

## Chapter 2

# Biodisposition in Relation to Actions

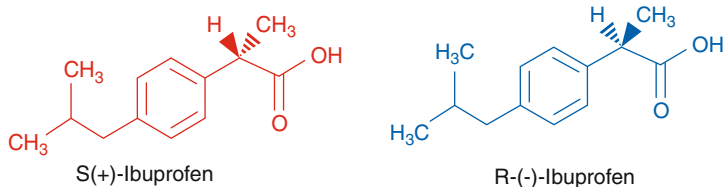
Like most NSAIDs, ibuprofen has multiple actions including the inhibition of prostaglandin (PG) production, and these activities underlie the clinical effects that are linked to its pharmacokinetic (PK) properties (Rainsford 1996, 1999b, 2009). In this chapter, the principal PK and pharmacodynamic (PD) 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 % of the R(–) form to the S(+) antipode, (b) oxidative conversion catalysed by cytochromes P<sub>450</sub> 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



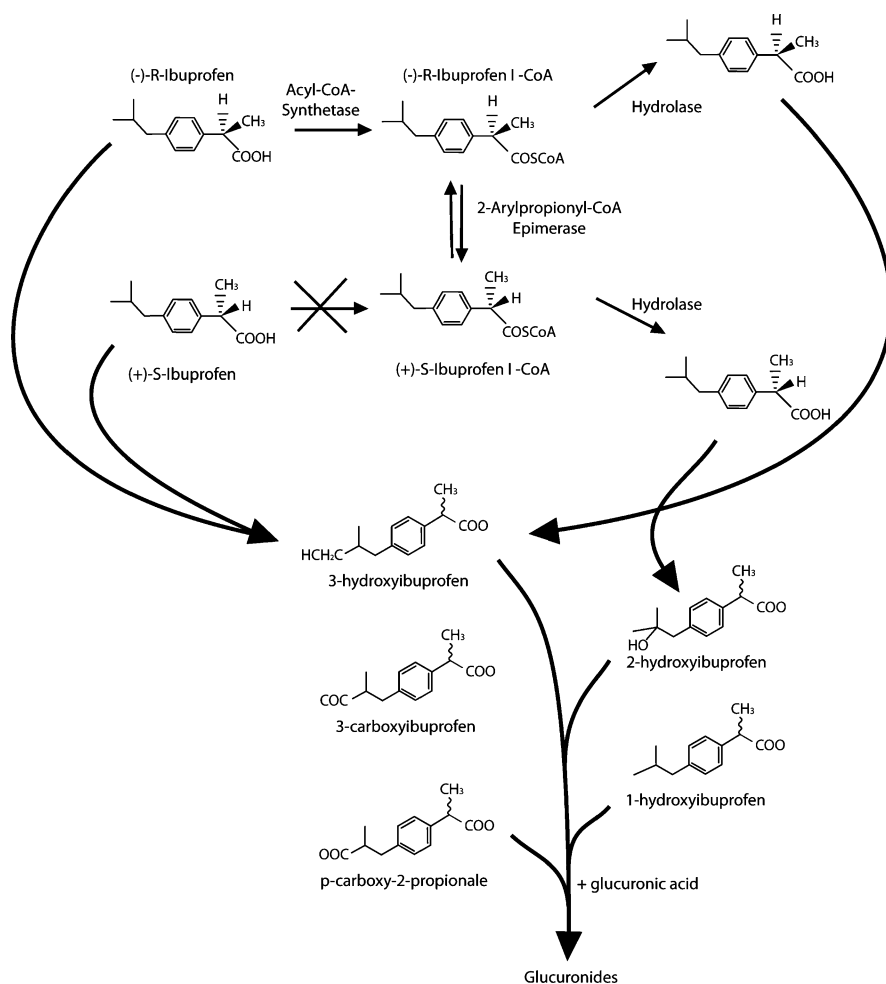
**Fig. 2.1** Chemical structures of the R(–)- and S(+)- isomers of ibuprofen (Nichol 1999). The ibuprofen molecule has a chiral centre at carbon-2 of the propionic acid group. This leads to the formation of two optical isomers or enantiomers. The (+) form (originally described as *d*- or *dextro*-) has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

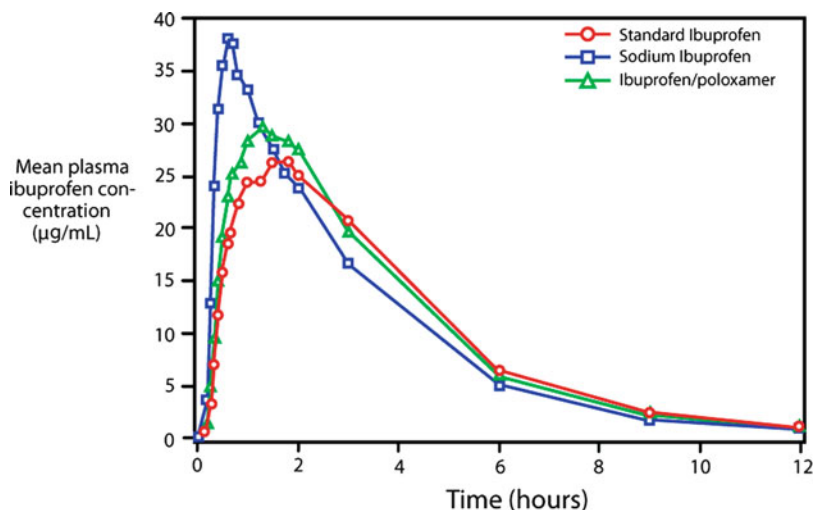
Ibuprofen is rapidly, and almost completely, absorbed from the upper gastrointestinal tract. As shown in Fig. 2.3 (Dewland et al. 2009), the plasma concentration profiles of ibuprofen can vary according to the drug formulation (Ceppi Monti et al. 1992; Brocks and Jamali 1999; Lötsch et al. 2001; Dewland 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-propionyl-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-hydroxy-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



