Effects of Org 7797 on early, late and inducible arrhythmias following coronary artery occlusion in rats and dogs

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1 The class Ic steroidal antiarrhythmic agent, Org 7797, was compared with two other Ic agents, flecainide and propafenone for intravenous activity against ischaemia-related cardiac arrhythmias and for electrophysiological actions *in vivo*. In addition the haemodynamic effects of Org 7797 were assessed in greyhounds.

2 Org 7797 (0.5 mg kg⁻¹) significantly reduced the expected incidence of early ischaemia-induced ventricular fibrillation (VF) in rats and greyhound dogs and at doses of 0.5–1.0 mg kg⁻¹ antagonized reperfusion-induced arrhythmias. Comparative studies in rats showed Org 7797 to be 2–4 times more potent than flecainide or propafenone.

3 Org 7797 (0.5 mg kg⁻¹) slowed intracardiac conduction in anaesthetized beagles and again was at least 2–4 times more potent than flecainide or propafenone.

4 Org 7797 (0.5 and 2.0 mg kg⁻¹), flecainide (1.0 and 2.0 mg kg⁻¹) or propafenone (0.5 and 2.0 mg kg⁻¹), did not significantly prevent induction of tachyarrhythmias (VT) in dogs with 5–6 day old myocardial infarcts although all 3 drugs appeared to prevent induced VF. All 3 drugs (notably flecainide) did however reduce the VT rate.

5 All 3 drugs (1–2 mg kg⁻¹) suppressed spontaneous tachyarrhythmias in conscious beagle dogs with 1–2 day old infarcts. Propafenone was the least effective.

6 In an antifibrillatory dose (0.5 mg kg⁻¹), the major haemodynamic effect of Org 7797 was a 10% increase in peripheral vascular resistance. Stroke volume, cardiac output and coronary blood flow were unchanged. In therapeutic doses, Org 7797 was also less negatively chronotropic than flecainide.

7 It was concluded that Org 7797 is a potent antifibrillatory agent which is haemodynamically well tolerated. Higher doses are required to suppress late ischaemia-induced tachyarrhythmias which suggest that its antifibrillatory effects are the consequence of an action other than, or in addition to, sodium channel block.

Keywords: Org 7797; Ic drugs; myocardial infarction; arrhythmias; inducibility; haemodynamics; electrophysiology

Introduction

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 currently undergoing clinical evaluation. This compound has been shown to be effective against aconitine-induced and ischaemia-induced arrhythmias in rodents and to inhibit the fast inward sodium current in guinea-pig atria (Campbell *et al.*, 1986). Org 7797 has been further subclassified as a Ic agent on the basis of the kinetics of onset of rate-dependent sodium channel block in porcine isolated cardiac tissue (Winslow *et al.*, 1989a) and on its electrophysiological actions *in vivo* (Campbell *et al.*, 1991). The aim of the present study was to explore the antiarrhythmic potential of this compound against ischaemia-related arrhythmias in more detail and to compare its activity with that of two other Ic agents, flecainide and propafenone. The ability of Org 7797 to antagonize the development of early arrhythmias evoked by acute coronary artery ligation in rats and dogs, to prevent reperfusion-induced arrhythmias, to suppress spontaneous late arrhythmias and to prevent electrical induction of arrhythmias in dogs with 5–6 day old myocardial infarcts was therefore assessed together with its haemodynamic actions. In addition, the electrophysiological actions of Org 7797 *in vivo* were compared with those of flecainide and propafenone. Part of this work has already been published in abstract form (Winslow *et al.*, 1989b).

Methods

Early ischaemia-induced and reperfusion-induced arrhythmias in rats

Male Wistar rats (235–350 g) obtained from Olac and fed on

Labsure CRMX pellets were anaesthetized with pentobarbitone sodium (60 mg kg⁻¹, i.p.) and prepared for coronary artery ligation as described by Clark *et al.* (1980). Arterial blood pressure and a limb lead II electrocardiogram (ECG) were recorded and the animals allowed to stabilize. Drugs (in 0.1 ml distilled water per 100 g body weight) or saline were given via the left femoral vein 15 min before occluding the main left descending coronary artery. Arrhythmias arising during the subsequent 30 min period were classified and analysed according to the Lambeth Conventions (Walker *et al.*, 1988). Rectal temperature was maintained at 37.0 $\pm$ 0.5°C.

