Electrophysiological effects of mexiletine in man¹

Julius C. Roos, Adolf C. A. Paalman, and Arend J. Dunning

From the Section of Cardiology, Department of Medicine, and the Laboratory for Clinical Pharmacy and Toxicology, University Hospital Binnengasthuis, Amsterdam, The Netherlands

The electrophysiological effects of intravenous mexiletine in a dose of 200 to 250 mg given over 5 minutes, followed by continuous infusion of 60 to 90 mg per hour, were studied in 5 patients with normal conduction and in 20 patients with a variety of disturbances of impulse formation and conduction, by means of His bundle electrography, atrial pacing, and the extrastimulus method. In all but 2 patients the plasma level was above the lower therapeutic limit. Mexiletine had no consistent effects on sinus frequency and atrial refractoriness. The sinoatrial recovery time changed inconsistently in both directions; however, of the 5 patients in whom an increase was evident, 3 had sinus node dysfunction. In most patients mexiletine increased the AV nodal conduction time at paced atrial rates and shifted the Wenckebach point to a lower atrial rate. The effective refractory period of the AV node was not consistently influenced, while the functional refractory period increased in 12 out of 14 patients. The HV intervals increased by a mean of 11 ms in 8 patients and were unchanged in 17. Both the relative and effective refractory period of the His-Purkinje system increased after mexiletine. Non-cardiac side effects occurred in 7 out of 25 patients, and cardiac side effects, including one serious, in 2.

The results indicate that mexiletine shares some electrophysiological properties with procainamide and quinidine, when given to patients with conduction defects, and that the drug should not be used in patients with pre-existing impairment of impulse formation or conduction. It has additional effects on AV nodal conduction which may be of value in the treatment of re-entrant tachycardias involving the AV node.

Mexiletine (Kö 1173, 1-(2',6'-dimethyl-phenoxy)2-aminopropane) is a new antiarrhythmic drug. Its chemical structure and its local anaesthetic properties closely resemble those of lignocaine. It has a strong antiarrhythmic effect in the experimental animal (Allen *et al.*, 1972; Singh and Williams, 1972) and in man (Campbell *et al.*, 1973; Talbot *et al.*, 1973; Talbot, 1975; Campbell *et al.*, 1975). Its clinical interest is based on its effectiveness in lignocaine-resistant arrhythmias (Campbell *et al.*, 1973), its strong antiarrhythmic potency in ouabain-induced arrhythmias in animals (Singh and Williams, 1972) and the feasibility of oral administration (Campbell *et al.*, 1973; Talbot *et al.*, 1973; Campbell *et al.*, 1975; Achuff *et al.*, 1975).

The purpose of this study is to analyse the electrophysiological effects of mexiletine on human

cardiac impulse formation and conduction by means of intracardiac electrocardiography.

Subjects and methods

Twenty-five patients were studied after informed consent had been obtained. Five patients (group A) had entirely normal impulse conduction, 13 patients (group B) had conduction defects in or distal to the His bundle, while in 7 patients (group C) conduction was delayed above the level of the His bundle.

Sinus node dysfunction was the major defect in 10 patients and 3 patients had complete heart block at the time of study. Four patients were studied within 72 hours of the onset of symptoms of acute myocardial infarction. The relevant clinical data are listed in Table 1. No patient was on digitalis treatment and other antiarrhythmic drugs were withheld for at least 24 hours before the time of study.

The study was performed after a light meal; most of the patients received 10 to 20 mg diazepam orally 30 minutes before catheterization.

Received 26 April 1976.

¹Part of this work was presented at the Symposium 'Mexitil in Ventricular Arrhythmias' held in Malta, 7 to 9 April 1976; an abstract of this will be published in *Postgraduate Medical Journal*.

TABLE 1 Clinical data

Case No.	Age (y)	Sex	Clinical characteristics	ECG diagnosis	Initial dose of mexiletine (mg)	Maintenance dose (mg/h)	Plasma level ($\mu\text{g/ml}$)	Side effects
<i>Group A: Normal conduction</i>								
1	58	M	Syncope	Within normal limits	200 mg/5 min	—	0.96	None
2	74	M	Syncope	Ventricular extrasystoles	200 mg/5 min	—	1.15	None
3*	69	M	Adams-Stokes attacks, old anterior myocard. infarct.	Sinus bradyarrhythmia, atrial flutter	250 mg/5 min	—	0.99	Nausea, vomiting, perspiration
4*	81	F	Adams-Stokes attacks	Sinus bradyarrhythmia, sinus arrest, AV junctional rhythm	250 mg/5 min	60	2.17	None
5	72	F	Angina, old inferior myocard. infarct.	Normal conduction	250 mg/5 min	—	0.72	Dizziness, nausea, vomiting, visual disturbance
<i>Group B: Infra-His conduction delay</i>								
6	76	F	Angina	LBBB, ventricular extrasystoles	250 mg/5 min	—	—	None
7	76	M	Recent anterior myocard. infarct.	RBBB, left anterior hemiblock	250 mg/5 min	90	4.2	None
8	67	F	Dizziness	Sinus bradyarrhythmia, atrial fibrillation, LBBB, RBBB	250 mg/5 min	90	6.2	None
9*	65	F	Adams-Stokes attacks	Brady-tachycardia syndrome, atrial fibrillation	250 mg/5 min	90	0.74	Nausea
10	33	M	Adams-Stokes attacks	Complete heart block	250 mg/5 min	90	0.66	None
11	88	F	Dizziness, intestinal haemorrhage	RBBB, LBBB, Mobitz-II block	125 mg/5 min	30	1.4	None
12*	81	F	Dizziness	2:1 sinoatrial block	250 mg/5 min	60	1.1	Nausea, vomiting, dizziness, nystagmus
13	52	M	Fatigue	Atrial fibrillation, complete AV block, LBBB	250 mg/5 min	60	0.86	None
14	74	M	Syncope	RBBB, left anterior hemiblock	250 mg/5 min	60	0.96	None
15	59	M	Recent inferior myocard. infarct.	RBBB	250 mg/5 min	60	—	None
16	54	M	Angina, recent myocard. infarct.	Rate-dependent RBBB	200 mg/5 min	60	0.78	None
17*	56	F	Dizziness, syncope	Sinus bradyarrhythmia, left anterior hemiblock	200 mg/5 min	—	1.28	Diplopia
18	78	F	Asymptomatic	Intermittent 5:1 AV block	200 mg/5 min	—	0.55	None
<i>Group C: Supra-His conduction delay</i>								
19*	77	M	Syncope, gastro-intestinal haemorrhage	Sinus bradyarrhythmia	250 mg/5 min	90	2.0	None
20*	70	M	Asymptomatic	Brady-tachycardia syndrome, LBBB	250 mg/5 min	1300**	—	None
21	80	F	Adams-Stokes attacks	1st degree AV block	250 mg/5 min	90	1.54	Nausea
22	62	M	Syncope	1st degree AV block	250 mg/5 min	60	0.92	None
23*	59	M	Recent inferior myocard. infarct.	Complete AV block, AV junctional rhythm, sinus arrest	250 mg/5 min	60	0.46	Asystolic arrest
24*	75	F	Mitral stenosis and regurgitation	Atrial quiescence	250 mg/5 min	60	1.33	Nausea, vomiting, dizziness, visual disturbance
25*	50	M	Dizziness	1st degree AV block, carotid hypersensitivity	200 mg/5 min	60	0.28	None

LBBB, left bundle-branch block; RBBB, right bundle-branch block.

*, patients with the sick sinus syndrome.

**, this patient accidentally received an additional 250 mg mexiletine in 11 minutes instead of the usual maintenance infusion.

After local analgesia with 100 mg lignocaine, two electrode catheters were introduced into the right femoral vein. A tripolar electrode wire was positioned against the high lateral wall of the right atrium. The two distal electrodes were used for bipolar atrial pacing, the proximal electrode for the recording of a unipolar high right atrial electrogram.

