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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was in marked contrast to findings in male rats where large amounts of plasma phenprocoumon metabolites were detected; unpublished observation).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 &

Table 1. *Pharmacokinetics of* R *and* S*-phenprocoumon in man after single oral dosing (50 mg).*

Subject	Weight (kg)	Enantiomer	Half-life* (h)	Zero-time plasma concn* (mg litre^{-1})	Apparent volume of distribution* (% body wt)	Clearance† (ml min^{-1} kg^{-1})
I	71	*R*	93	8·9	7·9	0·0098
		S	145	8·9	7·9	0·0062
II	77·7	*R*	101	6·3	10·2	0·0116
		S	104	9·1	7·1	0·0079
III	74	*R*	82	8·3	8·1	0·0116
		S	117	6·2	10·9	0·0110
IV	71	*R*	133	7·2	9·8	0·0085
		S	241	8·5	8·3	0·0039
V	73	*R*	145	5·3	12·9	0·0103
		S	115	7·0	9·8	0·0098
Mean with s.d.		*R*	110·8 s.d. 26·9	7·2 s.d. 1·46	9·78 s.d. 2·02	0·0103 s.d. 0·0013‡
		S	144·4 s.d. 56·1	7·94 s.d. 1·27	8·8 s.d. 1·53	0·0076 s.d. 0·0028

Plasma phenprocoumon was determined according Lewis & others (1970).
* Determined as described by Hewick & McEwen (1973).
† Calculated by dividing apparent volume of distribution (ml kg^{-1}) by half-life (min) and multiplying by 0·693.
‡ Significantly different (paired *t*-test) from corresponding value for *S*-phenprocoumon.

McEwen, 1973; Breckenridge, Orme & others, 1974; O'Reilly, 1974).

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Accumulation of cGMP in striatum of rats injected with narcotic analgesics: antagonism by naltrexone

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The stereospecific binding of some narcotic analgesics to a protein present in different amounts in homogenates of various brain structures has many physicochemical features expected of a drug binding to a specific site. Since the affinity constant for this binding in many drugs relates to their analgesic activity, the concentration of such receptors in brain structures reflects a site for the specific action of narcotic analgesics (Pert & Snyder, 1973). Although the necessary criteria that define ligand recognition have been satisfied (Creese, Pasternak & others, 1975), the molecular mechanisms that are regulated by the binding of opiates to this receptor are still undefined. It is possible that opiate receptors can be identified with specific postsynaptic receptors for a transmitter which carries information concerning pain. When the distribution of the opiate receptor in various nuclei of the cns is compared with that of known neurotransmitters a certain similarity can be found between the distribution of GABA (γ-aminobutyric acid) or acetylcholine and that of the opiate receptor (Snyder & Pert, 1975).

That a specific transmitter, involved in the mediation of pain sensation may be the natural agonist for opiate receptors is suggested by the following considerations: