Comparison of the electrophysiological effects of Org 7797, disopyramide, mexiletine and propafenone in anaesthetized dogs with myocardial infarcts

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1 The electrophysiological effects of intravenously administered Org 7797 were compared with those of disopyramide (class Ia), mexiletine (Ib) and propafenone (Ic) in anaesthetized dogs with 5–6 day-old left ventricular myocardial infarcts.

2 Org 7797 (0.5 mg kg^{-1}) slowed conduction at all levels of the myocardium as shown by increases in St-A, AH, HV and QRS intervals, very modestly prolonged atrial and ventricular refractory periods and slightly shortened ventricular repolarization. Sinus node recovery time was increased whilst the RR interval was unchanged. A higher dose (2 mg kg^{-1}) prolonged RR and rendered 5 out of 8 dogs unable to follow an atrial pacing stimulus of mean cycle length 322 ms.

3 Electrophysiological changes induced by propafenone (2 mg kg^{-1}) were qualitatively similar to those of Org 7797 (0.5 mg kg^{-1}).

4 Electrophysiological changes induced by mexiletine (2 mg kg^{-1}) were small or insignificant. The most noticeable effect was a modest increase in the St-A interval and a slight shortening of ventricular repolarization. A higher dose (8 mg kg^{-1}) additionally slowed conduction in the His-Purkinje system and in the ventricular myocardium.

5 Disopyramide (2 and 5 mg kg^{-1}) prolonged all cardiac intervals including JTc, QTc and QT during pacing and prolonged cardiac refractory periods.

6 It was concluded that the electrophysiological profile of Org 7797 is more like that of the Ic agent propafenone than that of the class Ia and Ib drugs, disopyramide and mexiletine.

Keywords: Electrophysiology; anaesthetized dog; myocardial infarction; Org 7797; propafenone; mexiletine; disopyramide

Introduction

Most clinically available antiarrhythmic agents block the fast inward sodium current in cardiac tissue (class I agents). However, individual class I agents display a variety of electrophysiological profiles and have been broadly subclassified into Ia, Ib and Ic agents on the basis of both their electrophysiological actions *in vivo* (Harrison, 1985) and on the speed at which they bind to and dissociate from cardiac sodium channels *in vitro* (Campbell, 1983). Org 7797 ((16 α ,17 β)-17-methylamino-oestra-1,3,5(10)-triene-3,16-diol(z)-2-butenedioate), is a new steroidal antiarrhythmic agent (Winslow *et al.*, 1989a; Janse *et al.*, 1990; Kirchhof *et al.*, 1991) currently undergoing clinical evaluation and which, in terms of its kinetics of sodium channel block in isolated porcine cardiac tissue has been subclassified as a Ic agent (Winslow *et al.*, 1989b). The aim of the present study was to evaluate and compare the electrophysiological actions of Org 7797 *in vivo* with those of disopyramide, mexiletine and propafenone, antiarrhythmic agents belonging to classes Ia, Ib and Ic respectively. Drug doses were chosen to include accepted therapeutic doses in man or in animal models of ischaemic-induced arrhythmias. Since electrophysiological results from clinical studies imply that the effects of sodium channel blocking agents on infra-nodal conduction may be enhanced in patients with existing conduction defects or coronary heart disease (Ross *et al.*, 1978; Marrot *et al.*, 1976), dogs with 5–6 day old myocardial infarcts were used for this study. Part of this work has already been published in abstract form (Winslow *et al.*, 1989a).

Methods

Beagle dogs of either sex (10.0 to 14.4 kg) were anaesthetized with sodium thiopentone (25 mg kg^{-1} , i.v.). Anaesthesia was

subsequently maintained with halothane (1–2%) in $\text{N}_2\text{O}/\text{O}_2$ (1:1). Using aseptic techniques, the left carotid artery was isolated and a guide catheter inserted and positioned at the left coronary ostium under fluoroscopic control. A Fogarty 2F embolectomy catheter was passed through the guide catheter into the left anterior descending coronary artery. The catheter balloon was inflated by injecting contrast medium to occlude the artery close to its origin. If ECG leads I, II or III showed no evidence of ischaemia 2 to 3 min after occlusion, the balloon was deflated and repositioned in the circumflex coronary artery. After 2 h of artery occlusion, the balloon was deflated, the guide and embolectomy catheters removed, the neck wound closed and the animal allowed to recover from anaesthesia. Xylocaine spray and acramide antibiotic powder were applied around the neck wound and ampicillin given intramuscularly. Heparin (1000 units i.v.) was administered prior to surgery to minimize the risk of thrombus formation around the catheters and lignocaine (8 mg kg^{-1} , i.m.) was given 5 min prior to reperfusion in an attempt to reduce the risk of fatal arrhythmias.

Five or six days after myocardial infarction, animals were re-anaesthetized with sodium pentobarbitone (30 mg kg^{-1} , i.v.). 6F quadripolar and bipolar intracardiac electrodes were positioned via the left jugular vein in the right atrium and right ventricle respectively. A bipolar electrode was positioned at the aortic root via the left femoral artery for His bundle recording. Electrophysiological measurements were made during normal sinus rhythm (NSR) and during pacing at a basic cycle length of 333 ms where possible, or, if not, at 20 ms less than the sinus cycle length. Atrial and ventricular effective refractory periods (ERP) were determined during atrial pacing or during simultaneous atrial and ventricular pacing respectively by interpolating an extra stimulus after every 12th basic stimulus.

The AH interval was measured from the first deflection of the atrial electrogram to the start of the largest His deflection. The HV interval was measured from the start of the largest His deflection to the start of the ventricular electrogram. The

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Table 1 Baseline values (ms) for electrophysiological parameters before drug administration

Normal sinus rhythm		HV	QRS	AH	PR	RR				
	n									
Org 7797	8	27 ± 3	45 ± 2	81 ± 4	90 ± 3	424 ± 19				
Propafenone	9	27 ± 1	44 ± 1	71 ± 4	85 ± 3	382 ± 20				
Mexiletine	7	25 ± 2	43 ± 3	78 ± 4	88 ± 4	387 ± 54				
Disopyramide	6	28 ± 1	50 ± 5	71 ± 2	82 ± 3	333 ± 21				
Pacing		HV	QRS	QT	VERP	AH	St-A	AERP	SNRT	RR
Org 7797	8	29 ± 3	45 ± 3	198 ± 8	154 ± 2	81 ± 4	24 ± 3	141 ± 7	473 ± 61	322 ± 7
Propafenone	9	26 ± 2	43 ± 1	201 ± 12	152 ± 7	67 ± 4	23 ± 2	130 ± 7	416 ± 24	319 ± 14
Mexiletine	7	27 ± 1	44 ± 6	201 ± 17	162 ± 9	70 ± 5	20 ± 3	148 ± 14	436 ± 38	321 ± 6
Disopyramide	6	28 ± 2	48 ± 3	195 ± 7	142 ± 2	65 ± 2	22 ± 2	120 ± 4	357 ± 9	306 ± 6

Values are the mean ± s.e.mean of *n* observations. VERP and AERP are the ventricular and atrial refractory periods respectively.

St-A interval was measured from the start of the stimulus artefact to the earliest atrial deflection. Sinus node recovery time (SNRT) was measured from the start of the last atrial complex during pacing to the beginning of the first atrial complex when normal sinus rhythm was resumed. The RR, QRS and QT intervals were measured from the lead II ECG. Derived intervals were:

$$QTc = QT \div \sqrt{RR}$$
$$JTc = (QT - QRS) \div \sqrt{RR}$$

Drugs were given over a 1 min period via the left femoral vein in a volume of 10–20 ml distilled water and electrophysiological measurements made before and 2, 5 and 10 min after administration. Refractory periods were determined 5 min after administration. Further doses of the same test drug were given when control values had been reattained. Each dog received only one drug.

At the end of each experiment, the heart was removed and perfused retrogradely via the aorta with triphenyltetrazolium for estimation of infarct size. Scores of 1, 2 or 3 were given for an endocardial infarct area of <10%, 10–25% and >25% of the total left ventricular endocardial surface respectively.

Statistical analysis of the results

Significant differences between pre- and post-drug values were determined by a paired *t* test. Results are presented as the mean % change to ease comparison of different drug-induced effects. Student's unpaired *t* test was used to detect significant differences in infarct size.

Drugs used

Drugs used were disopyramide phosphate (Searle), mexiletine hydrochloride (Boehringer Ingelheim), propafenone hydrochloride (Helopharm) and Org 7797 maleate (Organon). Doses quoted refer to the free base.

Results

Mean baseline values for each drug tested were within the normal range for pentobarbitone anaesthetized animals and are given in Table 1.

Electrophysiological effects during normal sinus rhythm

With the exception of the effect of propafenone on JTc, maximum changes in response to all 4 drugs were seen within 5 min of administration and are summarized in Table 2.

Org 7797 (0.5 and 2 mg kg⁻¹) dose-dependently lengthened the PR, AH, QRS and HV intervals whilst only the higher dose prolonged the RR interval. QTc was unchanged by the low dose and prolonged by the high dose but JTc was significantly shortened by both doses.

Propafenone (0.5 and 2 mg kg⁻¹) also dose-dependently prolonged PR, AH and HV but was about four times less potent than Org 7797. QRS was unchanged by the lower dose and only modestly (and insignificantly) prolonged by the higher dose. RR and QTc remained unchanged whilst a very small (2%) but significant shortening of JTc was seen 10 min after administration of the higher dose.

Mexiletine (0.5 and 2 mg kg⁻¹) induced only very small or insignificant effects. PR and QRS were minimally prolonged by 2 mg kg⁻¹ whilst QTc and JTc were, if anything, slightly shortened. A higher dose (8 mg kg⁻¹) induced prolongation of the QRS and HV intervals and slightly lengthened the PR interval; RR and AH remained unchanged, whilst QTc and JTc were shortened.

Disopyramide (2 and 5 mg kg⁻¹) dose-dependently prolonged all intervals.

Figure 1 compares the effects of 0.5 mg kg⁻¹ Org 7797 on intracardiac conduction and ventricular repolarisation over the 10 min observation period with those of 2 mg kg⁻¹ propafenone, mexiletine and disopyramide. The effects of all 4 drugs on conduction intervals declined with time as did shortening of JTc in response to Org 7797 and mexiletine. However, disopyramide-induced JTc lengthening was sustained.

Table 2 Mean maximum percentage changes in electrophysiological parameters during normal sinus rhythm

	Org 7797		Propafenone		Mexiletine			Disopyramide	
	0.5	2.0	0.5	2.0	0.5	2.0	8.0	2.0	5.0 mg kg ⁻¹
RR	+2 ± 2	+22 ± 2**	0 ± 3	+6 ± 4	+5 ± 2	-3 ± 2	+4 ± 2	+14 ± 2**	+43 ± 4**
PR	+15 ± 2**	+50 ± 3**	+4 ± 1**	+14 ± 3**	0 ± 1	+3 ± 1*	+7 ± 2*	+15 ± 3**	+37 ± 9**
AH	+15 ± 3**	+45 ± 7**	+2 ± 1*	+13 ± 3**	+3 ± 2	+1 ± 1	+2 ± 2	+11 ± 2**	+24 ± 3**
HV	+25 ± 2**	+119 ± 33**	+6 ± 1**	+18 ± 4**	+4 ± 3	+3 ± 2	+20 ± 3**	+15 ± 3**	+27 ± 4**
QRS	+30 ± 6**	+107 ± 17**	0 ± 2	+11 ± 5	+1 ± 5	+5 ± 1**	+21 ± 3**	+11 ± 3**	+36 ± 3**
QTc	+1 ± 1	+13 ± 2**	-1 ± 1	-1 ± 1	-6 ± 2	-4 ± 2	-7 ± 3*	+5 ± 1**	+6 ± 1**
JTc	-6 ± 1**	-5 ± 1**	-1 ± 1	-2 ± 1*	-5 ± 1*	-6 ± 3	-13 ± 4*	+6 ± 2*	+11 ± 3*

Results are the mean ± s.e.mean of 6–9 observations.
* *P* < 0.05 and ** *P* < 0.01 denote significant changes.

Figure 1 Comparative effects of 0.5 mg kg^{-1} Org 7797 (○) with those of 2 mg kg^{-1} propafenone (□), mexiletine (△) and disopyramide (×) on intracardiac conduction and ventricular repolarization during normal sinus rhythm. * $P < 0.05$ and ** $P < 0.01$ denote significant changes. Each result is the mean of from 6 to 9 observations.

