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Serum tocainide enantiomer concentrations in human subjects

Tocainide (2-amino-2',6'-propionoxylidide hydrochloride) is a new antiarrhythmic agent often effective in the treatment of life-threatening arrhythmias in man (Zipes & Troup, 1978; Sonnhag, 1980). The chemical structure of tocainide includes an asymmetric centre and the drug is used clinically in the racemic form. Although the antiarrhythmic properties of the tocainide enantiomers have not been studied in man, the R−(−) enantiomer is three times more potent than the S−(+) isomer as an antiarrhythmic agent in a mouse model (Byrnes *et al.*, 1979) and smaller differences in antiarrhythmic activity between the enantiomers have been demonstrated in coronary-ligated dogs (Byrnes *et al.*, 1979). In addition, stereoselective metabolism and renal excretion of tocainide in mice and rats also has been reported recently (Gal *et al.*, 1982). These reports prompted us to examine if differences in tocainide enantiomer pharmacokinetic and pharmacologic behaviour could complicate interpretation of total tocainide serum concentrations measured in human subjects.

Serum samples were obtained over a 3-year period from seven subjects at the Mayo Clinic, who were enrolled into an experimental protocol for the emergency administration of tocainide hydrochloride (Maloney *et al.*, 1980). All subjects had life-threatening ventricular arrhythmias which were unresponsive to conventional therapy. Serum tocainide concentrations were obtained at physician discretion, and tocainide enantiomer concentrations determined by a modification (Sedman & Gal, 1983) of a previously reported gas-liquid chromatographic procedure (Gal *et al.*, 1982).

Therapeutic total tocainide serum concentrations of 4–12 μg/ml (21–63 μmol/l) (Winkle *et al.*, 1978; Woosley *et al.*, 1977) were obtained in all patients (Table 1), utilizing racemic tocainide doses of 15–50 mg kg^{-1} day^{-1}. Ratios of S−(+) tocainide to R−(−) tocainide ranged from 1.3:1 to 4 : 1 in these same patients and intrasubject variability of enantiomer ratio was nearly as large as the variability between subjects. Clinical parameters such as tocainide dosage, other medications, or degree of congestive heart failure, renal failure or hepatic dysfunction, did not explain enantiomer variability, although the number of patients studied may be too small to elaborate such differences.

The results of this study demonstrate a large intra- and intersubject variability of tocainide enantiomer ratios and suggests that patients with identical, therapeutic total tocainide serum concentrations may have markedly different amounts of each enantiomer in their serum. For example, if the range of S−(+):R−(−) tocainide enantiomers of 1.3:1 to 4 : 1 is representative of that found in most patients, the amount of R−(−) enantiomer present at any total tocainide concentration may vary by up to 2.2 fold. There was no direct relationship observed between the total amount of tocainide and the S−(+):R−(−) ratio.

Since previous animal work (Byrnes *et al.*, 1979) suggests that tocainide antiarrhythmic activity may reside primarily with the R−(−) enantiomer, the large variability of tocainide enantiomer ratio would seem to preclude a high correlation of total tocainide serum concentration with therapeutic effect. The broad range previously reported for total tocainide therapeutic serum concentrations, 4–12 μg/ml, may be a result of this phenomenon and correlation of antiarrhythmic effect with the concentration of the active enantiomer (if only one enantiomer is active) would presumably improve therapeutic drug monitoring.

The drug, tocainide, was administered as a 1 : 1 (racemic) mixture of two enantiomers. After prolonged tocainide administration, the ratios of the two stereoisomers were markedly different than 1 : 1, thereby suggesting differences in enantiomer pharmacokinetics. Stereoselective differences in tocainide metabolism and/

Table 1 Tocainide serum concentrations in human subjects

Patients	*Sample day*[a]	*Tocainide dose* (*mg kg* $^{-1}$ *day*$^{-1}$)	*Total tocainide concentration*[b] (*μg/ml*)	*Ratio of tocainide enantiomers* (*S*−(+)/*R*−(−))
1	1	29	6.0	2.3
	4	29	10.5	2.1
	8	29	12.4	2.1
	35	24	6.0	3.8
	69	24	7.5	3.0
	138	22	8.2	2.5
2	9	25	10.3	1.4
	21	25	7.8	1.3
	71	25	6.7	1.8
	104	25	9.2	2.1
	132	25	10.5	1.7
3	585	15	5.9	2.0
	589	15	4.8	4.0
	683	15	5.0	2.0
4	417	27	9.8	1.6
	508	27	15.0	1.5
	577	31	12.7	1.5
5	173	22	5.6	1.5
	289	22	8.0	1.5
	365	30	7.4	1.6
6	3	32	9.2	2.1
	45	50	11.5	1.7
7	931	20	10.3	2.3

[a] Number of days patient had received tocainide
[b] Determined as described in text. Correlation with values determined by the method of Reece & Stanley (1980) was $y = 0.94x + 0.05$, $r = 0.96$.

or renal excretion (Gal *et al.*, 1982) are probably responsible for the change in enantiomer ratio, since the protein binding of the two stereoisomers is essentially the same (Sedman *et al.*, 1982), and enantiomeric differences in absorption and volume of distribution are unlikely. Therefore, disease states such as congestive heart failure and renal or hepatic dysfunction may alter the stereoselective elimination of tocainide and further complicate interpretation of total serum tocainide concentrations.

The clinical applicability of these findings and suppositions will depend on further studies which will define the pharmacological and pharmacokinetic behaviour of each stereoisomer in healthy subjects and those with disease states that influence tocainide disposition.

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