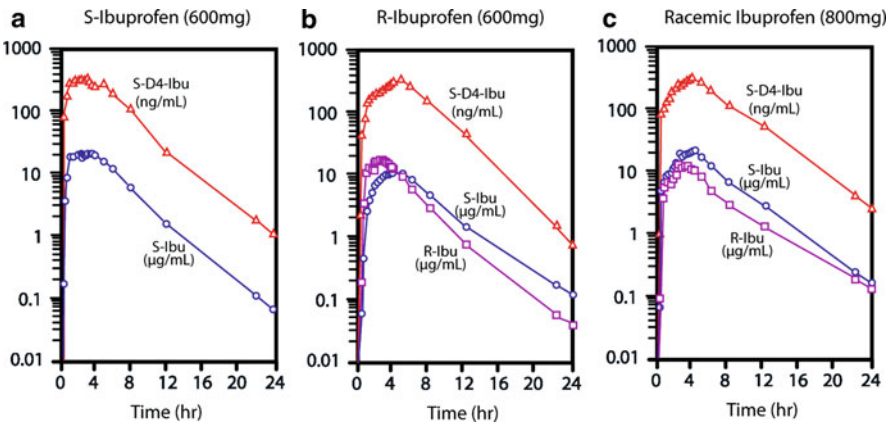
**Fig. 2.3** Mean plasma concentration profiles of racemic ibuprofen (determined by LC-MS) following oral ingestion of a single dose of: (a)  $2 \times 200$  mg tablets of ibuprofen acid [“standard ibuprofen” in the figure, i.e., Nurofen®], (b)  $2 \times 256$  mg tablets of sodium dihydrate ibuprofen [“sodium ibuprofen”, with the equivalent mass of ibuprofen to that in (a)], and (c)  $2 \times 200$  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  $\mu\text{g/mL}$ , compared with that of standard ibuprofen (acid) with a  $t_{\max}$  of 90 min and  $C_{\max}$  of 31.88  $\mu\text{g/mL}$ , while the ibuprofen/poloxamer had a  $t_{\max}$  of 75 min and a  $C_{\max}$  of 35.22  $\mu\text{g/mL}$ , 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  $\text{AUC}_{0-\infty}$  (range 117–122  $\mu\text{g/h/mL}$ ) and  $\text{AUC}_{0-4}$  (range 115–120  $\mu\text{g/h/mL}$ )], 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<sub>4</sub>-ibuprofen shown in *red*. Reproduced according to the proprietary rights and permission of The Journal of Pharmacology and Experimental Therapeutics

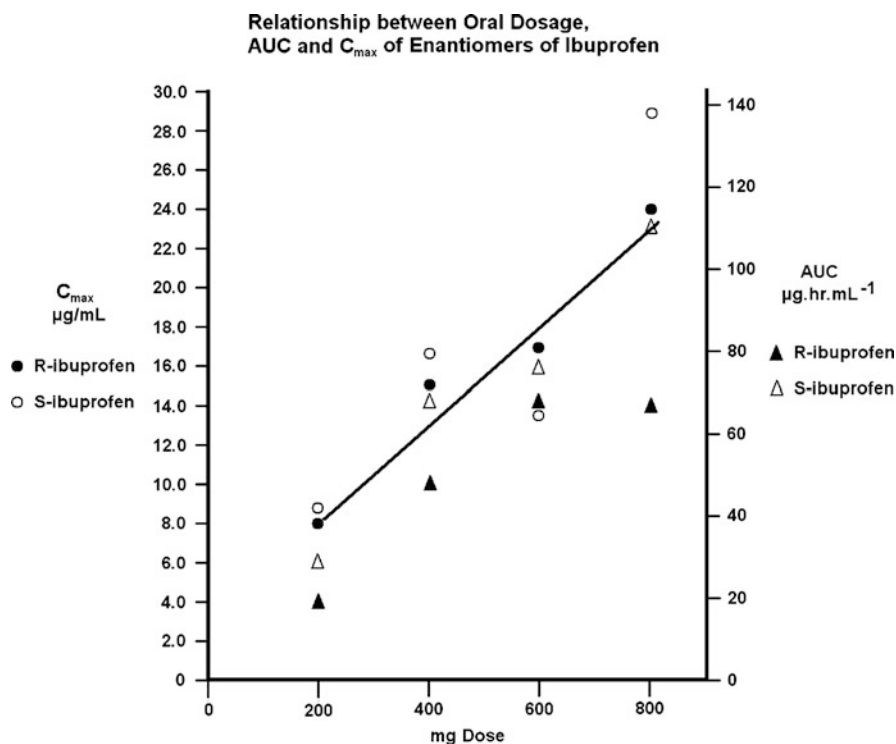
**Table 2.1** Pharmacokinetic parameters for oral ibuprofen (400 mg)

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

\*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<sup>-1</sup> 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<sub>0–8h</sub> 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.

