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# Stereoselective disposition of ibuprofen enantiomers in human cerebrospinal fluid

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Since both (R)- and (S)-enantiomers of ibuprofen may act on the central nervous system, we investigated their plasma and cerebrospinal fluid (CSF) concentrations in 46 patients with nerve-root compression pain requiring a lumbar puncture. Each patient received an oral dose of 800 mg *rac*-ibuprofen. A single blood and CSF sample was drawn concomitantly from each patient at intervals between 30 min and 8 h after dosing. Both isomers peaked later in the CSF (3 h) than in the plasma (1.5 h). Their CSF concentrations became higher than their concurrent free plasma concentrations after 90 min. The estimated elimination half-lives of (R)- and (S)-ibuprofen were 1.7 h and 2.5 h in plasma and 3.9 h and 7.9 h in CSF, respectively. The $AUC_{CSF}/AUC_{plasma}$ ratios (0, 8 h) were 0.009 and 0.015 for the (R)- and (S)-forms, respectively.

**Keywords** ibuprofen non-steroidal anti-inflammatory drugs plasma and CSF concentrations central nervous system

## Introduction

Ibuprofen is a 2-arylpropionic acid non-steroidal anti-inflammatory drug (NSAID) and it is generally accepted that the site of its antipyretic effect is in the brain [1]. There is also convincing evidence that a central component contributes to the overall analgesia provided by NSAIDs [2]. Furthermore, various central nervous system adverse reactions have been ascribed to NSAID therapy [3]. In this respect, ibuprofen may induce aseptic meningitis, particularly in patients with disturbed immunity [3]. Finally, NSAIDs can affect virtually any part of the neuraxis [2].

Since ibuprofen has one chiral carbon located on its propionic side chain, it exists in two stereoisomeric forms, S(+) and R(−). The current formulations of the drug are racemic mixtures. It is usually considered that the pharmacodynamic properties of ibuprofen reside almost exclusively in the (S)-enantiomer [4]. The latter was reported to be about 160 times more potent than (R)-ibuprofen in inhibiting prostaglandin synthesis *in vitro* [4] but there are conflicting data [5].

Since (R)- and (S)-ibuprofen exhibit enantioselective pharmacokinetics in man [4], the measurement of individual enantiomers has been recommended inasmuch as unidirectional metabolic inversion of about 60% of the (R)-isomer into the (S)-isomer occurs *in vivo* [6].

Based on the foregoing considerations, we investigated the total and free (unbound) plasma concentrations and the cerebrospinal fluid (CSF) concentrations of (R)- and (S)-ibuprofen in patients receiving a single oral dose of 800 mg of the racemate.

## Methods

### *Study design*

Forty-six in-patients (30 men, 16 women), aged 25 to 88 years (mean ± s.d. : 51 ± 15) and weighing from 45 to 99 kg (70 ± 13 kg) participated in the study after expressing informed consent in writing. The study protocol was approved by the University Hospital Ethics Committee of Nancy, France. The patients were suffering from nerve-root compression

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pain that required a lumbar puncture (analysis of the CSF, myelography, intrathecal injection of corticosteroids). Standard laboratory tests revealed no clinically significant abnormalities in any patient. The plasma concentrations of total protein (63.9 ± 5.4 g $l^{-1}$) and albumin (40.2 ± 4.0 g $l^{-1}$) were also within the normal range.

After an overnight fast, patients were given two tablets of 400 mg *rac*-ibuprofen (Brufen, Boots Pharma, France) with 100 ml tap water. A single blood (10 ml) and CSF (3 ml) sample was drawn concomitantly from each patient at intervals between 30 min and 8 h after drug administration. Thus, the following sampling times (4–6 subjects per time point) were allocated randomly: 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6 and 8 h.

Blood was collected in oxalate tubes and centrifuged. The CSF samples were divided in two aliquots : one (2 ml) was frozen with the plasma sample at −80° C until assayed, and the other (1 ml) was used for cytochemical analysis. The concentrations of total protein in CSF ranged from 0.21 to 1.31 g $l^{-1}$ (0.55 ± 0.25 g $l^{-1}$; normal 0.15–0.55 g $l^{-1}$). The CSF white blood cell counts were normal. Thus, the blood-brain barrier may be considered as virtually undamaged [7].

