Stereoselective disposition of indoprofen in surgical patients

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- 1 The pharmacokinetics of the enantiomers of indoprofen were determined after intravenous administration of the racemate to 10 surgical patients.
- 2 The mean volume of distribution was 8.97 ± 2.21 (s.d.) l for the pharmacologically active S(+)-enantiomer and 12.60 ± 4.21 l for the R(–)-enantiomer ($P < 0.001$).
- 3 The corresponding values for clearance were 32.2 ± 11.1 ml min⁻¹ and 48.8 ± 15.5 ml min⁻¹ ($P < 0.001$).
- 4 There was no significant difference in mean terminal half-life between the enantiomers.

Keywords indoprofen stereochemistry stereoselective disposition

Introduction

Indoprofen, 2-(4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)phenyl)-propionic acid, is a nonsteroidal anti-inflammatory drug (NSAID) used, in its racemic form, as a general analgesic agent (Bruni *et al.*, 1980). The pharmacokinetics of racemic indoprofen have been investigated (Fuccella *et al.*, 1973; Tamassia *et al.*, 1976; Caruso *et al.*, 1977). Of the two enantiomers, only the S(+)-isomer is pharmacologically active (Buttinoni *et al.*, 1983). It is therefore of interest to study the stereoselective disposition of indoprofen. A preliminary pharmacokinetic study in one subject (Tosolini *et al.*, 1974) showed that the S(+)-isomer is cleared more slowly than the inactive R(–)-isomer. A later study in six male, healthy volunteers (Tamassia *et al.*, 1984) substantiated this finding and showed, in addition, that the pharmacokinetic behaviour of the S(+)-enantiomer was the same when it was given as part of a racemic mixture as when it was given alone. However, since indoprofen was given orally, the only pharmacokinetic parameters that could be calculated for the enantiomers were $C_{\max}$, $t_{\max}$, area under the curve and terminal half-life. This paper presents the pharmacokinetics of the indoprofen enantiomers after intravenous administration, which allows the calculation of clearance and volume of distribution. Also, since the drug was given to surgical patients of varying age and body constitution, an indication could be obtained of the inter-

individual differences in the stereoselective disposition of indoprofen.

Methods

Blood samples were drawn from surgical patients undergoing cholecystectomy. The study was approved by the Ethics Committee of the University of Lund and by the Drug Division of the National Social Welfare Board. Informed consent was given by all patients. Eligible for inclusion in the study were patients of both sexes above 18 years of age. Patients with duodenal or gastric ulcer, hepatic or renal insufficiency, blood dyscrasias or coagulation disorders, severe concomitant disease, pregnancy or known allergy to anti-inflammatory drugs were excluded.

Surgery was performed under enflurane/nitrous oxide/oxygen anaesthesia after induction with thiopentone, 3–5 mg kg⁻¹. On recovery, racemic indoprofen, 400 mg, was given over 1 min as an intravenous injection. At the times indicated in Figure 1, blood samples (5–10 ml) were drawn from a peripheral vein into heparinized Venoject® blood collecting tubes. The plasma was collected after centrifugation of the samples and stored at –20°C until analysis.

The enantiomers of indoprofen were determined in the plasma samples by means of h.p.l.c. (Björkman, 1985). In brief, indoprofen and the

internal standard, indobufen, the butyric acid analogue of indoprofen, were extracted with diethyl ether after acidification of the plasma. On evaporation of the solvent, the extract was treated successively with ethyl chloroformate in acetonitrile/triethylamine and leucinamide in methanol to give diastereoisomeric indoprofen/indobufen leucinamide derivatives. Separation and quantitation of the derivatives were done on a 250×4 mm RP-18 column eluted with 38% acetonitrile in phosphate buffer, pH 6.5. Detection was by u.v. at 275 nm. The detection limit of the method is approximately 0.1 mg l^{-1} and its coefficient of variation is 1.0–1.3%, determined at 3.13 and 12.5 mg l^{-1} of each indoprofen enantiomer.

The plasma concentration curves were uniformly biphasic. For each curve, the area under the curve (AUC) from 0–10 h was calculated by the trapezoidal rule, and the residual 10 h to infinity by division of the plasma concentration at 10 h by the terminal elimination constant λ_z . The terminal half-life, $t_{1/2,z}$, and its corresponding rate constant, λ_z , were given by a regression line fitted to at least five datapoints. Total body clearance was calculated as dose/AUC and the apparent volume of distribution as clearance/ λ_z .

Results

The major pharmacokinetic parameters of S(+)- and R(-)-indoprofen are given in Table 1 and the mean plasma concentration curves are shown in Figure 1. Addition of the curves for the enantiomers gives pharmacokinetic parameters for the racemate which are consistent with previously reported results.

The S(+)-enantiomer had a significantly lower volume of distribution in all patients. The S(+)-enantiomer also had a lower total clearance than the R(-)-enantiomer in all patients, and the concentration ratio of S(+)- to R(-)-enantiomer increased with time also when distribution equilibrium had been achieved. There was no significant difference in terminal half-life between the enantiomers.

