	1,385/2,598	230/2,174	53	11	5.2(4.6–5.9)	2.3(2.2–2.5)
Aspirin	600/650	45	3,581	634/1,763	251/1,818	36	14	2.6(2.3–2.9)	4.5(4.0–5.2)
Aspirin	1,000	4	436	87/250	20/186	35	11	2.8(1.9–4.3)	4.2(3.2–6.0)
Celecoxib	200	3	423	94/282	01/02/41	41	1	16(5.1–49)	3.2(2.7–3.9)
Celecoxib	400	4	620	184/415	01/09/05	34	4	11(5.9–22)	2.5(2.2–2.9)
Codeine	60	15	1,146	79/573	52/573	14	9	1.5(1.1–2.1)	21(12–96)
Dexketoprofen	10/12.5	3	251	61/131	17/120	47	14	3.3(2.0–5.3)	3.1(2.3–4.6)
Dexketoprofen	20/25	4	322	82/176	17/146	47	12	4.5(2.8–7.2)	2.9(2.3–3.9)
Dextropropoxyphene (a)+ paracetamol	65+650	3	353	61/173	23/280	35	13	2.8(1.8–4.2)	4.6(3.2–7.2)
Diclofenac (b)	25	3	398	99/196	22/202	51	11	4.7(3.1–7.1)	2.5(2.1–3.2)
Diclofenac	50	9	1,119	378/678	82/441	56	19	3.0(2.4–3.7)	2.7(2.4–3.1)
Diclofenac	100	4	413	151/228	19/185	66	10	6.6(4.3–10)	1.8(1.6–2.1)
Diflunisal	500	3	220	61/112	19/108	55	18	3.1(2.0–4.8)	2.7(2.0–3.8)
Etodolac	100	4	418	80/211	34/207	38	16	2.3(1.6–3.3)	4.7(3.4–7.6)
Etodolac	200	7	670	145/333	44/337	44	13	3.3(2.5–4.5)	3.3(2.7–4.2)
Etodolac	400	2	149	43/85	01/03/64	51	5	11(3.5–18)	2.2(1.7–2.9)
Etoricoxib	120	4	500	233/326	16/174	71	9	8.0(5.0–13.0)	1.6(1.5–1.8)

Etoricoxib	180/240	2	199	129/150	01/06/49	79	12	6.4(3.1–14)	1.5(1.3–1.7)
Flurbiprofen	50	7	473	161/245	74/228	66	32	2.1(1.7–2.5)	3.0(2.0–4.0)
Flurbiprofen	100	6	354	119/184	48/170	65	29	2.4(1.9–3.1)	2.8(2.2–3.7)
Ketoprofen	12.5	3	274	77/138	18/136	56	13	4.2(2.7–6.6)	2.4(1.9–3.1)
Ketoprofen	25	6	452	153/239	26/213	64	12	5.2(3.6–7.5)	1.9(1.7–2.3)
Ketoprofen	50	3	190	61/98	01/06/92	62	6	9.0(4.2–19)	1.8(1.5–2.2)
Ketoprofen	100	3	195	79/97	01/10/98	72	10	7.3(4.0–13)	1.6(1.4–2.0)
Lornoxicam	8	3	273	71/155	13/118	46	11	4.7(2.7–8.1)	2.9(2.3–4.0)
Lumiracoxib	400	3	460	163/307	01/07/53	53	2	9.7(4.3–2.2)	2.1(1.8–2.7)
Naproxen	500/550	5	402	122/199	14/203	61	7	8.7(5.2–14)	1.8(1.6–2.1)
Oxycodone +paracetamol	10/650	6	673	252/496	01/11/77	51	6	6.8(3.9–12)	2.3(2.0–2.6)
Paracetamol	500	3	305	84/150	46/155	56	30	1.9(1.4–2.5)	3.8(2.7–6.4)
Paracetamol	600/650	10	1,276	225/638	74/638	35	12	3.1(2.4–3.8)	4.2(3.6–5.2)
Paracetamol	975/1,000	19	2,157	545/1,335	82/822	41	10	4.1(3.3–5.2)	3.2(2.9–3.6)
Rofecoxib	50	22	3,060	1,332/2,173	73/887	61	8	7.3(5.9–9.2)	1.9(1.8–2.0)
B. Other painful conditions									
Ibuprofen	200	2	220	42/110	01/05/10	38	5	7.7(3.2–18)	3.0(2.3–4.2)
Ibuprofen	400	12	1,047	277/580	103/467	48	22	2.2(1.8–2.6)	3.9(3.2–5.0)
Ibuprofen	200 soluble[c]	7	828	270/478	34/350	56	10	5.7(4.2–7.9)	2.1(1.9–2.4)
Ibuprofen	200 standard[c]	15	1,883	406/984	62/899	41	7	5.9(4.7–7.6)	2.9(2.6–3.2)
Ibuprofen	400 soluble[d]	9	959	361/550	41/409	66	10	6.5(4.8–8.9)	1.8(1.7–2.0)
Ibuprofen	400 standard[d]	46	4,772	1,385/2,598	230/2,174	53	11	5.2(4.6–5.9)	2.3(2.2–2.5)
Aspirin	600/650	19	1,384	349/733	128/651	48	20	2.4(2.0–2.8)	3.6(3.1–4.3)
Aspirin	1,000	4	334	91/166	35/168	55	21	2.6(1.9–3.6)	2.9(2.3–4.1)
Dextropropoxyphene (a)+paracetamol	65+650	3	610	123/305	51/305	40	15	2.4(1.8–3.2)	4.2(3.3–6.0)
Diclofenac	50	2	206	63/102	20/104	62	19	3.2(2.1–4.9)	2.4(1.8–3.3)

(continued)

Table 4.3 (continued)

				At least 50 % maximum pain relief over 4–6 h					
		Number of:		Number with outcome/ total		Percent with outcome		Relative benefit	
Drug	Dose (mg)	Studies	Participants	Active	Placebo	Active	Placebo	(95 % CI)	NNT (95 % CI)
Diclofenac	100	3	374	79/188	24/186	42	13	3.3(2.2–4.9)	3.4(2.7–4.9)
Diflunisal	500	3	171	42/86	01/08/85	49	9	5.3(2.7–10)	2.5(1.9–3.7)
Dipyrone	500	4	210	78/104	29/106	75	27	2.7(2.0–3.8)	2.1(1.7–2.8)
Flurbiprofen	50	3	219	84/108	34/111	78	31	2.5(1.9–3.3)	2.1(1.7–2.8)
Oxycodone +paracetamol	01/10/50	4	370	93/184	37/186	51	20	2.5(1.9–3.4)	3.3(2.5–4.7)

Reproduced from Moore et al. (2011) with permission of John Wiley and Sons, publishers of the Cochrane Database of Systematic Reviews
Data from Cochrane Collaboration® Review by Moore et al. (2011) see http://www.thecochranelibrary.com. Reproduced in part, with permission of John Wiley & Sons Ltd.
(a) Dextropropoxyphene now withdrawn.
(b) Data from sodium or potassium formulations of diclofenac not shown, but all these have comparable relative benefit or NNT to data in this table of diclofenac.
(c) Data judged by authors (Moore et al. 2011) to be of good standard.
(d) [a,b,c,d] These data are from direct comparisons of soluble and standard formulations.

with celecoxib (Derry et al. 2008), rofecoxib (Barden et al. 2002, 2004), diclofenac, and paracetamol combinations (Table 4.1). In general, these studies have shown that ibuprofen is either equivalent to or better than the comparator drugs (Tables 4.1 and 4.2).

4.2 Pain Relief at OTC Dosages

Ibuprofen is often a preferred drug among the OTC analgesics for treatment of tension-type headache and migraine (Verhagen et al. 2006; Table 4.2). A recent evidence-based consensus report (Haag et al. 2011) based on recommendations of the Deutsche Migräne und Kopfschmerzgesellschaft (DMKG), the Deutsche Gesellschaft für Neurologie (DGN), the Österreichische Kopfschmerzgesellschaft (ÖKSG) and the Schweizerische Kopfwehgesellschaft (SKG) rated ibuprofen 400 mg as a drug of first choice for self-treatment of tension-type headache and migraine attacks with or without aura, along with acetylsalicylic acid (aspirin) (900 1,000 mg), diclofenac (25 mg for headache alone), naratriptan (2.5 mg), paracetamol (1,000 mg), and phenazone (1,000 mg), as well as various fixed combinations of some of these drugs. As also shown in Table 4.3, there has been a large number of studies in which ibuprofen has clearly shown dose-related analgesia.

Ibuprofen is very effective in controlling fever both in adults and in children (Hersh et al. 2000b; Eccles 2006). It also has wide applications in the treatment of viral respiratory infections where there is an appreciable inflammatory component (Winter and Mygynd 2003). There are, however, some key points about the efficacy of ibuprofen which need to be emphasized in the context of the OTC use of this drug and comparisons with other analgesics.

Ibuprofen has rapid onset of analgesia, and this is maintained in parallel with the plasma elimination half-life of ibuprofen, which for both the active (S+) and inactive (R−) enantiomers is approximately 2 h (Graham and Williams 2004); the analgesia extends to approximately 6 h as evidenced by a number of analgesia models (e.g., third molar dental extraction pain model; Dionne and Cooper 1999; Table 4.1).

It has been observed that in acute pain there are alterations in the PKs of ibuprofen, resulting in decreased serum levels of the enantiomers after dental surgery (Jamali and Kunz-Dober 1999). Gender differences have been observed in response to acute pain in the dental pain model, with ibuprofen being more effective in men than in women (Walker and Carmody 1998). Other studies using a similar third molar extraction dental pain model have not revealed any gender differences in response to analgesia with ibuprofen (Averbuch and Katzper 2000). Aside from these factors, it appears therefore that variability in response to

analgesia with ibuprofen may relate to acute pain and altering the pharmacokinetics of the drug, and possibly to gender differences.

The relationship between plasma or serum concentrations of ibuprofen to the onset of analgesia has been the subject of much interest. Aside from knowledge that is of significance pharmacologically (i.e., relating PK of the drug to its PD properties) this is of significance in determining doses at which plasma/serum concentrations are achieved during therapy of different pain states (Rainsford 2009).

In order to derive values of the therapeutically relevant plasma concentrations (TRPC) of ibuprofen, data have been extracted from published studies in various acute and chronic (arthritis) studies and *acute* experimental pain models in humans in which plasma concentrations of the racemic or enantiomeric forms of the drug were compared with therapeutic response, comprising the relief of pain symptoms or the pharmacological actions as attributed to the S(+) and R(−) forms, as well as those components of ibuprofen required for reducing circulating levels of the cyclo-oxygenase products.

Therapeutically-relevant drug concentrations vary according to (a) the selection of pharmacokinetic (PK) parameters at which pain responses are evident, (b) the effects of the individual enantiomers concentrations to their pharmacodynamic (PD) activity with the S(+) isomer the active form for inhibiting both pain relief and prostaglandin synthesis inhibitory actions, and (c) the impact of different painful conditions on both the PK of ibuprofen and the analgesic responses.

In modelling of the data on PK in relation to PD from published studies, it is possible to take two approaches: (1) select data at the earliest period when there is significant increase in plasma concentrations, and relate this to the development of the analgesic response, or (2) to select data on the plasma concentrations of the drug, C_p, at the lowest effective dose of the drug (400 mg), and relate this to analgesic activity; the latter occurs mostly after the peak concentrations of the drug. Using data derived from the third molar dental surgery pain model, it has been possible to identify the earliest significant analgesic activity from ibuprofen 400 mg at 0.5 h, associated with serum concentrations of 17.5 μg/mL of racemic ibuprofen.

In less severe inflammatory conditions than observed in dental surgery, it is established that the lowest dose of 200 mg ibuprofen can be effective in relieving symptoms of mild pain (headache, colds, and acute injuries). Under these circumstances, lower TRPC is anticipated. Thus, in considering the TRPC of ibuprofen it is important to identify the degree of pain and inflammation accompanying the respective painful conditions.

From these and other data, it is proposed that the TRPC of racemic ibuprofen are within the range of 11 25 μg/mL and 10 15 μg/mL of S(+) ibuprofen following intake of 400 600 mg ibuprofen. These values are obtained from data on the optimal or lowest dose of the drug for acute pain relief, and the same or slightly higher concentrations required for relief of symptoms in arthritic pain. The values for the TRPC of ibuprofen correspond with those at which there is ex-vivo inhibition of COX-1 and COX-2 derived prostaglandin production in whole blood preparations. Fast-absorbing salts or other formulations enhance the onset of

analgesia, and the range of concentrations required for the early stages of onset is lower than observed above.

Recently, Li et al. (2012) have examined the onset and offset of dental pain relief by standard ibuprofen 400 mg (Nurofen) and an effervescent ibuprofen 400 mg tablet preparation in patients undergoing third molar extraction. They employed linear "hazard" models to determine the time of first perceptible pain relief (TFPR), the time to meaningful pain relief (TMPR), and the time to remedication (REMD), from ibuprofen in relation to placebo, and correlated these values with PK profiles. Maximum pain relief was obtained at drug concentrations of 10.2 μg/mL. This is within the same order as the TRPC concentrations calculated above. As expected, effervescent ibuprofen was more rapidly absorbed, and surprisingly was complete by 15 min. This rapid absorption resulted in earlier values of TMPR and lower REMD than standard ibuprofen. The authors have developed a series of nomograms which can be used to estimate pain responses in relation to plasma concentrations of ibuprofen for different immediate response (IR) formulations of ibuprofen.

Ibuprofen has been found to be effective in *chronic arthritic pain*, with associated improvement in joint inflammatory symptoms even at low (800 1,200 mg/day) doses (Grennan et al. 1983; Kean et al. 1999). Under these conditions paracetamol is less effective, and indeed, several studies have shown that it has no effects at all in controlling chronic inflammatory pain in rheumatic diseases at the recommended OTC dosages of 1,000 mg/day (Kean et al. 1999).

There is now unequivocal evidence for a dose response effect with ibuprofen in acute pain conditions (McQuay and Moore 2006; Li Wan Po 2007; Fig. 2.10), although the meta-analysis of McQuay and Moore (2006) only showed that 400 mg/day ibuprofen was superior to 200 mg. The studies by Schou et al. (1998) showed that there was a much greater range of dose response that extended from 100 to 400 mg (Fig. 2.10). The NNT for ibuprofen was in the range of 6 23 for the low high-dose comparisons, compared with that of paracetamol 1,000 mg compared with 500 mg which was 6 20; the inference is that there is no difference in the NNT between these two treatments. However, a consensus view is that in certain inflammatory pain conditions (e.g., dental surgery) ibuprofen is superior at its recommended OTC dosage of 200 400 mg per single treatment compared with that of paracetamol 500 1,000 mg (McQuay and Moore 1998; Dionne and Cooper 1999; Hargreaves and Keiser 2002).

In comparison with other NSAIDs, including the newer coxibs, ibuprofen has been shown in a variety of studies to be at least as effective as these drugs [with the possible exception that longer half-life drugs such as rofecoxib exhibit a longer duration of action (Dionne and Cooper 1999; Huber and Terezhalmi 2006; Hargreaves and Keiser 2002; Edwards et al. 2004)] as well as having been shown to be effective in a variety of acute pain conditions (Sachs 2005).

A key pharmacokinetic feature about the analgesic actions of ibuprofen is that the drug has the ability to penetrate the CNS, and is present in free concentrations in the CSF (Brocks and Jamali 1999; Graham and Williams 2004). In addition, ibuprofen accumulates and is retained in inflamed joints of arthritic patients (Brocks and Jamali 1999; Graham and Williams 2004). Thus, the drug is present in sites where analgesic and anti-inflammatory effects are required.

Recent reviews of the choice of analgesics for pain management have highlighted the fact that, although paracetamol may be useful and perhaps a choice initially for pain control, the safest and most effective of all NSAIDs is ibuprofen at doses of 400 mg for acute non-specific pain (Sachs 2005), and it is highly effective in tension-type headache (Verhagen et al. 2006). A particularly challenging view provided by a recent analytical review by Arora et al. (2007) suggested that oral ibuprofen is as effective in analgesia as parenteral ketolorac, a drug which is used in postoperative surgical pain control as well as in acute traumatic muscular skeletal pain conditions. Since ketolorac is amongst those NSAIDs the highest risks for causing upper gastrointestinal bleeding ulcers, it appears that substitution of oral ibuprofen in acute surgery and traumatic conditions may represent a valid alternative, with much lower risk that parenteral ketolorac.

4.3 Treatment of Pain in Osteoarthritis and Related Conditions

There are indications that ibuprofen is used quite extensively in some countries where it is available for OTC use for occasional treatment of osteoarthritis (OA) and other musculoskeletal conditions. Here, ibuprofen finds particular value in being more effective than paracetamol and having less GI symptoms than aspirin. Evidence in support of ibuprofen being effective in relieving pain and joint symptoms at OTC dosage in OA has come from various clinical trials; the earlier studies showing effectiveness in this condition were reviewed by Kean et al. (1999).

Among the more recent studies, Bradley et al. (1991) found that 1 month's treatment with ibuprofen 1,200 mg/day (referred to as an analgesic dose) had superior rest and walking pain scores and comparable Health Assessment Questionnaire (HAQ Stanford University) pain and walking scores with paracetamol (acetaminophen) 4,000 mg/day in patients (>70 % females; total number of 182 subjects) with OA of the knee. Adverse events were minor symptomatic and of comparable. The higher prescription level dose of 2,400 mg/day ibuprofen (referred to as an anti-inflammatory dose) resulted in increased pain and walking scores. A later re-analysis of this study by the same group (Bradley et al. 1992) attempted to resolve the issue of whether drug effects on joint tenderness and swelling, reflecting synovitis, were affected by "anti-inflammatory" doses of ibuprofen without any indications of these actions. A second re-evaluation of the earlier study by the same group (Bradley et al. 2001) showed that baseline pain could influence the anti-inflammatory/analgesic effects of ibuprofen, with better response being observed when there were higher levels of baseline pain. This is relevant, since there were indications that the original study population (Bradley et al. 1991) comprised patients with mild to moderate joint conditions. Thus, the effectiveness of ibuprofen is greater in patients with more pronounced joint symptoms.

The semantic definition of analgesic effects at OTC dosage of ibuprofen (1,200 mg) being separate from anti-inflammatory effects of the drug is probably not justified, since there are several studies in chronic arthritic conditions showing

that joint symptoms are significantly improved with 800 1,200 mg/day ibuprofen (Kean et al. 1999). Moreover, there is an important study performed by Deodhar et al. (1973) on the effects of ibuprofen 1,200 mg/day *for 1 week* on joint inflammation in RA patients, in which they investigated knee inflammation following i.v. injection of radioactive pertechnate (^{99m}Tc). The uptake of ^{99m}Tc uptake into knee joints was significantly reduced by ibuprofen compared with placebo. A correlation was observed between inflammatory indices of knee functions and ^{99m}Tc uptake. This is direct evidence for local anti-inflammatory effects of ibuprofen under conditions where there is effective relief of joint inflammatory symptoms and pain in arthritic diseases. Such relief of joint inflammatory pain is not evident with high doses of paracetamol.

In a short-term study designed to measure pain relief (measured using a 100 mm visual analogue scale, VAS) over the 8-h period following the first and sixth dose (total 1,200 mg/day) of ibuprofen 200 mg compared with placebo or ibuprofen + codeine (30 mg) to 29 patients with knee OA, Quiding et al. (1992) found that relatively rapid pain relief was evident with ibuprofen (as well as ibuprofen + codeine), and this was sustained throughout the 8-h period of evaluation. These results attest to the specific time-course effects of ibuprofen in relief of pain in OA.

Schiff and Minic (2004) compared the effects of 1,200 mg/day ibuprofen with naproxen sodium 660 mg/day at an OTC dose (another NSAID that is available OTC in some countries) and placebo for 7 days in two multicentre parallel group studies in 440 patients with knee OA. They found that both NSAIDs relieved joint symptoms, with naproxen being slightly more effective than ibuprofen, ibuprofen being, however, more effective in relief of day pain.

In another large multi-centre study (known as 'ibuprofen, paracetamol study in osteoarthritis' or IPSO) by Boureau et al. (2004) in 222 patients with OA of the hip (30 % patients) or knee (70 % patients), ibuprofen 400 mg taken as single or multiple (1,200 mg/day) doses was compared with paracetamol 1,000 mg single dose or 4,000 mg/day for relief of and pain joint symptoms, WOMAC (Western Ontario McMaster University) scores over 2 weeks. Significant reduction was observed in Pain Intensity Scores over the first 6-h period and then progressive reduction continued over the 2-week period with ibuprofen as compared with paracetamol. This study shows that ibuprofen is superior to paracetamol at OTC doses in relief of joint symptoms in both knee and hip OA. This conclusion is supported by a more general Cochrane Review of randomised and placebo-controlled trials in which NSAIDs (including ibuprofen) were superior to paracetamol in achieving reduction in pain, global efficacy assessments, and improvements in functional status (Towheed et al. 2006).

Thus, of the available OTC treatments, ibuprofen would appear to have particular advantage for self-treatment of joint pain and symptoms in OA in being superior in efficacy to paracetamol and preferable to aspirin because of a lower incidence of GI symptoms (see later section).

4.4 Paediatric Uses

The effectiveness of ibuprofen in headache and migraine has been demonstrated in a number of studies in children. Less is known about the mechanisms of action in these conditions, but it is probably due in part to S(+) ibuprofen affecting platelet activation and thromboxane A_2 production, and local vascular effects in the affected regions of brain vessels. It is significant that ibuprofen can penetrate into the CNS, so that this may contribute to the central analgesic effects including those in headache and migraine as a consequence of local accumulation of the drug. Several experimental studies suggest that S(+) ibuprofen administered intrathecally (i.a.) into the CNS has direct analgesic effects which are greater than the R(−) form.

4.4.1 Acute Fever in Children

Ibuprofen is widely used in the treatment of fever, and in the treatment of this condition carers can have a considerable involvement. Likewise, paediatricians and general physicians as well as pharmacists have a role in the administration or prescription of ibuprofen for the treatment of fever. While ibuprofen has had apparently a second place in the treatment of fever over the past three to four decades, paracetamol has found wide popular application, and is considered to be a safe and effective treatment for most febrile conditions. However, there is evidence from clinical trials that ibuprofen may be more effective than paracetamol (Table 4.4). There are also indications that alternating treatments with paracetamol and then ibuprofen or combinations of these two are becoming increasingly popular, especially amongst paediatricians and those involved in the treatment of children under emergency or outpatient conditions. The administration of combinations or alternating treatments with paracetamol and ibuprofen is highly controversial, and is regarded by most as having potential risks. Indeed this author believes that there is a major issue concerning potential toxicity in certain organs, for example in the liver and kidney, which may place paediatric patients who have very high febrile states that may lead to cytokine activation and precipitation of liver reactions. Monotherapy is generally preferred, and ibuprofen has a key place in treatment of fever in infants and children.

Amongst the most frequent indications for use of ibuprofen in children is for the treatment of fever. Since febrile conditions lead to elevation of febrile-inducing pro-inflammatory cytokines (especially IL-1β, TNFα, IL-6), and these can lead to alterations in the activities of drug-metabolizing enzymes, it is important to understand if the pharmacokinetics of antipyretic agents is altered in febrile conditions in children. Earlier reviews (e.g., Walson and Mortensen 1989) emphasized the lack of PK data in children, a situation that has been addressed more extensively in recent years, although there are still some gaps in knowledge of PKs of antipyretic/analgesic drugs, especially in infants.

Table 4.4 Comparative studies of ibuprofen and paracetamol in the treatment of acute fever

	Dose frequency	Age (years)	No of children	Dose of ibuprofen (mg/kg)	Dose of paracetamol (mg/kg)	Outcome
Sidler et al. (1990)	Multiple	1.25 13	90	7 or 10	10	Ibu 7 > Para Ibu 10 > Para
Wilson et al. (1991)	Single	0.25 12	178	5 or 10	12.5	Ibu 10 > Para
Autret et al. (1994)	Multiple 3 days	0.5 5	154	7.5	10	Ibu Para
Van Esch et al. (1995)	Multiple 3 days	0.25 4	70	7.5	10	Ibu > Para
Vauzelle Kervroedan et al. (1997)	Single	4 ± 0.6	116	10	10	Ibu Para
Autret et al. (1997)	Single	0.5 2	351	7.5	10	Ibu > Para

Reproduced with permission of the publishers from Rainsford (2009). *Ibu* Ibuprofen; *Para* Paracetamol

Nahata et al. (1991) studied the PK of ibuprofen in 17 patients (aged 3 10 years) with fever from streptococcal pharyngitis and otitis media, who received 5 mg/kg and 10 mg/kg liquid formulation of the drug (mean ages ± SD for this group being 6.7 ± 2.5 and 6.2 ± 2.1 years) The peak (mean ± SD) serum concentrations of the racemate in these two groups were 28.4 ± 7.5 and 43.6 ± 18.6 μg/mL, which were evident at 1.1 and 1.2 h respectively. The $t_{½}$s were 1.6 h in both groups and the rates of oral clearance 1.2 ± 0.4 1.4 ± 0.5 mL/min/kg respectively, showing that the serum PK are unaffected by the doses employed. An earlier study by Walson et al. (1989) using liquid ibuprofen in febrile children showed that the values for C_{max} were slightly lower at the 5 mg/kg dose than observed in the study by Nahata et al. (1991), but were within the same range.

A later study by the same group performed a randomized, double-blind, parallel-group placebo-controlled study in 56 infants and children (0.5 12 years) who were primarily investigated for antipyretic effects (Nahata et al. 1992). They were given 5 and 10 mg/kg ibuprofen suspension or placebo in separate groups but blood samples for PK assay of the plasma concentrations of the racemate in only 17 patients who received the drug alone. The mean maximal plasma concentration was 28.4 μg/mL and 43.6 μg/mL at 1.0 and 1.5 h for the 5 and 10 mg/kg dosage groups respectively. These plasma values (Nahata et al. 1992) correspond closely with those in serum which were obtained in the earlier study (Nahata et al. 1991), showing consistency both in plasma cf serum and between the studies.

Another study in febrile patients was performed by Kauffman and Nelson (1992) in 49 infants and children aged 3 months to 10.4 years, the primary purpose being to investigate the relationship between plasma concentration of the racemic form of the drug and antipyretic effects. Fever was diagnosed as arising from a variety of conditions including pneumonia, otitis media, upper respiratory tract infection, tonsillo-pharyngitis, and various other conditions. The dose of ibuprofen was

8 mg/kg, which is between that of 5 10 mg/kg used in the earlier studies. Further discussion about the therapeutic effects of this and other studies reported in this section will be considered in the next section. However, it was found that there was a delay in peak concentration of ibuprofen and maximal decrease in temperature, highlighting that the therapeutic benefit follows the peak or optimal plasma concentrations of the drug as shown in Chapter 3.

Despite these apparent benefits, the administration of antipyretic agents to treat fever in infants and children has not been without its critics; furthermore, parents and carers have been considered to have numerous misconceptions about what fever is and how it should be treated (Crocetti et al. 2001). Schmitt (1980) found that parents had many misconceptions about what fever really is in terms of temperature, and he coined the term "fever-phobia". In a survey of 340 carers in two urban-based paediatric clinics in the Baltimore region, MD, USA, Crocetti et al. (2001) found that care-givers varied considerably in their belief of potential harm of fever to their children, of what temperature range actually constitutes fever, and in the use of sponging and other treatments to control fever.

Hay and co-workers (2006) reviewed some of the recent studies on single and combination antipyretic therapies, and highlighted that the combination preparation's safety is limited. These authors also highlighted the occurrence of renal failure or renal tubular necrosis from ibuprofen, and the potential for nephrotoxic metabolite formation from paracetamol (quinine-imine paracetamol) in producing both nephrotoxicity and hepatic reactions. These authors also pointed out that the definition of clinically useful difference in temperature after treatment is still debatable. To achieve better understanding, continuous thermometry should be employed. Knapp-Długosz and co-authors (2006) have reviewed the appropriate use of non-prescription antipyretics in paediatric patients. They referred to the ongoing debate about whether and when to treat fever, but pointed out that clinicians agree that antipyretic therapy is important for febrile children who have (a) chronic cardio-pulmonary disease, metabolic disorders or neurological conditions, and (b) are at risk of febrile seizures. They point to the lack of guidelines on the use of antipyretic agents in other categories of fever in children. Thus, patient comfort is cited most often as the deciding factor. Moreover, there is little support for administering antipyretic agents when the temperature is less that at 101 °F unless the child is uncomfortable. None-the-less, they regard paracetamol and ibuprofen as effective agents for reducing fever, and this is supported by evidence from meta-analyses and other studies.

They point to risks of paracetamol hepatotoxicity, especially in children with diabetes, those with concomitant viral infections, patients with a family history of hepatotoxic reactions, obese children and chronically malnourished individuals. Dlugosz et al. (2006) also emphasized the precise dosing of paediatric patients with either ibuprofen or paracetamol, and in the case of a patient less than 6 months recommended consultation of physician.

The application of ibuprofen and other antipyretics to prevent the development of febrile seizures is now well-established treatment for this condition (van Stuijvenberg et al. 1998).

The question of precise dosage of antipyretics for treatment of fever and pain has been addressed by a number of experts and professional organisations. Among these, the Royal College of Paediatrics and Child Health with the Neonatal and Paediatric Pharmacists Group in their monograph "Medicines for Children" (2003) recommend for pyrexia and mild-to-moderate pain, where ibuprofen is given by the oral route, that the dosage should be by body weight (5 mg/kg) 3 4 times daily when treating infants or children from 1 month to 12 years of age. Dosage by age is recommended above 1 year: for 1 2 years 50 mg, 3 7 years 100 mg, and 8 12 years 200 mg of ibuprofen. In the 12 18 year age group, 200 600 mg ibuprofen is recommended 3 4 times daily.

In juvenile rheumatoid arthritis or juvenile arthritis, application of ibuprofen is recommended at the dose of 10 mg/kg for the 1-month- to 18-year-old group 3 4 times daily, or up to 6 times daily in systemic juvenile arthritis.

In Martindale's "The Complete Drug Reference" (Reynolds 2003), ibuprofen is not recommended for children below 7 kg bodyweight; in the same way as with the previous authors, dosage on a bodyweight basis is recommended in the range of 20 30 mg/kg/day in divided doses or alternatively in the 6 12 month age group 150 mg/day, 1 2 year 150 200 mg/day, 3 7 year 300 400 mg/day and 8 12 years of age 600 800 mg/day. These two authorities clearly differ in the precision in which they make recommendations for treating fever and pain in children on a dosage basis. Arguably, however, dose recommendations are probably rather similar, and it is a question of the application of information that is given to the carers.

The UK National Institute for Health and Clinical Excellence (NICE) has prepared recommendations for the assessment and management of children younger than 5 years in their report "Feverish Illness in Children" (National Institute for Health and Clinical Excellence 2007). In these guidelines, there is emphasis given on the detection of fever and the clinical assessment of the child with fever, as well as the relative roles of the non-paediatric practitioner and paediatric specialist. Surprisingly, the NICE recommendations state that antipyretics do not prevent febrile convulsions, and should not be used specifically for this purpose. This view is supported to some extent by a recent Cochrane analysis and review in which antipyretic - analgesic drugs, along with anti convulsants, appear to have limited benefit in treating febrile siezures in children (Offringa and Newton, 2012). Their recommendations also give a considerable number of clinical diagnostic indices for fever of various origins. Some of these recommendations are complex in themselves: "A Traffic-light System" for identifying risks of serious illness involving colour-coding of green for low risk, amber for intermediate risk, and red for high risk, with appropriate diagnostic and investigative procedures for identifying the origin of fevers.

The NICE recommendation for antipyretic interventions state that tepid sponging is not recommended for the treatment of fever. This is in contrast with recommendations of other authorities. On the question of the administration of antipyretic agents, these should be considered in children with fever who appear distressed or unwell. Antipyretic agents should not routinely be used with the sole aim for reducing temperature in children with fever who are otherwise well.

The views and wishes of parents and carers should be taken into consideration; this would in any physician's eyes be regarded as a statement of the obvious.

NICE recommendations are that either paracetamol or ibuprofen can be used to reduce temperature in children with fever, but that they should not be given at the same time or alternating the drugs. The only case for alternating of drug treatment would be considered for a child that does not respond to the first agent.

The guideline development group (GDG) of NICE has made a number of recommendations for research, based on the review of evidence to improve NICE guidance for patient care in the future, for example predictive values of heart rate, remote assessment, and a number of issues concerning diagnosis. They also recommend investigation of the administration of antipyretics in primary and secondary settings in relationship to the degree of illness.

Amdekar and Desai (1985) compared the antipyretic effects of ibuprofen with that of paracetamol in 25 children suffering from fever due to upper respiratory tract infection or systemic viral infections. There was a difference in the initial temperatures of patients that were treated for upper respiratory tract infection, in that the mean initial temperature was 39.9 ° in the ibuprofen group and 40.81 ° in the paracetamol group. Despite this variation, both ibuprofen and paracetamol produced statistically significant reductions in rectal temperatures following administration of 7 mg/kg of ibuprofen or 8 mg/kg of paracetamol in a random order. The initial reduction in temperatures of patients with upper respiratory tract infections incurred at about 0.5 h, with the maximum at 4 h after administration of both drugs. The level of antipyretic activity was evident up to 8 h, with patients having temperatures in the range of 37.5 °. In the group of children with fever due to viral infections, both the mean temperatures were comparable (40.51 ° 40.75 °), and similar results were observed to those in patients with upper respiratory tract infections, with the exception that by 8 h the temperatures had risen to 38.34 ° 38.77 °, which is somewhat higher than those observed in the patients with upper respiratory tract infections and probably reflects ongoing viral activities.

A single blind, parallel group investigation comparing the antipyretic properties of ibuprofen syrup versus aspirin syrup in 78 febrile children aged 6 months to 10 years was undertaken in two centres in Belgium by Heremans et al. (1988). At doses of ibuprofen syrup (6 mg/kg body weight) or aspirin (10 mg/kg bodyweight), significant reductions in rectal temperature were observed with both treatments, there being no statistically significant difference between the two. These patients had a greater variation of clinical history, although most were being treated for upper respiratory tract infections, in some cases with antibiotics being co-administered.

Significant reductions in temperatures were observed by 0.5 1 h with both treatments, with maximum reduction in rectal temperature being observed with both drugs at 4 h, and being maintained 6 h after administration.

A summary of more recent data from various studies reviewed by Autret-Leca (2003) is shown in Table 4.4. These studies were performed with modern methodologies, and in some cases Good Clinical Practice (GCP) conditions.

They show that ibuprofen is equal to or in some cases slightly more effective than paracetamol in relief of febrile symptoms in a variety of age groups in children.

There are three paediatric groups where ibuprofen has been investigated for therapeutic benefits in relation to pharmacokinetic properties. These are for relief of pain and joint symptoms in juvenile idiopathic (chronic) or juvenile rheumatoid arthritis (JIA, JRA respectively), the i.v. administration in patent ductus arteriosus (PDA), and in high doses in cystic fibrosis (CF). While both these treatments may be considered outside the norm, none-the-less they are potentially important uses of the drug in therapy. Moreover, they provide important therapeutic data on the pharmacokinetic properties of ibuprofen in extremes of dosage and administration which, with safety data, are important for giving outside values for indications for the drug.

4.4.2 Juvenile Idiopathic (Rheumatoid) Arthritis

This condition presents with a varying spectrum of clinical manifestations that include differing joint involvement including pauciarticular ($\leq$4 joints) and polyarticular ($\geq$5 joints), with juvenile rheumatoid arthritis (JRA; Still's Disease) as a subgroup of the latter resembling the adult disease (Dieppe et al. 1985; Klippel 1997). Pyrexia is common (50 %) along with lymphadenopathy, splenomegaly, pericarditis, and rashes (Dieppe et al. 1985). High doses of the NSAIDs, especially aspirin and other salicylates, have been widely used in the treatment of juvenile arthritis and more recently the coxibs (Ansell 1983; Hollingworth 1993; Klippel 1997; Eustace and O'Hare 2007).

Amongst the earlier studies on the effects of ibuprofen in JRA was that by Ansell (1973). She undertook an open-label investigation in 8 patients (aged 7 14 years; 5 female, 3 male), most of whom were treated because they were unable to tolerate aspirin and had a prior history of dyspepsia (5) or GI bleeding (2) or in one case where there was poor control. These patients received various doses of ibuprofen (13 32 mg/kg). Initially, they received 200 300 mg/day in those with body weight of 20 30 kg and 400 mg for those $<$30 kg. Later, all but one received 600 mg/day and one 1,200 mg/day for what appears to have been long periods of time (12 24 months). Satisfactory control of pain and stiffness was observed in 6/8 cases, although in 2 of these the dose had to be increased before this was achieved. Occult blood which had been observed in those patients who were on aspirin was negative with ibuprofen. In 6 patients, liver function tests were performed, and none showed increased SGOT, SGPT or alkaline phosphatase; some showed decrease in these values. This is important, since plasma/serum levels of elevated liver enzymes have been frequently observed in patients with JRA or JIA that have received aspirin, and ADRs in the GI tract and other systems are frequently observed with the salicylates and other NSAIDs in these conditions (Hollingworth 1993; Buchanan et al. 2004).

Giannini et al., with the Pediatric Rheumatology Collaborative Study Group (1990), undertook two studies one being a multi-centre, randomized,

double-blind study in 92 children (76 girls, 16 boys), mean age 7.7 years (range 1.8 15.1 years), mean body weight 26.4 (range 11.5 58.7) kg with JRA. Of these, 45 received ibuprofen suspension 30 mg/kg/day and 47 aspirin (200 mg tablets or 300 mg caplets) according to body weight (60 mg/kg/day) for 12 weeks. This was followed by an open-label study in 84 patients [aged 1 15 years, mean 5.3 years; average body weight 19.9 kg (range 10.0 58.0 kg)]. Ten patients failed to complete the double-blind study, 9 of whom had received aspirin and ibuprofen, while a further 6 patients were excluded from the aspirin group due to variations in diagnosis or disease condition. All the patients on ibuprofen showed reduction in all five joint parameters, while those that received aspirin showed significantly and clinically fewer reductions in joint inflammation and pain on motion, although the reduction in morning stiffness was the same in both groups.

In the open-label study, 3 dropped out and 16/84 failed to complete the 24 weeks of the study. Time dependent improvement in overall scores was observed in all 71 patients that completed the study, who received 30 50 mg/kg/day ibuprofen. One or more ADRs were observed in 55 % of patients, which were classified as possibly, probably, or definitely related to the drug. Upper GI disturbances were recorded in 31 % and 27 % in the lower tract, with dose-related effects in the former group. Of these, 3 patients had GI bleeding which resolved after discontinuing the drug. Increased serum alkaline phosphatase and bilirubin occurred in 2 patients who had 40 mg/kg/day ibuprofen.

Steans et al. (1990) examined the safety, efficacy, and acceptability of 10 (initially) to 40 mg (maximum)/kg/day ibuprofen syrup in 46 children with JIA (aged 18 months 13 years; mean 6.8 years) in a multicentre, open-label study that extended on average for 8 months (range 8 weeks to 2+ years). Six patients failed to complete the study, 2 of whom had suspected side-effects. Assessments of active joints and disease activity at monthly intervals over the first 3 months showed statistically significant reduction in numbers of swollen and/or tender joints at $\leq$2 months of therapy which progressed to 6 months, while the physician's VAS was reduced by 1 month and showed significant improvement thereafter, which was sustained at 4 6 months. Side-effects included gastritis (1 patient), abdominal pain (1 patient) and taste complaint and nausea (1 patient). Of the 39 children that completed the trial, 28 showed improvement on therapy, 7 were worse, and 4 remained unchanged.

The PK of ibuprofen in patients with juvenile idiopathic (or chronic) arthritis (JIA), aka juvenile rheumatoid arthritis (JRA), might be expected to be affected by production of pro-inflammatory cytokines, and other inflammatory reactions would be expected to have profound consequences for drug metabolism, biodisposition, or toxicological actions in these patients (Skeith and Jamali 1991; Furst 1992; Litalien and Jacqz-Aigrain 2001).

The dose of ibuprofen in JIA (30 40 mg/kg/day) is much higher than generally employed in infants and children for the treatment of fever and painful conditions (5 10 mg/kg/day), and is more in line with that employed in cystic fibrosis. Reference to the extensively studied PK properties of ibuprofen in CF may, therefore, be useful for relating to those in JIA.

Chapter 5
Drug Derivatives and Formulations

It is a special feature of ibuprofen that it is possible for it to be prepared as many derivatives and formulations, both for oral and parenteral administration. This is due to its unique physicochemical properties. As an organic acid with a pK_a of 4.4 5.2 (Boggara and Krishnamoorti 2010; Boggara et al. 2010), it is soluble in a wide variety of solvents and aqueous organic solvent systems. Like many NSAIDs, ibuprofen is amphiphilic, and this leads to unique interactions with lipid membranes (Boggara and Krishnamoorti 2010; Boggara et al. 2010). Although ibuprofen partitions into the liposoluble layer in organic solvent (e.g. *n*-octanol)-aqueous (or buffer) systems, it has detergent-like characteristics. These physicochemical properties of ibuprofen lend themselves to the development of a wide range of salts, complexes, and carboxylate or other chemical derivatives (Nichol 1999; Higton 1999).

5.1 Dexibuprofen

The development of dexibuprofen (i.e. S(+) ibuprofen) arose from the observations of Adams et al, (1976), subsequently verified and confirmed by others (Boneberg et al 1996; Evans 1996, 2001), that the S(+) isomer of ibuprofen was more active as a prostaglandin synthesis inhibitor, and could inhibit COX-1 and COX-2 with greater potency than the R(−) enantiomer. Based on these observations that S(+) ibuprofen was a more potent anti-inflammatory and analgesic than the R(−) enantiomer or *rac*-ibuprofen (Björkman et al. 1996; Rainsford 1999b; Evans 2001), it was suggested that S(+) ibuprofen was the pharmacologically active form (Evans 1996, 2001; Kaehler et al. 2003). Possibly, this statement needs modifying to say that S(+) ibuprofen, or dexibuprofen, is the PG synthesis inhibiting component of *rac*-ibuprofen, since it is known that R(−) ibuprofen has distinct non-prostaglandin-dependent mechanisms which may contribute to the overall anti-inflammatory properties of the racemate (Evans 1996, 2001; Rainsford 2009). Whatever the definition, dexibuprofen is more potent clinically in the

K.D. Rainsford, *Ibuprofen: Pharmacology, Therapeutics and Side Effects*,
DOI 10.1007/978 3 0348 0496 7 5,

treatment of acute pain or osteoarthritis than *rac*-ibuprofen on a weight for weight basis (Phleps 2001; Kaehler et al. 2003).

The physico-chemical properties of dexibuprofen differ considerably from those of *rac*-ibuprofen (Leising et al. 1996; Kaehler et al. 2003). Thus, the crystal structure, powder X-ray diffraction; thermodynamic, solubility, UV and photoluminescence emission spectra of dexibuprofen differ considerably from *rac*-ibuprofen.

These differences in physico-chemical properties of dexibuprofen and *rac*-ibuprofen translate into differences in their pharmacokinetics, principally their kinetics of oral absorption, plasma elimination half-lives, and also their metabolic (chiral inversion) profiles (Evans 1996; Kaehler et al. 2003). While dexibuprofen has almost complete bioavailability and is absorbed with a peak Cp in about 2 h (Evans 1996), this is somewhat longer than many formulations of racemic ibuprofen. The absence of the R(−) isomer in dexibuprofen means that this drug is not metabolised via hepatic fatty acyl CoA metabolism, but proportionately greater metabolism occurs via cytochrome P_{450} oxidation and glucuronidation mechanisms. S(+) ibuprofen is extensively bound to plasma proteins, with the fraction unbound (0.006) being greater than that of R(−) ibuprofen (Evans 1996). The half life of elimination of dexibuprofen is about 2 h, and contrasts with that of 1 2 h for *rac*-ibuprofen (or its R-enantiomer which is about 2 h) (Evans 1996).

Extensive clinical studies have shown the clinical effectiveness of dexibuprofen in acute oral surgery in a dose-related manner (Dionne and McCullagh 1998; Moore et al. 2011a, b), in several studies in patients with osteoarthritis of the hip or knee, rheumatoid arthritis, ankylosing spondilitis, lumbar vertebral pain, ankle joint injury, and dysmenorrhoea (Kaehler et al. 2003), and in febrile children with upper respiratory tract infections (Yoon et al. 2008a, b). It is approved (as Seractil®) for use in the treatment of pain and inflammation associated with OA and other musculoskeletal disorders, and in mild-to-moderate pain including dysmenorrhoea and dental pain in the UK (British National Formulary 2009), as well as in Austria and other countries of the EU.

An interesting property of dexibuprofen is that it has about twice the potency of *rac*-ibuprofen as a platelet aggregation inhibitor, and while reversible this is comparable with that of the irreversible inhibitor, aspirin (de la Cruz et al. 2010). Since extensive use of low-dose aspirin to control thrombo-embolic and CV conditions is associated with increased incidence of upper GI ADRs (see Chap. 7), especially when this drug is used in combination with other NSAIDs or coxibs for therapy of arthritis conditions, it might be preferable to consider the reversible anti-platelet anti-thrombotic actions of dexibuprofen with its analgesic and anti-inflammatory properties as cognate and coincident therapeutic properties, rather than using the combination of aspirin with other NSAIDs or the coxibs for treatment of arthritic patients at risk for developing CV disease.

There has been interest recently in the development of various oral formulations of dexibuprofen, among these an enhanced oral bioavailability/absorption self-emulsifying drug delivery system (Balakrishnan et al. 2009), extended-release tablets (Cox et al. 1999; Yi et al. 2008; Kim et al. 2011; Xu et al. 2011), and microencapsulation systems (Manjanna et al. 2010). These formulations open up

the possibility of modifying or optimising pain control using dexibuprofen for different acute and chronic painful states. The extended-release and microencapsulation systems may be useful for long-term therapy of rheumatic conditions, with the benefit of once or twice daily therapy coincident with less fluctuation in peak trough plasma concentrations, and, therefore, less variation in pain responses. An L-arginine complex with dexibuprofen has been found to be absorbed at a faster rate than the acid alone (Fornasini et al. 1997) and so may have utility as a rapidly acting analgesic for short-term use. The L-arginine may also have other actions relating to its stimulation of nitric oxide production.

5.2 Combinations with Caffeine

The rationale for addition of caffeine to ibuprofen and other analgesics has been based on the premise of raising the "analgesic ceiling" of the analgesic. The addition of caffeine to NSAIDs and paracetamol has been investigated for over three decades as an adjuvant to enhance pain relief (Aronoff and Evans 1982; Sunshine and Olson 1989; Zhang 2011). Combinations of caffeine and sodium salicylate and aspirin have been available in the UK since 1949, and have been mentioned in several pharmacopoeias (Martindale The Extra Pharmacopoeia 1958; Reynolds 1993). Caffeine is mentioned in the British National Formulary (2009) as a weak stimulant to enhance analgesia, but the alerting effect, mild habit-forming properties, and possible provocation of headache may not always be desirable. Earlier studies of the efficacy due to the addition of caffeine were largely negative, except the combination with paracetamol (Laska et al. 1983, 1984).

Ibuprofen caffeine combinations have been investigated by several workers for efficacy compared with that of ibuprofen (Stewart and Lipton 1989; Dionne and Cooper 1999). Combinations of ibuprofen with caffeine have been shown to be more effective than ibuprofen alone in the dental pain model (Forbes et al. 1990, 1991; McQuay et al. 1996). In particular, enhanced pain relief has been observed with doses of 100 mg caffeine and 200 400 mg ibuprofen (Forbes et al. 1990, 1991; McQuay et al. 1996; Dionne and Cooper 1999). Ibuprofen 400 mg with caffeine 200 mg has been found to give greater pain relief in the treatment of migraine than ibuprofen 400 mg alone (Stewart and Lipton 1989). Caffeine has also been found to enhance the pain relief with ibuprofen in tension headache (Diamond et al. 2000; Sparano 2001) and in children's headache (Dooley et al. 2007).

There are, however, several issues that are raised about the use of combinations of caffeine with ibuprofen, as well as with other non-narcotic analgesics/non-steroidal anti-inflammatory drugs (NSAIDs) which include:

(a) The pharmacological rationale for including caffeine; what is the pharmacological basis or mechanism for the enhanced analgesic activity?
(b) The confounding effects from the intake of caffeine-containing beverages, estimated to be of the order of 100 400 mg daily (Rall 1990; Reynolds, Martindale, The Extra Pharmacopoeia; Nawrot et al. 2003; Rainsford 2004a).

(c) The possibility of increased incidence of gastric adverse effects, especially in the stomach from stimulation of gastric acid secretion leading to gastric distress (Rainsford 2004a) or CNS toxicity (Thayer and Palm 1975; Christian and Brent 2001; Nawrot et al. 2003).

As a nervous system stimulant, caffeine acts by inhibiting phosphodiesterase, a well-known property which leads to an increase in the second messenger cyclic-3′,5′-adenosine monophosphate (cAMP), as well as acting as an antagonist of central adenosine receptors. Studies in laboratory animal models of analgesia show that caffeine, like that of some selective adenosine antagonists produces analgesic effects principally via central adenosine A1 receptors (Ahlijanian and Takemori 1985; Poon and Sawynok 1998), and this is the generally accepted mode of clinical analgesia (Dunwiddie and Masino 2001). Thus, from the viewpoint of contribution to the action of caffeine in the combination with ibuprofen, the focus would seem to be on the central actions as an A1 receptor agonist.

Cronstein and co-workers (1999) provided evidence from studies in mice, in which the genes for inflammatory cyclo-oxygenase-2 (COX-2) or transcription factor, nuclear kappa B ($NF_{\kappa}B$) proteins were selectively "knocked out", that the mode of acute anti-inflammatory actions of aspirin or salicylic acid was due to the anti-inflammatory effects of adenosine acting on the $NF_{\kappa}B$ signal transduction pathway. Using mice lacking the gene for the adenosine A_{2A}-receptor, Cadieux et al. (2005) have shown that their polymorphonuclear neutrophil leucocytes (PMNs) have diminished capacity to induce expression of COX-2, but not that in monocytes. This would suggest that adenosine receptor activation leads to increased COX-2-derived prostaglandins (PGs) from PMNs, so producing an increase in acute inflammatory reactions. A_{2A}-receptor agonists reduce expression of adhesion molecules and a range of pro-inflammatory mediators [e.g., reactive oxygen species, tumour necrosis factor-α (TNF_{α})] (Sullivan 2003). It is also known that adenosine A_1-receptors mediate plasma exudation in a non-prostaglandin, non-nitric oxide mediated fashion (Rubenstein et al. 2001). These effects are different from the effects of caffeine mediating analgesia in the central nervous system. However, as peripheral anti-inflammatory effects of NSAIDs are central to their analgesic actions (Rainsford 1999b, 2004c), it is possible that caffeine contributes to analgesic effects of NSAIDs or paracetamol *indirectly* via activation of adenosine A_2 receptors in both the peripheral and central nervous systems.

As far as adverse reactions are concerned, it appears that in the randomised controlled trials in acute pain models there are no appreciable adverse reactions from the ibuprofen caffeine combination compared with that of ibuprofen alone (McQuay et al. 1996). Some mild CNS effects have been reported, ranging from excitatory reactions and irritability; this may be especially evident in individuals who are genetically predisposed to these reactions (Ellinwood and Lee 1996).

A condition known as "caffeinism", which is a acute and chronic effect from intake of 500 600 mg caffeine per day (equal to approximately 7 9 cups of tea or 4 7 cups of coffee), is probably a health risk (Ellinwood and Lee 1996). Caffeine preparations in analgesics have 50 65 mg caffeine (Zhang 2001). At these doses

taken 4 6 times daily, the amount of caffeine taken would be within the intake of caffeine-containing beverages.

The common adverse events attributed to caffeine are: (1) associations with increased myocardial infarction, tachycardia, and increased blood pressure, (2) insomnia, anxiety, tremor, tenseness, and irritability, (3) increased free fatty acids and hyperglycaemia, (4) nausea, vomiting, and stimulation of gastric acid secretion, (5) increased diuresis, and (6) urticaria (Ellinwood and Lee 1996), gastro-oesophagal reflux, symptoms of anxiety and tachycardia in infants and children (Ellinwood and Lee 1996). With long-term intake of caffeine-containing analgesics, addiction may develop coincident with the analgesic abuse syndrome (Ellinwood and Lee 1996; Rainsford 2004c). There has been concern that drinking >7 8 cups of coffee per day may be associated with an increased incidence of stillbirths, pre-term deliveries, low birth weights of infants and spontaneous abortions, but other factors including intake of analgesics per se may contribute to these states (Beers and Berkow 1999). Concerns about the possibility of the risks of mutagenicity, genotoxicity, and carcinogenicity led to an assessment of these risks by the US Food and Drug Administration and several reviews (Thayer and Palm 1975). A variety of in-vitro and in-vivo experiments and studies had been reported since 1948 from which both positive and negative observations were recorded (Thayer and Palm 1975). A considerable number of animal studies of genetic changes, enhancement of dominant lethal changes, and teratogenic potential in rodents as well as in-vitro studies in cell lines, in relation to the pharmacokinetics and tissue/organ distribution of caffeine, were analysed and assessed by Thayer and Palm (1975) in their comprehensive review.

In conclusion, it appears that caffeine may have some moderate potentiating effects on analgesia from NSAIDs or paracetamol, but where these combinations are taken in large quantities for long periods of time there are risks of CNS adverse reactions, and at extremes analgesic abuse syndrome. Considering the availability of other combinations with ibuprofen (e.g., paracetamol, codeine) which are probably more effective than the ibuprofen caffeine combination, it would not seem of appreciable therapeutic benefit to use ibuprofen caffeine mixtures. It would appear just as simple and more pleasurable to take ibuprofen alone with coffee, tea or other caffeine-containing beverages.

5.3 Ibuprofen–Codeine Combinations

The combination of codeine with aspirin or paracetamol has been a popular and effective analgesic in moderate to severe pain for over 30 40 years (Reynolds 1993; Martindale; Cooper 1984). Combination of ibuprofen with codeine has been found to be more efficacious than either the drug alone, placebo or other NSAIDs in pain following episiotomy or gynaecological surgery (Norman et al. 1985; Cater et al. 1985; Sunshine et al. 1987), tonsillectomy (Pickering et al. 2002), post-operative dental pain (Mitchell et al. 1985; Giles et al. 1986; McQuay et al. 1989, 1992,

Walton and Rood 1990; Peterson et al. 1993), or in the treatment of OA pain (Quiding et al. 1992). Additionally, combinations of ibuprofen and hydrocodone have been shown to have greater pain relief than ibuprofen alone (Barkin 2001). In post-arthroplasty pain, ibuprofen 800 mg/codeine 60 mg was more effective than 800 mg ibuprofen alone (Dahl et al. 1995). A meta-analysis of the efficacy of adding codeine to ibuprofen for relief of surgical pain showed that addition of 60 mg codeine to 400 mg ibuprofen enhanced its analgesic effect by only 8 %, but also increased its side-effects (Li Wan Po and Zhang 1998). The possibility of pharmacokinetic interactions between ibuprofen and codeine has been investigated in 24 healthy human subjects, and no such interactions were observed (Kaltenbach et al. 1994).

Recently, there have been concerns about morbidity associated with codeine ibuprofen abuse in Victoria, Australia (Frei et al. 2010). Of 27 patients reviewed, most had no history of substance abuse. They had GI haemorrhage and opioid dependence associated with massive daily doses of 435 602 mg codeine and 6,800 9,000 mg ibuprofen. A study from New Zealand reported excess intake of codeine + ibuprofen in 7 patients, 6 of whom had a history of alcohol dependency. GI ulcers and bleeding and hepatotoxic reactions were reported (Robinson et al. 2010). There is a case report of 2 patients who had taken excessive amounts of codeine + ibuprofen associated with gastric ulcers (Dutch 2008). Another case was reported from Victoria, Australia where excess intake of ibuprofen + codeine together with a high caffeine-containing beverage (Red Bull®) was associated with hypokalaemia (Ernest et al. 2010). it was suggested that the mechanism of this reaction was due to ibuprofen causing type 2 renal acidosis and antagonism by caffeine of adenosine receptors or shift of K^+ into the extracellular space. Little evidence has been obtained for these proposed actions, the effects of codeine not being considered in this appraisal.

The mechanisms of analgesic effects of ibuprofen codeine combinations have been investigated in acetic acid-induced abdominal writhing in mice (Janovsky and Krsiak 2011). Codeine with ibuprofen showed a marked antinociceptive interaction which was not evident when the codeine was added to the COX-2 inhibitors, etoricoxib or celecoxib. This suggests that additional COX-1 and other cellular effects of ibuprofen contribute to the combined action of these two drugs.

Overall, it appears that although analgesic combinations have relatively acceptable safety profiles (Friedman et al. 1990a, b; Hersh et al. 2007), it is clear that in some societies this combination may, albeit rarely, be open to abuse potential with adverse consequences for GI and renal system.

In conclusion, of the available combination analgesics, the ibuprofen caffeine combination probably has little significant advantage. Ibuprofen codeine has some limited advantages, while ibuprofen paracetamol has potential for raising the analgesic ceiling while at the same time reducing ADRs that may occur with higher doses of these drugs alone which would be sufficient required to achieve the same degree of analgesia as the combination.

5.4 Ibuprofen–Paracetamol Combination

The combination of ibuprofen with paracetamol probably represents the most acceptable and useful of all combinations. There have been considerable number of attempts at examining the efficacy of combinations of the two drugs especially in children with fever (Cranswick and Coglan 2000; Erlewyn-Lajeunesse et al. 2006; Hay et al. 2008, 2009; Hollinghurst et al. 2008; Lal et al. 2000; Ong et al. 2010) or peri- or post-operative pain (Hyllested et al. 2002; Pickering et al. 2002; Kokki 2003; Gazal and Mackie 2007; Mehlisch et al. 2010a, b; Daniels et al. 2011). Some studies have also considered the efficacy of alternating ibuprofen and paracetamol for control of fever in children (Nabulsi et al. 2006), this regime being quite popular amongst paediatricians. In the study by Nabulsi et al. (2006), the ibuprofen treatment (10 mg/kg) followed 4 h later by paracetamol (15 mg/kg) was superior to ibuprofen/placebo in reducing rectal temperature after 6 8 h treatment. Unfortunately, the design of this study may have deviated from logic and accepted practice, since most would employ ibuprofen after paracetamol when there was poor reduction in temperature from paracetamol. The logic would be to employ the more potent antipyretic, i.e., ibuprofen, after first trying paracetamol.

The pharmacological basis for fixed combinations of ibuprofen and paracetamol was established by Miranda and co-workers (2006) in their investigations in the acetic acid induced constriction, or writhing assay in mice. The authors compared the effects of i.p. administration of various doses of paracetamol combinations with varying doses of NSAIDs, including ibuprofen; the anti-writhing results were compared with the effects of the drugs alone. To establish whether there were synergistic or additive effects with the drug combinations, the ED_{50} data of various ratios was subjected to isobolographic analysis. With this procedure, the ED_{50} data for the individual NSAID alone are plotted against the ED_{50}s of paracetamol being plotted separately. Where there is deviation from the linear relationship between the ED_{50}s for the respective NSAID and paracetamol, with the combination notably towards the origins, then this is evidence for synergistic interactions. Miranda and co-workers established a synergistic interaction between paracetamol and ibuprofen. The ED_{50} value for ibuprofen alone was 0.8 (0.12 6.1, 95 % CI) mg/kg, and that with paracetamol was 49.4 (33.4 59.1. 95 % CI) mg/kg, while the combination had an ED_{50} of 9.6 (8.3 11.1, 95 % CI) mg/kg, giving a ratio of 1:58.1 of ibuprofen to paracetamol, this ratio being the largest amongst the combinations of NSAIDs/paracetamol that were determined by these authors.

The mechanisms of this interaction in relation to effects of the drug combinations on the pain pathways has not been established, but it is considered that several sites of action in the nervous system and periphery may be affected differently by paracetamol and the individual NSAIDs. Thus, although paracetamol is relatively weak as a direct inhibitor of PG production and COX activities (Flower and Vane 1972, 1974; Tolman et al. 1983; Graham et al. 1999; Graham and Scott 2003), it exhibits inhibitory effects under differing oxidant conditions, which is effective in some tissues in vivo (Tolman et al. 1983; Graham et al. 1999;

Graham and Scott 2003; Hinz and Brune 2011). Another part of the effects of this drug is that it inhibits the peroxidative reactions in cyclo-oxygenases and PMN myeloperoxidases (Graham and Scott 2005; Lucas et al. 2005); the latter reactions are only affected by phenolic compounds, among them the salicylates (Rainsford 2004c). Ibuprofen would not appear to affect these peroxidative reactions.

It has been found that paracetamol selectively affects PG production in the brain and not in the spleen, suggesting that there may be selective effects of this drug in the CNS (Flower and Vane 1972). Paracetamol also inhibits COX-1 in the brain (or its splice variant, COX-3 *note however* that the latter not been found in humans), and PGE_2 concentrations have been shown to be reduced in the brains of mice in parallel with the reduction in writhing (Cashman 1996; Ayoub et al. 2004, 2006; Botting and Ayoub 2005; Ayoub and Botting 2010). Furthermore, activation of efferent opioid-pathways with increased activity of serotonergic (5-hydroxytryptamine) pathways and activation of 5-HT_{1B} and 5-HT_3 receptors which inhibit nociceptor signalling in the spinal cord (Alloui et al. 2002; Raffa et al. 2000, 2004; Bonnefont et al. 2003, 2005; Sandrini et al. 2003) may contribute to the analgesic effects of paracetamol. The central analgesic effects of paracetamol mediated through these pathways appear to be independent of any anti-oedemic activities of the drug (Alloui et al. 2002).