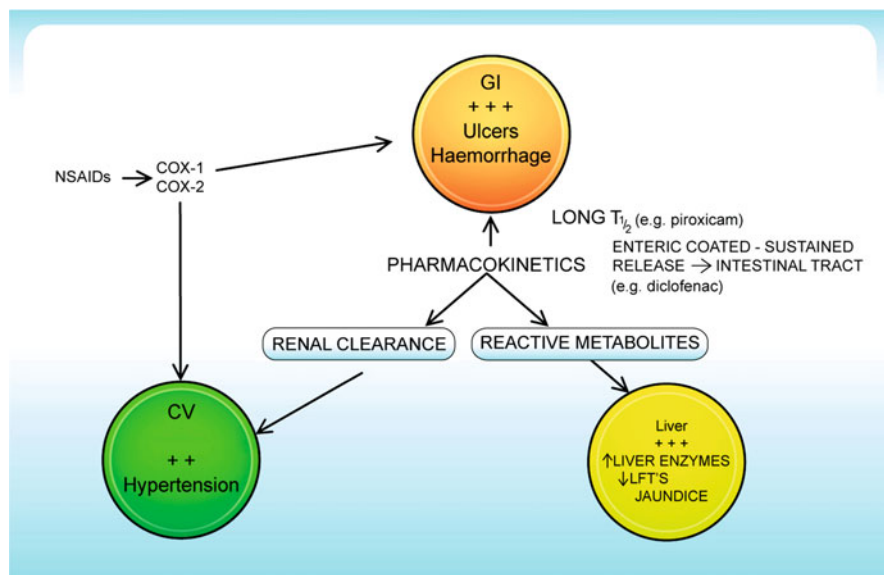
These studies on the kinetics and disposition of ibuprofen and its enantiomers in synovial fluids and the CNS form an important basis for understanding the analgesic actions of the drug in these compartments.

### ***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<sub>450</sub> 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  $t_{1/2}$  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  $t_{1/2}$ , 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  $\mu\text{g/mL}$  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.

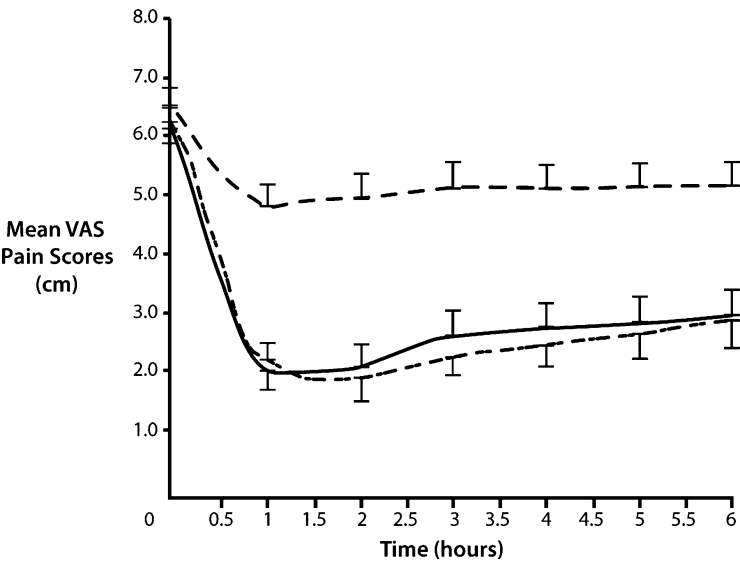
### **2.2.1 Dental Pain Model**

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).

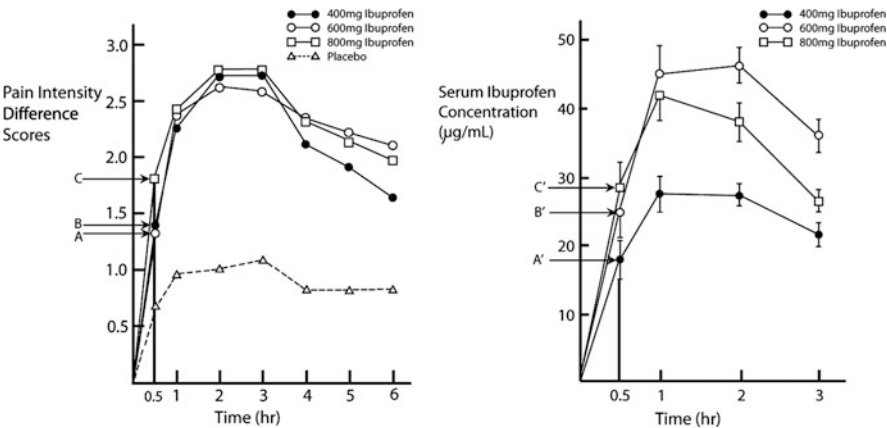
Most dental pain studies in which racemic ibuprofen has been administered within 30 min of pain show onset of analgesic activity within 30 min and peak activity at 2–3 h post drug administration (Cooper 1984; Cooper et al. 1989; Dionne and Cooper 1978, 1999; Laska et al. 1986; Jain et al. 1986; Seymour 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; Björnsson 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) ( $\pm$ 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

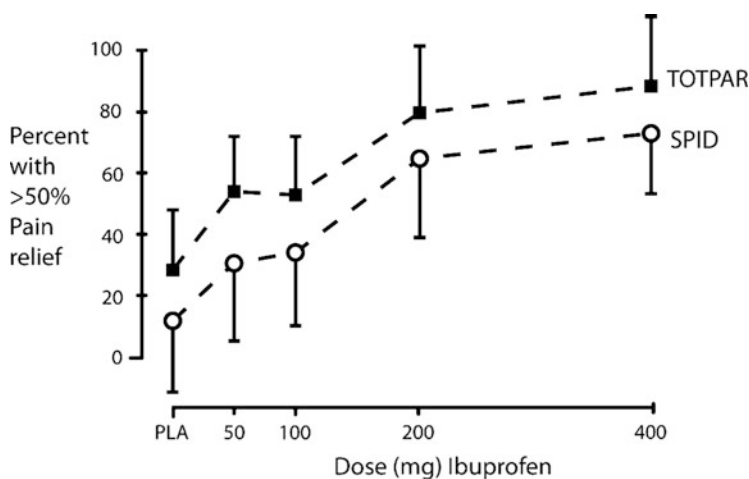
studies on the effects of ibuprofen in the third molar dental pain model have shown that effective doses for analgesia were 400 mg, with a few at 600 mg ibuprofen.

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:

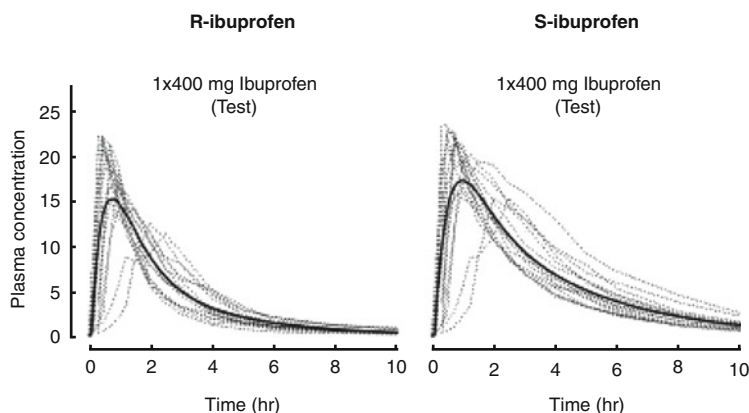
1. Taking data on serum concentrations at the earliest point at which there is a statistically significant difference in analgesic activity (i.e., pain intensity difference scores) (see Fig. 2.8), gives a time of 0.5 h. The right side graph in Fig. 2.8, gives values for the serum concentrations for the 400 mg dose of approximately 17.5  $\mu\text{g/mL}$ , for the 600 mg dose 24.8  $\mu\text{g/mL}$  and the highest dose of 800 mg gives 28.8  $\mu\text{g/mL}$ .
2. Taking the maximal serum concentrations of ibuprofen at 1 h those for the 400 mg dose would approximate to 27  $\mu\text{g/mL}$ ; at the 600 mg dose this would be 42  $\mu\text{g/mL}$  and at the 800 mg dose about 45  $\mu\text{g/mL}$  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  $\mu\text{g/mL}$  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  $\mu\text{g/mL}$  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  $2 \times 200$  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  $\mu\text{g/mL}$  for the racemate, 15  $\mu\text{g/mL}$  for the S(+) isomer and 14  $\mu\text{g/mL}$  for the R(–) isomer (see Fig. 2.10), based on the extrapolation of the time to reach specific concentrations. At least by 1 h ( $t_{\text{max}}$ ) the  $C_{\text{max}}$  value can be confidently used for calculations of the therapeutically-relevant concentrations at  $t_{\text{max}}$ .

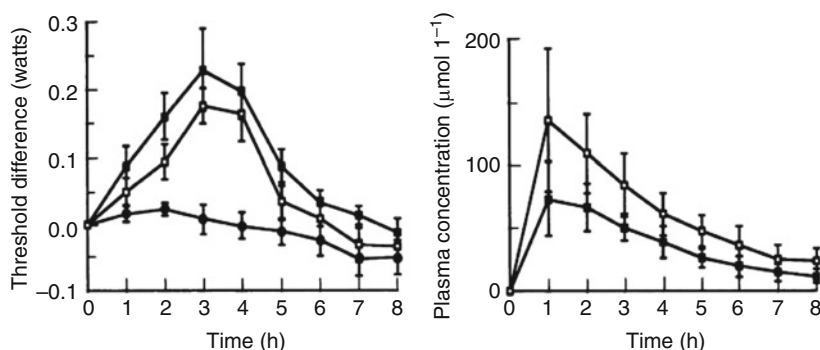


**Fig. 2.9** Dose–response of ibuprofen in the third molar dental pain model in which the percentage of patients showing greater than 50 % pain relief is shown in relation to data of Schou et al. (1998) on the sum of pain intensity difference (SPID) (*open circle*) and total pain relief (*filled circle*). 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  $\pm$  SEM, watts; *left graph*) and plasma concentrations ( $\mu\text{mol/L}$ ; *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  $C_{\text{max}}$  (at  $t_{\text{max}}$ ) 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  $\mu\text{g/mL}$  (from a 400 mg dose) and 27.8  $\mu\text{g/mL}$  (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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub> 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<sub>2</sub>-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 <sub>max</sub> (µg/mL)	Earliest time T <sub>max</sub> (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	
Jamali and Kunz-Dober (1999)	Third molar extraction	200		14[R(–)]	~18	1	
			N/A	N/A	6.3	1	[S(+)] 5.6 (0–2) Before Surg. 1.6 After Surg.
					3.9	6	
					6.1	1	[R(–)] 5.5 (0–2) Before Surg. 2.1 After Surg.
					5.3	6	
					14.5	1	[S(+)] 14.2 (0–2) Before Surg. 7.2 After Surg.
			N/A	N/A	11.1	4	
					14.8	1	[R(–)] 14.1 (0–2) Before Surg. 1.8 After Surg.
					13.4	4	
					18.2[S(+)]	1.4–1.5	
Nielsen et al. (1990)	Laser beam applied to right hand dorsum	400	3		27.8[S(+)]	1.2–1.5	
		800	3				

