Pharmacokinetics of (+)-, (−)- and (±)-hexobarbitone in man after oral administration

Since Knabe & Kräuter (1965) separated hexobarbitone into its optical antipodes, some reports on the activity and on the fate of the isomers in animals have appeared. Considerable differences in anaesthetic potency were shown in rats (Wahlström, 1966; Rummel, Brandenburger & Büch, 1967; Wahlström, Büch & Buzello, 1970). The (+)-isomer is the more active and the more rapidly metabolized in this species (Furner, McCarthy & others, 1969; Degkwitz, Ullrich & others, 1969; Büch, Knabe & others, 1970). These results were confirmed by us while studying the pharmacokinetics of the antipodes in the same rat and in the same isolated perfused rat liver (Breimer & van Rossum, unpublished). Data on the activity or fate of the hexobarbitone antipodes in man have so far not been recorded.

We have studied the plasma disappearance rate of racemic hexobarbitone and its optical antipodes in the same subjects. The specifications of the compounds were (+)-hexobarbitone: $[\alpha]_D^{20}$ + 11·4° (ethanol), m.p. 153° — 154°; (−)-hexobarbitone: $[\alpha]_D^{20}$ — 11·2° (ethanol), m.p. 152 — 153·5°; (±)-hexobarbitone: no optical rotation, m.p. 142°–144°. The particle sizes of the individual pulverized compounds were in the same range. The subjects were five healthy male volunteers (aged 20 to 25 years), who had not taken any drug for several days before administration of the compounds. The trials began in the morning after the subjects had been fasting overnight and 400 mg of each compound in powder form was administered orally together with 200 ml water. The interval between two consecutive experiments for each individual was at least two weeks. Blood samples were taken by venepuncture at 0·5, 1·0, 1·5, 2·0, 3·0, 4·0, 5·0, 7·0, 9·0 and 11·0 h after intake of drug. Plasma concentrations were determined by gas chromatography with nitrogen selective detection (alkali flame ionization detector, Hewlett and Packard); in this way concentrations as low as 50 ng ml^{-1} plasma can be measured. Details of the analytical procedure will be published elsewhere.

From Fig. 1 it can be concluded that the elimination of the three compounds from the body occurs according to a first-order process. The plasma half-lives can be determined from the descending part of the curves and are given in Table 1.

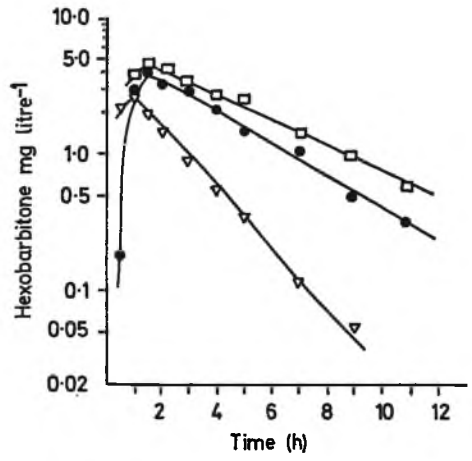

FIG. 1. Hexobarbitone plasma concentration curves on a semilogarithmic scale after oral administration of (+)-, □; (−)-, ▽ and (±)-hexobarbitone, ● (400 mg) to the same subject (IV). $t_{\frac{1}{2}}$ values. (+) = 3·5 h, (−) = 1·4 h, (±) = 2·6 h.

Table 1. *Plasma half-lives (h) of* (+)-, (−)- *and* (±)-*hexobarbitone in subjects I–V.*

Compound	I	II	III	IV	V	Mean
(+)	6·3	4·7	4·0	3·5	4·3	4·6
(−)	1·6	1·6	1·3	1·4	1·3	1·4
(±)	4·3	5·0	3·8	2·6	4·0	4·0
Ratio (+): (−)	3·9	2·9	3·1	2·5	3·3	3·2

It is evident that in man the (−)-hexobarbitone is eliminated much faster than the (+)-isomer, the mean half life ratio (+):(−) being 3·2. In rats the reverse occurs with the (+)-isomer being eliminated the faster.

Hardly any hexobarbitone is excreted unchanged in urine or faeces and there is no reason to assume that there will be a significant difference in apparent volume of distribution for the antipodes in the same subject. Therefore the differences in half life must be explained on the basis of a difference in rate of metabolism. The metabolic clearance constant for (−)-hexobarbitone in man must be approximately three times greater than for (+)-hexobarbitone. After intravenous infusion of racemic hexobarbitone sodium into man the value of this constant for the racemate was found to be approximately 250 ml min^{-1} (Breimer & van Rossum, unpublished). The much higher metabolic clearance for (—)-hexobarbitone makes a substantial "first-pass" effect for this compound very probable after oral administration (Rowland, 1972). Evidence in that direction can be deduced from the curves in Fig. 1, provided that the amount absorbed of the two antipodes has been the same.

The shape of the curve for the racemic mixture is interesting. While the (−)-isomer contributes to the elimination in the first few hours, this is also the time in which absorption takes place, the pure elimination phase having not yet been reached. The calculated half-lives are based on the points 2–3 h after administration and it can be deduced from the curves that in the period between 3 and 11 h, the plasma concentration of the (−)-, compared with the (+)-, isomer is so low that it hardly makes any contribution to the curve of the racemate.

With respect to hypnotic potency in man, the subjects experienced a very clear central depressive effect lasting for a few hours after 400 mg (+)-hexobarbitone, whereas after (−)-hexobarbitone hardly any effect was noticed. Although it seems likely that in man the (+)-isomer has a greater activity than the (−)-isomer, as is the case in rat, one must be aware of the fact that the above observation might also be explained on the basis of the differences in disappearance rate between the two isomers in man.

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