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The pharmacokinetics of R- and S-tocainide in patients with acute ventricular arrhythmias

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1 The pharmacokinetics of R(−) and S(+)- tocainide were studied in twelve patients requiring intravenous tocainide.

2 In all patients, a progressive increase in the S(+) : R(−) ratio was observed during the infusion. Mean ± s.d. ratios increased from 1.03 ± 0.05 at 2 min to 1.76 ± 0.35 at 48.5 h.

3 Data from eight patients were fitted to a two-compartment model and there was a significant difference (Wilcoxon matched-pairs test $P < 0.01$) in the clearance estimates for the two enantiomers. The median values were: S(+)- tocainide = 6.25 l h^{-1} and R(−)-tocainide = 9.31 l h^{-1}. There were no differences in V_1 or V_{ss}.

Keywords tocainide enantiomer pharmacokinetics antiarrhythmic drugs

Introduction

Drugs with Class 1B antiarrhythmic activity such as lignocaine remain the standard form of therapy in the treatment of acute ventricular arrhythmias. Tocainide is an antiarrhythmic drug which is structurally related to lignocaine, but unlike lignocaine, it is suitable for oral administration because it is not subjected to first pass metabolism (Lalka *et al.*, 1976). In patients who are acutely ill, tocainide may be given initially by intravenous bolus injection followed by a maintenance infusion (Morganroth *et al.*, 1984).

As the tocainide molecule contains an asymmetric carbon atom (Figure 1), the drug exists as two optically active enantiomers — the S(+) form and the R(−) form. In clinical practice, the drug is administered as the racemic mixture, but little is known about the relative potencies of the two enantiomers in man. In the chloroform mouse test (Byrnes *et al.*, 1979), the R(−) enantiomer was found to be three times more active than the S(+) enantiomer. However, the activities were similar in the coronary ligated dog preparation (Byrnes *et al.*, 1979).

Differences in the disposition of S(+) and R(−) tocainide have been demonstrated in both animals and man. Using rats and mice, Gal *et al.* (1982) showed differences in the elimination of the two isomers and stereoselective differences in clearance and volume of distribution were observed in a group of twelve healthy male volunteers (Edgar *et al.*, 1984). Examination of the S(+) : R(−) ratio in seven patients receiving tocainide for the treatment of ventricular arrhythmias, revealed that there was considerable inter- and intra-subject variability, with ratios ranging from 1.3 : 1 to 4 : 1 (Sedman *et al.*, 1984).

The stereoselective metabolism of tocainide has been explored further in the present study. The pharmacokinetics of S(+) and R(−) tocainide have been examined in twelve patients receiving intravenous tocainide for the treatment of life-threatening ventricular arrhythmias.

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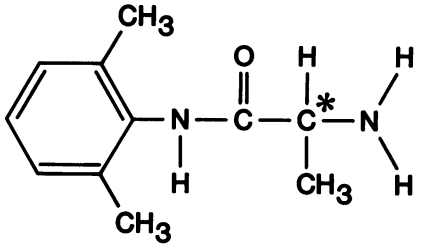

Figure 1 Structure of tocainide.

Methods

Patients

Twelve patients, seven male and five female, age range 45–81 years (mean 62 years), were studied. All patients had been admitted to the Coronary Care Unit (CCU) of Stobhill General Hospital. A decision to use parenteral antiarrhythmic therapy was made on the basis of arrhythmias observed during a period of electrocardiographic (ECG) monitoring; all patients had ventricular extrasystoles and three had ventricular tachycardia. Ischaemic heart disease was present in ten patients (three also sustained an acute myocardial infarction), one patient had rheumatic heart disease and one had cor pulmonale. Patients were excluded on the basis of cardiogenic shock, known allergy to amide-type local anaesthetics, hepatic or renal insufficiency, treatment with other Class I antiarrhythmics or concurrent illness which would have prevented adherence to the protocol. There were no restrictions placed on other relevant drug therapy. The study was approved by the Research and Ethics Committee of the Northern District of the Greater Glasgow Health Board and verbal consent was obtained from all patients prior to inclusion in the study.

Constant monitoring of the patients was performed in the Coronary Care Unit. Routine 12 lead ECGs and standard biochemical and haematological tests were also performed before and after drug administration. All adverse effects were recorded and heart rate and blood pressure were monitored routinely.

Drug administration

A 50% racemic mixture of tocainide hydrochloride (Tonocard, Astra) was given as a 250 mg bolus injection over 2 min, followed by an infusion of 500 mg over 30 min and then a maintainance infusion of 500 mg every 8 h for 48 h. A Tekmar infusion pump was used to deliver the drug. The infusion regimen was designed to achieve total tocainide steady state concentrations of 6 $\mu g\ ml^{-1}$ ('therapeutic range', 4–10 $\mu g\ ml^{-1}$) and was based on the data of Lalka *et al.* (1976). The infusion rate was altered (or stopped) if there were any adverse reactions which could be attributed to tocainide.

Blood samples and analysis

Blood samples (5 ml) were taken for analysis of S(+) and R(−) tocainide concentrations from an indwelling cannula (or by separate venepuncture) from the contralateral arm at the following times: predose, 2, 10, 20, 30, 45 and 60 min and at 2, 4, 8.5, 24.5, 32.5, 40.5 and 48.5 h after the start of the infusion. (Blood pressure and heart rate measurements were also made at these times). Samples were centrifuged immediately and the separated plasma was stored at −20°C prior to analysis. Concentrations of S(+) and R(−) tocainide were determined by a stereospecific gas chromatographic method (Antonsson *et al.*, 1984). The minimum detectable enantiomer concentration was 0.06 $\mu g\ ml^{-1}$.

Data analysis

Concentration-time data were fitted to both one-compartment (parameters k and V) and two-compartment (parameters λ_1, λ_2, k_{21} and V_1) pharmacokinetic models using a FORTRAN version of the extended least squares program ELSFIT (Sheiner, 1983). The equations used to model the data are shown in Appendix 1. The significance of any improvement in fit using the two compartment model was assessed by analysing the difference between the log likelihood values with the χ^2 test at a significance level of 0.05. Pharmacokinetic parameter estimates for S(+) and R(−) tocainide were compared by Wilcoxon matched-pairs test.

Results

Adverse effects and withdrawals

Four subjects were withdrawn from the study, either due to their clinical condition or because of adverse effects which could possibly be related to tocainide therapy. Details are given in Table 1. Patient number 2 who had been commenced on tocainide following a cardiac arrest associated with acute myocardial infarction, sustained a further cardiac arrest despite tocainide therapy and resuscitation was unsuccessful.

Table 1 Adverse effects and withdrawals

Patient	*Adverse effect*	*Time into infusion*	*S(+) concentration ($\mu g\ ml^{-1}$)*	*R(−) concentration ($\mu g\ ml^{-1}$)*
9	Hypotension	45 min	4.7	4.8
2	Cardiac arrest	1 h	3.6	3.5
7	Sweating-agitation	23 h	3.7	2.5
5	Bradycardia	41 h	3.5	2.1

Clinical and laboratory measurements

There were no significant differences in haematological or biochemical values before and after tocainide administration and there were no significant changes in heart rate or blood pressure other than those noted under adverse events.

Pharmacokinetic analysis

Data from all 12 patients were used in the analysis of the S : R ratio shown in Figure 2. As expected, the ratio was initially close to 1. However, it progressively increased in all patients during the course of the infusion (Figure 2) increasing from a mean (± s.d.) value of 1.03 ± 0.05 at 2 min to 1.76 ± 0.35 at 48 h.

Plasma concentration-time profiles of both the S(+) and R(−) enantiomers for eight of the 12 patients are shown in Figure 3. These data were used in the pharmacokinetic analysis. Two of the other four patients were excluded on the basis of insufficient data (numbers 2 and 9) and the other two patients (numbers 10 and 11) were excluded because technical problems with the infusion pumps led to uncertainty about the exact dosage input.

The data were found to be better fitted by a two-compartment model. Parameter estimates are shown in Table 2. In all patients the terminal rate constant (λ_2) was slower with the S(+) enantiomer than with the R(−) enantiomer and this difference was significant ($P < 0.01$). Estimated V_1 values and calculated V_{ss} values were essentially identical, but clearance values calculated from the fitted parameters were significantly different (Table 2).