In contrast, ibuprofen has been postulated to affect COX-1, COX-2, nNOS or iNOS $NF_{\kappa}B$ in the CNS as well as the serotinergic pathway activation (Rainsford 2007). The most potent effects of the racemic drug mediated centrally are due to the S(+)enantiomer, although R(−) ibuprofen also has demonstrable analgesic activity in laboratory models of analgesia (Wang et al. 1994; Björkman 1995a, b; Björkman et al. 1996). Both ibuprofen and paracetamol affect glutaminergic activation via effects on nitric oxide production (Björkman 1995a, b; Björkman et al. 1996). Most significantly, ibuprofen has been shown to inhibit the breakdown of the endogenous cannabinoid, anandamide (Fowler et al. 1997a, b, 2005; Tiger et al. 2000; Guindon et al. 2006) as well as interacting synergistically with this endocannabinoid (Guindon et al. 2006). These combined effects on CB_1 receptor activation in the spinal cord, dorsal root ganglia, and higher centres of the CNS, though not entirely unique to ibuprofen, may set this drug aside from paracetamol in relation to its analgesic actions. Furthermore, actions of ibuprofen on purinergic $P2X_3$ receptors in the dorsal root ganglia that are inhibited by ibuprofen (Wang et al. 2010), effects which like those on the anandamide pathway, have not been identified to be appreciably affected by paracetamol, which gives another possible basis for the differential actions of these two drugs. Thus, the combination of ibuprofen and paracetamol may lead to differential actions of these drugs, underlying their interactions on various pain pathways in the CNS that underlie the apparent synergy between these two drugs. There is a possibility that there may be local pharmacokinetic interactions between ibuprofen and paracetamol, bearing in mind that these drugs have differing localisation in the inflamed areas and the CNS (Graham and Hicks 2004; Graham and Williams 2004). In particular, the lack of accumulation of paracetamol in experimentally induced inflammatory sites, compared with that of acidic NSAIDs, differentiates paracetamol from NSAIDs (Graham and Hicks 2004; Graham et al. 2004).

In terms of total body PK, the serum kinetics and bioavailability of ibuprofen and paracetamol taken concurrently were not found to be different from the drugs taken alone in 20 normal healthy volunteers (Wright et al. 1983). A more detailed PK investigation of the potential effects on PK of combining these two drugs was recently undertaken by Tanner and co-workers (2010). They compared the effects of a standard OTC combination of 200 mg ibuprofen with that of 500 mg of paracetamol in 26 healthy human volunteers, 25 of whom were enrolled in a single dose study (study 1), and 26 in a two-way crossover repeat dose study (study 2). Subjects were either fed or fasted overnight before beginning of the study; the effects of food intake predictably reduced both the C_{max} and t_{max} of the drugs in combination. The results of this investigation showed that the fixed combination of ibuprofen and paracetamol did not show any significant differences in the PK parameters, t_{max}, C_{max}, $t_{½}$, AUC or k_{el} in study 1 and t_{max}, C_{max} and AUC in study 2, compared with that of the individual drugs.

To evaluate the analgesic efficacy of the fixed-dose combinations of ibuprofen and paracetamol that was employed in the abovementioned PK study (Tanner et al. 2010), two separate trials were undertaken by Mehlisch et al. (2010a, b), the first in two clinical research centres in Austin and San Marcos, TX, USA (Mehlisch et al. 2010a) and the second in the same cities but different locations as the first, and with an additional centre in Salt Lake City, UT, USA (Mehlisch et al. 2010b). The pain responses following surgical removal of 3 or 4 impacted molars (2 of which were mandibular) were initially graded and the subjects then randomised ($n = 234$ in the first study and 735 in the second) to ibuprofen 200 mg, ibuprofen 100 mg + paracetamol 250 mg, paracetamol 500 mg, or placebo; or in a separate comparison, ibuprofen 400 mg, ibuprofen 200 mg + paracetamol 500 mg, ibuprofen 400 mg + paracetamol 1,000 mg, paracetamol 1,000 mg (all at stage 1 for 8 h) followed by a second stage of treatment for 72 h with ibuprofen 100 mg/paracetamol 250 mg, ibuprofen 200 mg/paracetamol 500 mg or ibuprofen 400 mg/paracetamol 1,000 mg for those subjects that received either the respective doses of the individual or combination drugs in stage 1. The placebo group also received placebo in the second stage (Mehlisch et al. 2010b). The first proof of concept study (Mehlisch et al. 2010a) involved a 5-arm treatment with ibuprofen 400 mg, ibuprofen 200 mg/paracetamol 500 mg, ibuprofen 400 mg/paracetamol 1,000 mg, paracetamol 1,000 mg, or placebo. In both studies, the populations were predominantly female and in the first study were white. Overall, both studies showed that the fixed drug combinations (FDC) produced superior pain relief than when the drugs were given alone; this was particularly apparent in the second study which extended over 80 h, where the different FDCs had marked superiority over placebo. Therapy with the FDC of ibuprofen 200 mg/paracetamol 500 mg or ibuprofen 400 mg/paracetamol 1,000 mg was significantly more effective than with comparable doses of with either drug alone (Mehlisch et al. 2010b). The overall pain relief profiles in each of the studies showed slight differences in the ibuprofen 400 mg/paracetamol 1,000 mg or ibuprofen 200 mg/paracetamol 500 mg groups; in the first study, the differences between these two groups appeared greater than in the second. The responses to paracetamol alone were lower than those with ibuprofen alone.

A recent study examined the safety and efficacy of 10 days and 13 weeks daily treatment with ibuprofen 1,200 mg, paracetamol 3,000 mg, the FDC of ibuprofen 600 mg + paracetamol 1,500 mg in patients, and the FDC of ibuprofen 1,200 mg + paracetamol 3,000 mg in patients with osteoarthritis of the knee (Doherty et al. 2011). By 10 days the WOMAC scores for pain relief with the high dose combination exceed those for paracetamol. However, there were increases in the plasma levels of liver enzymes, ALT and γ-glutamyl transpeptidase, in patients that received paracetamol or the combinations, reflecting hepato-cellular injury. At 13 weeks treatment, there was a marked loss of haemoglobin (≥1 g/dL) in over one-third of patients that received the high dose combination of paracetamol and ibuprofen: this exceeding the loss in patients that had the other treatments. No investigations were undertaken to understand the basis to the marked loss of blood in these patients. It appeared that the effect of ibuprofen in the FDC was to enhance the analgesia by paracetamol.

In terms of achieving a maximal "analgesic ceiling", it appears that FDC of ibuprofen 400 mg/paracetamol 1,000 mg has higher and longer duration of analgesia than the other FDCs. The FDC had fewer adverse events, possibly as a result of slightly reduced facial swelling and GI symptoms (nausea, vomiting). Overall, these investigations suggest that the higher dose FDC is preferable therapeutically.

Another study compared the efficacy of one or two tablets of the FDC ibuprofen 200 mg/paracetamol 500 mg, two tablets of ibuprofen 200 mg/codeine 12.8 mg, two tablets of paracetamol 500 mg/codeine 15 mg, or placebo in the dental surgical pain model (Daniels et al. 2011). Treatment with two tablets of ibuprofen 200 mg/paracetamol 500 mg produced superior pain relief (measured as SPID, or pain relief scores) which lasted over a longer period (up to 8 12 h) than any of the other treatments or placebo.

A review by Ong and co-workers (2010) of paracetamol FDC involving ibuprofen in various surgical conditions showed that this combination produced superior pain relief over that of the individual drugs alone. A similar finding was obtained with other NSAIDs in combination with paracetamol over the individual drugs. A retrospective safety evaluation of ibuprofen and paracetamol taken concomitantly with that of the drugs alone was undertaken by de Vries and co-workers (2010), using 1.2 million patients from the UK General Practice Research Database (GPRD). The safety evaluations included gastrointestinal events, myocardial infarction, stroke, acute renal failure, congestive heart failure, intentional or accidental overdose, suicidal behaviours, and mortality, these being evaluated in relation to dose, duration, and exposure.

Of the patients analysed, 1.0 million had not been prescribed other NSAIDs including aspirin in the preceding 6 months. The patient population and frequency of prescribing ibuprofen and/or paracetamol were different between the groups. Ibuprofen was prescribed to a younger population (mean age 57.0 years) and less frequently than paracetamol alone (mean age 71.6 years), or concomitant ibuprofen and paracetamol (mean age 64.6 years).

The overall occurrence of upper GI events (RR = 1.18, 95 % CI 1.13, 1.24) was lower with ibuprofen than with paracetamol (RR = 1.36, 95 % CI 1.31, 1.41) or the

FDC (RR = 1.70, 95 % CI 1.32, 2.19). The rates of myocardial infarction, stroke, heart failure, and renal failure did not differ between the groups, and tended to be RR-1.1. The RR of suicidal behaviour or overdose was about 1.3, and did not differ between the groups. Mortality was notably higher with the FDC ibuprofen/paracetamol group (RR = 1.5, 95 % CI 1.34, 1.68) and paracetamol alone (RR = 1.28, 95 % CI 1.26, 1.68) compared with that of ibuprofen alone (RR = 1.12, 95 % CI 1.10, 1.15).

An interesting outcome from the time-course of these observations was that the crude hazard rates for all major adverse events (except overdose) appeared notably lower with ibuprofen alone or FDC ibuprofen than with paracetamol. It must be emphasised, however, that these data do not quantify the amount of drug taken, even though they highlight the apparent higher toxicity of paracetamol.

5.5 Amino Acid and Salt Formulations

A variety of salts of ibuprofen have been developed, among them salts of sodium or potassium, or combinations with aluminium, aminoethanol, meglumine, guaiacol, pyridoxine, and the amino acids arginine and lysine (Reynolds 1993). The lysine combination with ibuprofen (lysinate) is a (DL) lysine salt of ibuprofen [chemically 2-(4-isobutyl-phenyl) propionate (DL) lysine]. After oral ingestion, this complex dissociates into ibuprofen (acid) and DL-lysine. The gastric absorption of ibuprofen proceeds at a faster rate from the complex, due to rapid solubilisation and dissociation that is more than that of ibuprofen (acid) in tablets or caplets (Geisslinger et al. 1989). Once absorbed, ibuprofen assumes the pharmacokinetic properties of the conventional ibuprofen. It is unlikely that the DL-lysine influences any other pharmacokinetic processes.

DL-lysine is a 50:50 mix of the metabolisable, essential amino acid, L-lysine with the non-metabolisable D-isomer. The latter is not metabolised or incorporated into newly synthesised proteins in mammalian cells but may be oxidised by D-amino acid oxidases. It is presumably excreted unchanged after oral intake, and would be expected to have no metabolic or biochemical impact at the doses ingested with ibuprofen.

The L-enantiomer of lysine would be expected to be metabolised in the same way as that from dietary sources, and would be incorporated into newly synthesised proteins de novo. It is unlikely that the L-lysine component in the doses ingested would be expected to have any substantive effects on metabolic processes, as the relative amounts in the diet far exceed those in the ibuprofen lysine tablets. DL-lysine, like that of some other amino acids (e.g., arginine, glutamine) is widely used as a salt or pharmaceutical additive or excipient.

The rationale for development of the lysine salt of ibuprofen is to enable increased disintegration and solubilisation of the complex in GI tract following ingestion of the tablets, with consequent more rapid gastro-intestinal absorption than observed with ibuprofen acid. The pH-dissolution studies of Geisslinger et al.

(1989) show that there is appreciably greater dissolution of ibuprofen from ibuprofen lysine tablets (90 % after 90 min) at pH 4.0, compared with 15 % from conventional ibuprofen (acid) tablets under the same conditions.

The comparative pharmacokinetic properties of ibuprofen lysine studied by Klüglich et al (2005) showed bioequivalence of ibuprofen lysine formulations with that of ibuprofen acid. There appear to have been two formulations of ibuprofen lysine investigated, one known as Dolormin® (McNeil) and the other which is the Reckitt Benckiser/Boots formulation known as Nurofen® Express. The pharmaceutical properties of Dolormin® are described in the pharmacopoeal literature (e.g., "Martindale", Reynolds 1993) and it appears that Nurofen® Express is an improved formulation, more as a consequence of manufacture, stability, and dissociation characteristics.

Intravenous ibuprofen lysinate has been employed in the treatment of patent ductus arteriosus, where it has proven effective and safe (Poon 2007; Hirt et al. 2008; Aranda et al. 2009a, b).

The clinical PKs of the arginine salt of ibuprofen has been extensively investigated (Cattaneo and Clementi 2010). In human volunteers the arginine salt shows more rapid gastric absorption than the acid (Cattaneo and Clementi 2010). At a dose of 400 mg, it has been shown to produce effective pre-emptive or post-operative analgesia in the third molar dental pain model (Lau et al. 2009). The potential for arginine to generate nitric oxide (NO) has been found to be related to its enhanced acute and chronic anti-inflammatory effects in animal models compared with that of ibuprofen alone (De Palma et al. 2009). This suggests that the arginine ibuprofen combination may have greater anti-inflammatory effects compared with ibuprofen acid. A functional (or pharmacological) magnetic resonance imaging (MRI) double-blind, placebo-controlled study in healthy human volunteers in whom pain was elicited from right medial nerve stimulation indicated that blood oxygen level-dependent signalling was modified in relation to somatosensory pain evoked potentials by ibuprofen compared with placebo (Delli Pizzi et al. 2010). The authors considered this effect was due to arginine. However, since the effects of ibuprofen alone were not investigated in this study, it is not possible to conclude that the analgesic mechanism was related to the NO-donor effect of arginine.

5.6 Topical Formulations

Topical formulations of ibuprofen have found extensive application as OTC treatments of musculo-skeletal pain (Cross et al. 2005; Tiso et al. 2010). These treatments are particularly helpful for the elderly with knee or back pain, where they are likely to have fewer GI adverse reactions than with the oral drug (Cross et al. 2005; Carnes et al. 2008; Underwood et al. 2008a, b; McCarberg 2010). In Cochrane assessments, ibuprofen gel and other topical formulations are clearly superior to placebo, and are about comparable to some other effective NSAIDs (e.g., diclofenac) (Massey et al. 2010). Evidenced-based evaluation of pain relief

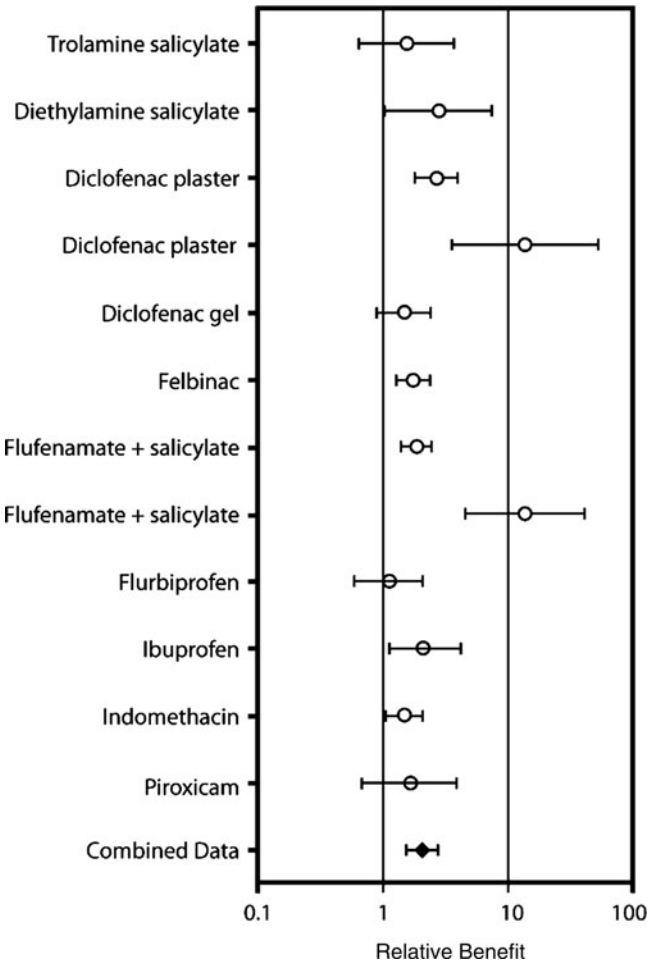


Fig. 5.1 Comparison of ibuprofen with some topical NSAIDs in placebo controlled trials in chronic pain conditions of 2 weeks duration. From: McQuay and Moore (1998). Reproduced with permission of one of the authors, Dr. Andrew Moore

from different formulations of NSAIDs has shown that ibuprofen has similar efficacy to other NSAIDs (Fig. 5.1; McQuay and Moore 1998).

Variation in the formulations and uptake of NSAIDs through different layers of skin and adjacent muscle determines the relative efficacy of these formulations (Rainsford et al. 2008a, b; Massey et al. 2010). Muscle pain appears well-controlled in mild moderate pain by ibuprofen, notably in elderly compared with younger subjects (Hyldahl et al. 2010). The issue of cost-effectiveness of topical versus oral ibuprofen has been examined (Castelnuova et al. 2008), and the cost benefits (at least within the UK National Health System) and results are equivocal and depend on the length of time of treatment. Long-term topical treatments (e.g., over a year or more) may not be as practical as taking the drug orally, since the repeated application may be accompanied by skin irritation and lack of compliance. It is clear,

however, that the more frequent occurrence of adverse events with the orally administered drug compared with the topically-applied formulation favours the latter, especially in the elderly who are most likely to have greater benefits in relation to adverse reactions from use of topical preparations (Carnes et al. 2008; Underwood et al. 2008a, b). The benefits to the elderly in whom topical ibuprofen appears as effective as the oral drug may depend on attention to close monitoring by health carers (Carnes et al. 2008).

Thus, topical ibuprofen has a place in therapy of mild moderate musculoskeletal pain, with the possibility of fewer GI and other adverse reactions than that with the oral drug. Recent development of novel dressings (Sibbald et al. 2007; Cigna et al. 2009; Arapoglou et al. 2011) or formulations, e.g., nanoscale emulsions (Abdullah et al. 2011), offer prospects for future development of more effective topical preparations.

Chapter 6
General Safety Profile

There were indications of a favourable safety profile for ibuprofen from the post-marketing data during the 15-year period after approval in the USA (Royer et al. 1984). This information was important in decisions made by the FDA in granting approval for OTC use in the USA (Rainsford 1999c).

Since then, the safety profile of ibuprofen has been compared with a range of other new and established NSAIDs on the basis of being a recognised "bench mark" for safety and efficacy comparisons (Kean et al. 1999). In particular, ibuprofen has been used as a comparator drug in several trials with the newer coxib class of NSAIDs; an aspect that will be considered later in this section and subsequent sections on the adverse events and toxicity in individual organ systems.

6.1 Introduction

6.2 Pharmacokinetic Aspects of Importance in the Safety of Ibuprofen

During the development of ibuprofen, pharmacokinetic issues were of particular importance, especially in the pre-clinical evaluation of the toxicity of the drug (Adams 1987; Rainsford 1999a). The Boots Company had already experienced problems with ibufenac in causing hepatic reactions in patients with rheumatoid arthritis during early-stage clinical trials. Furthermore, there was a major objective in the pre-clinical programme to discover a drug which was safer to the gastrointestinal tract than was evident with aspirin and some other NSAIDs at the time. Thus, to obviate the possibility of a new NSAID that was in discovery causing hepatic reactions, evidence for a lower rate of accumulation in the liver than was evident with ibufenac was obtained with ibuprofen.

K.D. Rainsford, *Ibuprofen: Pharmacology, Therapeutics and Side Effects*,
DOI 10.1007/978 3 0348 0496 7 6, © Springer Basel 2012

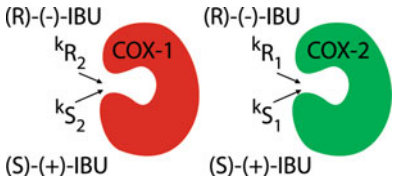


Fig. 6.1 Postulated competition between the R( ) and S(+) enantiomers of ibuprofen and the cyclo oxygenase (COX) isoenzymes in the upper gastrointestinal mucosa. There is no intestinal metabolism of R( ) ibuprofen to its S(+) antipode and possibly also in the stomach, this occurring principally in the liver. Thus, at least half of the racemic form of the drug, i.e., R( ), is available for competing with the inhibitory S(+) from active sites on COX isoenzymes in the stomach and intestinal mucosa. This masking of the COX active sites by R( ) ibuprofen effectively prevents appreciable inhibition of prostaglandin production in the gastrointestinal mucosa. This may account for the relatively low ulcerogenic activity and bleeding that is observed in clinico epidemiological and experimental studies (from Rainsford et al. 1997, 1999b, 2003). Reproduced with permission of Springer, publishers of Inflammopharmacology

What has emerged since ibuprofen was initially discovered is that (a) the drug undergoes metabolism of inactive R(−)-ibuprofen enantiomer (present as half the mass of ingested drug) to the prostaglandin synthesis inhibitory or active S(+) isomer, and (b) these isomers each have pharmacological effects of importance to the therapeutic actions of the drug, thus highlighting the inter-relationships between its metabolism and pharmacodynamic effects (Fig. 3.5) (Rainsford 1999b).

The presence of the R(−)-ibuprofen in the ingested drug may account for the low gastric irritancy of ibuprofen, by masking the interaction of the S(+)-isomer with the active site of COX-1 in the stomach and platelets circulating through the gastric circulation, so reducing the inhibitory potential of the latter isomer on production of gastric prostaglandins (Rainsford 1999b, 2003; Fig. 6.1).

In considering the pharmacokinetic profile of ibuprofen (Tables 2.1 and 6.1), there are several important features that should be noted:

1. The drug has a relatively short plasma elimination half-life ($t_{½}$) a feature which has been identified in comparative studies of gastrointestinal gastro-ulcerogenicity (Henry et al. 1996, 1998) which is probably a key safety feature. The plasma half-life of the drug averages between 2 and 3 h, with some inter-subject and intra-subject variability but not such that this vastly influences half-life values (Brocks and Jamali 1999; Graham and Williams 2004). Differences have also been observed in the bioconversion of the inactive (R−) enantiomers to (S+) enantiomers and in their clearance under conditions of acute surgical pain.
2. There is no evidence of increased accumulation in elderly or retention in specific body compartments. There is no evidence of formation of bio-reactive metabolites sufficient to cause covalent modification of liver, or other proteins that might contribute to toxicity of the kind seen in the case of paracetamol-induced irreversible hepatic injury (Graham and Hicks 2004). Glucuronide conjugates of ibuprofen represent the major metabolites of the drug, and it has

Table 6.1 Pharmacokinetic aspects affecting the safety of ibuprofen

General pharmacokinetic properties:
- Near complete bioavailability
- Low variability of PK parameters
- R( ) isomer protects against effects of S(+) in stomach
- Clearance not dependent on dose
- Little if any effects of food on gastric absorption
- Negligible excretion in milk
- Metabolised to pharmacologically inactive metabolites
- No evidence of appreciable systemic retention
- Little if any effects of gender
- Age: the elderly have increased unbound (albumin) fraction, clearance and V_d so overall may have higher exposure to drug than young adults
- Short plasma elimination half life ($T_{1/2}$)

  In healthy subjects:

  R 1.6 4.2 h

  S 1.9 3.4 h

  In osteoarthritis patients:

  R 1.7 2.9 h

  S 2.0 3.0 h

  In rheumatoid arthritis patients: more variable PK; AUC increased
- Hepato renal impairment:

  In liver disease: $T_{1/2}$ decreased, AUC increased, glucuronides decreased

  Renal clearance: variably affected by arthritic state

  and increased by 50 % at >70 years

  In renal insufficiency increase in AUC of S(+) with age and hypertension

  In painful states; delayed gastric absorption and increase renal clearance

Based on Jamali and Brocks (1999), Rainsford (2009). Reproduced with permission of Springer, publishers of Inflammopharmacology

been speculated that these conjugates might lead to formation of adducts such as are seen with other phenyl propionic and benzoic acid NSAIDs (Castillo et al. 1995). Whether these conjugates contribute to covalent modification of proteins that leads to toxicity is not known. There does not appear to be any indication of appreciable accumulation of ibuprofen in the liver and other organs, such as might result from such covalent modification. It is very likely that there is a considerable degree of spontaneous hydrolysis both of the glucuronides and the ibuprofenyl-derivatives of proteins.

Mild/moderate renal impairment does not appear to cause any elongation of the plasma elimination half-life, and there is little evidence of alterations in plasma pharmacokinetics in patients with mild hepatic disease. Clearly, patients with considerable renal impairment or liver malfunctions should not be taking ibuprofen as there would be an expected increase in risk of systemic accumulation, although this risk is probably of a low order in comparison with the short plasma half-life of the drug.

6.3 Pharmacokinetic Variations

The pharmacokinetic parameters obtained in studies with ibuprofen in normal subjects show relatively low variability (Table 6.2). This is illustrated in the mean values (±SD) or median and ranges of the various parameters obtained from a wide range of studies (Table 6.2).

As shown in Table 6.2, there is relatively little difference between the PKs in Western (or non-Chinese) populations compared with that from two studies performed in Chinese subjects (see also later section).

A major source of variability in the metabolism of ibuprofen, like that of other NSAIDs, is determined by the genetic variations in the cytochromes P_{450}, especially the CYP2C9 and CYP2C8 isoforms (Agundez et al. 2009).

The oxidative pathway of ibuprofen metabolism catalysed by the cytochrome P_{450}s constitutes a major Phase 1 pathway for the liver and intestinal detoxification of the drug (Brocks and Jamali 1999; Fig. 2.2). In recent years, it has become evident that there are genetic variants of those isoforms of cytochrome P_{450} that underlie the variation in catalytic activity, and consequently the metabolic clearance of ibuprofen as well as that of other NSAIDs and paracetamol (García-Martín et al. 2004; Agundez et al. 2009). These variations in cytochrome metabolism of NSAIDs and analgesics may be expected to have appreciable consequences for the safety and efficacy of these drugs (Agundez et al. 2009; Ali et al. 2009). Indeed, there is also evidence that there are marked differences in the frequency of alleles of those cytochromes involved in metabolism of these drugs in different ethnic populations worldwide (García-Martín et al. 2004; Agundez et al. 2009). Thus, the CYP2C9 and CYP2C8 isoforms are considered to have predominant roles in the metabolism of ibuprofen (as well as some other NSAIDs) (Agundez et al. 2009). CYP2C9 has particular prominence in variations in oxidative metabolism of ibuprofen, as it is the predominant isoform in the liver (Agundez et al. 2009). Allelic variants of both these isoforms may cause decreased, or rarely increased, enzyme activity, with consequent effects on the pharmacokinetics of ibuprofen or other NSAIDs metabolised by these isoforms (Agundez et al. 2009). Indeed, the dose-contributions of mutated heterozygous or homozygous CYP2C9 and CYP2C8 isoforms can have major consequences for the clearance of ibuprofen as well as some other NSAIDs.

The relative allelic frequencies of some of the principal CYP isoforms (i.e., CYP2C9*2, CYP2C9*3 and CYP2C8*3) vary considerably in different ethnic populations (Agundez et al. 2009). Although data in Chinese populations are sparse the allelic frequency of CYP2C9*3 is relatively low compared with that in some other populations (e.g., South and North Europeans, Caucasian Americans, and Asian Indians) (Agundez et al. 2009). This CYP variant which involves a single amino acid substitution of I359L is known to have decreased enzyme activity.

Table 6.2 Comparative pharmacokinetics of ibuprofen in normal Western subjects compared with those in Chinese [Data for Western subjects from Brocks and Jamali (1999)]

		C_{max} (μg/mL)		t_{max} (h)		AUC (μg/mL/h)		$t_{½}$ (h)		CL/F (L/h)		V_D/F (L)	
Author (year)—conditions	No. of subjects	S	R	S	R	S	R	S	R	S	R	S	R
Caucasians													
Jamali et al. (1988)	80	30	27.5	1.44		107	74.2	2.6	2.7	–	4.04	–	15.7
Levine et al. (1992)	11	38	25	1.3	1.2	127	74	2.1	1.7	–	4.05	–	9.64
With food		29	19	1.6	1.5	116	59	2.1	1.7	–	5.08	–	12.7
Jamali et al. (1992) solution	33					70.6	61.1	2.2	2.6	–	4.91	–	18.4
Tablets				2.17		70.8	52.7	2	2.1	–	5.69	–	17.3
Smith et al. (1994) solution	12	29	29.6	0.63	0.6	98.6	78.8	2.4	1.7	–	3.81	–	9.3
Oliary et al. (1992)	12	16.2	14	2.1	1.7	78.9	50.5	3.1	3.2	–	6.8	–	33
Li et al. (1993)	8	23.3	23.4	1.8	1.8	94.5	73.5	1.8	1.7	–	4.08	–	10
Geisslinger et al. (1990)	11	16.4	14.3	1.8	1.5	91.7	54.3	2.3	2.3	–	5.66	–	18.7
Geisslinger et al. (1989)	8	16.8	14.8	1.9	1.7	89.8	57	2.4	2.3	–	5.37	–	17.8
Mean		24.8	20.95	1.6	1.4	94.49	63.51	2.3	2.2	–	4.94	–	16.25
Median		26.15	21.2	1.8	1.5	93.1	60.05	2.25	2.2	–	4.99	–	16.5
SD		7.99	6.25	0.47	0.41	18.55	10.52	0.36	0.52	–	0.96	–	6.98
N		8	8	9	7	10	10	10	10		10		10
Min		16.2	14	0.63	0.6	70.6	50.5	1.8	1.7		3.81		9.3
Max		38	29.6	2.17	1.8	127	78.8	3.1	3.2		6.8		33
_75th % case 1–10		29.5	26.25	1.9	1.7	107	74	2.4	2.6		5.66		18.4
Chinese													
Chen and Chen (1995)	5 Male 5 Female					239.5	239.5	3.3	3.1		2.6		11
Ding et al. (2007)	12 Male	23.5	20.8	3	2.95	65.9	65.9			3.4	5.02	4.57	6.45

That the frequency of this variant is relatively low in Chinese populations suggests that ibuprofen metabolism is possibly less subject to impaired clearance. However, although more extensive data should be sought on other CYP2C9 and CYP2C8 variants in the Chinese before firm conclusions can be obtained.

The potential impact of variations in the CYP2C9*2 (as well as CYP2C9*3) variants on the risks of acute gastrointestinal (GI) bleeding is seen in data from meta-analyses (Agundez et al. 2009). Thus, for CYP2C9*2 associations it appears that the presence of this allelic variation confers about a 1.58-fold increase in the risk of GI bleeding with all NSAIDs, and 1.96 (CI 1.18 3.24) for NSAIDs that are CYP2C8 or CYP2C9 substrates; this would include ibuprofen. CYP2C9*2 and *3 polymorphisms are also related to excess of coagulation reactions due to warfarin (Lindh et al. 2005), and this may represent an added serious risk factor for bleeding if NSAIDs are taken with this drug.

Taking these data on GI risk together with data on allelic frequencies for CYP2C9*2, it would appear that although there is a risk of GI bleeding from individuals having this variant, the low frequency of this allelic variant in Chinese populations suggests that the likelihood of this genetic factor in determining risk of GI bleeding amongst the Chinese might be lower than that in Europeans, American Caucasians, or Asian Indians.

The most profound reduction in PK of both ibuprofen and other drugs in relation to allelic variations in CYP isoforms occurs in subjects with the CYP2C9*3 allele (López-Rodríguez et al. 2008; Vormfelde et al. 2009). With ibuprofen in Spanish populations, this variant leads to decreased metabolism of the R to S enantiomers, a 30 % increased AUC and 30 % reduced clearance of the drug compared with the most prevalent allelic variant CYP2C9*1. Subjects with CYP2C8*3 have reduced clearance and increased AUC and $t_{½}$ of R(−) ibuprofen, coincident with reduced ADRs. It must be cautioned, however, that the number of subjects was rather small in the CYP2C8*3 groups and so the statistical significance of data is limited.

The implications of allelic variations in CYPs for pharmacodynamics (PD) of ibuprofen were investigated in human volunteers by Kirchheiner et al. (2002), Lee et al. (2006), and López-Rodríguez et al. (2008). Since the PG synthesis inhibitory effects of ibuprofen are largely dependent upon the concentration of the active S(+)-isomer, and this is believed to affect both COX-1 and COX-2 (Rainsford 1999b, 2003, 2009), the variations in the R(−) to S(+) conversion would be expected to influence the total production of PGs and thromboxane B_2 (TXB_2). Kirchheiner et al. (2002) found that ex vivo production of TXB_2 via COX-1 in healthy volunteers that received a single dose of 600 mg racemic ibuprofen was significantly dependent on CYP2C9 polymorphisms. Greater inhibition of TXB_2 formation was evident in subjects with slow CYP2C9 phenotype metabolisers compared with the “wild” type CYP2C9*1; a similar trend was observed in COX-2 PGE_2 production ex vivo, but the wide variation in patterns of inhibition amongst subjects with CYP2CP variants meant that the results were less clear-cut.

6.4 Pharmacokinetics in Oriental Compared with Caucasian Populations

The possibility that there may be ethnic or environmental (e.g., dietary) differences in the PK of ibuprofen has been considered. The data considered here is from a few published investigations that have been reported in which the PK was determined of single OTC range dosage of racemic ibuprofen in normal volunteers. The PK data from these studies have been compared with pooled data (with statistical means, medians and errors or ranges of values) from studies in Western populations (Table 6.2; data from Brocks and Jamali 1999). These populations are presumed to comprise principally Caucasians, but also may include some Afro-Caribbean or Indo-Iranian populations.

Among these studies was an investigation by Chen and Chen (1995) in Taiwanese patients with varying hepato-renal conditions, cardiovascular, hyperlipidaemic, hyperuricaemic and diabetic conditions compared with 10 age-and sex-matched healthy volunteers. For the purpose of comparison with the studies in non-Chinese, predominantly Caucasian populations, only data from the normal volunteers is considered. The PKs of ibuprofen in patients with diseases or conditions that would be expected to confound the PKs of ibuprofen are considered separately later.

The main PK data from investigations by Chen and Chen (1995) are shown in Table 6.3. The values obtained in normal subjects are shown in Table 6.2 for comparison with data in non-Chinese populations. It appears that with the exception of the values for AUC (which were calculated to infinity values from linear extrapolation), the values of V_d, Cl, and $t_{½}$ for both enantiomers were within the ranges observed in non-Chinese populations (Table 6.3). The values for AUC in the Taiwanese all seem rather high in comparison with that in non-Chinese. An explanation for this is not obvious, except that in this study an 800 mg dose of ibuprofen was employed, whereas the other comparative data have been obtained from subjects that received 600 mg of the drug.

Ding and co-workers (2007) performed a study comparing the effects of an immediate release (IR) formulation of racemic ibuprofen with that of a sustained-release (SR) preparation in 12 healthy Han Chinese (Table 6.4). Both the racemic and the R(−) and S(+) enantiomers of ibuprofen, were determined by HPLC. The volunteers were fasted overnight, and then took 600 mg of one of the tablet formulations with water. No other foods or liquids were permitted for the next 4 h. Thereafter, hospital meals were allowed.

The serum concentrations of R(−) and S(+) ibuprofen following administration of 600 mg of the IR ibuprofen and the pharmacokinetic parameters are shown in Table 6.4. The time-dependent increase in the proportion of S(+) to R(−) ibuprofen reflects the well-known metabolic conversion of the R(−) form of the drug, and this appears to be in a similar proportion to that seen in Western populations (Ding et al. 2007).

Table 6.3 Pharmacokinetic parameters of ibuprofen enantiomers in Oriental patients admitted to National Taiwan University Hospital (1992–1994) with various cardiovascular and renal disorders compared with age-matched controls

Condition/age (years)	Cr (mg/dl)	$t_{½}^{(S)}$ (h)	$t_{½}^{(R)}$ (h)	$AUC^{(S)}$ (μg/mL/h)	$AUC^{(R)}$ (μg/mL/h)	$V_d/F^{(R)}$ (L)	$CL/F^{(R)}$ (L/h)
Diabetes mellitus							
63.8 ± 2.1	1.4 ± 0.2*	7.7 ± 1.4**	3.2 ± 0.5	715.8 ± 148.8*	338.1 ± 6.1	11.1 ± 2.1	1.7 ± 0.3
Hypertension							
59.6 ± 3.2	1.3 ± 0.1**	6.3 ± 1.2*	3.1 ± 0.5	800.6 ± 150.4**	396.3 ± 64.1	7.8 ± 1.4	1.4 ± 0.2
Hyperlipidaemia							
64.6 ± 4.7	2.1 ± 0.4*	3.3 ± 1.5	3.5 ± 0.8	780.5 ± 394.1*	374.9 ± 100.8	8.8 ± 3.3	1.4 ± 0.4
Hyperuricaemia							
67.3 ± 3.4	2.0 ± 0.5*	2.6 ± 0.4	4.3 ± 1.5	433.5 ± 123.4	490.1 ± 107.2	6.3 ± 2.8	1.0 ± 0.2*
Coronary artery disease							
63.2 ± 2.5	1.3 ± 0.1**	5.8 ± 1.6	3.9 ± 0.5	796.1 ± 203.0*	377.6 ± 64.0	9.2 ± 1.9	1.3 ± 0.2
Cerebral vascular disease							
60.5 ± 0.5	1.4 ± 0.1*	4.4 ± 0.5	3.6 ± 2.5	320.4 ± 171.3	212.4 ± 53.8	15.2 ± 9.2**	2.0 ± 0.5
Congestive heart failure							
68.5 ± 3.9	1.4 ± 0.1**	4.3 ± 1.1	3.9 ± 1.1	529.1 ± 86.3*	423.0 ± 114.0*	9.3 ± 3.4	1.1 ± 0.3
Coronary renal failure							
60.1 ± 3.7	2.0 ± 0.2**	4.5 ± 0.9	3.5 ± 0.7	768.3 ± 189.5*	436.1 ± 81.5*	8.8 ± 2.1	1.3 ± 0.3
Control							
57.9 ± 3.0	0.8 ± 0.1	3.3 ± 0.5	3.1 ± 0.6	286.8 ± 54.9	239.5 ± 45.4	11.0 ± 1.3	2.6 ± 0.7

V/*F* fractional volume of distribution calculated for (R)-ibuprofen, with dose calculated to one-half of administered racemate (800 mg)
From Chen and Chen (1995) with permission of the publishers

Table 6.4 Pharmacokinetic parameters of racemic and R ( ) and S (+) ibuprofen following oral administration of 600 mg immediate release (IR) preparation to 12 Han Chinese healthy male volunteers

	Enantiomer proportions		
	Racemate	R	S+
C_{max} (μg/mL)	46.21 ± 8.20***	20.82 ± 5.90**	23.46 ± 7.30**
t_{max} (h)	2.83 ± 1.03*	2.96 ± 1.18	3.00 ± 1.35*
AUC (μg/mL)	195.90 ± 31.69	65.94 ± 20.06	100.81 ± 32.28##
MRT (h)	4.34 ± 0.89***	3.43 ± 0.64***	4.51 ± 0.79***##
K_0 (h^{-1})			
k_a (h^{-1})	1.37 ± 2.12	1.32 ± 2.00	1.62 ± 2.06
Vd_G/F_G (L)			
Vd_T/F_T (L)	6.46 ± 2.13	6.45 ± 1.73	4.57 ± 2.47
K_{el} (h^{-1})	0.54 ± 0.16	0.58 ± 0.14	0.41 ± 0.12##
Tau (h)			
Lag $time_G$ (h)			
Lag $time_T$ (h)	0.95 ± 0.97	0.90 ± 0.82	1.10 ± 1.08#
CL/(F_G or F_T) (L/h)	3.14 ± 0.55	5.02 ± 1.81	3.40 ± 1.68
S/R AUC ratio			1.57 ± 0.45

C_{max} the maximum serum concentration, t_{max} the time to reach C_{max}, *AUC* area under the plasma concentration time curve, *MRT* mean residence time, k_0 zero order absorption rate constant, k_a first order absorption rate constant, Vd_G/F_G volume of distribution/fraction absorbed of SR preparation; Vd_T/F_T volume of distribution/fraction absorbed of IR preparation, k_{el} elimination rate constant, *Tau* drug release time of SR preparation, $Lagtime_G$ absorption lagtime of SR preparation, $Lagtime_T$ absorption lag time of IR preparation, CL/(F_G, or F_T) total body clearance/fraction absorbed IR preparation

Each value is the mean ± SD of results from 12 volunteers. From Ding et al. (2007) with permission of the publishers

Overall, it appears that the PK of racemic ibuprofen does not differ appreciably from that in other western populations.

Supporting evidence for the similarity of the PK properties of ibuprofen in Chinese compared with that in Western or Caucasian populations comes from another study by Zheng et al. (2008), as well as bioavailability studies in Chinese subjects in which various tablet formulations or suspensions of ibuprofen were compared (Table 6.5). Thus, Luan and co-workers compared the dissolution characteristics of three different ibuprofen formulations with that of a standard Boots preparation as a reference standard. They compared the bioequivalence of these preparations in volunteers using gas chromatography analysis of the racemic drug. The values for C_{max} for the 200 mg dose varied from 14.94 to 25.79 μg/mL for the three preparations under investigation compared with 20.96 to 24.46 μg/mL for three test preparations in comparison with the Boots product. Apart from one preparation (A) with a low value, the results were not significantly different from one another. The values for t_{max} ranged from 1.694 to 2.605 h for the three test preparations, and 1.737 to 2.126 h for the Boots preparation. The preparation (A) with the lowest C_{max} had the longest t_{max}, and this was statistically significant compared with the Boots preparation.

Table 6.5 Pharmacokinetics of various ibuprofen formulations in Chinese Subjects

Author's name (year)	Ibuprofen preparation	Dose (mg)	C_{max} (μg/mL)	T_{max} (h)	K_a (h^{-1})	AUC (μg/h/mL)	V_d (L)	Cl (L/h)	$t_{½}$ (h)	Other comments
Li and Chen (2001)	Sustained-release		22.7	3.5		150				Correlation between in vitro dissolution and PK
Wu et al. (2001)	Tablets multiple dose (q 6. 6d)		28.74	2.05		271.26(S.S.)				
	Sustained-release		18.42	7.47		263.31(S.S)				
Wang et al. (2002)	Tablets	400	42.43	2.68	0.7	237			1.92	Biovail. Susp/tabs. 102.8 %
	Suspension	400	52.62	1.55	1.65	242			1.89	No diff. PKs.
Wu and Kong (2004)	Tablets	600	13.56	1.76		44.13				Biovail. Susp/tabs. 104.3 %
	Suspension	600	14.46	1.21		46.76				
Zhao et al. (2004)	Ibu–arginine tabs	400	42.43	2.68	0.7	237			1.92	Biovail. Susp/tabs. 102.8 %
	Suspension	400	52.62	1.55	1.65	242			1.89	
Bao et al. (2006)	Hard capsules	400	32.77	2.83		147.57 (0-1)			2.39	Biovaol. Soft/hard capsules 103.5 %
	Soft capsules	400	34.94	2.78		157.43(0-00)			2.49	
Wang et al. (2006)	Tablets		28	2.7		148.49 (0-1)				
	Ibu–arginine syrup		47	0.6		157.28 (0-00)				
Xue (2006)	Sustained-release (Ref)	300 (S.D)	19.21	5		136 (0-10)			2.45	Biovail test/ref 101.74
		300 (M.D)	17.58	4.68		150 (0-10)			3.01	
	Sustained-release	300 (S.D)	16.86	4.85					3.42	
		300 (M.D)	14.46	4.68					3.6	
Wen et al. (2007)	Suspension ref test	400	34.6	2		125.4 (0-10)			2.1	Biovail test/ref (98.2 %)
		400	37.78	1.7		130.38 (0-10)			2.19	
Xu et al. (2009a, b)	Ibu–arginine tabs	400	50.6	0.51		118.63 (0-1) 121.18 (0-00)				Preparations bioequivalent
	Ibu–arginine granules	400	50.53	0.34		115.75 (0-1) 118.55				

The AUC values for the three test products varied from 58.37 to 122.8 μg/h/mL, compared with 78.41 to 109.8 μg/h/mL for the Boots preparation. These kinetic parameters have been related to mean dissolution times for the four preparations, with the preparation A being bio-inequivalent to the Boots preparation. It is significant that the values are, in general, within the range of racemic ibuprofen in other studies.

A study by Benjie and co-workers (2002) compared the bioequivalence of ibuprofen tablets (400 mg) with that of a suspension of the drug (400 mg) in Chinese volunteers. Serum levels of racemic ibuprofen were determined by HPLC. Values for C_{max} were 52.62 (±14.21 SEM) μg/mL for the suspension and 42.43 (±10.62 SEM) μg/mL for the tablets. The T_{max} was 1.55 (±0.70 SEM) h for the suspension and 2.68 (±0.86 SEM) h for the tablets. The values for AUC were 242.03 (±35.70 SEM) μg/h/mL for the suspension and 237.04 (±39.63 SEM) μg/h/mL for the tablets. The bioequivalence of the suspension was the same as that for the tablets, and was 102.8 (±11.45 SEM) %.

Overall, these data show that the PK parameters of various IR formulations and suspensions of ibuprofen are similar in Chinese subjects to those from a variety of studies in Western/Caucasian or other populations. However, other data from studies of bioavailability of different ibuprofen formulations available in China reported in Chinese journals shows there is a high degree of variability on the PK of preparations available in China (Rainsford 2011).

6.5 Influence of Disease States on PK of Ibuprofen

It is well-known that impaired hepatic and renal function can reduce the metabolism and clearance of ibuprofen (Brocks and Jamali 1999). In order to establish the influence of these and other diseases in Oriental populations and their impact on the rates of conversion of the R(−) to S(+) enantiomers of ibuprofen, Chen and Chen (1995) undertook a pharmacokinetic investigation in 32 Chinese patients in Taiwan compared with ten age-matched volunteers (Table 6.3). The patients had a variety of cardiovascular disorders: hypertension (46.9 %), hyperlipidaemia (15.6 %), hypercuricaemia (12.5 %), and diabetes mellitus (50 %), with or without complications including coronary artery disease (31.3 %), congestive heart failure (18.8 %), cerebrovascular disease (6.3 %) and chronic renal failure (37.5 %) with associated impaired renal function.

All the subjects received 2 × 400 mg of Boots racemic ibuprofen as a single dose (800 mg), without any dietary restriction but without regular medications. The PK data from this study are shown in Table 6.3. The most marked changes were evident in patients with compromised renal haemodynamics and especially patients with hyperuricaemia who showed reduced clearance of R(−) ibuprofen. Patients with most of the conditions showed increased AUC for S(+) and to some extent R(−) ibuprofen, this being most marked in patients with coronary vascular conditions. The fractional volume of distribution (V_d/F) for R(−) ibuprofen was very high in patients with cerebral vascular disease, but was somewhat lower, though not statistically significant from controls, in patients with hyperuricaemia. There was

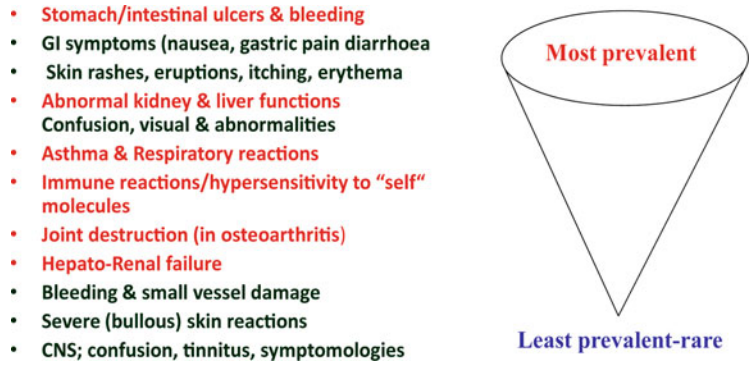


Fig. 6.2 Patterns of adverse reactions from the NSAIDs (Bjarnason et al. 2005). Adverse Reactions shown in red are most frequent.

a trend towards higher S/R AUC ratios in patients with renal insufficiency, diabetes mellitus, hypertension, hyperlipidaemia, and coronary artery disease, reflecting alterations in the renal and hepatic reactions in the disposition of the respective enantiomers. The exact nature of these altered functions in hepato-renal metabolism and elimination was not clear from these studies.

6.6 ADRs and Safety in Prescription-Level Doses

The overall pattern of adverse events from ibuprofen at prescription-level (Rainsford 1999b) probably conforms to that of all NSAIDs; a diagrammatic representation of the spectrum of adverse reactions from NSAIDs is shown in Fig. 6.2.

This has given rise to the concept that most NSAID adverse events can be considered as class-related. Within this concept, it is clear that NSAIDs vary considerably in their frequency or occurrence of individual side-effects. Some of these are mechanism-related, that is to say related to the effects on prostaglandin production via COX-1 inhibition for example in the GI tract and kidneys. However, it has been argued that in relation to some of these effects, there are important interactions between inhibition of COX-1 and COX-2, nitric oxide synthase and physico-chemical factors which are of significance in the development of these effects, so that they cannot all be considered to be mechanism-related.

6.7 Epidemiological Studies

A considerable number of studies have been performed since the introduction of ibuprofen examining the relative safety and adverse events attributed to ibuprofen compared with other NSAIDs. Many of these studies have involved examination of

the occurrence of adverse events e.g., in specific system organ classes (SOC) or individual reactions in organ systems (e.g., gastro-intestinal ulcers and bleeding). These studies are reviewed in subsequent sections of this report. There are relatively few studies where overall "toxicity" of NSAIDs has been examined in studies with any credibility that meet standards of epidemiological investigations (e.g., sufficient numbers of study subjects or validity of databases).

Among the earlier studies investigating the overall occurrence of serious adverse reactions was a study by Freis and co-workers (1991). They determined what they described as the relative toxicity of a range of NSAIDs used in the treatment of RA (rheumatoid arthritis) in the USA with data recorded in the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS). This is an extensive database developed by Fries and colleagues at Stanford University (Palo Alto, CA, USA), and has been extensively used as a research system, including for prospective comparative studies of drug toxicity factors accounting for the development of ADRs in rheumatic patients (Fries 1996, 1998; Fries et al. 1991, 2004; Singh et al. 1991; Fries and Bruce 2003).

It should be noted that at the beginning, these studies, patients (Fries 1996, 1998; Fries et al. 1991; Singh et al. 1991) were undertaken in what can be described as the "pre-coxib" era, i.e., before the introduction of the coxibs in 1999. This has significance, since the coxibs had an appreciable if variable share of the NSAID market world-wide, and thus influenced the overall patterns of use of the NSAIDs in rheumatic and other musculo-skeletal conditions.

A summary is shown in Table 6.6 of the Standardised Toxicity Index from 11 most-frequently prescribed NSAIDs including ibuprofen in RA patients adjusted for weightings, demographic factors etc., as part of a sensitivity analysis.

These data comprise toxicities from all patients in the database and those that are considered "drug starts". The results obtained with these differing periods of drug exposure were essentially similar. Ibuprofen was in a group with the two other salicylates, aspirin and salsalate, in having the lowest toxicity ratings. Other reports from the same group have confirmed the low relative toxicity of ibuprofen (Fries 1996, 1998).

An epidemiological safety investigation known as the Safety Profile of Antirheumatics in Long-term Administration (SPALA) was undertaken during the late 1980s to 1990 involving 30,000 rheumatic patients in participating centres in West Germany ($N = 9$), Switzerland ($N = 3$) and Austria ($N = 4$) (Brune et al. 1992). Of the ten most-frequently prescribed NSAIDs ($N = 36{,}147$ prescriptions), ibuprofen was the second most-frequently prescribed drug after diclofenac, and it ranked fourth in the overall total number of ADRs among the ten drugs. As shown in Table 6.7, ibuprofen was associated with the least number of reactions in the GI, liver and biliary, and body as a whole systems.

These two studies show that ibuprofen at prescription-level doses given to rheumatic patients has amongst the lowest toxicity ratings of frequently prescribed NSAIDs.

Table 6.6 Toxicity Indices of 11 most frequently prescribed NSAIDs, including ibuprofen in patients with rheumatoid arthritis in data derived from five centres in USA and Canada analysed from the ARAMIS database (Fries et al. 1991)

Drug	No. of courses	Standardised toxicity index score, ±SEM (rank)	No. of courses	Standardised toxicity index score, ±SEM (rank)
Aspirin	1,669	1.19 ± 0.10 (1)	410	1.37 ± 0.35 (1)
Salsalate	121	1.28 ± 0.34 (2)	107	1.30 ± 0.30 (2)
Ibuprofen	**503**	**1.94 ± 0.43 (3)**	**238**	**2.34 ± 0.55 (3)**
Naproxen	939	2.17 ± 0.23 (4)	327	3.43 ± 0.58 (4)
Sulindac	511	2.24 ± 0.39 (5)	220	2.89 ± 0.45 (5)
Piroxicam	790	2.52 ± 0.23 (6)	291	3.33 ± 0.46 (6)
Fenoprofen	161	2.95 ± 0.77 (7)	71	3.09 ± 0.65 (7)
Ketoprofen	190	3.45 ± 1.07 (8)	147	3.44 ± 0.78 (8)
Meclofenamate	157	3.86 ± 0.66 (9)	84	4.43 ± 0.84 (9)
Tolmetin	215	3.96 ± 0.74 (10)	120	4.83 ± 0.78 (10)
Indomethacin	386	3.99 ± 058 (11)	159	4.32 ± 0.60 (11)

Reproduced with permission of Springer, publishers of Inflammopharmacology

Table 6.7 Adverse Reactions from 3 most commonly preseneted NSAIDS in major organ systems in the safety profile of Antirhiumatics in Long Term Administration (SPALA) study

Organ system classes	Diclofenac	Ibuprofen	Indomethacin
No. of prescriptions	14,447	4,037	3,896
Gastrointestinal system	14.1 %	11.2 %	15.9 %
Skin and appendages	3.5 %	3.3 %	3.5 %
Central and peripheral NS	2.5 %	3.0 %	7.9 %
Liver and biliary system	2.2 %	0.7 %	1.8 %
Body as a whole general	2.7 %	2.2 %	3.1 %

Data from Brune et al. (1992); from Rainsford (2009). Reproduced with permission of Springer, publishers of Inflammopharmacology

6.8 Outcomes from Large-scale Clinical Trials

The studies with the coxibs conducted during the past decade were undertaken with large numbers of patients under modern standards of clinical investigation and with demanding requirements to establish safety in the GI, CV, and other organ systems where serious adverse events with the NSAIDs often occur at low frequencies. Ibuprofen was used in a number of these studies as a "bench standard" in recognition of it being accepted as amongst the safest of all NSAIDs that is still widely used in rheumatic and other musculo-skeletal conditions. These studies have afforded useful and high quality data for assessment of the adverse reaction and general safety profile of ibuprofen in a setting where the drug is critically evaluated against its competitors.

The individual adverse reactions in GI, CV, and other organ systems are reviewed in detail in later sections. Here, the adverse reaction profiles for ibuprofen and comparator drugs are viewed in a global sense, employing outcome measures

that are considered good indicators of overall patient and physician acceptability for safety and efficacy. It is important to note that withdrawal of an NSAID from use can be the moult of serious adverse events as well as lack of efficacy.

In an evaluation of the tolerability of adverse events in clinical trials conducted with the objective of assessing celecoxib (Celebrex®; Pfizer) in osteoarthritis and rheumatoid arthritis, Moore et al. (2005) used data from the manufacturer's database (Pfizer) of clinical trials for comparing the occurrence of responses and discontinuations in treatment in arthritis because of lack of efficacy or side-effects of celecoxib with those of ibuprofen, diclofenac, naproxen, paracetamol, and rofecoxib. Although there are limited data available on ibuprofen, the data reveals that adverse event discontinuation with ibuprofen following 12 or 24 plus weeks of treatment were similar to those from diclofenac or celecoxib when either the number of events or the percentage of discontinuations is compared (Table 6.8). These data should be evaluated in relation to the 95 % confidence interval ranges, which notably overlap. The lack of efficacy was lowest with rofecoxib and diclofenac and then ibuprofen, which had a low rate of discontinuation at what is effectively a prescription level of the drug, then followed by celecoxib at doses of 100 400 mg/day when all of these drugs have been taken for 12 weeks. There was a high rate of discontinuation when the drugs had been taken for 24 plus weeks (Table 6.8). These results suggest that ibuprofen has a relatively low rate of adverse event discontinuation compared with the other NSAIDs or coxibs, and that this is not impacted assessments off lack of efficacy.

Similar data available from a large-scale randomised trial of the efficacy and tolerability of rofecoxib versus ibuprofen in patients with osteoarthritis by Day and co-workers (2000) showed that patients who received ibuprofen 2,400 mg/day for 6 weeks had rates of discontinuation through adverse events of approximately 12 %, and through lack of efficacy of approximately 3 %, compared with those of rofecoxib where the discontinuations from adverse events were approximately half these values from ibuprofen whereas the lack of efficacy was comparable. This is an important observation, since it has often been argued that the lower rates of ADRs and toxicity of ibuprofen, including that in the GI tract, may be a consequence of the drug being less potent, or that it may have differing patterns of prescribing compared with that of other NSAIDs. The evidence is, however, that the anti-inflammatory and analgesic effects of ibuprofen are comparable to that of other NSAIDs when given at recommended prescription levels (Kean et al. 1999). It is true that drugs such as diclofenac and ketoprofen are more potent prostaglandin synthesis inhibitors than ibuprofen, and that the selective COX-2 activities of the coxibs such as celecoxib and etoricoxib may moult in greater efficacy of these drugs. However, it is more likely that the longer plasma half-lives of drugs such as naproxen and celecoxib may contribute to these drugs having more *sustained* analgesic and anti-inflammatory activity compared with that of ibuprofen, thus indicating that it may be a question of the duration in circulation of these drugs that accounts for any differences in their therapeutic effects. There is little available evidence to support these concepts, and therefore they can only be considered theoretical.

Table 6.8 Rates of discontinuation of NSAIDs during time of therapy of arthritis due to lack of efficacy or from adverse events[a]

Duration (weeks)	Treatment/dose (mg/day)	Percent discontinuations due to lack of efficacy (95 % CI)	Percent discontinuations due to adverse events (95 % CI)
2,6,11	Placebo	17.6 (15.8 19.4)	5.0(4.0 6.0)
	Celecoxib 400	7.7 (3.6 11.8)	3.2(0.5 5.9)
	Diclofenac 100/150	2.4 (1.0 3.8)	9.4(6.9 11.9)
	Naproxen 1,000	1.3 (0.1 2.5)	7.8(5.3 10.3)
	Paracetamol 4,000	11.0(8.3 13.7)	5.4(3.4 7.4)
	Rofecoxib 25[b]	1.6(0.8 2.4)	6.5(5.1 7.9)
12	Placebo	45.9(43.0 48.8)	6.2(4.8 7.6)
	Celecoxib 400	8.0(7.4 8.6)	9.6(8.8 10.4)
	Diclofenac 100/150	2.8(2.2 3.4)	7.8(7.0 8.6)
	Ibuprofen 2,400	4.1(1.9 6.3)	10.7(7.4 14.0)
	Naproxen 1,000	15.6(14.2 17.0)	13.2(11.8 14.6)
	Rofecoxib 25[b]	0.8(0.0 2.4)	9.8(4.7 14.9)
24	Placebo		
	Celecoxib 400	8.0(5.1 10.9)	10.4(7.1 13.7)
	Diclofenac 100/150	14.2(12.8 15.6)	25.5(23.7 27.3)
	Ibuprofen 2,400	23.0(21.2 24.8)	23.0(21.2 24.8)

From: Moore et al. (2005). Reproduced with permission of the publishers from Rainsford (2009)
[a]Data from Manufacturer's (Pfizer) database by Moore et al. (2005).
[b]Rofecoxib withdrawn in 2004.

In a large scale study the coxib, lumiracoxib 400 mg (Prexige®, Novartis) was compared with ibuprofen 2,400 mg and naproxen 1,000 mg taken for 52 weeks in 18,325 patients randomised for the treatment of osteoarthritis (Farkouh et al. 2004; Schnitzer et al. 2004). There were two major studies performed, one addressing the CV events (Farkouh et al. 2004) and the other GI safety (Schnitzer et al. 2004), with each of these having two sub-studies, one a comparison of lumiracoxib with ibuprofen and the other comparing the former with naproxen. Only the data from the ibuprofen sub-study is reviewed here, although it is interesting that aside from CV events ibuprofen had safety lower than or comparable with naproxen in the occurrence of other ADRs.

Here, the numbers of discontinuations and the reasons for withdrawal are considered (Table 6.9).

It is apparent from this data that there were similar rates of discontinuation from ibuprofen compared with that from lumiracoxib; the same was also evident with naproxen. The losses were mainly due to adverse events, these being relatively low compared with what might be expected in a study lasting 1 year. Likewise, the losses due to unsatisfactory therapeutic effects were low and comparable with one another.

These studies from large-scale clinical trials attest to the comparable rates for withdrawals from trials with ibuprofen and the coxibs. They show that the newer

Table 6.9 Percent discontinuations in the TARGET study: comparisons of ibuprofen with lumiracoxib

	Lumiracoxib vs ibuprofen sub study	
	Lumiracoxib (*n* 4,399)	Ibuprofen (*n* 4,415)
Discontinued	40 %	**44 %**
Reason for discontinuation		
Adverse events	16 %	**18 %**
Abnormal laboratory values	1 %	**1 %**
Abnormal test procedure results	<1 %	<**1 %**
Unsatisfactory therapeutic effect	9 %	**10 %**
Patient's condition no longer requires study drug	<1 %	<**1 %**
Protocol violation	4 %	**4 %**
Patient withdraw consent	8 %	**9 %**
Administrative problems	<1 %	**1 %**
Lost to follow up	<1 %	<**1 %**
Death	<1 %	<**1 %**

From Schnitzer et al. (2004). Reproduced with permission of the publishers from Rainsford (2009)

coxibs are neither more effective nor less likely to produce adverse reactions leading to withdrawals from studies comparing them with ibuprofen.

6.9 Adverse Events Attributed to Ibuprofen at Non-prescription (OTC) Dosages

A considerable number of studies have been reported comparing the adverse reactions from non-prescription (OTC) doses of ibuprofen with placebo, paracetamol (acetaminophen) or other analgesics. These studies have been performed using a variety of methodologies and study designs.

Earlier reviews of published literature have reported OTC ibuprofen causes adverse events (AEs) comparable with paracetamol or placebo (Furey et al. 1993; DeArmond et al. 1995; Moore et al. 1996).

