Pharmacological differences between the optical isomers of ibuprofen: evidence for metabolic inversion of the (—)-isomer

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Ibuprofen, 2-(4-isobutylphenyl)propionic acid, possesses an asymmetric carbon atom and can therefore occur either as the (+)- or (−)-isomer. It has been claimed by some workers that biological activity in certain other substituted phenylpropionic acids resides almost entirely in the (+)-isomer (Shen, 1967; Ham, Cirillo & others, 1972; Takeguchi & Sih, 1972; Tomlinson, Ringold & others, 1972; Greig & Griffin, 1975). The resolution of the drug was carried out with (−)-1-phenethylamine (Adams, Cliffe & others, 1967; Brooks & Gilbert, 1974). The (+)-isomer is believed to have the *S* configuration (Wechter, Loughhead & others, 1974). The purpose of this study has been to determine the contribution that the isomers of ibuprofen make to the activity of the normal compound, which is a racemic mixture.

Several groups of workers have shown that the ability of non-steroidal anti-inflammatory compounds to inhibit various prostaglandin synthetase systems *in vitro* bears a semi-quantitative relation to their ability to exert anti-inflammatory, analgesic and antipyretic actions *in vivo* (Ham & others, 1972; Takeguchi & Sih, 1972; Tomlinson & others, 1972; Flower, Gryglewski & others, 1972). Our own experience with selected members of the substituted phenylalkanoic acid series of anti-inflammatory compounds, using a bovine seminal vesicle microsomal preparation (BSVM) of prostaglandin synthetase *in vitro*, has shown that this relationship is extremely good. We have therefore examined the ability of ibuprofen and its isomers to inhibit this prostaglandin synthetase system.

The method and conditions of incubation used were identical to those of Tomlinson & others (1972) except that, because of the high potency of our enzyme preparation, we incubated substrate and enzyme for only 8 min instead of 1 h. We also introduced a 5-min preincubation period for drug and enzyme before adding [^{14}C]arachidonate substrate to the reaction mixture. Enzyme inhibition by drugs was measured by a decrease in the formation of [^{14}C]PGE_2.

The results in Table 1 indicate that the (+)-isomer was highly active but that very little activity occurred in the (−)-isomer. However, this large difference in potency between the two isomers was not found *in vivo* when they were compared simultaneously with the racemic substance in anti-inflammatory and analgesic tests. The experimental models used (Adams, McCullough & Nicholson, 1969) were ultraviolet erythema in the guinea-pig, acetylcholine-induced writhing in mice, and the pain threshold technique using the yeast-inflamed foot of the rat; the compounds were administered by mouth in suspension in either 10% acacia or 0·25% cellosize. The results shown in Table 2 indicate that, although there is a suggestion that the (+)-isomer may be marginally more potent than the (−)-isomer, there is in fact no significant difference between the potencies of the isomers and that of the racemic mixture.

Table 1. *Inhibitory potencies of ibuprofen and its optical isomers in a prostaglandin synthetase system* in vitro.

Compound	Prostaglandin synthetase enzyme system (BSVM[a]) ID50[b]	Potency
Ibuprofen	$8{\cdot}4 \times 10^{-5}$M	1
(−)-isomer	$8{\cdot}6 \times 10^{-3}$M	0·01 approx.
(+)-isomer	$5{\cdot}2 \times 10^{-5}$M	1·6 approx.

[a] Bovine seminal vesicle microsome preparation.
[b] The molar concentration which inhibits prostaglandin synthesis by 50%.

Table 2. *Relative pharmacological potencies of ibuprofen and its optical isomers after oral administration.*

Compound	Acetylcholine writhing (mouse)	Pain threshold (rat)	Ultraviolet erythema (guinea-pig)
Ibuprofen	1	1	1
(−)-isomer	0·90 (0·55–1·47)	0·87 (0·16–4·77)	1·07 (0·74–1·54)
(+)-isomer	1·24 (0·81–1·91)	1·25 (0·22–7·18)	1·20 (0·79–1·82)

95% confidence limits in parentheses.

Thus we have concluded that *in vivo* there is an almost complete inversion of the poorly active (−)- form to the much more active (+)-isomer in the three animal species used, i.e. the mouse, the rat and the guinea-pig.

An early observation by Adams & others (1967) that the human urinary metabolites of ibuprofen were dextrorotatory suggested that inversion might also occur in man, although later there was some indication that the inversion was incomplete (Mills, Adams & others, 1973). Recently, however, Wechter & others (1974) and VanGiessen & Kaiser (1975) have shown quite conclusively that in man the (−)-isomer is converted to the (+)-form.

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The plasma elimination of the enantiomers of phenprocoumon in man

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Like warfarin, the oral anticoagulant phenprocoumon (3-(α-ethylbenzyl)-4-hydroxycoumarin) is used clinically as the racemic mixture of the *R*-(+)- and *S*-(−)-enantiomers. In rats *S*-phenprocoumon is 3 to 5 times more potent than *R*-phenprocoumon as an anticoagulant (Eble & Barker, personal communication cited in West & Link, 1965) and has been reported to undergo slower urinary excretion (Goding & West, 1969). However, since no studies with the enantiomers have been reported in man, we have examined the plasma elimination of *R* and *S*-phenprocoumon in young male volunteers (aged 24 to 32 years).

The enantiomers ($[\alpha]_D^{20}$ + 98·4° and −117·3°; c2 95% ethanol) were prepared according to the method of West & Link (1965). Each subject was given 50 mg of *R*-phenprocoumon together with 50 mg vitamin K_1. Further vitamin K_1 (20 mg) was given on alternate days for 9 days. The same procedure was followed with *S*-phenprocoumon. All drugs were given orally. Plasma phenprocoumon was determined by the method of Lewis, Ilnicki & Carlstrom (1970). This spectrophotofluorimetric method originally developed for the assay of warfarin was found to be also satisfactory for assaying phenprocoumon. Under the assay conditions used the relative fluorescence intensity of phenprocoumon was about three times that of warfarin. The plasma samples were also analysed qualitatively; dichloroethane extracts of acidified plasma being examined using the thin-layer chromatographic systems developed by Haddock, Trager & Pohl (1975) for the separation of phenprocoumon and its hydroxylated metabolites. Chromatographic loci were located by viewing under ultraviolet light.

Qualitative thin-layer chromatographic analysis of plasma after phenprocoumon administration revealed chromatographic loci corresponding only to phenprocoumon; no metabolites were detected (this result was in marked contrast to findings in male rats where large amounts of plasma phenprocoumon metabolites were detected; unpublished observation).

Table 1 shows that there is no significant difference between the respective plasma half-lives or apparent volumes of distribution of the *R* and *S* enantiomers. However, the plasma clearances calculated from these values indicated that *R* is cleared slightly faster than *S*-phenprocoumon ($P < 0{\cdot}025$, paired *t*-test).

Therefore, in man there appears no marked difference between the pharmacokinetic properties of *R* and *S* phenprocoumon, and our mean values for the plasma half-lives of the enantiomers are in reasonable agreement with a mean value of about 156 h reported by Sieler & Duckert (1968) for racemic phenprocoumon. In comparison, the enantiomers of warfarin, which are structurally related to phenprocoumon, show a difference in plasma half-life and clearance; *S*-warfarin is cleared 40 to 70% faster than *R*-warfarin (Hewick &