*Sample analysis*

The concentrations of (R)- and (S)-ibuprofen were determined by h.p.l.c. The enantiomers were extracted from 200 µl acidified samples together with 0.1 µg of internal standard [(benzoyl-4-phenyl)-2-butyric acid, provided by Specia, Rhône Poulenc Rorer] by diethylether. The dried extract was derivatized by the method of Foster & Jamali [8]. Derivatized solution (50 µl) was then injected into a radial compression column (C18 Radial Pak, 100 × 8 mm). The mobile phase consisted of 50 mM $Na_2HPO_4$ buffer/acetonitrile/triethylamine (57:43:0.02, v/v; pH 7). (R)- and (S)-ibuprofen and both internal standard derivatives were eluted after 24, 26, 12 and 16 min, respectively (flow rate, 1 ml $min^{-1}$; wavelength of u.v. detector, 223 nm). The method was linear from 0.02 to 20 µg for each enantiomer. The limit of detection was 5 ng $ml^{-1}$. The reproducibility was assessed at 0.1, 1, and 10 µg. The intraassay coefficients of variation averaged 7.5%, 4.9%, and 2%, respectively. The interassay coefficients of variation were 14%, 6.7%, and 3.8%, respectively.

Plasma protein binding of (R)- and (S)-ibuprofen was determined by equilibrium dialysis at 37° C with a Dianorm apparatus equipped with 1 ml cells and Spectrapor-2 membranes (molecular weight cutoff, *circa* 12 000–14 000). Plasma samples were dialysed for 3 h against a 67 mM Sörensen phosphate buffer, pH 7.4.

*Data analysis*

The pharmacokinetic analysis was carried out with SIPHAR® software (Simed, Créteil, France) on a Vectra® microcomputer (Hewlett Packard). Individual data were pooled and the elimination half-lives in plasma and CSF were estimated by log linear regression. The area under the concentration-time curve (AUC) values were calculated by the linear trapezoidal rule from 0 to 8 h. Time to reach peak concentrations ($t_{max}$) and the peak concentrations ($C_{max}$) were the observed data in plasma and CSF.

## Results

The mean (± s.e. mean) plasma and CSF concentrations of ibuprofen enantiomers *vs* time are depicted in Figure 1. Their pharmacokinetic parameters are presented in Table 1. Both enantiomers crossed the blood-brain barrier. However, they were undetectable in the earliest samples of CSF taken 30 min after drug administration. $C_{max}$ values were later and

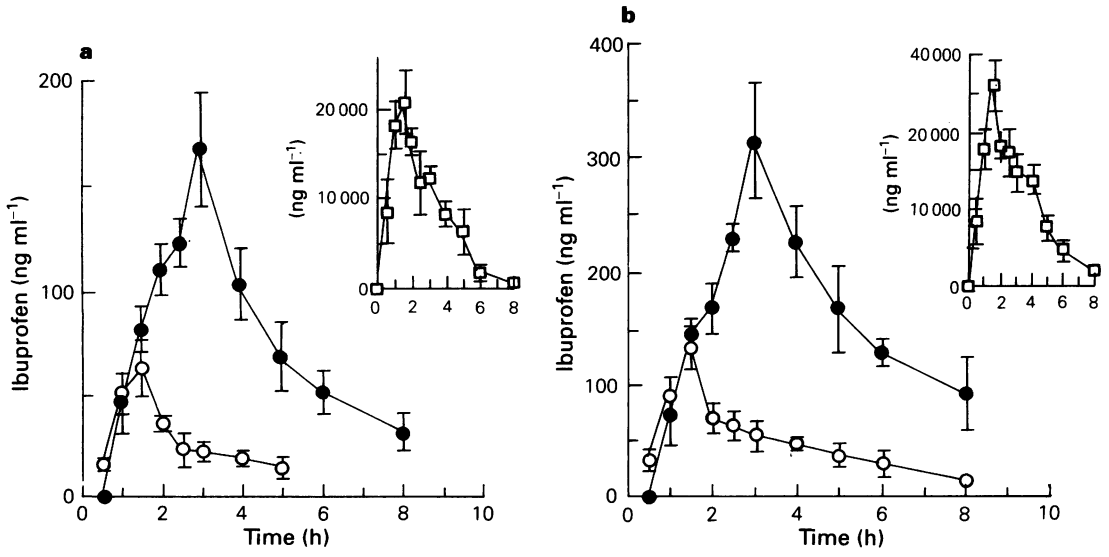


**Figure 1** Mean ± s.e. mean unbound plasma (○) and CSF (●) concentrations *vs* time curves for a) (R)- and b) (S)-ibuprofen after an oral dose of 800 mg *rac*-ibuprofen. Insets: total plasma concentrations of (R)- and (S)-ibuprofen.

