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COMPARATIVE ANTIDYSRHYTHMIC AND HAEMODYNAMIC EFFECTS OF ORALLY OR INTRAVENOUSLY ADMINISTERED MEXILETINE AND ORG 6001 IN THE ANAESTHETIZED RAT

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1 The antidysrhythmic and haemodynamic effects of the aminosteroid, Org 6001, were studied in the rat anaesthetized with pentobarbitone. Mexiletine was used for comparison.

2 Both Org 6001 (2–10 mg/kg) and mexiletine (1 mg/kg) given intravenously antagonized the development of dysrhythmias evoked by acute coronary artery ligation in rats.

3 In antidysrhythmic doses, Org 6001 and mexiletine exerted only moderate and transient hypotension and depression of cardiac contractility (assessed from LV $dP/dt\,max$). Org 6001 did, however, induce a more sustained bradycardia.

4 Effective oral doses of Org 6001 (20–100 mg/kg) were similar to those of mexiletine, disopyramide and propafenone.

5 Oral Org 6001 (100 mg/kg) was effective for 18 h whereas mexiletine (100 mg/kg) failed to protect against evoked dysrhythmias 3 h after dosing.

6 Org 6001 and mexiletine differed in their actions on ventricular fibrillation threshold (VFT). Org 6001 (100 mg/kg orally 12 h before ligation) prevented the decrease in VFT produced by coronary ligation whereas mexiletine (100 mg/kg orally) had no effect. When administered intravenously, mexiletine (but not Org 6001) increased VFT in normal ventricular muscle.

Introduction

Org 6001 (3α-amino-5α-androstan-2β-ol-17-one hydrochloride) is an experimental antidysrhythmic agent the electrophysiological actions of which resemble those of lignocaine and mexiletine (Singh & Hauswirth, 1974; Salako, Vaughan Williams & Wittig, 1976). The drug has been shown to be active when given orally in antagonizing the development of dysrhythmias evoked by aconitine in rats and mice (Vargaftig, Sugrue, Buckett & van Riezen, 1975; Winslow, 1980) or by acute coronary artery ligation in dogs (Marshall & Parratt, 1975) and rats (Kane, Lepran, McDonald, Parratt & Szekeres, 1980). Vargaftig *et al.* (1975) found that orally administered Org 6001 was effective against aconitine-induced dysrhythmias in rats for 18 h and Winslow (1980) found antidysrhythmic activity at 6 h (but not 18 h) after administration to mice. Marshall & Parratt (1975) demonstrated oral activity in dogs at least 4 h after dosing (later times were not studied). Org 6001 would therefore appear to possess a reasonably long duration of action. This agent has also been shown to exert only modest and/or transient cardiodepressant actions in dogs (Marshall & Parratt, 1975; Remme, Verdouw & Hagemeijer, 1976) in antidysrhythmic doses and to be at least as well tolerated as quinidine and procainamide in pigs (Verdouw, Remme, Beaune, Rutteman & Hagemeijer, 1976).

The initial aim of the present study was to investigate the oral efficacy and duration of action of Org 6001 against dysrhythmias evoked by acute coronary artery ligation in the rat and to examine its effects on the cardiovascular system of the rat following intravenous administration. Mexiletine was used for comparison. During the course of these studies, mexiletine administered 12 h before ligation was found to exacerbate the evoked dysrhythmias. This prompted further studies on the effects of the two drugs on ventricular fibrillation thresholds.

A preliminary account of these studies has been presented to the British Pharmacological Society (Marshall, Muir & Winslow, 1980).

Methods

Male Wistar rats (340–510 g) were anaesthetized with pentobarbitone sodium (60 mg/kg i.p.) and artificially ventilated with room air (Stroke volume, 4 ml; 48 strokes/min). Arterial blood pressure was recorded from the right carotid artery and the elec-

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trocardiogram (ECG) (Lead II) recorded from subcutaneous steel needle electrodes. Blood pressure (BP) and the ECG were displayed on a Mingograph 82 ink jet recorder (Elema-Schonander). A left thoracotomy was performed, the heart exteriorized, and a 6/0 silk suture placed under the main left coronary artery as described by Selye, Bajusz, Grasso & Mendell (1960). The heart was repositioned in the thoracic cavity and a stabilization period of 15 min allowed. Intravenously administered drugs were given via the left femoral vein 15 min before tightening the ligature. Ligation was performed 1 to 18 h after oral administration. The number of premature ventricular systoles (PVS) was counted and the incidence of ventricular fibrillo flutter (VFl) noted during the 0–30 min postligation period. The method has been described in full by Clark, Foreman, Kane, McDonald & Parratt (1980).

