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Dose independent pharmacokinetics of mexiletine in healthy volunteers

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In 12 healthy volunteers who received orally 100, 200, 300, 400 and 600 mg mexiletine at weekly intervals, the maximum plasma concentration of mexiletine and AUC increased linearly with the dose of mexiletine. Between doses there were no significant differences in the values for clearance and volume of distribution of mexiletine but there were for plasma elimination half-life. These results indicate that the kinetics of mexiletine are linear.

Keywords mexiletine pharmacokinetics

Introduction

Mexiletine is a Class I anti-arrhythmic drug effective in the suppression of ventricular ectopic beats in patients (Chew *et al.*, 1979). Mexiletine is extensively metabolised by the liver in man (Beckett & Chidomere, 1977). While preliminary studies indicated that there was a linear relationship between the dose and trough plasma concentration of mexiletine during steady state, no definite study has been made of the linearity of the kinetics of mexiletine (Campbell *et al.*, 1978). It was decided to undertake a formal study of the relationship between oral dose and the plasma concentration of mexiletine in normal healthy volunteers.

Methods

Observations were made in 12 healthy male volunteers who gave written informed consent. The study was approved by the Ethics Committee of the Queen's University, Belfast. No drugs were taken within 14 days of the test days and during the sampling period. Each subject received 100, 200, 300, 400 and 600 mg mexiletine supplied in capsules containing 100 mg mexiletine (Mexitil, Boehringer Ingelheim) at weekly intervals. The 600 mg dose was only given if there were no adverse effects after the 400 mg dose. The subjects fasted for at least 10 h and received the test drug together with 300 ml of water at 08.00 h; 4.5 h later a standard light meal was given. The subjects remained recumbent until 3 h after drug administration.

Recumbent heart rate and blood pressure were recorded prior to and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10 and 24 h after dosing, using an automatic recording device (Copal Digital Sphygmomanometer, Va 251). Any significant adverse reaction was recorded. Blood (10 ml) was drawn through an indwelling catheter or needle in a forearm vein and placed in a heparin-containing tube before, at each observation time and at 24, 32 and 48 h. The plasma was separated and stored at −18° C for analysis using high pressure liquid chromatography.

Mexiletine and betaxolol as internal standard were extracted from alkaline plasma into 4:1 ether/dichloromethane. After evaporation of the organic layer, 25 μl of acetic anhydride was added. Incubation for 5 min at 50° C was terminated by evaporation of the anhydride. The residue was reconstituted in 70 μl of 70:30 methanol/water for analysis by h.p.l.c. The column used was spherisorb 5 ODS (15 cm × 0.46 cm). The eluent was a mixture of 0.025% trichloroacetic acid, 0.15% octane sulphonic acid and 70% methanol in water. Detection was

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effected by a Pye-Unicam LCFL detector with excitation at 220 nm and emission at 310 nm. The coefficient of variation was 9.5% at 0.28 μg ml^{-1} and 2.6% at 1.93 μg ml^{-1}. Inter-day variation was 13.5% and 5.8% for the same concentrations over a 10 day period.

The following pharmacokinetic parameters were calculated from the plasma concentration time curve for each dose, for all subjects and expressed as mean ± s.e. mean: maximum plasma concentration (C_{max}), time to maximum plasma concentration, elimination rate constant (k_{el}: slope of terminal portion of the logarithm of the plasma concentration–time curve), plasma elimination half-life

$$(t_{½}: \frac{0.693}{k_{el}}),$$

the area under the plasma concentration–time curve from zero time to infinity (AUC: calculated using the trapezoidal rule), clearance

$$(CL = \frac{Dose}{AUC}),$$

and volume of distribution (V: CL/k_{el}). Bioavailability was assumed to be 100% in the calculation of clearance and volume of distribution (Prescott *et al.*, 1977).

The pharmacokinetic parameters were compared individually for each subject for each dose using two way analysis of variance and heart rate and systolic and diastolic pressure were compared by analysis of variance. Differences were regarded as significant at a P-value equal to or less than 0.05. Linear regression analyses for each subject at each dose were carried out on maximum plasma concentration (C_{max}) and AUC. The straight line describing the regression and the correlation coefficient were calculated by the method of least square regression analysis.

Results

All 12 subjects received 100, 200, 300 and 400 mg mexiletine but only 11 received 600 mg as one was unavailable for his final dose. There were no significant changes in heart rate or systolic and diastolic pressure after any dose. As the dose of mexiletine was increased there was a progressive increase in the maximum plasma concentration (Figure 1, Table 1). The correlation between maximum plasma concentration for each subject after each dose could be described by the equation $y = 2.15\ x - 41.8$ (y = maximum plasma concentration, x = dose) with a correlation coefficient of 0.815. The correlation between AUC for each subject and each dose is described by the straight line $y = 28.5\ x - 648$ (y = area under curve, x = dose) with a correlation coefficient of 0.756. No significant changes occurred in the clearance and volume of distribution between the doses. Significant differences ($P = 0.05$) occurred in the plasma elimination half-lives between doses (range 7.9 ± 0.6 to 11.3 ± 1.0 h).