Another tripolar electrode wire, with electrodes 10 mm apart, was positioned across the tricuspid valve in the His bundle region, as described by Scherlag *et al.* (1969). Standard leads I, II, III, a unipolar high right atrial electrogram, and a His bundle electrogram were recorded on an 8-channel

Elema recorder at a paper speed of 100 mm/s. Refractory periods were measured by the extra-stimulus technique with a modified Medtronic pulse generator (5837), delivering a premature beat with a variable coupling interval after every eighth beat of the basic driven cycle. All stimuli were delivered at twice diastolic threshold and a pulse duration of 2 ms. The atrium was driven at increasing rates with steps of 10 beats/min, beginning with a frequency as close as possible to the spontaneous sinus rate, until a rate of 200/min was reached or high degree AV block appeared. The mean sinoatrial recovery time was calculated from 5 successive determinations.

TABLE 2 Conduction intervals before and after mexiletine

Case No.	Basic cycle length (ms)	PA (ms)		AH (ms)		HV (ms)		HS (ms)		Wenckebach point		Pooled AH		Pooled HV		Sino-atrial recovery time*	
		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Group A : Normal conduction																	
1	720	70	70	140	135	45	45	140	150	140	150	1420	1405	405	405	1106	990
2	650	50	50	145	145	35	40	145	150	140	150	1435	1415	270	285	1400	1298
3†	750	70	70	95	90	45	55	135	145	>180	150	905	995	360	400	**	3287
4†	650	45	40	90	100	40	40	130	130	170	150	1070	1225	400	400	1284	1184
5	810	30	50	85	85	50	50	150	155	150	150	1255	1430	450	470	1552	1400
Group B : Infra-His conduction delay																	
6	900	50	**	90	**	55	55	225	235	**	**	**	**	**	**	**	**
7	750	30	30	90	90	65	65	165	170	130	130	1150	1420	520	520	1030	950
8	700	20	**	120	**	65	85	240	**	**	**	**	**	**	**	**	**
9†	260‡	**	**	**	**	45	60	145	200	**	**	**	**	**	**	**	**
10	720	30	30	80	80	~	~	~	~	140	140	955	985	—	—	1146	1090
11	700	50	50	80	80	60—	75—	180—	190—	170	140	750	745	120	160	998	835
						110	130	230	250								
12†	700	40	40	100	100	60	60	140	140	190	160	1125	1180	720	780	1348	1756
13	240‡	**	**	**	**	60	70	220	230	**	**	**	**	**	**	**	**
14	900	35	35	80	80	40	40	160	160	120	120	1175	1195	440	440	1354	1355
15	550	30	30	80	80	40	40	150	155	>190	>190	955	930	360	415	828	762
16	610	50	50	90	90	60	60	180	185	>190	>190	1206	1245	600	600	886	816
17†	960	50	50-90	120	115	50	50	150	150	100	100	1130	1215	350	350	1286	1430
18	650	50	50	105	115	55	55	130	130	170	150	965	1130	330	330	1074	988
Group C : Supra-His conduction delay																	
19†	750	30-50	50	160	150	50	50	170	170	120	160	1490	1535	400	400	1474	1562
20†	830	40	**	230	**	75	75	235	250	**	**	**	**	**	**	**	**
21	750	50	50	190	170	50	50	125	125	100	80	420	460	100	100	1110	1302
22	800	40	40	170—	195—	50§	50§	135§	145§	150	140	—	—	—	—	1286	1216
				255§	205§												
23†	700	30	30	~	140—	35	35	110	110	<80	¶	¶	¶	¶	¶	4480	¶
					250												
24†	680	††	††	††	550	50	60	140	150	††	110	††	††	††	††	††	††
25†	650	50	50	170	180	55	60	140	150	130	110	1055	1325	330	360	930	1158

*Mean of 5 determinations.

†Patients with the sick sinus syndrome.

‡Spontaneous atrial cycle length (ms).

§AH₁, H₂V, and H₂S intervals in Case 22 with split His bundle deflection (see text).

¶No values because of complete heart block and loss of atrial capture after mexiletine.

**No values because of atrial arrhythmias.

††No values because of atrial quiescence and absence of atrial capture.

~ No values because of complete heart block.

After completion of control measurements, 200 to 250 mg mexiletine was infused intravenously at a constant rate over a 5 minute period, followed by a maintenance infusion of 60 to 90 mg per hour. The dose each patient received is listed in Table 1. All measurements were repeated and completed within 20 minutes after the beginning of the infusion. One or more venous blood samples were obtained during the study for plasma mexiletine determination by gas-liquid chromatography, using a modification of the method described by Kelly *et al.* (1973).

Definition of terms

PA interval: time in ms between the stimulus artefact and the first sharp deflection of the P wave on the His bundle electrogram (normal 20 to 50 ms).

AH interval: time between the onset of the P wave on the His bundle electrogram and the onset of the His spike (normal 60 to 140 ms).

HV interval: time between the onset of the His

spike and the onset of the QRS complex in the standard leads (normal 30 to 55 ms).

HS interval: time between the onset of the His spike and the end of the QRS complex in the standard leads (normal 100 to 145 ms).

Pooled AH intervals: sum in ms of the AH times at each driven atrial rate with 1:1 or 2:1 AV conduction.

Pooled HV intervals: sum in ms of the HV intervals of each driven atrial rate with 1:1 conduction.

Wenckebach point: the highest driven atrial rate permitting 1:1 conduction. In patients with the Wenckebach phenomenon while in sinus rhythm the highest driven atrial rate permitting 2:1 conduction was taken as Wenckebach point.

Sinoatrial recovery time: the interval in ms between the last pacemaker spike and the first spontaneous P wave after abruptly turning off the external pacemaker 20 s after atrial pacing at a rate of 120/min (normal 954 ± 196 (SD) ms).

Effective refractory period of the atrium (ERP_a): the longest S_1 - S_2 interval at which S_2 does not propagate into the atrium.

Effective refractory period of the AV node (ERP_{avn}):

TABLE 3 Effects of mexiletine on refractory periods in 17 patients

Case No.	Basic cycle length (ms)	ERP_a Before	ERP_a After	ERP_{avn} Before	ERP_{avn} After	FRP_{avn} Before	FRP_{avn} After	RRP_{hps} Before	RRP_{hps} After	ERP_{hps} Before	ERP_{hps} After
Group A: Normal conduction											
1	720	<300	<320	340	340	470	450	+	+	+	+
2	650	230	240	330	315	460	465	+	+	+	+
3*	750	335	350	§	§	420	430	<420	480	+	+
4*	650	250	250	300	295	390	400	+	+	+	+
5	810	295	320	≤340	≤370	475	485	§	§	§	§
Group B: Infra-His conduction delay											
10	720	300	270	§	290	≤445	480	+	+	+	+
11†	700	290	250	<310	<310	≤420	≤430	520	680	420	570
12*	700	260	290	315	≤335	≤380	≤410	405	470	+	+
14	900	270	270	<340	330	515	490	§	+	§	+
15	550	220	240	<240	<250	330	350	<330	550	§	§
16	610	≤230	≤230	≤240	≤265	335	335	§	§	§	§
17*	960	320	360	525	440	575	580	+	+	+	+
18	650	200	220	275	280	370	390	390	520	375	475
Group C: Supra-His conduction delay											
19*	750	270	300 > 250	440	500	560	610	+	+	+	+
21	750	310	280	470	475	645	655	+	+	+	+
22	800	330	310	**	<340	**	**	≥790	**	≥790	**
23*	700	360	>750	¶	>750	¶	¶	+	+	+	+
25*	650	265	240	360	415	515	580	+	+	+	+

*Patients with the sick sinus syndrome.

†Because of 2:1 block distal to H the actual hps-refractoriness is >700 ms (basic paced cycle): the intervals presented were measured only when last beat of basic cycle before extra stimulus was blocked distal to H.

‡Study limited by AV nodal refractoriness.

§Study limited by atrial refractoriness.

¶Not performed because of complete AV nodal block and loss of atrial capture.

**Not obtained because of antegrade conduction bypassing the AV node.

Abbreviations as in text: see 'Definition of terms'.

the longest A_1 - A_2 interval at which A_2 fails to reach the His bundle.

Functional refractory period of the AV node (FRP_{avn}): the shortest interval between H_1 and H_2 , both of which are conducted from the atrium.

Effective refractory period of the His-Purkinje system (ERP_{hps}): the longest H_1 - H_2 interval at which H_2 fails to conduct to the ventricles.

Relative refractory period of the His-Purkinje system (RRP_{hps}): the longest H_1 - H_2 interval at which H_2 conducts to the ventricles with a longer HV interval and/or with an aberrant QRS complex.

Results

In Table 2 conduction intervals during atrial stimulation as close as possible to the spontaneous sinus rate before and after mexiletine are listed, together with the pooled AH intervals, pooled HV intervals, sinoatrial recovery time, and Wenckebach point during atrial pacing.

Table 3 summarizes the effects of mexiletine on the refractoriness of the His-Purkinje system, AV node, and atrium. Measurement of refractoriness was impossible in 1 patient because of atrial flutter and complete AV block, in another patient because of atrial quiescence with absence of atrial electrical activity, and in 4 patients because of atrial arrhythmias. In 1 patient (Case 7) only control values are available because of atrial flutter induced by an extrastimulus.

Interference with the results by the local anaesthesia with 100 mg lignocaine is unlikely, as has been shown earlier (Schwartz *et al.*, 1974; Roos and Dunning, 1975).

Sinus node function

In 15 patients sinus rate could be measured before, during, and immediately after the infusion of mexiletine.

The mean rate before mexiletine was 73.1 ± 13.0 (SD) and after mexiletine 75.3 ± 12.4 . This difference has no statistical significance. Atrial refractoriness (Fig. 1, Table 3) was not consistently affected by mexiletine. In 6 patients a mean increase of 24 ms occurred, in 2 patients there was no change, and in 6 patients atrial refractoriness decreased by a mean of 25 ms. The mean net change in all patients was -0.35 ms (not statistically significant).

The sinoatrial recovery time is an indicator of sinus node function and was recorded before and after mexiletine in 17 patients (Table 2). In 5 patients it increased (significantly in 1) and in 11 patients it decreased (significantly in 4). The mean sinoatrial recovery time before and after mexiletine was exactly the same ($1181 \text{ ms} \pm 211$ and 1181 ± 274 ms, respectively). Of the 5 patients who showed an increase after mexiletine, 3 had the sick sinus syndrome, and in only 1 patient with this syndrome did mexiletine decrease the sinoatrial recovery time.

FIG. 1 Refractory periods of the atrium, AV node, and His-Purkinje system before and after intravenous mexiletine. Abbreviations as in text: see 'Definition of terms'.

FIG. 2 Case 11. Panel A shows a paced atrial rate (cycle length 710 ms) with 2:1 HV block before mexiletine. The conducted beats show complete left bundle-branch block with a HV interval of 60 ms. Panel B shows the same paced atrial rate after intra-venous mexiletine. Again 2:1 HV block is present, but now right bundle-branch block with left anterior hemiblock is present, with considerable prolongation of the HV interval to 120 ms in the conducted beats. I, II, III: standard limb leads; A: atrial wave; AH: AH interval (ms); H: His bundle deflection; HBE: His bundle electrogram; HS: total intraventricular conduction (ms); HV: HV interval (ms); S: stimulus artefact; SS: interval between two atrial stimuli (ms); UAE: unipolar atrial electrogram.

AV nodal conduction

The AH interval, as measured during atrial pacing at a rate as close as possible to the spontaneous sinus frequency (Table 2) decreased in 5 patients (mean -9 ms), increased in 3 (mean $+10$ ms), and was unchanged in 8. The mean net change was -0.3 ms (not statistically significant). During atrial pacing, however, at increasing rates, the AH interval tended to become more prolonged after mexiletine. Thus, the pooled AH intervals (Table 2) increased in 12 patients, though in 5 patients a slight decrease

was observed. The mean change after mexiletine was $+8$ per cent. In 3 patients the Wenckebach point occurred at a higher atrial rate, in 5 patients it remained unchanged, and in 8 patients it was reached at a lower paced atrial rate (Table 2).

The effective refractory period of the AV node was not consistently influenced by mexiletine (Table 3, Fig. 1). In 4 patients the change was 5 ms or less, in 2 patients the ERP increased (mean 50 ms) and in 2 others it decreased (mean 57 ms). The mean net change was $+2.5$ ms (not statistically significant). The functional refractory period of the AV node increased more consistently in 11 patients (mean $+21.8$ ms) and decreased in 2 (mean -22.5 ms); the mean net change was $+14.2$ ms, but was not statistically significant.

His-Purkinje conduction

Of the 5 patients with normal conduction, 2 showed a minimal increase of the HV interval after mexiletine ($+5$ and $+10$ ms). One of these also showed a slight increase of the relative refractory period of the His-Purkinje system (Table 3). Six other patients showed an increase of the HV conduction time. Four of these had infra-His conduction defects (mean increase $+15$ ms) and 2 supra-His conduction delay (mean increase $+7.5$ ms) (Table 2). The mean increase of the HV interval was 3.3 ms, which was not statistically significant. In the 5 patients in whom the relative refractory period of the His-Purkinje system could be measured, a consistent and statistically significant increase (mean $+127$ ms, $P < 0.05$) was found after mexiletine. Four of these patients had infra-His conduction disturbances. In 2 patients (also with conduction delay below the His bundle) the effective refractory period of the His-Purkinje system increased (mean $+125$ ms). Some of the electrophysiological responses of these patients to mexiletine are illustrated in Fig. 2 and 3. Fig. 4 shows the effects of mexiletine on an antegrade AV nodal bypass tract in a patient with an intra-His conduction defect; the effective refractory period of this tract increased from 340 to 680 ms after mexiletine.

Complete heart block

Of the 3 patients with complete heart block, the effects of mexiletine could be assessed in 2, the third being completely pacemaker dependent. In Case 13, who had complete AV nodal block, the frequency of the AV junctional escape rhythm was not changed by mexiletine. The second patient (Case 23), also with complete AV nodal block, had a period of

FIG. 3 Case 18. Panel A shows the effective refractory period of the His-Purkinje system (H₁-H₂=375 ms) before mexiletine. Panel B shows a gap phenomenon: a premature beat with a shorter coupling interval than in panel A (285 ms) is now conducted to the ventricles because the H₁-H₂ interval increases to 410 ms because of functional AV nodal refractoriness. Panel D shows an increased effective refractory period of the His-Purkinje system (475 ms) after intravenous mexiletine. Panel C shows that before mexiletine a premature beat with the same H₁-H₂ interval of 475 ms is conducted to the ventricles. The basic cycle length in all panels is 650 ms. The His bundle deflection is fragmented, showing 3 separate spikes in all conducted beats; the blocked beats show only 1 spike, indicating intra-His conduction disturbance. Abbreviations and symbols as in Fig. 2.

FIG. 4 Case 22. Panel A shows a paced atrial rhythm with a cycle length of 500 ms before mexiletine. There is apparent 2:1 AV nodal block; however, when the cycle was shortened to a critical length of 400 ms (not shown in figure) a split His bundle deflection (H¹ and H²) appeared with a stable AH¹ interval of 160 ms, indicating normal AV nodal conduction and 2:1 intra-His block; apparently an AV nodal bypass tract existed (James bundle) which became refractory at a critical cycle length of 400 ms. Panel B shows the same cycle length of 500 ms after intravenous mexiletine. Because of refractoriness of the AV nodal bypass tract, conduction takes place through the AV node, unmasking a 2:1 intra-His block (every second beat being blocked distal to H¹), with a normal AH¹ interval at this rate of 140 ms. Abbreviations and symbols as in Fig. 2.

14 s total cardiac standstill after mexiletine; this patient is described in greater detail below.

Plasma mexiletine levels

Eighteen patients received an intravenous loading dose of 250 mg mexiletine in 5 minutes, followed by a continuous infusion of 60 to 90 mg per hour. The plasma levels at the time of study ranged from 0.46 to 6.2 $\mu\text{g/ml}$ (mean 1.65 ± 0.40 (SEM)). Six patients received a loading dose of 200 mg in 5 minutes, followed by a maintenance infusion of 60 mg per hour. The plasma levels ranged from 0.28 to 1.15 $\mu\text{g/ml}$ (mean 0.83 ± 0.14). Therapeutic plasma levels range from 0.5 to 2.0 $\mu\text{g/ml}$ (Talbot *et al.*, 1973). Two of our patients had plasma levels less than 0.5 $\mu\text{g/ml}$, and 2 had toxic levels (>3 $\mu\text{g/ml}$); all other patients had plasma levels within the therapeutic range.

Side effects

Eight patients suffered from side effects; 7 of them had received the higher loading dose of 250 mg in 5 minutes. Nausea was the most frequent symptom (6 out of 8 patients), followed by dizziness (3/8), vomiting (3/8), and visual disturbances (3/8), namely nystagmus, diplopia, and blurred vision. This high frequency of side effects is related to the dose and the rapidity with which the drug was in-

jected. Fig. 5 shows that when 250 mg mexiletine is injected in 5 minutes, the plasma level immediately after completion of the injection is above the upper therapeutic limit and clearly in the toxic range. During the next minutes the plasma levels rapidly come down to within the therapeutic range.

One patient (Case 23) had serious cardiac side effects. This patient was studied 48 hours after the onset of symptoms of acute inferior myocardial infarction, complicated by complete AV nodal block, with periods of sinus arrest and AV junctional escape rhythm. At the time of study complete heart block was present. During injection of mexiletine a Wenckebach type of block in the AV node developed, suggesting improved AV nodal conduction. Six and a half minutes after the beginning of the injection there was sudden cardiac standstill lasting for a period of 14 seconds, followed by a ventricular escape beat. Right ventricular pacing was then instituted and after 8 minutes the P waves returned. The plasma level at the time of this event was only 0.46 $\mu\text{g/ml}$, which is no more than the lower limit of the therapeutic range. Though this may have been coincidence, the sequence of events suggests that the injection of mexiletine was responsible for asystole in this case. Another patient (Case 12) with 3:2 sinoatrial block showed a reduction in the number of sinus beats from an average of 73 beats/min before to 40 beats/min 30 minutes after mexiletine, with periods of sinus arrest up to 3 seconds.

FIG. 5 This figure shows the mean plasma mexiletine levels ($\pm$ SEM) in 5 patients receiving 250 mg intravenously in 5 minutes, followed by a maintenance infusion of 90 mg/hour. Note that immediately after completion of the injection the plasma level is in the toxic range (>3 $\mu\text{g/ml}$).

Discussion

An ideal antiarrhythmic drug, that is effective, easy to administer, and without side effects and toxic reactions has not yet been produced. Lignocaine, probably the least toxic and certainly the most widely used drug in the coronary care unit, is not always effective and should be used cautiously in patients with distal conduction defects (Roos and Dunning, 1975); and it cannot be given orally. Procainamide, quinidine, phenytoin, and β -adrenergic blocking drugs, all of which can be administered orally, have more side effects than lignocaine, and especially in the long-term treatment of arrhythmias the incidence of adverse reactions is high. There is, therefore, a need for additions to our therapeutic armamentarium.

Mexiletine, originally developed as an anti-convulsant drug, has been studied in animals and in a limited number of patients. In animals (Allen *et al.*, 1972; Singh and Williams, 1972) mexiletine was effective in ventricular arrhythmias and especially in those provoked by ouabain. In the isolated rabbit atrium mexiletine reduced the maximum

frequency with which the atrium could be driven, raised the threshold for electrical stimulation, slowed conduction velocity, and depressed contraction. The drug reduced the maximum rate of rise of the action potential of rabbit atrial and ventricular muscle. The resting potential and action potential duration were not affected.

In the clinical studies of Campbell *et al.* (1973), Talbot *et al.* (1973), Campbell *et al.* (1975), and Achuff *et al.* (1975), mexiletine appeared to be effective against ventricular arrhythmias, both after acute myocardial infarction and in patients with chronic arrhythmias. When lignocaine failed, mexiletine was often successful. After intravenous administration a high percentage of patients had unacceptable side effects. On the other hand, mexiletine, when given orally, compared favourably with procainamide with respect to toxicity and was equally effective (Campbell *et al.*, 1975).

In this study, designed to analyse the electrophysiological properties of mexiletine, we did not find consistent effects on the spontaneous sinus rate at therapeutic plasma levels. Small and inconsistent changes in both directions of atrial refractoriness were found and the same was true for sinoatrial recovery times. No appreciable changes were found in atrial conduction time. Two patients, however, showed a striking reduction or even total absence of sinus activity after mexiletine. Both had pre-existent sinus node dysfunction. In animal experiments, mexiletine has been shown to cause sinus bradycardia, and bradyarrhythmias were described in man as a side effect (Campbell *et al.*, 1973; Talbot *et al.*, 1973). A possible explanation for the fact that sinus node function was not influenced by mexiletine in 23 of the 25 patients studied, could be that the drug has both a vagolytic activity and an intrinsic depressant effect. Such effects work in opposite directions and the net result depends on which of the two is stronger in an individual patient. Patients with sinus node dysfunction are known to respond to atropine-like drugs with only minimal increase in sinus frequency, and it is plausible that in these patients a depressant effect of mexiletine would become manifest.