Discussion

The differences in clearance and volumes of distribution between the two enantiomers are consistent with the differences in the areas under the curves reported by Tosolini *et al.* (1974) and Tamassia *et al.* (1984). A stereoselective clearance of an NSAID can be due to a stereoselective

elimination, to an inversion of R(-)-enantiomer to S(+)-enantiomer or to a combination of both. Stereospecific inversion of R-2-arylpropionic acids, notably ibuprofen (Wechter *et al.*, 1974; VanGiessen & Kaiser, 1975; Kaiser *et al.*, 1976), benoxaprofen (Bopp *et al.*, 1979; Simmonds *et al.*, 1980) and fenoprofen (Rubin *et al.*, 1985) to the S-enantiomers has been demonstrated to occur *in vivo* in humans. The net change in enantiomer ratio can be expressed as a half-life, after which the ratio has changed from 1:1 to 3:1 by the real or apparent inversion of half the amount of R(-)-enantiomer. This inversion half-life can be estimated at around 10 h for ibuprofen (VanGiessen & Kaiser, 1975) and for benoxaprofen it is a biphasic process with a terminal half-life of 108 ± 3 h (Simmonds *et al.*, 1980). The inversion of fenoprofen is so rapid that sometimes only the S(+)-enantiomer can be detected in plasma after oral administration of the racemate (Rubin *et al.*, 1985). Stereoselective inversion of indoprofen does not take place in man (Tamassia *et al.*, 1984) or in rats (Buttinoni *et al.*, 1983), and thus the apparent inversion half-life of indoprofen (50–60 h in the λ_z -phase of the curve) reflects a stereoselective elimination.

The elimination half-life of a drug is a function of clearance and distribution volume ($t_{1/2} = 0.693 V/CL$). For the indoprofen enantiomers, the differences in V and clearance tend to cancel each other out, and there was, in this study, no significant difference in elimination half-life between them. In contrast, Tamassia *et al.* (1984) found a slightly but significantly longer terminal half-life of the S(+)-enantiomer in their male volunteers. This discrepancy is probably accounted for by the different number of subjects in the two studies. If patients 1 and 10 had not participated in the present study, a highly significant difference in $t_{1/2}$ would have been found.

In spite of the wide range of ages and weights of the patients, the interindividual variation in the V ratios of the enantiomers was small, with a relative standard deviation of 12%. The same holds true for the clearance ratios, for which the relative s.d. was only 9%. Indoprofen is cleared virtually exclusively by glucuronidation (Fuccella *et al.*, 1973). There is no important age-dependent reduction in this reaction (Caruso *et al.*, 1977). Nor, as is shown here, does its stereoselectivity change with age.

The results of this work should be compared to the data available on some other anti-inflammatory drugs. A pharmacokinetic study on carprofen in three subjects (Stoltenborg *et al.*, 1981) showed a higher V and clearance for the R(-)-enantiomer and no clear difference in

Table 1 Pharmacokinetic parameters of the indoprofen enantiomers in 10 patients.

Patient	Age (years) and sex	Weight (kg)	Distribution volume, (l)		Clearance (ml min^{-1})		Half-life (min)		Ratio
			(+)	(-)	(+)	(-)	(+)	(-)	
1	86 F	67	9.85	16.75	27.0	36.0	253	322	0.79
2	61 F	59	6.37	8.08	16.1	22.7	275	247	1.11
3	57 M	87	9.05	12.01	34.1	48.2	184	172	1.07
4	62 F	61	7.56	9.70	34.7	52.8	151	127	1.19
5	40 F	75	6.98	9.30	25.7	41.6	188	155	1.21
6	31 F	60	7.44	9.12	27.4	44.1	188	143	1.31
7	25 F	57	7.58	9.06	33.3	51.9	158	121	1.31
8	67 F	70	11.20	15.12	34.1	51.3	227	204	1.11
9	22 F	54	10.31	17.12	30.4	56.1	234	211	1.11
10	60 M	72	13.39	19.73	59.4	82.9	156	165	0.95
Mean	51	66	8.97	12.60	32.2	48.8	201	187	1.12
s.d.	± 20.7	± 10.1	± 2.21	± 4.21	± 11.1	± 15.5	± 43.4	± 61.7	± 0.158
P^a			< 0.001			< 0.001		0.2	
P^b			< 0.05			< 0.05		0.6	

^a Student's *t*-test for paired samples.^b Student's *t*-test for unpaired samples.

Figure 1 Plasma concentration curves of the S(+)-enantiomer (▲) and R(-)-enantiomer (■) of indoprofen in ten patients. The bars show the standard deviation in each point. The inserted curve is a semi-logarithmic plot of S(+)- to R(-)-enantiomer ratio vs time.

terminal half-life between the enantiomers. A study on benoxaprofen in two volunteers gave analogous results (Bopp *et al.*, 1979). Ibuprofen, in a study on three subjects, showed a substantial difference in half-life between the S(+)-enantiomer (3.3 h) and the R(-)-enantiomer

(2.0 h), which at least in part was due to the rapid inversion of the latter isomer (VanGiessen & Kaiser, 1975). With fenoprofen, this inversion is very rapid (Rubin *et al.*, 1985). Thus, in all NSAID:s of the 2-arylpropionic acid type that have been studied so far, the active S(+)-enantiomer has the higher AUC and persists longer in the blood plasma than the inactive R(-)-enantiomer. The underlying pharmacokinetic reasons may, however, be different, and it is clear that each drug must be studied separately on a sufficient number of patients or volunteers.

In conclusion, in this group of surgical patients the enantiomers of indoprofen showed consistently different clearances and volumes of distribution and no significant differences in terminal half-life. In spite of the very heterogeneous patient sample, the inter-individual variations in stereoselectivity of indoprofen disposition were small.

The blood samples were taken during an unpublished clinical trial on indoprofen conducted by Drs Nils H Persson (Department of Surgery) and Lars Gisselsson (Department of Anaesthesiology) at Malmö General Hospital.

The skilful technical assistance of Miss Ulla Jönsson is gratefully acknowledged.

The indoprofen was a gift from Farmitalia Carlo Erba AB (Täby, Sweden).

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(Received 9 April 1985,
accepted 4 July 1985)