MEXILETINE DISPOSITION: INDIVIDUAL VARIATION IN RESPONSE TO URINE ACIDIFICATION AND ALKALINISATION

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- 1 The disposition of mexiletine has been studied in five subjects on two occasions with urine pH controlled at 5.0 and at 8.0.
- 2 With acid urine total plasma clearance was similar in all subjects (462 to 497 ml min⁻¹) and the plasma half-life ranged from 3.8 to 9.2 h (mean 6.7 h). With alkaline urine the total plasma clearance varied considerably (239 to 441 ml min⁻¹); the mean half-life, 9.7 h, (range 7.6 to 12.7 h) was not significantly different from that in the acid urine study.
- 3 Renal clearance fell greatly in every subject on alkalinisation of the urine. The total plasma clearance fell by a similar amount in two. In the remaining three the fall in total clearance was much smaller because of an increase in non-renal clearance. The reduction in total plasma clearance only just achieved statistical significance.
- 4 The increase in predicted steady-state plasma mexiletine concentrations during infusion with change in urine pH from 5 to 8 varied between +5% and +95% (mean +39%).
- 5 Changes in urine pH have a predictable effect upon renal clearance of mexiletine. However, disposition is changed in an unpredictable manner and inter-subject variation in distribution volume and non-renal clearance are important factors.

Keywords mexiletine urine pH drug disposition

Introduction

Mexiletine is an oral antiarrhythmic agent with a relatively long duration of action. It is eliminated mainly by metabolism (Beckett & Chidomere, 1977) and within the normal physiological range of urine pH about 10% of the administered dose is excreted unchanged, with substantial inter-subject variation (Kaye *et al.*, 1977; Prescott *et al.*, 1977; Haselbarth *et al.*, 1981). At the extreme urine pH values of 5.0 and 8.0 the percent excreted unchanged has been reported as 56% and 0.5% respectively (Kiddie *et al.*, 1974; Kaye *et al.*, 1977).

Mean mexiletine plasma half-lives in healthy subjects with uncontrolled urine pH are variously reported as 9.0 h (Beckett & Chidomere, 1977), 10.4 h (Prescott *et al.*, 1977), 6.3 h (Haselbarth *et al.*, 1981), 5.0 h (Johnston *et al.*, 1981) and 10.4 h (El Allaf *et al.*, 1982), whereas values as short as 2.8 h and 3.9 h have been described with urinary acidification (Kiddie *et al.*, 1974; Kaye *et al.*, 1977; Johnston *et al.*, 1981). This has been interpreted as evidence that physiological changes in urine pH will result in clinically significant changes in steady-state plasma concentration and has led to the recommendation that urine pH

be monitored during mexiletine therapy (Kaye *et al.*, 1977; Johnston *et al.*, 1979). However, our own observations led us to doubt whether this was necessary (Prescott *et al.*, 1977).

The steady-state plasma concentration and plasma half-life are determined by non-renal clearance and distribution volume as well as by renal clearance but the effects of changes in acid-base balance on these variables have not been reported previously for mexiletine. Accordingly, we have made a comprehensive study of the effects of urinary acidification and alkalinisation on the disposition of intravenous mexiletine in healthy subjects.

Methods

The subjects were five healthy fasting males (age 22 to 34 years, mean 26 years; weight 63 to 91 kg, mean 72.6 kg) who were not currently receiving any other drug therapy. After giving informed consent, each received intravenous mexiletine (3.0 mg base/kg infused over 30 min) on two separate occasions separated by at

least 7 days. The subjects were recumbent and no food or drink was permitted for the first 2 h of each study. Ammonium chloride (12 g daily in divided oral doses) was started 1 day before and continued for 2 days after the first infusion to acidify the urine. Similarly, sodium bicarbonate (16 g daily) was started 1 day before and continued for 5 days after the second infusion to make the urine alkaline.

Serial venous blood samples were taken for 24 h during and after the mexiletine infusion. Urine was collected at 2-hourly intervals for 12 h and then at increasing intervals for 48 h (acid study) or 120 h (alkaline study). Urine pH was measured without delay by pH-meter and plasma and urine were stored at -20°C prior to estimation of mexiletine by gas-liquid chromatography (Kelly *et al.*, 1973). Plasma mexiletine concentration-time data from the start of the infusion were fitted to a two- or three-compartment open model by non-linear regression analysis (Clements & Prescott, 1976). The area under the curve (AUC) was calculated by the trapezoidal rule with correction for area after the last sample. Half-life and total plasma clearance were derived from standard equations (Gibaldi & Perrier, 1975). The renal clearance was calculated as the product of total plasma clearance and the fraction of the dose excreted unchanged.

Model-independent steady-state distribution volume (V_{ss}) was calculated as:

$$V_{ss} = \frac{\text{Dose} \times \text{AUMC}}{\text{AUC}^2}$$

AUMC, the area under the first-moment curve, being calculated from:

$$\text{AUMC} = \int_0^{t'} \text{Cp} \cdot dt + \frac{t' \text{Cp}'}{\beta} + \frac{\text{Cp}'}{\beta^2} - \frac{\text{AUC} \tau}{2}$$

where Cp is the plasma concentration, Cp' is the concentration of the last sample at time t' , β is the slow disposition rate constant and τ is the infusion period (Benet & Galeazzi, 1979; Straughn, 1982). Predicted steady-state concentrations (C_{ss}) for an intravenous infusion were calculated from:

$$C_{ss} = \frac{\text{Infusion rate}}{\text{Total plasma clearance}}$$

Means are reported with s.e. mean and Student's t -test was used to test for the significance of differences between means.

Results

Plasma concentrations

Mean plasma mexiletine concentrations rose to peak values of 1.63 (acid urine) and 1.30 (alkaline urine)

$\mu\text{g ml}^{-1}$ at the end of the infusion and thereafter declined bi- (eight studies) or tri-exponentially (one study) (Figure 1). Data from the remaining study could not be satisfactorily fitted.

There was no significant difference between the mean mexiletine plasma half-life during the acid (6.7 h) and alkali (9.7 h) studies despite mean urine pH values of 5.26 and 7.95 over the first 24 h. Similarly there were no significant differences between the mean plasma concentrations at any time (except at 12 h), the AUC, the non-renal clearance or the steady-state distribution volume (Table 1).

Figure 1 Mean plasma mexiletine concentration ($\mu\text{g ml}^{-1}$) vs time (h) in five subjects for intravenous mexiletine (3 mg base/kg infused over 30 min) during acidification (○) and alkalisation (●) of urine. *denotes significant difference ($P < 0.05$).

Renal clearance

As expected the renal clearance of mexiletine was much higher with acid than with alkaline urine but the consequent increase in total plasma clearance was much smaller, although still significant (Table 1). The percentages of the dose excreted unchanged with acid and alkaline urine were 35.0 ± 1.1 and 1.1 ± 0.3 respectively ($P < 0.001$). There was a highly significant correlation between log renal clearance and urine pH ($r = -0.96$) but not between renal clearance and flow rate.

Over the period during which mexiletine could be measured in urine, the arithmetic mean urine pH was 5.24 (individual range 5.06 to 5.41) with ammonium chloride and 7.97 (range 7.84 to 8.11) with sodium

Table 1 Individual pharmacokinetic values in five subjects given intravenous mexiletine 3 mg kg⁻¹ infused over 30 min.

(a) Acid urine								
Subject	Clearance (ml min ⁻¹)			Mean urine pH	AUC (µg ml ⁻¹ min)	Half-life (h)	V _{ss} (l)	Steady-state concentration (µg ml ⁻¹)*
	Total	Renal	Non-renal					
1	497	178	319	5.42	452	7.4	267	1.51
2	462	114	348	5.02	590	8.4	277	1.97
3	477	151	326	5.37	434	9.2	329	1.45
4	467	171	296	5.10	417	3.8	137	1.39
5	488	224	264	5.31	387	4.5	177	1.29
Mean	478	168	311	5.24	456	6.7	237	1.52
s.e. mean	7	18	14	0.08	35	1.1	35	0.12
(b) Alkaline urine								
1	439	3	436	7.92	513	8.0	287	1.71
2	441	6	435	7.92	621	7.6	297	2.06
3	297	2	295	7.84	697	11.4	258	2.33
4	239	5	234	8.06	815	12.7	237	2.72
5	412	3	409	8.11	459	9.1	301	1.53
Mean	366	4	362	7.97	621	9.7	276	2.07
s.e. mean	41	1	41	0.05	64	1.0	12	0.21
P (paired t-test)	0.05 > P > 0.01	P < 0.001	NS	P < 0.001	NS	NS	NS	NS