To study reperfusion-induced arrhythmias, the procedure used was similar to that described above except that the ligature was tied around a small length of polythene tubing and 5 min after occlusion, the ligature released by sliding a scalpel blade over the tubing. The incidence of ventricular premature beats (VPBs), ventricular tachycardia (VT) and ventricular fibrillation (VF) consequent upon reperfusion were noted.

Haemodynamic measurements and early ischaemia-induced and reperfusion-induced arrhythmias in greyhound dogs

Experiments were carried out on greyhounds of either sex weighing between 21 and 35 kg. Anaesthesia was induced with intravenous sodium pentobarbitone (30–40 mg kg⁻¹) and maintained with additional barbiturate as required. Following endotracheal intubation, the dogs were artificially ventilated with room air using a positive pressure ventilation pump and stroke volume and rate adjusted to maintain arterial PO₂ between 90 and 100 mmHg (1 mmHg = 1.33 mbar) and blood pH between 7.35 and 7.45 pH units. Pancuronium bromide (3–4 mg) was given intramuscularly to prevent reflex muscular movements during surgery. Arterial blood pressure (BP), left

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ventricular pressure (LVP), cardiac output (CO) and left circumflex coronary blood flow (CBF) were recorded as described by Marshall & Muir (1981). A lead II ECG, from which heart rate (HR) was obtained, was recorded from adhesive limb electrodes.

Derived parameters were LV dP/dt P^{-1} (the rate of LVP development at a LVP of 40 mmHg), stroke volume (SV), peripheral vascular resistance (PVR) and external cardiac work (ECW).

A left thoracotomy was performed to expose the anterolateral aspect of the heart and the left anterior descending coronary artery (LAD) prepared for subsequent occlusion with a Diffenbach clamp at a point just distal to the septal branch. After a 30–40 min stabilization period, Org 7797 (in 10 ml distilled water) or 10 ml saline were given via the right femoral vein over a 2 min period and the LAD occluded 15 min later. Arrhythmias seen during the subsequent 30 min period of ischaemia were analysed as described for the rat. At the end of the occlusion period, reperfusion in surviving dogs (non-fibrillators) was accomplished by removing the clamp and gently stroking the artery. Reperfusion arrhythmias were assessed as described above. At the end of each experiment, blue dye was injected down the coronary artery at the level of the occlusion to assess the left ventricular 'area at risk'.

Statistics

In both the rat and dog studies, a Chi-square test was used to determine the significance of differences between the incidences of arrhythmias. A paired *t* test was used to detect significant drug-induced haemodynamic effects. All other comparisons were made with Student's *t* test.

Late ischaemia-induced arrhythmias in beagle dogs

Male or female beagle dogs (9–14 kg) were anaesthetized with halothane (1–2%) in N_2O/O_2 (1:1). Aseptic techniques were used to isolate the left carotid artery and a Fogarty 2F embolectomy catheter was manoeuvred into the LAD or circumflex coronary artery under fluoroscopic control. The catheter balloon was inflated to occlude the artery for 90 min after which time the catheter was removed and the neck wound closed. Details of the method are given by Winslow *et al.* (1990).

Spontaneous arrhythmias were recorded from conscious animals on the first or second day after surgery for a 30 min control period. Test drugs were then infused over 10 min periods in a volume of 6 ml distilled water via a brachial vein and the ECG continuously monitored until at least 50 min after the last dose of test compound was given. Each dog received only one drug. The number of sinus beats recorded during successive 2 min intervals was expressed as a percentage of the total number of beats recorded during the same period (% SB) and compared, by a paired *t* test, with the mean % SB obtained during the control period.

Electrophysiological recording and programmed electrical stimulation in beagles

Five or six days after induction of myocardial infarction, dogs (10–14 kg) were anaesthetized with sodium pentobarbitone (30 mg kg^{-1} , i.v.). Quadripolar and bipolar intracardiac electrodes (6F) were positioned in the right atrium and right ventricle respectively, via the left jugular vein. A bipolar electrode was positioned at the aortic arch via the left femoral artery for His bundle recording.