A systematic data analytical review of published studies compared OTC ibuprofen with paracetamol where the drugs were taken as single doses or daily dosages up to 10 days (Rainsford et al. 1997; Table 6.10; Fig. 6.3). The subjects in these studies were either healthy volunteers, or those who experienced various types of acute pain or chronic inflammatory conditions. Some studies involved comparisons with other analgesics/NSAIDs or placebo. Thus, there was a wide range of conditions in which the treatments were compared. The results showed that there were no significant differences between ibuprofen and paracetamol in occurrence of AEs after single or multiple daily doses taken for up to 10 days (Fig. 6.3) although there was a trend to increased GI AEs in both groups with increased duration of drug intake. There did not appear to be any discernible differences in AEs in

Table 6.10 Overall adverse event rates and exposure grouped by duration of dosing

Days dosed	Drug	No. of groups	Exposure[a]	Total number of patients	Overall percent with adverse events	Total number with adverse events[b]	Total number of adverse events[c]
1	Paracetamol	27	0	4,644	10	444	479
1	Ibuprofen	25	0	2,312	6	148	172
1	Paracetamol	11	420	420	10	43	49
1	Ibuprofen	5	215	215	8	18	22
2 7	Paracetamol	15	2,882	687	8	57	64
2 7	Ibuprofen	9	1,015	227	9	20	29
8 30	Paracetamol	6	5,496	207	19	39	39
8 30	Ibuprofen	9	5,960	272	19	52	52
31 90	Ibuprofen	5	6,504	85	29	25	29
Total	Paracetamol	59	8,798	5,958	10	583	631
Total	Ibuprofen	53	13,694	3,111	8	263	304

[a]Number of patient days.
[b]Adverse events grouped as the total number of patients having these events.
[c]Adverse events grouped as the total of all recorded adverse events.
From: Rainsford et al. (1997). Reproduced with permission of Springer, publishers of Inflammopharmacology

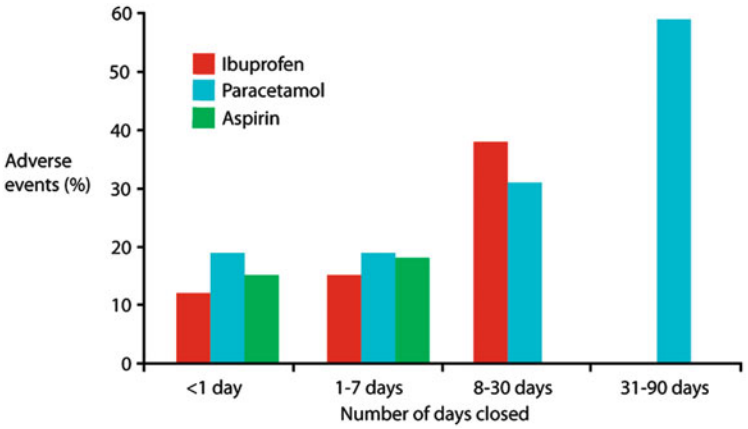


Fig. 6.3 Percent of ADRs reported in studies where OTC doses of ibuprofen were compared with aspirin and paracetamol (Rainsford 2011, unpublished)

different patient groups, although the number of patients in each of the groups was probably not sufficient to meet statistical requirements for being assessable. As paracetamol may be considered a "benchmark" drug for low propensity to cause serious GI events, this study suggests that as there was no differences in GI AEs between ibuprofen and paracetamol at OTC dosages, ibuprofen can be considered to have low risk of GI reactions comparable that are with paracetamol.

Table 6.11 Number (*N*) and percentage (%) of subjects experiencing a severe adverse reaction over all body systems, the digestive system, and the body as a whole system

All body systems			Digestive system		Body-as-a-whole system	
Pool studies	Placebo *N* (%)	Ibuprofen *N* (%)	Placebo *N* (%)	Ibuprofen *N* (%)	Placebo *N* (%)	Ibuprofen *N* (%)
Single-day studies	7/318 (2.2)	1/319 (0.3)	2/318 (0.6)	1/319 (0.3)	5/318 (1.6)	0/319 (0.0)
Multiple-day studies	59/775 (7.6)	38/775 (4.9)	21/775 (2.7)	14/775 (1.8)	36/775 (4.6)	21/775 (2.7)
All studies	66/1,093 (6.0)	39/1,094 (3.6)	23/1,093 (2.1)	15/1,094 (1.4)	41/1,093 (3.8)	21/1,094 (1.9)

From Kellstein et al. (1999). Reproduced with permission of the publishers from Rainsford (2009)

Using a similar analytical approach to data derived from various trials, these data have been updated and extended to include studies of comparisons of ibuprofen with aspirin as well as paracetamol (Rainsford 2011; unpublished studies).

Kellstein and co-workers (1999) performed a meta-analysis of reports of randomised, double-blind, placebo-controlled parallel-group studies, having initially reviewed published literature and established that only eight studies, all of which were *unpublished* but claimed as independent studies performed under the auspices of Whitehall Robbins Healthcare, met the criteria as specified above according to GCP conditions (Table 6.11). AEs were codified according to the conventional Coding Symbol Thesaurus for Adverse Reaction Terms (COSTART), with the exception of abdominal pain, which was "conservatively" assigned to "body as a whole" digestive system. This may in fact have disguised the importance of this AE, since it is a relatively frequent event in trials with NSAIDs and paracetamol.

The eight selected studies were in mixed patient groups comprising three in OA pain, two in delayed onset muscle soreness (DOMS), and one each in sore throat pain, dental pain, and a study of maximal use safety and tolerability (MUST) of non-prescription ibuprofen. The dosages ranged from 400 mg b.i.d. (800 mg/day; two studies) and 400 mg t.i.d. (1,200 mg/day; six studies) with a duration of intake between 1 and 10 days; the primary purpose was to compare the effects of single-dose with multiple daily doses of ibuprofen with placebo. The subjects covered a wide range of ages (12 97 years) and racial groups of both genders in a total of 1,094 ibuprofen and 1,093 placebo-treated subjects.

Table 6.11 summarises the serious AEs from this study. The principle outcomes can be summarised thus:

(a) The overall number of AEs, those in body-as-a-whole, and those in the digestive system were greater after multiple compared with single doses of ibuprofen and placebo.
(b) There were no differences in AEs in all body systems and in the digestive system after single doses of ibuprofen compared with placebo, or in the digestive system and body-as-a-whole after multiple doses.
(c) In an analysis of individual AEs by COSTART, dizziness was identified among the central nervous system reactions to be significantly increased after multiple doses in the ibuprofen (2.5 %) compared with placebo groups (1.4 %), there being no differences after single doses of the treatments.

(d) Overall tests for homogeneity among the study groups using the Breslow Day statistical test showed no significant differences between the occurrences of all individual AEs over all the study groups.
(e) Serious AEs over all categories were *fewer* in the ibuprofen compared with placebo groups in both the single and multiple dosage categories. Urinary tract infections, while rare, were more frequent in ibuprofen than placebo groups.

The reason for higher rates of AEs from placebo in "all body systems" and "body-as-a-whole" compared with ibuprofen is attributed to a larger number of patients in the placebo group reporting headaches, neck pain and malaise. The lower rates of these reactions in the ibuprofen groups are consistent with its analgesic activity.

While the studies employed in this meta-analysis are from unpublished investigations that have not been subjected to peer-review, they are none-the-less from investigations that were performed according to GCP requirements, and would have been in the company database that is subject to scrutiny by the US FDA.

Another study from the same company involved a prospective investigation of GI tolerability of the maximum daily OTC dose of 1,200 mg ibuprofen compared with placebo taken for 10 days in 1,246 healthy volunteers (Doyle et al. 1999). A total of 19 % of ibuprofen-treated subjects (67 of 413) and 16 % of placebo-treated individuals (161 of 833) experienced GI AEs, there being no significant differences between the two groups. The GI adverse reactions were dyspepsia, abdominal pain, nausea, diarrhoea, flatulence, and constipation. Occult blood tests were positive in 1.4 % of all subjects, there being no differences between the two treatments in the occurrence of these reactions. The results in this prospective study confirmed the data from previous retrospective studies, and showed that ibuprofen at OTC dosages has comparable GI reactions to placebo.

In a large-scale general practice based investigation (known as the PAIN Study) in 4,291 patients in France, Le Parc et al. (2002; Moore et al. 2002) compared the tolerability of 7 days treatment of ibuprofen (up to 1.2 g/day) with aspirin (up to 3 g/day) for relief of musculoskeletal conditions. So-called "significant" AEs were reported in 15.0 % of patients who took ibuprofen, 17 % on paracetamol and 20.5 % on aspirin; the difference between the ibuprofen and paracetamol groups being not statistically significant but significantly different from the aspirin group (Tables 6.12 and 6.13). GI AEs were fewer in the ibuprofen group (4.4 %) than in the paracetamol (6.5 %) or aspirin (8.6 %) groups, the differences in all groups being statistically significant from one another. In the non-musculoskeletal group there were similar trends, although there was no occurrence of serious digestive AEs.

Using the data acquired in the abovementioned PAIN Study, Moore and co-workers (2003) performed an assessment of risk factors that accounted for the development of, or association with AEs. By employing multivariant logistic regression analysis of 8,633 patients, they identified the following risk factors: (a) indication (e.g., musculo-skeletal pain, sore throat, colds and flu, menstrual pain, headache), (b) concomitant medications, (c) history of previous GI disorders, and

Table 6.12 Most frequent significant adverse events by COSTART body systems and terms

Systems/terms	Ibuprofen (%)	Aspirin (%)	Paracetamol (%)
Body as a whole	5.8	7.4	5.7
Digestive system	3.6	4.7	4.3
Nervous system	1.0	2.2	1.1
Respiratory system	1.2	1.5	1.3
Abdominal pain	2.4	5.1	2.7
Nausea	1.6	1.8	1.3
Dyspepsia	0.9	1.9	1.3
Headache	1.2	1.1	1.6

From Le Parc et al. (2002), Moore et al. (2002)

Table 6.13 Rates of adverse events by intensity

	Ibuprofen (%)	Aspirin (%)	Paracetamol (%)	*P* value (ibuprofen vs aspirin)	Confidence limit* (ibuprofen vs paracetamol)
SGAE	12.0	15.7	12.3	0.02	2.4
All AE	16.0	22.3	19.0	<0.001	0.1
Severe AE	3.6	3.7	2.9	NS	2.2
Moderate AE	6.9	10.3	8.5	<0.01	0.7
AE leading to discontinuation	4.3	6.5	5.1	0.033	0.9

Data from the PAIN studies by Moore et al. (2002) and Le Parc et al. (2002)
AE adverse event, *SGAE* significant adverse event
*One sided 96.5 % confidence limit for difference between ibuprofen and paracetamol; equivalence is concluded if the upper limit of the confidence interval of the difference is <2.7 %
Reproduced with permission of the publishers from Rainsford (2009).

(d) female sex. Age was not a risk factor. There were fewer clinically significant risk factors for GI AEs in the ibuprofen compared with paracetamol groups. The overall conclusion was that the main risk factor was concomitant medications.

A meta-analysis was undertaken by Ashraf and co-workers (2001) in elderly (>65 years) osteoarthritic patients in which the incidence of adverse events (COSTART-coded) from ibuprofen 1,200 mg daily with those that received placebo. Following an initial assessment of the quality of papers, three independent clinical trials that had been performed by Whitehall Robbins (USA) were selected in which the drug treatments were for ≤10 days. The pooled overall incidence of adverse events was 29.4 % with the ibuprofen group ($N = 197$ patients) and 29.0 % in the placebo group ($N = 210$ patients), with the three studies individually showing no statistically-significant differences. The percentages of adverse events in the organ systems were for: (a) "body as a whole" 12.7 % ibuprofen vs 9.5 % placebo, (b) digestive system 12.2 % ibuprofen vs 13.3 % placebo, and (c) nervous system 10.2 % ibuprofen vs 8.1 % placebo, the differences being not statistically significant. This study is important in showing that ibuprofen at OTC doses has a relatively low incidence of adverse events in elderly OA patients, a group who frequently self-administer the drug.

Several investigations have been performed in what could be regarded as "at risk" patients; either those admitted to hospitals for clinical investigation (and who could be regarded as being at "suspect" risk because of indicative symptoms requiring investigation), or patients with rheumatic diseases. The focus of these studies has been to identify the risks of serious AEs in the GI tract from intake of OTC analgesics. The rheumatic patients may have increased susceptibility to GI events from intake of NSAIDs as a consequence of their disease, concurrent disease (e.g., diabetes, CHD), concomitant medications (either anti-rheumatic, e.g., steroids, or other agents to control diabetes, hypertension, CV disorders, or subnormal renal function), as well as socio-psychological stress or *Helicobacter pylori* infection. Since many patients with rheumatic disorders take OTC analgesic medications on a self-administered p.r.n. basis and as a reflection on costs of prescription NSAIDs which for the elderly or members of lower socio-economic classes could be a major issue, use of OTC analgesics in these patients can be regarded as one of the "real-world" uses of these drugs.

Among the reports in GI suspect risk patients, Blot and McLaughlin (2000) reported investigations conducted by a mail survey of members of the American College of Gastroenterology, ACG, designed to identify risks of GI bleeding associated with intake of analgesics at OTC dosages within the previous week of drug intake. The methodology involved data collected from the ACG Registry ($N = 627$ patients) and "procedure-matched" endoscopy controls. Suspect factors (e.g., tobacco, alcohol intake, etc.) were also identified. These hospitalised patients had a variety of upper or lower GI conditions that led to bleeding in the OTC analgesic group but no bleeding in the control group. The number of patients in these groups might be considered relatively small, and questions can be raised about the statistical validity of the subgroup analysis of risk factors. Moreover, the nature of the data collection increases the bias in the cohorts examined.

The cases tended to be older subjects (mean 60 years) compared with controls (55 years), with 45 % cases being over 65 years compared with 33 % controls, and they were more often male cases (63 %) compared with controls (49 %). The balance of races was comparable, with about two-third being non-Hispanic whites. GI risk, especially in the upper tract, was greater in those that had consumed alcoholic beverages, this being increased in smokers, but cigarette smoking was unrelated to GI risks.

Of the major analgesics, reported intake of drugs was associated with GI bleeding in 9.5 % aspirin-takers, 4.2 % ibuprofen- takers, and 5.4 % paracetamol-users. A considerable number of patients had taken mixtures of two analgesics or prescribed NSAIDs. It should be emphasised that the numbers of patients were relatively small among the single-analgesic users (56 on aspirin, 25 on ibuprofen, and 32 on paracetamol), so it is questionable to ascribe causality to individual drugs. None-the-less, these data are instructive at least for assessment of potential GI bleeding in at-risk patients. It is interesting that paracetamol was associated with GI bleeding, as it is normally considered a low-risk GI "safe" drug. In this complex group of patients with evident underlying disease, it was clear that ibuprofen is somewhat safer than the other two analgesics.

In conclusion: (a) the studies at prescription-level doses show that ibuprofen has amongst the lowest risks for adverse events, (b) this drug is as good in safety and efficacy terms as any of the newer coxibs (which were designed to have lower incidence of adverse reactions), and serious events are rare, and (c) at OTC doses ibuprofen has low or at least amongst the lowest rating for risks of developing adverse reactions compared with other analgesics.

6.10 ADR Risks in Oriental Populations

Shi and co-workers (2003) reported a meta-analysis of adverse drug reactions and efficacy of NSAIDs in patients with osteoarthritis and rheumatoid arthritis in clinical trials that were reported in 19 articles in Chinese medical journals in the period 1990 2001. A total of 2,925 patients were enrolled for safety evaluation and 1,723 for efficacy. The therapeutic effectiveness rates were somewhat comparable, being in a range of about 65 79 % across all seven NSAIDs. Ibuprofen was amongst the more efficacious drugs with an efficacy rating of 77 % (95 % CI 70.7 83.8 %) and was only slightly, but not statistically significantly, exceeded by nimesulide with a rating of 79.8 % (95 % CI 75.7 84.0 %). The rates of ADRs were about 10 20 %, with ibuprofen being 16.7 %, all these reactions being time-dependent.

The same group performed a retrospective risk factor analysis of arthritic patients who were receiving long-term treatment over the period of Jan 1, 1996 to Jan 1, 2001 with ibuprofen which was obtained from outpatient clinics of hospitals in the Shanghai region (Shi et al. 2004a). Extensive clinical, demographic, and socio-economic data were collected, and risk factors were calculated using univariate correlation analysis. Of 447 patients enrolled in the study, 144 (32.3 %) had ADRs to ibuprofen. The female to male ratio was approximately 77 %. Approximately half of the patients had epigastric distress, and a further one-fifth had other GI symptoms. Malaena was present in two subjects (1.4 %). Overall, gastrointestinal toxicity was evident in 115 patients (79.9 %) and was severe in three subjects. Most of the ADRs were assessed to be mild (45.8 %) to moderate (44.1 %), and 9.7 % were severe. The dosage level varied considerably, from 300 to 1,800 mg/day. Risk factor analysis from this study is summarised in Table 6.14.

It is important to note that most of the patients were receiving second-line anti-rheumatic drugs as well as Chinese traditional medicines (CTM). This multiple use of drugs contributed to the incidence of ADRs, as noted in Table 6.15. Most of the patients were older (>55 years). The average period of dosage was around 2 years, with the shortest being 1 and the longest being 5 years. Various factors contributed to the development of ADRs, including smoking and stress. These data suggest that the patients were quite severely rheumatic, as they required other anti-rheumatic drugs along with a range of doses of ibuprofen. Being outpatients, they presumably were being treated for rheumatic conditions in the long-term. The period of dosage

Table 6.14 Odds ratios (OR) of risk factors from ADRs attributed to ibuprofen in rheumatic outpatients from hospitals in Shanghai

			95 % confidence interval	
No.	Variables	OR	Upper limit	Lower limit
1	Concomitant drug therapy	0.25	0.122	0.512
2	Smoking	0.564	0.334	0.915
3	Acceptance to unchangeable things	0.587	0.398	0.864
4	In general, how would assess your health	2.047	1.217	3.44
5	Do you drink cola everyday?	1.303	1.012	1.677
6	Compared to 6 months ago, how would you rate your health in general now?	1.006	1.341	2.352
7	Impact of health status on activity (first principle component)?	0.815	0.72	0.921
8	Impact of financial stress on your QOL	1.114	1.017	1.22

From Shi et al. (2004a). The variables relate to answers from questions presented to patients

with ibuprofen (1 5 years) was quite extensive. The occurrence of GI ADRs was similar to that in non-Chinese populations, although it is not known if the severity of the arthritic condition contributed to the development of the ADRs.

In another study in which the same methodology was employed, Shi et al. (2004b), examined the effects of 12 NSAIDs (including aspirin) in 1,002 patients with arthropathies, principally with RA (84.5 %) and a lesser number with OA (5.7 %) and other miscellaneous conditions. The study was a retrospective epidemiological survey performed according to ICH GCP guidelines, and involved structured patient interviews. Ibuprofen was the second most-frequently taken of the six NSAIDs. The occurrence of ADRs in patients who took ibuprofen was 32.3 %, compared with diclofenac 42.5 %, indomethacin 48.6 %, nimesulide 44.7 %, meloxicam 39.9 % and nabumetone 33.8 %. The most frequent ADRs were stomach discomfort (33.0 %), and other GI symptoms and gastric bleeding occurred in 2.1 % of patients. Most patients had taken the drugs for about 2 years. When the risk factors were taken into account, those patients that took ibuprofen showed significant benefit and quality of life benefits. The authors point out that this was the first and most extensive study of the effects of NSAIDs in chinese arthritic patients. The results show a pattern of ADRs not unlike that seen in studies in other parts of the world. Thus, the predominance of GI effects is apparent in rheumatic patients receiving NSAIDs. The occurrence of other ADRs seems lower than that seen in other studies, but this may reflect the sensitivity of the epidemiological procedures that were employed.

In a literature analysis of 80 cases of ADRs associated with ibuprofen, Liu and co-workers (2008) undertook a survey of Chinese medical journals using literature identified in the Chinese Journal Net. The patients who received ibuprofen had a wide variety of conditions. Most took a sustained-release formulation (76.25 %) and the remainder took conventional tablets (22.5 %) and other types. About 11 % of patients took combinations of ibuprofen with other drugs, including some NSAIDs. The most common ADRs were allergic reactions (36.25 %) and those

Table 6.15 Twenty five most frequent adulterants in traditional Chinese medicines

Rankings of adulterations	Detected synthetic therapeutic substances	Frequency of detection
1	Caffeine	213
2	Paracetamol/acetaminophen	167
3	Indomethacin	152
4	Hydrochlorothiazide	127
5	Prednisolone	91
6	Chlorzoxazone	87
7	Ethoxybenzamide[a]	66
8	Phenylbutazone	26
9	Betamethasone	23
10	Theophylline	22
11	Dexamethasone	20
11	Diazepam	20
13	Bucetin	19
14	Chlorpheniramine maleate	16
14	Prednisone	16
16	Oxyphenbutazone	14
17	Diclofenac sodium	13
17	Ibuprofen	13
19	Cortisone	11
19	Ketoprofen	11
21	Phenobarbital	10
22	Hydrocortisone acetate	9
24	Niflimic acid[a]	9
25	Diethylpropion	6
25	Mefenamic acid	6
25	Piroxicam	6
25	Salicylamide	6

[a]*Synthetic therapeutic substances not available in the United States.*

The remaining frequencies of adulterations detected (FAD) in this survey are:

FAD 4: methylprednisolone, nicotinamide

FAD 3: alluprinol, aminophylline, diphenhydramine, chlordiazepoxide, propanolol, raniditine

FAD 2: amino, aspirin, chlormezanone, dextromethorphan, methyltestosterone, oxymetholone, sorbic acid, stulfanilamide, thiamine disulfide, thiamin propyldisulfide

FAD 1: acetohexamide, barbital, benzafibrate, carbazepine, carisoprodol chloramphenicol, cholione bitartrate, cimetidine, cyproheptadine, dilantin, flopropeione, flourouracil, glibenamide, hydrazine, lorazepam, mephenesin, meprobamate, methocarbamol, phenacetin, phenylephrine, riboflavin, tetracycline, vitamin E

From Huang et al. (1997) with permission of Sage Publications, publishers of Journal of Clinical Pharmacology

in the digestive system (13.75 %), including four cases of GI haemorrhage, five cases of asthma (including one fatality), and a variety of other conditions. The ADRs occurred predominantly in the elderly, and most patients had rheumatic disease, with others having complex histories. Cases of hypersensitivity with angioedema and urticaria have been reported in patients from Singapore receiving

Table 6.16 Source of traditional Chinese medicines and frequency of adulterations from each source

Source	No. of samples (%)	No. of adulterated samples (%)	Percentage of adulteration
TCM hospitals	111 (4.3)	10 (1.6)	9
TCM clinics	860 (33.0)	177 (28.6)	20.6
TCM drugstores	478 (18.0)	122 (19.7)	25.5
Chiropractors	200 (7.7)	92 (14.9)	46
Herbalists	81 (3.1)	28 (4.5)	34.6
Peddlers	46 (1.8)	22 (3.6)	47.8
Quacks	179 (6.7)	59 (9.5)	33
Others	654 (25.1)	108 (17.5)	16.5
Total	2,609 (100.0)	618 (100.0)	23.7

TCM Traditional Chinese medicine
Reproduced from Huang et al. (1997) with permission of Sage Publications, publishers of Journal of Clinical Pharmacology

NSAIDs and paracetamol (Kidon et al. 2005). It may be that young Asian children who are atopic have hypersensitivity to NSAIDs. There was no attempt to link these hypersensitivity events to particular drugs. Likewise, retrospective studies have identified NSAIDs among a range of drugs that are associated with angioedema in Thai subjects, with diclofenac and ibuprofen being the most frequently implicated (Leeyaphan et al. 2010). The frequency of this association may be related to these drugs being employed most for therapy. HLA phenotypes and cytokines have been linked to drug sensitivities in Chinese populations (Kim et al. 2010), though the exact basis of this and drug types have not been fully evaluated.

6.11 Potential Concerns with Chinese Traditional and Herbal Medicines

The data available on the associations of ibuprofen with the occurrence of specific adverse events in Chinese populations is relatively limited. This is partly because of: (a) variations in the regulatory requirements for reporting ADRs in different countries with Chinese populations, (b) differences in the nature of the databases in various countries, whether these are maintained by government agencies and/or companies, and (c) the patterns of drug prescribing, dispensing and use of concomitant medications. The latter aspect is particularly relevant, since physicians in these countries frequently prescribe or recommend and patients frequently self-medicate with traditional medicines (CTM). Among these are a wide range of Chinese herbal medicines (Ergil et al. 2002), many of which are widely used for treating pain and inflammatory conditions, especially in Hong Kong (Lam et al. 1994). Chinese patients base their decisions about using herbal medicines on family traditions and self-medication, as well as professional and quasi-professional advice and

recommendations (Ergil et al. 2002). CTM is legal in Hong Kong, China, Taiwan, Vietnam, Japan, Korea, and many countries in Europe, as well as in the USA (Ergil et al. 2002). Quasi-professional advice is normally given in traditional herb stores, and this has been widespread among Chinese communities worldwide for centuries (Ergil et al. 2002). In contrast to the professional training by CTM practitioners, that of quasi-professionals varies considerably (Ergil et al. 2002). It is against this background of the established use of CTM that various potential aspects concerning herb ibuprofen interactions require consideration.

One major issue deserves consideration and this concerns the evidence for the widespread practice of adulteration of Chinese herbal preparations, both with NSAIDs (including ibuprofen) but also a wide range of other established medicines (Huang et al. 1997; Ergil et al. 2002; Li et al. 2007; Lu et al. 2010; Table 6.16) and natural product components (including steroids) which have varying anti-inflammatory activities (Zheng et al. 2003; Sato et al. 1998; Wang et al. 1997; Wang and Mineshita 1996; Gong and Sucher 2002; Yang et al. 2006; Liu et al. 2007, 2008; Xie et al. 2008; Wang et al. 2009; Xu et al. 2009a, b).

In an extensive survey of the adulteration of CTMs with established therapeutic medications, Huang et al. (1997) showed that these were available from both professional and quasi-professional sources as well as from herbalists, "peddlers", and "quacks" (Table 6.16).

The potential for untoward herb NSAID or herb medication interactions is highlighted in Table 6.17 (Ergil et al. 2002). The toxicity of aconitine (present in Cao Wu; Chan et al. 1993) is of particular concern, especially as small amounts of this material which have not been properly prepared (i.e., by aqueous hydrolysis to aqlycone) can be fatal. Gastrointestinal irritation is evident from the anthroquinone glycosides and oxalic in rhubarb (of Da Huang; Table 6.17) and may exacerbate the GI effects of ibuprofen and other NSAIDs. The vascular effects of *Ephedra sinica* and *Glyechiza glabara* (Table 6.18) might be expected to interact with the prostaglandin-inhibitory actions of NSAIDs such as ibuprofen. Moreover, the effects of herbal medicines on the functions of cytochromes P_{450} (Foster et al. 2002), especially the CYP2C9 (Mo et al. 2009) and CYP C28 (Lai et al. 2009) isoforms, may have particular consequences for the cytochrome oxidative metabolism of ibuprofen and other NSAIDs that are oxidised via these pathways.

These issues about herbal drug interactions that may affect the safety and efficacy of ibuprofen are highlighted because there may be a case for recommending that CTM practitioners, quasi-professionals, pharmacists, and herbalists should be specifically educated and trained to advise patients or customers that they should not take CTMs with ibuprofen and other NSAIDs or analgesics because of the risks of herbal preparations interacting in an untoward manner with these drugs. Moreover, labelling of packages and advice to patients taking ibuprofen (as well as other NSAIDs or paracetamol) should include specific warnings not to take these drugs with CTMs/herbal preparations.

Table 6.17 Risks of reactions or drug-herb interactions from constituents of Chinese herbal medicines (TCM)

TCM Medicinal agent	Common name	Plant species	Relevant constituent	Risk/interaction
Ma Huang	Ephedra	*Ephedra sinica*	Ephedrine, pseudoephedrine	Can exacerbate hypertension, palpitations, and dizziness. May interact with monoamine oxidase inhibitors, sympathomimetics, and epinephrine
Du Huo	Pubescent angelica	*Angelica pubescens*	Effect may be associated with furocoumarins	Potentially photosensitizing
Cao Wu	Aconite	*Aconitum carmichaeli*, *A. kuspexoffi*	Aconitine	Highly toxic in unprepared form; death can occur as a result of small doses of unprepared forms
Gau Cau	Licorice	*Glycrrhiza glabra*	Glycyrrhizin, glycrrhetinic acids	Hypokalemia, sodium retention producing hypertension, edema, and headache with prolongled use or a high dose. Synergistic effects with prednisolone, hydrocortisone, and thiazides. May counteract oral contraceptives
Da Huang	Rhubarb		Anthroquinone glycosides, oxalic acid	Irritation of gastrointestinal tract, abdominal cramping, nausea, kidney irritation; should be avoided in pregnancy
Ren Shen	Ginseng	Panax ginseng	Ginsenosides	Ginseng Abuse Syndrome (contraversial syndrome, since may due to adulterants; syndrome, rarely reported, is considered to include hypertension, anxiety, insomnia); interaction with phenelzine sulfate reported

TCM Traditional Chinese medicine

Reproduced from Huang et al. (1997) with permission of Sage Publications, publishers of Journal of Clinical Pharmacology

Table 6.18 Incidence rates of adverse experiences between ibuprofen and paracetamol by age

		Younger children		Older Children	
Body system	Type of AE	Ibuprofen (%) (n 7,381)	Paracetamol (%) (n 9,600)	Ibuprofen (%) (n 12,730)	Paracetamol (%) (n 3,133)
Any	Any	17.6*	15.0*	11.9*	10.7
Body as a whole	Pain in office	0.4*	0.2*	0.2	0.1
	Procedure	0.0**	0.01	0.01 n/c	0
Digestive	Any	3	2.1	2.1*	1.2
	Abdominal pain	0.5*	0.1	0.6*	0.2
Nervous	Hyperkinesia	0.7*	0.1	0.4	0.4
	Insomnia	0.6*	0.1	0.2	0.1
	Stupor	0.0**	0.01	0.0 n/c	0
	Twitch	0.0**	0.01	0.0 n/c	0
Respiratory	Rhinitis	2.1	3.5	1.1*	1.5
	Atelectasis	0.0*	0.03	0.0 n/c	0
Skin	Any	2.6*	1.3	1.3	1.4
	Sweat	0.05*	0	0.0 n/c	0
Special senses	Any	3.9**	3.8	2	1.9
	Otitis media	3.5*	3.4	1.7	1.4

*Statistically significant at $P \leq 0.05$.
P values based upon CMH test controlling for health status at enrolment and first time use of study education
**$P \leq 0.001$.
*$P \leq 0.01$ or 0.05.
N/c not computed

6.12 Adverse Events and Safety in Paediatric Populations

The safety profile of ibuprofen has been extensively evaluated in paediatric clinical trials of fever and/or pain and in a number of trials or in critical reviews (Walson et al. 1989; Rainsford et al. 1997, 1998, 1999, 2001; Diez-Domingo et al. 1998). All have shown the low incidence of serious and non-serious adverse events (AEs) with ibuprofen. While these data are useful, it is only in large-scale population-based studies that it is possible to accrue sufficient data to obtain a sound basis for safety evaluation.

In a series of publications, Lesko and Mitchell (1995, 1997; Lesko et al. 2002) have compared the safety of ibuprofen and paracetamol with a focus in particular on ibuprofen, in practitioner-based clinical trials, the methodologies of which were reviewed by Lesko and Mitchell (1995). These studies have been supported by both leading companies producing the antipyretics in the USA as well as the US FDA, US NIH, and other pharmaceutical companies supporting the Sloane Epidemiology Unit of Boston University School of Medicine (Brookline, MA, USA) where these studies have been based. Among these studies, the use of advisory groups has been employed, which helps retain the abilities to critically assess data and ensure proper conduct of trials.

In their practitioner-based population study of 2,015 primary care physicians throughout the continental United States of America, Lesko and Mitchell (1995) undertook a randomised, double-blind, office-based paracetamol (acetaminophen)-controlled trial: a total of 84,192 patients aged 6 months to 12 years of age were randomly assigned to receive ibuprofen at 5 or 10 mg/kg suspensions (Children's Motrin®, McNeill), or 12 mg/kg paracetamol suspension (Calpol®, Burroughs Wellcome) for the treatment of acute febrile illness. The study provided for a 4-week follow-up period to determine the occurrence of side-effects. The primary outcome measures were hospitalisations for acute GI bleeding, acute renal failure, and anaphylaxis. The occurrence of Reye's syndrome was also monitored. Secondary outcomes included identification of previously unrecognised serious reactions. Two patients died; one who had received paracetamol who died in a road accident, and the other who had ibuprofen who died from bacterial meningitis; both these fatalities could be considered to be unrelated to the drugs. A total of 1 % of the patients were admitted to hospital in the 4 weeks following enrolment. Four children were hospitalised for acute GI bleeding that was due to ibuprofen (two from 10 mg/kg and two from 5 mg/kg of the drug) giving a risk of GI bleeding as 7.2 per 100,000 (95 % CI 2 38 per 1,000,000) with the risk from paracetamol being zero, the difference being not statistically significant. Gastritis/vomiting was observed in 20 patients that had received ibuprofen, with a risk of 36 per 100,000 (95 % CI 22 55) and in six patients on paracetamol, with a risk of 21 per 100,000 (95 % CI 7.9 46). There were 24 patients who had received paracetamol who had asthma (RR = 85, 95 % CI 55 150) and 44 on ibuprofen (RR = 80 per 100,000; 95 % CI 57 110), thus showing there was no difference in risks between the two drugs. There was no risk from Reye's syndrome, acute renal failure, or anaphylaxis among 55,785 children that received ibuprofen. Low white blood cell count was observed in eight children that had received ibuprofen (but the causality could not be established) and none in the paracetamol group. The authors considered that the risks from less severe outcomes could not be ascertained because of the statistical statistical power of the study. This study attests to the low risks for serious GI, renal, or anaphylactic events from ibuprofen, and a lack of association with severe renal or asthmatic events.

In what is probably the largest study designed to investigate the safety of analgesics in children $\leq$2 years old, Lesko and Mitchell (1999) used data from the Boston Collaborative Fever Study in a total of 27,065 febrile children who were randomised to receive 5 mg/kg or 10 mg/kg ibuprofen or 12 mg/kg paracetamol suspensions.

The study was double-blind and practitioner-based, with children being eligible if, in the opinion of the attending physician, their illnesses warranted treatment with an antipyretic; duration and height of fever were not criteria for participation. Follow-up was achieved by mailed questionnaire or telephone interviews. The most common cause of fever in children $\leq$6 months was otitis media (45 %), upper respiratory tract infection (40 %), pharyngitis (15 %), lower respiratory tract infection (7.4 %), and gastro-intestinal infection (2.2 %). Data from the two doses of ibuprofen were combined because there were no discernible differences

between the groups; thus, the size of the ibuprofen group is about twice that of the paracetamol group.

The risk of hospitalisation for any reason in the 4 weeks after enrolment ($N = 385$ patients in total) was the same in the ibuprofen group (relative risk, RR=1.1 (0.9 1.3) compared with that of the paracetamol group as a reference, RR = 1.0). The absolute risks were 1.5 % (1.3 1.6, 95 % CI) for the ibuprofen group and 1.4 % (1.1 1.6 %) for the paracetamol group. None of the study participants was hospitalised for acute renal failure, anaphylaxis, or Reye's syndrome. Three children who received ibuprofen were hospitalised for evidence of GI bleeding; these were non-serious, and were resolved with conservative management. The risk of hospitalisation from GI bleeding was estimated to be 11 per 100,000 (95 % CI 2.2 32 per 100,000) for antipyretic assignment and 17 per 100,000 (95 % CI, 3.5 49 per 100,000) in those children $\leq$2 years who received ibuprofen.

Among children <6 months of age, there was no observed risk for hospitalisation for any of the primary outcomes.

The risks for hospitalisation for asthma/bronchiolitis for ibuprofen were 0.9 (95 % CI, 0.5 1.4) compared with paracetamol, a total of 65 children being hospitalised for this group of conditions (they were grouped together because of frequent misdiagnosis of these two conditions). Of nine children hospitalised for vomiting or gastritis, the risk did not vary according to antipyretic assignment.

Of the 385 who were hospitalised, those in whom creatinine levels were available (29 % of total) and was considered to be only of borderline statistical significance between the ibuprofen and paracetamol groups. There was no significant differences between these two treatment groups when age, weight, sex, or admission diagnosis of dehydration. When alternate cut-off points were used to define an elevated creatinine level (44 or 53 μmol/L for the two treatment groups respectively), there were no significant differences between the antipyretic groups.

While this was the largest controlled study ever undertaken of antipyretic use in children $\leq$6 months of age, the authors admitted that the power to detect serious adverse events is limited (especially those that occur infrequency). Some clinical and demographic information suggested that the study participants probably reflected a wide spread of febrile illnesses in the view of the authors, even though socioeconomic data were limited.

These data are important in showing that there is a remarkably low incidence of serious and even non-serious ADRs in children $\leq$2 years and especially $\leq$6 months who receive antipyretic therapy for febrile illness.

Another large investigation into the overall safety of ibuprofen in paediatric populations was performed by Ashraf et al. (1999). This study, known as the Children's Analgesic Medicines Project (CAMP), was a prospective, multicentre, all-comers, multi-dose, open-randomised and open-label study designed to compare the safety of ibuprofen (Children's Advil®) with that of paracetamol (Children's Tylenol®) given for relief of pain and/or fever. A total of 41,810 children aged 1 18 years were enrolled in a naturalistic outpatient paediatric setting (PEGASUS Research Inc., Salt Lake City, UT, USA) involving 68 clinics in the

USA. Among 30,144 children who took one dose of either ibuprofen or paracetamol, 14,281 were "younger" aged $\leq$2 years and 15,863 were "older" and aged 2 12 years. There were no serious AEs in $\geq$1 % of patients in either group. There were no cases of Reye's syndrome, gastric bleeding and/or ulceration, renal failure, necrotising fasciitis, Stevens Johnson, or Lyell's syndromes, anaphylaxis, or any other serious condition that are known to be associated with either drug in any population.

Small but clinically non-significant differences were observed in AEs in both age groups that received ibuprofen, compared with those that had paracetamol being 17.6 % vs 15 % respectively in the younger and 11.9 % and 10.7 % respectively in the older groups. The increased incidence of AEs in the ibuprofen groups was related to the greater disease severity in those groups. Four deaths were recorded (herpes encephalitis, sepsis due to *Staphyloccocus pneumoniae*, medulloblastoma, and sudden death syndrome) and were unrelated to the study medications but were related to the special senses followed by the digestive and respiratory systems and skin (all in 3 4 % approximately in the younger and slightly lower in the older group).

Chapter 7
Gastro-Intestinal Toxicity

Serious GI ADRs (upper GI bleeding and ulcers) are a major cause of concern and in the past three to four decades have aroused much interest among clinicians, experimentalists and regulators (Voutilainen et al. 1998; Wolfe et al. 1999; Lewis et al. 2005; Schaffer et al. 2006; Arroyo and Lanas 2006; Lanas et al. 2006; Laine et al. 2006; Lanas 2010). The problems are particularly apparent in rheumatic patients (Singh et al. 1996; Singh and Rosen Ramey 1998) and the elderly (Griffin et al. 1988; Beyth and Shorr 1999; Seinelä and Ahvenainen 2000; Mamdani et al. 2002; Kean et al. 2008). Definitions vary on what constitutes the elderly, but most agree on >65, a time that seems to have been derived over a century ago from Otto von Bismarck who required Prussian officers to retire at this age (Kean and Buchanan 1987; Buchanan 1990). Early studies indicated that ibuprofen was well-tolerated in elderly patients (Buckler et al. 1975).

A range of factors influence the development of NSAID-associated GI ulcerations and bleeding (Table 7.1; Figs. 7.1 and 7.2). This makes it difficult to ascribe a quantitative component of the NSAID to the occurrence of serious GI events.

Several studies have reported that prescription doses of ibuprofen produce time- and dose-dependent blood loss (assessed using the radiochromium blood loss technique) from the GI tract of volunteers or patients (Teixeira et al. 1977; Warrington et al. 1982; Aabakken et al. 1989a; Hunt et al. 2000; Bowen et al. 2005) and mild moderate endoscopic changes compared with other NSAIDs in fasted human volunteers (Lanza et al. 1979, 1981, 1987, 2008; Aabakken et al. 1989a; Friedman et al. 1990b; Bergmann et al. 1992; Roth et al. 1993; Müller et al. 1995) or those with rheumatic diseases (Teixeira et al. 1977). There appears to be an inherent variability in the blood loss both within and between subjects (Bowen et al. 2005), the reasons for which are not fully understood. The extent of the loss of blood may be overestimated using the radiochromium technique, as a consequence of loss of ^{51}Cr from the labelled red cells and subsequent biliary excretion of the radiolabelled chromium (De Medicinis et al. 1988; Rainsford 2004a). Moreover, some drugs such as the salicylates are choleretics and may stimulate biliary flow (Schneider et al. 1990; Rainsford 2004a). The extent of the mucosal changes

K.D. Rainsford, *Ibuprofen: Pharmacology, Therapeutics and Side Effects*,
DOI 10.1007/978 3 0348 0496 7 7, © Springer Basel 2012

Table 7.1 Risk factors for the development of NSAID associated gastro duodenal ulcers

Established risk factor	Possible risk factor
Advancing age	High alcohol consumption
High dose NSAID or paracetamol	Cigarette smoking
Use of more than two NSAIDs	*Helicobacter pylori* infection
Concurrent paracetamol	
Concurrent anti coagulants	
Concurrent aspirin (even low dose)	
Prior history of peptic ulcer disease	
Rheumatoid arthritis	

Based on Wolfe et al. (1999), Wolfe (2003) and Laine (2001); modified and with additional information from Rainsford (2004a, 2005b)

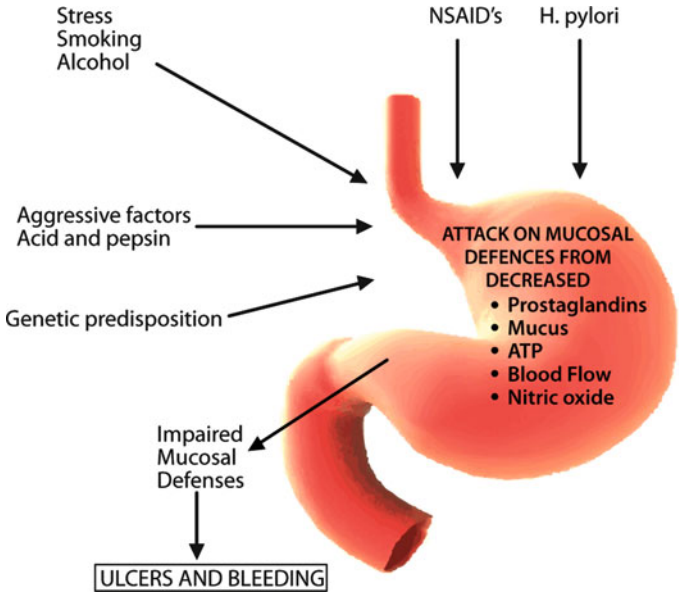


Fig. 7.1 Summary of factors involved in the development of gastric mucosal injury. Based on Lanas (2010) and Rainsford (2009)

(lesions, ulcers) compared with blood loss varies considerably with different NSAIDs, and is not always comparable (Aabakken et al. 1989b). The blood loss from ibuprofen is relatively low compared with other NSAIDs, but is above that of placebo and paracetamol (Rainsford 1999c).

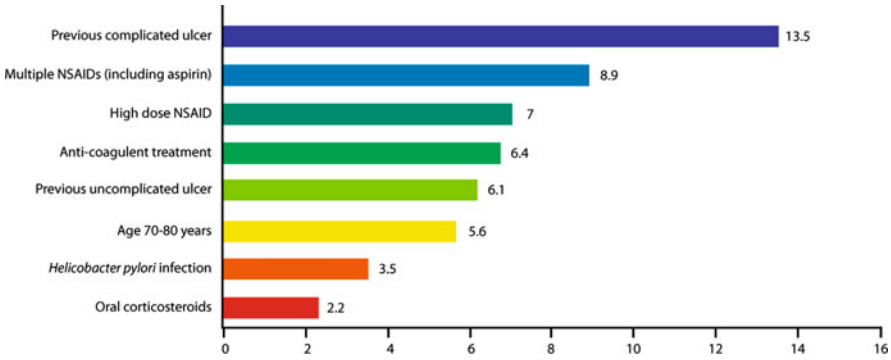


Fig. 7.2 Relative contributions of complicating factors in the occurrence of upper GI haemorrhage or ulcers. Reproduced from Lanas (2010) with permission of Oxford University Press, publishers of Rheumatology

7.1 Epidemiological Studies

A considerable number of population studies have been reported over the past two to three decades comparing the occurrence of serious GI events from ibuprofen and other NSAIDs, at prescription-level dosages, with some studies being dose-ranging (Kaufman et al. 1993; Langman et al. 1994; Henry et al. 1996; Henry and McGettigan 2003; Hippisley-Cox et al. 2005; Thomsen et al. 2006; see also Table 7.2). The study designs, outcome measures, and variables (dosage and duration) vary considerably among these studies. Some measures have included the occurrence of peptic ulcer bleeds (PUBs), upper GI bleeding, ulcers viewed at endoscopy (usually investigated as a consequence of clinical symptoms or as part of a planned investigation), or the more general grouping of "serious events". While these studies vary considerably, they are useful in comparing the risks of serious GI events attributed to ibuprofen with that of a range of other NSAIDs with known ulcerogenicity.

A summary of some of the population studies reported in the 1990s in the period before the introduction of the newer class of coxib NSAIDs is shown in Table 7.2.

In a meta-analysis of published studies comparing the GI ADRs for various NSAIDs, Henry et al. (1996, 1998) were able to show that the relative risks of these events from different NSAIDs ranged considerably (Fig. 7.3). They found that ibuprofen had the lowest risks for developing GI complications (Fig. 7.4).

Henry and co-workers also observed (a) dose-related occurrence of GI complications with ibuprofen, naproxen, and indomethacin (Fig. 7.4), and (b) the ranking of GI complications was directly related to the plasma elimination half-life ($t_{1/2}$) of the individual NSAIDs (Table 7.3). As in the overall analysis, ibuprofen had the lowest rates of occurrence of GI complications, this being attributed to its short $t_{1/2}$ (~2 h). Thus, there is a good pharmacokinetic rationale to account for the low GI ADRs with ibuprofen.

Table 7.2 Serious outcome gastro intestinal toxicity ranking of NSAIDs

Drug	Kaufman et al. (1993)	Henry et al. (1993)	Langman et al. (1994)	Rodriguez et al. (2001)	Henry et al. (1996)	MacDonald et al. (1997)
Aspirin					10	
Azapropazone			1		1	2
Diclofenac	6	7	6	7	9	4
Diflunisal		1		8	7	
Fenbufen						11
Fenoprofen	4			5	11	1
Ibuprofen	7	8	7	9	12	8
Indomethacin	5	3	4	4	5	9
Ketoprofen	1	2	2	2	2	5
Nabumetone						10
Naproxen	3	4	5	3	6	6
Mefenamic acid						7
Piroxicam	2	5	3	1	3	3
Sulindac		6		6	8	
Tolmetin					4	

Toxicity rankings of NSAIDs, with those associated with the greatest risk of ulcer complication being given the number 1. The studies used different methodologies. Reproduced with permission of the publishers from Rainsford (2009)

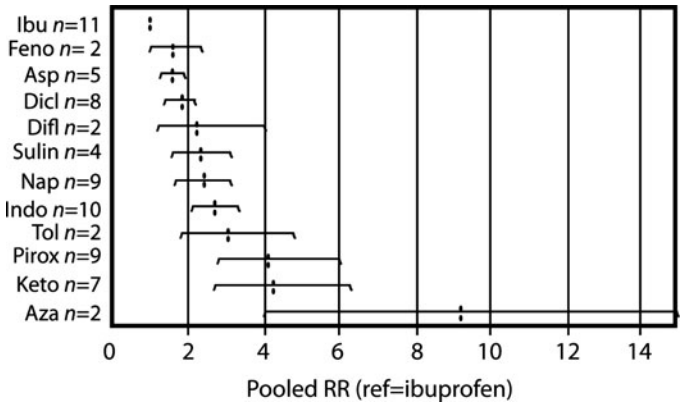


Fig. 7.3 Redrawn from Henry et al. (1998)

Among the most comprehensive studies that have been performed to evaluate overall adverse drug reactions in European populations was the study by Lugardon and co-workers (2004). These authors undertook an analysis of spontaneous reports to the French pharmacovigilance network, which is probably one of the most extensive and comprehensive pharmacovigilance systems in Europe. A summary of the data shown in the Table 7.4 compares the reporting odds ratios for GI events of heteroarylacetic acids, which include ibuprofen, diclofenac, naproxen, and ketoprofen with that of the two principal coxibs, rofecoxib and celecoxib, as well

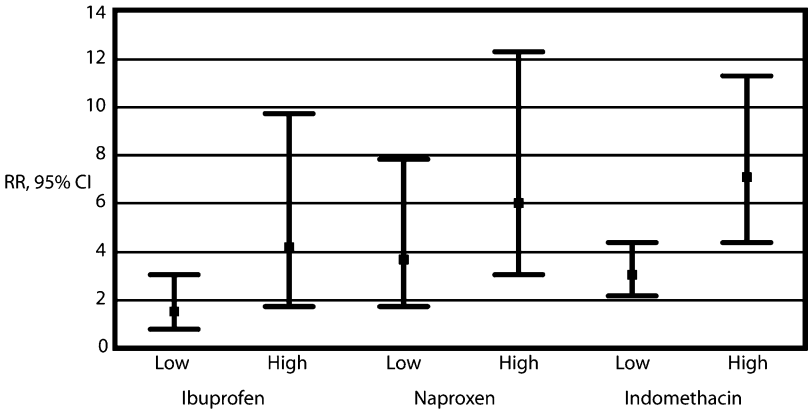


Fig. 7.4 Dose related development of GI haemorrhage associated with low and high doses of ibuprofen, indomethacin and naproxen. Redrawn from Henry et al. (1998)

Table 7.3 Ranking of GI complications from NSAIDs with plasma elimination half life ($t_{1/2}$) of the drugs

GI safety, dose and plasma half life of NSAIDs
Ranking of RR of Ulcers compared with $t_{1/2}$ (h):
Ibuprofen (2.5) < Diclofenac (1.5 5) < Diflunisal (10.8) < Fenprofen (2.2) < Aspirin (0.5 4.5) < Sulindac (14.0) < Naproxen (14.0) < Indomethacin (3.8) < Piroxicam (48.0) < Ketoprofen (8.5) < Tometin (6.8) < Azapropazone (22.0)
Dose relationships low compared with high dose:
Ibuprofen RR 1.8 4.0
Naproxen RR 3.8 6.0
Indomethac in RR 2.3 6.5

From: Henry et al. (1998) and from Rainsford (2009) with permission of the publishers, Kluwer Academic Publishers, now owned by Springer AG.

as the oxicams, principally meloxicam, piroxicam, and tenoxicam. The unadjusted and adjusted odds ratios for ibuprofen ADRs are the lowest amongst all the drugs that were studied by Lugardon and co-workers (2004).

A similar conclusion can be drawn from the case-control study of Laporte et al. (2004), as shown in Table 7.5.

Case-control investigations by Garcia-Rodriguez and Hernandez-Diaz (2001) using data from the UK General Practice Database also show the low risks of GI events with ibuprofen in contracts with those from various doses and periods of taking NSAIDs and aspirin (Table 7.6). These data have also instructive in highlighting that high-dose paracetamol (hitherto regarded as a GI-safe drug) when taken at doses of >2 g/day alone or in combination with NSAIDs is associated with relative risks >2 (alone) or >6 (combination with NSAIDs) of causing haemorrhage.

In rheumatic patients, Singh (2000) has produced data from the ARAMIS (a rheumatic disease patient) database showing relatively high risks of GI bleeding (or peptic ulcer bleeds) from all NSAIDs, with little difference between individual

Table 7.4 Adverse drug reaction reporting odds ratio (OR) (with their 95 % confidence interval) according to main classes of non steroidal anti inflammatory drugs (NSAIDs) from the French pharmacovigilance database

Drugs	Adjusted OR[a] (95 % CI)	Adjusted OR[b] (95 % CI)
Coxibs	4.6 (3.3 6.5)*	14.9 (9.3 23.7)*
Rofecoxib	5.2 (3.1 8.7)*	21.0 (10.6 41.6)*
Celecoxib	3.7 (2.4 5.8)*	11.7 (6.6 20.9)*
Oxicams	12.2 (6.7 22.2)*	25.3 (11.9 53.6)*
Heteroarylacetic acids		
Ibuprofen	4.5 (3.2 8.8)*	7.3 (3.2 16.6)*
Diclofenac	3.9 (2.1 7.2)*	9.2 (3.8 22.2)*
Naproxen	10.6 (4.7 23.7)*	17.9 (6.7 47.6)*
Ketoprofen	8.6 (5.3 13.9)*	19.9 (10.7 37.0)*

*$P < 0.0001$.

[a]Adjustment for matching factors (age, gender, period of occurrence).

[b]Adjustment for matching factors (age, gender, period of occurrence) and confounding factors (regional pharmacovigilance centre, work place of health professional and drug exposure: anticoagulants, antiplatelet drugs, aspirin, gastroprotective and other NSAIDs).

Reproduced from Lugardon et al. (2004) with permission of Springer, publishers of the European Journal of Clinical Pharmacology

Table 7.5 Gastro intestinal bleeding from NSAIDs in a multicentre case control study in Spain and Italy

Drug	Cases [no (%)]	Controls [no (%)]	Odds ratio (95 % CI)	Population attributable risk (%)
NSAIDs				
Aceclofenac	15 (0.5)	30 (0.4)	1.4 (0.6, 3.3)	
Aspirin (acetylsalicylic acid)	591 (21.1)	403 (5.7)	8.0 (6.7,9.6)	18.5
Dexketoprofen	16 (0.6)	8 (0.1)	4.9 (1.7, 13.9)	0.5
Diclofenac	100 (3.6)	98 (1.4)	3.7 (2.6, 5.4)	2.6
Ibuprofen	60 (2.1)	58 (0.8)	3.1 (2.0, 4.9)	1.5
Indomethacin	29 (1.0)	16 (0.2)	10.0 (4.4, 22.6)	0.9
Ketoprofen	16 (0.6)	9 (0.1)	10.0 (3.9, 25.8)	0.5
Ketorolac	33 (1.2)	6 (0.1)	24.7 (8.0, 77.0)	1.1
Meloxicam	14 (0.5)	11 (0.2)	5.7 (2.2, 15.0)	0.4
Naproxen	52 (1.9)	27 (0.4)	10.0 (5.7, 17.6)	1.7
Nimesulide	48 (1.7)	46 (0.6)	3.2 (1.9, 5.6)	1.2
Piroxicam	119 (4.3)	40 (0.6)	15.5 (10.0, 24.2)	4
Rofecoxib	10 (0.4)	10 (0.1)	7.2 (2.3, 23.0)	0.3
Other NSAIDs	34 (1.2)	33 (0.5)	3.6 (2.0, 6.8)	0.9
NSAIDs + antiplatelet drugs	140 (5.0)	54 (0.8)	16.6 (11.3, 24.2)	4.7
Analgesics				
Lysine clonixinate	26 (0.9)	47 (0.7)	1.3 (0.7, 2.6)	
Metamizole	117 (4.2)	155 (2.2)	1.9 (1.4, 2.6)	2
Paracetamol (acetaminophen)	376 (13.4)	612 (8.6)	1.2 (1.0, 1.5)	
Propyphenazone	17 (0.6)	38 (0.5)	1.3 (0.6, 2.8)	

From: Laporte et al. (2004). Reproduced with permission of Springer International Publishing AG, for Adis Press, publishers of Drug Safety

Table 7.6 Epidemiological data from General Practice Database (UK) and other sources on peptic ulcer bleeding risks from aspirin and other NSAIDs and paracetamol

Drug	Usage/factor	Relative risk	
Ibuprofen		**Lowest risk (dose-dependent)**	**~1.0 2.0**
Aspirin	Overall use	Users	2.0
		Non users	1.0
		Recent users	1.5
		Past users	1.1
	Dose	75 300 mg/day	2.1
		>400 mg/day	3.1
		<50 mg/day	0.7
	Period of use	1 60 day	4.5
		61 180 day	2.7
		181 730 day	1.0
		>730 day	1.6
Paracetamol		<1 g/day	1.0
		1 2 g/day	0.9
		2 4 g/day	3.4
		>4 g/day	6.5
		2 g with NSAID	4.2
		>2 g with NSAID	13.5
		cf. NSAID alone	3.5
NSAIDs		Low dose	2.5
		High dose	5.0
	Duration	1 30 days	4.3
		>730 days	3.5
	Formulation	Plasma $T_{½}$	
		<12 h (high dose)	4.2
		≥12 h (slow release)	5.4
			6.2
		<12 h (low dose)	2.4
		≥12 h	2.8

Data from Garcia Rodriguez and Hernandez Diaz (2001). Reproduced with permission of the publishers from Rainsford (2009)

NSAIDs (including ibuprofen). Lower risks were associated with paracetamol. While there have been claims made by this author that the GI risks are similar to those from OTC dosages of these analgesics, there is little information available on their duration of use, concomitant medications, and other risk factors.

More insight into the GI risks associated with OTC analgesics/NSAIDs has been provided by Lewis and co-workers (2005) in a case-control study of hospitalised patients recruited from 28 hospitals. The cases ($N = 359$) had upper GI bleeding, benign gastric outlet obstructions or perforations, while controls ($N = 1{,}889$) were obtained from random-digit phone dialling in the same region. Use of OTC doses of non-aspirin NSAIDs ≥4 days in the past week was associated with an adjusted odds ratio of 1.83 (95 % CI 1.14 2.95), the risks from ibuprofen being much lower. Risks were increased with higher doses of the drugs, confirming what has been well-

Table 7.7 Upper gastro intestinal bleeding from low dose (OTC ibuprofen and naproxen) in relation to age in UK population

Drug (daily dose)	Age (years)	Number of users	Number of cases	Incident rate/104 users	95 % CI
Ibuprofen (<1,200 mg)	<70	47,323	1	0.2	0.01 1.20
(90 % used 1,200 mg)	≥70	7,505	1	1.3	0.03 7.40
	All	54,830	2	0.4	0.04 1.30
Diclofenac (<75 mg)	<70	18,407	3	1.6	0.3 4.80
(90 % used 75 mg)	≥70	3,739	1	2.7	0.1 14.9
	All	22,946	4	1.8	0.3 4.6
Naproxen (<750 mg)	<70	39,720	5	1.3	0.4 2.9
(60 % used 750 mg)	≥70	7,199	6	8.3	3.1 18.1
	All	46,919	11	2.3	1.2 4.2

Overall, ibuprofen showed the lowest risks for upper GI bleeds, with an increased risk in over 70 year olds, a trend which was also seen with the other frequently prescribed NSAIDs
Data derived from the UK General Practice Research Database (GPRD) from patients that received prescriptions for ibuprofen, diclofenac, and naproxen for 30 days
From: Pérez Gutthann et al. (1999)

known about the dose response relationships among most NSAIDs being associated with serious GI AEs (Henry et al. 1996, 1998).

Estimations of the relationship between age and dose-related occurrence of upper GI bleeding can be seen in data from the UK General Practice Research Database (Table 7.7) which was analysed by Pérez-Gutthann and co-workers (1999).

7.2 GI Risks in Coxib Studies at Prescription Doses

The data on ulcer complications in the CLASS study observed at 6 months showed there were differences between celecoxib and NSAIDs (Silverstein et al. 2000). However, as pointed out by Jüni et al. (2002) these differences were not apparent at 12 months (Table 7.8), suggesting there are time-dependent factors that are significant in considering ulcer incidence with both coxibs and NSAIDs. The clinical significance of these data, like that from other long-term studies, is that when coxibs are taken for relatively short periods of time (2 4 weeks) they are less likely to cause less ulcer complications than NSAIDs such as naproxen and diclofenac than if they are taken for several months or longer. There is also the issue of what has been described as "channelling", where patients with a history of GI complaints or GI ulcer disease may be prescribed coxibs in the belief that they will be "gastric-safe"; this may be such that benefits for using these drugs may be less apparent and the patients may require anti-ulcer co-therapy (e.g., with H_2 receptor antagonists or PPIs). The cost benefit of coxib therapy may prove less favourable, as not only are these drugs notably more expensive than conventional NSAIDs, but if PPIs or other anti-ulcer therapies have to be employed they may as well be given with cheaper

Table 7.8 Summary of adverse events in the CLASS study

Event %	Celecoxib	Diclofenac	**Ibuprofen**
GI	45.6	55.0	**46.2**
→withdrawal	12.2	16.6*	**13.4**
Renal	6.8	6.7	**10.3***
→withdrawal	1.0	0.6	**1.3**
CV non aspirin	1.6	1.2	**0.4**
Hepatic	1.8	6.9*	**1.9**
→withdrawal	0.3	3.5*	**0.3**

*Significantly different compared with celecoxib. $p < 0.05$
Based on data published by Silverstein et al. (2000). Reproduced with permission of the publishers from Rainsford (2009)

Table 7.9 Estimation of serious gastrointestinal reactions from the CLASS trial of celecoxib compared with NSAIDs

In the CLASS Trial (non aspirin using patients only)			
Percentage of patients with serious NSAID associated gastrointestinal complications was:			
Celecoxib	0.44 % diclofenac	0.48 %	
(no statistically significant difference between diclofenac and celecoxib)			
Celecoxib	0.44 % Ibuprofen	1.14 %	
ARR	1.14 %	0.44 %	0.7 %
NNT	1/0.7 %	1/0.007	143
RRR	1.14 %	0.44 %/1.14 %	61 %

Results are reported as serious NSAID associated gastro intestinal complications (i.e., gastro intestinal bleeds, perforations, and obstructions) per 100 patient years. *ARR* absolute risk reduc tion, *RRR* relative risk reduction, *NNT* number needed to treat
From: Schoenfeld (2001). Reproduced with permission of Springer, publishers of Inflammopharmacology

NSAIDs, especially those with a lower propensity to cause CV complications (e.g., naproxen) or combinations with aspirin for cardioprotection.