Ventricular electrophysiological effects during pacing

Two to three minutes after administration, 7 of the 8 dogs given the high dose of Org 7797 (2 mg kg^{-1}) were unable to follow the atrial pacing stimulus and by 5 min only 3 dogs had recovered this ability. Two of the dogs given the lower dose (0.5 mg kg^{-1}) failed to follow the driving stimulus 2 min after dosing in comparison with 2/9 and 1/7 dogs given 2 mg kg^{-1} propafenone and 8 mg kg^{-1} mexiletine respectively. However, these drug effects had worn off by 5 min. The high dose of disopyramide (5 mg kg^{-1}) also rendered 3/6 dogs unresponsive to atrial pacing 5 min after administration. Also 2 dogs developed transient episodes of ventricular tachycardia.

Figure 2 compares mean maximum changes in HV, QRS and QT induced by 0.5 mg kg^{-1} Org 7797, with those of propafenone, mexiletine and disopyramide. Both Org 7797 and propafenone increased HV and QRS whilst QT was not significantly changed. Again the effect of Org 7797 on QRS appeared more pronounced than that seen in response to propafenone.

Mexiletine induced a dose-dependent increase in HV and QRS but only the higher dose (8 mg kg^{-1}) induced changes comparable to those of Org 7797 and propafenone. QT was, if anything, slightly and dose-dependently shortened.

Disopyramide dose-dependently increased HV, QRS and QT Figure 3 compares effects on the ventricular effective refractory period (ERP). Org 7797 induced only a small (4%) but significant increase in ERP whilst propafenone and disopyramide at 2 mg kg^{-1} induced more marked increases (9%). The high dose of disopyramide prolonged ERP by 21% whilst mexiletine (2 and 8 mg kg^{-1}) if anything, shortened the refractory period.

Supraventricular electrophysiological effects during pacing

Mean maximum changes in AH, St-A intervals and atrial effective refractory periods are summarized in Figure 4. Org 7797 (0.5 mg kg^{-1}) induced a marked increase in St-A (81%) and modestly prolonged the AH interval (16%) but caused only a small increase in the effective refractory period (8%). Propafenone (2 mg kg^{-1}) increased AH to a similar extent (22%) as Org 7797 but induced more marked prolongation of the refractory period (26%). Mexiletine 2 mg kg^{-1} was without effect on AH or ERP but modestly prolonged St-A (by 19%). At the higher dose (8 mg kg^{-1}), St-A and ERP were markedly increased (by 78 and 28% respectively) whilst only a modest and non-significant increase in AH was observed (15%).

Disopyramide (2 and 5 mg kg^{-1}) also lengthened AH, St-A and ERP but unlike the other 3 drugs its effects on AH and the refractory period were more pronounced than its effects on St-A.

Effects on sinus node recovery time are summarized in Figure 5. Org 7797 and 2 mg kg^{-1} propafenone or disopyramide induced modest increases in SNRT although the result obtained with propafenone did not reach statistical significance. Mexiletine even at a high dose was without effect.

Infarct size

All dogs used in the study were found to have an infarct. Mean infarct size was similar in all groups (scores of 2.3 ± 0.3 , 2.3 ± 0.3 , 2.5 ± 0.2 and 2.7 ± 0.2 in the Org 7797, propafenone, mexiletine and disopyramide groups respectively).

Discussion

The results of the present study suggest that the *in vivo* electrophysiological profile of Org 7797 is more like that of the Ic

Figure 2 Maximum drug-induced effects on HV, QRS and QT intervals during pacing. Doses (mg kg^{-1}) used are denoted by $\square$ (0.5 Org 7797); $\square$ and $\square$ (0.5 and 2.0 propafenone); $\square$, $\square$ and $\square$ (0.5, 2.0 and 8.0 mexiletine); $\square$ and $\square$ (2.0 and 5.0 disopyramide). Each result is the mean of from 6 to 9 observations; vertical bars show s.e.mean. * $P < 0.05$ and ** $P < 0.01$ denote significant changes.

drug propafenone than of either mexiletine (Ib) or disopyramide (Ia). Org 7797 was some 4 times more potent than propafenone. Org 7797 (2 mg kg^{-1}) rendered 5 out of 8 dogs unable to follow an atrial pacing stimulus of mean cycle length 322 ms and induced substantial bradycardia. At a lower dose, shown previously to prevent ischaemia-induced ventricular fibrillation in dogs (Winslow *et al.*, 1989a), Org 7797 (0.5 mg kg^{-1}), like propafenone (2 mg kg^{-1}), slowed conduction at all levels of the myocardium. This was shown by prolongation of St-A (81%), AH (16%), HV (22%) and QRS (37%) intervals reflecting slowing of conduction in the atria, AV node, His-Purkinje system and ventricular myocardium respectively. Only small increases in the ventricular and more noticeably the atrial effective refractory period (of 4 and 8% respectively) were seen in response to Org 7797 whereas, relative to effects on ventricular and intraatrial conduction, refractory periods were increased to a greater extent by propafenone (9 and 26% respectively) than by Org 7797. The

electrophysiological effects of both drugs were seen in the absence of significant changes in QTc or paced QT and are qualitatively similar to clinical findings with propafenone (Waleffe *et al.*, 1981; Doherty *et al.*, 1984; Hammill *et al.*, 1987). Neither drug altered sinus cycle length but sinus node recovery time (SNRT) was significantly increased by Org 7797 and appeared to increase following propafenone. A similar dose of propafenone in man has been variably reported to have either no effect or to slightly increase SNRT (Shen *et al.*, 1984; Breithardt *et al.*, 1984). In the high range of therapeutic doses, propafenone has ancillary β -adrenoceptor blocking activity (Brown *et al.*, 1986) an action expected to oppose sodium channel-mediated shortening of cardiac action potentials. This may explain the very small shortening effect of propafenone on JTc observed in our study, in which the combination of myocardial infarction and pentobarbitone anaesthesia enhances sympathetic tone (Alter III *et al.*, 1979). On the other hand, β -adrenoceptor blockade might be expected to contribute to prolongation of cardiac refractory periods.

The results obtained with propafenone differ from those obtained by Karaguezian *et al.* (1984) in non-infarcted pentobarbitone-anaesthetized dogs where 4 mg kg^{-1} propafenone, whilst slowing atrial conduction (by 50%) and prolonging AV nodal refractoriness, failed to prolong either the HV interval or the ventricular effective refractory period. However, clinical studies have demonstrated that propafenone-induced slowing of conduction in the His-Purkinje system is enhanced in patients with underlying conduction abnormalities (Seipel & Breithardt, 1984; Connolly *et al.*, 1983a,b). Our use of dogs with left ventricular infarcts may therefore explain the prominent effects we found on HV conduction with a relatively low dose of the drug.

In the present study electrophysiological responses to an antiarrhythmic dose of mexiletine (2 mg kg^{-1}) were small compared to those of propafenone (2 mg kg^{-1}) and Org 7797 (0.5 mg kg^{-1}).

The most noticeable effect of this dose of mexiletine was a modest increase (19%) in St-A reflecting slowing of intraatrial

Figure 3 Changes in ventricular effective refractory periods 5 min after drug administration. Each result is the mean of from 6 to 9 observations; vertical bars show s.e.mean. * $P < 0.05$ and ** $P < 0.01$ denote significant changes.

Figure 4 Maximum drug-induced effects on AH, St-A and the atrial effective refractory period (ERP) during pacing. Doses (mg kg^{-1}) used are denoted by $\square$ (0.5 Org 7797); $\square$ and $\boxtimes$ (0.5 and 2.0 propafenone); $\square$ and $\boxtimes$ (2.0 and 5.0 mexiletine); $\square$ and $\boxtimes$ (2.0 and 5.0 disopyramide). Each result is the mean of from 6 to 9 observations; vertical bars show s.e.mean. * $P < 0.05$; ** $P < 0.01$ and *** $P < 0.001$ denote significant changes.

conduction together with a modest but non-significant increase in HV (10%) and a small but significant increase in QRS (5–6%). JTc was, if anything, shortened but no other electrophysiological changes were seen. Intravenous ($2\text{--}3 \text{ mg kg}^{-1}$) canine studies (Yoon & Han, 1982; Costard-Jackle & Franz, 1989), intravenous clinical studies (Seipel & Breithardt, 1978; Jewitt, 1978) and clinical oral studies (reviewed by Kreuger *et al.*, 1987; Nestico *et al.*, 1988) have reported little or no effect of mexiletine on intracardiac conduction, refractory periods or repolarization although shortening of the latter has sometimes been observed. Experimental studies using 2 mg kg^{-1} do however suggest that mexiletine may slow ventricular conduction (Bajaj *et al.*, 1987) and prolong the ventricular refractory period (Costard-Jackle & Franz, 1989) but only at cycle lengths substantially shorter than those used in our study whilst at long cycle lengths, prominent short-

ening of ventricular repolarization is seen. Our results are in general agreement with those obtained by others but deviate in that we found a definite slowing of conduction in both atria and ventricular tissue at physiological pacing rates. Again, this may be due to the presence of infarction.

A dose of mexiletine (8 mg kg^{-1}) close to that which produces convulsions in conscious dogs (10 mg kg^{-1} , Hashimoto *et al.*, 1984) produced some effects similar to those of Org 7797 and propafenone (slowing of conduction in ventricular, His-Purkinje and especially atrial tissue and a marked increase in the atrial effective refractory period) whilst repolarization during normal sinus rhythm was shortened. Responses to this dose of mexiletine differed from those to Org 7797 and propafenone in that neither the ventricular refractory period, SNRT nor AV nodal conduction were significantly altered. These results suggest that even at a high dose, the profile of mexiletine differs from that of Org 7797.

In contrast to Org 7797, disopyramide (2 mg kg^{-1}) in anti-arrhythmic doses (Marshall & Parratt, 1979; Hashimoto *et al.*, 1982) increased JTc (by 6%) and QT during pacing (by 16%) indicating a clear prolongation of ventricular repolarization. The ventricular refractory period was lengthened to a greater extent (9%) than that seen in response to Org 7797 whilst effects on His-Purkinje and ventricular conduction were less pronounced (HV and QRS during pacing were lengthened by 13 and 17% respectively). In comparison to Org 7797, disopyramide markedly prolonged the atrial refractory period (by 30%) whilst its effect in slowing intraatrial conduction was much less prominent (St-A increased by only 13%). This dose of disopyramide also prolonged the RR interval. However, increases in SNRT and the AV interval in response to both drugs were of similar magnitude. Three of the six dogs given the higher dose of disopyramide (5 mg kg^{-1}) failed to follow the atrial pacing stimulus and two others responded to ventricular pacing with transient episodes of ventricular tachycardia suggesting that this dose is close to toxic levels.

Figure 5 Maximum drug-induced changes in sinus node recovery time. Each result is the mean of from 6 to 9 observations; vertical bars show s.e.mean. * $P < 0.05$ and ** $P < 0.01$ denote significant changes.

The effects of disopyramide on ventricular repolarization, atrial conduction and refractory periods are similar to those reported from both canine (Guimond *et al.*, 1982; Giacomini *et al.*, 1985; Kidwell *et al.*, 1989) and clinical (Dreifus *et al.*, 1976; Marrott *et al.*, 1976) studies using i.v. doses of 1.5–4.0 mg kg⁻¹. However, results from non-infarcted animal studies including those of Lee *et al.* (1985) have shown either no change or only very small increases in HV and QRS in response to 4 mg kg⁻¹ disopyramide or doses giving mid-therapeutic plasma levels (3–6 mg ml⁻¹), results in agreement with clinical studies using 1.5–1.7 mg kg⁻¹ (Dreifus, 1975; Dreifus *et al.*, 1976). However Ross *et al.* (1978) and Marrott *et al.* (1976) both report an increase in the HV interval at doses of 1.5–2 mg kg⁻¹ in patients with intraventricular conduction defects or suspected coronary heart disease. Again, these findings and the results of our studies seem to suggest that left ventricular infarction increases sensitivity to sodium channel blocking agents.

In clinical studies RR and SNRT are either unchanged or shortened by disopyramide, effects which are probably a consequence of the well-documented anticholinergic actions of

this agent (Mirro *et al.*, 1980). However in experimental studies using pentobarbitone-anaesthetized dogs in which vagal activity is already depressed, disopyramide, as in our study, prolongs both RR and SNRT (Kidwell *et al.*, 1989).

In conclusion, the results of these studies suggest that in agreement with *in vitro* studies (Winslow *et al.*, 1989b), Org 7797 can be classified as a Ic agent. According to Harrison's clinical classification (1985), Ic agents widen QRS and slow conduction at low doses, have little effect on repolarization and induce only small increases in refractory periods. This is the profile observed with Org 7797 in these studies. Propafenone exerted similar effects but relative to its effects on conduction, refractory periods were more prolonged than with Org 7797. Class Ia agents prolong both repolarization and refractory periods at low doses whilst Ib agents have a limited effect on QRS and conduction and shorten repolarization, effects essentially observed with disopyramide and mexiletine, respectively, in this study. Our results also suggest that left ventricular infarction may enhance slowing of conduction induced by class Ia, Ib or Ic antiarrhythmic agents.

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