Electrophysiological measurements were made during normal sinus rhythm (NSR). The HV interval was measured from the start of the largest His deflection to the start of the ventricular electrogram. RR, QRS and QT intervals were measured from the lead II ECG and effects on repolarization assessed from JTc where

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

The ventricular effective refractory period (ERP) was determined during simultaneous atrial and ventricular pacing with a basic cycle length 20 ms shorter than the spontaneous sinus cycle length.

All measurements were made immediately before and 10 min after intravenous drug administration at which time programmed electrical stimulation (PES) was started. A BBC microcomputer, specially designed software and a Grass S88 stimulator were used to deliver up to 3 premature stimuli during normal sinus rhythm and/or during simultaneous atrial and ventricular pacing at a basic cycle length of 250 ms. The PES protocol is described in detail by Winslow *et al.* (1990).

The duration of the premature stimuli was 1 ms and the voltage was twice threshold (1–4 V). The PES protocol was invoked until sustained ventricular tachycardia (SVT) or VF was induced or until the protocol was exhausted. Non-sustained VT (NSVT) was defined as VT terminating spontaneously within 20 s. Termination of SVT sometimes required overdrive pacing or direct current (d.c.) conversion. If d.c. conversion was required, dogs were allowed to recover for at least 1 h before further challenge.

A paired *t* test was used to compare pre- and post-drug electrophysiological measurements.

Results

Early ischaemia-induced arrhythmias in anaesthetized rats

Results are summarized in Table 1. At doses of 2 mg kg^{-1} , Org 7797, flecainide and propafenone all abolished the development of VF and reduced the number of VPBs contributing to VT. However, unlike flecainide and propafenone, significant antifibrillatory effects were also seen at a dose of 0.5 mg kg^{-1} Org 7797 and the higher dose additionally reduced the number of single VPBs and salvos.

Table 1 Early ischaemia-induced arrhythmias in anaesthetized rats during the first 30 min of occlusion

Treatment	(mg kg^{-1})	n	VPBs			Total	% VF	% death
			Single	Salvo	VT			
Saline		17	150 ± 24	64 ± 17	397 ± 142	612 ± 171	53	29
Org 7797	0.5	10	197 ± 68	36 ± 20	182 ± 127	415 ± 205	10*	10
	2.0	10	55 ± 37*	5 ± 3**	123 ± 10*	72 ± 41**	0*	0
Flecainide	0.5	10	178 ± 52	78 ± 39	494 ± 217	751 ± 280	40	10
	2.0	10	276 ± 99	66 ± 29	90 ± 39*	431 ± 143	0*	0
Propafenone	0.5	9	152 ± 36	82 ± 28	1055 ± 473	1289 ± 495	33	22
	2.0	10	227 ± 80	116 ± 75	111 ± 43*	453 ± 175	0*	0

Each result under the VPB heading is the mean ± s.e.mean of results obtained from surviving animals in each group.

n refers to the total number of animals (survivors and non-survivors) included in each group.

* *P* < 0.05 and ** *P* < 0.01 denote significant differences from the appropriate control values.

Figure 1 Effects of saline (hatched columns), Org 7797 (solid columns) and propafenone (stippled columns) on the % incidence of reperfusion-induced ventricular premature beats (VPBs), ventricular tachycardia (VT) and ventricular fibrillation (VF) in anaesthetized rats. * $P < 0.01$ and *** $P < 0.001$ denote significant differences from the appropriate control group. The number of animals in each group is shown in the VPB columns.

No sustained changes in blood pressure ($115 \pm 8/95 \pm 7$ mmHg in controls) were seen following administration of any of the 3 drugs. However, significant ($P < 0.01$) decreases in heart rate were observed following 2 mg kg^{-1} Org 7797, flecainide and propafenone (from 419 ± 9 , 402 ± 17 and 415 ± 13 beats min^{-1} respectively to 402 ± 11 , 370 ± 15 and 384 ± 15 15 min after administration) and following the lower dose of flecainide (from 441 ± 10 to 412 ± 12 beats min^{-1}).

Reperfusion-induced arrhythmias in anaesthetized rats

Both Org 7797 and propafenone ($1\text{--}2 \text{ mg kg}^{-1}$) dose-dependently reduced the expected incidences of reperfusion-induced VF, VT and VPBs although Org 7797 was approximately twice as potent as propafenone (Figure 1).

Ischaemia-induced and reperfusion-induced arrhythmias in anaesthetized greyhound dogs

During the 30 min occlusion period, 9 out of 18 control animals developed VF whereas none of the 7 animals pretreated with 0.5 mg kg^{-1} Org 7797 fibrillated ($P < 0.05$) (Figure 2). Analysis of arrhythmias seen in non-fibrillating

Figure 2 Early ischaemia-induced and reperfusion-induced arrhythmias in greyhound dogs: (a) shows the total number of ventricular premature beats (VPBs) and the % incidence of ventricular fibrillation (VF) recorded from animals pretreated with either 0.5 mg kg^{-1} Org 7797 (open columns) or 10 ml saline (hatched columns). Total VPBs have also been subdivided into single VPBs, salvos or ventricular tachycardia (VT) and the results expressed as the mean (s.e. mean shown by vertical bars) of 9 control dogs and 7 drug-treated dogs. (b) Shows the % incidence of single VPBs, VT and VF consequent upon reperfusion at the end of the 30 min occlusion period.

* $P < 0.05$ denotes a significant difference between Org 7797 and saline-treated dogs.

dogs showed no significant differences between the control and drug-treated groups. Of the 9 surviving control animals, 7 developed VF and 2 developed VT following reperfusion. Of the 7 Org 7797-treated dogs, 3 developed VF, 3 developed VT and 1 responded with only a few premature beats on reperfusion. However, these differences were not statistically significant. The area at risk was similar in control and drug-treated animals (33.9 ± 1.0 and $34.5 \pm 1.4\%$ of the left ventricle respectively).

Late-ischaemia-induced arrhythmias in conscious beagles

Org 7797, flecainide and propafenone (1 followed by 2 mg kg^{-1}) all significantly increased the number of sinus beats compared to pretreatment values (Figure 3). Quantitatively similar responses were obtained to Org 7797 and flecainide both of which appeared more potent and longer acting than equivalent doses of propafenone.

Inducibility of arrhythmias in anaesthetized beagles with 5–6 day old myocardial infarcts

None of the three drugs (Org 7797, 0.5 mg kg^{-1} ; flecainide, 1.0 mg kg^{-1} ; propafenone, 0.5 mg kg^{-1}) was particularly effective in this model (Figure 4). VT or VF could still be induced in 4 out of 6 dogs following Org 7797, in 4 out of 5 dogs following propafenone and in 6 out of 6 dogs following flecainide. However, sustained VT/VF in one dog in each of the

Figure 3 Effects of intravenous infusion of Org 7797 (a), flecainide (b) or propafenone (c) on the percentage of sinus beats (columns) assessed over successive 2 min intervals in conscious beagles 1 to 2 days after myocardial infarction. Heart rate is shown by the horizontal line. The horizontal bars denote the period during which 1.0 followed by 2.0 mg kg^{-1} of each drug was infused. Each result is the mean of 6 to 7 observations; vertical bars show s.e. mean.

* $P < 0.05$ and ** $P < 0.01$ denote significant differences from pretreatment values.

Figure 4 Arrhythmias induced by programmed electrical stimulation before (Pre) and after (Post) administration of Org 7797 (0.5 mg kg^{-1}), flecainide (1.0 mg kg^{-1}) and propafenone (0.5 mg kg^{-1}) to each of 5–6 anaesthetized beagles. The y-axis denotes the severity of the induced arrhythmia. NSVT, SVT and VF are nonsustained ventricular tachycardia, sustained tachycardia and fibrillation respectively; (●) and (○) denote the type of arrhythmia induced (VF or VT respectively).

Org 7797 and propafenone groups was converted to non-sustained VT whilst VF in 3 out of 3 flecainide-treated, 2 out of 3 Org 7797-treated and 2 out of 3 propafenone-treated animals was prevented. Higher doses (2 mg kg^{-1}) of Org 7797 or flecainide did not confer additional protection against inducibility of arrhythmias whilst dog 2 (see Figure 4) in the propafenone group became non-inducible and the response in dog 4 was converted to non-sustained VT.