* Predicted steady-state mexiletine plasma concentration during i.v. infusion of 10 µg kg⁻¹ min⁻¹.

bicarbonate. The mean flow rates were 70.7 ml h⁻¹ (range 60.5 to 87.8) and 64.8 ml h⁻¹ (range 51.5 to 93.0), respectively, and these values did not differ significantly.

Predicted plasma concentrations

In each subject the predicted steady-state plasma concentration resulting from an intravenous infusion of 10 µg kg⁻¹ min⁻¹ was higher with alkaline than with acid urine although the means did not differ significantly (Table 1). In subjects 1, 2 and 5 the changes were unimportant. In subjects 3 and 4 the increases were substantial and clearly of clinical significance. Interestingly, the individual differences in response were not due to changes in the renal clearance of mexiletine since this fell markedly in all subjects with alkalinisation of the urine. In subjects 1, 2 and 5 the non-renal clearance increased with alkalinisation and this compensated for the fall in renal clearance. As a result there was little change in total plasma clearance or in predicted steady-state plasma concentrations. In contrast, in subjects 3 and 4, both non-renal and renal clearance decreased with alkalinisation, producing a substantial fall in total plasma clearance and an increase in the predicted steady-state plasma concentrations.

Discussion

As in previous studies, urinary acidification produced a large and consistent increase in the renal clearance of mexiletine. There was no significant decrease in mean plasma half-life, AUC or non-renal clearance but the number of subjects studied was small. We found that the effects of extreme changes in urine pH on total mexiletine clearance, distribution volume and half-life were surprisingly unpredictable. Thus renal clearance fell in every subject with the change from acid to alkaline urine whereas the total plasma clearance fell by a similar amount in only two. In the remainder, the fall in renal clearance was partially offset by an increase in non-renal clearance and as a result there was little change in total plasma clearance. In three subjects the plasma mexiletine half-life was similar at both extremes of urine pH. In the other two the half-life was much shorter with acid urine; this reduction was due not only to a higher total clearance but also to a decrease in distribution volume.

Predicted steady-state plasma mexiletine concentrations (Table 1) during an infusion at 10 µg kg⁻¹ min⁻¹ increased by a mean of 39% with a change in urine pH from 5 to 8. However in three subjects the increase was less than 20%, whereas in the others it was 61% and 96%. Clearly, factors other than renal

clearance influence the disposition of mexiletine under these conditions. Changes in half-life, when they occurred, were not always due to changes in total plasma clearance because of the unpredictable effects of acidification on distribution volume.

The renal contribution to elimination of mexiletine is minor and the plasma kinetics are not influenced by mild to moderate renal failure (El Allaf *et al.*, 1982). Conversely, the elimination of mexiletine is significantly enhanced by microsomal enzyme induction produced by rifampicin (Pentikainen *et al.*, 1982) and is significantly impaired in patients with liver disease (Nitsh *et al.*, 1982). Hence in most subjects normal physiological changes in urine pH seem unlikely to have a clinically significant effect on mexiletine steady-state plasma concentrations or half-life (Prescott *et al.*, 1977; El Allaf *et al.*, 1982). However, we found, as did Johnston *et al.* (1979) that in some individuals

the changes are greater and could affect the outcome of therapy.

There is considerable individual variation in plasma mexiletine concentrations resulting from a given dose in patients with cardiac arrhythmias (Prescott *et al.*, 1977; Vozeh *et al.*, 1982) and as shown here and in previous studies (Prescott *et al.*, 1977) inter-subject variation in distribution volume is an important factor that must be taken into account. Alteration of urine pH (through diurnal variation or after antacid administration) may affect plasma mexiletine clearance in an individual, and measurement of urine pH may provide an explanation for observed deviations from expected steady-state concentrations. However, changes in mexiletine disposition cannot be predicted accurately from urine pH measurements, and dosage can only be adjusted reliably by measurement of plasma concentrations.

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