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# THE CLINICAL PHARMACOLOGY OF MEXILETINE

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**1** Mexiletine was given to 156 patients by intravenous or oral routes of administration.

**2** There was great interpatient variation in kinetics and plasma concentrations with both routes of administration.

**3** The mean volume of distribution was 6.63 l/kg. The mean plasma elimination half-life after chronic oral therapy was 11.31 h.

**4** Plasma concentrations between 0.75 and 2.00 μg/ml were usually effective. Within this therapeutic range severe side effects were uncommon.

**5** Plasma concentrations within this range were achieved in 72% of patients when doses of 10–14 $mg^{-1}$ $kg^{-1}$ day were given orally.

## Introduction

Mexiletine is an effective antiarrhythmic drug. It controls ventricular dysrhythmias when given intravenously or orally (Campbell, Chaturvedi, Kelly, Strong, Shanks & Pantridge, 1973; Talbot, Clark, Nimmo, Neilson, Julian & Prescott, 1973; Talbot, Julian & Prescott, 1976). In this study, we report the plasma concentrations observed after giving various dosage regimes of mexiletine to patients admitted to the Coronary Care Unit of the Royal Victoria Hospital, Belfast. We have also correlated the clinical effects of the drug with its plasma concentrations.

## Methods

One hundred and fifty-six patients, of whom 153 had ischaemic heart disease, received mexiletine. The majority of the patients required treatment for ventricular dysrhythmias complicating a recent myocardial infarction. Thirty-three patients had persistent ST segment displacement following acute myocardial infarction (Wilson & Pantridge, 1973) and were treated prophylactically before dysrhythmias were detected. Mexiletine was given by two routes of administration.

### *Intravenous administration*

*(a) Single intravenous injection.* Ten patients received mexiletine 200 mg as a single intravenous injection over 5 minutes. Blood samples for estimation of plasma mexiletine concentrations were withdrawn at 5, 10, 15, 20, 25 and 30 min and at 1, 2, 4, 8, 12, 16 and 24 h after the start of the injection.

*(b) Intravenous injection with continuous infusion.* Nine patients received mexiletine 200 mg as a single intravenous injection over 5 min and a continuous infusion of the drug was started immediately after the injection. The infusion was at a rate of 3 mg/min for the first hour, 1.5 mg/min for the next 3 h, and thereafter at 1 mg/min.

Blood samples for estimation of plasma mexiletine concentrations were taken from these patients at 10, 15, 20, 30, 45, 65, 125, 185 and 245 min after the start of the injection.

### *Oral administration*

*(a) Oral administration following a loading dose.* Thirty-three patients were studied: 25 were convalescent following an acute myocardial infarction. All received an initial dose of 400 mg mexiletine followed by one of four drug regimes. In three of these, the doses of mexiletine were fixed but in the fourth the attending physician was allowed to vary the dose. In all four groups, a total of three doses were given in the 16 h of the study. The initial 400 mg dose was followed by doses at 2 h and 8 h. Doses (in mg) were in the following order (number of patients in brackets).

A. 400, 400, 400 (5).
B. 400, 200, 300 (5).
C. 400, 200, 200 (7).
D. 400, variable (16).

The 16 patients in Group D received a flexible dosage schedule in an attempt to tailor the dose to the requirements of the patient. Thus, at 2 h a choice of giving 200 mg or 300 mg was made and at 8 h a choice of giving 300 mg or 400 mg was made by the attending physician. On each occasion the lower dose was given if the patient weighed less than 57 kg, was aged more than 65 years, was receiving other potentially hypotensive drugs, e.g. lignocaine or $\beta$-adrenoceptor blocking agents, or had side effects. Blood samples were taken at 30 min and at 1, 2, 3, 4, 8 and 16 h during the study.

*(b) Oral administration with no loading dose.* Eighteen patients received maintenance doses of mexiletine without an initial loading dose. Treatment was started within a fortnight of the onset of myocardial infarction. The three doses used, 200 mg, 250 mg, or 300 mg, three times a day, were each given to six patients.

The trough plasma concentrations of mexiletine were determined from blood samples taken on the second, third, fifth and seventh days of therapy. In the twelve patients receiving 200 mg or 250 mg, three times a day, further samples were taken on the fourteenth day of therapy.

*(c) Longterm oral maintenance therapy.* Observations were made in 88 patients, all of whom had been receiving mexiletine for at least 5 days and usually for considerably longer. Plasma concentrations were determined just prior to an oral dose after at least 5 days' treatment with a fixed dosage schedule. After stopping mexiletine in 30 of these patients who had been receiving the drug for at least 2 weeks, blood samples were taken just before and 1, 2, 4, 8, 12, 16 and 24 h after the last dose. In 20 of these 30 patients, urine was collected for 48 h after stopping the drug.

Additional observations were made in 149 of the 156 patients. Plasma concentrations which were measured during the course of oral or intravenous therapy were assessed to see whether ventricular dysrhythmias were controlled and whether adverse effects were present. In 113 of these patients, the concentrations were measured during the studies of dosage regimes which have been described already. The drug was judged effective when ventricular dysrhythmias were not detected on the 12-lead electrocardiogram, on continuous oscilloscopic monitoring of the electrocardiogram, or on a continuously recorded electrocardiogram. Side-effects were classed as mild or severe. Mild side effects were considered to be minor subjective complaints, often not mentioned by the patients unless directly questioned, or slight objective abnormalities causing little impairment of function. Severe adverse effects were usually mentioned spontaneously and produced obvious clinical abnormalities.

The plasma concentration of mexiletine was determined from venous blood samples. Plasma was separated by centrifugation and was stored frozen. Unchanged mexiletine was measured by gas-liquid chromatography (Kelly 1977). Urine was collected over 24 h periods and measured portions were stored frozen. The concentration of the drug in the urine was measured by gas-liquid chromatography or by a spectrofluorometric method (Kelly, Nimmo, Rae, Shanks & Prescott, 1973; Kelly, 1977).

From the studies in which a single 200 mg injection was given intravenously, the slopes ($\alpha$ and $\beta$) of the early and late phases of distribution were determined using linear least squares regression analysis. Alpha was determined using points derived by a standard curve peeling method. From these results the half lives of both phases ($T_{\frac{1}{2}}\alpha$ and $T_{\frac{1}{2}}$) were determined. The total volume of distribution ($V_d$) and total body clearance (C) were calculated using the relationships:

$$V_d = \frac{\text{Dose}}{\beta\, AUC_{0-\infty}}$$

$$C = \frac{\text{Dose}}{AUC_{0-\infty}}$$

where $AUC_{0-\infty}$ = the area under the plasma concentration—time curve extrapolated to infinity (Greenblatt & Koch-Weser, 1975).

The significance of differences between groups and of paired differences within groups was evaluated by means of Student's *t*-test.

## Results

Following single intravenous injections of mexiletine, plasma concentrations in patients fell rapidly for one

**Table 1** Pharmacokinetic indices of mexiletine in ten patients who received 200 mg intravenously

| *Patients* | $T_{\frac{1}{2}}\alpha$ *(min)* | $T_{\frac{1}{2}}$ *(h)* | $V_d$ *(l/kg)* | $C$ *(ml min$^{-1}$ kg$^{-1}$* |
|---|---|---|---|---|
| A | 6.2 | 9.32 | 4.45 | 5.51 |
| L | 9.9 | 23.89 | 11.00 | 5.32 |
| T | 6.9 | 7.13 | 8.29 | 13.41 |
| R | 10.7 | 10.17 | 10.02 | 11.37 |
| T | 5.7 | 11.03 | 4.30 | 4.50 |
| D | 12.0 | 10.75 | 2.67 | 2.87 |
| McC | 3.5 | 15.52 | 4.84 | 3.60 |
| S | 7.6 | 8.99 | 7.65 | 9.82 |
| A | 7.1 | 18.35 | 8.68 | 5.45 |
| H | 5.1 | 17.20 | 4.38 | 2.94 |
| Mean | 7.5 | 13.24 | 6.63 | 6.48 |
| | 0.84 | 1.67 | 0.90 | 1.17 |

$T_{\frac{1}{2}}\alpha$ = half-life of the early phase of distribution. $T_{\frac{1}{2}}$ = plasma elimination half-life. $V_d$ = volume of distribution C = total body clearance.

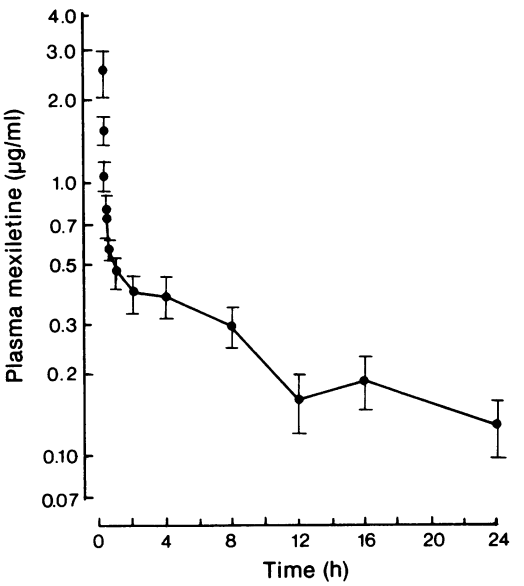


**Figure 1** Plasma concentrations of mexiletine (mean ± s.e. mean) in ten patients who received a 200 mg intravenous injection over 5 min.

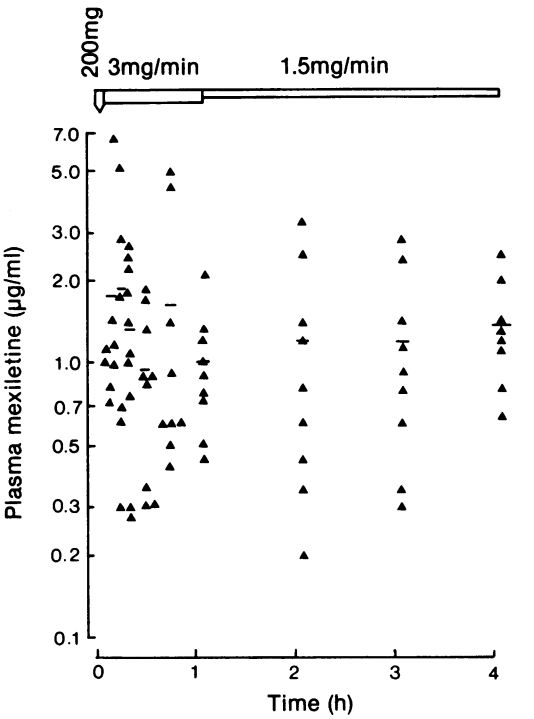


**Figure 2** Plasma concentrations of mexiletine in nine patients who received a 200 mg injection followed by a continuous infusion of the drug. Each triangle represents the concentration for one patient. The horizontal bars show the mean values.

hour and then more slowly during the remainder of the study (Figure 1). $T_{\frac{1}{2}}\alpha$, half-life of elimination ($T_{\frac{1}{2}}$), volume of distribution, and clearance varied widely in the ten patients (Table 1). The mean elimination half-life was 13.24 h.

Figure 2 shows the results of giving mexiletine as a single intravenous injection combined with an intravenous infusion. Plasma mexiletine concentrations varied widely in these patients. One patient developed a concentration of 5.0 μg/ml mexiletine at 45 min. The mean concentrations remained between 0.9 and 1.9 μg/ml.

Mean plasma concentrations following the various oral loading regimes are shown in Figure 3. Absorption in Group B was slower than in the other groups but after 2 h there was no significant difference in concentrations between the four groups. At 8 and 16 h all groups except Group C (who received the lowest total dose) had mean plasma mexiletine concentrations in excess of 1.0 μg/ml. Among the patients who received variable doses

**Table 2** Trough plasma concentrations of mexiletine (mean ± s.e. mean) in eighteen patients receiving oral therapy without a loading dose

| *Dose (mg 8-hourly)* | *Days of therapy* 2 | 3 | 5 | 7 | 14 |
|---|---|---|---|---|---|
| | *Trough plasma mexiletine(μg/ml)* | | | | |
| 300 | 1.36 ±0.18 | 2.05 ±0.30 | 1.65 ±0.27 | 1.75 ±0.26 | — — |
| 250 | 1.07 ±0.10 | 1.15 ±0.12 | 1.39 ±0.22 | 1.01 ±0.22 | 0.91 ±0.22 |
| 200 | 1.03 ±0.26 | 1.33 ±0.36 | 1.13 ±0.44 | 1.38 ±0.39 | 0.94 ±0.21 |

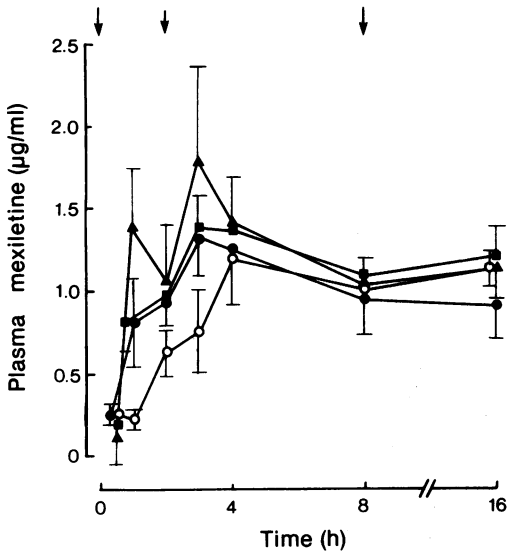


**Figure 3** Plasma concentrations of mexiletine (mean ± s.e. mean) in 33 patients receiving four different oral loading regimes (Group A (▲), Group B (○), Group C (●) and Group D (■). For explanation of loading regimes see **Methods**). The arrows show the times of administration of the drug.

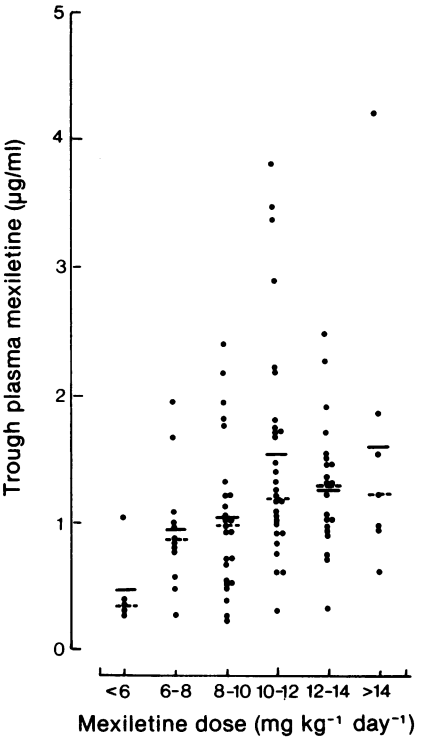


**Figure 4** Trough plasma concentrations of mexiletine in 88 patients after at least 5 days' therapy. Each dot represents the plasma concentration in one patient. The solid and interrupted horizontal bars show the mean and median concentrations for each dose range respectively. Seventy-nine patients received a single dosage regime. Seven patients received two regimes and two received three.

(Group D) 69% of plasma concentrations were within the range 0.75–2.00 μg/ml. All the other groups had lower proportions within this range (52%, 62%, and 60% respectively for Groups A, B, and C).

Table 2 shows the mean trough plasma concentrations in patients receiving oral therapy without a loading dose. With each dose, mean plasma concentrations rose gradually until the third day. Between the second and third day of treatment there was a significant increase in plasma mexiletine concentrations in patients receiving 300 mg three times a day, ($P < 0.05$). There was a significant fall in plasma mexiletine concentrations in patients receiving 250 mg three times a day, between the fifth and fourteenth days ($P < 0.05$). Since no further increase in the plasma concentrations occurred after the fifth day of therapy, it was assumed that steady state plasma concentrations had been reached.

In a total of 88 patients, trough plasma concentrations were available after 5 days' treatment with different oral regimes (Figure 4). The results are widely scattered, although there is a significant linear correlation between plasma concentration and daily dose of mexiletine ($r = 0.34$; $P < 0.001$).

The mean ± s.e. mean half-life of elimination in 30 patients after oral therapy was 11.31 ± 0.71 (range 5.3–23.3 h) (Figure 5). The half-life was not significantly prolonged in six patients with clinical evidence of congestive heart failure at the time of withdrawal. The mean ± s.e. mean difference between minimum and maximum concentrations at withdrawal was 0.98 ± 0.13 μg/ml. On average 14 ± 3% of the total daily dose was excreted unchanged in the urine during the 48 h after the last dose (range 2–48%). There was a significant linear correlation between the recovery in the urine of the unchanged drug and the output of urine ($r = 0.813$: $P < 0.001$).

The relationship between plasma concentrations of mexiletine and its clinical effects in 149 patients is shown in Figure 6. In the range 0.75–1.00 μg/ml, 77% of plasma concentrations were effective. Eighty per cent of concentrations ⩾2.00 μg/ml were effective but 30% were associated with adverse effects and in 19% of these concentrations, severe ill effects were seen. These included hypotension with or without bradycardia, atrio-ventricular dissociation, vomiting,

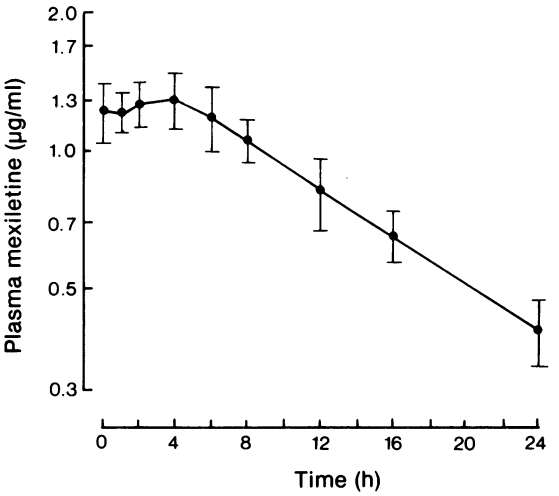


**Figure 5** Plasma concentrations of mexiletine (mean ± s.e. mean) after chronic oral therapy.

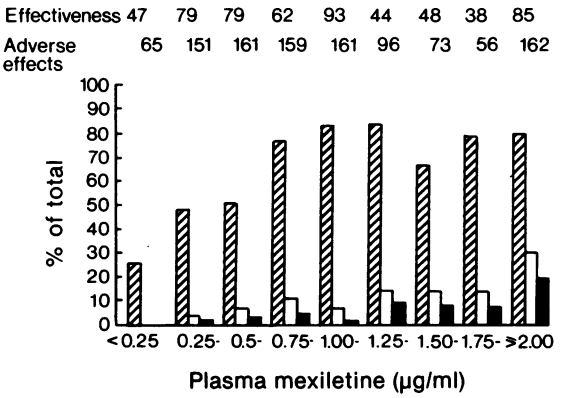


**Figure 6** The Y axis shows the percentages of plasma concentrations within each dose range which were effective or produced adverse effects. The figure above the columns show the number of concentrations assessed. However, when the drug was given prophylactically (before any rhythm disturbances were detected) its effectiveness could not be judged. Thus, more concentrations were assessed for adverse effects than for effectiveness. (▨) % effective, (□) % total adverse effects, (■) % severe adverse effects.

tremor, and toxic confusional states. Side effects were not seen with concentrations $< 0.25$ μg/ml. Seventy-nine per cent of concentrations within the range 0.75–2.00 μg/ml were effective and 5.5% were associated with severe adverse effects.