These calculations (Table 7.9) show that although the percentage of relative risk reduction (RRR) for celecoxib cf. NSAIDs (ibuprofen, diclofenac) is 61 % and for rofecoxib cf. naproxen is 60 %, the values for absolute risk reduction (ARR) are relatively small, being 0.7 % and 0.8 % respectively for the two trials. The latter values represent the fact that the percentage incidence of GI complications for the NSAID as well as for the two coxibs is in the low end range of 0.4 1.14 %, which are very low percentages. Thus, with such small differences, calculations of RRR are meaningless, and give a false impression of improved benefit to the GI tract of the coxibs. This approach of using RRR percentage benefits has been extensively exploited in published data on coxib trials and must, therefore, be regarded as suspect statistical treatment of data which has little relevance clinically. Indeed *clinical significance* in many coxib trials has rarely been considered in contrast to *statistical significance* (Rainsford 2009).

In another large scale coxib study, Sikes et al. (2002) compared the incidence of gastric and duodenal ulcers from two dose levels of valdecoxib (10 and 20 mg/day)

Table 7.10 Percentage incidence rate of upper gastrointestinal ulcers

	Placebo	Valdecoxib 10 mg daily	Valdecoxib 20 mg daily	Ibuprofen 800 mg three times daily	Diclofenac 75 mg twice daily
12 week cohort					
No. patients	123	142	157	149	145
Gastroduodenal	7	5	4	16[a,b,c]	17[a,b,c]
Gastric	5	4	4	14[a,b,c]	14[a,b,c]
Duodenal	2	1	1	4	5[c]
ITT cohort [*n* (%)]					
No. patients	178	189	198	184	187
Gastroduodenal	4	4	4	14[a,b,c]	13[a,b,c,]
Gastric	3	3	3	11[a,b,c]	11[a,b,c]
Duodenal	2	1	1	3	5[c]

[a]Significantly different from placebo at $P > 0.05$.
[b]Significantly different from valdecoxib 10 mg daily at $P > 0.05$.
[c]Significantly different from valdecoxib 20 mg daily at $P > 0.05$.
12 week cohort includes patients who took the study medication for the entire 12 week period
ITT cohort includes all patients who had a post treatment endoscopy irrespective of whether they completed 12 weeks of treatment
Summary of data in modified form from Sikes et al. (2002) with permission of Wolters Kluwer Health Publishers of European Journal of Gastroenterology and Hepatology

with that from ibuprofen 2,400 mg/day and diclofenac 150 mg/day taken for 12 weeks. This study is shorter than the other coxib studies reviewed previously. There is a trend noted by Jüni et al. (2002) for differences in GI events between celecoxib and the NSAIDs to become smaller with time, especially after 6 months therapy, coinciding with an increase in GI events from celecoxib approaching those from the NSAIDs. Thus, at the shorter time period it might have been expected that if valdecoxib had a favourable GI profile, it would show a lower incidence of GI events compared with the two comparator NSAIDs. The data in Table 7.10 shows that there was a somewhat higher incidence of gastric and duodenal ulcers and all GI ulcers from ibuprofen compared with valdecoxib, but these were fewer than seen with diclofenac.

This study is of significance in that there was separate analysis of ulcer incidence in (a) *Helicobacter pylori* negative and *H. pylori* positive subjects, and (b) aspirin takers (for CV prophylaxis) and non-takers.

The data in Table 7.11 shows that *H. pylori* status made little if any difference to the ulcer incidence in subjects who received any of the drugs, but taking aspirin did increase the incidence of ulcers in the ibuprofen and naproxen groups, and to a lesser extent in the valdecoxib groups.

From the point of view of GI safety, there may have been pathological consequences of hepato-renal ADRs and hypertension that contributed to the vascular aetiology of upper GI ulcer disease (Fig. 2.6), as well as the consequences of treatment with diuretics and anti hypertensive drugs (which, as noted earlier, increase the risk for developing ulcers) as well as interactions between NSAIDs and drugs that patients with hepato-renal conditions and hypertension received for

Table 7.11 Gastroduodenal ulcer incidence [*n* (%)] by aspirin use, age, or *Helicobacter pylori* status

	Placebo	Ibuprofen 800 mg three times daily	Diclofenac 75 mg twice daily	Valdecoxib 20 mg daily
H. pylori positive	4/46 (9)[a,b]	9/45 (20)	11/54 (20)	2/49 (4)[a,b]
H. pylori negative	4/119 (3)[a,b]	15/123 (12)	14/122 (12)	5/136 (4)[a,b]
H. pylori status unknown	0/2 (0)	0/7 (0)	0/5 (0)	0/6 (0)
Taking aspirin	0/26 (0)[a,b]	10/31 (32)[c]	10/33 (30)[c]	2/29 (7)[a,b]
Not taking aspirin	8/141 (6)[a,b]	14/144 (10)	15/148 (10)	5/162 (3)[a,b]
Age ≥65 years	4/65 (6)[a,b]	15/71 (21)[d]	14/78 (18)	3/67 (5)[a,b]
Age >65 years	4/102 (4) [a,b]	9/104 (9)	11/103 (11)	4/124 (3)[a,b]

[a]$P \leq 0.014$ vs ibuprofen, [b]$P \leq 0.008$ vs diclofenac; [c]$P \leq 0.017$ vs not taking aspirin; [d]$P \leq 0.025$ vs age < 65 years.

Summary of data in modified form from Sikes et al. (2002). Reproduced in modified form by permission of Wolters Kluwer Health Publishers of European Journal of Gastroentrology and Hepatology

treatment of these conditions. In the end, from what has emerged in the safety analysis of the coxibs (summarised in Table 7.7), it is clear that the benefits of what now are classed as "first generation" coxibs (celecoxib, rofecoxib, valdecoxib) may have been marginal compared with *some* conventional NSAIDs, among which etodolac, ibuprofen, nabumetone, and possibly diclofenac (although the intestinal ulceration and hepatotoxicity from this drug limits it being considered to have a favourable safety profile).

An interesting and possibly important point that should be considered is the arthritic condition in the CLASS study, as well as other studies with coxibs. Patients in the VIGOR study only had RA, whereas those in the CLASS study had both RA and OA. It has been claimed that there were no differences in ulcer complications between patients with OA versus RA. This is in one sense surprising, since as noted earlier it has been speculated that patients with RA may be more susceptible to NSAIDs than those with OA. It could be that the selection criteria for patients entered in the CLASS Study were such that RA as well as OA patients were relatively "fit", and without complicating chronic conditions that inevitably occur in older more infirm patients, especially those with RA.

Indeed the ulcer incidence in the CLASS study (Tables 7.8 and 7.9) as well as in the meta analysis of celecoxib trials by Moore et al. (2005) reveals a remarkably low incidence in placebo and NSAID groups. This gives support to the view that patients selected for inclusion in these studies may have been of relatively favourable health. Another issue is that if there were any real differences in data of ulcer complications in, say, a proportion of patients with RA versus those with OA, these could have had been disguised in the grouping of data together such as in the CLASS results.

In conclusion, the epidemiological and large-scale clinical trials show that ibuprofen has amongst the lowest risk of NSAIDs for serious GI events. The additional intake of aspirin may raise the risk of GI complications in a similar way to that seen with celecoxib and rofecoxib.

7.3 GI Symptomatic Adverse Reactions

Meta-analysis of the tolerability and adverse events from a range of trials of celecoxib compared with NS-NSAIDs, paracetamol, and placebo (using data from the published and unpublished trials from Pfizer) (Moore et al. 2005) revealed some interesting features and trends concerning the occurrence of GI symptoms, notably nausea, dyspepsia, diarrhoea, abdominal pain, and vomiting. These constitute main reasons (other than ulcer/bleeds or other serious ADRs) for withdrawal from therapy, and indeed the data by Moore et al. confirmed this pattern.

Data on the GI symptoms from NSAIDs and coxibs summarised in the report by Moore et al. (2005) highlight that (1) the occurrence and relative risks of most GI symptoms in patients receiving celecoxib, rofecoxib, or paracetamol are greater than that of placebo, (2) while there are trends for a lower incidence of some symptoms with low-dose celecoxib, the differences are less distinct with higher-dose celecoxib, and (3) the data on confidence intervals in relative risks with most comparisons often overlaps to the extent that it is doubtful whether any differences, especially those favouring celecoxib, have any meaning. Moore et al. (2005) noted that the proportion of patients having dyspepsia was about 7 %, and that there were no differences in comparison with placebo, paracetamol, or rofecoxib, but there were more patients on NSAIDs. Celecoxib was responsible for abdominal pain in about 5 % of patients, there being no difference compared with placebo or paracetamol, but more patients on NSAIDs and rofecoxib experienced this adverse effect. In these and other GI symptomatic effects as well as overall GI tolerability, there were trends in favour of celecoxib in comparison with the other treatments, but the 95 % confidence intervals for relative risk often overlapped those of comparator drugs. Making much of what are relatively small values for incidence and percentage differences of symptomatic GI ADRs such as that of clinical ulcers and bleeds in this meta analysis (Moore et al. 2005) is probably of limited value.

7.4 GI Events at OTC Dosages

GI symptoms (nausea, epigastric or abdominal pain, dyspepsia, diarrhoea, flatulence, and constipation) are among more frequent reactions observed with OTC use of ibuprofen as well as with paracetamol and aspirin, and generally the symptoms are of the same order as in subjects who have received placebo (Rainsford et al. 1997, 2001; Doyle et al. 1999; Kellstein et al. 1999; Ashraf et al. 2001; Le Parc et al. 2002; Boureau et al. 2004; Biskupiak et al. 2006).

The occurrence of GI symptoms with ibuprofen has often been found to be lower than with aspirin, and comparable with those from paracetamol (Rainsford et al. 1997; Moore et al. 1999; Le Parc et al. 2002; Boureau et al. 2004). Serious GI reactions are rare, and have not been reported in significant numbers in trials with OTC ibuprofen (Doyle et al. 1999; Kellstein et al. 1999; Ashraf et al. 2001;

Table 7.12 Endoscopically observed ulcers and erosions from OTC ibuprofen compared with naproxen and celecoxib

	Treatment (dose mg/d)			
	Placebo	Ibuprofen (1200)	Celecoxib (200)	Naproxen (1000)
No. subjects	40	39	39	40
No. ulcers/subject (range)	0.03(0 1)	0.59(0 15)	0.3(0 1)	1.03(0 20)
No. erosions/subject (range)	0	0.62(0 9)	0.15(0 3)	3.98(0 21)

Normal healthy volunteers (*N* 20) treatment group took the drugs for 10 days in a US based multi centre, outpatient randomised, double blind, 2 way crossover study with a 4 5 week washout period. Although subjects were stratified for presence of *H. pylori*, this varied from 13 to 26.9 % subjects
From: Scheiman et al. (2004)

Le Parc et al. 2002; Boureau et al. 2004). Thus, it may be concluded that GI events are essentially non-serious with OTC ibuprofen, are probably reversible upon cessation of the drug (an action likely to be taken by most subjects), and are no different than with paracetamol and less so than with aspirin. Epidemiological studies in general practice patients (Table 7.7; Pérez-Gutthann et al. 1999) have shown that there is a small age-related increase in GI bleeding in patients who took ibuprofen at about OTC doses, but this is a small risk and much less than with diclofenac and naproxen, the latter being amongst the most frequently prescribed NSAIDs in general practice after ibuprofen.

Endoscopy studies using OTC doses of ibuprofen have shown that there is a small increase in lesions or ulcers above placebo or low-dose celecoxib, but less so than observed with naproxen (Scheiman et al. 2004; Table 7.12). While this study was performed in healthy volunteers, an appreciable proportion of these subjects were infected with the ulcerogenic bacterium *H. pylori*. The data from subjects that had taken ibuprofen overlapped that from celecoxib in respect of confidence intervals, showing that there was no significant difference between these treatment groups and placebo. It should also be noted that subjects undergoing endoscopy will have been fasted overnight, and the procedure can be regarded as stressful such that it could have led to exacerbation of mucosal ulceration from the NSAIDs.

7.5 GI Safety in Paediatric Populations

In the large-scale paediatric study by Lesko and Mitchell (1995), four children were hospitalised for acute GI bleeding that was due to ibuprofen (two from 10 mg/kg and two from 5 mg/kg of the drug), which gives a risk of GI bleeding of 7.2 per 100,000 (95 % CI 2 38 per 1,000,000 patients), with the risk from paracetamol being zero, the difference being not statistically significant. Gastritis/vomiting were observed in 20 patients that had received ibuprofen, with a risk of 36 per 100,000

patients (95 % CI 22 55), and in six patients on paracetamol, with a risk of 21 per 100,000 patients (95 % CI 7.9 46).

In their later study on ≤2 year olds, Lesko and Mitchell (1999) observed that three children who received ibuprofen were hospitalised due to evidence of GI bleeding, these cases being non-serious and resolved with conservative management. The risk of hospitalisation from GI bleeding was estimated to be 11 per 100,000 (95 % CI 2.2 32 per 100,000) for antipyretic assignment, and 17 per 100,000 (95 % CI, 3.5 49 per 100,000) in those children ≤2 years who received ibuprofen.

As noted earlier in the discussion of the large-scale paediatric study by Ashraf et al. (1999), no occurrences of gastric bleeding or ulcers were observed with either ibuprofen or paracetamol. The incidence of adverse events (AEs) in the digestive system was 3.0 % and 2.1 % in the younger group (≤2 years) that received ibuprofen or paracetamol, and 2.1 % and 1.2 % for these drugs in the older group (2 12 years); the statistical tests showed the former to be non-significant, and the latter statistically significant. Abdominal pain occurred in 0.6 % of the younger patients who had ibuprofen compared with 0.1 % that had paracetamol, while in the older group the incidence was 0.6 % and 0.2 % for ibuprofen and paracetamol respectively.

These results attesting to the gastric safety of ibuprofen in comparison with paracetamol accord with earlier investigations (Walson et al. 1989; Rainsford et al. 1997; Diez-Domingo et al. 1998), and confirm the safety of both drugs to be comparable and relatively low adverse events in the open clinical paediatric setting.

7.6 Reducing GI Risks

An obvious way of reducing GI risks from ibuprofen, like that from other NSAIDs, is to take note of the risk factors for developing NSAID-induced GI injury (Table 7.1; Figs. 7.1 and 7.2) and adopt preventative strategies (educational, patient advisory leaflets and advice on packaging). One suggestion that is frequently made is to take ibuprofen with food or drinks. In a review, the evidence in support of this suggestion was analysed (Rainsford and Bjarnason 2012).

In essence, the evidence reviewed addressed issues concerning recommendations to take OTC ibuprofen with food, or at various times before during or after meals. This question has arisen as a result of some EU drug regulatory agencies requiring a specific warning on labels to take the drug with food.

In order to gain scientific insight into what the benefits are from intake of ibuprofen with food or at various stages around mealtimes, the published evidence was reviewed for the effects on the pharmacokinetics, pharmacological, therapeutic actions and safety of various ibuprofen formulations when taken orally with food or fasting, and intake of the drug around mealtimes. The main conclusions were:

1. The recommendations to take ibuprofen with food or meals have raised a number of important issues:
   (a) The impact of intake of food, at various stages during meals and intake of liquids on the absorption pharmacokinetics and the bioavailability of ibuprofen in relation to the various formulations of the drug that may be taken OTC.
   (b) The types of food and the timing of drug intake in relation to that of foods, the volumes and types of liquids may influence the pharmacokinetics, therapeutic actions, and safety of various ibuprofen formulations that may affect the advice which should be covered by any such recommendations.
   (c) Current recommendations by various authorities and regulatory agencies on the intake of ibuprofen formulations with food, at mealtimes, with fluids or liquid foods (e.g., milk) or as a consequence of fasting.
   (d) The evidence for any apparent safety benefits, which are assumed to be in preventing gastro-intestinal symptoms, which may arise from intake of the drug with food, at various stages in mealtimes, and/or with fluids.
   (e) Influence of intake of food on gastric acidity and effects of ibuprofen on acid production, both factors that are important in the pH-dependent gastro-duodenal absorption of ibuprofen.
   (f) Practical impact of any recommendations to take ibuprofen with food or at various stages around mealtimes or with fluids or liquid foods.
2. The evidence shows that taking standard or conventional immediate-release (IR) and extended (or modified) release (MR or SR) ibuprofen, or the lysine or sodium salts of ibuprofen tablets during or after meals, delays the gastric absorption of the drug but not its total bioavailability. However, the gastric absorption of IR ibuprofen is not affected when taken immediately before meals. The total bioavailability of the drug is generally unaffected when it is taken at any stage with meals compared with that following fasting.
3. The extent of reduction in the maximal plasma or serum concentrations of ibuprofen when the IR or solubilised formulations (e.g., sodium or lysine salts or "liquigel" formulations) are taken with food or under conditions of fasting followed by intake of meals is relatively small (~20 30 %).
   Since the total bioavailability is unaffected, it is unlikely that conditions of food intake have any pronounced negative impact on the therapeutic efficacy of the IR or solubilised formulations of the drug, although these conditions may have greater effects on ER or MR formulations, based on what is known about the impact of food on the oral pharmacokinetics of these forms.
4. The evidence from published studies in various acute pain states (five of which were in dental surgical pain) suggests that the lysine salt of ibuprofen has a faster onset of action (approximately 30 45 min in dental pain studies) than conventional ibuprofen IR tablets and, in some studies, compared with paracetamol or aspirin (about 0.75 2 h), or placebo. The pain relief from ibuprofen lysine in the dental pain studies extended to about 6 h. This is in accord with the absorption profile of this salt, but principally in the fasted state. In the absence

of any information on the instructions to subjects taking these drugs at various stages under fasting or fed conditions (especially in the dental pain studies), it can only be assumed that the presence of food in the stomach had little influence on the speed of onset of analgesia of the lysine salt, and that this was faster than that from conventional ibuprofen (acid) tablets or that from the other analgesics.

5. There is no published evidence available to indicate whether there are any perceived benefits in reducing GI irritation or symptoms from taking ibuprofen formulations with food or milk or other fluids. Indeed, the recommendations of drug regulatory agencies or those in authoritative literature (formularies, leading clinical pharmacological texts, or advisory notices from agencies) are inconsistent, and are not substantiated by any published recommendations or investigations. Some of these sources recommend intake of ibuprofen (which includes the conventional immediate-release or coated formulations) with meals or milk in individuals prone to upset stomach or epigastric pain. This may be regarded as "common sense", but there is no evidence to support these recommendations. There may be important "consumer-related" issues that influence whether the public are prepared to take tablets with food, as this may be a bulky combination and not pleasant, especially in the elderly or those patients with some degree of dysphagia.
6. The absorption pharmacokinetics of extended- or modified-release formulations (i.e., ER or MR) of ibuprofen appears to be more markedly reduced than that of the immediate release or solubilised formulations. Thus, any recommendations to take these formulations of ibuprofen with food or at mealtimes could reduce the therapeutic efficacy if viewed from the negative influence of food on pharmacokinetics of these formulations. However, there is no evidence to suggest that there is reduced efficacy or risks of GI events from of intake of ER or MR formulations with food or milk.
7. There is no clear indication of when ibuprofen formulations should be taken with individual types of food (with variations in carbohydrates, proteins, fats) or with milk, based on the available evidence. The conclusions are that there is insufficient evidence to warrant mandatory warnings or statements to indicate that ibuprofen formulations should be taken with meals, milk, or water to reduce the likelihood or occurrence of GI upsets or severe GI adverse events. Whether a consensus recommendation to take these products with food or milk in individuals who are likely to have upset stomach might be voluntarily applied in conformity with the recommendations, on the basis of this being a common-sense recommendation, is debatable but may be useful to the patient.

Given the limited amount of data available, which suggests that the intake of food has little if any clinically significant effects on the speed of onset of analgesia from ibuprofen lysine and that the overall bioavailability of the drug is unaffected, the issue of food intake does not represent a major issue for recommended usage of this salt, nor indeed that of any other IR formulation of the drug.

Further investigations on the effects of intake of ibuprofen before during or after food or various compositions would be necessary to determine the relative gastro-protective effects of intake of food compared with the onset of analgesia in these fed compared with fasted states.

In essence, therefore, there is no evidence to support the beneficial effects of taking ibuprofen with foods or drink.

Chapter 8
Cardiovascular Safety

There are three main issues concerning cardio-vascular (CV) safety of ibuprofen. The first of these concerns the possible risks of triggering serious CV conditions such as congestive heart failure (CHF) and myocardial infarction (MI), a situation which has arisen as a consequence of the re-evaluation of risks of MI from all NSAIDs following the identification of risks of this condition with rofecoxib and other coxibs. The second concerns the effects of NSAIDs, including ibuprofen, on blood pressure in hypertensive individuals, elevation of blood pressure being regarded as a surrogate marker for risks of MI or stroke. Linked to the effects of NSAIDs in elevating blood pressure are their effects on renal functions, which can contribute to their hypertensive potential as a consequence of inhibition of renal prostaglandin production. This has given rise to the so-called "cardio-renal" syndrome of NSAIDs, and again has come from recognition of the pronounced renal effects of coxibs as a consequence of inhibition of COX-2 in the macula densa (Harris et al. 1994; Haas et al. 1998; Khan et al. 1998; Inoue et al. 1998; Ichihara et al. 1999; Wolf et al. 1999; Roig et al. 2002); aspects of this are discussed in Chap. 9. The third issue is the possibility that ibuprofen might reduce the anti-platelet effects of aspirin, and thus reduce the anti-thrombotic effectiveness of the latter.

8.1 Disease-related Issues

There is a fundamental *disease-related* issue with regard to the effects of coxibs and NSAIDs in producing the range of cardio-vascular symptoms and life-threatening conditions such as myocardial infarction, stroke, and congestive heart failure. The emphasis since the identification of increased risks of these CV conditions has been on the actions of the drugs per se. However, there is substantial evidence that in RA and other rheumatic conditions these CV conditions are risk factors in themselves, along with the influence of diabetes mellitus, hypertension, systemic inflammation, and obesity (Turesson et al. 2004, Panoulas et al. 2007; Peters et al. 2009; Freise

K.D. Rainsford, *Ibuprofen: Pharmacology, Therapeutics and Side Effects*,
DOI 10.1007/978 3 0348 0496 7 8, © Springer Basel 2012

et al. 2009; Mathieu and Lemieux 2010; Rho et al. 2010). Indeed, there is growing evidence that RA, like diabetes mellitus, may be an independent risk factor for CV disease (Peters et al. 2009). Allied with this is the evidence that COX-2 inhibition by coxibs, and NSAIDs may result in a shift in Th1-type immuno-inflammatory response that is prevalent in atherosclerosis to produce instable atheromatous plaque in coronary arterial disease which is associated with a Th2-type immunological response (Padol and Hunt 2010). Furthermore, concomitant infections with *Helicobacter pylori,* Chlamydia, and other microbial agents may enhance the risk of developing CV conditions (Miragliotta and Molineaux 1994; Gunn et al. 2000; Freise et al. 2009; Rainsford 2010). *H. pylori* is prevalent in patients with arthritic disease; this organism has been shown to have pro-thrombotic activity (Miragliotta and Molineaux 1994) and to cause shifts in Th1/Th2 subsets (Rainsford 2010), and the CagA positive pathogenic strain is associated with increased risks of premature myocardial infarction (MI), thus making this organism a prime candidate for being associated with MI and other CV conditions. As suggested, "the gun must be loaded (i.e., presence of prior disease or infections) for the coxibs to pull the trigger and produce CV disease" (Rainsford 2010).

The available evidence reviewed here shows that ibuprofen has low CV risks, although this drug may have effects on blood pressure (Durrieu et al. 2005; Panoulas et al. 2007) and on the actions of drugs used to control blood pressure.

8.2 Heightened Concerns from the Coxib Studies

Serious CV events, principally ischaemic heart conditions, were initially highlighted by the initial long-term studies with rofecoxib, but then followed with other coxibs and later some of the NSAIDs (Strand and Hochberg 2002; Topol 2004, 2005; Khanna et al. 2005; Östör and Hazleman 2005; Rainsford 2005a). The CV events included myocardial infarction and hypertension, and were noted with rofecoxib (VIOXX®) in the VIGOR study as well as in a number of other studies. They were of sufficient concern for the company producing this drug, Merck Sharp & Dohme, to withdraw it from the market on 29 September 2004 (Topol 2004, 2005; American College of Rheumatology, Hotline 2005; Psaty and Furberg 2005). In the wake of the issues surrounding withdrawal of rofecoxib, the FDA determined that valdecoxib (Pfizer) had similar CV risks, as well as the skin reactions that emerged with this drug, which led to its withdrawal in 2005.

The FDA and other agencies worldwide were alerted and sufficiently concerned with the CV ADRs with rofecoxib, such that extensive reviews were undertaken by these agencies world-wide of both coxibs and NSAIDs based on the somewhat unfounded premise that inhibition of COX-2 which occurs with all these drugs might well underlie the increased risks of MI and elevation of blood pressure. It is important to note that the VIGOR study investigating the long-term GI effects of rofecoxib was performed in patients with rheumatoid arthritis (RA). RA patients are known to have a markedly higher risk of developing MI and other serious CV

events (Nurmohamed et al. 2002; Assous et al. 2007), and this is not a feature generally recognized in the assessment of CV risks of coxibs and NSAIDs.

Subsequent analysis of clinical trials performed with rofecoxib has confirmed the higher risk of CV toxicity with this drug, especially in the high-dose range (≥50 mg/day) (Kerr et al. 2007; Strand 2007; Baron et al. 2008; Table 8.1). Furthermore, there are indications from studies performed with the coxibs in long-term preventative studies in cancers or Alzheimer's disease that high doses of these drugs were employed, and the patients were clearly very sick.

Etoricoxib (Arcoxia®) also developed by Merck Sharp and Dohme as a second-generation coxib is probably the most selective inhibitor of COX-2 of those drugs that have been developed to date. Large-scale trials have given indications that GI and CV events from etoricoxib may be lower than with NSAIDs, such as diclofenac, as well as celecoxib (Cannon et al. 2006).

Lumiracoxib (Prexige®; Novartis), although classed possibly incorrectly as a coxib, is not chemically like other coxibs, as it is a derivative of diclofenac. It also does not have the high COX-2 selectivity of etoricoxib or rofecoxib. In view of commercial interest in the CV issue with NSAIDs, Novartis have undertaken large-scale studies to determine the CV safety with lumiracoxib, which was compared with ibuprofen and naproxen, all at prescription-level dosages (Schnitzer et al. 2004; Matchaba et al. 2005; Stricker et al. 2008).

Likewise, Pfizer through its collaborations undertook an extensive evaluation of their data on celecoxib to determine the CV risks in clinical trials on patients exposed to this drug compared with some other NSAIDs and rofecoxib (Moore et al. 2005; White et al. 2007; Solomon et al. 2008a, b). Some of the data from these large-scale clinical trials and subsequent analysis of CV risks of NSAIDs and coxibs have featured comparisons with ibuprofen.

Thus, these data as well as that from large-scale epidemiological studies are useful as a basis for determining the relative CV safety of ibuprofen compared with its competitors including the coxibs (Table 8.1). Overall these data show that although there is some variability in risk assessments between the studies while ibuprofen has a relatively low CV risk.

8.3 Epidemiological Studies

The awareness of CV risks from coxibs and NSAIDs has led to a substantial number of studies reported in which the risks of MI or other serious CV accidents have been examined (McGettigan and Henry 2006; Antman et al. 2007; Waksman et al. 2007; Ray et al. 2009; Ray 2010; Table 8.1).

Among these studies, that by Garcia-Rodriguez and co-workers (2004) employed data from the UK General Practice Research Database (GPRD) which records reports from GPs sent anonymously to the UK MHRA. This database records demographic and patient data, and over 90 % of GP referrals along with prescription details. The associations of MI with various patient and risk factors was

Table 8.1 Meta analysis, case–control and cohort studies of cardiovascular risk with ibuprofen and COX-2 (Coxib) inhibitors

		Relative Risks (95 % CI)				
Authors (year)	Study type	Ibuprofen	Celecoxib	Rofecoxib (all doses)	Naproxen	Diclofenac
Gislason et al. (2006)	Cohort	1.390 (1.27–1.53)	2.06 (1.73–2.45)	2.29 (1.99–2.65)	–	–
MacDonald and Wei (2003)		1.73 (1.05–2.84)	–	–	–	0.80 (0.49–1.31)
Ray et al. (2002)		0.91 (0.7–1.06)	0.96 (0.76–1.21)	1.70 (0.98–2.95)	0.93 (0.82–1.06)	–
Curtis et al. (2003)		0.84 (0.7–1.01)	–	–	–	–
Ray et al. (2003)		1.15 (1.02–1.28)	–	–	0.95 (0.82–1.09)	–
Summary relative risk		1.12 (0.90–1.38)	1.22 (0.69–2.16)	1.51 (0.73–3.13)	0.94 (0.85–1.04)	1.36 (0.51–3.65)
Hippisley-Cox and Coupland (2005)	Case–control studies	1.24 (1.11–1.39)	1.21 (0.96–1.54)	1.32 (1.09–1.61)	1.27 (1.01–1.60)	1.55 (1.39–1.72)
Graham et al. (2005)		1.06 (0.96–1.17)	0.84 (0.67–1.04)	1.34 (0.98–1.82)	1.14 (1.00–1.30)	1.60 (0.96–1.17)
McGettigan et al. (2006)		0.98 (0.53–1.81)	1.11 (0.59–2.11)	0.63 (0.31–1.28)	–	–
Kimmel et al. (2004)		0.52 (0.39–0.69)	0.43 (0.23–0.79)	1.16 (0.70–1.93)	0.48 (0.28–0.82)	–
Singh et al. (2006)		1.11 (1.01–1.22)	1.09 (1.02–1.15)	1.32 (1.22–1.42)	1.08 (0.95–1.22)	–
Fischer et al. (2005)		1.16 (0.92–1.46)	–	–	0.96 (0.66–1.38)	1.23 (1.00–1.51)
García Rodríguez et al. (2004)		1.06 (0.87–1.29)	–	–	0.89 (0.64–1.24)	1.18 (0.99–1.40)
Bak et al. (2003)		1.30 (1.00–1.60)	–	–	0.70 (0.40–1.10)	1.10 (0.70–1.17)
Solomon et al. (2002)		1.02 (0.88–1.18)	–	–	0.84 (0.72–0.98)	–
Schlienger et al. (2002)		1.17 (0.87–1.58)	–	–	0.68 (0.42–1.13)	1.38 (1.08–1.77)
Watson et al. (2002)		0.74 (0.35–1.55)	–	–	0.57 (0.31–1.06)	1.68 (1.14–2.49)
Summary relative risk		1.06 (0.95–1.18)	1.01 (0.90–1.13)	1.21 (1.08–1.36)	0.96 (0.84–1.10)	1.36 (1.21–1.54)
Overall summary relative risk		1.07 (0.97–1.18)	1.06 (0.91–1.23)	1.35 (1.15–1.59)	0.97 (0.87–1.07)	1.40 (1.16–1.70)
Antman et al. (2007)	Meta analysis of RCTs (vascular events)	1.51 (0.96–2.37)	–	–	0.92 (0.67–1.26)	1.63 (1.12–2.37)
	(Observational events Mostly MI)	1.07 (0.97–1.18)	–	–	0.97 (0.87–1.07)	1.40 (1.16–1.70)
	Registry recurrent MI	1.25 (1.07–1.46)	–	–	–	1.54 (1.23–1.93)
	Registry mortality	1.50 (1.36–1.67)	–	–	–	2.49 (2.09–2.80)

Modified from Strand (2007) with additional data from Antman et al. (2007)

Data on summary relative risks for celecoxib, rofecoxib, naproxen and diclofenac represents all trials analysed by Strand (2007)

examined in this study. The odds ratios (ORs) for development of MI after multivariant adjustment with current use of NSAIDs were found to have an OR = 1.06 (0.87 1.29; 95 % CI values) for ibuprofen, contrasted with those at the upper end of risk with piroxicam with an OR of 1.25 (0.69 2.25). Prior history of CHD or concomitant intake of aspirin did not increase the risk of MI from ibuprofen.

Jick and co-workers (2006) performed a case control analysis of data from the UK GPRD; they did not find any increased risk of acute MI with either ibuprofen or naproxen, but did find increased risks with diclofenac, rofecoxib, and celecoxib.

Kimmel et al. (2004) performed a study of hospitalized patients for MI in a 5-county region around Philadelphia (USA). They observed reductions in the risks of MI among non-aspirin NSAID users. This reduction was also observed with ibuprofen, with the adjusted OR being 0.52 (0.39 0.69; 95 % CI) compared with that of 0.53 (0.42 0.67) for aspirin and 0.48 (0.28 0.82) for naproxen, a drug which has often been found to have low CV risk and in fact may have some cardioprotective effects (Topol 2004, 2005; Khanna et al. 2005).

In a nested case control study of data from a leading US health maintenance organization, Kaiser Permanente, Graham and co-workers (2005) examined 8,143 cases of serious coronary disease (from 2,302,029 patient-years follow-up). They found that the adjusted OR for ibuprofen for current use was 1.26 (1.00 1.60), compared with that of naproxen OR = 1.36 (1.06 1.75) and rofecoxib low dose (<25 mg/day) OR = 1.47 (0.99 2.17) and high dose (>25 mg/g) OR = 3.58 (1.27 10.11). For "remote" use, the OR for ibuprofen was 1.06 (0.96 1.17), contrasted with that of rofecoxib (high dose, >25 mg/day) with an OR of 3.0 (1.09 8.31) and naproxen.

In a combined study of CV and GI events in 49,711 US Medicare beneficiaries (>65 years of age), Schneeweiss et al. (2006) found that the risks of acute MI was 1.20 with ibuprofen, compared with 1.01 with naproxen, 1.54 with diclofenac, 1.58 with celecoxib, and 1.56 with rofecoxib.

A summary of the risk calculations associated with the occurrence of these conditions is shown in Table 8.2. Overall the data show that ibuprofen was amongst the drugs with the risks of serious GI and CV events in these elderly patients (Table 8.2). It should be noted that there is a degree of overlap in the confidence intervals of relative or risk differences in these data. To overcome complications in data analysis arising from unmeasured variables, the authors undertook an instrumental analysis of the data in which confounding variables were removed (see Footnotes Table 8.2 for details). The results show that ibuprofen was amongst the group of lower-risk drugs, and notably this was more striking in comparison with diclofenac (high risk for both GI and MI events) and rofecoxib (high risk of MI, but lower risk of GI complications, Table 8.2).

In another nested case control study using clinical records of the UK general practice database known as QRESERCH, Hippisley-Cox and Coupland (2005) found that recent use (<3 months) of ibuprofen was associated with an adjusted OR of 1.24 (1.11 1.39), compared with that of diclofenac, which had an OR of 1.55 (1.39 1.72), naproxen 1.09 (0.96 1.24), celecoxib 1.14 (0.93 1.40), and rofecoxib 1.05 (0.89 1.24). The lack of signals with rofecoxib and to some extent with

Table 8.2 Risks and adjusted relative or risk differences for GI complications and acute MI after 180 days, stratified by NSAID group and calculated for GI and MI groups

	[a]GI complications				[b]Acute MI			
Drug	Events	Exposed	Risk	Rel diff/100[c] (95 % CI)	Events	Exposed	Risk	Rel diff/100[c] (95 % C.I.)
Ibuprofen	68	5,353	1.27	0.88 (−1.93, 3.68)	64	5,353	1.2	−0.01 (2.49, 2.46)
Celecoxib	291	19,842	1.47	0 (reference)	313	19,842	1.58	0 (reference)
Diclofenac	29	1,817	1.6	5.09 (−1.18, 11.36)[d]	28	1,817	1.54	6.07 (−0.02, 12.15)[d]
Naproxen	60	4,139	1.45	0.74 (−2.04, 3.52)	42	4,139	1.01	−0.30 (−2.74, 2.14)
Rofecoxib	212	12,232	1.73	0.30 (−1.28, 1.89)	191	12,232	1.56	1.4 (−0.20, 3.01)
Other NSAIDs	86	6,328	1.36		60	6,328	0.95	

[a]*GI* gastrointestinal, [b]*MI* myocardial infarction, *95 % CI* 95 % confidence interval.

[c]Relative (or risk) difference obtained in an instrumental variable model for differences in risks of GI and HI events, adjusted for age, sex, race, hypertension, congestive heart failure, coronary heart disease, past and concurrent gastroprotective drug use, peptic ulcer disease, rheumatoid arthritis, osteoarthritis, warfarin use, steroid use, Charlson index, physician visits, hospitalizations, and nursing home residence.

[d]Statistically significant difference by Sargan test.

From Schneeweiss et al. (2006), with modifications

celecoxib is odd, but may reflect more limited use of this drug according to the guidelines by the UK National Institute for Clinical Excellence (NICE).

A recent retrospective study of hospitalization records of ≥65-year-old patients admitted for acute MI (as well as GI events) in Québéc (Canada) by Rahme and Nedjar (2007) showed that the adjusted hazard ratios (HR) were 1.05 (0.74 2.41) for ibuprofen, 1.69 (1.35 2.10) for diclofenac, 1.59 (1.31 1.93) for naproxen, 1.34 (1.19 1.52) for celecoxib, 1.27 (1.13 1.42) for rofecoxib, and 1.29 (1.17 1.42) for paracetamol.

Another large-scale epidemiological study undertaken using a US patient database was performed by Motsko et al. (2006) using the US Department of Veterans Affairs (VA) Veterans Integrated Service Network 17, in which Medicare data and Texas Department of Health Mortality data was incorporated in order to capture events outside the VA network. Of 12,188 exposure periods to the NSAIDs (in 11,930 persons), long-term and ≤180 days, data from intake of ibuprofen were used to set the data reference point at 1.0, with the other NSAIDs and two coxibs being compared with this value. Thus, the CV risks (MI, stroke and MI-related deaths) with long-term celecoxib and rofecoxib were associated with an appreciably greater hazard ratio (HR) of 3.64 (95 % CI 1.36) and 6.64 (95 % CI 20.28) respectively. The risks were greater in patients aged ≤65 years. In contrast, long-term intake of etodolac and naproxen short- or long-term resulted in HR values within those of ibuprofen. Thus, none of these three drugs were associated with any cardio-negative or cardio-protective effects (Motsko et al. 2006).

A study undertaken by Huang et al. (2006) in Taiwan is of particular interest, in the context of establishing if the CV risks from NSAIDs and celecoxib that are evident in Western/US-European populations are also observed in Oriental communities (Tables 8.3 and 8.4). These authors undertook a population-based analysis using data from the Taiwanese Bureau of National Health Insurance (NHI) (Taipei); this health insurance system covers ≤99 % of Taiwan's population of 23 million (data obtained in the period 2001 2003). This NHI database also contains comprehensive records of diagnosis, treatment, and the occurrence of clinical adverse events and other outcomes. A total of 16,326 patients (of equal numbers of both sexes) were identified who received long-term treatment with ibuprofen (32.09 % of patients), celecoxib (23.04 % of patients), etodolac (12.34 % of patients), nabumetone (13.86 % of patients) and naproxen (18.68 % of patients). The overall prevalence of acute MI, angina, cerebro-vascular accident (CVA), and transient ischaemic attack (TIA) was higher in long-term users of these drugs who had a prior history of CV disease (Table 8.3).

The data in Table 8.4 shows the prevalence of the individual CV events with intake of the NSAIDs and celecoxib. The HR values for AMI, CVA, and TIA NSAIDs were similar for all four NSAIDs, and in some cases higher for celecoxib. Ibuprofen had a somewhat lower risk of angina (HR 0.78 [95 % CI 0.63 0.93]).

These data on the risk factors (Table 8.4) show that risk of CV events is greater in subjects that are at CV-risk, and the pattern of CV events may be similar in the population of Taiwanese compared with that in Western populations. As expected, patients with diabetes mellitus and chronic renal disease were at highest risk for

Table 8.3 Cardiovascular events (CVDs) in long term >180 days users of one of four nonselective NSAIDs (etodolac, nabumetone, ibuprofen, or naproxen) or the cyclooxygenase-2 inhibitor, celecoxib, in Taiwan

	Etodolac		Nabumetone		Ibuprofen		Naproxen		Celecoxib		All patients	
CVD	History of CVD	No history of CVD	History of CVD	No history of CVD	History of CVD	No history of CVD	History of CVD	No history of CVD	History of CVD	No history of CVD	History of CVD	No history of CVD
AMI												
Events per subgroup, no (%)	1/38 (2.63)	22/1,976 (1.11)	3/31 (9.68)	32/2,231 (1.43)	1/33 (3.03)	40/5,206 (0.77)	2/31 (6.45)	31/3,018 (1.03)	3/77 (3.90)	34/3,685 (0.92)	10/210 (4.76)	159/16,166 (0.99)
Duration of use, mean (SD), d	363.24 (204.22)	396.23 (207.54)	393.39 (233.43)	425.01 (234.18)	402.00 (201.45)	347.19 (200.18)	349.90 (178.54)	418.23 (240.62)	381.36 (173.65)	383.56 (176.00)	378.46 (192.99)	385.60 (211.28)
Angina												
Events per subgroup, no (%)	3/78 (3.85)	14/1,936 (0.72)	2/68 (2.94)	4/2,194 (0.18)	3/55 (5.45)	22/5,184 (0.42)	2/60 (3.33)	12/2,989 (0.40)	6/128 (4.69)	16/3,634 (0.44)	16/389 (4.11)	68/15,937 (0.43)
Duration of use, mean (SD), d	360.12 (199.47)	397.04 (207.72)	372.96 (210.83)	426.18 (234.70)	368.38 (231.69)	347.32 (199.87)	348.88 (199.87)	418.91 (240.73)	371.83 (158.22)	383.93 (176.53)	365.65 (193.25)	385.99 (211.45)
CVA												
Events per subgroup, no (%)	23/266 (8.65)	26/1,748 (1.49)	14/202 (6.93)	39/2,060 (1.89)	12.177 (6.78)	58/5,062 (1.15)	16.136 (11.76)	51/2,913 (1.75)	23.256 (6.46)	55/3,406 (1.61)	88/1,137 (7.74)	229/151,889 (1.51)
Duration of use, mean (SD), d	374.47 (183.58)	398.82 (210.74)	418.13 (226.64)	425.21 (234.92)	423.14 (245.59)	344/89 (197.95)	414.68 (240.47)	417.67 (240.17)	346.39 (151.03)	387.40 (177.91)	385.48 (211.63)	385.82 (203.26)
TIA												
Events per subgroup, no (%)	2/48 (4.17)	16/1,966 (0.81)	2/37 (5.41)	14/2,225 (0.63)	0.35 (0)	18/5,204 (0.35)	2/40 (5.00)	17/3,009 (0.56)	4/88 (4.55)	18/3,674 (0.49)	10.248 (4.03)	83/16,078 (0.52)
Duration of use, mean (SD), d	318.79 (128.13)	397.48 (208.71)	372.54 (234.8)	425.44 (234.09)	384.49 (209.28)	347.29 (200.15)	395.28 (219.12)	417.83 (240.44)	351.91 (147.52)	384.27 (176.50)	385.90 (211.45)	360.17 (181.93)

CVD cardiovascular disease, *AMI* acute myocardial infarction, *CVA* cerebrovascular accident, *TIA* transient ischaemic attack
Source: Taiwanese Bureau of National Health Insurance database, January 1, 2001 to December 31, 2003
From Huang et al. (2006)

Table 8.4 Potential risk factors for cardiovascular events in long-term (>180 days) users of one of four nonselective NSAIDs (etodolac, nabumetone, ibuprofen, or naproxen) or a cyclooxygenase (COX)-2 inhibitor (celecoxib) in Taiwan

	AMI			Angina			CVA			TIA		
Variable	HR	95 % CI	*P*	HR	95 % CI	*P*	HR	95 % CI	*P*	HR	95 % CI	*P*
Age	1.05	1.04–1.06	<0.01	1.02	1.01–1.04	0.01	1.05	1.04–1.05	<0.01	1.04	1.02–1.06	<0.01
Male sex[a]	1.22	1.05–1.41	0.01	1.02	0.83–1.25	0.87	1.04	0.93–1.15	0.5	1.14	0.94–1.38	0.18
Medication prescribed[b]												
Etodolac	1.09	0.89–1.34	0.41	1.1	0.83–1.45	0.52	1.07	0.93–1.24	0.35	1.07	0.81–1.40	0.64
Nabumetone	0.98	0.84–1.14	0.78	1.08	0.90–1.30	0.43	0.96	0.87–1.07	0.48	1.08	0.90–1.29	0.42
Ibuprofen	1.07	0.98–1.18	0.14	0.78	0.63–0.96	0.02	0.99	0.92–1.07	0.79	0.98	0.85–1.12	0.75
Naproxen	1.02	0.94–1.10	0.71	0.99	0.88–1.12	0.89	1.02	0.97–1.08	0.41	0.98	0.89–1.09	0.72
Prescription duration	1	1.00–1.00	0.01	1	1.00–1.00	0.41	1	1.00–1.00	0.01	1	1.00–1.00	0.21
History of CVD[c]	2.29	1.22–4.32	0.01	6.19	3.56–10.78	<0.01	3.56	2.80–4.52	<0.01	6.6	3.72–11.73	<0.01
Preexisting medical condition												
CHF[d]	2.17	1.38–3.39	<0.01	2.04	1.08–3.85	0.03	1.46	1.01–2.10	0.04	0.86	0.37–2.00	0.73
Chronic renal disease[e]	1.81	1.17–2.81	0.01	1.73	0.88–3.37	0.11	1.24	0.85–1.82	0.26	0.97	0.45–2.11	0.94
Diabetes mellitus	1.62	1.18–2.23	<0.01	1.26	0.78–2.02	0.35	1.41	1.11–1.7	<0.01	1.74	1.15–2.64	0.01
Hypertension[f]	1.41	1.04–1.92	0.03	1.12	0.72–1.73	0.62	1.21	0.97–1.50	0.09	1.38	0.93–2.06	0.11
Dyslipidemia[g]	1.09	0.63–1.90	0.75	2.79	1.60–4.86	<0.01	0.77	0.48–1.23	0.27	0.67	0.27–1.66	0.39

AMI acute myocardial infarction; CVA cerebrovascular accident; *TIA* transient ischemic attack; *HR* hazard ratio; *CVD* cardiovascular disease; *CHF* congestive heart failure

[a]Female sex.

[b]The COX-2 inhibitor.

[c]No recurrence.

[d]No preexisting CHF.

[e]No preexisting chronic renal disease, no preexisting diabetes mellitus.

[f]No preexisting hypertension.

[g]No preexisting dyslipidemia (all, HR-1.00).

Based on data in Huang et al. (2006)

AMI, angina, and CVA. Those with hypertension notably showed risk for AMI but not for other CV conditions.

Gislason and colleagues (2006) employed data from the nationwide Danish National Patient Registry, which since 1978 has registered all hospital admissions in Denmark. Since 1995, the Danish Registry of Medicinal Product Statistics has kept records of all prescriptions dispensed by pharmacies in Denmark. In addition to recording data on the dispensed medication, the registry includes patient data. The authors identified all patients with first-time MI between 1995 and 2002, and determined the risk of death and hospitalization associated with use of NSAIDs or COX-inhibitors. Of 58,432 patients (with first MI) who were discharged alive, 9,773 were subsequently re-hospitalized for MI and a total of 16,573 died. The HR for death following any use of ibuprofen was 1.5 (95 % CI 1.36 11.67), celecoxib 2.57 (95 % 2.15 3.08), diclofenac 2.40 (95 % CI 2.09 2.80), rofecoxib 2.80 (95 %CI 2.41 3.25), and for all other NSAIDs 1.29 (1.16 1.43).

The Cox Proportional Hazards analysis for HRs for death and rehospitalisation for MI showed that there was a significantly increased risk of death associated with all the NSAIDs and coxibs. This analysis applied to high and low intake dosages showed there was a clear dose-related response. Of particular interest is that the daily intake of $\leq$1,200 mg ibuprofen was associated with an HR for death of 0.75 (95 % CI 0.61 0.92) compared with no use of drug, which was not observed with the other drugs. This same dosage of ibuprofen was associated with an HR for hospital re-admission for MI of 1.28 (95 % CI 1.03 1.60) compared with the reference of no use of NSAIDs. Both rofecoxib and celecoxib showed notably higher HRs for both categories, and this was dose-related. High dose ($\leq$100 mg/day) was also associated with higher HRs in both categories, which is of the same order as that observed with high doses of the coxibs.

In an Expert Opinion article, Fosbøl et al. (2010) stated inter alia ". . .Studies on the cardiovascular safety of NSAIDs in healthy people have recently underlined that healthy people (sic) are also at risk of cardiovascular adverse events. The results showed increased risk with the use of selective COX-2 inhibitors and also the traditional NSAID diclofenac. The results showed dose-dependency.

Ibuprofen in low doses ($<$1,200 mg/day) and naproxen seem to be safe alternatives with regard to cardiovascular safety."

The reference by Fosbøl et al. (2010) to "healthy people (sic) " raises the issue that the authors may consider that those who have no CV condition, even if it arises with drugs, can hardly be described as healthy any longer!! It is, therefore, questionable whether the so-called "healthy" individuals were in fact healthy.

These data need to be interpreted in the context of being in high-risk patients. They show that on a nationwide basis in this European population, OTC dosage of ibuprofen is probably associated with the lowest risk for MI-related rehospitalisation and death. Even at higher doses ($\geq$1,200 mg/day), the risks of death from ibuprofen, though higher than those in the lower dose or no-use categories, are about twofold lower than associated with intake of the other drugs.

Dose-related incidence of myocardial infarction in patients taking NSAIDs is shown in the data from van Staa et al. (2008) in Table 8.5.

Table 8.5 Relative risk (RR) of myocardial infarction in relation to dose of NSAID current users compared with control patients

		NSAID vs. Control cohort	
NSAID use	Number of cases	Age sex year adjusted RR[a] (95 % CI)	Fully adjusted RR[b] (95 % CI)
Current	5,690[c]	1.31 (1.27 1.36)	1.12 (1.08 1.17)
Ibuprofen (mg per day)	1,913	1.22 (1.16 1.28)	1.04(0.98 1.09)
<1,200	176	1.29(1.10 1.50)	1.05(0.91 1.22)
1,200	600	1.21(1.11 1.31)	1.02(0.94 1.11)
1,201 2,399	146	1.42(1.20 1.67)	1.22(1.03 1.44)
>2,400	10	2.28(1.23 4.24)	1.96(1.05 3.65)
Diclofenac (mg per day)	2,033	1.40(1.33 1.47)	1.21(1.15 1.28)
<150	675	1.30(1.20 1.40)	1.13(1.04 1.22)
150	650	1.50(1.38 1.62)	1.28(1.18 1.39)
150 299	35	1.35(0.97 1.88)	1.18(0.85 1.65)
>300	10	2.28(1.23 4.24)	2.03(1.09 3.77)
Naproxen (mg per day)	526	1.22(1.12 1.3)	1.03(0.94 1.13)
<1,000	155	1.19(1.01 1.40)	0.99(0.85 1.17)
1,000	250	1.31(1.15 1.48)	1.12(0.98 1.27)
>1,000	10	1.14(0.61 2.11)	0.92(0.49 1.71)

[a]Age and sex, with years on therapy Adjusted Relative Risk
[b]Fully adjusted for all variables Relative Risk
[c]Represents all patients in study, some of whom received other NSIADs and were current or past NSAID users. RR= relative risk
Reproduced from van Staa et al. (2008) with permission of John Wiley and Sons, publishers of Journal of Internal Medicine

This retrospective cohort study using the UK GPR database performed by van Staa et al. (2008) involved a total of 729,294 users of NSAIDs and 443,047 controls. The relative rate for MI increased with cumulative and daily dose. Ibuprofen and naproxen users had lower risks of MI than those that took diclofenac; these drugs being amongst the most frequently prescribed NSAIDs in the UK. Indeed, the risks with 0 4 prescriptions were around unity. In comparing the hazard rates (i.e., the absolute risk) there were no overall differences between these three drugs. The authors suggested that the increased risk of MI in these patients may relate to the underlying disease severity.

The data in Table 8.5 show that ibuprofen at OTC doses ($\leq$1,200 mg/day) has low relative risks (fully adjusted RR) comparable to low-dose (OTC) naproxen, a drug which has been indicated from several epidemiological studies to be amongst the lowest risk for MI of any type.

Congestive heart failure (CHF) has been observed in patients taking NSAIDs (Mamdani et al. 2004; McGettigan et al. 2008). In hospital-based case control studies in Newcastle (New South Wales) Australia during 2002 2005, involving 285 admissions for CHF. McGettigan et al. (2008) observed that celecoxib and rofecoxib were amongst the most frequently associated NSAIDs in first and recurrent admission cases of CHF, and that there was a dose-related association. Also,

Table 8.6 Odds ratios and 95 % confidence intervals for recurrent congestive heart failure in patients exposed to current nonsteroidal anti inflammatory drugs compared with current celecoxib exposure

	Crude odds ratio	Adjusted odds ratio[a]	95 % Confidence interval
Celecoxib	Reference		
Naproxen	1.05	1.05	0.59 1.86
Diclofenac	0.92	0.82	0.51 1.33
Ibuprofen	1.29	1.46	0.66 3.21
Indomethacin	1.87	2.04	1.16 3.58
Rofecoxib	1.51	1.58	1.19 2.11
Acetaminophen	1.19	1.15	0.92 1.44
Nonexposed	0.9	0.93	0.75 1.15

[a]Adjusted for age, sex, length of stay, dose, comorbidities, physician characteristics, and medications to treat congestive heart failure.

Reproduced from Hudson et al. (2007) with permission of John Wiley and Sons, publishers of Arthritis and Rheumatism

paracetamol was amongst the most frequently associated drug overall, but this was no different than in controls. Ibuprofen showed no difference in association between cases and controls (being approximately 31 32 % in all categories). These data suggest that ibuprofen has a relatively low association with CHF in comparison with celecoxib and rofecoxib.

Hudson and co-workers (2007) performed a nested case control analysis of a hospital administrative database in the Province of Québec, Canada in which records for the health insurance agency covering inpatients and outpatients were examined. The population cohort comprised 8,512 cases and 34,048 controls. As shown in Table 8.6, the data from this study showed that there was a greater risk of CHF in patients who have taken any NSAID (including coxibs) or paracetamol (acetaminophen) compared with that in subjects who were not exposed to these drugs. The incidence from intake of ibuprofen is lower than that of indomethacin and rofecoxib, but slightly higher than diclofenac and naproxen (Table 8.6).

Overall, therefore, these epidemiological investigations highlight (with admittedly some variability of ORs) the relatively *low to moderate risk* of ibuprofen at prescription level dosages being associated with serious CV conditions such as MI. These observations contrast with the higher risks with diclofenac, the coxibs, and in one study with paracetamol, and variable risks with naproxen. The risks of cardiovascular events from ibuprofen at OTC dosages are appreciably lower than with higher prescription dosages of this and other NSAIDs or the coxibs.

8.4 Recent Clinical Trials and Meta-Analyses

The CLASS study (Table 7.8) showed that ibuprofen had relatively low incidence of cardiovascular events, and this has been confirmed in a number of other studies comparing it with coxibs. These large-scale studies are valuable for highlighting

Table 8.7 Relative risks of acute cardiovascular events in randomized controlled trials of COX-2 (Coxib) inhibitors and NSAIDs

			Ibuprofen (comparator drug)				Coxib (investigational drug)				
Authors (year)	Study	Analysis	Dose	Number of subjects	Number of events	Number of events per 100 patient years	Dose	Number of subjects	Number of events	Number of events per 100 patient years	Relative risk 95 % CI
Silverstein et al (2000)	CLASS	Original	800 mg t i d	1,985	20	1 8	Celecoxib 400 mg b d	3,987	34	1 5	0 83
Strand and Hochberg (2002)		APTC	800 mg t i d	1,985	21	1 9	Celecoxib 400 mg b d	3,987	52	2 24	1 18
Farkouh et al (2004)	TARGET	APTC	800 mg t i d	4,397	23	0 52	Lumiracoxib 400 mg o d	4,376	19	0 43	0 76 (0 41–1 40)

APTC Antiplatelet Trialists' Collaboration

In the CLASS and TARGET trials, 22 % of patients took aspirin. In the TARGET trial comparison, naproxen 500 mg b.d. showed number of events per 100 patient years was 0.57, and this was comparable with ibuprofen (0.52/100 patient years). Relative risks are investigational of comparator drugs. These were crude risks in CLASS trial. Modified from Strand (2007)

Table 8.8 Cardiovascular events in patients receiving NSAIDs or coxibs: "Network" meta analysis rate ratio (95 % CI)

Drug	Myocardial infarction	Cardiovascular death
Celecoxib	1.35 (0.71 2.72)	2.07 (0.98 4.55)
Diclofenac	0.82 (0.29 2.20)	3.98 (1.48 12.70)
Etoricoxib	0.75 (0.23 2.39)	4.07 (1.23 15.70)
Ibuprofen	1.61 (0.50 5.77)	2.39 (0.69 8.64)
Lumiracoxib	2.00 (0.71 6.21)	1.89 (0.64 7.09)
Naproxen	0.82 (0.37 1.67)	0.98 (0.41 2.37)
Rofecoxib	2.12 (1.26 3.56)	1.58 (0.88 2.84)
Drug	*Platelet Trialists' Collaboration	Stroke
Celecoxib	1.43 (0.94 2.16)	1.12 (0.60 2.06)
Diclofenac	1.60 (0.85 2.99)	2.86 (1.09 8.36)
Etoricoxib	1.53 (0.74 3.17)	2.67 (0.82 8.72)
Ibuprofen	2.26 (1.11 4.89)	3.36 (1.00 11.60)
Lumiracoxib	2.04 (1.13 4.24)	2.81 (1.05 7.48)
Rofecoxib	1.44 (1.00 1.99)	1.07 (0.60 1.82)

Rate ratios for the occurrence of various cardiovascular conditions in patients receiving NSAIDs and coxibs compared with placebo, based on "network" meta analysis of large scale randomised con trolled trials

* Based on methodology of the Platelet Trialists' Collaboration assessments of CV events.

Reproduced from Trelle et al. (2011) with permission of the BMJ Publishing Group Ltd., publishers of the British Medical Journal

under control conditions in clinical trials in patients with rheumatic disease that ibuprofen has a low risk of developing cardiovascular effects.

An evaluation of the cardiovascular risks with coxibs and NSAIDs undertaken by Antman et al. (2007), which was a study under the auspices of the American Heart Association, has been instructive in critically evaluating and offering a clear statement of cardiovascular risks of all NSAIDs including coxibs. As shown in Table 8.7, which is a summary of the cardiovascular risk reported in randomized placebo-controlled clinical trials with the non-selective NSAIDs, the various outcome measures and natures of assessment from either randomized controlled trials, observational studies, or registry data, showed that there is some variability in cardiovascular risk with the different NSAIDs (Antman et al. 2007). Overall, ibuprofen has a slightly lower relative risk than diclofenac, but naproxen has a notably lower risk of cardiovascular events. Indeed, in the VIGOR study and several other studies that were reviewed back in 2004, it was found that naproxen had the lowest overall risk of all NSAIDs for developing CV events. For ibuprofen, the relative risks range from 1.07 for all CV, mostly MI, to all vascular events 1.51. However, the confidence intervals for these risks overlap considerably, and are approximately unity in comparison with placebo.

A recent meta-analysis of published and unpublished randomised placebo-controlled clinical trials (Trelle et al. 2011; Table 8.8) shows that the there is with some data a relatively high confidence interval (or what is described as the credibility interval, CI), making it difficult to ascribe clinical significance to some of these data. The data from the Antiplatelet Trialists' Collaboration suggests there

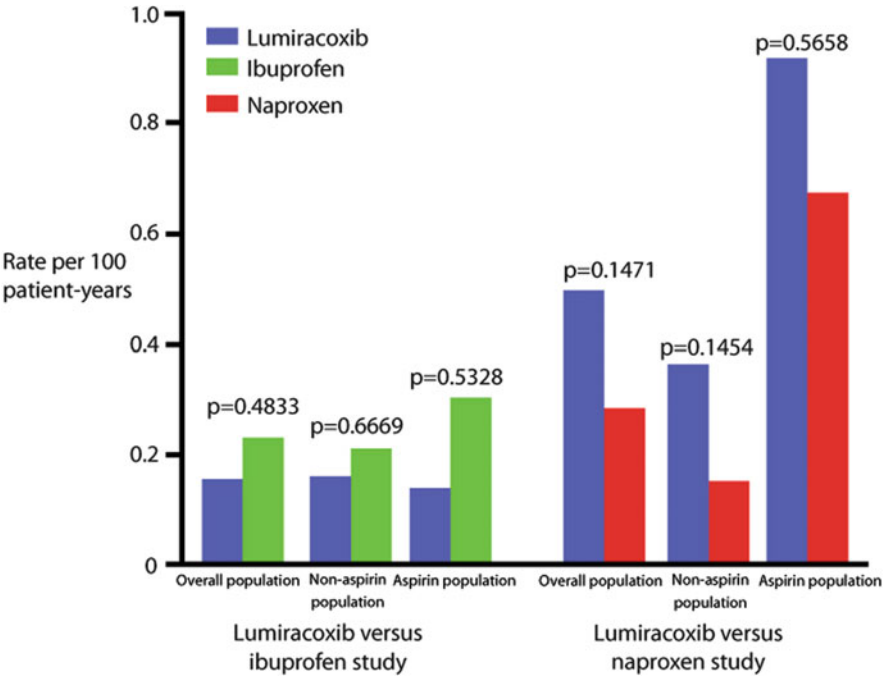


Fig. 8.1 Incidence of confirmed or probable myocardial infarctions (clinical and silent), from ibuprofen compared with lumiracoxib and naproxen by sub study and aspirin use. Reproduced from Naldi et al. (1999) with permission of John Wiley and Sons, publishers of the British Journal of Clinical Pharmacology

is an overall trend in favouring placebo with nearly all the drugs. The data on MIs with rofecoxib show the most significant trend in increased risk, while the other NSAIDs (including ibuprofen) show variable risks. Diclofenac, etoricoxib, and celecoxib show the highest risks of CV death, with a lower trend being shown with ibuprofen in MI, stroke and the APTC data.

8.4.1 Individual Trials

In the large multicentre trial intended to establish the risks of CV events from lumiracoxib with those from ibuprofen or naproxen in some 14,000 patients, it was found that the number of confirmed or probable myocardial infarctions and ischaemic events in the ibuprofen group was comparable with that from lumiracoxib as well as the naproxen treatment group (Fig. 8.1; Table 8.9; Farkouh et al. 2004). These data suggest that ibuprofen is no more likely to be a risk of CV events over that of the other drugs.