No subjects reported any adverse effects after 100, 300 and 400 mg. One subject complained of slight nausea after 200 mg mexiletine and two after 600 mg. Two had slight dizziness and one moderately severe dizziness and blurred vision after 600 mg.

Discussion

In the present experiments as the dose of mexiletine was increased there was a progressive and

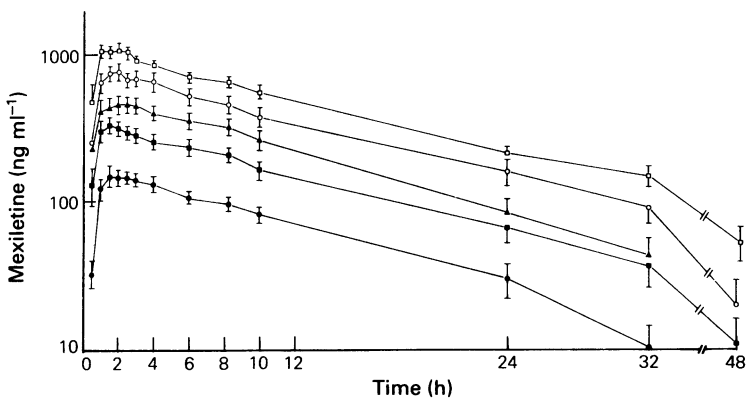

Figure 1 Plasma concentrations of mexiletine (mean ± s.e. mean ng ml^{-1}) during the 48 h period following oral doses of 100 (●), 200 (■), 300 (▲), 400 (○) and 600 (□) mg mexiletine in each of 12 healthy volunteers.

Table 1 Pharmacokinetic parameters of mexiletine after single oral doses of 100, 200, 300, 400 and 600 mg to 12 healthy male subjects. Results are expressed as mean ± s.e. mean.

Parameter	*Parameter value at indicated dose (mg)*				
	100	*200*	*300*	*400*	*600**
C_{max} (ng ml^{-1})	177 ± 18	381 ± 41	560 ± 81	885 ± 100	1223 ± 112
Time to C_{max} (h)	1.9 ± 0.2	1.8 ± 0.3	2.0 ± 0.3	2.6 ± 0.6	1.8 ± 0.2
k_{el} (h^{-1})	0.067 ± 0.006	0.078 ± 0.01	0.093 ± 0.007	0.077 ± 0.007	0.068 ± 0.005
$t_{½}$ (h)	11.3 ± 1.0	10.8 ± 1.2	7.9 ± 0.6	9.5 ± 0.7	10.7 ± 0.8
AUC (ng ml^{-1} h)	2511 ± 324	5094 ± 785	6870 ± 1195	11,373 ± 1714	16,438 ± 1760
CL (l h^{-1})	45.9 ± 4.6	52.2 ± 9.7	57.0 ± 8.2	46.7 ± 7.8	40.4 ± 3.8
V (l)	707 ± 80	695 ± 91	592 ± 60	580 ± 60	591 ± 43

*Mean of 11 subjects.

linear increase in the maximum plasma concentration and in AUC. The clearance of the drug ranged from 40.4 ± 3.8 to 57.0 ± 8.2 l h^{-1} (mean ± s.e. mean) with no significant differences between doses. There were small but not significant differences between the values for the volume of distribution after different doses. There was no evidence that the rate of metabolism of mexiletine was impaired or saturated at the higher doses. Thus the kinetics of mexiletine are quite different to those of aprindine (Kobari *et al.*, 1984) and phenytoin, antiarrhythmic drugs exhibiting dose-dependent pharmacokinetics (Richens & Dunlop, 1975).

There were significant differences between the plasma elimination half-lives of mexiletine for different doses but not between subjects (7.9 ± 0.6 h after 300 mg and 11.3 ± 1.0 h after 100 mg). The reason for this difference is not apparent.

The therapeutic plasma concentration of mexiletine is in the range 0.75 to 2.0 μg ml^{-1} (Prescott *et al.*, 1977; Campbell *et al.*, 1978). In the present study the mean plasma concentrations were in the therapeutic range after 400 and 600 mg although some subjects had plasma concentrations above 0.75 μg ml^{-1} after 300 mg while others had values below this value after 400 and 600 mg.

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