**Table 1** Pharmacokinetic parameters of ibuprofen enantiomers in plasma and CSF following administration of 800 mg *rac*-ibuprofen to 46 patients

| *Parameters* | *Plasma* | | *CSF* | |
|---|---|---|---|---|
| | *R (−)* | *S (+)* | *R (−)* | *S (+)* |
| $f_u$ | 0.002 ± 0.001 ($n$ = 37) | 0.005 ± 0.002 ($n$ = 43) | | |
| $C_{max}$ (ng ml$^{-1}$) | 20712 ± 7035 | 26103 ± 6391 | 168 ± 61 | 315 ± 116 |
| $Cu_{max}$ (ng ml$^{-1}$) | 63 ± 28 | 133 ± 39 | | |
| $t_{max}$ (h) | 1.5 | 1.5 | 3 | 3 |
| $t_{1/2}$ (h) | 1.7 [1.4–2.3] | 2.5 [1.9–3.8] | 3.9 [2.7–7.0] | 7.9 [4.2–75.2] |
| AUC(0,8 h) (ng ml$^{-1}$ h) | 65470 | 85547 | 595 | 1241 |
| $AUC_u$(0,8 h) (ng ml$^{-1}$ h) | 164 | 375 | | |

$f_u$ = unbound fraction. Values are given as mean ± s.d. except $t_{max}$ which is the median. 95% confidence intervals are given in brackets.

peaked at lower concentrations in the CSF than in the plasma. The estimated elimination half-lives of both enantiomers appeared to be more rapid in plasma than in the CSF. The $AUC_{CSF}/AUC_{total\ plasma}$ ratios were 0.009 and 0.015 for the (R)- and the (S)- forms, respectively.

In view of the low protein content of the CSF, drugs are usually assumed to be largely in the unbound form in this compartment [7]. Subsequently, the CSF concentrations were compared with the corresponding unbound plasma concentrations (Figure 1). As such, the CSF concentrations of both enantiomers were higher than their concurrent free plasma concentrations from 1.5 to 8 h. Finally, the $AUC_{CSF}/AUC_{free\ plasma}$ ratios were 3.6 and 3.3 for the (R)- and (S)-forms, respectively.

## Discussion

After a single oral dose of *rac*-ibuprofen, the concentration-time curves of (R)- and (S)-enantiomers in the CSF lag behind those in plasma. This pattern is compatible with a mechanism of drug transfer across the blood-brain barrier being primarily passive diffusion [7, 9, 10]. Accordingly, the lipophilicity of the drug plays a major role in its rate of entry into the CSF [7, 9, 11]. Both (R)- and (S)-ibuprofen, which necessarily have the same oil-water partition coefficient, are highly lipophilic. The logarithm of their n-octanol-water partition coefficient (log P) was reported to be equal to 3.51 [12]. The $AUC_{CSF}/AUC_{plasma}$ ratio quantifies the overall drug transit from plasma to CSF in single dose studies [10]. As these ratios were threefold higher than the corresponding plasma unbound fraction ($f_u$) for both enantiomers, they appear to enter the CSF in relatively large amounts.

The CSF concentrations of (R)- and (S)-ibuprofen exceeded free plasma concentrations from 1.5 h. This phenomenon has already been described after a single administration of other drugs, including NSAIDs [9, 10]. It may be related to the slower disappearance of drugs from the CSF as compared with their elimination from the central compartment [10, 11]. Furthermore, ibuprofen enantiomers may be partly bound to proteins in the CSF, as previously reported for indomethacin [13]. Thus, the CSF concentrations may be higher than the free plasma concentrations at equilibrium [13].

Our study does not allow any direct conclusion to be drawn regarding the possible central beneficial or detrimental effects of ibuprofen enantiomers. Neither systemic nor intrathecal administration of (R)-ibuprofen was effective on hyperalgesia elicited by subcutaneous injection of formalin in rats [14]. On the other hand, experimental and clinical data suggest strongly that the (S)-form displays a central analgesic activity [2, 14]. Interestingly, the time-course of ibuprofen enantiomers in the CSF resembles that of their pharmacodynamics in febrile children [1].

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