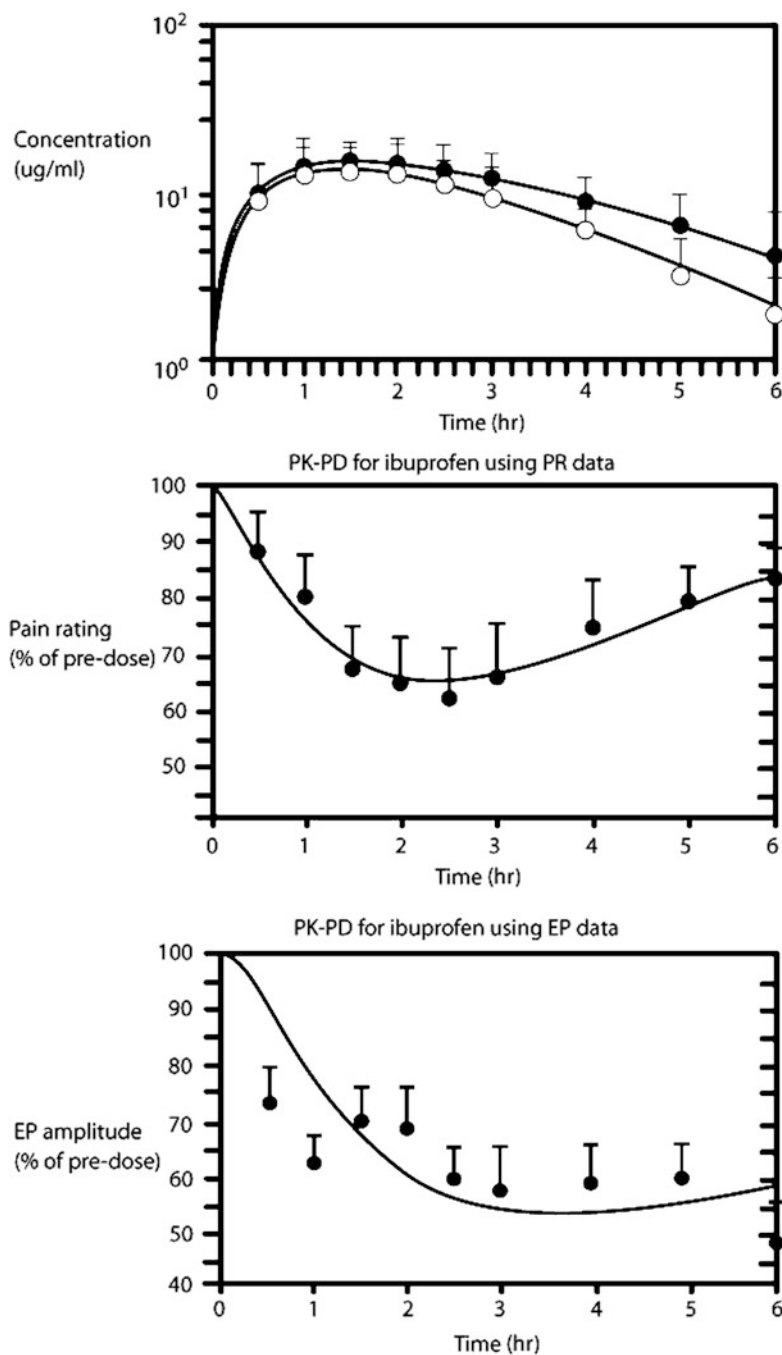
to the type and severity of the painful stimulus, given that the inflammatory pain in the third molar extraction model is appreciably greater than the CO<sub>2</sub>-stimulus model.

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  $\mu\text{g/mL}$ ) and evoked potential ( $EC_{50}$  set to 8.71  $\mu\text{g/mL}$ ) 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:

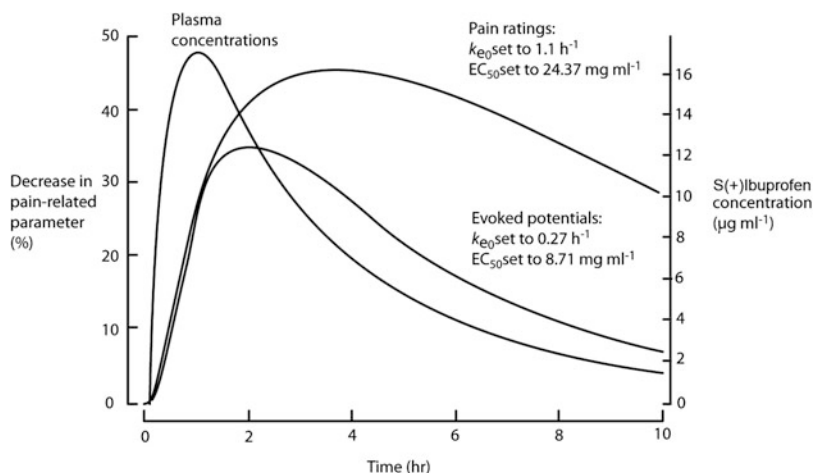
1. Plasma concentrations of S(+) ibuprofen peak and are ahead of the peak pain-related parameters. Thus, peak concentrations of S(+) ibuprofen occur at 1 h, while that of the evoked potentials is at 2 h and the subject-assessed pain ratings follow at a peak at 3 h. The latter extends for a longer period, and the AUC for the pain ratings extends over a much longer period than 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  $\mu\text{g/mL}$  then it would be safe to assume this value approximated to 24  $\mu\text{g/mL}$  as the effective therapeutic concentration. The lower value of the  $EC_{50}$  being 8.71  $\mu\text{g/mL}$  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  $\mu\text{g/mL}$  while those of the active S(+) isomer after 200 mg of the racemate are ~14  $\mu\text{g/mL}$  and after 400 mg of this are 25  $\mu\text{g/mL}$ .
- (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- $\alpha$ ) on hypothalamic pathways leading to PGE<sub>2</sub> production. Thus, a model of antipyretic effects of NSAIDs, including ibuprofen, focuses principally on the direct inhibition of hypothalamic PGE<sub>2</sub>, 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<sub>50</sub> [the plasma concentration that elicits half maximal drug effect, or  $E_{\max}$ ] for reduction of temperature at 6.18  $\mu\text{g/mL}$ . 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:

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

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  $\mu\text{g/mL}$ . 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 ( $t_{\text{max,ef}}$ ) 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  $C_{\text{max}}$  for total racemic ibuprofen was 26.67  $\mu\text{g/mL}$  and those for S(+) ibuprofen were 13.8  $\mu\text{g/mL}$  and for R(–) ibuprofen 13.39  $\mu\text{g/mL}$  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  $C_{\text{max}}$  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  $\mu\text{g/mL}$ , and (c) coincided with reduction in VAS estimates of pain and articular indices. There were no differences in the time of  $C_{\text{max}}$  (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  $20.3 \pm 5.3 \mu\text{g/mL}$  S(+) ibuprofen and 17.7  $\mu\text{g/mL}$  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  $\mu\text{g/mL}$  for S(+) ibuprofen and 8.8  $\mu\text{g/mL}$  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  $\mu\text{g/mL}$  S(+) ibuprofen and 6.5  $\mu\text{g/mL}$  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  $C_{\text{max}}$  for racemic ibuprofen was 31.1–35.6  $\mu\text{g/mL}$  and was achieved at  $t_{\text{max}}$  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  $\mu\text{g/mL}$  of the racemate and approximately 10–20  $\mu\text{g/mL}$  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  $\mu\text{g/mL}$  and 10–15  $\mu\text{g/mL}$  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 overall ( <i>n</i> = 45)
	300 mg ( <i>n</i> = 8)	600 mg ( <i>n</i> = 7)	300 mg ( <i>n</i> = 21)	600 mg ( <i>n</i> = 24)	
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)
<i>C</i> <sub>max</sub> (mg/L)	11.1 (5.3)	13.8 (8.5)	12.7 (5.4)	18.2 (6.8)	
<i>T</i> <sub>max</sub> (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)	
<i>t</i> <sub>1/2</sub> (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)
<i>C</i> <sub>max</sub> (mg/L)	10.5 (3.8)	16.4 (8.5)	12.0 (4.9)	18.7 (7.4)	
<i>T</i> <sub>max</sub> (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)	
<i>t</i> <sub>1/2</sub> (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*<sub>max</sub> maximum serum concentration, *T*<sub>max</sub> time to *C*<sub>max</sub>, *Css.av* average steady state serum concentration, *t*<sub>1/2</sub> 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*<sub>max</sub> and *t*<sub>max</sub> 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
<i>PK Parameters</i>	Placebo			
$C_{\max}$ ( $\mu\text{g/mL}$ )	–	$19.4 \pm 6.8$	$18.2 \pm 4.0$	$17.5 \pm 3.9$
AUC ( $\mu\text{g/mL/min}$ )	–	$3,042 \pm 966$	$5,564 \pm 1,152$	$7,962 \pm 1,653$
$t_{\max}$ (min)	–	$61.4 \pm 18.1$	$56.9 \pm 12.4$	$58.3 \pm 13.9$
<i>Clinical responses</i>	(vs. placebo)			
VAS pain	–	NS	$<0.005$	$\leq 0.005$
Articular index	–	NS	$<0.01$	$\leq 0.005$
Pain scores	–	NS	$<0.05$	$\leq 0.02$
Thermographic index	$445.4 \pm 188.5$	$429 \pm 220.2$	$443.3 \pm 204.6$	$462 \pm 203.9$