The median pharmacokinetic parameters based on total tocainide concentrations (S(+) + R(−)) were as follows: $\lambda_1 = 9.67\ h^{-1}$, $\lambda_2 = 0.053\ h^{-1}$, $k_{21} = 2.06\ h^{-1}$ and $V_1 = 23.5$ l.

Discussion

The importance of distinguishing between optically active enantiomers in understanding pharmacokinetics and pharmacodynamics is now being recognised. Indeed, a recent review article criticised clinical pharmacological research

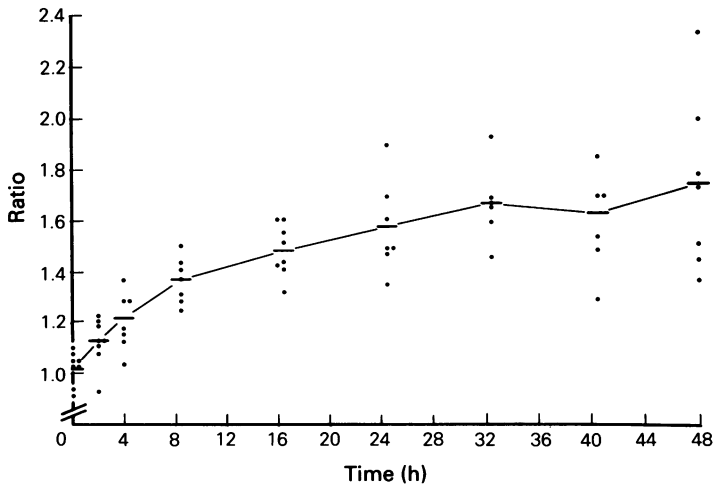

Figure 2 Ratio of S(+) to R(−) tocainide in all patients during infusion of a 50% racemic mixture of tocainide.

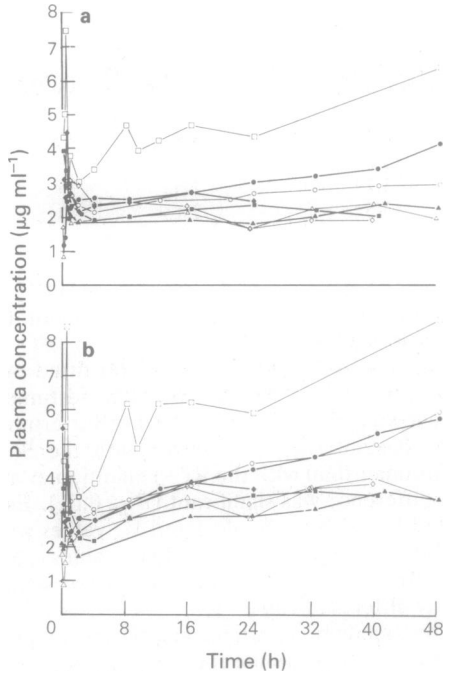

Figure 3 Plasma concentration-time profiles of (a) R(−) and (b) S(+)-tocainide in eight patients receiving tocainide infusion.

which failed to take into account the contribution of separate enantiomers to overall pharmacological response (Ariens, 1984) and studies with warfarin have previously emphasised the clinical importance of considering the enantiomers of a drug separately (Breckenridge *et al.*, 1974). Stereoselectivity in the disposition of tocainide has been observed in animal studies (Gal *et al.*, 1982) and to a limited extent, in human studies (Edgar *et al.*, 1984; Sedman *et al.*, 1984). The contribution of the separate enantiomers to clinical effect has not been established, however, and animal studies have produced inconclusive results (Gal *et al.*, 1982).

