Long-term oral antiarrhythmic therapy with mexiletine

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SUMMARY Forty-eight patients with ischaemic heart disease received oral mexiletine for the control or prevention of ventricular arrhythmias. The most frequently used doses were 200, 250, and 300 mg 8-hourly. The treatment period varied from 2 days to more than 1 year (median 3 months). No ventricular arrhythmias were detected in more than one-half of the patients. Severe side effects occurred in 15 (31%) of the 48 patients. Major ventricular arrhythmias were observed in 14 (29%) of the 48 patients at a time when the majority had plasma concentrations within the therapeutic range. The value of mexiletine in the management of patients at risk of sudden death is likely to be limited.

Nearly two-thirds of premature deaths from coronary artery disease occur within one hour of the onset of symptoms (Bainton and Peterson, 1963). The majority of these deaths result from ventricular fibrillation (Adgey *et al.*, 1969; Cobb *et al.*, 1971).

Identification of those at high risk of sudden death from ventricular fibrillation is of the utmost concern. Despite earlier findings, sudden death is relatively infrequent among patients with unstable angina (Fulton *et al.*, 1972; Duncan *et al.*, 1976). However, survivors of acute infarction have a yearly incidence of sudden death approaching 5 per cent (Koch-Weser, 1972). Ventricular ectopics on a routine electrocardiogram recorded at least 3 months after myocardial infarction were a significant predictor of sudden death (Coronary Drug Project Research Group, 1973). The significance of ventricular ectopics may be increased if they are precipitated by stress or exercise (Lown *et al.*, 1969; Lown, 1971) or if they are repetitive or fall early in the cycle (Lown and Wolf, 1971; Han and Goel, 1972; Lown *et al.*, 1975).

Many antiarrhythmic agents are available for the management of ventricular arrhythmias in the coronary care unit but there is no satisfactory oral preparation for long-term prophylactic therapy. Procainamide was ineffective as an antiarrhythmic agent in a significant proportion of patients with sporadic ventricular arrhythmias when effectiveness was assessed by exercise stress testing or 24-hour

ambulatory monitoring (Jelinek *et al.*, 1974). Long-term oral administration of procainamide is associated with significant side effects. Most of these are related to the development of systemic lupus erythematosus. Quinidine was ineffective in ambulatory patients with sporadic ventricular ectopics, and moderate or severe adverse effects occurred in 29 per cent of the patients (Jelinek *et al.*, 1974). Diphenylhydantoin is ineffective in prevention of sudden death and its long-term use is associated with significant adverse effects (Lovell, 1975). The role of beta-blocking agents in the prevention of sudden death from ischaemic heart disease is still uncertain though it has been suggested that alprenolol and practolol reduce the incidence of sudden death in patients discharged from hospital after myocardial infarction (Ahlmark *et al.*, 1974; Wilhelmsson *et al.*, 1974; Multicentre International Study, 1975).

Mexiletine—a type 1 antiarrhythmic agent with local anaesthetic effect (Singh and Vaughan Williams, 1972)—has been found to control ventricular arrhythmias in both the experimental and clinical situations (Allen *et al.*, 1972; Campbell *et al.*, 1973; Talbot *et al.*, 1973; Campbell *et al.*, 1975; Talbot, 1975; Talbot *et al.*, 1976). It has been claimed that when the drug is given orally adverse effects are infrequent (Campbell *et al.*, 1975; Talbot, 1975; Talbot *et al.*, 1976). The purpose of this study was to assess the effectiveness of long-term oral therapy with mexiletine and the side effects associated with its administration.

Patients and methods

Over a 14-month period from June 1973 to August 1975, 53 patients were started on maintenance treatment with oral mexiletine. The drug was stopped in error in 5 patients and these have been excluded from the subsequent analysis. Details of the remaining 48 patients are given in Table 1. Thirty-nine patients had had a recent myocardial infarction and 9 had chronic ischaemic heart disease. Thirty-seven received the drug because of ventricular ectopics, ventricular tachycardia, or ventricular fibrillation. Ventricular ectopics were considered to require therapy when they were more than 5 per minute, consecutive, multifocal, or R on T. Ventricular tachycardia was defined as 5 or more consecutive ventricular ectopics. Mexiletine was given to 11 patients with acute myocardial infarction who had persistent ST segment elevation considered to be a harbinger of late ventricular arrhythmias (Wilson and Pantridge, 1973). Fifteen of the patients with acute myocardial infarction and 7 of those with chronic ischaemic heart disease had suffered a previous myocardial infarction. There was clinical and/or radiological evidence of mild or moderate left ventricular failure in 34 patients. Thirty patients had previously received 1 or more antiarrhythmic drugs (quinidine, procainamide, lignocaine, verapamil). These had proved ineffective or had produced adverse effects. At the time of entry into the study only 2 patients were receiving an antiarrhythmic drug.