Table 8.9 Percentage of confirmed or probable ischaemic events including myocardial infarctions (clinical and silent), from ibuprofen compared with lumiracoxib and naproxen by sub study and aspirin use

	Both sub studies		Lumiracoxib vs ibuprofen sub study	
	Lumiracoxib	NSAIDs	Lumiracoxib	Ibuprofen
Number of patients in non aspirin population	6,950	6,968	3,401	3,431
Patients with confirmed or probable ischaemic events	0.49	0.39	0.38	0.35
All myocardial infarctions	0.20	0.13	0.12	0.15
Clinical	0.20	0.07	0.12	0.09
Silent	0	0.06	0	0.06
Ischaemic stroke	0.17	0.11	0.18	0.06
Unstable angina	0.07	0.07	0.03	0.12
Transient ischaemic attack	0.04	0.07	0.06	0.03
Number of patients in aspirin population	2,167	2,159	975	966
Patients with confirmed or probable ischaemic events	1.34	1.11	0.92	0.93
All myocardial infarctions	0.42	0.37	0.10	0.21
Clinical	0.28	0.32	0.10	0.21
Silent	0.14	0.05	0	0
Ischaemic stroke	0.51	0.42	0.21	0.41
Unstable angina	0.23	0.28	0.31	0.31
Transient ischaemic attack	0.18	0.05	0.31	0

Data are percentage (%) of patients with event. *NSAIDs* non steroidal anti inflammatory drugs
Reproduced in part from Farkouh et al. (2004) with permission of Elsevier, publishers of The Lancet

Table 8.10 Combined incidence of gastrointestinal and cardiovascular events from lumiracoxib, compared with ibuprofen and naproxen, by sub study (Safety Population) (Schnitzer et al. 2004)

Both substudies[†]	Number of patients with events/number at risk (%)	Hazard ratio (95 % CI)	p[a]
Lumiracoxib	89/9,117 (0.98 %)	0.65 (0.49 0.84)	0.0014
Non steroidal anti inflammatory drugs	133/9,127 (1.46 %)		
Lumiracoxib vs ibuprofen substudy[‡]			
Lumiracoxib	30/4,376 (0.69 %)	0.50 (0.32 0.79)	0.0025
Ibuprofen	56/4,397 (1.27 %)		
Lumiracoxib vs naproxen substudy[‡]			
Lumiracoxib	59/4,741 (1.24 %)	0.75 (0.53 1.05)	0.0961
Naproxen	77/4,730 (1.63 %)		

[a]Based on Wald X^2 statistic for treatment group comparison. Cox proportional hazards models include, in addition to treatment group, the factors [†]sub study, low dose aspirin, and age; and [‡]low dose aspirin and age.
Reproduced from Schnitzer et al. (2004) with permission of Elsevier, publishers of The Lancet

The combination of the risks of CV and GI events has been considered a major element in determining the overall safety of coxibs and NSAIDs (Antman et al. 2007). To exemplify this, Schnitzer and co-workers attempted an analysis of the combined risks of these drugs. A summary of their data showing the combined GI and CV events is shown in Table 8.10 (Schnitzer et al. 2004). These data show that the hazard ratio is significantly lower for lumiracoxib than the two NS-NSAIDs, although there is considerable overlap of the values of the 95 % confidence intervals. These data do show, however, that the combined risks of serious CV and GI events with ibuprofen are relatively low. Overall, therefore, these studies show that ibuprofen has a low risk of developing cardiovascular events, principally serious conditions such as myocardial infarction, although vascular events might be slightly increased in risk.

8.5 Interaction of Ibuprofen with the Anti-platelet Effects of Aspirin

Low-dose (75 100 mg daily) aspirin has been found to reduce established coronary, cerebrovascular, and peripheral vascular disease, including secondary myocardial infarction (Webert and Kelton 2004). Although it is arguable that aspirin exerts a range of non-platelet effects (e.g., actions on coagulation factors), its vascular preventative actions are primarily due to the inhibition of thromboxane A_2 and consequent platelet aggregation (Webert and Kelton 2004). However, it is possible that ibuprofen may interfere with the anti-platelet effects of aspirin (Catella-Lawson et al. 2001). This drug interaction was investigated by Catella-Lawson and co-workers (2001), who studied the effects of intake of aspirin (81 mg) 2 h before ibuprofen (400 mg) each morning for 6 days. After this treatment, the order of taking the two drugs was reversed, and a similar design was incorporated with paracetamol 1,000 mg. Serum thromboxane B_2 levels, determined as an indicator of COX-1 activity in platelets, were found to be inhibited. Platelet aggregation was found to be significantly inhibited by aspirin; the maximum inhibition being evident on day 6 when the drug was taken alone. When aspirin was given, followed by ibuprofen before taking aspirin, there was complete inhibition of the effect of aspirin on serum thromboxane B_2 and platelet aggregation. This impairment of platelet aggregation and thromboxane production by ibuprofen was not evident with paracetamol, diclofenac, or rofecoxib.

The consequence of these studies was that there were a considerable number of pharmaco-epidemiological investigations to establish if NSAIDs would in general impair the anti-thrombotic potential of aspirin and its prevention of myocardial infarction. Thus, MacDonald and Wei (2003) analysed data from the Scottish Administrative Pharmacy Database, and found that patients with cardiac disease who had been prescribed combinations of ibuprofen and aspirin had an increase in

cardiovascular mortality compared with that of patients who had taken aspirin alone. This effect was not evident when diclofenac was taken with aspirin.

Kurth and co-workers (2003) published data from patients enrolled in the Physicians Health Study whom had been randomized to receive aspirin and NSAIDs, and who were at increased risk of cardiovascular events compared with patients who did not use NSAIDs. The increased risk of NSAIDs causing increased risk of adverse events when given with aspirin while dose-dependence was relatively small, and required the drugs to be used for long periods. The study by Kimmel et al. (2004) which has already been mentioned was interesting, because this managed to put a completely different slant on the whole story. In patients with no history of coronary artery disease, the use of aspirin was associated with the lower risk of myocardial infarction as expected, but this benefit was not seen in patients who took any NSAIDs in addition to aspirin. Patients who had established coronary disease who used aspirin with NSAIDs were at similar risk at developing myocardial infarction to those patients who had taken aspirin alone. Thus, there is an important issue relating to whether patients have coronary disease or not in this effect of NSAIDs. It should be noted that the earlier study of Catella-Lawson et al. (2001) had been undertaken in normal subjects.

In a study in elderly patients who had already experienced a myocardial infarction, the mortality of those who had received aspirin and a non-steroidal was similar to that of patients who been prescribed aspirin alone (Curtis et al. 2003; Ko et al. 2002). No apparent differences were observed in the mortality and analysis of patients who had been prescribed aspirin and ibuprofen compared with those prescribed aspirin alone (Curtis et al. 2003).

As a follow-up to the study by Catella-Lawson and co-workers (2001), Cryer et al. (2005) investigated the effects of ibuprofen on aspirin-induced thromboxane B_2 production in 51 volunteers in a double-blind randomized parallel placebo-controlled study. The objections to the Catella-Lawson study were that it did not feature a placebo group, and there were issues about the study population. The basis of single measurement of thromboxane production is that this correlates to a high degree to the inhibition of platelet aggregation when aspirin is taken. Thromboxane production was measured over 10 days at 1, 3, and 7 days (in the period prior to randomization to treatment with ibuprofen or placebo) during 8 days treatment with 81 mg aspirin once daily in the morning. This resulted in greater than 90 % thromboxane inhibition. On the 9th day and subsequently for 10 days, the subjects were randomly assigned to receive ibuprofen or placebo, and their thromboxane B_2 levels were measured on days 0, 1, 3, 7, and 10. In both groups there was greater than or equal to 98 % inhibition of thromboxane B_2 production, although there was a small but clinically non-significant difference between the two treatment groups of thromboxane inhibition on day 7; but since this was already in a group who had greater than 98 % mean inhibition of thromboxane production, this could not be regarded as clinically significant (Cryer et al. 2005). These results show that prior treatment for 8 days with aspirin is not affected by subsequent ibuprofen treatment in terms of platelet thromboxane production. A similar study was performed by

Pongbhaesaj and co-workers (2003) and published in abstract form, which showed almost identical results.

Recently, Schuijt et al. (2009) investigated the effects of 7 days treatment with ibuprofen 2,400 mg t.i.d. or diclofenac 150 mg t.i.d. alone or taken concomitantly with aspirin 80 mg o.d., or 30 mg aspirin o.d. alone, in normal healthy volunteers. Aspirin 80 mg reduced thromboxane levels to about 90.3 % of baseline. However, they found that while diclofenac reduced serum thromboxane B_2 less than ibuprofen but with a high variability compared with baseline (range 69.7 97.7 %), diclofenac with aspirin 80 mg reduced the thromboxane B_2 levels to the same extent as aspirin 80 mg, while ibuprofen with aspirin reduced these levels to 86.6 %, but with a wider range (77.6 95.1 %) than observed with aspirin alone (97.2 98.9 %). While the authors suggested that the concomitant treatment with diclofenac and aspirin had less of an effect in reducing the production of thromboxane B_2 than ibuprofen with aspirin, it is surprising from these studies that the impairment of platelet thromboxane B_2 production is not as striking as in the earlier studies of Catella-Lawson et al. (2001). Indeed, using thromboxane B_2 levels as a surrogate for anti-platelet effects of aspirin, it would appear that although there is some variability in the effects of ibuprofen with aspirin, the anti-platelet effects are not totally negated and indeed might be clinically significant. It is also possible that by increasing the dose of aspirin to say 100 150 mg, the negative effects of ibuprofen might be overcome. Moreover, in the context of the wide occurrence of platelet unresponsiveness to aspirin or even the more effective antiplatelet drug, clopidogrel (Galdding et al. 2008), the variability in effects of either ibuprofen or diclofenac on aspirin-induced thromboxane B_2 would appear to be manageable. This could be achieved as suggested by either by upward dose adjustment with aspirin and/or careful point-of-care platelet function technology to discriminate aspirin-resistance (Gladding et al. 2008a).

Studies with other NSAIDs have shown that the impairment of aspirin-induced platelet function ex vivo observed with ibuprofen were also observed with other NSAIDs (indomethacin, naproxen, and tiaprofenac acid), but not with celecoxib or sulindac (Galdding et al. 2008). While the antiplatelet effects of aspirin were reduced by the former three drugs, they did not abolish the effects of aspirin, but only showed wider variability (Galdding et al. 2008).

A consensus view would appear to suggest that the mode of action of ibuprofen in impairing platelet function inhibited by aspirin is that there is competition between ibuprofen and the active site of COX-1, which is irreversibly inhibited by covalent modification by the acetyl group of aspirin at or near the active site (Curtis and Krumholz 2004; Gaziano and Gibson 2006; Armstrong et al. 2008).

The US Food and Drug Administration (2006) have provided information for healthcare professionals with regard to the concomitant use of ibuprofen and aspirin, and have stated that with occasional use of ibuprofen, there is minimal risk from any attenuation of the anti-platelet effect of low-dose aspirin, because of its long-lasting effect on platelets. Moreover, patients who use immediate-release aspirin (not enteric-coated) and take a single dose of ibuprofen should take the latter

at least 30 min or longer after ingestion of aspirin, or more than 8 h before aspirin to avoid attenuation of the effects of aspirin.

Thus, it may be concluded that the *timing of aspirin and ibuprofen intake* may have considerable bearing on the interaction of ibuprofen with aspirin on platelets. The clinical significance of this in terms of the prevention of cardiovascular disease in patients, especially those taking OTC ibuprofen, that are at risk of developing these conditions clearly is of low grade when viewed in the context of the study by Kimmel and co-workers (2004).

Another important aspect arising from these studies is that ibuprofen itself inhibits platelet aggregation or functions (Brooks et al. 1973; McIntyre et al. 1978; Barclay 2005). The mechanisms of the inhibition of platelet aggregation by ibuprofen are, however, different from those of aspirin. Thus, Brooks et al. (1973) observed that 4 weeks treatment of male volunteers with ibuprofen 1,800 mg/day reduced aggregation induced by collagen and ADP, but not in recalcificated prior-citrated blood (a thrombin-induced reaction that is inhibited by aspirin). Platelet aggregation was inhibited, in blood drawn 40 minutes after 7 days treatment with ibuprofen, but this returned to normal after 24 h; a situation where it would normally be expected that aspirin would have produced 90 % inhibition of aggregation and prolongation of bleeding time. Moreover, ibuprofen does not cause inhibition of coagulation in recalcificated prior-citrated blood or increased prothrombin times (Brooks et al. 1973).

Notwithstanding the obvious differing basis of the aspirin ibuprofen interaction, the US FDA pronounced a warning on the concomitant use of aspirin and ibuprofen in patients who may be taking aspirin for the prevention of coronary vascular disease (Ellison and Dager 2007). Indeed, the FDA has published on its MedWatch Web site (http://www.fda.gov/medwatch/report.htm) information for health care professionals and drug facts with regard to warning of the concomitant use of ibuprofen and aspirin. In the information for healthcare professionals, it is stated that with occasional use of aspirin there is likely to be a minimal risk from any attenuation of the anti-platelet effects of low-dose aspirin because of the long-lasting effect of aspirin on platelets. Moreover, they state that patients who use immediate release aspirin (not enteric-coated) and take a single dose of ibuprofen 400 mg should take the dose of ibuprofen at least 30 min or longer after the aspirin ingestion, and not more than 8 hours before aspirin ingestion to avoid attenuation of the effect of aspirin on platelets. They state that recommendations about the timing of concomitant use of ibuprofen and *enteric-coated* low-dose aspirin cannot be made on the basis of available data. Thus, on the basis of information from the FDA and the available published literature, it is clear that separation of the dose of aspirin from that of ibuprofen is a practical means of being able to avoid the potential for impairment of the anti-platelet effect of aspirin by ibuprofen.

It should be noted that an earlier study in patients with rheumatoid arthritis by Grennan et al. (1979) showed that high-dose aspirin (3.6 g/day), but not a lower dose of 2.4 g/day in combination with high- or low-dose ibuprofen, had a weak clinical additive effect on indices of articular function and pain; this appeared to be related to an increase in serum ibuprofen by aspirin, but ibuprofen administration

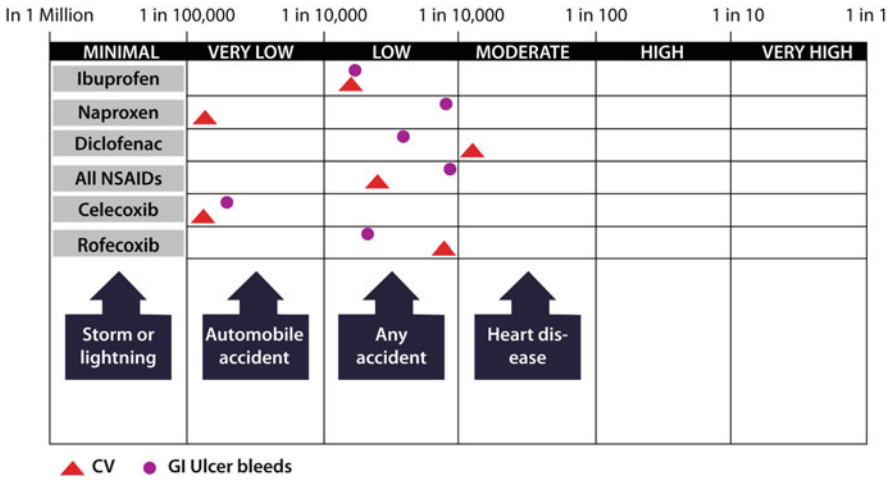


Fig. 8.2 Risks of death from cardiovascular and gastro intestinal reactions to NSAIDs related to life events. Redrawn from Moore et al. (2008)

did not affect serum salicylate levels. Thus, high doses of aspirin (not those usually used for anti-thrombotic effects) may have some impact on the clinical efficacy of ibuprofen in a positive way, but this is related to effects on ibuprofen concentration in the plasma.

8.6 Effects in Hypertension

Elevation of blood pressure is regarded as a surrogate for CV risk, especially in patients who are at risk of CV events. Studies with the coxibs, especially rofecoxib, indicated that they could increase blood pressure and produce oedema in patients with rheumatic conditions (Topol 2004, 2005; Khanna et al. 2005; Östör and Hazleman 2005; Rainsford 2005a; Antman et al. 2007). NSAIDs, including ibuprofen, cause little or no increase in blood pressure in normotensive individuals (Pope et al. 1993; Johnson et al. 1994; Miwa and Jones 1999; Nurmohamed et al. 2002). This has been confirmed in extensive meta-analyses of various clinical trials (Johnson et al. 1994). The issue is, however, that NSAIDs interfere with the actions of β-blockers (Johnson et al. 1994). In a controlled clinical trial in patients with mild to moderate hypertension receiving anti-hypertensive medications (β-blockers and diuretics), 3 weeks treatment with ibuprofen 1,200 mg/day caused an increase in supine blood pressure of 5.3 mmHg and in sitting mean arterial pressure of 5.8 mmHg, compared with placebo (Radack et al. 1987). Similarly, increased blood pressure was noted in a placebo-controlled clinical trial in patients receiving hydrochlorothiazide and 1,800 mg/day ibuprofen (Gurwitz et al. 1996). However, in a study in stage 1 and 2 hypertensive patients on low- and high-sodium diets

receiving the angiotensin-converting enzyme (ACE) inhibitor enalapril, ibuprofen 1,200 mg/day did not affect systolic or diastolic blood pressure, although in another study indomethacin reduced the effects of capropril (Velo et al. 1987). NSAIDs are well-known to interfere with the actions of ACE inhibitors (Badin et al. 1997). Calcium channel blockers do not appear to be affected by ibuprofen and other NSAIDs in hypertensive patients (Miwa and Jones 1999).

8.7 Congestive Heart Failure and Cardio-Renal Effects

Several studies have indicated that use of NSAIDs in patients with a history of heart disease may cause an increased risk of congestive heart failure (McGettigan et al. 2000, 2008). It appears that this effect of NSAID intake may be a class effect, and confined to patients that have been taking the normal anti-arthritis doses of these drugs. The risk of increased occurrence of congestive heart failure is overall an odds ratio of 2.8, but for those with a history of heart disease this may be increased to 10.5. It appears that plasma half-life of elimination plays a role in the risk of coronary heart failure, inasmuch as this risk seems to be doubled in long half-life versus short half-life NSAIDs (McGettigan et al. 2000; McGettigan et al. 2008).

Since inevitably the interference by NSAIDs in prostaglandin-dependent processes including haemostasis, vasodilation, vasoconstrictor balance, and renal functions including electrolyte balance influences the potential for cardiac toxicity via renal effects, this class effect with NSAIDs usually seen at high doses of NSAIDs with long half-lives may be a significant feature in the increase in hypertension and subsequent risk of cardiovascular disease (McGettigan et al. 2000).

8.8 Balancing CV and GI Risks of NSAIDs

To give some perspective of the concept of risk associated with GU and MI events, Moore and co-workers (2008) attempted to rate the risks of events against known life events (Fig. 8.2). Their estimates suggest that ibuprofen, like several other NSAIDs, with the exception of the risks of a heart attack with diclofenac, and celecoxib have *relatively* low risks for CV and GI events. This kind of analysis may be helpful to the public but may well disguise inherent risks, many of which have been discussed earlier.

Chapter 9
Renal Toxicity

Renal effects of ibuprofen are common to all those syndromes that are known to be produced by NSAIDs (Dunn et al. 1984; Breyer 1999; Murray and Brater 1999; Mounier et al. 2006). The four main primary types of renal impairments observed by NSAIDs are: (1) acute ischaemic renal insufficiency, (2) effects on sodium potassium and water homeostasis with interference with the effects of diuretics and anti-hypertensive therapy, (3) acute interstitial nephritis, and (4) renal papillary necrosis. The association of ibuprofen intake with the development of adverse renal effects is probably due to its widespread use rather than any particular characteristic of the drug per se, since irreversible effects are rare (Murray and Brater 1999). Renal dysfunction may be more pronounced in patients that have known risk factors including prior renal disease, stress, or impaired renal function (for example, changes in creatinine clearance) (Chen et al. 1994; Bennett 1997; Castellani et al. 1997; Galzin et al. 1997; Schwartz et al. 2002). The issue is probably of greater concern in elderly subjects, because of the higher prevalence of arthritic disease among them and the greater need for NSAID therapy (Murray and Brater 1999). On rare occasions, serious renal pathology has been observed with ibuprofen (Carmichael and Shankel 1985; Radford et al. 1996; Cook et al. 1997; Silvarajan and Wasse 1997; Murray and Brater 1999), but this has not been observed in trials with OTC ibuprofen (Whelton et al. 1990; Whelton 1995), and the evidence from literature analysis and clinical trials suggests OTC use of ibuprofen has not been found to cause significant renal injury (Rainsford et al. 1997, 2001; Doyle et al. 1999; Kellstein et al. 1999; Hersh et al. 2000a; Ashraf et al. 2001; Le Parc et al. 2002; Boureau et al. 2004).

Griffin and co-workers (2000), using Tennessee (USA) Medicaid US Federal State Program Database with patients at greater than 65 years of age, undertook an analysis of the effects of NSAIDs on the development of acute renal failure in these elderly patients. Their analysis included consideration of conventional population variables as well as the concomitant intake of prescription drugs and aspirin. In their study they identified 1,799 persons aged greater than 65 years of age with a community-acquired pre-renal failure or intrinsic renal failure that required hospitalization for varying periods of time. Patients with acute renal failure differed from

K.D. Rainsford, *Ibuprofen: Pharmacology, Therapeutics and Side Effects*,
DOI 10.1007/978 3 0348 0496 7 9, © Springer Basel 2012

controls in a variety of population-related and drug-related factors. NSAIDs featured in the increasing risk for pre-renal failure among those without any underlying renal insufficiency. The data on the odds-ratio estimates and the confidence intervals of 95 % of the risk of association between use of individual NSAIDs and hospitalization for acute renal failure among this population in a case-control comparison showed that ibuprofen had an odds ratio of 1.63 (1.23 2.08 95 % CI), exceeded only by piroxicam, fenoprofen and several other single or multiple-use NSAIDs. The slightly higher risk associated with ibuprofen intake may be a reflection of its widespread use.

In relation to over-the-counter use of ibuprofen and its possible association with the development of nephrotoxicity adverse reactions, it is been noted that analgesic nephropathy is not a widely recognized or reported effect of OTC ibuprofen (Mann et al. 1993), and certainly this is only infrequently reported in ADR reports made to the UK CSM (Prescott and Martin 1992). In the analysis of risks of renal side-effects of ibuprofen by Mann et al. (1993), it was found that the renal effects are dose-dependent, and that these effects are almost exclusively in elderly subjects with low intravascular volume and low cardiac output. Furey et al. (1993) observed that renal-vascular effects of OTC ibuprofen in elderly patients with mild thiazide-treated hypertension and renal insufficiency do not appear to be a risk factor for the development of renal compromise or hypertension.

Farquhar et al. (1999) and Farquhar and Kenney (1999) have shown that OTC dose of ibuprofen (1.2 g/day) in normal subjects subjected to heat-stress, low-sodium diet or dehydration may cause impairment of renal blood flow, glomerular filtration and electrolyte excretion which is related to inhibition of prostaglandin production. Studies in rabbits suggest that those with pre-existing renal failure receiving ibuprofen may have alterations in the pharmacokinetics of the two enantiomers of the drug (Chen et al. 1994), with the active (S+) isomer clearance being significantly impaired in this model of renal dysfunction. Thus, there may be increased prostaglandin inhibition in the renal tubular systems in individuals with renal impairment.

Overall, these studies suggest that OTC ibuprofen is a low risk factor for developing acute or chronic renal conditions, but that as with other NSAIDs there is increasing risk, particularly in elderly individuals or those with compromised renal function when the drug is taken at high prescription anti-arthritic doses.

Chapter 10
Hepatic Toxicity

Hepatic reactions have been of concern because of serious liver injury being reported with some NSAIDs and coxibs, e.g., diclofenac, sulindac (in the USA), celecoxib, and lumiracoxib (O'Brien and Bagby 1985; O'Brien 1987; Stricker 1992; Cameron et al. 1996; Tolman 1998; Zimmerman 2000; Lacroix et al. 2004; Bannwarth and Berenbaum 2005; Chang and Schiano 2007), as well as paracetamol even at usual OTC doses (Watkins et al. 2006; Heard et al. 2006, 2007). The problem with attributing hepatic reactions to a particular drug, whether it be an NSAID or otherwise, is that there are so many commonly used drugs that are hepatotoxic, especially those drugs used by rheumatic patients, e.g., antibiotics, anti-hypertensives, statins etc. (Stricker 1992; Cameron et al. 1996; Zimmerman 2000; Motola et al. 2007). Moreover, the pattern of hepatopathies varies considerably among the different drugs which may be taken with ibuprofen (or other NSAIDs) and that are associated with hepatoxicity (Sabaté et al. 2007).

As illustrated in Fig. 2.6, the complexities of the demands on the liver metabolism of so many commonly used drugs inevitably make for complex interactions leading to hepatotoxicity.

To obtain some indication of the incidence of hepatic reactions in patients taking NSAIDs, Traversa et al. (2003) investigated the occurrence of hepatotoxicity in a cohort study in Umbria (Northern Italy) in subjects that had recently taken NSAIDs. A total of two events were recorded as "all hepatopathies" (of 122 cases that had taken NSAIDs) and two with liver injury associated with recent use of ibuprofen (of 126 cases that had NSAIDs). Considering the extensive use of ibuprofen, this is a low incidence.

In a "case/non-case" compilation of reports extracted from the FDA and WHO (NIMBUS) databases, Sanchez-Matienzo and co-workers (2006) of the Pfizer Global Epidemiology group in Barcelona (Spain) attempted to give proportional estimates of the occurrence of different liver reactions attributed to individual NSAIDs. Tables 10.1 and 10.2 summarise data from Sanchez-Matienzo et al. Unfortunately, there are a number of critical issues about this data, among them: (a) there are no assessments of the likelihood of the event being associated with intake of a specific drug, (b) there is no information on confounding

K.D. Rainsford, *Ibuprofen: Pharmacology, Therapeutics and Side Effects*,
DOI 10.1007/978 3 0348 0496 7 10, © Springer Basel 2012

Table 10.1 Proportion of reports (PRs) of various hepatic disorders among cyclo oxygenase (COX) 2 selective inhibitors and NSAIDs in the World Health Organization Uppsala Monitoring Centre data source, updated to the end of quarter 3 of 2003

Drug	Overall hepatic disorders	Abnormal hepatic function	Jaundice	Hepato-cellular damage	Non-infectious hepatitis	Hepatic failure	Total no. of reports	Rank
Bromfenac	20.7	10.8	3.2	3.5	4.3	2.2	2,057	14
Celecoxib	2.1	1.3	0.4	0.2	0.5	0.2	17,748	12
Diclofenac	4.7	3.2	1.0	0.2	1.4	0.1	21,082	5
Etodolac	3.6	2.5	1.0	0.4	1.2	0.3	3,553	9
Ibuprofen	1.8	1.1	0.4	0.2	0.5	0.1	32,973	13
Indomethacin	1.8	1.0	0.5	0.1	0.5	0.1	14,576	7
Ketorolac	0.6	0.4	0.1	0.1	0.1	0.2	1,867	6
Meloxicam	0.8	0.4	0.1	0.0	0.4	0.0	3,042	11
Multiple NSAIDs[a]	5.0	3.1	1.2	0.4	1.4	0.4	33,660	4
Naproxen	1.6	0.8	0.3	0.2	0.3	0.1	13,646	1
Nimesulide	14.4	7.2	2.0	1.0	5.7	0.4	1,057	3
Proxicam	2.0	1.2	0.4	0.1	0.6	0.1	13,973	8
Rofecoxib	1.5	0.8	0.2	0.1	0.4	0.1	20,429	2
Sulindac	9.9	5.2	3.2	0.5	3.1	0.2	5,777	10

Values are percentages

PRs of concomitant use of other hepatotoxic drugs excluded

[a]Includes reports involving >1 COX 2 selective inhibitor and/or NSAID.

Reproduced from Sanchez Matienzo et al. (2006) with permission of Elsevier, publishers of Clinical Therapeutics

Table 10.2 Frequencies of potential confounders in the US Food and Drug Administration (under Freedom of Information) (FDA/FOI) and World Health Organization Uppsala Monitoring Centre (WHO/UMC) data sources

	Concomitant use of hepatotoxic drugs		Age ≥65 years	
Drug	FDA/FOI	WHO/UMC	FDA/FOI	WHO/UMC
Nimesulide	46.8	13.2	27.8	20.3
Celecoxib	35.0	17.4	35.3	34.2
Sulindac	31.0	16.7	33.4	33.2
Meloxicam	30.1	5.9	38.0	13.5
Diclofenac	29.4	11.0	34.0	17.6
Etodolac	28.0	13.5	29.8	21.7
Indomethacin	27.9	17.1	25.0	18.0
Ibuprofen	25.0	18.1	17.6	13.8
Rofecoxib	20.9	5.8	38.4	21.4
Piroxicam	19.4	7.5	29.4	17.9
Naproxen	18.7	15.3	21.6	16.7
Ketorolac	17.6	69.6	22.0	19.1
Bromfenac	15.5	8.7	8.7	9.1
Multiple NSAIDs[a]	48.1	15.0	34.8	22.5

Values are percentages

[a]Includes reports involving >1 cyclooxygenase 2 selective inhibitor and/or non selective NSAID.

Reproduced from Sanchez Matienzo et al. (2006) with permission of Elsevier, publishers of Clinical Therapeutics

Table 10.3 Percent liver reactions in rheumatoid- and osteo-arthritis patients in randomised-controlled trials (% of patients, 95 % CI)

	Condition/reaction				
Treatment	Elevated aminotransferases >3X, ULN	Liver-related discontinuations	Liver-related SAEs	Liver-related hospitalisation	Liver-related deaths
Ibuprofen	0.43 (0.26–0.70)	0.06 (0.02–0.23)	0	0	0
Celecoxib	0.42 (0.32–0.54)	0.08 (0.04–0.15)	0	0	0
Diclofenac	3.55 (3.12–4.03)	2.17 (1.78–2.64)	0.04 (0.01–0.16)	0	0
Meloxicam	0.19 (0.12–0.03)	0	0	0	0
Naproxen	0.43 (0.30–0.63)	0.06 (0.03–0.14)	0.06 (0.02–0.15)	0.01 (0.00–0.08)	0.01 (0.00–0.05)
Rofecoxib	1.80 (1.52–2.13)	0.16 (0.09–0.26)	0.05 (0.02–0.14)	0	0
Valdecoxib	0.04 (0.01–0.22)	N/A	0.02 (0.00–0.13)	0	0
Placebo	0.29 (0.17–0.51)	0.08 (0.02–0.29)	0	0	0

Reproduced from Rostrom et al. (2005) with permission from Elsevier, publishers of Clinical Gastroenterology and HepatologyThe data are principally from patients with osteo-arthritis. Analysis by arthritis type did not influence the overall results. One patient in the VIGOR trial, which involved rofecoxib, had toxic hepatitis and died from hepatic failure. This patient had received methotrexate and paracetamol, both established hepatotoxic drugs

Data derived from literature searches ($N = 67$ articles), the Cochrane Library and US Food and Drug Administration public archives ($N = 65$ studies)

ULN = upper limit of normal

SAEs = serious adverse events

patient-, disease- or drug-related factors, (c) there is probably considerable double counting between the FDA and WHO data, (d) there is no information on the intake of drugs in Defined Daily Doses (DDD)/100,000 patients, and (e) these data are in no sense quantitative, and the WHO cautions especially on the use of the data from what are spontaneous reports. At best, these data only give signals. Thus, the data only show that ibuprofen has been reported to produce liver reactions with concomitant use of hepatotoxic drugs being implicated in a considerable proportion of cases.

An extensive bibliographic analysis by Rostom and co-workers (2005) highlighted the differing liver reactions from NSAIDs from what is effectively a large database (Table 10.3). These data show that diclofenac and rofecoxib have the highest incidence of severe liver reactions requiring discontinuation of the drug, and also cause a high frequency of elevated transaminases. Meloxicam and valdecoxib (now discontinued) have the lowest incidence of liver reactions. Ibuprofen like several other NSAIDs showed low moderate reactions. The variations in the incidence of these liver reactions may reflect patterns and total use of the drugs.

In patients with rheumatoid arthritis and ankylosing spondilitis who receive methotrexate, this hepatotoxic drug may complicate the associations with NSAIDs and liver reactions (Colebatch et al. 2011). However, the numbers of liver reactions reported implicating NSAIDs and methotrexate appear small, and are most significant for aspirin (Colebatch et al. 2011).

Overall, the available data suggest that hepatic reactions are probably rarely associated with ibuprofen. Since there have been no specific indications of reports of hepatic reactions with OTC use of ibuprofen from trials (Doyle et al. 1999; Kellstein et al. 1999; Boureau et al. 2004) or in literature analyses (Whelton 1995; Rainsford et al. 1997), it is likely that hepatotoxicity is not a significant risk factor at OTC dosages.

Hepatic reactions do not appear to have been reported in any of the large-scale hospitalisation practitioner-based studies in children (Lesko and Mitchell 1995, 1999; Ashraf et al. 1999) or in critical reviews of clinical trials (Rainsford et al. 1997, 1999b, 2001). Hepatitis has been frequently reported in trials of NSAIDs including ibuprofen and aspirin in JRA or JIA (Giannini et al. 1990), but in a small long-term study, Ansell (1973) found that liver function tests were unaltered in these patients. The risks of liver reactions, especially in JRA or JIA, would appear to be low except where concomitant hepatotoxic drugs are taken (e.g., paracetamol, methotrexate) (Furst 1992; Hollingworth 1993).

Chapter 11
Other Adverse Reactions

Rare adverse events that have been reported at prescription level doses with ibuprofen, and less frequently with OTC doses, are common to those seen with all NSAIDs. Among these are thrombocytopaenia, agranulocytosis, anaemia, aseptic meningitis, and anaphylactoid reactions, interactions with the immune, endocrine, and metabolic systems, central nervous system and ocular effects, and some skin conditions including erythema multiforme, bullus dermatitis, Stevens-Johnson and Lyell's syndromes (Hoffman and Gray 1982; O'Brien and Bagby 1985; Haupt et al. 1991; Miwa and Jones 1999; Jackson et al. 2006; Layton et al. 2006; Neuman and Nicar 2007). Most but not all of these adverse events are rare, with the exception of allergies including aspirin-sensitive asthma, especially with OTC dosages of ibuprofen.

11.1 Hypersensitivity Reactions and Asthma

NSAIDs are associated with the development of a range of hypersensitivity reactions including asthma. The symptoms of intolerance to these drugs range from severe bronchospasm that is often associated with nasal polyposis, rhino-conjunctivitis, urticaria, cervico-facial erythema, angio-oedema, hypotension, and digestive disturbances (Arnaud 1995). These symptoms may occur individually or in any combination (Arnaud 1995; de Weck et al. 2006). The symptoms may be manifest within a few minutes to several hours after ingestion of the drug.

Recently, Nanau and Neuman (2010) described features of a type B hypersensitivity reaction which is idiosyncratic and is observed with NSAIDs including ibuprofen. These reactions occur in susceptible individuals, and are characterized by systemic disease involving a triad of fever, rash, and 'internal organ involvement' which is initiated from day 1 up to 12 weeks following drug intake. Host-dependent reactions involve a combination of T-cell and the effects on the production of cytokines and chemokines which exacerbate immune reactions.

K.D. Rainsford, *Ibuprofen: Pharmacology, Therapeutics and Side Effects*,
DOI 10.1007/978 3 0348 0496 7 11, © Springer Basel 2012

Hypersensitivity reactions of the respiratory system have been frequently reported with aspirin, and the terms "aspirin-associated asthma", "aspirin-sensitive asthma" or "aspirin-interant asthma (AIA)" have been employed to describe the association of symptoms of asthma with aspirin (Arnaud 1995; Rainsford 2004a: de Weck et al. 2006; Quiralte et al. 2007). In patients with ASA, small doses of aspirin can lead to severe attacks. Frequently, sensitivity to NSAIDs overlaps that with aspirin, as well as with ibuprofen (Jenkins et al. 2004). This has given rise to the concept of sensitization and the use of desensitizing procedures to treat this condition (Rainsford 2004a; Jenkins et al. 2004; de Weck et al. 2006; Quiralte et al. 2007). Paracetamol has been found to be tolerated in some patients with NSAID intolerance, but has in recent years been reported to be associated with asthma and hypersensitivity reactions (Arnaud 1995).

The incidence of NSAID intolerance has been variously estimated depending on the method of evaluation, study design, and population. Overall, the incidence can be 0.6 2.5 % of the general population (de Weck et al. 2006). The incidence is 4 % when asthmatic patients are interviewed, and can range up to 10 29 % in adult patients with asthma or those that have been challenged for presence of allergies (Arnaud 1995; de Weck et al. 2006). Hypersensitivity to NSAIDs usually appears in the second or third decade, and occurs in atopic subjects over the age of 40 years, this reaction being more common in females than males (Arnaud 1995; de Weck et al. 2006). Aspirin or NSAID intolerance is occurs infrequently in children (de Weck et al. 2006). AIA does not normally involve sensitization through IgE (Arnaud 1995; de Weck et al. 2006).

The mechanisms of NSAID sensitivity have been debated over the years but there is some consensus that it is due to COX inhibition in susceptible individuals, leading to over-production of peptidoleukotrienes causing bronchoconstriction and other asthmatic symptoms (Arnaud 1995; Rainsford 2005b). Other hypotheses suggest that there may be genetic influences relating to variability in leukotriene or prostanoid receptors (de Weck et al. 2006). Altered expression of COX-1, but not COX-2 with LT synthases have been considered as underlying the development of AIA (Harrington et al. 2008; Dobovišek et al. 2011). In a theoretical study, decreased expression of PGH synthase-1 and increased leukotriene C_4 synthase were considered key factors in the development of AIA (Dobovišek et al. 2012). In AIA, patients being given either aspirin or ibuprofen followed by a PGE_2 analogue enabled both drugs to be administered (Dobovišek et al. 2012), implying that regulating the immunopathogenic basis of AIA might be achieved via PGE_2.

Asthma and hypersensitivity reactions have long been a cause for concern in children, and the cross-reactions of ibuprofen with aspirin-sensitive asthma have been highlighted by several authors (Body and Potier 2004; Kidon et al. 2005; Mascia et al. 2005; Debley et al. 2005; Kanabar et al. 2007; Ponvert and Scheinmann 2007; Bousquet et al. 2009). On rare occasions, deaths have been reported in children or adults from intake of ibuprofen (Ayres et al. 1987; Antonicelli and Tagliabracci 1995). In a study in Finland, it was suggested that one death from ibuprofen might have been in a child that had a previous history of

allergy (Malmström et al. 2007). These authors also considered drugs were acting as triggers in some patients.

Two large-scale studies in febrile asthmatic children (McIntyre and Hull 1996; Lesko et al. 2002) found that ibuprofen, far from being associated with increased risk of asthma compared with paracetamol, actually showed a slightly reduced risk. Debley et al. (2005) performed a randomised, double-blind, placebo-controlled, crossover bronchoprovocation challenge study in 100 pre-screened school-aged children (6 18 years) and found that ibuprofen-induced bronchospasm was prevalent in 2 % of asthmatic subjects. Another 2 % had clinically relevant decreases in spirometric measurements after ibuprofen administration, but these did not meet the authors' a priori criteria for a positive challenge test. These authors considered that ibuprofen-sensitive asthma has a low prevalence, but nonetheless ibuprofen-induced bronchospasm should be considered as a risk in childhood asthma.

Literature reviews of clinical trials (Kanabar et al. 2007) have indicated that there is a low risk for asthma with ibuprofen, and that in contrast paracetamol might be associated with wheezing in children. Ibuprofen might have protective effects in some subjects with asthma, in contrast to paracetamol (Mazur 2002; Kanabar et al. 2007), but caution should be emphasized in any attempts to exploit this suggestion by trying ibuprofen in children with asthma.

11.2 Cutaneous Reactions

Minor or "non-serious" skin reactions are among the more frequent reactions observed with NSAIDs including ibuprofen (Bigby and Stern 1985; O'Brien 1987; Ponvert and Scheinmann 2007). The risks of various skin reactions occurring with "ibuprofen-containing medications" have been highlighted by Sánchez-Borges et al. (2005). Their review drew attention to the different types of skin reactions and the lack of quantitative information on the associations with ibuprofen.

A case control study performed in a region in Denmark of the occurrence of angio-oedema among NSAID and coxib users in hospital admissions by Downing et al. (2006) showed that the relative risks for this condition were higher in coxib users than in those taking traditional NSAIDs. There were 25 cases out of a total of 377 patients.

Data from reports of serious and non-serious cutaneous reactions for NSAIDs reported in Italy as part of an overall programme of drug surveillance by Naldi and co-workers (1999) are shown in Fig. 11.1.

These show that ibuprofen ranked in the mid-range of reports.

Ibuprofen, like other NSAIDs, is associated with the occurrence of skin reactions, many of which can be rated as mild. Serious ADRs in the skin are rare. There have been occasional reports of Stevens Johnson and Lyell's syndromes as well as severe bullous reactions (Bigby and Stern 1985; Miwa and Jones 1999; Sánchez-Borges et al. 2005). However, these serious conditions have not been reported in controlled trials or in literature with OTC events with ibuprofen

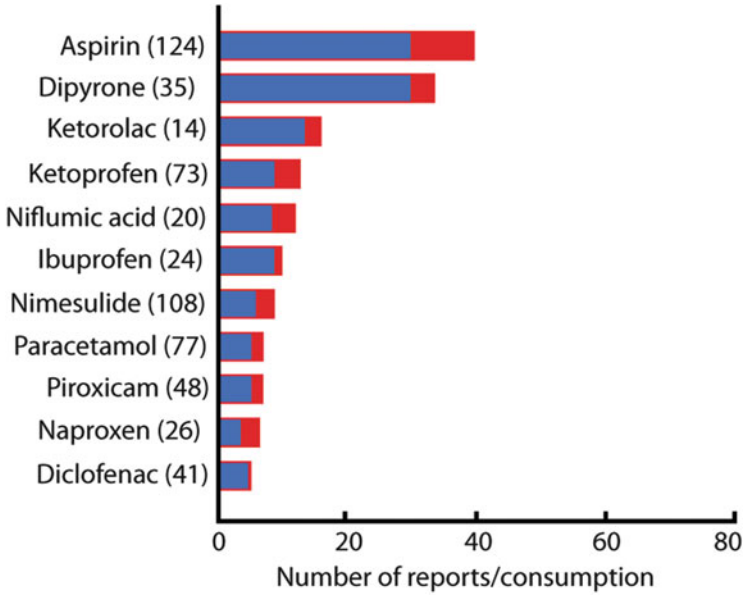


Fig. 11.1 Reporting rates of serious (*black bars*) and non serious cutaneous reactions to NSAIDs and analgesics compared with reports/consumption in DDD's/1,000 inhabitants/day in four regions in Italy. Drug consumption data was derived from pharmacy sales data or hospital pharmacies. Numbers of reports for each drug are shown in *brackets*. Redrawn from Naldi et al. (1999) with permission of Wiley Blackwell for the British Journal of Clinical Pharmacology

(Rainsford et al. 1997, 2001; Doyle et al. 1999; Kellstein et al. 1999; Hersh et al. 2000a; Ashraf et al. 2001; Le Parc et al. 2002; Boureau et al. 2004).

In their large-scale Boston University Fever studies, Lesko, Mitchell and colleagues (Lesko and Mitchell 1995; Lesko et al. 2002; Lesko 2003) did not observe any hospitalizations for anaphylaxis. However, three cases of erythema multiforme occurred in patients that had received ibuprofen and one that had received paracetamol, thus making the risks of these events very low (Lesko and Mitchell 1995). Ashraf et al. (2001) in their large-scale OA trial also noted there were no cases of Stevens Johnson syndrome among their patients.

11.3 Risk of Fractures

The possibility of fractures being associated with NSAID use has been identified in patients with rheumatoid and osteoarthritis (Vestergaard et al. 2006). In these epidemiological studies, adjustments were made for stratifying two cumulative daily dosages (defined daily dose DDD) and other confounders. There was an odd disease association that was observed in these studies, in that osteoarthritis was associated with a decreased risk of any fracture, and rheumatoid arthritis was

associated with increased development of fractures. These studies highlighted that high-dosage intake of aspirin, paracetamol, diclofenac, meloxicam, and some other NSAIDs but not coxibs was associated with an increased risk of fractures. Ibuprofen showed an odd inverse dose-related effect, in as much as the adjusted odds ratios (less than or 20 74 DDDs, approx. 1.8 1.82) were higher than those where the drug was taken in greater quantities (1.42). Thus, hip fractures and other bone fractures being a risk factor in elderly rheumatic patients taking NSAIDs for long periods of time may be more a class indication as distinct from a specific risk factor associated with any one drug.

Using the UK General Practice Research Database, Van Staa et al. (2000) examined the factor risk of being exposed to NSAIDs, using a case control approach. Regular NSAID intake was associated with an increase of risk compared with control of 1.47 (1.42 1.52 95 % CI) for non-vertebral fractures, while the risk of hip fractures was relatively low, being 1.08 (0.9 1.19 95 % CI). It appeared from this study that ibuprofen had the lowest risk of non-vertebral fractures, as it was used as the reference, but there was a larger number of cases of ibuprofen compared with other NSAIDs, probably reflecting a wider-spread use. In contrast to these observations in development of fractures, studies by Persson and co-workers (2005) suggest that long-term treatment of patients with who have undergone surgical revision of hip arthroplasty.

Chapter 12
Global Assessment of Adverse Reactions and Human Toxicology

In this chapter, experience in the regulation of ibuprofen by international drug regulatory agencies is reviewed and analyzed. In this review, some of the major issues are highlighted which have occurred over the two and a half decades since ibuprofen was first approved for OTC use in the UK and USA, and how these have been assessed and managed. Recent experience in Australia is reviewed, where the drug was granted GSL status having been previously pharmacy-only sale at the accepted OTC dosage (1,200 mg/day) in that country.

12.1 Initial Basis for Approval for OTC sale in UK and USA

It is now nearly 30 years since ibuprofen has been approved in the UK for non-prescription OTC sale to the public (Rainsford 1999a). This was undoubtedly a landmark decision, based on a review of safety data that had been accrued from a relatively large number of studies where the drug had been taken at or below the 1,200 mg/day dose in earlier trials in rheumatic diseases and later, following dose-incrementation, at the upper dose level of 2,400 mg/day for these conditions (Rainsford 1999a, 2003). While dose-incrementation had been largely physician-led, in the belief that patients (especially those with RA) might have better response to the drug in more painful inflammatory conditions, the lower dose was still regarded as being effective for control of pain and joint symptoms in mild moderate rheumatic conditions; higher dosage was needed, it was perceived, in patients with more severe rheumatoid arthritis (RA). In the determination of safety of the drug, a large body of evidence was accumulated at the 1,200 mg/day dosage in rheumatic disease. This showed that the drug had low ADRs and a favourable safety profile.

In the assessment of the suitability of ibuprofen for over-the-counter sale, the UK Dunlop Committee (later the Committee on the Safety of Medicines, CSM), considered a priori the safety of ibuprofen as its efficacy was accepted and not of concern. Since the data on 1,200 mg/day dosage was primarily derived from patients with RA, a condition that is well-known today to have profound systemic consequences,

K.D. Rainsford, *Ibuprofen: Pharmacology, Therapeutics and Side Effects*,
DOI 10.1007/978 3 0348 0496 7 12, © Springer Basel 2012

leading to increase risks of gastrointestinal (GI) hepato-renal and cardiovascular (CV) conditions, it would appear in retrospect that the data on safety would have been derived from a critical patient group. If any untoward effect should occur or be evident, then it would surely have been revealed in this patient group.

Thus, the approval by the UK CSM in 1983 enabled ibuprofen to be made available, initially in pharmacies, but during the growth of supermarket chains during the last one to two decades, in this retail outlet direct to the public without intervention specifically of the pharmacist.

In practice, ibuprofen was effectively the third choice by the public after aspirin and paracetamol for use by nearly all age groups except infants. The wave of concern about the risks of Reye's syndrome in the 1980s, with its relatively high fatal outcome in children receiving aspirin, led to extensive publicity and later proscribing of the use of aspirin in children. It is possible that there was a shift in use of paracetamol, especially in paediatric formulations, to replace aspirin use in children with febrile conditions, but ibuprofen was only "second choice".

In 1984, ibuprofen was approved by the FDA for OTC sale in the USA. The application was made by Upjohn (Kalamazoo, MI, USA) who had licensed the drug from Boots Pharmaceuticals (Nottingham, UK) and had performed extensive investigations on ibuprofen, including a considerable number of large-scale clinical trials (Altman 1984). In these studies in RA patients, the drug dosage was increased to 3.4 g daily, which was exceptional. The reasons for undertaking studies at this high dose level are not clear, except to prove a perceived unmet need for a highly effective pain-relieving drug in rheumatic disease. The majority of doses in the trials in the USA were at $\leq$2.4 g/day.

Again, as with the UK CSM, the decision to allow ibuprofen to be granted OTC status by the FDA was based a priori on safety. It was given that the drug worked in pain relief and in controlling the fever symptoms in respiratory and other mild febrile conditions. Doubtless, reasoning in a consumer society such as in the USA would be that patients would not buy the drug if it was ineffective.

Since these two landmark approvals, ibuprofen has been granted OTC approval in a number of countries. In Canada, impetus for OTC approval was from the legislation designed to promote the use of generic drugs with their lower costs to the consumer and healthcare systems, this legislation being enacted in the late 1980s. Several countries in Europe have granted P to GSL status.

12.2 Experience in the UK

The UK Medicines and Healthcare Products Regulatory Agency (MHRA), formerly the Committee on the Safety of Medicines (CSM) operates an ADR reporting system through the UK Department of Health. Medical practitioners, pharmacists, and other healthcare professionals are encouraged to report adverse reactions to this agency through what is termed the "yellow card" system. The reports are evaluated by experts, and assessments are made regarding possible causality.

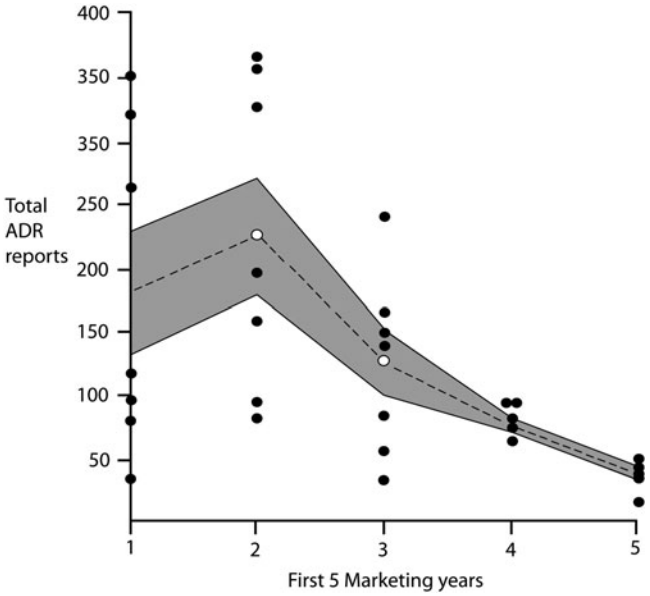


Fig. 12.1 Pattern of adverse drug reaction reporting to the UK CSM for a range of NSAIDs in the first 5 years post marketing. Redrawn from Weber (1984), reproduced with permission of Springer, owners of Raven Press

In more recent years, more critical attention has been given to assessment of ADRs, but even so the reliability of reporting and the quality of reports can vary. Also, as noted by one of the Department of Health scientists, Dr JCP Weber, there are a variety of factors influencing reporting of ADRs in the yellow card system (Weber 1984). Amongst these, reports of ADRs for anti-inflammatory/analgesic drugs often peak at about 2 years after the introduction of a new drug, then taper off (Fig. 12.1).

Such features as the "novelty" of the reaction, concerns about the occurrence of particular reactions, "awareness" by physicians or other healthcare professionals, and even commercial interests may influence reporting frequencies.

A summary of the adverse events recorded in the UK from ibuprofen, aspirin, and paracetamol covering the period of 1963 2010 are summarized in Fig. 12.2. It should be noted that these data have been obtained from all dose levels (i.e., prescription as well and non-prescription or OTC doses) and for varying periods of time.

This covers the period of 1963 2010, and there is no differentiation according to period or amount of drug taken. There is, however, discrimination of data according to (a) single active constituent, (b) multiple active constituent (i.e., intake with other medications), and (c) total of what is described as unique reports, a term which is not clearly defined but presumably related to toxic phenomena which may be related to the specific drug. Fatal and non-fatal reports are shown. Fatal and non-fatal reports data are presented graphically in Fig. 12.2.

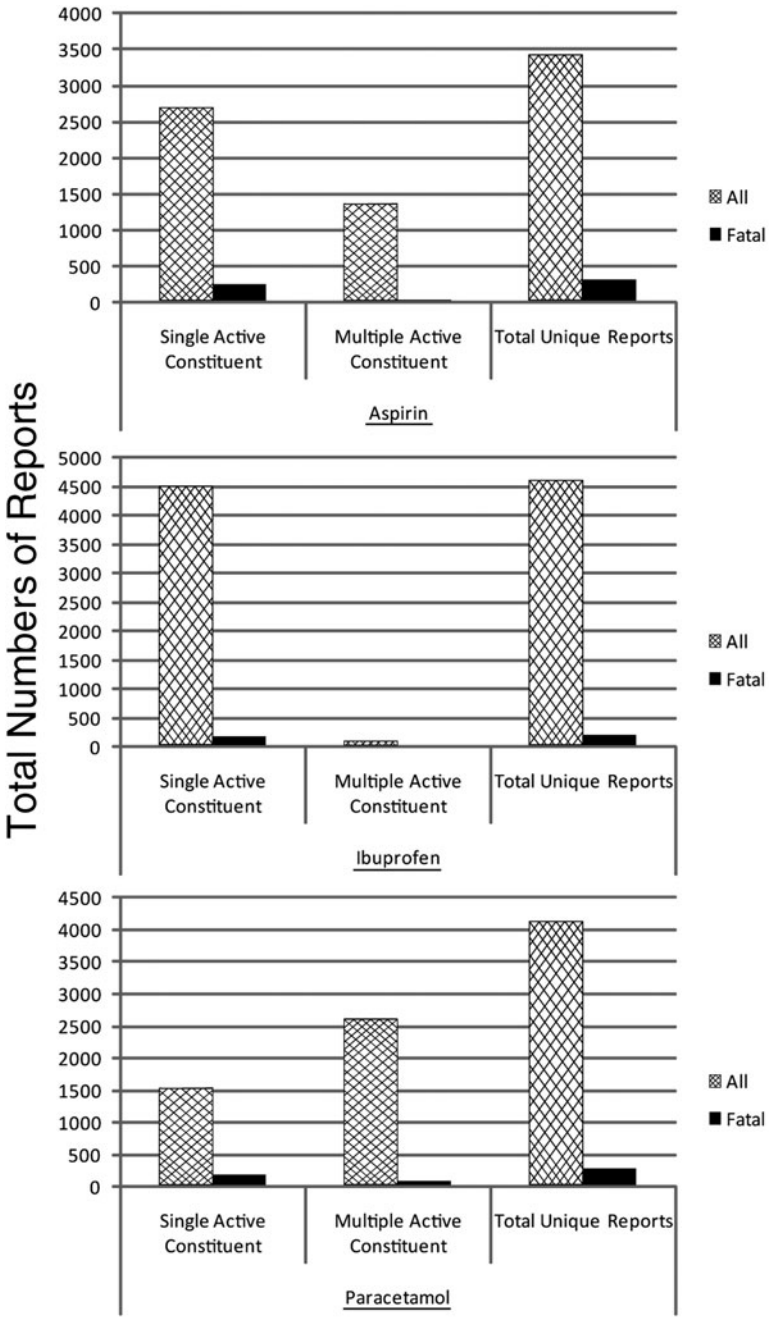


Fig. 12.2 Reports of adverse events to the UK Medicines and Healthcare Products Agency (MHRA, formerly the Committee on the Safety of Medicine, CSM) attributed to aspirin, ibuprofen, and paracetamol. The data were obtained from the UK MHRA courtesy of Dr. Phil Berry, Reckitt Benckiser Healthcare. Total unique reports refers to those in which drug is suspected

Taking the data from single active constituent, the total and percentage of total reactions primarily involve GI disorders in decreasing order with aspirin, ibuprofen, and to a lesser extent with paracetamol. This is in accordance with what would be expected. This order of data also parallels the number and percent of fatal ADRs involving GI disorders. The number of reaction fatalities and number of ADR reports associated with hepatic disorders is relatively low with ibuprofen and aspirin, but as expected is relatively higher than with paracetamol. Skin, blood, and CNS disorders appear more prevalent with ibuprofen and paracetamol, but the number of fatalities is low with all three drugs.

The number of reaction fatal reports and ADR reports in the category of Unique Reports predominates in the GI tract, in parallel with the reports under single active constituent. Likewise the low prevalence of liver disorders with aspirin and ibuprofen contrasts with the high prevalence associated with paracetamol.

Considering the period of 37 years over which this data has been accumulated, the total number of fatal reports from ibuprofen (199) contrasts with those from paracetamol (289) and aspirin (310).

It should be emphasized that these data can only be interpreted quantitatively with estimates of drug intake on a defined daily dose intake (DDD).

It is not possible to determine incidence rates for ADRs reported or attributed to ibuprofen, since no denominator information is available about the population size or drug packs consumed by the subjects from whom reports have been volunteered.

These data, when considered in relation to widespread use of the drug, show that there is a relatively low occurrence of major adverse events attributed to ibuprofen in the UK.

12.3 Cases of Poisoning in UK

As noted earlier, the number of reports to the NPIS (the main referral centre in the UK for enquiries and reports of poisonings) about ibuprofen are now second to those for paracetamol.

Reviews by Volans (2001, 2012) and Volans and Fitzpatrick (1999) serve as background information on poisoning cases from the drug, principally in the period when the drug was prescription or P-only in the UK, although more recent information up to the time of writing at the beginning of 1999 contained early observations in the period after 1996 when there was P to GSL reclassification in the UK. Dr. Volans notes the following key points:

(a) The switch to GSL licence in 1996 doubled sales of ibuprofen, but this was without a corresponding increase in ADRs reported to the MHRA.
(b) The shift to GSL in Australia in January 2004 has not resulted in increasing reports of poisonings.
(c) Poisonings in the USA have not been seen to be a major concern in that country, where OTC ibuprofen has been widely available OTC for two decades or more.
(d) There is evident low toxicity from overdose of ibuprofen.

With respect to the last point, it is clear from a large number of studies (Rainsford 1999b, 2004a, 2009) that ibuprofen has the lowest toxicity of all analgesics. Mechanistically, there is no evidence of irreversible toxic actions that would be attributed to the covalent modification of endogenous biomolecules analogous to that observed in the liver toxicity from the quinine imine metabolite of paracetamol (Graham and Hicks 2004), or the GI ulceration and bleeding arising from irreversible acetylation of platelets and other cyclo-oxygenases or biomolecules from the acetyl-moiety of acetylsalicylic acid (aspirin) (Rainsford et al. 1981; Rainsford 2004a).

12.4 Limitations on Analgesic Pack Sizes in UK

During the 1990s, there was growing concern in the UK about the toxicity to the liver from paracetamol. This drug is known to cause irreversible liver damage, often with fatal outcome in poisoning. There is also evidence that paracetamol may cause severe liver injury in certain conditions in doses $\geq$4 g/day. As a consequence of these concerns, the UK MHRA reviewed the safety of all analgesics, since there have also been ongoing concerns about gastro-intestinal and renal effects of aspirin in particular, and to a lesser extent from ibuprofen.

A consequence of this was that legislation was introduced in September 1998 to limit the general sales and sales by pharmacies of paracetamol and aspirin by restricting the pack size (Hawton et al. 2001; Morgan et al. 2007). Ibuprofen, with or without codeine, had already been sold in small pack sizes consistent with its OTC labelling. The limitation of pack sizes of paracetamol and aspirin has had a significant impact in reducing cases of poisoning, accidental or deliberate, with a trend to reducing serious outcomes including deaths (Hawton et al. 2001; Morgan et al. 2007).

Statistics from the UK National Poisonings Information Service (Anonymous 2006) show that over 115,000 enquiries have been received about paracetamol annually, which comprised 99,000 visits to paracetamol poisoning information on TOXBASE the NPIS's online information database and about 16,000 telephone calls. In comparison, 42,000 enquiries were received by the NPIS about ibuprofen and 25,000 about aspirin.

12.5 Concerns About Misuse of Analgesics in USA

During the early part of this decade, the US FDA has been increasingly concerned about the safety of OTC analgesics. Initially, concern was about the dangers of paracetamol causing hepatotoxicity and deaths in an increasing number of reports. However, the GI and renal effects of OTC NSAIDs (which include naproxen and ketoprofen as well as aspirin and ibuprofen) were also highlighted. Among the

reviews of safety issues of OTC analgesics was a meeting of the Nonprescription Drugs Advisory Committee (FDA) on September 19 20, 2002 with experts from other advisory committees to the FDA, who reviewed and discussed available data on US case reports regarding accidental and unintentional overdoses with paracetamol and NSAID-related GI bleeding and renal toxicity. A number of actions resulted from these discussions, including:

- A national education campaign on the safe use of OTC pain relief products which was announced in January 2004 (http://www.fda.gov/fdac/features/2004/204 otc.html).
- A Letter to State Boards of Pharmacy highlighting and advising especially about the danger of hepatotoxicity in association with paracetamol and GI and renal effects of NSAIDs (http://www.fda.gov/cder/drg/analgesics/letter.html).

Chapter 13
Overall Assessment

It is clear from this review of available evidence on the safety and efficacy of ibuprofen that this drug is amongst the safest and most effective of the analgesics available to the public for relief of symptoms of mild to moderate pain and inflammation.

The evidence of the adverse reaction profile from ibuprofen has been derived from published studies at the prescription dose level (1,800 2,400 mg/day). The higher prescription-level dose range gives information that in relation to the OTC level can be regarded as the upper limit of toxic reactions that are likely from this drug. In terms of dose response, the most frequent adverse reactions are seen in the GI tract, skin, and possibly renal systems.

While serious GI events (GI ulceration, bleeding) occur with prescription-level ibuprofen, the consensus of data support the conclusion that ibuprofen has the lowest GI risk of all NSAIDs, although this is dose-related. The low OTC dosage studies in controlled clinical trials show that GI and other ADRs are rare and have minor outcomes (Rainsford et al. 1997; Doyle et al. 1999; Rainsford 1999a, b, c; Ashraf et al. 2001; Le Parc et al. 2002; Moore et al. 1999, 2002, 2003).

13.1 Spontaneous ADRs and Toxicity

Spontaneous events from OTC ibuprofen in the UK, the USA, and Australia indicate that serious ADRs are rare. Most involve the GI system, renal, and respiratory systems. Oedema and minor respiratory reactions along with some minor skin reactions occur infrequently asthma, bronchoconstriction, and cardiovascular events are rare.

Relatively few deaths have been noted with ibuprofen, and mostly in patients with other serious complications.

While an increase in cases of ibuprofen poisoning has been reported to the National Poisons Advisory Service, London, in the period post-1996 when ibuprofen was granted GSL status in the UK, this has not been accompanied by serious

K.D. Rainsford, *Ibuprofen: Pharmacology, Therapeutics and Side Effects*,
DOI 10.1007/978 3 0348 0496 7 13, © Springer Basel 2012

outcomes or deaths. Indeed, OTC ibuprofen has very rarely ever produced deaths, even in accidental or deliberate acute overdose.

Ibuprofen must, in comparison with paracetamol or aspirin (let alone other analgesics), be considered a drug least likely to result in mortality in overdose. It is associated with morbidity from GI haemorrhage at OTC doses, but very rarely has this resulted in fatality.

In comparison with paracetamol and aspirin, ibuprofen has the lowest risks of GI, CV, and hepato-renal toxicities. While GI toxicity is probably the most significant, it is markedly less than that of aspirin, but more than that from paracetamol. However, the pharmacoepidemiologic observations (Henry et al. 1996, 1998; Garcia-Rodriguez and Hernandez-Diaz 2001; Bjarnason 2007), supported by studies in laboratory animal models of GI toxicity, suggest that under some conditions paracetamol may not be entirely without GI toxicity (e.g., in certain patients with hypersecretory functions in the stomach, those with profound inflammatory conditions, or those taking NSAIDs concomitantly) (Whitehouse and Rainsford 2006). Serious GI reactions may occur, but are relatively rare and are dose- and time-dependent (Bjarnason 2007).

In contrast to the situation of liver toxicity associated with paracetamol, and to a lesser extent with aspirin, serious liver reactions are rare with ibuprofen. Indeed, it should be recalled that ibuprofen was developed as a drug without liver toxicity, in the light experience with its progenitor, ibufenac (Rainsford 1999a).

Renal effects of low-dose NSAIDs may contribute to reversible alterations in excretion of sodium and potassium, and reduction in the efficacy of anti-hypertensive agents and diuretics as a consequence of inhibitory effects on renal prostaglandin production (Brater 1998). This also applies to ibuprofen. Consequent exacerbation of hypertension in patients with this and related CV conditions may represent a risk factor. However, even at prescription-level doses the risk of serious CV reactions is low, and certainly not in the order of those for coxibs (Antman et al. 2007; Strand 2007; Trelle et al. 2011).

Concerns have been raised about ibuprofen affecting the anti-platelet, and thus anti-thrombotic activity of aspirin, especially at low dose. It appears this may possibly occur when the two drugs are taken concomitantly. The suggestion has been made to recommend that these two drugs not be taken concomitantly, but to separate the time of taking these drugs. Certainly, this would appear to make sense pharmacokinetically and pharmacodynamically. The short plasma elimination half-life of ibuprofen, and the short period (~15 30 min) when aspirin acetylates platelets COX-1 would seem to make this a feasible recommendation. It has been postulated that ibuprofen interferes with aspirin, at the level of competing with the COX-1 binding site for aspirin. Given this specific nature of the pharmacodynamic interference, it is likely that even short periods of separation of the intake of these two drugs will notably reduce the risk of ibuprofen interfering with the anti-thrombotic effects of aspirin. It would also be preferable to take the dose of aspirin before ibuprofen.

It does seem that as aspirin increases the risk of NSAIDs causing serious GI reactions, taking aspirin and ibuprofen would not seem a safe procedure.

Another aspect that has not been considered is the possibility that use of aspirin to prevent platelet aggregation in patients with thrombo-embolic diseases may not be necessary in patients taking ibuprofen, since it has been shown that ibuprofen can inhibit certain components of platelet aggregation. The clinical significance of this effect in prevention of CV disease has not been explored. It has, however, been noted that naproxen has low CV risks, and this may be related to the inhibition of platelet aggregation by this drug.

Meta-analysis studies in the large-scale coxib trials suggest that ibuprofen has low CV risk, which in most studies does not appear to have been greater that a RR of unity (Antman et al. 2007; Trelle et al. 2011), so that this component of the overall safety of ibuprofen would appear to be a low possibility with ibuprofen.

13.2 Benefit/Risk Analysis

In terms of benefits, ibuprofen at OTC recommended doses has been proven to have either comparable or in many cases superior therapeutic effects to those of other NSAIDs or analgesics in the treatment of a wide variety of painful and associated inflammatory conditions, including the following:

- Inflammatory arthropathies and other musculo-skeletal conditions
- Dental pain
- Primary dysmenorrhoea
- Upper respiratory tract infections, colds and influenza
- Sports and other minor injuries

In most of the conditions where there is a *pronounced inflammatory component*, ibuprofen is superior to the alternative analgesic, paracetamol, because of its substantial anti-inflammatory component. Paracetamol does not have appreciable anti-inflammatory activity. Ibuprofen is more potent than aspirin as an analgesic and anti-inflammatory agent. Thus, in respect of therapeutic benefits ibuprofen is *clinically superior* to the other two OTC analgesics. It clearly affords *an important therapeutic alternative for the public* which is widely recognized in the UK, North America, Australia, New Zealand, Switzerland, and many other European, Central and South American as well as Asian countries. In these countries, it is widely recognised for its relative safety which is clearly superior to that of (a) paracetamol, especially in relation to the hepatic risks factors from this drug, and (b) aspirin, where there are appreciable GI risks.

13.3 Assessment of Risks and Procedures for Their Reduction

The potential risks to the public taking ibuprofen at OTC doses arise from:

- Upper GI distress comprising principally dyspepsia and epigastric or abdominal pain, as well nausea, diarrhoea, and to a lesser extent vomiting. The evidence suggests that the risk of serious upper GI events is low at OTC doses. In "real-world" situations, OTC ibuprofen has been found to have relatively few reports of serious GI ADRs, cutaneous reactions, and superficial oedema, which are reversible upon cessation of the drug. Warning the patient of the occurrence of these symptoms should be adequate to prevent their occurrence.
- On rare occasion, renal and hepatic reactions, which in the normal course of events would inevitably lead the patient to seek medical advice. Some precautions might be advisable to warn of the risks of taking medications that are known to affect these organ systems.
- The risks of symptomatic events (dyspepsia, pain, nausea, etc.) are more common with ibuprofen but no different than those of paracetamol (which has been used in extensive studies as a bench-mark for comparison) and placebo in those studies where this has been employed as a basis of comparison. These ADRs can be considered largely "self-limiting", inasmuch as they mostly result in cessation of use of the drug.

Well-known factors are associated with increased risks of all NSAIDs in developing serious GI reactions, among them (a) concurrent high intake of alcohol, corticosteroids, other ulcerogenic drugs, (b) ageing and impaired hepato-renal functions, (c) presence of *Helicobacter pylori*, (d) long plasma elimination half-life, and (e) high relative potency as inhibitors of COX-1 derived mucosal protective prostaglandins.

Some of these factors can be reduced by recommending avoidance of intake of drugs such as those in (a) above, and patients who are "at risk" such as in (b). The properties of being a short half-life drug and relatively low potency as a cox inhibitor (especially as it is reversible, in contrast to many NSAIDs and coxibs that have pseudo-irreversible inhibitory properties) reduces the likelihood of these factors underlying the development of serious GI events with ibuprofen. *H. pylori* is a different matter. This may only emerge when there are untoward upper GI events that highlight the need to investigate for the presence of this pathologic organism.

Risk reduction also involves advising patients with pre-existent states, e.g., history or presence of peptic ulcer disease, renal, and hepatic diseases from taking ibuprofen.

Clearly, safety is a feature of ibuprofen that is to its advantage, but use of the drug by patients that may be at risk of developing a particular side-effect raises the prospect that there may be "channelling" of high-risk subjects. There is also an important role for education in risk reduction. This may take several forms, e.g., advertising and publicity directed to the public, package labelling, and patient information leaflets.

Many of these educational issues have application to the safe use of all analgesic preparations and not to ibuprofen alone. Some of the principles and suggestions outlined here could well apply to aspirin and paracetamol in particular.

However, this could be made a generic approach, especially when cautioning on drug interactions, prior- or concurrent conditions likely to exacerbate or trigger adverse reactions, and appropriate use of these medications.

It is possible that some members of the public who may not be adequately in formed or appreciate the problems with taking medications that are available in stores or even pharmacies may be at risk because of lack of knowledge, literacy, or understanding (cognition). It is of course a world-wide problem that there are different levels of literacy in various socio-economic classes or groups. This situation has been highlighted in relation to concomitant intake of Chinese Traditional medicines CTMs and other herbal remedies, which raises issues about herbal drug interactions that may affect the safety and efficacy of ibuprofen (Sect. 6.10). There may be a case for recommending that CTM practitioners, quasi-professionals, pharmacists, and herbalists should be specifically educated and trained to advise patients or customers not to take CTMs with ibuprofen and other NSAIDs or analgesics because of the risks of herbal preparations interacting in an untoward manner with these drugs. The labelling of packages and advice to patients taking ibuprofen as well as other NSAIDs or paracetamol should include specific warnings not to take these drugs with CTMs/herbal preparations.

An approach to improve understanding by members of the public when not to take analgesics, and when it is appropriate for them to do so, is to simplify and make more meaningful recommendations on the package as well in the patient information leaflets (PILS).

13.4 Examples of Advice for Ibuprofen Packages and PILs

Don't take this pain-killer with

- Alcohol (beer, wine, whiskey)
- Other pain killers
- If you have stomach pains
- If you take blood thinners
- If you are receiving treatment for cancer, heart disease, or other serious diseases unless specifically advised by your doctor
- If you have problems or reactions to this drug, then immediately consult your pharmacist or doctor
- Chinese traditional medicines or herbal preparations

Many examples of complex labelling and PILS derive from over-riding concerns that statements made on packs and PILS should be legally sound, without

consideration of the perception of the confusing nature of information which is often provided with medications. For analgesics this is a particular issue, and one which could be addressed by having simple do's and don'ts, even the use of iconic easy-to-understand symbols.

Chapter 14
Summary

Ibuprofen has become one of the most widely used analgesic and anti-inflammatory drugs in the world today. In the USA alone, this drug is the largest selling analgesic sold over the counter (OTC) for non-prescription use. Its success as an OTC drug has been due partly to its relative effectiveness and safety in low dosages, and the low risks of serious toxicity in the population at large. Moreover, as a prescription-only drug taken at higher doses for the treatment of arthritic and related chronic inflammatory diseases, it still has wide acceptability for short-term use, despite competition from the newer non-steroidal anti-inflammatory drugs (NSAIDs), including the coxibs, as well as the non-narcotic analgesics (including paracetamol or acetaminophen).

This book reviews the mechanisms of action of ibuprofen, and its therapeutic applications in a wide variety of painful and inflammatory diseases. Aspects of the safety of this drug are reviewed, including (a) the *overall* safety profile of ibuprofen at current prescription dosage 1,800 2,400 mg/day, wherein the drug is recommended for the short- and long-term treatment of acute and chronic moderate to severe inflammatory pain conditions, including rheumatoid- and osteoarthritis, spondylo-arthropathies and other rheumatic conditions, (b) *specifically* the safety of ibuprofen $\leq$1,200 mg/day for a maximum dosage period of 7 14 days, which in over 80 countries worldwide is sold as an OTC analgesic for the relief of mild to moderate painful conditions, many of which have a moderate acute inflammatory component, (c) the efficacy and therapeutic activities of ibuprofen principally at OTC dosage, and (d) assessment of the risks/benefits of ibuprofen compared with other analgesics (paracetamol) and OTC NSAIDs (ketoprofen, naproxen) that are also sold as OTC analgesics in some countries.

The main conclusions are that:

1. Ibuprofen at OTC doses has low risks of developing serious GI events, renal and associated CV events, cutaneous and hepatic injury. Among the NSAIDs sold for prescription use, ibuprofen has the lowest risks of developing these and other adverse effects observed with NSAIDs in general. Thus, at the high end of the

K.D. Rainsford, *Ibuprofen: Pharmacology, Therapeutics and Side Effects*,
DOI 10.1007/978 3 0348 0496 7 14, © Springer Basel 2012

prescription doses employed therapeutically, ibuprofen is of low overall relative risk.
2. Ibuprofen OTC does not represent a risk for developing liver injury, especially the irreversible liver damage observed with paracetamol and the occasional liver reactions from aspirin.
3. The pharmacokinetic properties of ibuprofen, especially short plasma half-life of elimination, and lack of development of pathologically-related metabolites (e.g., covalent modification of liver proteins by the quinine imine metabolite of paracetamol or irreversible acetylation of biomolecules by aspirin), are support for the view that these pharmacokinetic and notably metabolic effects of ibuprofen favour its low toxic potential.
4. Moderate inhibition of COX-1 and COX-2, combined with low residence time of the drug in the body, may account for the low GI, CV, and renal risks from ibuprofen, especially at OTC doses.
5. Despite ethnic differences in cytochrome P_{450} metabolism, this does not appear of major significance in the overall safety profile of the drug in different populations in relation to its pharmacokinetic parameters.

The place of OTC ibuprofen in OTC as a pain-relieving drugs for use by the population at large should be considered in relation to cautious use, and recognition of adverse symptoms when they occur. Like all drugs, ibuprofen can have untoward reactions when used inappropriately or in those at risk of developing known side-effects (e.g., in the gastro-intestinal tract, cardiovascular system, skin, or the hepato-renal systems). This book reviews the case for safe use of ibuprofen and understanding of its modes of action.

References

Aabakken L, Dybdahl JH, Larsen S, Mowinckel P, Osnes M, Quiding H (1989a) A double blind comparison of gastrointestinal effects of ibuprofen standard and ibuprofen sustained release assessed by means of endoscopy and ^{51}Cr labelled erythrocytes. Scand J Gastroenterol 24:307 313

Aabakken L, Dybdahl JH, Eidsaunet W, Haaland A, Larsen S, Osnes M (1989b) Optimal assessment of gastrointestinal side effects induced by non steroidal anti inflammatory drugs. Endoscopic lesions, faecal blood loss, and symptoms not necessarily correlated, as observed after naproxen and oxindanac in healthy volunteers. Scand J Gastroenterol 24:1007 1013

Aarons L, Grennan DM, Rajapakse C, Brinkley J, Siddiqui M, Taylor L, Higham C (1983) Anti inflammatory (ibuprofen) drug therapy in rheumatoid arthritis rate of response and lack of time dependency of plasma pharmacokinetics. Br J Clin Pharmacol 15:387 388

Abdullah GZ, Abdulkarim MF, Salman IM, Ameer OZ, Yam MF, Mutee AF, Chitneni M, Mahdi ES, Basri M, Sattar MA, Noor AM (2011) In vitro permeation and in vivo anti inflammatory and analgesic properties of nanoscaled emulsions containing ibuprofen for topical delivery. Int J Nanomed 6:387 396

Adams SS (1987) Non steroidal anti inflammatory drugs, plasma half lives, and adverse reactions. Lancet 2(8569):1204 1205

Ad Giles, Hill CM, Shepherd JP, Stewart DJ, Pickvance NJ (1986) A single dose assessment of an ibuprofen/codeine combination in postoperative dental pain. Int J Oral Maxillofac Surg 15:727 732

Adams SS, Breslof P, Mason CG (1976) Pharmacological differences between the optical isomers of ibuprofen: evidence for metabolic inversion of the ( ) isomer. J Pharm Pharmacol 28:256 257

Agundez JAG, Garcia Martin E, Martinez C (2009) Genetically based impairment CYP2C8 and CYP2C dependent NSAID metabolism as a risk factor for gastrointestinal bleeding: is a combination of pharmacogenomics and metabolomics required to improve personalized medicine? Expert Opin Drug Metab Toxicol 5:1 14

Agus B, Nelson J, Kramer N, Mahal SS, Rosenstein ED (1990) Acute central nervous system symptoms caused by ibuprofen in connective tissue disease. J Rheumatol 17:1094 1096

Ahlijanian MK, Takemori AE (1985) Effects of ( ) N6 (R phenylisopropyl) adenosine (PIA) and caffeine on nociception and morphine induced analgesia, tolerance and dependence in mice. Eur J Pharmacol 112:171 179

Ahlström U, Kahnberg KE, Roos BE (1974) Pentazocine and aspirin for pain following oral surgery. Acta Pharmacol Toxicol (Copenh) 35(4):325 336

Aiache JM (1990) French and/or European perspectives on biopharmaceutical characterization of drug dosage forms. J Pharm Biomed Anal 8:499 506

Albert KS, Gernaat CM (1984) Pharmacokinetics of ibuprofen. Am J Med 77:40 46

DOI 10.1007/978 3 0348 0496 7, © Springer Basel 2012

Albert KS, Gillespie WR, Wagner JG, Pau A, Lockwood GF (1984) Effects of age on the clinical pharmacokinetics of ibuprofen. Am J Med 77(1A):47 50

Ali ZK, Kim RJ, Ysla FM (2009) CYP2C9 polymorphisms: considerations in NSAID therapy. Curr Opin Drug Disc Devel 12:108 114

Alloui A, Chassaing C, Schmidt J, Ardid D, Dubray C, Cloarec A, Eschalier A (2002) Paracetamol exerts a spinal, tropisetron reversible, antinociceptive effect in an inflammatory pain model in rats. Eur J Pharmacol 443:71 77

Altman RD (1984) Review of ibuprofen for osteoarthritis. Am J Med 77(1A):10 18

Amdekar YK, Desai RZ (1985) Antipyretic activity of ibuprofen and paracetamol in children with pyrexia. Br J Clin Pract 39:140 143

American College of Rheumatology, Hotline (2005) The safety of COX 2 inhibitors. Deliberations from the February 16 18, 2005, FDA Meeting. http://www.rheumatology.org/publications/hotline/0305COX2.asp?aud+mem. Accessed 16 Jan 2007

Amir R, Argoff CE, Bennett GJ, Cummins TR, Durieux ME, Gerner P, Gold MS, Porreca F, Strichartz GR (2006) The role of sodium channels in chronic inflammatory and neuropathic pain. J Pain 7(Suppl 3):S1 S29

Angst MS, Clark JD, Carvalho B, Tingle M, Schmelz M, Yeomans DC (2007) Cytokine profile in human skin in response to experimental inflammation, noxious stimulation, and administration of a COX inhibitor: a microdialysis study. Pain 139:15 27

Anonymous (2006) Pharm J 277:321

Ansell BM (1973) Ibuprofen in the management of Still's disease. Practitioner 211:659 663

Ansell BM (1983) The medical management of chronic arthritis in childhood. Ann Acad Med Singapore 12:168 173

Antman EM, Bennett JS, Daugherty A, Furberg C, Roberts H, Taubert KA, American Heart Association (2007) Use of nonsteroidal antiinflammatory drugs: an update for clinicians: a scientific statement from the American Heart Association. Circulation 115:1634 1642

Antonicelli L, Tagliabracci A (1995) Asthma death induced by ibuprofen. Monaldi Arch Chest Dis 50:276 278

Aranda JV, Thomas R (2006) Systematic review: intravenous Ibuprofen in preterm newborns. Semin Perinatol 30:114 120

Aranda JV, Varvarigou A, Beharry K, Bansal R, Bardin C, Modanlou H, Papageorgiou A, Chemtob S (1997) Pharmacokinetics and protein binding of intravenous ibuprofen in the premature newborn infant. Acta Paediatr 86:289 293

Aranda JV, Beharry KD, Valencia GB (2009a) Nonsteroidal anti inflammatory drugs (NSAIDs) in the newborn which ones? J Matern Fetal Neonatal Med 22(Suppl 3):21 22

Aranda JV, Clyman R, Cox B, Van Overmeire B, Wozniak P, Sosenko I, Carlo WA, Ward RM, Shalwitz R, Baggs G, Seth A, Darko L (2009b) A randomized, double blind, placebo controlled trial on intravenous ibuprofen L lysine for the early closure of nonsymptomatic patent ductus arteriosus within 72 hours of birth in extremely low birth weight infants. Am J Perinatol 26:235 245

Arapoglou V, Katsenis K, Syrigos KN, Dimakakos EP, Zakopoulou N, Gjødsbøl K, Glynn C, Schäfer E, Petersen B, Tsoutos D (2011) Analgesic efficacy of an ibuprofen releasing foam dressing compared with local best practice for painful exuding wounds. J Wound Care 20:319 320, 322 325

Armstrong PCJ, Truss NJ, Ali FY, Dhanji AA, Vojnovic I et al (2008) Aspirin and the in vitro linear relationship between thromboxane A_2 mediated platelet aggregation and platelet production on thromboxane A_2. J Thromb Haemost 6:1933 1943

Arnaud A (1995) Allergy and intolerance to nonsteroidal anti inflammatory agents. Clin Rev Allergy Immunol 13:245 251

Aronoff GM, Evans WO (1982) Evaluation and treatment of chronic pain at the Boston Pain Center. J Clin Psychiatry 43(8 Pt 2):4 9

Arora S, Wagner JG, Herbert M (2007) Myth: parenteral ketorolac provides more effective analgesia than oral ibuprofen. CJEM 9:30 32

Arranz I, Martín Suárez A, Lanao JM, Mora F, Vázquez C, Escribano A, Juste M, Mercader J, Ripoll E (2003) Population pharmacokinetics of high dose ibuprofen in cystic fibrosis. Arch Dis Child 88:1128 1130

Arroyo M, Lanas A (2006) NSAID induced gastrointestinal damage. Minerva Gastroenterol Dietol 52:249 259

Ashraf E, Ford L, Geetha R, Cooper S (1999) Safety profile of ibuprofen suspension in young children. Inflammopharmacology 7:219 225

Ashraf E, Cooper S, Kellstein D, Jayawardena S (2001) Safety profile of non prescription ibuprofen in the elderly osteoarthritic patient: a meta analysis. Inflammopharmacology 9:35 41

Assous N, Touzé E, Meune C, Kahan A, Alloanore Y (2007) Cardiovascular disease in rheumatoid arthritis: single center hospital based cohort in France. Joint Bone Spine 74(1):66 72

Autret E, Breart G, Jonville AP, Courcier S, Lassale C, Goehrs JM (1994) Comparative efficacy and tolerance of ibuprofen syrup and acetaminophen syrup in children with pyrexia associated with infectious diseases and treated with antibiotics. Eur J Clin Pharmacol 46:197 201

Autret E, Reboul Marty J, Henry Launois B, Laborde C, Courcier S, Goehrs JM, Languillat G, Launois R (1997) Evaluation of ibuprofen versus aspirin and paracetamol on efficacy and comfort in children with fever. Eur J Clin Pharmacol 51:367 371

Autret E, Reboul Marty J, Henry Launois B, Laborde C, Courcier S, Goehrs JM, Autret Leca E, Gibb IA, Goulder MA (2007) Ibuprofen versus paracetamol in pediatric fever: objective and subjective findings from a randomized, blinded study. Curr Med Res Opin 23:2205 2211

Autret Leca E (2003) A general overview of the use of ibuprofen in paediatrics. Int J Clin Pract Suppl (135):9 12

Averbuch M, Katzper M (2000) A search for sex differences in response to analgesia. Arch Intern Med 160:3424 3428

Averbuch M, Katzper M (2003) Severity of baseline pain and degree of analgesia in the third molar post extraction dental pain model. Anesth Analg 97:163 167

Ayoub SS, Botting RM (2010) Iloprost induced nociception: determination of the site of anti nociceptive action of cyclooxygenase inhibitors and the involvement of cyclooxygenase products in central mechanisms of nociception. Methods Mol Biol 644:207 215

Ayoub SS, Botting RM, Goorha S, Colville Nash PR, Willoughby DA, Ballou LR (2004) Acetaminophen induced hypothermia in mice is mediated by a prostaglandin endoperoxide synthase 1 gene derived protein. Proc Natl Acad Sci USA 101:11165 11169

Ayoub SS, Colville Nash PR, Willoughby DA, Botting RM (2006) The involvement of acyclooxygenase 1 gene derived protein in the antinociceptive action of paracetamol in mice. Eur J Pharmacol 538:57 65

Ayres JG, Fleming DM, Whittington RM (1987) Asthma death due to ibuprofen. Lancet 1(8541):1082

Badin C, Chambrier C, Anouifi A, Boucaud C, Bouletreau P (1997) Non steroidal anti inflammatory agents and angiotensin converting enzyme inhibitor: a dangerous combination during postoperative period. Ann Fr Anesth Reanim 16:55 57

Balakrishnan P, Lee BJ, Oh DH et al (2009) Enhanced oral bioavailability of dexibuprofen by a novel solid self emulsifying drug delivery system (SEDDS). Eur J Pharm Biopharm 72:539 545

Bak S, Andersen M, Tsiropoulos I, García Rodríguez LA, Hallas J, Christensen K, Gaist D (2003) Risk of stroke associated with nonsteroidal anti inflammatory drugs: a nested case control study. Stroke 34:379 386

Ballou LR, Botting RM, Goorha S, Zhang J, Vane JR (2000) Nociception in cyclo oxygenase isoenzymes deficient mice. Proc Natl Acad Sci USA 97:10272 10276

Bannwarth B, Berenbaum F (2005) Clinical pharmacology of lumiracoxib, a second generation cyclooxygenase 2 selective inhibitor. Expert Opin Investig Drugs 14:521 533

Bannwarth B, Lapicque F, Pehourcq F, Gillet P, Schaeverbeke T, Laborde C, Dehais J, Gaucher A, Netter P (1995) Stereoselective disposition of ibuprofen enantiomers in human cerebrospinal fluid. Br J Clin Pharmacol 40:266 269

Bao L d et al (2006) Bioavailability of ibuprofen soft capsules in healthy volunteers. Chin J New Drugs. doi:CNKI:SUN:ZXYZ.0.2006 23 021

Barclay L (2005) Platelet function may normalize by 24 hours after last ibuprofen dose. Medscape Medical News. http://www.medscape.com/viewarticle/502566?src mp. Accessed 15 Apr 2005

Barden J, Edwards JE, McQuay HJ, Moore RA (2002) Single dose rofecoxib for acute postoperative pain in adults: a quantitative systematic review. BMC Anesthesiol 2:4

Barden J, Edwards JE, McQuay HJ, Wiffen PJ, Moore RA (2004) Relative efficacy of oral analgesics after third molar extraction. Br Dent J 197(7):407 411

Barkin RL (2001) Acetaminophen, aspirin, or ibuprofen in combination analgesic products. Am J Ther 8:433 442

Baron JA, Sandler RS, Bresalier RS, Lanas A, Morton DG, Iverson ER, Riddell R, DeMets D (2008) Cardiovascular events associated with rofecoxib: final analysis of the APPROVe trial. Lancet 372:1756 1764

Beaver W (2003) Review of the analgesic efficacy of ibuprofen. Int J Clin Pract S135:13 17

Beers MH, Berkow R (1999) The Merck manual of diagnosis and therapy, 17th edn. Merck Research Laboratories, Whitehouse Station, NJ, pp 2026 2027

Benjie W, Meiyuan N, Ruichen G (2002) Bioavailability of ibuprofen suspension and tablets in healthy volunteers. Chin J Clin Pharm. doi:cnkr ISSN 1007 4406 0 2002 01 011

Bennett WM (1997) Drug interactions and consequences of sodium restriction. Am J Clin Nutr 65:678S 681S

Bergmann JF, Chassany O, Geneve J, Abiteboul M, Caulin C, Segrestaa JM (1992) Endoscopic evaluation of the effect of ketoprofen, ibuprofen and aspirin on the gastroduodenal mucosa. Eur J Clin Pharmacol 42:685 688

Bergogne Bérézin E, Bryskier A (1999) The suppository form of antibiotic administration: pharmacokinetics and clinical application. J Antimicrob Chemother 43:177 185

Beyth RJ, Shorr RI (1999) Epidemiology of adverse drug reactions in the elderly by drug class. Drugs Aging 14:231 239

Bigby M, Stern R (1985) Cutaneous reactions to nonsteroidal anti inflammatory drugs. A review. J Am Acad Dermatol 12:866 876

Biskupiak JE, Brixner DI, Howard K, Oderda GM (2006) Gastrointestinal complications of over the counter nonsteroidal anti inflammatory drugs. J Pain Palliat Care Pharmacother 20:7 14

Bjarnason I (2007) Ibuprofen and gastrointestinal safety: a dose duration dependent phenomenon. J R Soc Med 100:11 14

Bjarnason I, Rainsford KD (2001) COX 2 inhibitors and the gastrointestinal tract. Gut 48:451

Bjarnason I, Bissoli F, Conforti A, Maiden L, Moore N, Moretti U, Rainsford KD, Takeuchi K, Velo GP (2005). Adverse reactions and their mechanisms from nimesulide. In: Rainsford KD (ed) Nimesulide: actions and uses. Birkhäuser, Basel, pp 315 415

Bjarnason I, Scarpignato C, Takeuchi K, Rainsford KD (2007) Determinants of the short term gastric damage caused by NSAIDs in man. Aliment Pharmacol Ther 26:95 106

Björkman R (1995a) Central nociceptive effects of non steroidal anti inflammatory drugs and paracetamol. Acta Anaethesiol Scand 39(Suppl 103):9 44

Björkman R (1995b) Central antinociceptive effects of non steroidal anti inflammatory drugs and paracetamol. Experimental studies in the rat. Acta Anaesthesiol Scand Suppl 103:1 44

Björkman R, Hallman KM, Hedner J, Hedner T, Henning M (1996) Nonsteroidal antiinflammatory drug modulation of behavioral responses to intrathecal N methyl D aspartate, but not to substance P and amino methyl isoxazole propionic acid in the rat. J Clin Pharmacol 36(12 Suppl):20S 26S

Bjørnsson GA, Haanaes HR, Skoglund LA (2003) A randomized, double blind crossover trial of paracetamol 1000 mg four times daily vs. ibuprofen 600 mg: effect on swelling and other postoperative events after third molar surgery. Br J Clin Pharmacol 55:405 412

Bak S, Andersen M, Tsiropoulos I, García Rodríguez LA, Hallas J, Christensen K, Gaist D (2003) Risk of stroke associated with nonsteroidal anti inflammatory drugs: a nested case control study. Stroke 34:379 386

Blain H, Boileau C, Lapicque F, Nédélec E, Loeuille D, Guillaume C, Gaucher A, Jeandel C, Netter P, Jouzeau JY (2002) Limitation of the in vitro whole blood assay for predicting the COX selectivity of NSAIDs in clinical use. Br J Clin Pharmacol 53:255 265

Bliddal H, Rosetzsky A, Schlichting P, Weidner MS, Andersen LA, Ibfelt HH, Christensen K, Jensen ON, Barslev J (2000) A randomized, placebo controlled, cross over study of ginger extracts and ibuprofen in osteoarthritis. Osteoarthritis Cartilage 8:9 12

Blot WJ, McLaughlin JK (2000) Over the counter non steroidal anti inflammatory drugs and risk of gastrointestinal bleeding. J Epidemiol Biostat 5:137 142

Blot WJ, Fischer T, Nielsen GL, Friis S, Mumma M, Lipworth L et al (2004) Outcome of upper gastro intestinal bleeding and use of ibuprofen versus paracetamol. Pharm World Sci 26:319 323

Boardman PL, Nuki G, Hart FD (1967) Ibuprofen in the treatment of rheumatoid arthritis and osteo arthritis. Ann Rheum Dis 26:560 561

Body R, Potier K (2004) Best evidence topic report. Non steroidal anti inflammatory drugs and exacerbations of asthma in children. Emerg Med J 21:713 714

Boggara MB, Krishnamoorti R (2010) Partitioning of nonsteroidal anti inflammatory drugs in lipid membranes: a molecular dynamics simulation study. Biophys J 98:586 595

Boggara MB, Faraone A, Krishnamoorti R (2010) Effect of pH and ibuprofen on the phospholipid bilayer bending modulus. J Phys Chem 114:8061 8066

Boneberg EM, Zou MH, Ullrich V (1996) Inhibition of cyclooxygenase 1 and 2 by R(+) and S(+) ibuprofen. J Clin Pharmacol 36(12) (Suppl S):S16 S19

Bonnefont J, Alloui A, Chapuy E, Clottes E, Eschalier A (2003) Orally administered paracetamol does not act locally in the rat formalin test: evidence for a supraspinal, serotonin dependent antinociceptive mechanism. Anesthesiology 99:976 981

Bonnefont J, Chapuy E, Clottes E, Alloui A, Eschalier A (2005) Spinal 5 HT1A receptors differentially influence nociceptive processing according to the nature of the noxious stimulus in rats: effect of WAY 100635 on the antinociceptive activities of paracetamol, venlafaxine and 5 HT. Pain 114:482 490

Bonta IL, Parnham MJ (1981) Prostaglandins, essential fatty acids and cell tissue interactions in immune inflammation. Prog Lipid Res 20:617 623

Boström AA, Forbes JA, Adolfsson C, Beaver WT, Bell WE (1994) Evaluation of bromfenac and ibuprofen for pain after orthopedic surgery. Pharmacotherapy 14(3):305 313

Botting R, Ayoub SS (2005) COX 3 and the mechanism of action of paracetamol/acetaminophen. Prostaglandins Leukot Essent Fatty Acids 72:85 87

Boureau F (1998) Multicentre study of the efficacy of ibuprofen compared with paracetamol in throat pain associated with tonsillitis. In: Rainsford KD, Powanda MC (eds) Safety and efficacy of non prescription (OTC) analgesics and NSAIDs. Kluwer Academic, Dordrecht, pp 119 121

Boureau F, Schneid H, Zeghari N, Wall R, Bourgeois P (2004) The IPSO study: ibuprofen, paracetamol study in osteoarthritis. A randomised comparative clinical study comparing the efficacy and safety of ibuprofen and paracetamol analgesic treatment of osteoarthritis of the knee or hip. Ann Rheum Dis 63:1028 1034

Bousquet PJ, Demoly P, Romano A, Aberer W, Bircher A, Blanca M, Brockow K, Pichler W, Torres MJ, Terreehorst I, Arnoux B, Atanaskovic Markovic M, Barbaud A, Bijl A, Bonadonna P, Burney PG, Caimmi S, Canonica GW, Cernadas J, Dahlen B, Daures JP, Fernandez J, Gomes E, Gueant JL, Kowalski ML, Kvedariene V, Mertes PM, Martins P, Nizankowska Mogilnicka E, Papadopoulos N, Ponvert C, Pirmohamed M, Ring J, Salapatas M, Sanz ML, Szczeklik A, Van Ganse E, De Weck AL, Zuberbier T, Merk HF, Sachs B,

Sidoroff A, Global Allergy, Asthma European Network (GALEN) and Drug Allergy and Hypersensitivity Database (DAHD) and the European Network for Drug Allergy (ENDA) (2009) Pharmacovigilance of drug allergy and hypersensitivity using the ENDA DAHD database and the GALEN platform. The Galenda project. Allergy 64:194 203

Bowen B, Yuan Y, James C, Rashid F, Hunt RH (2005) Time course and pattern of blood loss with ibuprofen treatment in healthy subjects. Clin Gastroenterol Hepatol 3:1075 1082

Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI (1991) Comparison of an anti inflammatory dose of ibuprofen, an analgesic dose of ibuprofen and acetaminophen in the treatment of patients with osteoarthritis of the knee. N Engl J Med 325:87 91

Bradley JD, Brandt KD, Katz BP, Kalasinski LA, Ryan SI (1992) Treatment of knee osteoarthritis: relationship of clinical features of joint inflammation to the response to a nonsteroidal anti inflammatory drug or pure analgesic. J Rheumatol 19:1950 1954

Bradley JD, Katz BP, Brandt KD (2001) Severity of knee pain does not predict a better response to an anti inflammatory dose of ibuprofen than to analgesic therapy in patients with osteoarthritis. J Rheumatol 28:1073 1076

Brater DC (1998) Renal safety of ibuprofen: pharmacokinetic aspects. In: Rainsford KD, Powanda MC (eds) Safety and efficacy of non prescription (OTC) analgesics and NSAIDs. Kluwer Academic, Dordrecht, pp 73 76

Breyer M (1999) Editorial. COX 2 selective NSAIDs and renal function: gain without pain? Kidney Int 55:738 739

British National Formulary (2009) BNF 57. BMJ Group & RPS, London

Brocks D, Jamali F (1999) The pharmacokinetics of ibuprofen in humans and animals. In: Rainsford KD (ed) Ibuprofen: a critical bibliographic review. Taylor & Francis, London, pp 89 142

Brooks CD, Schlagel CA, Sekhar NC, Sobota JT (1973) Tolerance and pharmacology of ibupro fen. Curr Ther Res Clin Exp 15:180 190

Brooks P, Emery P, Evans JF, Fenner H, Hawkey CJ, Patrono C, Smolen J, Breedveld F, Day R, Dougados M, Ehrich EW, Gijon Banos J, Kvien TK, Van Rijswijk MH, Warner T, Zeidler H (1999) Interpreting the clinical significance of the differential inhibition of cyclooxygenase 1 and cyclooxygenase 2. Rheumatology (Oxford) 38:779 788

Broome JR, Stoneham MD, Beeley JM, Milledge JS, Hughes AS (1994) High altitude headache: treatment with ibuprofen. Aviat Space Environ Med 65:19 20

Brown RD, Wilson JT, Kearns GL, Eichler VF, Johnson VA, Bertrand KM (1992) Single dose pharmacokinetics of ibuprofen and acetaminophen in febrile children. J Clin Pharmacol 32:231 241

Brune K (2007) Persistence of NSAIDs at effect sites and rapid disappearance from side effect compartments contributes to tolerability. Curr Med Res Opin 23:2985 2995

Brune K, Fenner H, Kurowski M, Lanz R, and members of the SPALA Group (1992) Adverse reactions to NSAIDs: consecutive evaluation of 30,000 patients in rheumatology. In: Rainsford KD, Velo GP (eds) Side effects of anti inflammatory drugs 3. Kluwer Academic, Dordrecht, pp 33 42

Brunton L, Parker K, Blumenthal D, Buxton I (2008) Goodman and Gilman's manual of pharma cology and therapeutics. McGraw Hill Medical, New York

Buchanan WW (1990) Implications of NSAID therapy in elderly patients. J Rheumatol 17:29 32

Buchanan WW, Kean WP (2002) Osteoarthritis: clinical therapeutic trials and treatment. Inflammopharmacology 10:79 155

Buchanan WW, Kean WF, Rainsford KD (2004) Use of salicylates in rheumatic and related conditions. In: Rainsford KD (ed) Aspirin and related drugs. Taylor & Francis, London, pp 636

Buchheit D, Dragan CA, Schmitt EI, Bureik M (2011) Production of ibuprofen acyl glucuronides by human UGT2B7. Drug Metab Dispos 39:2174 2181

Buckler JW, Hall JE, Rees JA, Sheldrake FE, Miller AC (1975) The tolerance and acceptability of ibuprofen ('Brufen') in the elderly patient. Curr Med Res Opin 3:558

Cadieux JS, Leclerc P, St Onge M, Dussault AA, Laflamme C, Picard S, Ledent C, Borgeat P, Pouliot M (2005) Potentiation of neutrophil cyclooxygenase 2 by adenosine: an early anti inflammatory signal. J Cell Sci 118:1437 1447

Cameron RG, Feuer G, de la Iglesia FA (eds) (1996) Drug induced hepatotoxicity. Handbook of experimental pharmacology, vol 121. Springer, Berlin

Cannon CP, Curtis SP, FitzGerald GA, Krum H, Kaur A, Bolognese JA, Reicin AS, Bombardier C, Weinblatt ME, van der Heijde D, Erdmann E, Laine L (2006) Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatosis arthritis in the multinational etoricoxib and diclofenac arthritis long term (MEDAL) programme: a randomised comparison. Lancet 368:1771 1781

Carmichael J, Shankel SW (1985) Effects of non steroidal anti inflammatory drugs on prostaglandins and renal function. Am J Med 78:992 1000

Carnes D, Anwer Y, Underwood M, Harding G, Parsons S, TOIB study team (2008) Influences on older people's decision making regarding choice of topical or oral NSAIDs for knee pain: qualitative study. Br Med J 336(7636):142 145

Cashman JN (1996) The mechanisms of action of NSAIDs in analgesia. Drugs 52(suppl 5):13 23

Castellani S, Ungar A, LaCava G, Cantini C, Stefanile C, Camaiti A, Messeri G, Coppo M, Vallotti B, DiSerio C, Brocchi A, Masotti G (1997) Renal adaptation to stress: a possible role of endothelial release and prostaglandin modulation in human subjects. J Lab Clin Med 129:462 469

Castelnuovo E, Cross P, Mt Isa S, Spencer A, Underwood M, TOIB study team (2008) Cost effectiveness of advising the use of topical or oral ibuprofen for knee pain; the TOIB study [ISRCTN: 79353052]. Rheumatology (Oxford) 47:1077 1081

Castillo M, Lam YW, Dooley MA, Stahl E, Smith PC (1995) Disposition and covalent binding of ibuprofen and its acyl glucuronide in the elderly. Clin Pharmacol Ther 57:636 644

Catella Lawson F, Reilly MP, Kapoor SC, Cucchiara AJ, DeMarco S, Tournier B, Vyas SN, FitzGerland GA (2001) Cyclooxygenase inhibitors and the antiplatelet effects of aspirin. N Engl J Med 345:1809 1817

Cater M, O'Brien PM, Pickvance MJ (1985) A double blin comparison of the new ibuprofen codeine phosphate combination, zomepirac, and placebo in the relief of postepisiotomy pain. Clin Ther 7:442 447

Cattaneo D, Clementi E (2010) Clinical pharmacokinetics of ibuprofen arginine. Curr Clin Pharmacol 5(4):239 245

Caunedo Alvarez A, Gomez Rodriguez BJ, Romero Vasquez J et al (2010) Macroscopic small bowel mucosal injury caused by chronic nonsteroidal anti inflammatory drugs (NSAIDs) use as assessed by capsule endoscopy. Rev Esp Enferm Dig 102:80 85

Ceppi Monti N, Gazzaniga A, Gianesello V, Stroppolo F, Lodola E (1992) Activity and pharma cokinetics of a new oral dosage form of soluble ibuprofen. Arzneimittelforschung 42(4):556 559

Chan TY, Tomlinson B, Critchley JA (1993) Aconitine poisoning following the ingestion of Chinese herbal medicines: a report of eight cases. Aust NZ J Med 23:268 271

Chang CY, Schiano TD (2007) Review article: drug hepatotoxicity. Aliment Pharmacol Ther 25:1135 1151

Chen CY, Chen CS (1995) Stereoselective disposition of ibuprofen in patients with compromised renal haemodynamics. Br J Clin Pharmacol 40(1):67 72

Chen CY, Pang VF, Chen SS (1994) Assessment of ibuprofen associated nephrotoxicity in renal dysfunction. J Pharmacol Exp Ther 270:1307

Cheng JWM (2006) Use of non aspirin nonsteroidal anti inflammatory drugs and the risk of cardiovascular events. Ann Pharmacother 40:1785 1796

Chico TJA, Milo M, Crossman DC (2010) The genetics of cardiovascular disease: new insights from emerging approaches. J Pathol 220:186 197

Christian MS, Brent RL (2001) Teratogen update: evaluation of the reproductive and develop mental risks of caffeine. Teratology 64:51 78

Cigna E, Tarallo M, Bistoni G, Anniboletti T, Trignano E, Tortorelli G, Scuderi N (2009) Evaluation of polyurethane dressing with ibuprofen in the management of split thickness skin graft donor sites. In Vivo 23:983 986

Clark E, Plint AC, Correll R, Gaboury I, Passi B (2007) A randomized, controlled trial of acetaminophen, ibuprofen and codeine for acute pain relief in children with musculoskeletal trauma. Pediatrics 119:460 467

Codispoti JR, Prior MJ, Fu M, Harte CM, Nelson EB (2001) Efficacy of non prescription doses of ibuprofen for treating migraine headache. A randomized controlled trial. Headache 41:665 679

Colebatch AN, Marks JL, Edwards CJ (2011) Safety of non steroidal anti inflammatory drugs, including aspirin and paracetamol (acetaminophen) in people receiving methotrexate for inflammatory arthritis (rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, other spondyloarthritis). Cochrane Database Syst Rev (11):CD008872

Cook ME, Wallin JD, Thakur VD, Kadowitz PJ, McNamara DB, Garcia MM, Lipani JA, Poland M (1997) Comparative effects of nabumetone, sulindac, and ibuprofen on renal function. J Rheumatol 24:1137 1144

Cooper SA (1984) Five studies on ibuprofen for postsurgical dental pain. Am J Med 77(1A):70 77

Cooper SA (1986) The relative efficacy of ibuprofen in dental pain. Compend Contin Educ Dent 7(8):578, 580 581, 584 588 passim

Cooper SA, Needle SE, Kruger GO (1977) Comparative analgesic potency of aspirin and ibuprofen. J Oral Surg 35:898 903

Cooper SA, Schachtel BP, Goldman E, Gelb S, Cohn P (1989) Ibuprofen and acetaminophen in the relief of acute pain: a randomized, double blind, placebo controlled study. J Clin Pharmacol 29:1026 1030

Cox SR, Brown MA, Squires DJ, Murrill EA, Lednicer D, Knuth DW (1988) Comparative human study of ibuprofen enantiomer plasma concentrations produced by two commercially available ibuprofen tablets. Biopharm Drug Dispos 9(6):539 549

Cox SR, Gall EP, Forbes KK, Gresham M, Goris G (1991) Pharmacokinetics of the R( ) and S(+) enantiomers of ibuprofen in the serum and synovial fluid of arthritis patients. J Clin Pharmacol 31(1):88 94

Cox PJ, Khan KA, Munday DL, Sujja areevath J (1999) Development and evaluation of a multiple unit oral sustained release dosage form of S(+) ibuprofen: preparation and release kinetics. Int J Pharm 193:73 84

Cranswick N, Coglan D (2000) Paracetamol efficacy and safety in children: the first 40 years. Am J Ther 7:135 141

Crocetti M, Moghbeli N, Serwint J (2001) Fever phobia revisited: have parental misconceptions about fever changed in 20 years? Pediatrics 107:1241 1246

Crockford DJ, Maher AD, Ahmadi KR, Barrett A, Plumb RS, Wilson ID, Nicholson JK (2008) ^{1}H NMR and UPLC MS^{E} statistical heterospectroscopy: characterization of drug metabolites (xenometabolome) in epidemiological studies. Anal Chem 80:6835 6844

Cronstein BN, Montesinos MC, Weissmann G (1999) Sites of action for future therapy: an adenosine dependent mechanism by which aspirin retains its antiinflammatory activity in cyclooxygenase 2 and NFkappaB knockout mice. Osteoarthritis Cartilage 7:361 363

Cross PL, Ashby D, Harding G, Hennessy EM, Letley L, Parsons S, Spencer AE, Underwood M, TOIB Study Team (2005) Are topical or oral ibuprofen equally effective for the treatment of chronic knee pain presenting in primary care: a randomised controlled trial with patient preference study [ISRCTN79353052]. BMC Musculoskelet Disord 6:55

Cryer B, Feldman M (1998) Cyclooxygenase 1 and cyclooxygenase 2 selectivity of widely used nonsteroidal anti inflammatory drugs. Am J Med 104:413 421

Cryer B, Berlin RG, Cooper SA, Hsu C, Wason S (2005) Double blind, randomized, parallel, placebo controlled study of ibuprofen effects on thromboxane B_2 concentrations in aspirin treated healthy adult volunteers. Clin Ther 27:185 191

Curtis JP, Krumholz HM (2004) The case for an adverse interaction between aspirin and non steroidal anti inflammatory drugs: is it time to believe the hype? J Am Coll Cardiol 43:991 993

Curtis JP, Wang Y, Portnay EL, Masoudi FA, Havranek EP, Krumholz HM (2003) Aspirin, ibuprofen, and mortality after myocardial infarction: retrospective cohort study. Br Med J 327:1322 1323

Dahl V, Raeder JC, Drosdal S, Wathne O, Brynildsrud J (1995) Prophylactic oral ibuprofen or ibuprofen codeine versus placebo for postoperative pain after hip arthroplasty. Acta Anaesthisiol Scand 39:323 326

Dalton JD Jr, Schweinle JE (2006) Randomized controlled noninferiority trial to compare extended release acetaminophen and ibuprofen for the treatment of ankle sprains. Ann Emerg Med 48:615 623

Daniels S, Reader S, Berry P, Goulder M (2009) Onset of analgesia with sodium ibuprofen, ibuprofen acid incorporating poloxamer and acetaminophen a single dose, double blind, placebo controlled study in patients with post operative dental pain. Eur J Clin Pharmacol 65:343 353

Daniels SE, Goulder MA, Aspley S, Reader S (2011) A randomised, five parallel group, placebo controlled trial comparing the efficacy and tolerability of analgesic combinations including a novel single tablet combination of ibuprofen/paracetamol for postoperative dental pain. Pain 152:632 642

Davies NM (1998) Clinical pharmacokinetics of ibuprofen. Clin Pharmacokinet 34:101 154

Day RO, Williams KM, Graham GG, Lee EJ, Knihinicki RR, Champion GD (1988) Stereoselective disposition of ibuprofen enantiomers in synovial fluid. Clin Pharmacol Ther 43:480 487

Day R, Morrison B, Luza A, Castaneda O, Strusberg A, Nahir M, Helgetveit KB, Kress B, Daniels B, Bolognese J, Krupa D, Seidenberg B, Ehrich E (2000) A randomized trial of the efficacy and tolerability of the COX 2 inhibitor rofecoxib vs ibuprofen in patients with osteoarthritis. Arch Intern Med 160:1781 1787

De la Cruz JP, Reyes JJ, Ruiz Moreno MI et al (2010) Differences in the in vitro antiplatelet effect of dexibuprofen, ibuprofen, and flurbiprofen in human blood. Anesth Analg 111:1341 1346

De Medicinis R, LeBel E, Rioux A et al (1988) Biliary excretion of radiochromium. Am J Med 85:276

De Palma C, Di Paola R, Perrotta C, Mazzon E, Cattaneo D, Trabucchi E, Cuzzocrea S, Clementi E (2009) Ibuprofen arginine generates nitric oxide and has enhanced anti inflammatory effects. Pharmacol Res 60:221 228

De Vries F, Setakis E, van Staa TP (2010) Concomitant use of ibuprofen and paracetamol and the risk of major clinical safety outcomes. Br J Clin Pharmacol 70:429 438

de Weck AL, Gamboa PM, Esparza R, Sanz ML (2006) Hypersensitivity to aspirin and other nonsteroidal anti inflammatory drugs (NSAIDs). Curr Pharm Des 12:3347 3358

DeArmond B, Francisco CA, Lin JS, Huang FY, Halladay S, Bartziek RD, Skare KL (1995) Safety profile of over the counter naproxen sodium. Clin Ther 17:587 601

Debley JS, Carter ER, Gibson RL, Rosenfeld M, Redding GJ (2005) The prevalence of ibuprofen sensitive asthma in children: a randomized controlled bronchoprovocation challenge study. J Pediatr 147:233 238

Delli Pizzi S, Mantini D, Ferretti A, Caulo M, Salerio I, Romani GL, Del Gratta C, Tartaro A (2010) Pharmacological functional MRI assessment of the effect of ibuprofen arginine in painful conditions. Int J Immunopathol Pharmacol 23:927 935

Deodhar SD, Dick WC, Hodgkinson R, Buchanan WW (1973) Measurement of clinical response to anti inflammatory drug therapy in rheumatoid arthritis. Q J Med New Ser 166:387 401

Derry S, Barden J, McQuay HJ, Moore RA (2008). Single dose oral celecoxib for acute postoper ative pain in adults. Cochrane Database Syst Rev (4):CD004233

Dewland PM, Reader S, Berry P (2009) Bioavailability of ibuprofen following oral administration of standard ibuprofen, sodium ibuprofen or ibuprofen acid incorporating poloxamer in healthy volunteers. BMC Clin Pharmacol 9:19

Diamond S (1983) Ibuprofen versus aspirin and placebo in the treatment of muscle contraction headache. Headache 23:206 210

Diamond S, Balm TK, Freitag FG (2000) Ibuprofen plus caffeine in the treatment of tension type headache. Clin Pharmacol Ther 68:312 319

Diener HC, Bussone G, de Liano H, Eikermann A, Englert R, Floeter T, Gallai V, Gobel H, Hartung E, Jimenez MD, Lange R, Manzoni GC, Mueller Schwefe G, Nappi G, Pinessi L, Prat J, Puca FM, Titus F, Voelker M (2004) Placebo controlled comparison of effervescent acetylsalicylic acid, sumatriptan and ibuprofen in the treatment of migraine attacks. Cephalalgia 24:947 954

Dieppe PA, Doherty M, Macfarlane D, Maddison P (1985) Rheumatological medicine. Churchill Livingstone, Edinburgh

Dieppe PA, Harkness JAL, Higgs ER (1989) Osteoarthritis. In: Wall PD, Melzack R (eds) Textbook of pain, 2nd edn. Churchill Livingstone, Edinburgh, pp 306 326

Díez Domingo J, Plannelles MV, Baldo JM, Ballester A, Nunez F, Jubert A, Domínguez Granados R (1998) Ibuprofen prophylaxis from adverse reactions to diphtheria tetanus pertussis vacci nation. Curr Ther Res Clin Exp 59:588 597

Ding C G, He R, Chen Y A, Zhong H L (1997) Pharmacokinetics and relative bioavailability of ibuprofen effervescent tablets. Chin J Clin Pharmacol. doi:CNKI:SUN:GLYZ.0.1997 02 007

Ding G, Liu Y, Sun J, Takeuchi Y, Toda T, Hayakawa T, Fukushima S, Kishimoto S, Lin W, Inotsume N (2007) Effect of absorption rate on pharmacokinetics of ibuprofen in relation to chiral inversion in humans. J Pharm Pharmacol 59(11):1509 1513

Dionne RA (1998) Evaluation and analgesic mechanisms and NSAIDs for acute pain using the oral surgery model. In: Rainsford KD, Powanda MC (eds) Safety and efficacy of non prescription (OTC) analgesics and NSAIDs. Kluwer Academic, Dordrecht, pp 105 117

Dionne RA, Cooper SA (1999) Use of ibuprofen in dentistry. In: Rainsford KD (ed) Ibuprofen: a critical bibliographic review. Taylor & Francis, London, pp 409 430

Dionne RA, Cooper SA (1978) Evaluation of preoperative ibuprofen for postoperative pain after removal of third molars. Oral Surg Oral Med Oral Pathol 45:851 856

Dionne RA, McCullagh L (1998) Enhanced analgesia and suppression of plasma β endorphin by the S(+) isomer of ibuprofen. Clin Pharmacol Ther 63:694 701

Dlugosz CK, Chater RW, Engle JP (2006) Appropriate use of nonprescription analgesics in pediatric patients. J Pediatr Health Care 20:316 325

Dobovišek A, Fajmut A, Brumen M (2011) Role of expression of prostaglandin synthases 1 and 2 and leukotriene C4 synthase in aspirin intolerant asthma: a theoretical study. J Pharmacokinet Pharmacodyn 38:261 278

Dobovišek A, Fajmut A, Brumen M (2012) Strategy for NSAID administration to aspirin intolerant asthmatics in combination with PGE2 analogue: a theoretical approach. Med Biol Eng Comput 50:33 42

Doherty M, Hawkey C, Goulder M, Gibb I, Hill N, Aspley S, Reader S (2011) A randomised controlled trial of ibuprofen, paracetamol or a combination tablet of ibuprofen/paracetamol in community derived people with knee pain. Ann Rheum Dis 70:1534 1541

Dominkus M, Nicolakis M, Kotz R, Wilkinson FE, Kaiser RR, Chlud K (1996) Comparison of tissue and plasma levels of ibuprofen after oral and topical administration. Arzneimittel forschung 46:1138 1143

Dong JQ, Ni L, Scott CS, Retsch Bogart GZ, Smith PC (2000) Pharmacokinetics of ibuprofen enantiomers in children with cystic fibrosis. J Clin Pharmacol 40(8):861 868

Dooley JM, Gordon KE, Wood EP, Brna PM, MacSween J, Fraser A (2007) Caffeine as an adjuvant to ibuprofen in treating childhood headaches. Pediatr Neurol 37:42 46

Dotzel MM (2002) Internal Analgesic, antipyretic, and antirheumatic drug products for over the counter human use; Proposed amendment of the tentative final monograph, and related labeling. Food and Drug Administration 21CFR Parts 201 abd 343 [Docket No. 77N 0941] RIN 0910 AA01. Fed Reg 67(162):54139 54159

Downing A, Jacobsen J, Sorensen HT, McLaughlin JK, Johnsen SP (2006) Risk of hospitalization for angio oedema among users of newer COX 2 selective inhibitors and other nonsteroidal anti inflammatory drugs. Br J Clin Pharmacol 62:496 501

Doyle G, Furey S, Berlin R, Cooper S, Jayawardena S, Ashraf E, Baird L (1999) Gastrointestinal safety and tolerance of ibuprofen at maximum over the counter dose. Aliment Pharmacol Ther 13:897 906

Doyle G, Jayawardena S, Ashraf E, Cooper SA (2002) Efficacy and tolerability of nonprescription ibuprofen versus celecoxib for dental pain. J Clin Pharmacol 42:912 919

Du L, Liu X, Huang W, Wang E (2006) A study on the interaction between ibuprofen and bilayer lipid membrane. Electrochim Acta 51:5754 5760

Dunn MJ, Scharschmidt L, Zambraski E (1984) Mechanisms of nephrotoxicity if non steroidal anti inflammatory drugs. Arch Toxicol 7:328 337

Dunwiddie TV, Masino SA (2001) The role and regulation of adenosine in the central nervous system. Annu Rev Neurosci 24:31 55

Durrieu G, Olivier P, Montastruc JL (2005) COX 2 inhibitors and arterial hypertension: an analysis of spontaneous case reports in the pharmacovigilance database. Eur J Clin Pharmacol 61:611 614

Dutch MJ (2008) Nurofen Plus misuse: an emerging cause of perforated gastric ulcer. Med J Aust 188:56 57

Eccles R (2006) Efficacy and safety of over the counter analgesics in the treatment of common cold and flu. J Clin Pharm Ther 31:309 319

Edwards IR, Biriell C (2007) WHO Programme global monitoring. In: Mann RD, Andrews EB (eds) Pharmacovigilance. Wiley, Chichester, pp 151 166

Edwards JE, Moore RA, McQuay HJ (2004) Individual patient meta analysis of single dose rofecoxib in postoperative pain. BMC Anesthesiol 4:1 10

Edwards IR, Olsson S, Lindquist M, Hugman B (2006). Global drug surveillance: The WHO Programme for international drug monitoring. In: Strom BL, Kimmel SE (eds) Textbook of pharmacoepidemiology. Wiley, Chichester, pp 117 136

Ehrlich EW, Dallob A, De Lepeleire I, Van Hecken A, Riendeau D, Yuan W et al (1999) Characterization of rofecoxib as a cyclooxygenase 2 isoform inhibitor and demonstration of analgesia in the dental pain model. Clin Pharmacol Ther 65:336 347

Eller MG, Wright C III, Della Coletta AA (1989) Absorption kinetics of rectally and orally administered ibuprofen. Biopharm Drug Dispos 10:269 278

Ellinwood EH, Lee TH (1996) Central nervous system stimulants and anorectic agents. In: Dukes MNG (ed) Meyler's side effects of drugs, 13th edn. Elsevier, Amsterdam, pp 1 30

Ellison J, Dager W (2007) Recent FDA warning of the concomitant use of aspirin and ibuprofen and the effects on platelet aggregation. Prev Cardiol 10:61 63

Elmquist WF, Chan KK, Sawchuk RJ (1994) Transsynovial drug distribution: synovial mean transit time of diclofenac and other nonsteroidal antiinflammatory drugs. Pharm Res 11(12):1689 1697

EMSASI Study Group: Diener HC, Bussone C, de Liano H, Eikermann A, Englert R, Floeter T, Gallai V et al (2004) Placebo controlled comparison of effervescent acetylsalicylic acid, sumatripan and ibuprofen in the treatment of migraine attacks. Cephalagia 24:947 954

Ergil KV, Wang CB, Ng AT (2002) Chinese herbal medicines. West J Med 176:275 279

Erlewyn Lajeunesse MD, Coppens K, Hunt LP, Chinnick PJ, Davies P, Higginson IM, Benger JR (2006) Randomised controlled trial of combined paracetamol and ibuprofen for fever. Arch Dis Child 91:4141 4416

Ernest D, Chia M, Corallo CE (2010) Profound hypokalaemia du to Nurofen Plus® and Red Bull® misuse. Crit Care Resusc 12:109 110

Eustace N, O'Hare B (2007) Use of nonsteroidal anti inflammatory drugs in infants. A survey of members of the Association of Paediatric Anaesthetists of Great Britain and Ireland. Paediatr Anaesth 17:464 469

Evans AM (1996) Pharmacodynamics and pharmacokinetics of the profens: enantioselectivity, clinical implications, and special reference to S(+) ibuprofen. J Clin Pharmacol 36(12 Suppl): 7S 15S

Evans AM (2001) Comparative pharmacology of S(+) ibuprofen and (RS) ibuprofen. Clin Rheumatol Suppl 1:S9 S14

Farkouh ME, Kirshner H, Harrington RA, Ruland S, Verheugt FWA, Schnitzer TJ, Burmester GR, Mysler E, Hochberg MC, Doherty M, Ehrsam E, Gitton X, on behalf of the TARGET Study Group (2004) Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial. Lancet 364:675 684