## Discussion

Prescott, Pottage & Clements (1977) have described the distribution and elimination of mexiletine. They observed a volume of distribution often exceeding 500 l in both patients and healthy volunteers. In patients receiving the drug intravenously, the mean total body clearance was 415 ml/min and the mean plasma half-life was 16.7 h. After chronic oral therapy the mean half-life was 12.1 h. The results of the present investigation are similar. The mean volume of distribution was 6.63 l/kg and the clearance 6.48 ml $min^{-1}$ $kg^{-1}$. In a 70 kg man these are 464.101 and 454 ml/min respectively. The mean half-life was 13.24 h after a single intravenous dose and 11.31 h after longterm oral administration. Between individual patients there were great variations in the kinetics with all modes of administration and this was reflected in the great variation in plasma concentrations. Kiddie, Kaye, Turner & Shaw (1974) suggested that this variation might partly be due to fluctuations in urinary pH. They showed that altering the pH of the urine markedly affected the elimination half-life of mexiletine by altering the urinary excretion of unchanged drug. Prescott *et al.* (1977) have disagreed. They suggested that normal physiological variation in urinary pH was unlikely to have a marked effect on steady state plasma concentrations or on elimination half-life. Our study was not designed to resolve this controversy. We did observe great variation in the amount of the drug excreted in the urine (2–48% of the daily dose) though urinary recovery was closely correlated with urine flow. As on average less than 15% of the daily dose was excreted unchanged in the urine, in most patients this is unlikely to be a major excretory route. Beckett & Chidomere (1977) have demonstrated that mexiletine is extensively metabolized in the body.

With many drugs a range of plasma concentrations exists within which desired effects are common and adverse effects rare. Campbell, Talbot, Dolder, Murray, Prescott & Julian (1975) suggested that with mexiletine this range was between 0.75 and 2.00 μg/ml. Our results confirm this. Seventy-nine per cent of the concentrations within this range were effective and 5.5% of the concentrations were associated with severe side effects. When the concentrations rose to 2.00 μg/ml or more there was no increase in effectiveness but the incidence of severe adverse effects was 19%. In the dose range 0.50–0.75 μg/ml the drug was effective in 51% of observations. Fewer than 50% of concentrations of less than 0.50 μg/ml were effective.

When given in a maintenance dose by mouth, no further significant increase in mean plasma concentration occurred after the third day. The small but significant fall in trough plasma concentrations in some patients between the fifth and fourteenth day of

treatment may have been due to their improving clinical condition. With longterm oral therapy it was assumed that steady state plasma concentrations were reached by the fifth day of treatment. A statistically significant relationship existed between plasma concentration and daily dose (per kg body weight). Nevertheless, prediction of the required dose for a given patient is difficult because of the great individual variation. A dose of between 10 and 14 mg $kg^{-1}$ $day^{-1}$ is a reasonable initial choice as when it was used 72% of trough plasma concentrations were within the therapeutic range. The drug should be given in divided doses. Six- and 8-hourly administration gave a mean swing in plasma concentrations of 0.98 μg/ml. Twelve-hourly dosage, though theoretically possible because of the long half-life, would produce even greater variations. This is undesirable.

Where a rapid effect is required, a loading dose by mouth may be given. An initial 400 mg was followed by further doses after 2 and 8 h. Plasma concentrations within the therapeutic range were most often produced when the second and third doses varied with the individual patient's clinical features. The majority of the patients in our study received the drug when convalescent after acute myocardial infarction. Pottage (1977) has shown that the absorption of mexiletine may be delayed in patients treated soon after the onset of acute myocardial infarction, particularly if narcotic analgesics have been given. In such patients, larger doses may be required.

In this paper we have outlined our experience with various dosage regimes of mexiletine. Because of the great interpatient variation these schedules can only serve as approximate guides. In individual patients the dose must be adjusted according to the clinical effects. As a clear relationship exists between the plasma concentration of the drug and its effects, measurement of concentrations should be of help in the control of therapy.

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