In this study, patients with acute ventricular arrhythmias were given tocainide by an infusion regimen designed to achieve and maintain concentrations within the therapeutic range for total tocainide. The parameters used to generate the infusion regimen were based on previous data from normal subjects (Lalka *et al.*, 1976), but even in this group of acutely ill patients, the total tocainide pharmacokinetic parameters compared well with Lalka's values (λ_1 = 3.14 h^{-1}, λ_2 = 0.06 h^{-1}, k_{21} = 2.22 h^{-1} and V_1 = 74.7 l, although the volume of the central compartment was much lower (24 l compared to 75 l). Mean

Table 2 Pharmacokinetic parameters for S- and R-tocainide

	S-tocainide						*R-tocainide*						
Patient	λ_1 (h^{-1})	λ_2 (h^{-1})	k_{21} (h^{-1})	V_1 (*l*)	V_{ss} (*l*)	*CL* (*l* h^{-1})	$t_{½}$ (*h*)	λ_1 (h^{-1})	λ_2 (h^{-1})	k_{21} (h^{-1})	V_1 (*l*)	V_{ss} (*l*)	*CL* (*l* h^{-1})	$t_{½}$ (*h*)
1	6.78	0.033	1.25	15.6	82.8	2.97	21.0	4.67	0.041	0.99	21.6	98.5	5.17	16.9
3	66.9	0.038	13.7	30.8	150	6.03	18.2	81.8	0.068	13.6	27.5	164	11.5	10.2
4	9.18	0.073	1.89	19.9	97.5	7.12	9.49	11.2	0.107	1.86	18.2	104	11.7	6.48
5	5.52	0.043	0.97	26.6	153	6.47	16.1	5.36	0.077	0.90	26.1	145	12.0	9.00
6	8.37	0.045	2.28	44.1	163	7.24	15.4	9.49	0.081	2.80	45.2	150	12.5	8.56
7	16.9	0.060	2.20	14.3	110	6.59	11.6	15.3	0.092	2.13	16.2	112	10.7	7.53
8	20.8	0.025	3.51	24.8	147	3.69	27.6	23.1	0.049	4.28	27.9	149	7.42	14.1
12	7.74	0.037	1.47	22.7	120	4.46	18.7	7.98	0.072	1.52	24.9	126	9.40	9.62
Median	8.77	0.041*	2.04	23.7	134	6.25*	17.1*	10.3	0.075*	1.99	25.5	136	11.1*	9.31*

* significant difference between S- and R-enantiomers $P < 0.01$

profiles of total tocainide (S(+) + R(−)) were within the therapeutic range.

Pharmacokinetic analysis of the S(+) and R(−) enantiomer data revealed higher clearance estimates for the R(−) compared to the S(+) enantiomer. No differences in volume of distribution were obtained however. These results conflict with those of Edgar *et al.*, (1984) who reported differences in both clearance and volume of distribution in a group of healthy volunteers. However, their results were based on the measurement of V_{area} whose calculation depends on an assessment of the elimination rate constant. In this study, kinetic comparisons were based on measurement of V_{ss} which does not depend directly on elimination. The clearance of the S(+) enantiomer in this patient group was similar to that observed in volunteers: 104 ml min^{-1} compared to 106 ml min^{-1} but the R(−) enantiomer clearance was slightly lower: 155 ml min^{-1} compared to 197 ml min^{-1}.

About 40–50% of a dose of tocainide is cleared unchanged by the kidney and about 30% is metabolized to the glucuronide of *N*-carboxytocainide (Elvin *et al.*, 1980). Two other metabolites, lactylxylidide (Ronfeld *et al.*, 1980) and tocainide oxime (Holmes *et al.*, 1983) have also been identified. Edgar *et al.*, (1984) showed that the renal clearances of the two enantiomers was essentially the same and Gal *et al.* (1982) demonstrated stereoselective elimination in animals. Stereospecific metabolism has therefore been proposed as a likely mechanism for differences in the disposition of S(+) and R(−) tocainide. Based on the data of Sedman *et al.* (1982), it is unlikely that protein binding differences contribute to the differences in the disposition of the enantiomers. S(+) tocainide was found to have slightly greater binding than R(−) tocainide but this was considered to be clinically insignificant.

In conclusion, this study has confirmed previously reported differences in the pharmacokinetics of S(+) and R(−) tocainide and identified the relevant parameters in a group of eight patients with acute ventricular arrhythmias. As yet, the clinical significance of changes in the S(+) : R(−) ratio has not been established and further studies will be required to identify stereoselective effects on activity and toxicity.