Farkouh ME, Grennberg JD, Jeger RV, Ramanathan K, Verheugt FWA, Chesebro JH et al (2007) Cardiovascular outcomes in high risk patients with osteoarthritis treated with ibuprofen, naproxen or lumiracoxib. Ann Rheum Dis 66:764 770

Farquhar WB, Kenney WL (1999) Age and renal prostaglandin inhibition during exercise and heat stress. J Appl Physiol 86:1936 1943

Farquhar WB, Morgan AL, Zambraski EJ, Kenney WL (1999) Effects of acetaminophen and ibuprofen on renal function in the stressed kidney. J Appl Physiol 86:598 604

Fields HL (1987) Pain. McGraw Hill, New York

Fischer LM, Schlienger RG, Matter CM, Jick H, Meier CR (2005) Current use of nonsteroidal antiinflammatory drugs and the risk of acute myocardial infarction. Pharmacotherapy 25:503 510

Florence AT, Attwood D (1998) Physicochemical principles in pharmacy, 3rd edn. Macmillan, Houndmills Basingstoke, pp 441 446

Flower RJ, Vane JR (1972) Inhibition of prostaglandin synthetase in brain explains the anti pyretic activity of paracetamol (4 acetamidophenol). Nature 240:410 411

Flower RJ, Vane JR (1974) Inhibition of prostaglandin biosynthesis. Biochem Pharmacol 23:1439 1450

Forbes JA, Jones KF, Kehm CJ, Smith WK, Gongloff CM, Zeleznock JR, Smith JW, Beaver WT, Kroesen M (1990) Evaluation of aspirin, caffeine, and their combination in postoperative oral surgery pain. Pharmacotherapy 10(6):387 393

Forbes JA, Beaver WT, Jones KF, Kehm CJ, Smith WK, Gongloff CM, Zeleznock JR, Smith JW (1991) Effect of caffeine on ibuprofen analgesia in postoperative oral surgery pain. Clin Pharmacol Ther 49:674 684

Fornasini G, Monti N, Brogin G, Gallina M, Eandi M, Persiani S, Bani M, Della Pepa C, Zara G, Strolin Benedetti M (1997) Preliminary pharmacokinetic study of ibuprofen enantiomers after administration of a new oral formulation (ibuprofen arginine) to healthy male volunteers. Chirality 9:297 302

Fosbøl EL, Køber L, Torp Pedersen C, Gislason GH (2010) Cardiovascular safety of non steroidal anti inflammatory drugs among healthy individuals. Expert Opin Drug Saf 9:893 903

Foster BC, Vandenhoek S, Tang R, Budzinski JW, Krantis A, Li KY (2002) Effect of several Chinese natural health products of human cytochrome P450 metabolism. J Pharm Pharm Sci 5:185 189

Fowler CJ, Stenström A, Tiger G (1997a) Ibuprofen inhibits the metabolism of the endogenous cannabinimetic agent anandamide. Pharmacol Toxicol 80(2):103 107

Fowler CJ, Tiger G, Stenström A (1997b) Ibuprofen inhibits rat brain deamidation of anandamide at pharmacologically relevant concentrations. Mode of inhibition and structure activity relationship. J Pharmacol Exp Ther 283(2):729 734

Fowler CJ, Holt S, Nilsson O, Jonsson KO, Tiger G, Jacobsson SO (2005) The endocannabinoid signaling system: pharmacological and therapeutic aspects. Pharmacol Biochem Behav 81:248 262

Frei MY, Nielsen S, Dobbin MD, Tobin CL (2010) Serious morbidity associated with misuse over the counter codeine ibuprofen analgesics: a series of 27 cases. Med J Aust 193:294 296

Freis JF, Williams CA, Bloch DA (1991) The relative toxicity of nonsteroidal antiinflammatory drugs. Arth Rheum 34:1353 1360

Freise J, Bernau I, Meier S, Zeidler H, Kuipers JG (2009) Detection of Chlamydia trachomatis DNA in synovial fluid: evaluation of the sensitivity of different DNA extraction methods and amplification systems. Arth Res Ther 11:R175

Friedman H, Seckman C, Stubbs C, Oster H, Royer G (1990a) Multiple dose safety study of ibuprofen/codeine and aspirin/codeine combinations. J Clin Pharmacol 30:65 69

Friedman H, Seckman C, Lanza F, Royer G, Perry K, Francom S (1990b) Clinical pharmacology of predisintegrated ibuprofen 800mg tablets: an endoscopic and pharmacokinetic study. J Clin Pharmacol 30:57 63

Fries J (1996) Toward an understanding of NSAID related adverse events: the contribution of longitudinal data. Scand J Rheumatol Suppl 102:3 8

Fries JF (1998) The epidemiology of NSAID gastropathy: the ARAMIS experience. J Clin Rheumatol 4(5 Suppl):s11 s16

Fries JF, Bruce B (2003) Rates of serious gastrointestinal events from low dose use of acetylsalicylic acid, acetaminophen, and ibuprofen in patients with osteoarthritis and rheumatoid arthritis. J Rheumatol 30(10):2226 2233

Fries JF, Williams CA, Bloch DA (1991) The relative toxicity of nonsteroidal antiinflammatory drugs. Arthritis Rheum 34(11):1353 1360

Fries JF, Murtagh KN, Bennett M, Zatarain E, Lingala B, Bruce B (2004) The rise and decline of nonsteroidal antiinflammatory drug associated gastropathy in rheumatoid arthritis. Arthritis Rheum 50(8):2433 2440

Furey SA, Waksman JA, Dash BH (1992) Nonprescription ibuprofen: side effect profile. Pharma cotherapy 12:403 407

Furey SA, Vargas R, McMahon FG (1993) Renovascular effects of non prescription ibuprofen in elderly hypertensive patients with mild renal impairment. Pharmacotherapy 13:143 148

Furst DE (1992) Toxicity of antirheumatic medications in children with juvenile arthritis. J Rheumatol Suppl 33:11 15

Furst D (1994) Are there differences among nonsteroidal anti inflammatory drugs? Comparing acetylated salicylates, nonacetylated salicylates, and nonacetylated nonsteroidal anti inflammatory drugs. Arth Rheum 37:1 9

Galdding PA, Webster MWI, Farrell HB, Zeng ISL, Park R, Ruijne N (2008) The antiplatelet effect of six non steroidal anti inflammatory drugs and their pharmacodynamic interaction with aspirin in healthy volunteers. Am J Cardiol 101:1060 1063

Gallin JI, Goldstein IM, Snyderman R (eds) (1992) Inflammation. Basic principles and clinical correlates, 2nd edn. Ravel, New York

Gallo JM, Gall EP, Gillespie WR, Albert KS, Perrier D (1986) Ibuprofen kinetics in plasma and synovial fluid of arthritic patients. J Clin Pharmacol 26(1):65 70

Galzin M, Brunet P, Burtey S, Dussol B, Berland Y (1997) Tubular necrosis after non steroidal anti inflammatory agents and acute alcoholic intoxication. Nephrologie 18:113 115

García Rodríguez LA, Varas Lorenzo C, Maguire A, González Pérez A (2004) Nonsteroidal antiinflammatory drugs and the risk of myocardial infarction in the general population. Circulation 109:3000 3006

García Martín E, Martínez C, Tabarés B, Frías J, Agúndez JA (2004) Interindividual variability in ibuprofen pharmacokinetics is related to interaction of cytochrome P450 2C8 and 2C9 amino acid polymorphisms. Clin Pharmacol Ther 76(2):119 127

Garcia Rodriguez LA, Hernandez Diaz S (2001) The risk of upper gastrointestinal complications associated with nonsteroidal anti inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents. Arthritis Res 3:98 101

Garg V, Jusko WJ (1994) Pharmacodynamic modelling of nonsteroidal anti inflammatory drugs: antipyretic effect of ibuprofen. Clin Pharmacol Ther 55:87 88

Gazal G, Mackie IC (2007) A comparison of paracetamol, ibuprofen or their combination for pain relief following extractions in children under general anaesthesia: a randomized controlled trial. Int J Paediatr Dent 17:169 177

Gaziano JM, Gibson CM (2006) Potential for drug drug interactions in patients taking analgesics for mild to moderate pain and low dose aspirin for cardioprotection. Am J Cardiol 97(9A):23 29

Ge L, Jin R, Lu Y (1995) The bioavailability and pharmacokinetics of ibuprofen grantile in young healthy volunteers. J Chin Pharm. doi:cnki:ISSN:10010408.0.1995 06 018

Geisslinger G, Dietzel K, Bezler H, Nuernberg B, Brune K (1989) The therapeutic relevant differences in the pharmacokinetical and pharmaceutical behaviours of ibuprofen lysinate as compared to ibuprofen acid. Int J Clin Pharmacol Ther Toxicol 27:324 328

Geisslinger G, Schuster O, Stock KP, Loew D, Bach GL, Brune K (1990) Pharmacokinetics of *(S)* (+) and *(R)* ( ) ibuprofen in volunteers and first clinical experience in rheumatoida arthritis. Eur J Clin Pharmacol 38:493 497

Geisslinger G, Stock KP, Loew D, Bach GL, Brune K (1993) Variability in the stereoselective disposition of ibuprofen in patients with rheumatoid arthritis. Br J Pharmacol 35:603 607

Ghislandi V, La Manna A, Azziolino O, Gazzaniga A, Vercesi D (1982) Configurational relationships in antiphlogistic hydratopic acids. Il Farmaco (Edizione Scientifica) 37:81 92

Giannini EH, Brewer EJ, Miller ML, Gibbas D, Passo MH, Hoyeraal HM, Bernstein B, Person DA, Fink CW (1990) Ibuprofen suspension in the treatment of juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. J Pediatr 117:645 652

Gilroy D, Lawrence T (2008) The resolution of acute inflammation: a 'tipping point' in the development of chronic inflammation. In: Rossi AG, Sawatzky DA (eds) The resolution of inflammation. Birkhäuser, Basel, pp 1 18

Giles AD, Hill CM, Shepherd JP, Stewart DJ, Pickvance NJ (1986) A single dose assessment of an ibuprofen/codeine combination in postoperative dental pain. Int J Oral Maxillofac Surg 15:727 732

Gislason GH, Jacobsen S, Rasmussen JN, Rasmussen S, Buch P, Friberg J, Schramm TK et al (2006) Risk of death or reinfarction associated with the use of selective cyclooxygenase 2 inhibitors and nonselective nonsteroidal anti inflammatory drugs after acute myocardial infarction. Circulation 113:2906 2913

Gladding P, Webster M, Ormiston J, Olsen S, White H (2008a) Antiplatelet unresponsiveness. Am Heart J 155:591 599

Glass RC, Swannell AJ (1978) Concentrations of ibuprofen in serum and synovial fluid from patients with arthritis. Br J Clin Pharmacol 6:453P 454P

Głowka FK (2000) Stereoselective pharmacokinetics of ibuprofen and its lysinate from suppositories in rabbits. Int J Pharm 199:159 166

Goldstein J, Silberstein SD, Saper JR, Ryan RE, Lipton RB (2006) Acetaminophen, aspirin, and caffeine in combination versus ibuprofen for acute migraine: results from a multicentre, double blind, randomized, parallel group, single dose, placebo controlled study. Headache 46:444 453

Gong X, Sucher NJ (2002) Stroke therapy in traditional Chinese medicine (TCM): prospects for drug discovery and development. Phytomedicine 9:478 484

Graff J, Skarke C, Klinkhardt U, Watzer B, Harder S et al (2007) Effects of selective COX 2 inhibition on prostanoids and platelet physiology in young healthy volunteers. J Thromb Haemost 5:2376 2385

Graham GG (1988) Kinetics of non steroidal anti inflammatory drugs in synovial fluid. In: Brooks PM, Day RO, Williams K, Graham G (eds) Basis for variability of response to anti rheumatic drugs. Brikhäuser, Bael, pp 66 75

Graham GG, Hicks M (2004) Pharmacokinetics and metabolism of paracetamol (acetaminophen). In: Rainsford KD (ed) Aspirin and related drugs. Taylor & Francis, London, pp 182 213

Graham GG, Scott KF (2003) Mechanisms of action of paracetamol and related analgesics. Inflammopharmacology 11:401 413

Graham GG, Williams KM (2004) Metabolism and pharmacokinetics of ibuprofen. In: Rainsford KD (ed) Aspirin and related drugs. Taylor & Francis, London, pp 157 180

Graham GG, Day RO, Milligan MK, Ziegler JB, Kettle AJ (1999) Current concepts of the actions of paracetamol (acetaminophen) and NSAIDs. Inflammopharmacology 7:255 263

Graham GG, Roberts MS, Day RO, Rainsford KD (2004) Pharmacokinetics and metabolism of the salicylates. In: Rainsford KD (ed) Aspirin and related drugs. Taylor & Francis, London, pp 97 155

Graham DJ, Campen D, Hui R, Spence M, Cheetham C, Levy G, Shoor S, Ray WA (2005) Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo oxygenase 2 selective and non selective non steroidal anti inflammatory drugs: nested case control study. Lancet 365:475 481

Grennan DM, Ferry DG, Ashworth ME, Kenny RE, Mackinnon M (1979) The aspirin ibuprofen interaction in rheumatoid arthritis. Br J Clin Pharmacol 8:497 503

Grennan DM, Aarons L, Siddiqui M, Richards M, Thompson R, Higham C (1983) Dose response study with ibuprofen in rheumatoid arthritis: clinical and pharmacokinetic findings. Br J Clin Pharmacol 15(3):311 316

Griffin MR, Ray WA, Schaffner W (1988) Nonsteroidal anti inflammatory drug use and death from peptic ulcer in elderly persons. Ann Intern Med 109:359 363

Griffin MR, Yared A, Ray WA (2000) Nonsteroidal anti inflammatory drugs and acute renal failure in elderly persons. Am J Epidemiol 15:488 496

Grillo MP, Hua F (2008) Enantioselective formation of ibuprofen S acyl glutathione in vitro in incubation of ibuprofen with rat hepatocytes. Chem Res Toxicol 21:1749 1759

Growcott JW, Stone A, Beise R, Stammer H, Tetzloff W, Demey C (2000) Sensitivity of repeated interdigital web pinching to detect antinociceptive effects of ibuprofen. Br J Clin Pharmacol 49:331 336

Guindon J, De Lean A, Beaulieu P (2006) Local interactions between anandamide, an endocannabinoid, and ibuprofen, a nonsteroidal anti inflammatory drug, in acute and inflam matory pain. Pain 121:85 93

Gunn M, Stephens JC, Thompson JR, Rathbone BJ, Samani NJ (2000) Significant association of cagA positive helicobacter pylori strains with risk of premature myocardial infarction. Heart 84:267 271

Gurwitz JH, Everitt DE, Monane M, Glynn RJ, Choodnovskiy I, Beaudet MP, Avorn J (1996) The impact of ibuprofen on the efficacy of antihypertensive treatment with hydrochlorothiazide in elderly persons. J Gerontol A Biol Sci Med Sci 51:M74 M79

Haag G, Diener H C, May A, Meyer C, Morck H, Straube A, Wessely P, Evers S (2011) Self medication of migraine and tension type headache: summary of the evidence based recommendations of the Deutsche Migräne und Kopfschmerzgesselschaft (DMKG), the Deutsche Gesselschaft für Neurologie (DGN), the Österreichische Kopfschmerzgesselschaft (ÖKSG) and the Schweizerische Kopfwehgessellschaft (SKG). J Headache Pain 12:201 217

Haas M, Moolenaar F, Meijer DK, Jong PE, de Zeeuw D (1998) Renal targeting of a non steroidal anti inflammatory drug: effects on renal prostaglandin synthesis in the rat. Clin Sci 95:603 609

Haase W, Fischer M (1991) Statistical meta analysis of multicenter clinical studies of ibuprofen with regard to cohort size. Z Rheumatol 50(Suppl 1):77 83

Hadas D, Youngster I, Cohen A, Leibovitch E, Shavit I, Erez I, Uziel Y, Berkovitch M (2011) Premarketing surveillance of ibuprofen suppositories in febrile children. Clin Pediatr (Phila) 50:196 199

Hamman MA, Thompson GA, Hall SD (1997) Regioselective and stereoselective metabolism of ibuprofen by human cytochrome P450 2C. Biochem Pharmacol 54:33 41

Hargreaves KM, Keiser K (2002) Development of new pain management strategies. J Dent Educ 66:113 121

Harrington LS, Lucas R, McMaster SK, Moreno L, Scadding G, Warner TD, Mitchell JA (2008) COX 1, and not COX 2 activity, regulates airway function: relevance to aspirin sensitive asthma. FASEB J 22:4005 4010

Harris RC, McKanna JA, Akai Y, Jacobson HR, Duboois RN, Breyer MD (1994) Cyclooxygenase 2 is associated with the macula densa of rat kidney and increases with salt restriction. J Clin Invest 94:2504 2510

Harris NS, Wenzel RP, Thomas SH (2003) High altitude headache: efficacy of acetaminophen vs, ibuprofen in a randomized, controlled trial. J Emerg Med 24:383 387

Haupt MT, Jastrmski MS, Clemmer TP, Metz CA, Goris GB (1991) Effect of ibuprofen in patients with severe sepsis: a randomized, double blind, multicentre study. The ibuprofen study group. Crit Care Med 19:1339 1347

Havanka Kanniainen H (1989) Treatment of acute migraine attack: ibuprofen and placebo com pared. Headache 29:507 509

Hawton K, Townsend E, Deeks J, Appleby L, Gunnell D, Bennewith O, Cooper J (2001) Effects of legislation restricting pack sizes of paracetamol and salicylate on self poisoning in the United Kingdom: before and after study. Br Med J 322:1203 1207

Hay AD Costelloe C, Redmond NM, Montgomery AA, Fletcher M, Hollinghurst S, Peters TK (2008) Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): randomised controlled trial. Br Med J 337:a1302 (erratum Br Med J 339:b3295)

Hay AD, Redmond N, Fletcher M (2006) Antipyretic drugs for children. Br Med J 333:4 5

Hay AD, Redmond NM, Costelloe C, Montgomery AA, Fletcher M, Hollinghurst S, Peters TK (2009) Paracetamol and ibuprofen for the treatment of fever in children: the PITCH randomised controlled trial. Health Technol Assess 13:iii iv, ix x, 1 163

Heard K, Sloss D, Weber S, Dart RC (2006) Overuse of over the counter analgesics by emergency department patients. Ann Emerg Med 48:315 318

Heard K, Green JL, Bailey JE, Bogden GM, Dart RC (2007) A randomized trial to determine the change in alanine aminotransferase during 10 days of paracetamol (acetaminophen) in subjects who consume moderate amount of alcohol. Aliment Pharmacol Ther 26:283 290

Henry D, McGettigan P (2003) Epidemiology overview of gastrointestinal and renal toxicity of NSAIDs. Int J Clin Pract Suppl (135):43 49

Henry DA, Dobson A, Turner C (1993) Variability in the risk of major gastrointestinal complications from non aspirin nonsteroidal anti inflammatory drugs. Gastroenterology 105:1078 1088

Henry D, Lim LL Y, Garcia Rodriguez LA, Perez Gutthann S, Carson JL, Griffin M, Savage R, Logan R, Moride Y, Hawkey C et al (1996) Variability in risk of gastrointestinal complications with individual non steroidal anti inflammatory drugs: results of a collaborative meta analysis. Br Med J 312:1563 1566

Henry DA, Drew A, Beuzeville S (1998) Adverse drug reactions in the gastrointestinal system attributed to ibuprofen. In: Rainsford KD, Powanda MC (eds) Safety and efficacy of non prescription (OTC) analgesics and NSAIDs. Kluwer Academic, Dodrecht, pp 19 45

Heremans G, Dehaen F, Rom N, Ramet J, Verboven M, Loeb H (1988) A single blind parallel group study investigating the antipyretic properties of ibuprofen syrup versus acetylsalicylic acid syrup in febrile children. Br J Clin Pract 42:245 247

Hermann TW, Gtówka FK, Garrett ER (1993) Bioavailability of racemic ibuprofen and its lysine from suppositories in rabbits. J Pharm Sci 82:1102 1111

Hernandez Diaz S, Varas Lorenzo C, Garcia Rodriguez LA (2006) Non steroidal anti inflammatory drugs and the risk of acute myocardial infarction. Basic Clin Pharmacol Toxicol 98:266 274

Hersh EV, Cooper S, Betts N, Wedell D, MacAfee K, Quinn P, Lamp C, Gaston G, Bergman S, Henry E (1993) Single dose and multidose analgesic study of ibuprofen and meclofenamate sodium after third molar surgery. Oral Surg Oral Med Oral Pathol 76(6):680 687

Hersh EV, Moore PA, Ross GL (2000a) Over the counter analgesics and antipyretics: a critical assessment. Clin Ther 22:500 548

Hersh EV, Levin LM, Cooper SA, Doyle G, Waksman J, Wedell D, Hong D, Secreto SA (2000b) Ibuprofen liquigel for oral surgery pain. Clin Ther 22:1306 1318

Hersh EV, Pinto A, Moore PA (2007) Adverse drug interactions involving common prescription and over the counter analgesic agents. Clin Ther 29:2477 2497

Higton F (1999) The pharmaceutics of ibuprofen. In: Rainsford KD (ed) Ibuprofen. A critical bibliographic review. Taylor & Francis, London, pp 53 86

Hinz B, Brune K (2012) Paracetamol and cyclooxygenase inhibition: is there a cause for concern? Ann Rheum Dis 71:20 25

Hippisley Cox J, Coupland C (2005) Risk of myocardial infarction in patients taking cyclo oxygenase 2 inhibitors or conventional non steroidal anti inflammatory drugs: population based nested case control analysis. Br Med J 330:1366

Hippisley Cox J, Coupland C, Logan R (2005) Risk of adverse gastrointestinal outcomes in patients taking cyclo oxygenase 2 inhibitors or conventional non steroidal anti inflammatory drugs: population based nested case control analysis. Br Med J 331:1310 1316

Hirt D, Van Overmeire B, Treluyer JM, Langhendries JP, Marguglio A, Eisinger MJ, Schepens P, Urien S (2008) An optimized ibuprofen dosing scheme for preterm neonates with patent ductus arteriosus, based on a population pharmacokinetic and pharmacodynamic study. Br J Clin Pharmacol 65:629 636

Hoffman M, Gray RG (1982) Ibuprofen induced meningitis in mixed connective tissue disease. Clin Rheumatol 1:128 130

Hollinghurst S, Redmond N, Costelloe C, Montgomery A, Fletcher M, Peters TJ, Hay AD (2008) Paracetamol plus ibuprofen for the treatment of fever in children (PITCH): economic evalua tion of a randomised controlled trial. Br Med J 337:a1490

Hollingworth P (1993) The use of non steroidal anti inflammatory drugs in paediatric rheumatic diseases. Br J Rheumatol 32(1):73 77

Holmes E, Loo RL, Cloarec O, Coen M, Tang H, Maibaum E, Bruce S, Chan Q, Elliott P, Stamler J, Wilson ID, Lindon JC, Nicholson JK (2007) Detection of urinary drug metabolite (xenometabolome) signatures in molecular epidemiology studies via statistical total correlation (NMR) spectroscopy. Anal Chem 79:2629 2640

Holt S, Paylor B, Boldrup L, Alajakku K, Vandevoorde S, Sundström A, Cocco MT, Onnis V, Fowler CJ (2007) Inhibition of fatty acid amide hydrolase, a key endocannabinoid metabolizing enzyme, by analogues of ibuprofen and indomethacin. Eur J Pharmacol 565(1 3):26 36

Hopkinson JH 3rd, Bartlett FH Jr, Steffens AO, McGlumphy TH, Macht EL, Smith M (1973) Acetaminophen versus propoxyphene hydrochloride for relief of pain in episiotomy patients. J Clin Pharmacol 13(7):251 263

Huang WF, Wen KC, Hsiao ML (1997) Adulteration by synthetic therapeutic substances of traditional Chinese medicines in Taiwan. J Clin Pharmacol 37:344 350

Huang WF, Hsiao FY, Wen YW, Tsai YW (2006) Cardiovascular events associated with the use of four nonselective NSAIDs (etodolac, nabumetone, ibuprofen, or naproxen) versus a cyclooxygenase 2 inhibitor (celecoxib): a population based analysis in Taiwanese adults. Clin Ther 28:1827 1836

Huber MA, Terezhalmi GT (2006) The use of COX 2 inhibitors for acute dental pain. J Am Dent Assoc 137:480 487

Hudson M, Rahme E, Richard H, Pilote L (2007) Risk of congestive heart failure with nonsteroidal anti inflammatory drugs and selective cylooxygenase 2 inhibitors: a class effect? Arth Rheum 57:516 523

Hunt RH, Bowen B, Mortensen ER, Simon TJ, James C, Cagliola A, Quan H, Bolognese JA (2000) A randomized trial measuring faecal blood loss after treatment with rofecoxib, ibuprofen, or placebo in healthy subjects. Am J Med 109:201 206

Huntjens DR, Danhof M, Della Pasqua OE (2005) Pharmacokinetic pharmacodynamic correlations and biomarkers in the development of COX 2 inhibitors. Rheumatology (Oxford) 44:846 859

Hummel T, Cramer O, Mohammadian P, Geisslinger G, Pauli E, Kobal G (1997) Comparison of the antinociception produced by two oral formulations of ibuprofen: ibuprofen effervescent vs ibuprofen tablets. Eur J Clin Pharmacol 52:107 114

Hyldahl RD, Keadle J, Rouzier PA, Pearl D, Clarkson PM (2010) Effects of ibuprofen topical gel on muscle soreness. Med Sci Sports Exerc 42:614 621

Hyllested M, Jones S, Pedersen JL, Kehlet H (2002) Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. Br J Anaesth 88:199 214

Ichihara A, Imig JD, Navar LG (1999) Cyclooxygenase 2 modulates afferent arteriolar responses to increases in pressure. Hypertension 34:843 847

Ikegawa S, Murao N, Oohashi J, Goto J (1998) Separatory determination of diastereomeric ibuprofen glucuronides in human urine. Biomed Chromatogr 12:317 321

Inoue T, Mi Z, Gillesoie DG, Jackson EK (1998) Cyclooxygenase inhibition reveals synergistic action of vasoconstrictors on mesangial cell growth. Eur J Pharmacol 361:285 291

Jackson LA, Dunstan M, Starkovich P, Dunn J, Yu O, Nelson JC, Rees T, Zavitkovsky A (2006) Prophylaxis with acetaminophen or ibuprofen for prevention of local reaction to the fifth diphtheria tetanus toxoids acellular pertussis vaccination: a randomized, controlled trial. Pediatrics 117:620 625

Jacqz Aigrain E, Anderson BJ (2006) Pain control: non steroidal anti inflammatory agents. Semin Fetal Neonat Med 11:251 259

Jain AK, Ryan JR, McMahon FG, Kuebel JO, Walters PJ, Noveck C (1986) Analgesic efficacy of low dose ibuprofen in dental extraction pain. Pharmacotherapy 6(6):318 322

Jamali F, Singh NN, Pasutto FM, Russell AS, Coutts RT (1988) Pharmacokinetics of ibuprofen enantiomers in humans following oral administration of tablets with different absorption rates. Pharm Res 5:40 43

Jamali F, Aghazadeh Habashi A (2008) Rapidly dissolving formulations for quick absorption during pain episodes: ibuprofen. Int J Clin Pharmacol Ther 46:55 63

Jamali F, Kunz Dober CM (1999) Pain mediated altered absorption and metabolism of ibuprofen: an explanation for decreases serum enantiomer concentration after dental surgery. Br J Clin Pharmacol 47:391 396

Janovsky M, Krsiak M (2011) Codeine did not increase analgesic efficacy of coxibs in contrast to that of paracetamol or ibuprofen: isobolographic analysis in mice. Neuro Endocrinol Lett 32(2):164 169

Jenkins C, Costello J, Hodge L (2004) Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. Br Med J 328:434

J h Wen, X h Cheng et al (2007) Pharmacokinetics and bioequivalence of ibuprofen tablet in healthy volunteers. Acta Academiae Medicinae Jiangxi 47:30 32. doi:CNKI:SUN:JXYB.0.2007 06 009

Ji MC, Chen B Y, Du Y, Cheng N N, Wamg Y M (1999) Relative bioavailability after p.o. ibuprofen sustained release suspension in healthy volunteers. Chin J Clin Pharmacol. doi:cnki: ISSN:1001 6821.0.1999 04 009

Jian L (1996) Pharmacokinetics and relative bioavailability of ibuprofen dry syrup. J Shenyang Pharm Univ. doi:cnki:ISSN:10062858.0.1996 02 004

Jick H, Kaye JA, Russmann S, Jick SS (2006) Nonsteroidal antiinflammatory drugs and acute myocardial infarction in patients with no major risk factors. Pharmacotherapy 26:1379 1387

Johnson AG, Nguyen TV, Day RO (1994) Do nonsteroidal anti inflammatory drugs affect blood pressure? A meta analysis. Ann Intern Med 121:289 300

Johnson CH, Wilson ID, Harding JR, Stachulski AV, Iddon L, Nicholson JK, Lindon JC (2007) NMR spectroscopic studies on the in vitro glucuronide migration kinetics of ibuprofen ((+/) (R, S) 2 (4 sobutylphenyl) propanoic acid), its metabolites and analogues. Anal Chem 79:8720 8727

Jones K, Seymour RA, Hawkesford JE (1997) Are the pharmacokinetics of ibuprofen important determinants for the drug's efficacy in postoperative pain after third molar surgery? Br J Oral Maxillofac Surg 35:173 176

Jorgensen B, Friis GJ, Gottrup F (2006) Pain and quality of life for patients with venous leg ulcers: proof of concept of the efficacy of Biatain® ibu, a new pain reducing would dressing. Wound Rep Reg 14:233 239

Jüni P, Rutjes AWS, Dieppe PA (2002) Are selective COX 2 inhibitors superior to traditional nonsteroidal anti inflammatory drugs. Br Med J 324:1287 1288

Kaehler ST, Phleps W, Hesse E (2003) Dexibuprofen: pharmacology, therapeutic uses and safety. Inflammopharmacology 11:371 383

Kaka JS, Tekle A (1992) Bioavailability of ibuprofen from oral and suppository preparations in rats. Res Commun Chem Pathol Pharmacol 76:171 182

Kaltenbach ML, Mohammed SS, Mullersman G et al (1994) Pharmacokinetic evaluation of two ibuprofen codeine combinations. Int J Clin Pharmacol Ther 32:210 214

Kanabar D, Dale S, Rawat M (2007) A review of ibuprofen and acetaminophen use in febrile children and the occurrence of asthma related symptoms. Clin Ther 29:2716 2723

Kauffman RE, Nelson MV (1992) Effect of age on ibuprofen pharmacokinetics and antipyretic response. J Pediatr 121:969 973

Kaufman DW, Kelly JP, Sheehan JE, Laszlo A, Wiholm BE, Alfredsson L, Koft RS, Shapiro S (1993) Nonsteroidal anti inflammatory drug use in relation to major gastrointestinal bleeding. Clin Pharmacol Ther 53:485 494

Kean WF, Buchanan WW (1987) Antirheumatic drug therapy in the elderly: a case of failure to identify the correct issues? J Am Geriatr Soc 35:363 364

Kean WF, Buchanan WW, Rainsford KD (1999) Therapeutics of ibuprofen in rheumatic and other chronic and painful diseases. In: Rainsford KD (ed) Ibuprofen: a critical bibliographic review. Taylor & Francis, London, pp 279 353

Kean WF, Kean R, Buchanan WW (2004) Osteoarthritis: symptoms, signs and source of pain. Inflammopharmacology 12:3 31

Kean WF, Kean IRL, Rainsford KD (2008) Gastrointestinal complications of anti rheumatic drugs. In: Font J, Ramos Casals M, Rodes J (eds) Handbook of systemic autoimmune diseases, vol 8. Digestive involvement in systemic autoimmune diseases. Elsevier, Amsterdam, pp 243 275

Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C (2006) Do selective cyclo oxygenase 2 inhibitors and traditional non steroidal anti inflammatory drugs increase the risk of atherothrombosis? Meta analysis of randomised trials. Br Med J 332:1302 1308

Kelley MT, Walson PD, Edge JH, Cox S, Mortensen ME (1992) Pharmacokinetics and pharma codynamic of ibuprofen isomers and acetaminophen in febrile children. Clin Pharmacol Ther 52:181 189

Kellstein DE, Waksman JA, Furey SA, Binstok G, Cooper SA (1999) The safety profile of nonprescription ibuprofen in multiple dose use: a meta analysis. J Clin Pharmacol 39:520 532

Kellstein DE, Lipton RB, Geetha R, Koronkiewicz K, Evans FT, Stewart WF, Wilkes K, Furey SA, Subramanian T, Cooper SA (2000) Evaluation of a novel solubilized formulation of ibuprofen in the treatment of migraine headache: a randomized, double blind, placebo controlled, dose ranging study. Cephalalgia 20:233 243

Kerola M, Vuolteenaho K, Kosonen O, Kankaanranta H, Sarna S, Moilanen E (2008) Effects of nimesulide, acetylsalicylic acid, ibuprofen and nabumetone of cyclooxygenase 1 and cyclooxygenase 2 mediated prostanoid production in healthy volunteers ex vivo. Basic Clin Pharmacol Toxicol 104:17 21

Kerr DJ, Dunn JA, Langman MJ, Smith JL, Midgley RSJ, Stanley A et al (2007) Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. N Engl J Med 357:360 369

Khan KN, Venturini CM, Bunch RT, Brassard JA, Koki AT, Morris DL, Trump BF, Maziasz TJ, Alden CL (1998) Interspecies differences in renal localization of cyclooxygenase isoforms: implications in nonsteroidal anti inflammatory drug related nephrotoxicity. Toxicol Pathol 26:612 620

Khanna D, Khanna PP, Durst DE (2005) COX 2 controversy: where are we and where do we go from here? Inflammopharmacology 13:395 402

Kidon MI, Kang LW, Chin CW, Hoon LS, See Y, Goh A, Lin JTP, Chay OM (2005) Early presentation with angioedema and urticaria in cross reactive hypersensitivity to nonsteroidal antiinflammatory drugs among young, Asian, atopic children. Pediatrics 116:e675 e680

Kim S H, Ye T M, Palikhe NS, Kim J E, Park H S (2010) Genetic and ethnic risk factors associated with drug hypersensitivity. Curr Opin Allergy Clin Immunol 10:280 290

Kim SR, Kim JK, Park JS, Kim CK (2011) Dry elixir formulations of dexibuprofen for controlled release and enhanced oral bioavailability. Int J Pharm 404:302 307

Kimmel SE, Berlin JA, Reilly M, Jaskowiak J, Kishel L, Chittams J, Strom BL (2004) The effects of nonselective non aspirin non steroidal anti inflammatory medications on the risk of nonfatal myocardial infarction and their interaction with aspirin. J Am Coll Cardiol 43:985 990

Kirchheiner J, Meineke I, Freytag G, Meisel C, Roots I, Brockmöller J (2002) Enantiospecific effects of cytochrome P450 2C9 amino acid variants on ibuprofen pharmacokinetics and on the inhibition of cyclooxygenases 1 and 2. Clin Pharmacol Ther 72(1):62 75

Klippel JH (ed) (1997) Primer on the rheumatic diseases. Arthritis Foundation, Altanta, GA

Kloster R, Nestvold K, Vilming ST (1992) A double blind study of ibuprofen versus placebo in the treatment of acute migraine attacks. Cephalalgia 12:169 171

Klüglich M, Ring A, Scheuerer S, Trommeshauser D, Schuijt C, Liepold B, Berndl G (2005) Ibuprofen extrudate, a novel, rapidly dissolving ibuprofen formulation: relative bioavailability compared to ibuprofen lysinate and regular ibuprofen, and food effect on all formulations. J Clin Pharmacol 45:1055 1061

Ko D, Wang Y, Berger AK, Radford MJ, Krumholz HM (2002) Nonsteroidal anti inflammatory drugs after acute myocardial infarction. Am Heart J 143:475 481

Kobal G, Hummel C, Gruber M, Geisslinger G, Hummel T (1994) Dose related effects of ibuprofen on pain related potentials. Br J Clin Pharmacol 37:445 452

Koelsch M, Mallak R, Graham GG, Kajer T, Milligan MK, Nguyen LQ, Newsham DW, Keh JS, Kettle AJ, Scott KF, Ziegler JB, Pattison DI, Fu S, Hawkins CL, Rees MD, Davies MJ (2010) Acetaminophen (paracetamol) inhibits myeloperoxidase catalyzed oxidant production and biological damage at therapeutically achievable concentrations. Biochem Pharmacol 79:1156 1164

Koga T, Fujiwara R, Nakajima M, Yokoi T (2011) Toxicological evaluation of acyl glucuronides of nonsteroidal anti inflammatory drugs using human embryonic kidney 293 cells stably expressing human UDP glucuronyltransferase and human hepatocytes. Drug Metab Dispos 39:54 60

Kokki H (2003) Nonsteroidqal anti inflammatory drugs for postoperative pain: a focus on children. Peaediatr Drugs 5:103 123

Kokki H, Kampulainen E, Lehtonen M, Laisalmi M, Heikkinen M, Savolainen J, Rautio J (2007) Carebrospinal fluid distribution of ibuprofen after intravenous administration in children. Pediatrics 120:21002 21008

Konstan MW, Hoppel CL, Chai BL, Davis PB (1991) Ibuprofen in children with cystic fibrosis: pharmacokinetics and adverse effects. J Pediatr 118:956 964

Konstan MW, Byard PJ, Hoppel CL, Davis PB (1995) Effect of high dose ibuprofen in patients with cystic fibrosis. N Engl J Med 332:848 854

Kubitzek F, Ziegler G, Gold MS, Liu J MH, Ionescu E (2003) Low dose diclofenac potassium in the treatment of episodic tension type headache. Eur J Pain 7:155 162

Kurth T, Glynn RJ, Walker AM, Chan KA, Buring JE, Hennekens CH, Gaziano JM (2003) Inhibition of clinical benefits of aspirin on first myocardial infarction by nonsteroidal antiinflammatory drugs. Circulation 108:1191 1195

Kyllönen M, Olkkola KT, Seppälä T, Ryhänen P (2005) Perioperative pharmacokinetics of ibuprofen enantiomers after rectal administration. Paediatr Anaesth 15:566 573

Lacroix I, Lapeyre Mestre M, Bagheri H, Pathak A, Montastruc JL, Club de Relexion des Cabinets de Groupe de Gastro Enterologie (GREGG): General Practitioner Networks (2004) Nonsteroi dal anti inflammatory drug induced liver injury: a case control study in primary care. Fundam Clin Pharmacol 18:201 206

Lai XS, Yang LP, Li XT, Liu JP, Zhou ZW, Zhou SF (2009) Human CYP2C8: structure, substrate specificity, inhibitor selectivity, inducers and polymorphisms. Curr Drug Metab 10(9):1009 1047

Laine L (2001) Approaches to nonsteroidal anti inflammatory drug use in the high risk patient. Gastroenterology 120:594 606

Laine L, Smith R, Min K, Chen C, Dubois RW (2006) Systematic review: the lower gastrointestinal adverse effects of non steroidal anti inflammatory drugs. Aliment Pharmacol Ther 24:751 767

Lal A, Gomber S, Talukdar B (2000) Antipyretic effects of nimesulide, paracetamol and ibuprofen paracetamol. Indian J Pediatr 67:865 870

Lam CLK, Catarivas MG, Munro C, Lauder IJ (1994) Self medication among Hong Kong Chinese. Soc Sci Med 39:1641 1647

Lambert GP, Boylan M, Laventure JP, Bull A, Lanspa S (2007) Effects of aspirin and ibuprofen on GI permeability during exercise. Int J Sports Med 28:722 726

Lanas A (2010) A review of the gastrointestinal safety data a gastroenterologist's perspective. Rheumatology 49(Suppl 2):ii3 ii10

Lanas A, Garcia Rodriguez LA, Arroyo MT, Gomollon F, Feu F, Gonzalez Perez A, Zapata E, Bastida G, Rodrigo L, Santolaria S, Güell M, de Argila CM, Quintero E, Borda F, Pique JM (2006) Risk of upper gastrointestinal ulcer bleeding associated with selective cyclo oxygenase 2 inhibitors, traditional non aspirin non steroidal anti inflammatory drugs, aspirin and combinations. Gut 55:1731 1738

Lange R, Lentz R (1995) Comparison of ketoprofen, ibuprofen and naproxen sodium in the treatment of tension type headache. Drugs Exp Clin Res 21:89 96

Langman MJS, Weil J, Wainwright P, Lawson DH, Rawlins MD, Logan RFA, Murphy M, Vessey MP, Colin Jones DG (1994) Risk of bleeding peptic ulcers associated with individual non steroidal anti inflammatory drugs. Lancet 343:1075 1078

Lanza FL, Royer GL, Nelson RS, Chen TT, Seckman CE, Rack MF (1979) The effects of ibuprofen, indomethacin, aspirin, naproxen, and placebo on the gastric mucosa of normal volunteers. A gastroscopic and photographic study. Dig Dis Sci 24:823 828

Lanza FL, Royer GL, Nelson RS, Chen TT, Seckman CE, Rack MF (1981) A comparative endoscopic evaluation of the damaging effects of nonsteroidal anti inflammatory agents on the gastric and duodenal mucosa. Am J Gastroenterol 75:17 21

Lanza F, Rack MF, Lynn M, Wolf J, Sanda M (1987) An endoscopic comparison of the effects of etodolac, indomethacin, ibuprofen, naproxen, and placebo on the gastrointestinal mucosa. J Rheumatol 14:338 341

Lanza FL, Marathi UK, Anand BS, Lichtenberger LM (2008) Clinical trial: comparison of ibuprofen phosphatidylcholine and ibuprofen on the gastrointestinal safety and analgesic efficacy in osteoarthritic patients. Aliment Pharmacol Ther 28:431 442

Laporte J R, Ibanez L, Vidal X, Vendrell L, Leone R (2004) Upper gastrointestinal bleeding associated with the use of NSAIDs. Newer versus older agents. Drug Saf 27:411 420

Laska EM, Sunshine A, Zighelboim I, Roure C, Marrero I, Wanderling J, Olson N (1983) Effect of caffeine on acetaminophen analgesia. Clin Pharmacol Ther 33(4):498 509

Laska EM, Sunshine A, Mueller F, Elvers WB, Siegel C, Rubin A (1984) Caffeine as an analgesic adjuvant. JAMA 251:1711 1718

Laska EM, Sunshine A, Marrero I, Olson N, Siegel C, McCormick N (1986) The correlation between blood levels of ibuprofen and clinical analgesic response. Clin Pharmacol Ther 40:1 7

Lau SL, Chow RL, Yeung RW, Samman N (2009) Pre emptive ibuprofen arginate in third molar surgery: a double blind randomized controlled crossover clinical trial. Aust Dent J 54:355 360

Layton D, Marshall V, Boshier A, Friedmann P, Shakir SA (2006) Serious skin reactions and selective COX 2 inhibitors: a case series from prescription event monitoring in England. Drug Saf 29:687 696

Le Parc JM, Van Ganse E, Moore N, Wall R, Schneid H, Verrière F (2002) Comparative tolerability of paracetamol, aspirin and ibuprofen for short term analgesia in patients with musculoskeletal conditions: results in 4291 patients. Clin Rheumatol 21:28 31

Lee YS, Kim H, Wu TX, Wang XM, Dionne RA (2006) Genetically mediated interindividual variation in analgesic responses to cyclooxygenase inhibitory drugs. Clin Pharmacol Ther 79(5):407 418

Leeyaphan C, Kulthanan K, Jongjarearnprasert K, Dhana N (2010) Drug induced angioedema without urticaria: prevalence and clinical features. J Eur Acad Dermatol Venereol 24:685 691

Leising G, Resel R, Stelzer F, Tasch S, Lanziner A, Hantich G (1996) Physical aspects of dexibuprofen and racemic ibuprofen. J Clin Pharmacol 36(12 Suppl):3S 6S

Lesko SM (2003) The safety of ibuprofen suspension in children. Int J Clin Pract Suppl 135:50 53

Lesko SM, Mitchell AA (1995) An assessment of the safety of pediatric ibuprofen. A practitioner based randomized clinical trial. JAMA 273:929 933

Lesko SM, Mitchell AA (1997) Renal function after short term ibuprofen use in infants and children. Pediatrics 100:954 957
Lesko SM, Mitchell AA (1999) The safety of acetaminophen and ibuprofen younger than two years old. Pediatrics 104(4):e39
Lesko SM, Louik C, Vezina RM, Mitchell AA (2002) Asthma morbidity after the short term use of ibuprofen in children. Pediatrics 109:E20
Levine MA, Walker SE, Paton TW (1992) The effect of food or sucralfate on the bioavailability of S(+) and R( ) enantiomers of ibuprofen. J Clin Pharmacol 32:1110 1114
Lewis JD, Kimmel SE, Localio AR, Metz DC, Farrar JT, Nessel L, Brensinger C, McGibney K, Strom BL (2005) Risk of serious upper gastrointestinal toxicity with over the counter nonas pirin nonsteroidal anti inflammatory drugs. Gastroenterol 129:1865 1874
Li G, Treiber G, Maier K, Walker S, Klotz U (1993) Disposition of ibuprofen in patients with liver cirrhosis: stereochemical considerations. Clin Pharmacokinet. 25:154 163
Li Wan Po AW (2006) Dose response of minor analgesics in acute pain. Br J Clin Pharmacol 63:268 270
Li Wan Po A, Zhang WY (1998) Analgesic efficacy of ibuprofen alone and in combination with codeine or caffeine in post surgical pain: a meta analysis. Eur J Clin Pharmacol 53:303 311
Li X, Chen W L (2001) In vivo and vitro correlation of domestic sustained release tablets of ibuprofen. Chin J Hosp Pharm. doi:cnki:ISSN:1001 5213.0.2001 04 002
Li S, Le J, Chen GL, Chai YF, Lu F (2007) Discrimination of adulterated traditional Chinese medicines by infrared spectroscopy two dimensional correlation analysis. Guang Pu Xue Yu Guang Pu Fen Xi 27:2212 2215
Li H, Mandema J, Wada R, Jayawardena S, Desjardins P, Doyle G, Kellstein D (2012) Modeling the onset and offset of dental pain relief by ibuprofen. J Clin Pharmacol 52:89 101
Lichtenberger LM, Barron M, Marathi U (2009) Association of phosphatidylcholine and NSAIDs as a novel strategy to reduce gastrointestinal toxicity. Drugs Today 45:877 890
Lindh JD, Lundgren S, Holm L, Alfredsson L, Rane A (2005) Several fold increase in risk of overanticoagulation by CYP2C9 mutations. Clin Pharmacol Ther 78:540 550
Lipworth L, Friis S, Blot WJ, McLaughlin JK et al (2004) A population based cohort study of mortality among users of ibuprofen in Denmark. Am J Ther 11:156 163
Litalien C, Jacqz Aigrain E (2001) Risks and benefits of nonsteroidal anti inflammatory drugs in children: a comparison with paracetamol. Paediatr Drugs 3(11):817 858
Liu L, Li K, Zhang G, He G, Sun C (1998) Relative bioavailability of the sustained release capsule of ibuprofen. Chin Pharm. doi:CNKI:SUN:ZGYA.0.1998 03 016
Liu J, Wang ZT, Ji LL (2007) In vivo and in vitro anti inflammatory activities of neoandro grapholide. Am J Chin Med 35:317 328
Liu J, Wang ZT, Ge BX (2008) Andrograpanin, isolated from Andrographis paniculata, exhibits anti inflammatory property in lipopolysaccharide induced macrophage cells through down regulating the p38 MAPKs signaling pathways. Int Immunopharmacol 8:951 958
Llorca CS, Serra MPM, Donat FJS (2008) Interactions between ibuprofen and antihypertensive drugs: incidence and clinical relevance in dental practice. Med Oral Pathol Oral Cir Bucal 13:E717 E721
London RS, Sundaram GS, Feldman S, Goldstein PJ (1983) Aspirin in the treatment of episiotomy pain. South Med J 76(7):844 845
López Rodríguez R, Novalbos J, Gallego Sandín S, Román Martínez M, Torrado J, Gisbert JP, Abad Santos F (2008) Influence of CYP2C8 and CYP2C9 polymorphisms on pharmacokinetic and pharmacodynamic parameters of racemic and enantiomeric forms of ibuprofen in healthy volunteers. Pharmacol Res 58(1):77 84
Lötsch J, Muth Selbach U, Tegeder I, Brune K, Geisslinger G (2001) Simultaneous fitting of R and S ibuprofen plasma concentrations after oral administration of the racemate. Br J Clin Pharmacol 52:387 398
Lu YL, Zhou NL, Liao SY, Su N, He DX, Tian QQ, Chen B, Yao SZ (2010) Detection of adulteration of anti hypertension dietary supplements and traditional Chinese medicines with

synthetic drugs using LC/MS. Food Addit Contam A Chem Anal Control Expo Risk Assess 27:893 902
Lucas R, Warner TD, Vojnovic I, Mitchell JA (2005) Cellular mechanisms of acetaminophen: role of cyclo oxygenase. FASEB J 19:635 637
Lugardon S, Lapeyre Mestre M, Montastruc JL (2004) Upper gastrointestinal adverse drug reactions and cyclo oxygenase 2 inhibitors (celecoxib and rofecoxib): a case/non case study from the French Pharmacovigilance Database. Eur J Clin Pharmacol 60:673 677
Lui S, Mo H, Pan Q, Li (2008). Literature analysis on 80 cases of adverse drug reactions caused by ibuprofen. Chin Pharm 17:48 49.
Maaliki H, Church L (2002) Which is better for the management of postpartum perineal pain: ibuprofen or acetaminophen with codeine? J Fam Pract 51:207
MacDonald TM, Wei L (2003) Effect of ibuprofen on cardioprotective effect of aspirin. Lancet 361:573 574
MacDonald TM, Wei L (2006) Is there an interaction between the cardiovascular protective effects of low dose aspirin and ibuprofen? Basic Clin Pharmacol Toxicol 98:275 280
MacDonald TM, Morant SV, Robinson GC, Shield MJ, McGilchrist MM, Murray FE, McDevitt DG (1997) Association of upper gastrointestinal toxicity of non steroidal anti inflammatory drugs with continued exposure: Cohort study. Br Med J 315:1333 1337
Mahboob A, Haroon TS (1998) Drugs causing fixed eruptions: a study of 450 cases. Int J Dermatol 37(11):833 838
Mahler DL, Forrest WH Jr, Brown CR, Shroff PF, Gordon HE, Brown BW Jr, James KE (1976) Assay of aspirin and naproxen analgesia. Clin Pharmacol Ther 19(1):18 23
Makela AL, Lempiainen YT (1979) Ibuprofen in the treatment of juvenile rheumatoid arthritis: metabolism and concentrations in synovial fluid. Br J Clin Pract (Suppl) 23 27
Mäkelä AL, Lempiäinen M, Ylijoki H (1981) Ibuprofen levels in serum and synovial fluid. Scand J Rheumatol Suppl 39:15 17
Malmberg AB, Yaksh TL (1992a) Antinociceptive actions of spinal non steroidal anti inflammatory agents on the formalin test in the rat. J Pharmacol Exp Ther 263:136 146
Malmberg AB, Yaksh TL (1992b) Hyperalgesia mediated by spinal glutamate or substance P receptor blocked by spinal cyclo oxygenase inhibition. Science 257:1276 1279
Malmstrom K, Sapre A, Couglin H, Agrawal NG, Mazenko RS, Fricke JR Jr (2004) Etoricoxib in acute pain associated with dental surgery: a randomized, double blind, placebo and active comparator controlled dose ranging study. Clin Ther 26:667 679
Malmström K, Kaila M, Kajosaari M, Syvänen P, Juntunen Backman K (2007) Fatal asthma in Finnish children and adolescents 1976 1998: validity of death certificates and a clinical description. Pediatr Pulmonol 42:210 215
Mamdani M, Rochon PA, Juurlink DN, Kopp A, Anderson GM, Naglie G, Austin PC, Laupacis A (2002) Observational study of upper gastrointestinal haemorrhage in elderly patients given selective cyclo oxygenase 2 inhibitors or conventional non steroidal anti inflammatory drugs. Br Med J 325:624 629
Mamdani M, Juurlink DN, Lee DS, Rochon PA, Kopp A, Naglie G, Austin PC, Laupacis A, Stukel TA (2004) Cyclo oxygenase 2 inhibitors versus non selective non steroidal anti inflammatory drugs and congestive heart failure outcomes in elderly patients: a population based cohort study. Lancet 363:1751 1756
Mangoni AA, Woodman RJ, Gaganis P, Gilbert AL, Knights KM (2009) Use of non steroidal anti inflammatory drugs and risk of incident myocardial infarction and heart failure, and all cause mortality in the Australian veteran community. Br J Clin Pharmacol 69:689 700
Manjanna KM, Shivakumar B, Pramod Kumar TM (2010) Microencapsulation: an acclaimed novel drug delivery system for NSAIDs in arthritis. Crit Rev Ther Drug Carrier Syst 27:509 545
Mann JF, Goerig M, Brune K, Luft FC (1993) Ibuprofen as an over the counter drug: is there a risk for renal injury? Clin Nephrol 39:1 6

Mascia K, Haselkorn T, Deniz YM, Miller DP, Bleecker ER, Borish L, TENOR Study Group (2005) Aspirin sensitivity and severity of asthma: evidence for irreversible airway obstruction in patients with severe or difficult to treat asthma. J Allergy Clin Immunol 116:970 975

Martindale (1958) The extra pharmacopœia. The Pharmaceutical Press, London

Massey T, Derry S, Moore RA, McQuay HJ (2010). Topical NSAIDs for acute pain in adults. Cochrane Database Syst Rev (6):CD007402

Masso Gonzalez EL, Patrignani P, Tacconelli S, Garcia Rodriguez LA (2010) Variability among nonsteroidal antiinflammtory drugs in risk of upper gastrointestinal bleeding. Arthritis Rheum 62:1592 1601

Matchaba P, Gitton X, Krammer G, Ehrsam E, Sloan VS, Olson M, Mellein B, Hoexter G, Orloff J, Garaud JJ (2005) Cardiovascular safety of lumiracoxib: a meta analysis of all randomized controlled trials > or 1 week and up to 1 year in duration of patients with osteoarthritis and rheumatoid arthritis. Clin Ther 27:1196 1214

Mathieu P, Lemieux Despres J P (2010) Obesity, inflammation, and cardiovascular risk. Clin Pharmacol Ther 87:407 416

Mazur LJ (2002) Ibuprofen was more protective against asthma morbidity than acetaminophen in asthmatic children with fever. ACP J Club 137:108

McCarberg BH (2010) Acute back pain: benefits and risks of current treatments. Curr Med Res Opin 26:179 190

McCormack K, Brune K (1991) Dissociation between the anti nociceptive and anti inflammatory effects of the nonsteroidal anti inflammatory drugs: a survey of their analgesic efficacy. Drugs 41:533 547

McGettigan P, Henry D (2006) Cardiovascular risk and inhibition of cyclooxygenase. JAMA 296:1633 1644

McGettigan P, Platona A, Henry DA (2000) Renal and cardiovascular toxicity of non steroidal anti inflammatory drugs. Inflammopharmacology 8:1 18

McGettigan P, Han P, Henry D (2006) Cyclooxygenase 2 inhibitors and coronary occlusion exploring dose response relationships. Br J Clin Pharmacol 62:358 365

McGettigan P, Han P, Jones L, Whitaker D, Henry D (2008) Selective COX 2 inhibitors, NSAIDs and congestive heart failure: differences between new and recurrent cases. Br J Clin Pharmacol 65:927 934

McIntyre J, Hull D (1996) Comparing efficacy and tolerability of ibuprofen and paracetamol in fever. Arch Dis Child 74:164 167

McIntyre BA, Philp RB, Inwood MJ (1978) Effect of ibuprofen on platelet function in normal subjects and haemophiliac patients. Clin Pharmacol Ther 24:616 621

McQuay H, Moore A (eds) (1998) An evidence based resource for pain relief. Oxford University Press, Oxford

McQuay HJ, Moore RA (2006) Dose response in direct comparisons of different doses of aspirin, ibuprofen and paracetamol (acetaminophen) in analgesic studies. Br J Clin Pharmacol 63:271 278

McQuay HJ, Moore RA (2007) Dose response in direct comparisons of different doses of aspirin, ibuprofen and paracetamol (acetaminophen) in analgesic studies. Br J Clin Pharmacol 63:271 278

McQuay HJ, Poppleton P, Carroll D, Summerfield RJ, Bullingham RE, Moore RA (1986) Ketorolac and acetaminophen for orthopedic postoperative pain. Clin Pharmacol Ther 39(1):89 93

McQuay HJ, Carroll D, Watts PG, Juniper RP, Moore RA (1989) Codeine 20mg increases pain relief from ibuprofen 400mg after third molar surgery. A repeat dosing comparison of ibuprofen and an ibuprofen codeine combination. Pain 37:7 13

McQuay HJ, Carroll D, Guest P, Juniper RP, Moore RA (1992) A multiple dose comparison of combinations of ibuprofen and codeine and paracetamol, codeine and caffeine after third molar surgery. Anaesthesia 47:672 677

McQuay HJ, Carroll D, Guest PG, Robson F, Wiffen PJ, Juniper RP (1993) A multiple dose comparison of ibuprofen and dihydrocodeine after third molar surgery. Br J Oral Maxillofac Surg 31:95 100

McQuay HJ, Angell K, Carroll D, Moore RA, Juniper RP (1996) Ibuprofen compared with ibuprofen plus caffeine after third molar surgery. Pain 66:247 251

Mehlisch DR, Aspley S, Se Daniels, Bandy DP (2010a) Comparison of the analgesic efficacy of concurrent ibuprofen and paracetamol with ibuprofen or paracetamol alone in the management of moderate to severe acute postoperative dental pain in adolescents and adults: a randomized, double blind, placebo controlled, parallel group, single dose, two centre, modified factorial study. Clin Ther 32:882 895

Mehlisch DR, Aspley S, Daniels SE, Southerden KA, Christensen KS (2010b) A single tablet fixed dose combination of racemic ibuprofen/paracetamol in the management of moderate to severe postoperative dental pain in adult and adolescent patients: a multicentre, two stage, randomized, double blind, parallel group, placebo controlled, factorial study. Clin Ther 32:1033 1049

Miragliotta G, Molineaux N (1994) Helicobacter pylori infection and coronary heart disease. Lancet 344:751

Miranda HF, Puig MM, Prieto JC, Pinardi G (2006) Synergism between paracetamol and nonsteroidal anti inflammatory drugs in experimental acute pain. Pain 121:22 28

Mitchell DA, Ward Booth P, Saymour RA (1985) A comparative study of the efficacy of aspirin and an ibuprofen/codeine combination in patients treated pre operatively with methylprednis olone acetate. Br Dent J 159:78 81

Mitchell JA, Akarasereenont P, Thiemermann C, Flower RJ, Vane JR (1994) Selectivity of nonsteroidal anti inflammatory drugs as inhibitors of constituitive and inducible cyclooxygen ase. Proc Natl Acad Sci USA 90:11693 11697

Mitchell JA, Lucas R, Vojnovic I, Hasan K et al (2006) Stronger inhibition by nonsteroid anti inflammatory drugs of cyclooxygenase 1 in endothelial cells than platelet offers an explanation for increased risk of thrombotic events. FASEB J 20:2468 2475

Miwa LJ, Jones JK (1999) Adverse drug reactions attributed to ibuprofen: effects other that gastrointestinal. In: Rainsford KD (ed) Ibuprofen: a critical bibliographic review. Taylor & Francis, London, pp 499 538

Mo S L, Zhou Z W, Yang L P, Wei MQ, Zhou S F (2009) New insights into the structural features and functional relevance of human cytochrome P450 2C9. Part 1. Curr Drug Metab 10:1075 1126

Monti NC, Gazzaniga A, Gianesello V, Stroppolo F, Lodola E (1992) Activity and pharmacoki netics of a new oral dosage form of soluble ibuprofen. Arzneim Forsch 42:556 559

Moore N, Noblet C, Breemeersch C (1996) Focus on the safety of ibuprofen at the analgesic antipyretic dose. Therapy 51:458 463

Moore N, Van Ganse E, Le Parc J M et al (1999) The PAIN study (Paracetamol, Aspirin and Ibuprofen New Tolerability study): a large scale randomised clinical trial comparing the tolerability of aspirin, ibuprofen, and paracetamol for short term analgesia. Clin Drug Invest 28:89 98

Moore N, Le Parc JM, van Ganse E, Wall R, Schneid H, Cairns R (2002) Tolerability of ibuprofen, aspirin and paracetamol for the treatment of cold and flu symptoms and sore throat pain. Int J Clin Pract 56:732 734

Moore N, Charlesworth A, Van Ganse E, LeParc JM, Jones JK, Wall R, Schneid H, Verrière F (2003) Risk factors for adverse events in analgesic drug users: results from the PAIN study. Pharmacoepidemiol Drug Saf 12:601 610

Moore A, Derry S, Makinson GT, McQuay HJ (2005) Tolerability and adverse events in clinical trials of celecoxib in osteoarthritis and rheumatoid arthritis: systematic review and meta analysis of information from company clinical trials reports. Arthritis Res Ther 7:R644 R665

Moore RA, Derry S, McQuay HJ, Paling J (2008) What do we know about communicating risk? A brief review and suggestion for contextualising serious, but rare, risk, and the example of COX 2 selective and non selective NSAIDs. Arthritis Res Ther 10(1):R20

Moore RA, Derry S, McQuay HJ (2009) Single dose oral dexibuprofen S(+) ibuprofen) ibuprofen from acute postoperative pain in adults. Cochrane Database Syst Rev (8):CD007550

Moore RA, Derry S, McQuay HJ, Wiffen PJ (2011) Single dose oral analgesics for acute postoperative pain in adults (Review). The Cochrane Collaboration. Cochrane Database Syst Rev (9):CD008659. doi:10.1002/14651858.CD008659.pub2.Chichester

Morelli MS, O'Brien FX (2001) Stevens Johnson syndrome and cholestatic hepatitis. Dig Dis Sci 46(11):2385 2388