During the initial administration of the drug, the electrocardiogram was continuously monitored. In those with acute myocardial infarction, monitoring was continuous for at least the first week of treatment. A loading dose of mexiletine was administered, either intravenously or by mouth, to 29 patients. These patients received 800 to 1100 mg during the first 8 hours of therapy. At the start of the study, the oral maintenance dose was 300 mg 8-hourly. Later, doses of 250 or 200 mg were more commonly used. The dose was adjusted during therapy as the clinical situation demanded. Other drugs given to patients receiving mexiletine included digoxin, diuretics, diazepam, bronchodilators, and anticoagulants. Prolonged electrocardiographic monitoring was only possible when patients were in hospital. Out-patient evaluation was limited to 12-lead electrocardiograms.

Patients were fully assessed after 1 to 2 weeks, 4 weeks, 2 months, and 3 months on each individual regimen. Thereafter, they were reviewed at 3-monthly intervals. At review, the clinical examination was usually carried out 1 to 2 hours after their last dose. The blood pressure was measured both lying and standing. Inquiry was made about possible adverse reactions. Blood was taken for haematological and biochemical assessment and for detection of antinuclear factor. After 6 months of treatment, the serum B12 and folic acid were determined. At each examination, blood was withdrawn immediately before, and 1 and 2 hours after a dose of the drug. After centrifugation the plasma was stored frozen and subsequently analysed for mexiletine (Kelly *et al.*, 1973).

Therapy was maintained until stopped electively or stopped because of ineffectiveness, adverse reactions, or other complications such as further myocardial infarction. Adverse reactions have been classified as mild or severe. The former included minor subjective complaints, often not mentioned by the patients unless directly questioned, or slight objective abnormalities such as nystagmus or tremor. Severe side effects were usually associated with specific complaints or caused obvious clinical abnormalities, for example hypotension. With the exception of 1 man who refused readmission to hospital, patients were admitted at the time of drug withdrawal. The electrocardiogram was monitored continuously for at least 24 hours after the drug was stopped. One to 3 months after cessation of the drug therapy the patients were reassessed.

Results

Among patients with acute myocardial infarction, the median time from the onset of symptoms to

Table 1 *Clinical details of patients receiving long-term oral mexiletine*

Age* (y)	Wt* (kg)	Sex		Pathological condition		Site of infarction					Reason for antiarrhythmic therapy		
		M	F	Recent myocardial infarction	Chronic IHD	Ant	Post	Ant+post	SE	LBBB	Persistent ST segment elevation	VES	VT and/or VF
57·6 ±1·5	70·0 ±1·41	45	3	39	9	23	9	3	3	1	11	19	18

*Mean ±SEM.
Ant, anterior; Ant+post, combined anterior and posterior; IHD, ischaemic heart disease; LBBB, left bundle-branch block; Post, posterior; SE, subendocardial; VES, ventricular ectopics; VF, ventricular fibrillation; VT, ventricular tachycardia.

starting treatment was 7 days (range 5½ hours to 6 weeks). The duration of therapy for the 48 patients varied from 2 days to more than 1 year: median time was 3 months.

It was possible to continue the treatment for as long as considered necessary in 25 patients. In 23 patients, it was stopped prematurely (Table 2). In 8, it was stopped because of suspected adverse reactions, though in 3 of the 8 it was subsequently found that the adverse reactions were unlikely to be associated with mexiletine therapy. The drug was stopped in 7 patients because of failure to control arrhythmias: in 5 because of ventricular tachycardia or ventricular fibrillation and in 2 because of ventricular ectopics. It was found that 3 of these 7 patients had plasma concentrations of less than 0·75 μg/ml. In 4 patients, mexiletine was stopped for other reasons. One developed a positive antinuclear factor and thrombocytopenia, 1 had congestive heart failure, 1 had a further myocardial infarction, and 1 developed signs of motor neurone disease. Four patients died while on treatment. One died in left ventricular failure and another from a further coronary occlusion. In the latter, the terminal rhythm was asystole. Two died at home: 1 of these deaths occurred suddenly in association with chest pain.