In a separate group of animals, the carotid artery catheter was advanced into the left ventricle to allow recordings of left ventricular pressure (LVP) and left ventricular dP/dt ($LVdP/dt$), using an Elema-Schonander differentiating circuit.

For determination of ventricular fibrillation thresholds (VFT) ribs 2, 3 and 4 were cut close to the left side of the sternum and the chest walls retracted. Two platinum electrodes (6 mm apart) embedded in a narrow rubber strip were positioned on the left ventricular anterior wall such that the anode was approximately 3 mm below the atrioventricular ring and the cathode on or near the apex. The rubber strip was held in place by means of anchoring threads. Square wave pulses (0.8 ms duration; 50 Hz) delivered from a Nihon Kohden (SEN-1101) stimulator were passed through a constant current stimulus isolation unit (SS-101J) to give an initial current intensity of 100 μA. Current intensity was then gradually increased until ventricular fibrillation (VF) developed at which point the stimulation was stopped and the current intensity read. Drugs or vehicle were given intravenously 10 min after the control determination and VFT redetermined 20 min after drug administration.

In oral studies, VFT was determined 20 min before and 3 to 4 min after ligation. This study was performed 'blind'.

A Chi-square test was used to detect significant differences in the incidence of VFl between control and drug-treated animals. In all other experiments, significant differences between means of drug-treated and control groups or intergroup differences were determined by Student's t test.

Drugs used were propafenone hydrochloride (Helopharm), disopyramide phosphate (Searle), mexiletine hydrochloride (Boehringer Ingleheim) and Org 6001 hydrochloride (Organon).

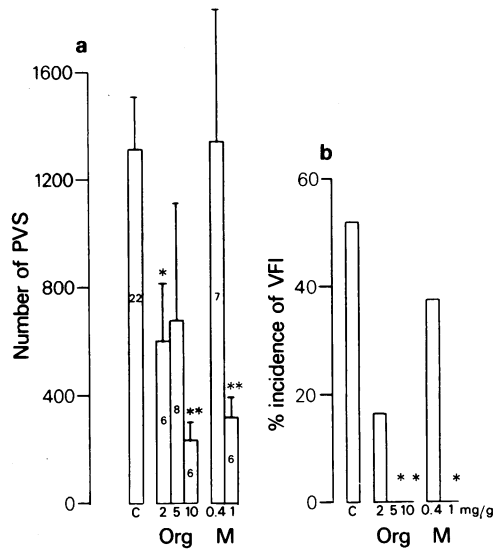

Figure 1 Effects of intravenously administered Org 6001 (Org) and mexiletine (M) on the number of premature ventricular systoles (PVS) and the incidence of ventricular fibrillo flutter (VFl) observed during the 30 min period following coronary artery ligation in the anaesthetized rat. C is the control. Each column in (a) is the mean of the number of observations (shown in each column); vertical lines show s.e.mean. *($P<0.05$) and **($P<0.01$) denote significant differences from the control value. In (b) a Chi square test was applied to detect significance (*denotes $P<0.05$).

Results

Antidysrhythmic and haemodynamic effects of bolus intravenous injections of Org 6001 or mexiletine

Figure 1 compares the mean number of PVS and the incidence of VFl recorded during the first 30 min of ligation in control animals and in animals given Org 6001 (2, 5 and 10 mg/kg) or mexiletine (0.4 and 1 mg/kg). The mean number of PVS in the control group was 1312 ± 196 and the incidence of VFl was 52%. The mean ectopic count was significantly lower in animals given 2 or 10 mg/kg Org 6001 and doses of 5 and 10 mg/kg completely prevented the development of VFl. In 7 rats, mexiletine at a dose of 0.4 mg/kg failed to influence the severity of the dysrhythmias. In one other rat the ectopic count was 4732 beats which was above the range encountered in control animals (249–3308). This animal has not been included in the summarized results. However, mexiletine in a dose of 1 mg/kg markedly reduced the number of PVS (to 319 ± 74) and abolished the development of VFl.

Table 1 Maximum haemodynamic effects of intravenously administered Org 6001

	Control	% change 2	5	10 mg/kg
Systolic blood pressure (mm Hg)	143 ± 8	− 3 ± 2 (7)	− 8 ± 4 (7)	** − 26 ± 3 (9)
Diastolic blood pressure (mm Hg)	105 ± 9	− 6 ± 4 (7)	− 22 ± 5 (7)	*** − 44 ± 4 (9)
Heart rate (beats/min)	450 ± 10	− 3 ± 1 (7)	− 9 ± 2 (8)	** − 20 ± 3 (9)
Left ventricular systolic pressure (mm Hg)	136 ± 12	− 12 ± 2 (5)	− 13 ± 3 (5)	− 14 ± 5 (5)
Left ventricular $dP/dt\,max$ (mm Hg/s)	4205 ± 439	* − 12 ± 4 (5)	* − 14 ± 2 (5)	* − 19 ± 2 (5)

Results of the mean ± s.e.mean of from 4 to 9 observations (n).
Significant differences from the controls denoted: $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.
1 mm Hg = 1.333 mbar.

The haemodynamic effects of Org 6001 and mexiletine are summarized in Tables 1 and 2. Both drugs induced a dose-dependent decrease in BP, LVP and LV$dP/dt$ *max*. Org 6001 also caused a dose-dependent decrease in heart rate whereas mexiletine produced very little change. Comparison of the haemodynamic effects of the highest doses of each drug used showed that mexiletine (1 mg/kg) and Org 6001 (10 mg/kg) depressed BP and LV$dP/dt\,max$ to a similar extent. These responses were transient and by 15 min only a small residual depression of cardiac rate (5%) was apparent following the highest dose of Org 6001 used.

Antidysrhythmic effects of orally administered drugs

Figure 2 compares the mean number of PVS and the incidence of VFl recorded from animals given 0.9% w/v NaCl solution (saline, 1 ml/kg), Org 6001, mexiletine, disopyramide or propafenone 1 h before ligation. The mean number of PVS was significantly less than the mean control value (1458 ± 206) in rats given 20 mg/kg Org 6001 or 50 mg/kg mexiletine, disopyramide or propafenone. The development of VFl (44% in the control group) was prevented by 20 mg/kg Org 6001, 50 mg/kg mexiletine or 100 mg/kg disopyramide and reduced (but not significantly) by 100 mg/kg propafenone. Again, one animal given the low dose of mexiletine (20 mg/kg) developed a greater number of PVS (4943 beats) following ligation than that observed in the control animals.

In all drug-treated groups, mean systolic and diastolic arterial blood pressures recorded before ligation were similar to those recorded in control animals (123 ± 9/100 ± 9 mm Hg) whereas heart rates were moderately lower in animals which received the largest dose of each drug used. The decrease in heart

Table 2 Maximum haemodynamic effects of intravenously administered mexiletine

	Control	% change 0.4	1.0 mg/kg
Systolic blood pressure (mm Hg)	134 ± 6	** − 20 ± 3 (8)	* − 24 ± 6 (6)
Diastolic blood pressure (mm Hg)	107 ± 5	*** − 32 ± 4 (8)	** − 32 ± 6 (6)
Heart rate (beats/min)	421 ± 9	− 6 ± 1 (8)	− 8 ± 1 (6)
Left ventricular systolic pressure (mm Hg)	130 ± 13	− 13 ± 5 (4)	− 25 ± 6 (5)
Left ventricular $dP/dt\,max$ (mm Hg/s)	3898 ± 497	− 9 ± 3 (4)	* − 24 ± 5 (5)

Results are the mean ± s.e.mean of from 4 to 9 observations (n).
Significant differences from the controls denoted: $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$.
1 mm Hg = 1.333 mbar.

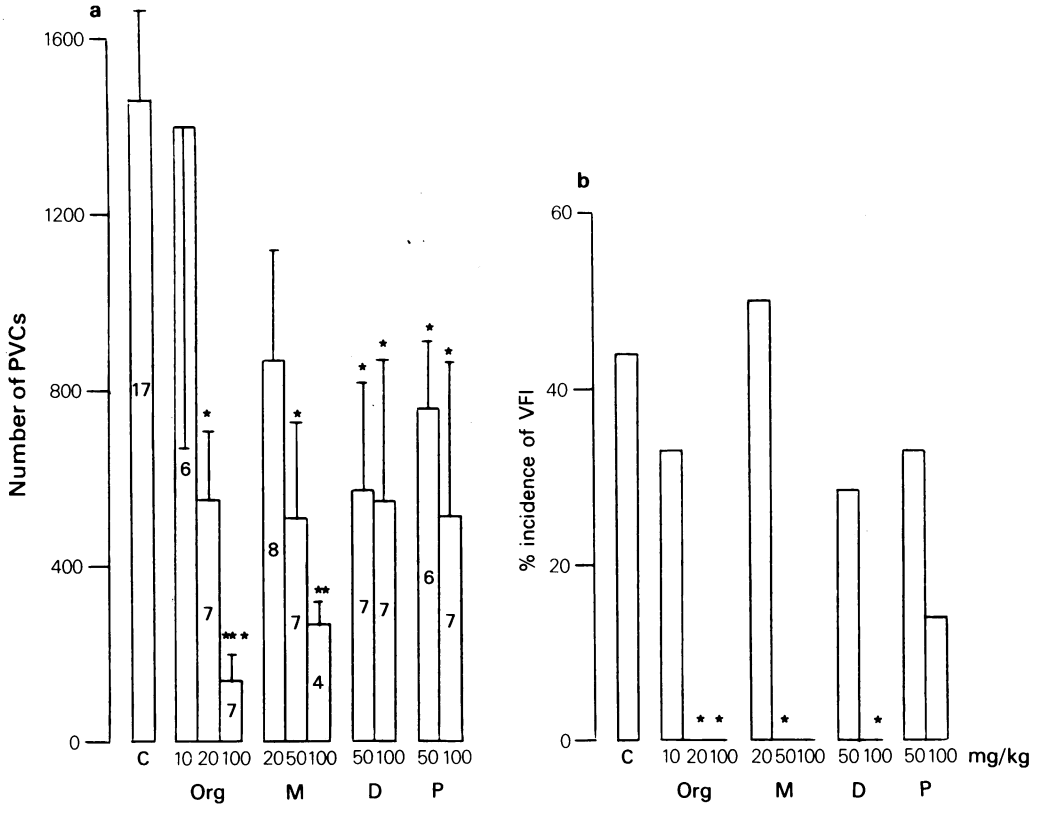

Figure 2 Effects of orally administered Org 6001 (Org), mexiletine (M), disopyramide (D) and propafenone (P) on the number of premature ventricular systoles (PVS) and the incidence of ventricular fibrillo-flutter (VFl) observed during the 30 min period following coronary artery ligation in the anaesthetized rat. C is the control. Each column in (a) is the mean of the number of observations (shown in each column); vertical lines show s.e.mean. *($P<0.05$), **($P<0.01$) and ***($P<0.001$) denote significant differences from the control value. In (b) a Chi square test was applied to detect significance (*denotes $P<0.05$).

rate reached significance ($P<0.05$) for the Org 6001 (100 mg/kg) and disopyramide (100 mg/kg) groups. Mean preligation values of heart rates in these groups were 405 ± 8 and 394 ± 13 beats/min respectively compared to 443 ± 6 in the control animals. Heart rates recorded 30 min after ligation were similar in the drug-treated and control groups (413 ± 8 beats/min).

Comparative duration of action of Org 6001 and mexiletine given orally

The ectopic count and the incidence of VFl in animals given 20 mg/kg Org 6001, 12 h before ligation, were 1315 ± 277 and 57% respectively ($n=7$). Corresponding values from animals given 25 or 50 mg/kg mexiletine were 1336 ± 301; 29%; $n=7$ and 1006 ± 353; 25%; $n=8$ respectively. None of these values were significantly different from the controls.

Figure 3 compares the number of PVS and the incidence of VFl in animals pretreated with these drugs at doses of 100 mg/kg. Ligation was performed 1, 3, 12 or 18 h after drug administration. A marked and significant reduction in the number of dysrhythmias was apparent when ligation was performed 1, 12 or 18 h after Org 6001. The numbers of PVS in these groups were 142 ± 59, 23 ± 11 and 211 ± 194 respectively and VFl was not seen in any Org 6001-treated animal.