Morgan O, Hawkins L, Edwards N, Dargan P (2007) Paracetamol (acetaminophen) pack size restrictions and poisoning severity: time trends in enquiries to a UK poisons centre. J Clin Pharm Ther 32:449 455

Motola G, Russo F, Mazzeo F, Rinaldi B, Capuano A, Rossi F, Filippelli A (2001) Over the counter oral nonsteroidal anti inflammatory drugs: a pharmacoepidemiologic study in southern Italy. Adv Ther 18:216 222

Motola D, Vargiu A, Leone R, Cocci A, Salvo F, Ros B, Meneghelli I, Venegoni M, Cutroneo PM, Vaccheri A, Velo G, Montanaro N (2007) Hepatic adverse drug reactions: a case/non case study in Italy. Eur J Clin Pharmacol 63:73 79

Motsko SP, Rascati KL, Busti AJ, Wilson JP, Barner JC, Lawson KA, Worchel J (2006) Temporal relationship between use of NSAIDs, including selective COX 2 inhibitors, and cardiovascular risk. Drug Saf 29(7):621 632

Mounier G, Guy C, Berthoux F, Beynes MN, Ratrema M, Ollagnier M (2006) Severe renal adverse events with arylcarboxylic non steroidal anti inflammatory drugs: results on an eight year French national survey. Therapie 61:255 266

Müller P, Koch EMW, Simon B (1995) Schutzwirkung von Ranitidin bei Ibuprofen Gastroduodenopathie. Arzneim Forsch/Drug Res 45:601 603

Murray MD, Brater DC (1999) Renal effects of ibuprofen. In: Rainsford KD (ed) Ibuprofen: a critical bibliographic review. Taylor & Francis, London, pp 459 495

Mutchba P, Gitton X, Krammer G, Ehrsam E, Sloan VS, Olson M, Mellein B, Hoexter G, Orloff J, Garaud JJ (2005) Cardiovascular safety of lumiracoxib: a meta analysis of all randomized controlled trials > or 1 week and up to 1 year in duration of patients with osteoarthritis and rheumatoid arthritis. Clin Ther 27:1196 1214

Nabulsi MM, Tamim H, Mahfoud Z, Itani M et al (2006) Alternating ibuprofen and acetamino phen in the treatment of febrile children: a pilot study [ISRCTN30487061]. BMC Med 4:4

Nahata MC, Durrell DE, Powell DA, Gupta N (1991) Pharmacokinetics of ibuprofen in febrile children. Eur J Clin Pharmacol 40:427 428

Nahata MC, Powell DA, Durrell DE, Miller MA, Gupta N (1992) Efficacy of ibuprofen in pediatric patients with fever. Int J Clin Pharmacol Ther Toxicol 30:94 96

Naldi L, Conforti A, Venegoni M, Troncon MG, Caputi A, Ghiotto E, Cocci A, Moretti U, Velo G, Leone R (1999) Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. Br J Clin Pharmacol 48:839 846

Nanau RM, Neuman MG (2010) Ibuprofen induced hypersensitivity syndrome. Transl Res 155:275 293

National Institute for Health and Clinical Excellence (2007) Feverish illness in children. Guideline No CG47. Royal College of Obstetrics and Gynecology, RCOG, London. http://guidance.nice.org.uk/CG47/Guidance/pdf/English

Nawrot P, Jordan S, Eastwood J, Rotstein J, Hugenholtz A, Feeley M (2003) Effects of caffeine on human health. Food Addit Contam 20:1 30

Nebe J, Heier M, Diener HC (1995) Low dose ibuprofen in self medication of mild to moderate headache: a comparison with acetylsalicylic acid and placebo. Cephalagia 5:531 535

Nelson SL, Brahim JS, Korn SH, Greene SS, Suchower LJ (1994) Comparison of single dose ibuprofen lysine, acetylsalicylic acid, and placebo for moderate to severe postoperative dental pain. Clin Ther 16:458 465

Neuman M, Nicar M (2007) Apoptosis in ibuprofen induced Steven Johnson syndrome. Transl Res 149:254 259

Nichol KJ (1999) The medicinal chemistry of ibuprofen. In: Rainsford KD (ed) Ibuprofen. A critical bibliographic review. Taylor & Francis, London, pp 27 51
Nielsen JC, Bjerring P, Arendt Nielsen L, Petterson KJ (1990) A double blind, placebo controlled, cross over comparison of the analgesic effect of ibuprofen 400 mg and 800 mg on laser induced pain. Br J Clin Pharmacol 30:711 715
Nørholt SE, Aagaard E, Svensson P, Sindet Pedersen S (1998) Evaluation of trismus, bite force, and pressure algometry after third molar surgery: a placebo controlled study of ibuprofen. J Oral Maxillofac Surg 56:420 427
Norman SL, Jeavons BI, O'Brien PM et al (1985) A double blind comparison of a new ibuprofen codeine phosphate combination, codeine phosphate, and placebo in the relief of postepisiotomy pain. Clin Ther 7:549 554
Noro S, Komatsu Y, Uesugi T (1982a) Studies on pharmaceutical drug design for suppositories. I. Effect of physicochemical properties of surfactants and polymers on emulsion type bases. Chem Pharm Bull (Tokyo) 30:2900 2905
Noro S, Komatsu Y, Uesugi T (1982b) Studies on pharmaceutical drug design for suppositories. II. Rheological properties of emulsion type suppository bases. Chem Pharm Bull (Tokyo) 30(8):2906 2911
Noyelle RM et al (1987) Ibuprofen, aspirin, and paracetamol compared in a community study. Pharm J 238:561 564
Nurmohamed MT, van Halm VP, Dijkmans BA (2002) Cardiovascular risk profile of antirheumatic agents in patients with osteoarthritis and rheumatoid arthritis. Drugs 62:1599 1609
O'Brien WM (1987) Rare adverse reactions to non steroidal anti inflammatory drugs. In: Rainsford KD, Velo GP (eds) Side effects of anti inflammatory drugs 3. Kluwer Academic, Dordrecht, pp 73 98
O'Brien W, Bagby GF (1985) Rare adverse reactions to nonsteroidal anti inflammatory drugs. J Rheumatol 12:1 24
Offringa M, Newton R (2012) Prophylactic drug management for febrile seizures in children. Cochrane Database Syst Rev 4:CD003031
Oliary J, Tod M, Nicolas P, Petitjean O, Caillé G (1992) Pharmacokinetics of ibuprofen enantiomers after single and repeated doses in man. Biopharm Drug Dispos 13(5):337 344
Ong CKS, Seymour RA, Lirk P, Merry AF (2010) Combining paracetamol (acetaminophen) with nonsteroidal anti inflammatory drugs: a qualitative systematic review of analgesic efficacy for acute postoperative pain. Anesth Analg 110:1170 1179
Orme MCL'E (1990) Plasma concentrations and the therapeutic effect of anti inflammatory and anti rheumatic drugs. In: Orme M (ed) Anti rheumatic drugs. Pergamon, New York, pp 217 233
Östör AJK, Hazleman BL (2005) The murky waters of the coxibs: a review of the current state of play. Inflammopharmacology 13:371 380
Owen Smith BD, Burry HC (1972) Ibuprofen in the management of osteoarthrosis of the hip. Rheumatol Phys Med 11:281 286
Pachkoria K, Lucena MI, Ruiz Cabello F, Crespo E, Cabello MR, Andrade RJ, Spanish Group for the Study of Drug Induced Liver Disease (Grupo de Estudio para las Hepatopatías Asociadas a Medicamentos) (2007a) Genetic polymorphisms of CYP2C9 and CYP2C19 are not related to drug induced idiosyncratic liver injury (DILI). Br J Pharmacol 150:808 815
Pachkoria K, Lucena MI, Molokhia M, Cueto R, Carbollo AS, Carvajal A, Andrade RJ (2007b) Genetic and molecular factors in drug induced liver injury: a review. Curr Drug Saf 2:281 286
Packman B, Packman E, Doyle G, Cooper S, Ashraf E, Koronkiewicz K, Jayawardena S (2000) Solubilized ibuprofen: evaluation of onset, relief, and safety of a novel formulation in the treatment of episodic tension type headache. Headache 40:561 567
Padol IT, Hunt RH (2010) Association of myocardial infarctions with COX 2 inhibition may be related to immunomodulation towards Th1 response resulting in atheromatous plaque instability: an evidence based interpretation. Rheumatology 49:837 843

Palangio M, Damask MJ, Morris E et al (2000) A combination hydrocodone and ibuprofen versus combination codeine and acetaminophen fro the treatment of chronic pain. Clin Ther 22:879 892

Panoulas VF, Douglas KMJ, Milionis HJ, Stravropoulos Kalinglou A, Nightingale P, Kita MD, Tselio AL, Metsios GS, Elisaf MS, Kitas GD (2007) Prevalence and associations of hyperten sion and its control in patients with rheumatoid arthritis. Rheumatology 46:1477 1482

Parkhouse J, Rees Lewis M, Skolinik M, Peters H (1968) The clinical dose response to aspirin. Br J Anaesth 40(6):433 441

Patel RM, Marfatia YS (2008) Clinical study of cutaneous drug eruptions in 200 patients. Indian J Dermatol Venereol Leprol 74(4):430

Patel HB, Dawson B, Humbly F, Blades M, Pitzalis C, Burnet M, Seed M (2010) Animal models of rheumatoid arthritis. In: Serhan CN, Ward PA, Gilroy DW (eds) Fundamentals of inflam mation. Cambridge University Press, Cambridge

Paulus HE (1990) FDA Arthritis Advisory Committee meeting: guidelines for approving nonste roidal anti inflammatory drugs for over the counter use. Arthritis Rheum 33:1056 1058

Perez Gutthann S, Garcia Rodriguez LA, Duque Oliart A, Varas Lorenzo C (1999) Low dose diclofenac, naproxen and ibuprofen cohort study. Pharmacotherapy 19:854 859

Pernerstorfer T, Schmid R, Bieglmayer C, Eichler H G, Kapiotis S, Jilma B (1999) Acetamino phen has greater antipyretic efficacy than aspirin in endotoxemia: a randomized, double blind, placebo controlled trial. Clin Pharmacol Ther 66:51 57

Perrone MG, Scilimati A, Simone L, Vitale P (2010) Selective COX 1 inhibition: a therapeutic target to be reconsidered. Curr Med Chem 17:3769 3805

Persson PE, Nilsson OS, Berggren AM (2005) Do non steroidal anti inflammatory drugs cause endoprosthetic loosening? A 10 year follow up of a randomized trial on ibuprofen for preven tion of heterotopic ossification after hip arthroplasty. Acta Orthop 76:735 740

Peter EA, Janssen PA, Grange CS, Douglas MJ (2001) Ibuprofen versus acetaminophen with codeine for the relief of perineal pain after childbirth: a randomized controlled trial. CMAJ 165:1203 1209

Peters MJL, van Halm VP, Voskuyl AE, Smulders YM, Boers M, Lems WF et al (2009) Does rheumatoid arthritis equal diabetes mellitus as an independent risk factor for cardiovascular disease? A prospective study. Arth Rheum 61:1571 1579

Peterson GM (2005) Selecting non prescription analgesics. Am J Ther 12:67 79

Peterson JK, Hansson F, Strid S (1993) The effect of an ibuprofen codeine combination for the treatment of patients with pain after removal of lower third molars. J Oral Maxillofac Surg 51:637 640

Phleps W (2001) Overview on clinical data of dexibuprofen. Clin Rheumatol 20(Suppl 1):s15 s21

Pickering AE, Bridge HS, Nolan J, Stoddart PA (2002) Double blind, placebo controlled analge sic study of ibuprofen or rofecoxib in combination with paracetamol for tonsillectomy in children. Br J Anaesth 88:72 77

Pongbhaesaj P, Yamwong P, Chattanamatta P et al (2003) Effects of ibuprofen and different doses of aspirin on platelet aggregation. Artherosclerosis Suppl 4:247 (Abstract # 3P 0841)

Ponvert C, Scheinmann P (2007) Les reactions allergiques et pseudoallergiques aux antalgiques, antipyrétics et anti inflammatoires non stéroïdiens. Allergic and pseudoallergic reactions to antalgics, antipyretics and non steroidal anti inflammatory drugs. Archives de Pédaitrie 14:507 512

Poon G (2007) Ibuprofen lysine (NeoProfen) for the treatment of patent ductus arteriosus. Proc (Bayl Univ Med Cent) 20:83 85

Poon A, Sawynok J (1998) Antinociception by adenosine analogs and inhibitors of adenosine metabolism in an inflammatory thermal hyperalgesia model in the rat. Pain 74:235 245

Pope JE, Anderson JJ, Felson DT (1993) Meta analysis of the effects of non steroidal anti inflammatory drugs on blood pressure. Arch Intern Med 22:477 484

Prescott LF, Martin U (1992) Current status of nephrotoxicity caused by non steroidal anti inflammatory drugs. In: Rainsford KD, Velo GP (eds) Side effects of anti inflammatory drugs 3. Kluwer Academic, Dordrecht

Psaty BM, Furberg CD (2005) COX 2 inhibitors lessons in drug safety. N Engl J Med 352:1133 1135
Quiding H, Grimstad J, Rusten K, Stubhaug A, Bremnes J, Breivik H (1992) Ibuprofen plus codeine, ibuprofen, and placebo in a single and multidose cross over comparison for coxarthrosis pain. Pain 50:303 307
Quiralte J, Blanco C, Delgado J, Ortega N, Alcntára M, Castillo R, Anguita JL, de San Sáenz, Pedro B, Carrillo T (2007) Challenge based clinical patterns of 223 Spanish patients with nonsteroidal anti inflammatory drug induced reactions. J Investig Allergol Clin Immunol 17:182 188
Radack KL, Deck CC, Bloomfield SS (1987) Ibuprofen interferes with the efficacy of antihyper tensive drugs. A randomized, double blind, placebo controlled trial of ibuprofen compared with acetaminophen. Ann Intern Med 107:628 635
Radford MG, Holley KE, Grande JP, Larson TS, Wagoner RD, Donadio JV, McCarthy JT (1996) Reversible membranous nephropathy associated with the use of nonsteroidal anti inflammatory drugs. JAMA 276:466 469
Raffa RB, Stone DJ Jr, Tallarida RJ (2000) Discovery of "self synergistic" spinal/supraspinal antinociception produced by acetaminophen (paracetamol). J Pharmacol Exp Ther 295:291 294
Raffa RB, Walker EA, Sterious SN (2004) Opioid receptors and acetaminophen (paracetamol). Eur J Pharmacol 503:209 210
Ragot JP (1991) Comparison of analgesic activity of mefenamic acid and paracetamol in treatment of pain after extraction of impacted lower 3d molars. Inf Dent 73(21):1659 1664
Rahme E, Nedjar H (2007) Risks and benefits of COX 2 inhibitors vs non selective NSAIDs: does their cardiovascular risk exceed their gastrointestinal benefit? A retrospective cohort study. Rheumatology 46:435 438
Rainsford KD (ed) (1984) Aspirin and the salicylates. Butterworth, London
Rainsford KD (1987) Introduction and historical aspects of the side effects of anti inflammatory analgesic drugs. In: Rainsford KD, Velo GP (eds) Side effects of anti inflammatory drugs. Part 1. Clinical and epidemiological aspects. MTP Press, Lancaster, pp 3 26
Rainsford KD (1996) Mode of action, uses and side effects of anti rheumatic drugs. In: Rainsford KD (ed) Advances in anti rheumatic therapy. CRC, Boca Raton, FL, pp 59 111
Rainsford KD (1999a) History and development of ibuprofen. In: Rainsford KD (ed) Ibuprofen: a critical bibliographic review. Taylor & Francis, London, pp 3 24
Rainsford KD (1999b) Pharmacology and toxicology of ibuprofen. In: Rainsford KD (ed) Ibuprofen: a critical bibliographic review. Taylor & Francis, London, pp 145 275
Rainsford KD (1999c) Safety and efficacy of non prescription (OTC) ibuprofen. In: Rainsford KD (ed) Ibuprofen: a critical bibliographic review. Taylor & Francis, London, pp 357 405
Rainsford KD (2003) Discovery, mechanisms of action and safety of ibuprofen. Int J Clin Pract S135:3 8
Rainsford KD (2004a) Side effects and toxicology of the salicylates. In: Rainsford KD (ed) Aspirin and related drugs. Taylor & Francis, London, pp 367 554
Rainsford KD (2004b) Inhibitors of eicosanoids. In: Curtis Prior P (ed) The eicosanoids. Wiley, Chichester, pp 189 210
Rainsford KD (2004c) Pharmacology and biochemistry of salicylates and related drugs. In: Rainsford KD (ed) Aspirin and related drugs. Taylor & Francis, London, pp 215 366
Rainsford KD (2005a) Introduction The coxib controversies. Inflammopharmacology 13:331 341
Rainsford KD (ed) (2005b) Nimesulide. Actions and uses. Birkhäuser, Basel
Rainsford KD (2007) Anti inflammatory drugs in the 21st century. Subcell Biochem 42:3 27
Rainsford KD (2009) Ibuprofen: pharmacology, efficacy and safety. Inflammopharmacology 17:275 342
Rainsford KD (2010) Cardiovascular adverse reactions from NSAIDs are more than COX 2 inhibition alone. Rheumatology 49:834 836

Rainsford KD (2011) Fifty years since the discovery of ibuprofen. Inflammopharmacology 19:293 297

Rainsford KD, Schweitzer A, Brune K (1981) Autoradiographic and biochemical observations on the distribution of non steroid anti inflammatory drugs. Arch Int Pharmacodyn Ther 250:180 194

Rainsford KD, James C, Johnson DM, Stetsko PI, Hill RE, Salena BJ, Hunt RH (1993) Effects of chronic NSAIDs on gastric mucosal injury related to mucosal prostanoids, and plasma drug concentrations in human volunteers. Agents Actions 39(Spec No):C21 C33

Rainsford KD, Roberts SC, Brown S (1997) Ibuprofen and paracetamol: relative safety in non prescription dosages. J Pharm Pharmacol 49:345 376

Rainsford KD, Adesioye J, Dawson S (2001) Relative safety of NSAIDs and analgesics for non prescription use or in equivalent doses. Inflammopharmacology 8:351 359

Rainsford KD, Kean WF, Ehrlich GE (2008a) Review of the pharmaceutical properties and clinical effects of the topical NSAID formulation, diclofenac epolamine. Curr Med Res Opin 24:2967 2992

Rainsford KD, Kean WF, Ehrlich GE (2008b) Triad (GI, CV, Hepatic) composite toxicity ratings for use in assessing the overall safety of NSAIDs. Intern Med J 38(suppl 2):A32 (Abstract No. ARP71)

Rainsford KD, Bjarnason I (2012) NSAIDs: take with food or after fasting? J Pharm Pharmacol 64:465 469

Raksha MP, Marfatia YS (2008) Clinical study of cutaneous drug eruptions in 200 patients. Indian J Dermatol Venereol Leprol 74(1):80

Rall TW (1990) Drugs used in the treatment of asthma. In: Goodman GA, Rall TW, Nies AS, Taylor P (eds) Goodman and Gilman's the pharmacological basis of therapeutics, 8th edn. Pergamon, New York, pp 618 637

Rang HP, Dale MM, Ritter JM, Moore PK (2003) Pharmacology, 5th edn. Churchill Livingstone, Edinburgh

Rau R, Berner G, Wagener HH, Vögtle Junkert U (1989) Konzentrationen von Ibuprofemn und Eiweiβ Gehalt sowie pH Wert in Kniegelenksergu β und plasma nach oraler Gabe von Ibuprofen bei Arthritis Patienten. Arzneim Forsch 39:1166 1168

Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR (2002) COX 2 selective non steroidal anti inflammatory drugs and risk of serious coronary heart disease. Lancet 360:1071 1073

Ray W, Stein CM, Hall K, Daugherty JR, Griffin MR (2003) Non steroidalanti inflammatory drugs and the risks of serious coronary heart disease: an observational study. Lancet 359:118 123

Ray WA (2010) Cardiovascular safety of NSAIDs: the cardiovascular risks should prompt evaluation of a broader range of alternatives. Br Med J 342:116 117

Ray WA, Varas Lorenzo C, Chung CP, Castellsague J, Murray KT, Stein CM, Daugherty JR et al (2009) Cardiovascular risks of nonsteroidal anti inflammatory drugs in patients after hospitali zation for serious coronary heart disease. Circ Cardiovasc Qual Outcomes 2:155 163

Re E, Pariente Khayat A, Gouyet L, Vauzelle Kervroëdan F, Pons G, D'Athis Ph, Dubois MC, Murat I, Lassale C, Goehrs M, Cl Sainst Maurice, Olive G (1994) Stereoselective disposition of ibuprofen enantiomers in infants. Br J Clin Pharmacol 38:375 378

Reichel C, Brugger R, Bang H, Geisslinger G, Brune K (1997) Molecular cloning and expression of a 2 arylpropionyl Coenzyme A epimerase: a key enzyme in the inversion metabolism of ibuprofen. Mol Pharmacol 51:576 582

Reynolds JEF (ed) (1993) Martindale. The extra pharmacopoeia, 13th edn. The Pharmaceutical Press, London

Reynolds JEF (2003) Martindale. The complete drug reference. The Pharmaceutical Press, London

Rho YH, Chung CP, Sulos J, Raggi P, Oeser A, Gebretsadik T, Shintani A, Stein CM (2010) Adipokynotines, insulin resistance, and coronary atherosclerosis in rheumatoid arthritis. Arthritis Rheum 62:1259 1264

Robinson GM, Robinson S, McCarthy P, Cameron C (2010) Misuse of over the counter codeine containing analgesics: dependence and the adverse effects. NZ Med J 123:59 64
Rodger IW (2009) Analgesic targets: today and tomorrow. Inflammopharmacology 17:151 161
Rodrigues LAG, Jick H (1994) Risk of upper gastrointestinal bleeding and perforation associated with individual non steroidal anti inflammatory drugs. Lancet 343:769 772
Rodriguez F, Llinas MT, Moreno C, Salazar FJ (2001) Role of cyclooxygenase 2 derived metabolites and NO in renal response to bradykinin. Hypertension 37:129 134
Roig F, Llinas MT, Lopez R, Salazar FJ (2002) Role of cyclooxygenase 2 in the prolonged regulation of renal function. Hypertension 40:721 728
Rostom A, Goldkind L, Laine L (2005) Nonsteroidal anti inflammatory drugs and hepatic toxicity: a systematic review of randomized controlled trials in arthritis patients. Clin Gastroenterol Hepatol 3:489 498
Rostom A, Muir K, Dube C, Jolicoeur E et al (2007) Gastrointestinal safety of cyclooxygenase 2 inhibitors: a Cochrane Collaboration systematic review. Clin Gastroenterol Hepatol 5:818 828
Roth SH, Tindall EA, Jain AK, McMahon FG, April PA, Bockow BI, Cohen SB, Fleischmann RM (1993) A controlled study comparing the effects of nabumetone, ibuprofen, and ibuprofen plus misoprostol on the upper gastrointestinal tract mucosa. Arch Intern Med 153(22):2565 2571
Royer GL, Seckman CE, Welshman IR (1984) Safety profile: fifteen years of clinical experience with ibuprofen. Am J Med 77(1A):25 34
Royer GL, Seckman CE, Schwartz JH, Bennett K (1985) Effects of ibuprofen on normal subjects: clinical and routine and special laboratory assessments. Curr Ther Res 37:412 426
Rubenstein I, Chandilawa R, Dagar S, Hong D, Gao XP (2001) Adenosine A_1 receptors mediate plasma exudation from the oral mucosa. J Appl Physiol 91:552 560
Rudy AC, Bradley JD, Ryan SI, Kalasinski LA, Xiaotao Q, Hall SD (1992) Variability in the disposition of ibuprofen enantiomers in osteoarthritis patients. Ther Drug Monit 14:464 470
Sabaté M, Ibánez L, Pérez E, Vidal X, Buti M, Xiol X, Mas A, Guarner C, Forné M, Solà R, Castellote J, Rigau J, Laporte JR (2007) Risk of acute liver injury associated with the use of drugs: a multicentre population survey. Aliment Pharmacol Ther 25(12):1401 1409
Sachs CJ (2005) Oral analgesics for acute non specific pain. Am Fam Phys 71:913
Saini SD, Schoenfeld P, Fendrick AM, Scheiman J (2008) Cost effectiveness of proton pump inhibitor cotherapy in patients taking long term, low dose aspirin for secondary cardiovascular prevention. Arch Intern Med 168:1684 1690
Sánchez Borges M, Capriles Hulett A, Caballero Fonseca F (2005) Risk of skin reactions when using ibuprofen based medicines. Expert Opin Drug Saf 4:837 848
Sanchez Matienzo D, Arana A, Castellsague J, Perez Gutthann S (2006) Hepatic disorders in patients treated with COX 2 selective inhibitors or nonselective NSAIDs: a case/noncase analysis of spontaneous reports. Clin Ther 28:1123 1132
Sandrini G, Franchini S, Lanfranchi S, Granella F, Manzoni GC, Nappi G (1998) Effectiveness of ibuprofen arginine in the treatment of acute migraine attacks. Int J Clin Pharmacol Res 18:145 150
Sandrini M, Pini LA, Vitale G (2003) Differential involvement of central 5 HT1B and 5 HT3 receptor subtypes in the antinociceptive effect of paracetamol. Inflamm Res 52:347 352
Sato K, Shimizu T, Tomioka H, Kawahara S (1998) Effects of half sized secretory leukocyte protease inhibitor and Chinese traditional medicines, yokuinin and mao bushi saishin to, on therapeutic efficacies of benzoxazinorifamycin KRM 1648 against Mycobacterium avium complex infection induced in mice. Kekkaku 73:501 506
Schachtel BP, Thoden WR (1993) A placebo controlled model for assaying systemic analgesics in children. Clin Pharmacol Ther 53:593 601
Schachtel BP, Fillingim JM, Thoden WR, Lane AC, Baybutt RI (1988) Sore throat pain in the evaluation of mild analgesics. Clin Pharmacol Ther 44:704 711
Schachtel BP, Cleves GS, Konerman JP, Brown AT, Markham AO (1994) A placebo controlled model to assay the onset of action of nonprescription strength analgesic drugs. Clin Pharmacol Ther 55:464 470

Schachtel BP, Furey SA, Thoden WR (1996) Nonprescription ibuprofen and acetaminophen in the treatment of tension type headache. J Clin Pharmacol 36:1120 1125

Schlienger RG, Jick H, Meier CR (2002) Use of nonsteroidal anti inflammatory drugs and the risk of first time acute myocardial infarction. Br J Clin Pharmacol 54:327 332

Schachtel BP, Pan S, Kohles JD, Sanner KM, Schachtel EP, Bey M (2007) Utility and sensitivity of the sore throat pain model: results of a randomized controlled trial on the COX 2 selective inhibitor valdecoxib. J Clin Pharmacol 47:860 870

Schaffer D, Florin T, Eagle C, Marschner I, Singh G, Grobler M, Fenn C, Schou M, Curnow KM (2006) Risk of serious NSAID related gastrointestinal events during long term exposure: a systematic review. Med J Aust 185:501 506

Scheiman JM, Cryer B, Kimmey MB, Rothstein RI, Riff DS, Wolfe MM (2004) A randomized, controlled comparison of ibuprofen at the maximal over the counter dose compared with prescription dose celecoxib on upper gastrointestinal mucosal injury. Clin Gastroenterol Hepatol 2:290 295

Schiff M, Minic M (2004) Comparison of the analgesic efficacy and safety of non prescription doses of naproxen sodium and ibuprofen in the treatment of osteoarthritis of the knee. J Rheumatol 31:1373 1383

Schleier P, Prochnau A, Schmidt Westhausen AM, Peters H, Becker J, Latz T, Jackowski J, Peters EU, Romanos GE, Zahn B, Ludemann J, Maares J, Petersen B (2007) Ibuprofen sodium dihydrate, an ibuprofen formulation with improved absorption characteristics, provides faster and greater pain relief than ibuprofen acid. Int J Clin Pharmacol Ther 45:89 97

Schmitt BD (1980) Fever fobia: misconceptions of parents about fever. Am J Dis Child 134:176 181

Schneeweiss S, Solomon DH, Wang PS, Rassen J, Brookhart MA (2006) Simultaneous assessment of short term gastrointestinal benefits and cardiovascular risks of selective cyclooxygenase 2 inhibitors and nonselective nonsteroidal antiinflammatory drugs: an instrumental variable analysis. Arthritis Rheum 54:3390 3398

Schneider HT, Nernberg B, Dietzel K, Brune K (1990) Biliary elimination on non steroidal anti inflammatory drugs in patients. Br J Clin Pharmacol 29:127 131

Schnitzer TJ, Burmester GR, Mysker E, Hochberg MC, Doherty M, Ehrsam E, Gitton X, Krammer G, Meillein B, Matchaba P, Gimona A, Hawkey CJ (2004) Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastroin testinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial. Lancet 364:665 674

Schoenfeld P (2001) An evidence based approach to the gastrointestinal safety profile of COX 2 selective anti inflammatories. Gastroenterol Clin North Am 30:1027 1044

Schou S, Nielsen H, Nattestad A, Hillerup S, Ritzau M, Branebjerg PE, Bugge C, Skoglund LA (1998) Analgesic dose response relationship of ibuprofen 50, 100, 200, and 400 mg after surgical removal of third molars: a single dose, randomized, placebo controlled, and double blind study of 304 patients. J Clin Pharmacol 38:447 454

Schuijt MP, Huntjens Fleuren HWHA, de Metz M, Vollard EJ (2009) The interaction of ibuprofen and diclofenac with aspirin in healthy volunteers. Br J Pharmacol 157:931 934

Schwartz JI, Vandormael K, Malice MP, Kalyani RN, Lasseter KC, Holmes GB, Gertz BJ, Gottesdiener KM, Laurenzi M, Redfern K J, Brune K (2002) Comparison of rofecoxib, celecoxib, and naproxen on renal function in elderly subjects receiving normal salt diet. Clin Pharmacol Ther 72:50 61

Seibel K, Schaffler K, Reeh P, Reitmeir P (2004) Comparison of two different preparations of ibuprofen with regard to the time course of their analgesic affect. A randomised, placebo controlled, double blind cross over study using laser somatosensory evoked potentials obtained from UW irritated skin in healthy volunteers. Arzneimittelforsch 54:444 451

Seideman P, Graham GG, Lohrer F, Duncan MW, Williams KM, Day RO (1994) The stereoselective disposition of the enantiomers of ibuprofen in blood, blister and synovial fluid. Br J Clin Pharmacol 38:221 227

Seinelä L, Ahvenainen J (2000) Peptic ulcer in the very old patients. Gerontology 46:271 275
Seymour RA, Hawkesford JE, Weldon M, Brewster A (1991) An evaluation of different ibuprofen preparations in the control of postoperative pain after third molar surgery. Br J Clin Pharmacol 31:83 87
Seymour RA, Ward Booth P, Kelly PJ (1996) Evaluation of different doses of soluble ibuprofen and ibuprofen tablets in postoperative dental pain. Br J Oral Maxillofac Surg 34(1):110 114
Seymour RA, Frame J, Negus TW, Hawkesford JE, Marsden J, Matthew IR (1998) The compara tive efficacy of aceclofenac and ibuprofen in postoperative pain after third molar surgery. Br J Oral Maxillofac Surg 36:375 379
Seymour RA, Hawkesford JE, Hill CM, Frame J, Andrews C (1999) The efficacy of a novel adenosine agonist (WAG 994) in postoperative dental pain. Br J Clin Pharmacol 47:675 680
Shah A, Woodruff M, Agarwal V, Liu P, Sundaresan P (2001) Pharmacokinetics, safety, and tolerability of BAY 12 9566 and non steroidal anti inflammatory agents (naproxen, ibuprofen) during coadministration in patients with osteoarthritis. J Clin Pharmacol 41:330
Sharma PK, Garg SK, Narang A (2003) Pharmacokinetics of oral ibuprofen in premature infants. J Clin Pharmacol 43:968 973
Shi W, Wang Y m, Cheng N n, Chen B y, Li D (2003) Meta analysis on the effect and adverse reaction on patients with osteoarthritis and rheumatoid arthritis treated with non steroidal anti inflammatory drugs.Chin J Epidemiol [Zhonghua Liuxingbing Xue Zazhi] 24(11):1044 1048
Shi W, Wan Y m, Chen B y, Li, Cheng N N (2004a).Risk factor analysis and discrimination of adverse reactions to ibuprofen. Chin J New Drugs [Zhongguo Xinyao yu Linchuang Zazhi] 23(2):67 72
Shi W, Y m Wang, S l Li, Yan M, Li D, B y Chen, N n Cheng (2004b) Risk factors of adverse drug reactions from non steroidal anti inflammatory drugs in Shanghai patients with arthropa thy. Acta Pharmacol Sin 25(93):357 365
Sibbald RG, Coutts P, Fierheller M, Woo K (2007) A pilot (real life) randomised clinical evaluation of a pain relieving foam dressing: (ibuprofen foam versus local best practice). Int Wound J 4(Suppl 1):16 23
Sidler J, Frey B, Baerlocher K (1990) A double blind comparison of ibuprofen and paracetamol in juvenile pyrexia. Br J Clin Pract Suppl 70:22 55
Sikes DH, Agrawal NM, Zhao WW, Kent JD, Recker DP, Verburg KM (2002) Incidence of gastroduodenal ulcers associated with valdecoxib compared with that of ibuprofen and diclofenac in patients with osteoarthritis. Eur J Gastroenterol Hepatol 14:1101 1111
Silvarajan M, Wasse L (1997) Perioperative renal failure associated with preoperative intake of ibuprofen. Am Soc Anesthesiol 86:1390 1392
Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, Makuch R, Eisen G, Agrawal NM, Stenson WF, Burr AM, Zhao WW, Kent JD, Lefkowith JB, Verburg KM, Geis GS (2000) Gastrointestinal toxicity with celecoxib vs nonsteroidal anti inflammatory drugs for osteoarthritis and rheumatoid arthritis. JAMA 284:1247 1255
Simmons DL, Wagner D, Westover K (2000) Nonsteroidal anti inflammatory drugs, acetamino phen, cyclooxygenase 2, and fever. Clin Infect Dis 31:S211 S218
Singer F, Mayrhofer F, Klein G, Hawel R, Kollenz CJ (2000) Evaluation of the efficacy and dose response relationship of dexibuprofen (S(+) ibuprofen) in patients with osteoarthritis of the hip and comparison with racemic ibuprofen using the WOMAC osteoarthritis index. Int J Clin Pharmacol Ther 38:15 24
Singh G (2000) Gastrointesstinal complications of prescription and over the counter nonsteroidal anti inflammatory drugs: a view from the ARAMIS database. Arthritis, Rheumatism, and Aging Medical Information System. Am J Ther 7:115 121
Singh G, Rosen Ramey D (1998) NSAID induced gastrointestinal complications: the ARAMIS perspective 1997. Arthritis, Rheumatism, and Aging Medical Information System. J Rheumatol Suppl 51:8 16

Singh G, Fries JF, Williams CA, Zatarain E, Spitz P, Bloch DA (1991) Toxicity profiles of disease modifying antirheumatic drugs in rheumatoid arthritis. J Rheumatol 18(2):188 194

Singh G, Ramey DR, Morfeld D, Shi H, Hatoum HT, Fries JF (1996) Gastrointestinal tract complications of nonsteroidal anti inflammatory drug treatment in rheumatoid arthritis. A prospective observational cohort study. Arch Intern Med 156(14):1530 1536

Singh G, Wu O, Langhorne P, Madhok R (2006) Risk of acute myocardial infarction with nonselective non steroidal anti inflammatory drugs: a meta analysis. Arthritis Res Ther 8:R153

Skeith KJ, Jamali F (1991) Clinical pharmacokinetics of drugs used in juvenile arthritis. Clin Pharmacokinet 21:129 149

Smith DE, Paliwal JK, Cox SR, Berardi RR, Dunn Kucharski VA, Elta GH (1994) The effect of competitive and non linear plasma protein binding on the stereoselective disposition and metabolic inversion of ibuprofen in healthy subjects. Biopharm Drug Dispos 15:545 561

Smith DE, Paliwal JK, Cox SR, Berardi RR, Dunn Kucharski VA, Elta GH (1994) The effect of competitive and non linear plasma protein binding on the stereoselective disposition and metabolic inversion of ibuprofen in healthy subjects. Biopharm Drug Dispos 15:545 561

Solomon DH, Glynn RJ, Levin R, Avorn J (2002) Nonsteroidal anti inflammatory drug use and acute myocardial infarction. Arch Int Med 162:1099 1104

Solomon DH, Glynn RJ, Rothman KJ, Schneeweiss S et al (2008a) Subgroup analyses to determine cardiovascular risk associated with nonsteroidal anti inflammatory drugs and coxibs in specific patient groups. Arthritis Rheum 59:1097 1104

Solomon SD, Wittes J, Finn PV, Fowler R, Viner J, Bertagnolli MM, Arber N, Levin B, Meinert CL, Martin B (2008b) Cardiovascular risk of celecoxib in 6 randomized placebo controlled trials. The cross trial safety analysis. Circulation 117:2104 2113

Sparano N (2001) Is the combination of ibuprofen and caffeine effective for the treatment of a tension type headache? J Fam Pract 50(1):10

Speed WC, Kang SP, Tuck DP, Harris LN, Kidd KK (2009) Global variation in *CYP2C8 CYP2C9* functional haplotypes. Pharmacogenomics J 9:283 290

Steans A, Manners PJ, Robinson IG (1990) A multicentre, long term evaluation of the safety and efficacy of ibuprofen syrup in children with juvenile chronic arthritis. Br J Clin Pract 44:172 175

Steen Law SL, Southard KA, Law AS, Logan HL, Jakobsen JR (2000) An evaluation of preoperative ibuprofen for treatment of pain associated with orthodontic separator placement. Am J Orthod Dentofacial Orthop 118:629 635

Steiner TJ, Lange R, Voelker M (2003) Aspirin in episodic tension type headache: placebo controlled dose ranging comparison with paracetamol. Cephalalgia 23(1):59 66

Sternlieb P, Robinson RM (1978) Stevens Johnson syndrome plus toxic hepatitis due to ibuprofen. NY State J Med 78(8):1239 1243

Stewart WF, Lipton RB (1989) Ibuprofen plus caffeine in the treatment of migraine. In: Rainsford KD, Powanda MC (eds) Safety and efficacy of non prescription (OTC) analgesics and NSAIDs. Kluwer Academic, Dordrecht, pp 123 124

Strand V (2007) Are COX 2 inhibitors preferable to non selective non steroidal anti inflammatory drugs in patients with risk of cardiovascular events taking low dose aspirin? Lancet 370:2138 2151

Strand V, Hochberg MC (2002) The risk of cardiovascular thrombotic events with selective cyclooxygenase 2 inhibitors. Arthritis Rheum 47:349 355

Stricker BHCh (1992) Drug induced hepatic injury. Elsevier, Amsterdam

Stricker K, Yu S, Krammer G (2008) A 6 week, multicentre, randomised, double blind, double dummy, active controlled, clinical safety study of lumiracoxib and rofecoxib in osteoarthritis patients. BMC Musculoskel Dis 9:118

Strom BL, Schinnar R, Bilker WB, Feldman H, Farrar JT, Carson JL (1997) Gastrointestinal tract bleeding associated with naproxen sodium vs ibuprofen. Arch Intern Med 157:2626 2631

Sullivan GW (2003) Adenosine A2A receptor agonists as anti inflammatory agents. Curr Opin Investig Drugs 4:1313 1319

Sunshine A, Olson NZ (1989) Non narcotic analgesics. In: Wall PD, Melzack R (eds) A textbook of pain, 2nd edn. Churchill Livingstone, Edinburgh, pp 670 685

Sunshine A, Roure C, Olson N, Laska EM, Zorilla C, Rivera J (1987) Analgesic efficacy of two ibuprofen codeine combinations for the treatment of postepisiotomy and postoperative pain. Clin Pharmacol Ther 42:374 380

Suri A, Grundy BL, Derendorf H (1997a) Pharmacokinetics and pharmacodynamics of enantiomers of ibuprofen and flurbiprofen after oral administration. Int J Clin Pharmacol Ther 35:1 8

Suri A, Estes KS, Geisslinger G, Derendorf H (1997b) Pharmacokinetic pharmacodynamic relationships for analgesics. Int J Pharmacol Ther 35:307 323

Sycha T, Gustorff B, Lehr S, Tanew A, Eichler HG, Schmetterer L (2003) A simple pain model for the evaluation of analgesic effects of NSAIDs in healthy subjects. Br J Clin Pharmacol 56:165 172

Tanner T, Aspley S, Munn A, Thomas T (2010) The pharmacokinetic profile of a novel fixed dose combination tablet of ibuprofen and paracetamol. BMC Clin Pharmacol 10:10

Teixeira AV, Abrunhosa R, Poças L (1977) Observations on the gastric mucosa of rheumatic patients before and after ibuprofen administration as studied by the pentagastrin test, endos copy, and light and electron microscopy. Int J Med Res 5:243 252

Thayer PS, Palm PE (1975) A current assessment of the mutagenic and teratogenic effects of caffeine. CRC Crit Rev Toxicol 3:345 369

Thomsen RW, Riis A, Munk EM, Nørgaard M, Christensen S, Sørensen HT (2006) 30 day mortality after peptic ulcer perforation among users of newer selective COX 2 inhibitors and traditional NSAIDs: a population based study. Am J Gastroenterol 101:2704 2710

Tiger G, Stenström A, Fowler CJ (2000) Pharmacological properties of rat brain fatty acid amidohydrolase in different subcellular fractions using palmitoylethanolamine as substrate. Biochem Pharmacol 59:647 653

Tiso RL, Tong Ngork S, Fredlund KL (2010) Oral versus topical Ibuprofen for chronic knee pain: a prospective randomized pilot study. Pain Phys 13:457 467

Tolman KG (1998) Hepatotoxicity of non narcotic analgesics. Am J Med 105:13S 19S

Tolman EL, Fuller BL, Marinan BA, Capetola RJ, Levinson SL, Rosenthale ME (1983) Tissue selectivity and variability of effects of acetaminophen on arachidonic acid metabolism. Prostaglandins Leukot Med 12:347 356

Topol EJ (2004) Failing the public health rofecoxib, Merck, and the FDA. N Engl J Med 351:1707 1709

Topol EJ (2005) Arthritis medicines and cardiovascular events “house of coxibs”. JAMA 293 (3):366 368

Towheed TE, Maxwell L, Judd MG, Catton M, Hochberg MC, Wells G (2006) Acetaminophen for osteoarthritis. Cochrane Database Syst Rev (1):CD004257

Traversa G, Bianchi C, Da Cas R, Abraha I, Menniti Ippolito F, Venegoni M (2003) Cohort study of hepatotoxicity associated with nimesulide and other non steroidal anti inflammatory drugs. Br Med J 327:18 22

Trelle S, Reichenbach S, Wandel S, Hildebrand P, Tschannen B, Villiger PM, Egger M, Jüni P (2011) Cardiovascular safety of non steroidal anti inflammatory drugs: network meta analysis. Br Med J 342:7086

Troconiz I, Armenteros S, Planelles MV, Benitez J, Calvo R, Dominguez R (2000) Pharmacokinetic pharmacodynamic modelling of the antipyretic effect of two oral formulations of ibuprofen. Clin Pharmacokinet 38:505 518

Turesson C, Jarenros A, Jacobsson L (2004) Increased incidence of cardiovascular disease in patients with rheumatoid arthritis: results from a community based study. Ann Rheum Dis 63:952 955

Uhler ML, Hsu JW, Fusher SG, Zinaman MJ (2001) The effect of non steroidal anti inflammatory drugs in ovulation: a prospective, randomized clinical trial. Fertil Steril 76:957 961

Underwood M, Ashby D, Cross P, Hennessy E, Letley L, Martin J, Mt Isa S, Parsons S, Vickers M, Whyte K, TOIB study team (2008a) Advice to use topical or oral ibuprofen for chronic knee pain in older people: randomised controlled trial and patient preference study. Br Med J 336 (7636):138 142

Underwood M, Ashby D, Carnes D, Castelnuovo E, Cross P, Harding G, Hennessy E, Letley L, Martin J, Mt Isa S, Parsons S, Spencer A, Vickers M, Whyte K (2008b) Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study. Health Technol Assess 12(22):iii iv, ix 155

US Food and Drug Administration (2006) Information for healthcare professionals: concomitant use of ibuprofen and aspirin New Information [9/2006]. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatients. Accessed 11 Mar 2011

Van Esch A, Van Steensel Moll HA, Steyerberg EW, Offringa M, Habbema JD, Derksen Lubsen G (1995) Antipyretic efficacy of ibuprofen and acetaminophen in children with febrile seizures. Arch Pediatr Adolesc Med 149:632 637

Van Ganse E, Jones JK, Moore N, Le Parc JM, Wall R, Schneid H (2005) A large simple clinical trial prototype for assessment of OTC drug effects using patient reported data. Pharmacoe pidemiol Drug Saf 14:249 255

Van Hoogdalem EJ, de Boer AG, Breimer DD (1991) Pharmacokinetics of rectal drug adminis tration, Part II. Clinical applications of peripherally acting drugs, and conclusions. Clin Pharmacokinet 21:110 128

Van Overmeire B, Touw D, Schepens PJ, Kearns GL, van den Anker JN (2001) Ibuprofen pharmacokinetics in preterm infants with patent ductus arteriosus. Clin Pharmacol Ther 70:336 343

van Staa TP, Leufkens HGM, Cooper C (2000) Use of non steroidal anti inflammatory drugs and risk of fractures. Bone 27:563 568

van Stuijvenberg M, Derksen Lubsen G, Steyerberg EW, Habbema JD, Moll HA (1998) Randomized, controlled trial of ibuprofen syrup administered during febrile illnesses to prevent febrile seizure recurrences. Pediatrics 102(5):e51

van Staa TP, Reitbrock S, Setakis E, Leufkens HGM (2008) Does the varied use of NSAIDs explain the differences in the risk of myocardial infarction? J Intern Med 264(5):481 492

Vanderhoeven SJ, Lindon JC, Troke J, Nicholson JK, Wilson ID (2006) NMR spectroscopic studies of the transacylation reactivity of ibuprofen 1 beta O acyl glucuronide. J Pharm Biomed Anal 41:1002 1006

Vane JR, Botting RM (eds) (2001) Therapeutic roles of selective COX 2 inhibitors. William Harvey, London

Vauzelle Kervroëdan F, d'Athis P, Pariente Khayat A, Debregeas S, Olive G, Pons G (1997) Equivalent antipyretic activity of ibuprofen and paracetamol in febrile children. J Pediatr 131:683 687

Velo GP, Minuz P, Arosio E, Capuzzo MG, Covi G, Lechi A (1987) Interaction between non steroidal anti inflammatory drugs and angiotensin converting enzyme inhibitors. In: Rainsford KD, Velo GP (eds) Side effects of anti inflammatory drugs, Part 1: Clinical and epidemiological aspects. MTP, Lancaster, pp 195 201

Verhagen AP, Damen L, Berger MY, Passchier J, Merlijn V, Koes BW (2006) Is any one analgesic superior for episodic tension type headache? J Fam Pract 55:1064 1072

Vestergaard P, Rejnmark L, Mosekilde L (2006) Fracture risk associated with use of nonsteroidal anti inflammatory drugs, acetylsalicylic acid, and acetaminophen and the effects of rheumatoid arthritis and osteoarthritis. Calcif Tissue Int 79:84 94

Viitanen H, Tuominen N, Vääräniemi H, Nikanne E, Annila P (2003) Analgesic efficacy of rectal acetaminophen and ibuprofen alone or in combination for paediatric day case administration. Br J Anaesthes 91:363 367

Volans G (2001) Current issues on the safety of non prescription NSAIDs. Inflammophar macology 9:43 49

Volans G, Fitzpatrick R (1999) Human toxicity of ibuprofen. In: Rainsford KD (ed) Ibuprofen: a critical bibliographic review. Taylor & Francis, London, pp 541 559
Vormfelde SV, Brockmöller J, Bauer S, Herchenhein P, Kuon J, Meineke I, Roots I, Kirchheiner J (2009) Relative impact of genotype and enzyme induction on the metabolic capacity of CYP2C9 in healthy volunteers. Clin Pharmacol Ther 86(1):54 61
Voutilainen M, Sokka T, Juhola M, Färkkilä M, Hannonen P (1998) Nonsteroidal anti inflammatory drug associated upper gastrointestinal lesions in rheumatoid arthritis patients. Relationships to gastric histology, Helicobacter pylori infection, and other risk factors for peptic ulcer. Scand J Gastroenterol 33:811 816
Waksman JC, Brody A, Phillips SD (2007) Nonselective nonsteroidal anti inflammatory drugs and cardiovascular risk: are they safe? Ann Pharmacother 41:1163 1173
Waldburger JM, Firestein GS (2009) Signalling pathways in rheumatoid arthritis. In: Parnham MJ (eds) New therapeutic targets in rheumatoid arthritis. Birkhäuser Verlag, Basel, p 251
Walker JS, Carmody JJ (1998) Experimental pain in healthy human subjects: gender differences in nociception and in response to ibuprofen. Anesth Analg 86:1257 1262
Walker JS, Arroyo JF, Nguyen T, Day RO (1993a) Analgesic efficacy of non steroidal anti inflammatory drugs in experimental pain in humans. Br J Clin Pharmacol 36:417 425
Walker JS, Knihinicki RD, Seideman P, Day RO (1993b) Pharmacokinetics of ibuprofen enantiomers in plasma and suction blister fluid in healthy volunteers. J Pharm Sci 82:787 790
Wall PD, Melzack R (eds) (1989) Textbook of pain. Churchill Livingstone, Edinburgh
Wallis WJ, Simpkin PA (1983) Antirheumatic drug concentrations in human synovial fluid and synovial tissue: observations on extravascular pharmacokinetics. Clin Pharmacokinet 8:496 522
Walson PD, Mortensen ME (1989) Pharmacokinetics of common analgesics, anti inflammatories and antipyretics in children. Clin Pharmacokinet 17(Suppl 1):116 137
Walson PD, Galletta G, Braden NJ, Alexander L (1989) Ibuprofen, acetaminophen, and placebo treatment of febrile children. Clin Pharmacol Ther 46:9 17
Walton GM, Rood JP (1990) A comparison of ibuprofen and ibuprofen codeine combination in the relief of post operative oral surgery pain. Br Dent J 169:245 247
Wang LM, Mineshita S (1996) Preventive effects of unsei in and oren gedoku to, Chinese traditional medicines, against rat paw oedema and abdominal constriction in mice. J Pharm Pharmacol 48:327 331
Wang B, Tu X, Lu Z, Zhu J (1989) Development and pharmacokinetic study of sustained release ibuprofen pellets. J Chin Pharm Univ. doi:CNKI:SUN:ZGYD.0.1989 05 002
Wang BC, Li D, Budzilovich G, Hiller JM, Rosenberg C, Hillman DE, Turndorf H (1994) Antinociception without motor blockade after subarachnoid administration of S(+) ibuprofen in rats. Life Sci 54:715 720
Wang RL, Dong WL, Feng CM (1997) Pharmacokinetics and relative bioavailability of ibuprofen syrup. Chin Pharm J. doi:CNKI:SUN:ZGYX.0.1997 10 009
Wang B, Ni M, Guo R (2002) Bioavailability of ibuprofen suspension and tablets in healthy volunteers. Chin J Clin Pharm. doi:cnki:ISSN:1007 4406.0.2002 01 011
Wang RL, Q w Zhang, J r Yang et al (2006) Pharmacokinetics and bioequivalence of arginine ibuprofen syrup vs ibuprofen tablet in healthy volunteers. Chin J New Drugs Clin Remed. doi:CNKI:SUN:XYYL.0.2006 01 016
Wang C, He L, Wang N, Liu F (2009) Screening anti inflammatory components from Chinese traditional medicines using a peritoneal macrophage/cell membrane chromatography offline GC/MS method. J Chromatogr B Anal Technol Biomed Life Sci 877:3019 3024
Wang Y, Zhang X, Guo QL, Zou WY, Huang CS, Yan JQ (2010) Cyclooxygenase inhibitors suppress the expression of P2X(3) receptors in the DRG and attenuate hyperalgesia following chronic constriction injury in rats. Neurosci Lett 478:77 81
Wanwimolruk S, Brooks PM, Birkett DJ (1983) Protein binding of non steroidal anti inflammatpry drugs in plasma and synovial fluid of arthritic patients. Br J Clin Pharmacol 15:91 94

Warner TD, Giuliano F, Vojnovic I, Bukasa A, Mitchell JA, Vane JR (1999) Nonsteroid drug selectivities for cyclo oxygenase 1 rather than cyclo oxygenase 2 are associated with human gastrointestinal toxicity: a full in vitro analysis. Proc Natl Acad Sci USA 96:7563 7568

Warrington SJ, Halsey A, O'Donnell L (1982) A comparison of gastrointestinal bleeding in healthy volunteers treated with tiaprofenic acid, aspirin or ibuprofen. Rheumatology 7:107 110

Watson DJ, Rhodes T, Cai B, Guess HA (2002) Lower risk of thromboemboloc cardiovascular events with naproxen among patients with rheumatoid arthritis. Arch Intern Med 162:1105 1110

Watkins PB, Kaplowitz N, Slattery JT, Colonese CR, Colucci SV, Stewart PW, Harris SC (2006) Aminotransferase elevations in healthy adults receiving 4 grams of acetaminophen daily: a randomized controlled trial. JAMA 296:87 93

Weber JCP (1984) Epidemiology of adverse drug reactions to nonsteroidal antiinflammatory drugs. In: Rainsford KD, Velo GP (eds) Side effects of antiinflammatory/analgesic drugs. Raven, New York, pp 1 7

Weber JCP (1987) Epidemiology in the United Kingdom of adverse drug reactions from nonste roidal antiinflammatory drugs. In: Rainsford KD, Velo GP (eds) Side effects of antiinflammatory drugs. Part 1: Clinical and epidemiological aspects. MTP Press, Lancaster, pp 27 35

Webert KE, Kelton JG (2004) Acetylsalicylic acid fro the prevention and treatment of thrombo embolic diseases. In: Rainsford KD (ed) Aspirin and related drugs. Taylor and Francis, London, pp 619 633

Wen J H, Cheng X H, Cai J, Li Y Y, Xiong Y Q (2007) Pharmacokinetics and bioequivalence of ibuprofen tablet in healthy volunteers. Acta Academiae Medicinae Jiangxi. doi:CNKI:SUN:JXYB.0.2007 06 009

Whelton A (1995) Renal effects of over the counter analgesics. J Clin Pharmacol 35:454 463

Whelton A, Stout RL, Spilman PS, Klassen DK (1990) Renal effects of ibuprofen, piroxicam, and sulindac in patients with asymptomatic renal failure. A prospective, randomized, crossover comparison. Ann Intern Med 113:481 482

White WB, West CR, Borer JS, Gorelick PB, Lavange L, Pan SX, Weiner E, Verburg KM (2007) Risk of casrdiovascular events in patients receiving Celecoxib: a meta analysis of randomized clinical trials. Am J Cardiol 99:91 98

Whitehouse MW, Rainsford KD (2006) Paracetamol (acetaminophen) induced gastrotoxicity: revealed by induced hyperacidity in combination with acute or chronic inflammation. Inflammopharmacology 54:150 154

Whitlam JB, Brown KF, Crooks MJ, Room GF (1981) Transsynovial distribution of ibuprofen in arthritic patients. Clin Pharmacol Ther 29(4):487 492

Wiholm BE, Myrhed M, Ekman E (1987) Trends and patterns in adverse drug reactions to non steroidal anti inflammatory drugs reported in Sweden. In: Rainsford KD, Velo GP (eds) Side effects of antiinflammatory drugs. Part 1: Clinical and epidemiological aspects. MTP Press, Lancaster, pp 55 72

Williams K, Day R, Knihinicki R, Duffield A (1986) The stereoselective uptake of ibuprofen enantiomers into adipose tissue. Biochem Pharmacol 35(19):3403 3405

Wilson JT, Brown RD, Kearns GL, Eichler VF, Johnson VA, Bertrand KM, Lowe BA (1991) Single dose, placebo controlled comparative study of ibuprofen and acetaminophen antipyresis in children. J Pediatr 119:803 811

Wilson AW, Medhurst SJ, Dixon CI, Bontoft NC et al (2006) An animal model of chronic inflammatory pain: pharmacological and temporal differentiation from acute models. Eur J Pain 10:537 549

Winter B, Mygynd N (2003) Potential benefits of ibuprofen in the treatment of viral respiratory infections. Inflammopharmacology 11:445 453

Wolf K, Castrop H, Hartner A, Goppelt Strübe M, Hilgers K, Kurtz A (1999) Inhibition of the renin angiotensin system upregulates cyclooxygenase 2 expression in the macula densa. Hypertension 34:503 507

Wolfe MM (2003) Risk factors associated with the development of gastroduodenal ulcers due to the use of NSAIDs. Int J Clin Pract Suppl 135:32 37

Wolfe MM, Lichtenstein DR, Singh G (1999) Gastrointestinal toxicity of nonsteroidal anti inflammatory drugs. N Engl J Med 340:1888 1899

Wright CE III, Antal EJ, Gillepie WR, Albert KS (1983) Ibuprofen and acetaminophen kinetics when taken concurrently. Clin Pharmacol Ther 34:707 710

Wu X, Kong D m (2004) Pharmacokinetics and relative bioavailability of a suspension formula tion of ibuprofen in normal volunteers. Modern Med Health. doi:cnki:ISSN:1009 5519.0.2004 14 011

Wu L H, Zhao H G, Fan H W et al (2001) Pharmacokinetics and relative bioavailability after multiple doses oral of sustained release and conventional tablets of ibuprofen in male volunteers. Chin J Clin Pharmacol. doi:cnki:ISSN:1001 6821.0.2001 02 013

Xie F, Zhang M, Zhang CF, Wang ZT, Yu BY, Kou JP (2008) Anti inflammatory and analgesic activities of ethanolic extract and two limonoids from Melia toosendan fruit. J Ethnopharmacol 117:463 466

Xu GL, Li G, Ma HP, Zhong H, Liu F, Ao GZ (2009b) Preventive effect of crocin in inflamed animals and in LPS challenged RAW 264.7 cells. J Agric Food Chem 57:8325 8330

Xu J y, Liang Y, Zhao X et al (2009a) Bioequivalence of arginine ibuprofen tablets and granules in Chinese healthy volunteers. Chin J Clin Pharmacol. doi:CNKI:SUN:GLYZ.0.2009 03 008

Xu MJ, Zou C, Chu H, Wu T et al (2011) Pharmacokinetics and bioequivalence of single dose and multiple doses of immediate and extended release formulations of dexibuprofen in healthy Chinese subjects. Int J CLin Pharmacol Ther 49:237 246

Xue H Y (2006) Pharmacokinetics and relative bioequivalence of single and multiple oral disease of ibuprofen sustained release capsules. Chin J Pharm 30:693 696. doi:CNKI:SUN: ZHOU.0.2006 10 016

Yang L, Qin LH, Bligh SW, Bashall A, Zhang CF, Zhang M, Wang ZT, Xu LS (2006) A new phenanthrene with a spirolactone from Dendrobium chrysanthum and its anti inflammatory activities. Bioorg Med Chem 14:3496 3501

Yi HG, Chi MH, Kim YI, Woo JS, Park ES (2008) Formulation of a extended release tablet containing dexibuprofen. Arch Pharm Res 31:1637 1643

Yong CS, Oh YK, Jung SH, Rhee JD, Kim HD, Kim CK, Choi HG (2004) Preparation of ibuprofen loaded liquid suppository using eutectic mixture system with menthol. Eur J Pharm Sci 23:347 353

Yoon JS, Jeong DC, Oh JW, Lee KY et al (2008a) The effects and safety of dexibuprofen compared with ibuprofen in febrile children caused by upper respiratory tract infection. Br J Clin Pharmacol 66:854 860

Yoon JS, Jeong D C, Oh J W, Lee K Y, Lee HS, Koh YY, Kim JT, Kang JH, Lee JS (2008b) The effects and safety of dexibuprofen compared with ibuprofen in febrile children caused by upper respiratory tract infection. Br J Clin Pharmacol 66:854 860

Yoshino H, Kobayashi M, Samejima M (1983) Influence of fatty acid composition on the properties and polymorphic transition of fatty suppository bases. Chem Pharm Bull (Tokyo) 31:237 246

Zhang WY (2001) A benefit risk assessment of caffeine as an analgesic adjuvant. Drug Saf 24:1127 1142

Zhang WY, Li Wan Po A (1998) Efficacy of minor analgesics in primary dysmenorrhoea: a systematic review. Br J Obstet Gynecol 105:780 789

Zhao X, P h Sun, Zhou Y, Y w Liu, D f Zhao, Y m Cui, Z m Sun (2004) Determination of ibuprofen in human serum by HPLC. Chin J Clin Pharmacol. doi:cnki:ISSN:1001 6821.0.2004 04 014

Zheng J, Wu LJ, Zheng L, Wu B, Song AH (2003) Two new monoterpenoid glycosides from Mentha spicata L. J Asian Nat Prod Res 5:69 73

Zheng C, Hao H, Wang G, Sang G, Sun J, Li P, Li J (2008) Chiral separation of ibuprofen and chiral pharmacokinetics in healthy Chinese volunteers. Eur J Drug Metab Pharmacokinet 33(1):45 51

Zhou H, Cao W, Mao G et al (1997) Relative bioavailability and pharmacokinetics of ibuprofen suspension. Chin J Hosp Pharm. doi:CNKI:SUN:ZGYZ.0.1997 10 000

Zhou Y, Hancock JF, Lichtenberger LM (2010) The nonsteroidak anti inflammatory drug indo methacin induces heterogeneity in lipid membranes: potential implication for its diverse biological action. PLoS One 5:e8811

Zimmerman HJ (2000) Hepatotoxicity. The adverse effects of drugs and other chemicals on the liver, 2nd edn. Lippincott, Williams & Wilkins, Philadelphia

Zohmann A, Hawel R, Klein G, Kullich W, Lötsch G (1998) S(+) ibuprofen (dexibuprofen) excellent tolerance has not to be combined with poor clinical efficacy. Inflammopharmacology 6:75 79

Index

K.D. Rainsford, *Ibuprofen: Pharmacology, Therapeutics and Side Effects*,
DOI 10.1007/978 3 0348 0496 7,