Arthritis patients ( $N = 20$  total) took either placebo or ibuprofen 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 ( $0.19 \mu\text{g/mL}$ ) do not differ significantly from those in plasma ( $0.25 \mu\text{g/mL}$ ) 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 <sup>-1</sup> (h) or MTT (h)	AUC (μg/mL/h)	Author(s)
400–1,200 mg	<u>rac</u>	Syn fluid	4.0–63 <sup>a</sup> [0.6–1.6]			Wallis and Simpkin (1983)
800 mg	<u>rac</u>	Syn tissue	126–150			
	<u>rac</u>	Syn fluid	11S(+)			Cox et al. (1991)
600 mg	<u>rac</u>	Syn fluid	6.4R(–) 9.7 S(+) <sup>b</sup> 8.6 R(–)			Geisslinger et al. (1993)
400 mg	S(+)	Syn fluid	10.6(S+) <sup>c</sup>			
40 mg/kg Children JCA <sup>d</sup>	<u>rac</u>	Syn fluid	20			
1,200	<u>rac</u>	Syn fluid	3.3–4.9 S(+)	$K = 0.45; 0.29 \text{ sp}$ $MTT = 2.22, 3.44$ $K_i = 0.29$ $K_0 = 0.36^e$	110 ± 28 <sup>e</sup>	Elmqvist et al. (1994)
			2.4–4.4 R(–)	$K_i = 0.19$ $K_0 = 0.34$	56 ± 8	Seideman et al. (1994)
		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	<u>rac</u>	Lumbar CSF	1.5			Bannwarth et al. (1995)

<sup>a</sup>Free concentrations from estimates of free fraction ~0.026.

<sup>b</sup> $t_{max} \sim 2.4 \text{ h}$ .

<sup>c</sup> $t_{max} \sim 2.3 \text{ h}$ .

<sup>d</sup>JCA children with juvenile chronic arthritis; data from Mäkelä et al. (1981).

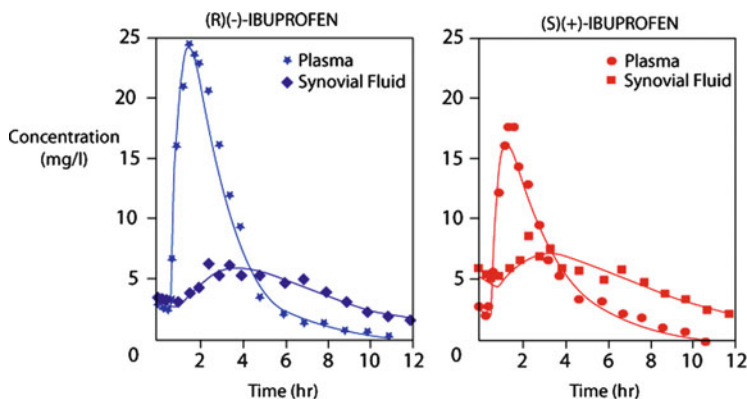
<sup>e</sup>Rate constants, k<sup>-1</sup> (h) as  $K_i$  = inward,  $K_0$  = outward of synovial fluid or blister fluid values of  $K_i$  or  $K_0$  and AUCs of synovial fluids not significantly different from blister fluids.

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  $\mu\text{g/mL}$  (45.6  $\mu\text{M}$ ), compared with those in plasma at that time which were 15.45  $\mu\text{g/mL}$  (75  $\mu\text{M}$ ), 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 ( $k_{\text{sp}}$ ) are the sum of the rate constants for both diffusion and lymphatic blood flow out of the synovial space (Elmqvist et al. 1994). The mean residence times ( $\text{MTT}_{\text{synovial}}$ ) can be calculated in relation to the exit rate constants. Using partial-areas analysis, Elmqvist et al. (1994) calculated the  $k_{\text{sp}}$  for ibuprofen as  $0.29 \text{ h}^{-1}$  and the  $\text{MTT}_{\text{synovial}}$  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  $\text{MTT}_{\text{synovial}}$  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 ( $t_{1/2}$ ) 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 ( $\mu\text{g/mL}$ )	80.7 (6)	28.7 (28)	50.3 (36)	19.2 (63)
AUC ( $\mu\text{g/mL/h}$ )	2.7			
0–12	197.8 (12)	164.2 (21)	172.5 (36)	97.6 (73)
0– $\infty$	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 ( $\text{h}^{-1}$ )	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  $C_{\text{max}}$  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<sup>®</sup> (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  $t_{\text{max}}$  in infants for the ratio of R/S enantiomers of ibuprofen was 1.6–3.3 h, and the  $t_{1/2}$  for absorption was 1.9–2.9 h. In four of the youngest group of infants (1–7 weeks; group 1), the  $t_{\text{max}}$  was similar to that in those where the suppository was not fully retained in situ, even though the  $C_{\text{max}}$  values were about 40 % less than in the retained suppository group. The only differences in  $t_{\text{max}}$  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 ( <i>n</i> = 5) suppository retained				
<i>C</i> <sub>max</sub> (mg/L)	29.3 ± 16.2	23.8 ± 9.4	49.2 ± 20.7	1.7 ± 1.1
<i>T</i> <sub>max</sub> (h)	2.2 ± 1.0 <sup>b</sup>	1.8 ± 1.3 <sup>b</sup>	1.9 ± 1.2 <sup>b</sup>	
Chronological <i>t</i> <sub>1/2</sub> (h)	2.9 ± 1.8	3.2 ± 2.7	4.6 ± 5.1	
Physiological <i>t</i> <sub>1/2</sub> (h)	5.8 ± 3.5 <sup>b</sup>	6.6 ± 5.4 <sup>b</sup>	8.9 ± 10.1	
AUC (mg/L × h)	159 ± 81 <sup>a</sup>	112 ± 54	299 ± 69 <sup>a</sup>	
Group 1 ( <i>n</i> = 4) suppository expelled				
<i>C</i> <sub>max</sub> (mg/L)	12.4 ± 6.4	13.4 ± 8.1	25.7 ± 14.2	1.6 ± 1.4
<i>T</i> <sub>max</sub> (h)	1.9 ± 0.9	1.9 ± 0.9	1.9 ± 0.9	
Chronological <i>t</i> <sub>1/2</sub> (h)	3.8 ± 2.9	3.1 ± 2.4	2.9 ± 2.1	
Physiological <i>t</i> <sub>1/2</sub> (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 ( <i>n</i> = 8)				
<i>C</i> <sub>max</sub> (mg/L)	38.5 ± 20.7	40.0 ± 21.8	75.6 ± 44.6	1.1 ± 0.2
<i>T</i> <sub>max</sub> (h)	1.6 ± 0.7 <sup>b</sup>	1.4 ± 0.8 <sup>b</sup>	1.6 ± 0.7 <sup>b</sup>	
Chronological <i>t</i> <sub>1/2</sub> (h)	1.7 ± 0.4	2.2 ± 0.7	1.9 ± 0.5	
Physiological <i>t</i> <sub>1/2</sub> (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 ( <i>n</i> = 7)				
<i>C</i> <sub>max</sub> (mg/L)	42.7 ± 16.0	49.7 ± 23.3	87.9 ± 36.6	1.1 ± 0.4
<i>T</i> <sub>max</sub> (h)	1.7 ± 0.3 <sup>b</sup>	1.6 ± 0.7 <sup>b</sup>	1.6 ± 0.3 <sup>b</sup>	
Chronological <i>t</i> <sub>1/2</sub> (h)	2.8 ± 1.3	1.8 ± 0.4	2.1 ± 0.7	
Physiological <i>t</i> <sub>1/2</sub> (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 ( <i>n</i> = 7)				
<i>C</i> <sub>max</sub> (mg/L)	30.1 ± 12.5	30.1 ± 9.9	63.8 ± 20.4	0.9 ± 0.1
<i>T</i> <sub>max</sub> (h)	3.5 ± 0.8	2.9 ± 1.0	3.3 ± 0.8	
Chronological <i>t</i> <sub>1/2</sub> (h)	2.1 ± 0.3	2.5 ± 0.7	2.2 ± 0.4	
Physiological <i>t</i> <sub>1/2</sub> (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.

<sup>a</sup>Significantly (*P* > 0.05) different from the corresponding value in group 1 where the suppository was expelled.

<sup>b</sup>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.

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

From Autret-Leca (2003) and Rainsford (2009)

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

The population PK properties of ibuprofen in children (aged  $\geq 6$  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 ( $\pm$ 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  $t_{1/2}$  (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  $t_{1/2}$  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  $t_{1/2}$  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  $t_{1/2}$  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  $t_{1/2}$  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)
<i>Ibuprofen</i>	i.v.	2.06 (0.33)	0.062 (0.004)	30.5
22–31 weeks <sup>a</sup>	i.v.	9.49 (6.82)	0.357 (0.121)	43.1 (26.1)
28.6 (1.9) weeks <sup>a</sup>	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) <sup>SE</sup>	0.16 (0.02) <sup>SE</sup>	1.44 (0.15)
3 mo–12 years	Suspension	110 (10) <sup>SE</sup>	0.22 (0.02) <sup>SE</sup>	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) <sup>-1</sup>	(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 distribution,  $V_{ss}$  volume of distribution at steady state,  $V_c$  initial volume of distribution,  $V_p$  apparent volume of distribution of peripheral compartment, SE standard error.

<sup>a</sup>Age is gestation age (GA, weeks).

<sup>b</sup>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  $35.8 \pm 16.7$  (mean  $\pm$  SD) at  $0.7 \pm 0.5$  h (mean  $\pm$  SD). The absorption was faster than that found in earlier studies, and similarly the half-life of absorption was fast ( $t_{1/2abs}$   $0.3 \pm 0.3$  h). The plasma elimination  $t_{1/2}$  was  $1.6 \pm 0.7$  (mean  $\pm$  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  $33.5 \pm 14.7$  (mean  $\pm$  SD)  $\mu$ g/mL and  $t_{max}$  being  $60 \pm 19.7$  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  $7.6 \pm 0.3$  mg/kg ibuprofen suspension post-operatively (Re et al. 1994). The values of racemic S(+) and R(–) were  $24.4 \pm 6.6$ ,  $9.7 \pm 2.9$  and  $11.8 \pm 4.4$   $\mu$ g/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  $t_{1/2}$  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  $t_{1/2}$  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 ( $6.1 \pm 1.7$ ; mean  $\pm$  SD mg/min/mL) were significantly lower than in controls ( $11.3 \pm 3.4$ , mean  $\pm$  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  $t_{1/2}$  was (mean  $\pm$  SD)  $30.5 \pm 4.2$  h, which was appreciably longer than in infants, children, or adults (approximately 1–2 h). The percentage binding to cord plasma was significantly lower ( $94.98 \pm 0.39$  %, mean  $\pm$  SD) compared with that in adult plasma ( $98.73 \pm 0.31$  %, mean  $\pm$  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 ( $2.06 \pm 0.33$  mL/kg/h, mean  $\pm$  S.D.) compared with that in infants through to adults. It was suggested that the prolonged  $t_{1/2}$  and Cl may reflect immaturity in the formation of cytochrome P<sub>450</sub> 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.

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