Six patients received the drug for less than 1 week. The mean trough concentration of mexiletine during treatment of the remaining 42 patients was 0·85 ±0·04 (SEM) μg/ml. There was a significant linear correlation between the total daily dose per kg body weight and the trough plasma concentration (r=0·37: P<0·01). Using the highest of the concentrations measured at each visit, the mean peak concentration was found to be 1·45 ±0·06 (SEM) μg/ml. A more accurate estimate of peak concentration was obtained in 27 patients as the drug was withdrawn. Samples were taken before and 1, 2, 4, 6, and 8 hours after the last dose. From these results, the mean difference between the lowest (trough) and the peak concentrations was 0·76 ±0·11 (SEM) μg/ml. The range did not differ significantly whether the last dose was 200, 250, or 300 mg. Peak concentrations were generally observed within 2 hours of the last dose. In a few patients (16%) the peak was delayed for 6 hours or more.

VENTRICULAR ARRHYTHMIAS DURING THERAPY

Ventricular arrhythmias were detected in 23 patients, either during their hospital stay or at the out-patient clinic (Table 3). Major ventricular arrhythmias (ventricular tachycardia or ventricular fibrillation) were observed in 14 patients. Three of these patients developed ventricular tachycardia

Table 2　*Mexiletine discontinued prematurely in 23 patients*

Suspected adverse reactions	Ineffective	Others	Patients died			
			LVF	Asystole	Died at home	Total
8	7	4	1	1	2	4

LVF, left ventricular failure.

Table 3　*Ventricular arrhythmias in patients receiving mexiletine*

	VES	VT or VF
Total patients	16*	14*
Mean plasma concentration (μg/ml)	1·00 (N=11)	1·68 (N=10)

*7 patients had VES and VT detected on separate occasions.
N, number of patients where plasma concentrations were determined; VES, ventricular ectopics; VF, ventricular fibrillation; VT, ventricular tachycardia.

outside hospital. In 8, it was possible to prevent further recurrence of arrhythmias, either by continuing mexiletine (2) or by giving it in combination with other drugs, that is verapamil, practolol, diphenylhydantoin, disopyramide, procainamide, or quinidine (6). One patient died in left ventricular failure before his treatment could be altered. In the remaining 5, mexiletine was stopped and other treatment instituted. In 11 of the 14 patients, ventricular tachycardia or ventricular fibrillation occurred more than 3 weeks after the onset of acute myocardial infarction. The mean plasma concentration of mexiletine which failed to prevent major ventricular arrhythmias in 10 patients was 1·68 μg/ml (range 0·57 to 3·20 μg/ml). In 6 of these 10 patients, the concentrations were ≥1·60 μg/ml.

Ventricular ectopics were detected in 16 patients, despite a mean plasma concentration of 1·00 μg/ml (range 0·22 to 2·24 μg/ml). In 5 of the patients, the plasma concentration was less than 0·75 μg/ml. In 10 of the patients, the ventricular ectopics were observed on the electrocardiogram recorded at the out-patient clinic.

ELECTROCARDIOGRAPHIC, BIOCHEMICAL, AND HAEMATOLOGICAL FINDINGS

No statistically significant changes were observed in the PR interval or in the duration of QRS or QTc in the 12-lead electrocardiogram. There were no significant differences between the biochemical and haematological results after mexiletine was stopped compared with those at the end of at least 2 months' treatment. Antinuclear factor was detected in 6 patients during treatment: in 1 patient the amount of fluorescence graded visually was + +

out of $+++$. The antibody titre was not determined. Later, the platelet count in this patient fell to less than 100 000/mm³. Three months after stopping the drug the platelet count was normal and antinuclear factor was present in smaller amounts. This patient had previously had an allergic reaction to quinidine.

ADVERSE REACTIONS

Adverse reactions were attributed to mexiletine in 31 (65%) of the 48 patients (Table 4). After excluding those in whom other possible causes of the adverse effects might have operated, 26 (54%) of the 48 patients had adverse effects. The most common side effects were tremor, nausea, and dyspepsia. Individual patients often had more than 1 adverse effect. Undoubtedly, severe side effects occurred in 15 (31%) of the 48 patients. Adverse cardiovascular effects were observed in 4 patients. In 3, bradycardia (heart rate of 50 per minute or less) was associated with a systolic blood pressure of 70 mmHg or lower. All 3 patients had had an anterior myocardial infarction. The bradycardia with hypotension occurred during the third week after the onset of symptoms of myocardial infarction. At the time of onset of bradycardia, none of these patients was receiving other antiarrhythmic drugs or digitalis. Postural hypotension in the absence of bradycardia was observed in 2 patients. In 14 of the 15 patients with severe side effects, the drug was stopped (5) or the dose reduced (9). Reduction in dosage resulted in the suppression or reduction in the severity of side effects. However, in 4 patients arrhythmias recurred. In 1 patient, no alteration was made because of the severity of the arrhythmias. No interactions were observed when mexiletine was given to patients already on other drugs, including antiarrhythmic agents.

The incidence of undoubted adverse effects was not related to the time the drug was given after the onset of acute myocardial infarction. Undoubted adverse effects occurred in 13 (38%) of 34 patients treated within 4 weeks of the onset of symptoms and in 11 (34%) of 32 treated after 4 weeks. Severe side effects occurred in 6 (18%) treated early and in 4 (12%) treated after 4 weeks.

After 4 weeks or more of treatment and despite

Table 5 *Incidence of adverse effects related to trough plasma concentrations of mexiletine; side effects due to gastrointestinal irritation were excluded*

	Plasma concentrations (µg/ml)			
	< 0·5	0·5–	1·0–	⩾1·5
Number of concentrations	30	73	45	30
Severe side effects	0	3 (4%)	1 (2%)	6 (20%)
Total side effects	2 (7%)	13 (18%)	12 (27%)	16 (53%)

Table 6 *Clinical details, plasma concentrations, and side effects of mexiletine using different initial doses*

Dose (mg) given 8-hourly	No. of patients	Age† (y)	Wt† (kg)	Mean trough plasma concentration ±SEM (µg/ml)	Undoubted severe side effects
300	14	58·6 ±3·2	70·4 ±2·3	1·15* 0·13	6 (43%)
250	17	52·3 ±3·8	74·0 ±1·8	0·77* ±0·06	3 (18%)
200	16	58·2 ±2·5	67·6 ±2·9	0·90 ±0·09	4 (25%)

*P < 0·01.
†Mean ±SEM.

some adjustment of the dose, side effects remained as common as in the first weeks of treatment. However, the incidence of undoubted severe adverse effects was reduced from 11 of 48 (23%) to 5 of 37 (14%) but the difference was not statistically significant.

There was considerable variation in the plasma levels which could be tolerated. Some patients developed adverse effects with concentrations of less than 1·0 µg/ml. Others had none, despite levels of more than 2·50 µg/ml. When side effects resulting from gastrointestinal irritation were excluded, undoubted adverse effects occurred in association with a mean trough concentration of 1·03 ±0·18 (SEM) µg/ml and a mean peak level of 1·77 ±0·19 (SEM) µg/ml. However, severe side effects occurred at a higher mean peak concentration than that associated with mild side effects (2·11 ±0·37 (SEM) µg/ml compared with 1·54 ±0·18 (SEM) µg/ml). The difference, however, failed to reach significance. The frequency of adverse effects was related to trough plasma concentrations (after at least 1 week

Table 4 *Side effects observed in patients receiving mexiletine*

	Tremor and/or nystagmus	Indigestion	Nausea	Bradycardia and hypotension	Postural hypotension	Others*	Total patients
Mild	22 (19)	6 (5)	4 (3)	0	0	6 (1)	26 (22)
Severe	9 (9)	4 (4)	6 (4)	3 (3)	2 (2)	7 (2)	17 (15)

*For examples, dizziness, twitching movements, dysphasia, and congestive heart failure.
Figures in parentheses indicate the number of patients in whom mexiletine was considered to be the only possible cause of the side effects.

of therapy) (Table 5). Twenty per cent of trough concentrations ≥1·5 µg/ml were associated with severe adverse effects.