We would like to thank the nursing staff of the Coronary Care Unit, Stobhill General Hospital, for their help in this study. We also acknowledge the assistance of Astra Pharmaceuticals in the analysis of the blood samples and financial support from the British Heart Foundation.

Appendix 1

(a) One compartment model

$$C = \frac{R_o}{V.k}(1 - e^{-kt}) + \frac{A_{10}}{V} e^{-kt} \qquad (1)$$

where R_o = infusion rate
V = Volume of distribution
k = elimination rate constant
t = time
A_{10} = amount of drug in body at end of previous infusion ($A_{10} = 0$ at start of first infusion).

(b) two compartment model

(i) Equation for modelling contribution of 'current' infusion:

$$C_1 = \frac{R_o}{V_1}\left[\frac{k_{21}}{\lambda_1\lambda_2} - \frac{(\lambda_1 - k_{21})}{\lambda_1(\lambda_1 - \lambda_2)} e^{-\lambda_1 t} + \frac{\lambda_2 - k_{21}}{\lambda_2(\lambda_1 - \lambda_2)} e^{-\lambda_2 t}\right] \qquad (2)$$

(ii) Equation for modelling decline from end of previous infusion:

$$C_1^* = \frac{A_{10}}{V_1}\left[\frac{k_{21}-\lambda_1}{\lambda_2-\lambda_1} e^{-\lambda_1 t} - \frac{k_{21}-\lambda_2}{\lambda_2-\lambda_1} e^{-\lambda_2 t}\right] + \frac{k_{21}A_{20}}{(\lambda_2-\lambda_1)V_1} (e^{-\lambda_1 t} - e^{\lambda_2 t}) \qquad (3)$$

where concentration in central compartment during any infusion = $C_1 + C_1^*$

R_o = infusion rate
V_1 = Volume of central compartment
k_{21} = Intercompartmental rate constant
λ_1 = Rate constant during distribution phase
λ_2 = Terminal elimination rate constant
A_{10} = Amount in central compartment at end of previous infusion ($X_{10} = 0$ at start of first infusion)
A_{20} = Amount in peripheral compartment at end of previous infusion ($X_{20} = 0$ at start of first infusion)
t = time

Amounts in each compartment are also modelled to obtain values for X_{10} at start of 2nd, 3rd, ... etc. infusions, i.e.

$$A_1 = A_{10}\left[\frac{(k_{21}-\lambda_1)}{\lambda_2-\lambda_1}e^{-\lambda_1 t} - \frac{(k_{21}-\lambda_2)}{\lambda_2-\lambda_1}e^{-\lambda_2 t}\right] + \frac{k_{21}A_{20}}{\lambda_2-\lambda_1}(e^{-\lambda_1 t} - e^{-\lambda_2 t}) + R_o\left[\frac{k_{21}}{\lambda_1\lambda_2} - \frac{\lambda_1-k_{21}}{\lambda_1(\lambda_1-\lambda_2)}e^{-\lambda_1 t} + \frac{\lambda_2-k_{21}}{\lambda_2(\lambda_1-\lambda_2)}e^{-\lambda_2 t}\right] \quad (4)$$

$$A_2 = \frac{k_{21}A_{10}}{\lambda_2-\lambda_1}(e^{-\lambda_1 t} - e^{-\lambda_2 t}) + k_{12}R_o\left[\frac{1}{\lambda_1\lambda_2} + \frac{e^{-\lambda_1 t}}{\lambda_1(\lambda_1-\lambda_2)} - \frac{e^{-\lambda_2 t}}{\lambda_2(\lambda_1-\lambda_2)}\right] + \frac{k_{12}k_{21}A_{20}}{(k_{21}-\lambda_2)(\lambda_1-k_{21}(\lambda_1-\lambda_2)}\left[(k_{21}-\lambda_2)e^{-\lambda_1 t} + (\lambda_1-k_{21})e^{-\lambda_2 t} - (\lambda_1-\lambda_2)e^{-k_{21}t}\right] + A_{20}e^{-k_{21}t} \quad (5)$$

(Where A_{10} and $A_{20} = 0$ at start of first infusion

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