Conduction time through the AV node was not influenced by mexiletine at driven atrial rates close to the spontaneous sinus rate. However, at higher frequencies the pooled AH times tended to increase and the Wenckebach point shifted to a lower atrial rate in the majority of the patients. The effective refractory period of the AV node changed only slightly, and in both directions, while AV nodal functional refractoriness increased. Measurements of the three variables reflecting AV nodal conduction (functional refractory period, Wenckebach point, and

pooled AH intervals) were available in 14 patients before and after mexiletine. In 11 out of these 14 patients, 2 or 3 of these measurements indicated depressed conduction after mexiletine; in 2 patients the Wenckebach point was unchanged, while the 2 other variables changed in opposite directions; in only 1 patient did all 3 measurements indicate improved conduction. The exact mechanism by which mexiletine influences AV nodal function is not clear. The net effect in the majority of patients, both with normal and abnormal AV nodal conduction, is decreased conduction. Again this may be the resultant of a vagolytic and an (in most of the patients apparently dominating) intrinsic depressant action. In Case 23 the sequence of events (improved AV nodal conduction followed by cardiac standstill) is consistent with the view that mexiletine has such a dual action. The net effect of mexiletine on AV nodal conduction could be of value in the treatment of re-entrant tachycardias involving the AV node. Its possible usefulness in tachycardias associated with pre-excitation is illustrated by one patient in our study (Fig. 5). Two patients in this study, with atrial tachycardias occurring during catheterization, reverted to sinus rhythm after mexiletine; another patient, not in this study, with paroxysmal supraventricular tachycardia, resistant to all conventional drugs, has now been free of attacks for 1½ years on treatment with oral mexiletine.

In this study mexiletine appeared to produce a small increase in total intraventricular conduction time in the majority of the patients. In some patients (most of them with pre-existing infra-His conduction defects) the HV interval increased and/or His-Purkinje refractoriness increased. These results are in agreement with those of Lang, Just, and Limbourg (1975), who also found delayed infra-His conduction in some of their patients. In this respect, mexiletine resembles procainamide (Josephson *et al.*, 1974a) and quinidine (Josephson *et al.*, 1974b) and should be classified as a class IA antiarrhythmic drug (Singh and Hanswirth, 1974). McComish *et al.* (1975), however, found, in patients with normal cardiac conduction, a slight but statistically significant decrease of the relative refractory period of the His-Purkinje system after mexiletine.

The mechanism by which mexiletine exerts its antiarrhythmic effect thus seems to be a complicated one. It seems likely that mexiletine, like lignocaine, acts differently on normal and diseased conduction tissue.

Like Campbell *et al.* (1973) and Talbot *et al.* (1973) we found a high incidence of side effects after intravenous injection of mexiletine (8 out of 25 patients). Two patients had a cardiotoxic reaction which was severe in one of these. Seven of the 8

patients who suffered from side effects had received the higher dose of 250 mg infused over 5 minutes, while only 1 patient, who received 200 mg in 5 minutes, showed mild symptoms (diplopia). The side effects were thus related to the dose and the rapidity of intravenous injection and were confined to a period of 5 to 20 minutes after the loading dose was given.

Like Talbot *et al.* (1973) our experience with oral mexiletine indicates that side effects do not occur or only rarely do so with this route of administration. The apparent effects on intracardiac conduction and the described adverse effects in 2 patients make the drug less suitable for treatment of patients with pre-existing disturbances of impulse formation and/or infra-His conduction.

We thank Mr. J. Siebeling of Boehringer Ingelheim for providing the mexiletine.

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Requests for reprints to Dr. Julius C. Roos, Section of Cardiology, Binnengasthuis, 10 Grimborgwal, Amsterdam, The Netherlands.