When comparing the effects of different dosages, only the regimens used first in each patient were considered (Table 6). There was wide interpatient variation in plasma concentrations for all dosages. Mean trough plasma concentrations were lower in those receiving 250 mg 8-hourly than in those on 200 mg 8-hourly. This difference may have occurred because those receiving the lower dose weighed less and were in the higher age range. Severe side effects followed the plasma concentrations and were, thus, least common in those receiving the 250 mg 8-hourly regimen.

Discussion

Mexiletine has advantages as an oral antiarrhythmic agent. The mean biological half life for mexiletine in patients is 11·3 hours (N. P. S. Campbell, 1977, unpublished observations). Eight-hourly administration resulted in plasma concentrations within the therapeutic range (Campbell et al., 1977). Ventricular arrhythmias were not detected in more than half of the patients in this study during therapy.

It has been found that the intravenous administration of mexiletine is associated with a high incidence of adverse effects (Campbell et al., 1973; Talbot et al., 1973; Roos et al., 1976). However, when given orally to patients with acute myocardial infarction, it has been reported that adverse effects were infrequent though the drug has a narrow therapeutic index (0·75 to 2·00 µg/ml) (Campbell et al., 1975, 1977) and was given in a fixed dosage (Campbell et al., 1975). Thirty-one (65%) of the 48 patients in this study had adverse effects attributed to mexiletine. Adverse effects occurred in 26 (54%) of the patients when other possible causes of such effects were excluded. In 15 patients (31%), the adverse effects were severe. All these severe side effects occurred more than 2 weeks after the onset of acute myocardial infarction. Other workers report an incidence of 29 per cent of adverse effects necessitating stopping the drug or reducing the dosage (Talbot et al., 1976).

The majority of the adverse effects encountered in this study have previously been described (Campbell et al., 1973). Though other workers have not reported adverse cardiovascular effects when mexiletine was given by mouth (Talbot et al., 1973; Campbell et al., 1975; Talbot et al., 1976), 3 patients in this study developed bradycardia and hypotension during therapy. All had had an anterior myocardial infarction at least 2 weeks before the

development of hypotension. Two patients had received therapy for 2 weeks. Postural hypotension, which was observed in 2 patients, has not been previously documented. Saunamäki (1975) has described a fall in the peripheral resistance in patients given the drug intravenously. The drug has been reported to have negative inotropic effects (Shaw et al., 1973; Saunamäki, 1975). Though 4 patients in this study developed heart failure while on treatment, it was impossible to attribute this to mexiletine with certainty. One patient developed a positive test for antinuclear factor and thrombocytopenia which may have been caused by mexiletine.

Adverse effects are frequently dose related and in individual patients it is frequently possible to arrive at a suitable dose (Talbot et al., 1976; Campbell et al., 1977). In this study, after dosage adjustment undoubted severe adverse effects due to mexiletine occurred in 5 (14%) of 37 patients continuing on the drug for 4 weeks or longer.

The therapeutic plasma concentration of mexiletine lies between 0·75 and 2·00 µg/ml (Campbell et al., 1975, 1977). We have shown that, using 10 to 14 mg/kg per day orally, 72 per cent of steady state plasma concentrations lie within this range (Campbell et al., 1977). In this study, important side effects occurred at a mean peak concentration of 2·11 µg/ml. The mean difference between trough and peak concentrations was 0·76 µg/ml. This suggests that plasma concentrations associated with adverse effects will often occur if trough concentrations of 1·50 µg/ml are exceeded. Twenty per cent of trough concentrations of ≥1·5 µg/ml were associated with severe adverse effects (Table 5). It was disappointing that major ventricular arrhythmias were not prevented by plasma concentrations of 1·60 µg/ml or greater. Talbot et al. (1976) found that in 18 patients with ventricular arrhythmias associated with ischaemic heart disease or acute myocardial infarction, the mean minimum effective therapeutic concentration of mexiletine was 1·60 µg/ml.

The observations among patients in this study, many of whom had cardiac failure and arrhythmias resistant to other antiarrhythmic drugs, suggest that mexiletine may be used for long-term oral therapy. Though side effects are frequent, they are usually dose related. Careful titration of the dose may allow therapy to continue but the margin between therapeutic effect and toxicity is small. Major ventricular arrhythmias (ventricular tachycardia or fibrillation) were detected in 14 patients (29%) at a time when the majority of plasma concentrations lay within the therapeutic range. Failure to prevent major ventricular arrhythmias casts doubt on the value of mexiletine in the prevention of sudden death.

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