In contrast a significant decrease in the expected number of PVS was only seen in response to mexiletine when ligation was performed 1 h after dosing. At 3, 12 or 18 h after administration of mexiletine, the number of PVS and the incidence of VFl were not significantly different from control values. However, in the 12 h mexiletine group, all the animals which developed fibrillo-flutter died (63%) whereas only 7% mortality was recorded in the control group.

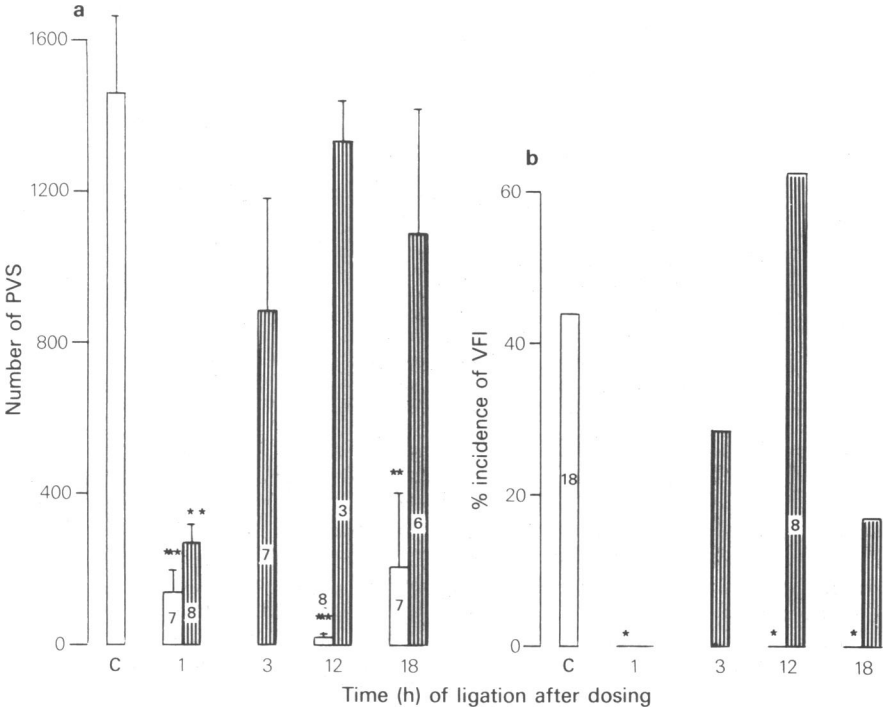

Figure 3 The number of prèmature ventricular systoles (PVS) and the incidence of ventricular fibrilloflutter (VFl) recorded during the 0–30 min period following coronary artery ligation in animals orally pretreated with Org 6001 (100 mg/kg, open columns) or mexiletine (100 mg/kg, lined columns) 1, 3, 12 or 18 h before ligation. Each column in (a) is the mean of the number of observations (shown in each column); vertical lines show s.e.mean. *($P<0.05$), **($P<0.01$) and ***($P<0.001$) denote significant differences from the control value (C). In (b) a Chi square test was applied to detect significance (*denotes $P<0.05$).

Mean arterial blood pressures in all groups of treated animals were similar to control values when compared both before and 30 min after ligation ($123\pm9/100\pm9$ and $87\pm9/64\pm8$ mm Hg respectively). Heart rates were also within normal limits although moderate but significant ($P<0.05$) reductions were seen in the 12 h Org 6001 group, both before and 30 min after ligation. At these times heart rates were 360 ± 21 and 341 ± 14 beats/min respectively whereas values recorded from control animals were 443 ± 6 and 413 ± 8 beats/min respectively.

Examination of the ECG showed that 12 h after Org 6001 (100 mg/kg) the PR, QRS and QT intervals were all significantly longer than those recorded from control animals whereas in the 100 mg/kg mexiletine group only the QT interval was lengthened (Table 3).

Effects of mexiletine and Org 6001 on ventricular fibrillation thresholds

VFT was determined before and after coronary artery ligation in animals dosed 12 h previously with saline, Org 6001 or mexiletine (both 100 mg/kg). The results are summarized in Table 3. In the control group VFT fell significantly after coronary artery ligation whereas no change in VFT occurred in the animals given Org 6001. The mean VFT recorded before ligation in the mexiletine group was significantly lower than the preligation control value. Coronary occlusion in this group resulted in a further, although statistically insignificant, decrease in VFT. The mean postligation VFT value in the mexiletine group was significantly less than the value recorded preligation in both the control and Org 6001-treated groups and also significantly smaller than the postligation VFT value in the Org 6001 group.

In a second series of experiments the effects of intravenously administered mexiletine (0.2 and 1 mg/kg) on VFT of non-ischaemic hearts were compared to those of Org 6001 (0.5 and 5 mg/kg). The results are summarized in Table 4. The low dose of mexiletine (0.2 mg/kg) and Org 6001 at either dose were without effect on VFT. The higher dose of mexiletine increased VFT by a mean of $50\pm18\%$ ($P<0.05$; paired t test).

Table 3 PR, QT and QRS intervals and the effects of coronary artery ligation on ventricular fibrillation thresholds (VFT) in animals pretreated with saline (4 ml/kg), Org 6001 (100 mg/kg) or mexiletine (100 mg/kg) 12 h before ligation

Treatment	*PR* (ms)	*QT* (ms)	*QRS* (ms)	*VFT* (μA) *Preligation*	*3–4 min postligation*
Saline	44 ± 1 (7)	78 ± 3 (7)	13.5 ± 0.4 (7)	††549 ± 69	†332 ± 59
Mexiletine	44 ± 2 (7)	*88 ± 2 (7)	14.0 ± 0.8 (7)	†363 ± 48	†279 ± 43
Org 6001	***52 ± 1 (8)	*96 ± 6 (8)	***18.9 ± 0.8 (8)	††421 ± 48	††493 ± 69

*($P<0.05$) and ***($P<0.001$) denote significant differences from the corresponding saline values; †denotes a significant difference from the preligation control value and ††denotes a significant difference from the postligation value in the mexiletine group. Number of observations in parentheses.

Discussion

The results of the present study indicate that Org 6001 administered orally (1 h before ligation) in doses comparable to those of other known antidysrhythmic agents (mexiletine, propafenone and disopyramide) is effective in antagonizing the development of dysrhythmias evoked by acute coronary artery ligation in the anaesthetized rat. Comparison with mexiletine suggests that whereas this agent is 5–10 times more potent than Org 6001 following intravenous administration, the oral potency of Org 6001 is marginally greater than that of mexiletine. An oral dose of 20 mg/kg Org 6001 completely prevented the development of VFl whereas a similar oral dose of mexiletine was ineffective. Studies on the duration of action of the two drugs suggest that Org 6001 is the longer acting in this species. Marked antidysrhythmic activity was still present 18 h after dosing with Org 6001 (100 mg/kg) whereas 3 h after a similar dose of mexiletine only minimal and insignificant antidysrhythmic activity could be demonstrated.

The development of ligation-induced dysrhythmias 12 h after oral administration of mexiletine yielded unexpected results; mortality from VFl increased from 7% in the controls to 63%. Comparison of ventricular fibrillation thresholds at this time revealed that the mean VFT in the mexiletine group was significantly lower than that recorded in the group of animals given saline 12 h before ligation. These results suggest an increased vulnerability to ventricular fibrillation in these animals. Since arterial blood pressure and heart rate were not different from the control values at this time and no obvious signs of toxicity were observed, it seems unlikely that overdosage with mexiletine was responsible for the increased susceptibility to dysrhythmias. It should also be noted that lower doses of mexiletine (25 and 50 mg/kg) did not enhance the development of dysrhythmias when ligation was carried out at 12 h nor was such an effect seen 18 h after receipt of 100 mg/kg. Indeed it could be argued that mexiletine afforded protection in these groups since the incidence of VFl was lower, although not significantly, than control incidence. Increased vulnerability to ligation-induced dysrhythmias in the 100 mg/kg (12 h) group could, perhaps, be explained by an effect of sub-threshold plasma levels of mexiletine at this time although measurement of plasma drug

Table 4 The effects of intravenously administered Org 6001 and mexiletine on ventricular fibrillation thresholds (VFT) of non-ligated hearts

Drug (mg/kg)	n	*VFT* (μA) *Before treatment*	*20 min after treatment*
Saline (1 ml/kg)	9	469 ± 33	496 ± 51
Mexiletine (0.2)	8	410 ± 40	418 ± 45
Mexiletine (1.0)	7	517 ± 83	788 ± 133*
Org 6001 (0.5)	6	458 ± 66	423 ± 49
Org 6001 (5.0)	8	421 ± 42	444 ± 59

Each result is the mean ± s.e.mean of *n* observations.
$P<0.05$; paired *t* test.

levels would be necessary to state this with any certainty. Yamada, Ikeda, Goto, Okuma, Inamura, Toyoshima, Toyama & Harumi (1978) have shown that low concentrations of mexiletine shorten the transmembrane action potential duration and the effective refractory period of dog Purkinje fibres whilst Arita, Goto, Nagmoto & Saikawa (1979) have demonstrated enhanced conduction of propagated premature action potentials. Although improved conduction of premature stimuli has been suggested as a possible mechanism to explain the suppression of ventricular dysrhythmias (Bigger, Bassett & Hoffman, 1968) such an action could equally well be regarded as proarrhythmogenic. Our own observation that the QT interval but not the PR or QRS duration was prolonged 12 h after oral mexiletine may indicate an increased inhomogeneity in refractoriness of cardiac tissue. Exacerbation of early post-infarction dysrhythmias is not unique to mexiletine and has also been found in response to other antiarrhythmic drugs, e.g. lignocaine (Zipes & Troup, 1978) and aprindine (Nattel, Pedersen & Zipes, 1979).

In contrast to the results obtained from the 12 h oral study with mexiletine, a marked degree of protection was seen in animals similarly pretreated with Org 6001. Ligation-induced VFl was completely prevented and the development of PVS almost completely suppressed by 100 mg/kg Org 6001. Moreover, the decrease in VFT recorded after ligation in the control animals was prevented by this agent. Mean arterial blood pressure was similar to that observed in control animals whereas heart rate was 19% lower and the PR, QT and QRS intervals significantly greater. These effects on the rat ECG are consistent with those of antidysrhythmic agents which induce membrane stabilization and slow conduction (Singh & Hauswirth, 1974; Kuhl, Buschman & Budden, 1980). Although exacerbation of dysrhythmias by Org 6001 was not seen in the present study, it remains possible that plasma levels outside the 'therapeutic' range may exert effects similar to those reported for mexiletine.

Although the fall in VFT associated with ligation was prevented by Org 6001, VFT recorded before ligation was not significantly different from the control values, suggesting that VFT of normal myocardium is little influenced by Org 6001. This agent was similarly without effect on VFT of non-ligated hearts following intravenous administration. On the other hand, mexiletine produced a significant increase in VFT, an observation similar to that made by Allen, Kofi, Ekue, Shanks & Zaidi (1972) in the dog. The differential effects of Org 6001 and mexiletine in VFT may reflect differences in the electrophysiological profiles of the two drugs. Whereas mexiletine increases the effective refractory period of dog ventricular muscle cells (Yamaguchi, Singh & Mandel, 1979; Anta *et al.*, 1979), Org 6001 has been shown to have no effect on refractoriness of normal human ventricular muscle (Kane, 1980). In contrast, the fall in VFT following coronary artery ligation was prevented by Org 6001 suggesting that the membrane stabilizing actions are more manifest in ischaemic tissue.

In antidysrhythmic doses both Org 6001 (2–10 mg/kg) and mexiletine (1 mg/kg) given intravenously induced only moderate and transient reductions in BP, LVP and LVPdP/dt *max*. These results agree with the reported haemodynamic effects of Org 6001 in dogs (Marshall & Parratt, 1975; Remme *et al.*, 1976) and pigs (Verdouw *et al.*, 1976) and suggest that in antidysrhythmic doses, Org 6001 is devoid of marked cardiodepressant actions. However, Org 6001 induced a more marked and longer lasting bradycardia, an effect that was also apparent 12 h after oral dosing with 100 mg/kg.

In conclusion, the duration of action of the antidysrhythmic effect of orally administered Org 6001 in the rat is longer than that of mexiletine. In antidysrhythmic doses, Org 6001 (like mexiletine) exerts only modest and transient haemodynamic effects but causes a more pronounced and prolonged bradycardia.

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