The induced VT rate was reduced by the lower dose of flecainide (from 410 ± 33 to 370 ± 27 beats min^{-1} , $P < 0.05$) but not by the lower doses of either Org 7797 or propafenone. Flecainide, Org 7797 and propafenone, all at 2 mg kg^{-1} , significantly ($P < 0.05$) reduced VT rate from 410 ± 33 , 418 ± 27 and 412 ± 38 beats min^{-1} respectively to 338 ± 14 , 370 ± 26 and 329 ± 31 beats min^{-1} .

Electrophysiological effects

Table 2 gives mean control values of RR, QRS, HV, ERP and JTc obtained before drug administration.

The RR interval was unchanged by propafenone (0.5 or 2 mg kg^{-1}) or the lower doses of Org 7797 (0.5 mg kg^{-1}) and flecainide (1.0 mg kg^{-1}) whilst 2 mg kg^{-1} Org 7797 and flecainide modestly but significantly ($P < 0.05$) prolonged RR by 9 ± 2 and $10 \pm 3\%$ respectively. Org 7797 and flecainide dose-dependently prolonged QRS and HV and to a much lesser extent prolonged ERP whilst JTc was unaltered (Figure 5). The lower dose of propafenone was without significant electrophysiological effects whilst the higher dose failed to prolong QRS significantly. However, HV and ERP were lengthened whilst again JTc was unchanged. The effects of Org 7797 on conduction were much more prominent than those of either flecainide or propafenone.

Haemodynamic effects of Org 7797 in anaesthetized greyhounds

The immediate haemodynamic effects of a bolus injection of Org 7797 (0.5 mg kg^{-1}) were small but significant. These were

Table 2 Baseline values (ms) for electrophysiological parameters recorded from beagle dogs pre-drug administration

	n	RR	QRS	HV	JTc	ERP
Org 7797	6	393 ± 9	45 ± 2	27 ± 3	275 ± 9	158 ± 2
Propafenone	5	398 ± 34	45 ± 1	24 ± 1	266 ± 11	162 ± 9
Flecainide	6	347 ± 5	35 ± 0	25 ± 0	279 ± 11	144 ± 2

Values are the mean $\pm$ s.e.mean of *n* observations.

Figure 5 Electrophysiological effects of Org 7797 (0.5 and 2.0 mg kg^{-1}) (hatched columns), flecainide (1.0 and 2.0 mg kg^{-1}) (stippled columns) and propafenone (0.5 and 2.0 mg kg^{-1}) (solid columns) 10 min after administration to anaesthetized beagles. Each result is the mean of the % change from pre-drug values in 5–6 animals; vertical bars show s.e.mean.

* $P < 0.05$ and ** $P < 0.01$ denote significant changes from pretreatment values.

decreases in heart rate (5%) and LV dP/dt P^{-1} (11%) and increases in left ventricular end-diastolic pressure (LVEDP) and peripheral vascular resistance of 23% and 7% respectively ($P < 0.05$). These effects were sustained for at least 10 min at which time systolic blood pressure was also modestly but significantly increased (Table 3). Cardiac output, stroke volume and coronary blood flow were not significantly altered.

Discussion

Results of the present study have shown that Org 7797 has potent antifibrillatory properties in myocardial infarction. At an intravenous dose of 0.5 mg kg^{-1} , Org 7797 significantly prevented early ischaemia-induced VF in anaesthetized rats and greyhound dogs and prevented electrical induction of VF in 2 out of 3 beagle dogs with established infarcts. This dose also halved the expected incidence of reperfusion-induced VF in the greyhound (from 78 to 43%) although the result did not reach statistical significance whilst a higher dose (1 mg kg^{-1}) abolished the development of reperfusion-induced VF in the rat. Comparative antiarrhythmic studies in rats suggest that Org 7797 is approximately 2 to 4 times more potent than either flecainide or propafenone. The superior potency of Org 7797 was confirmed in electrophysiological studies in anaesthetized beagles in which conduction in both the His-Purkinje system and the ventricular myocardium (reflected in the HV and QRS intervals) was significantly slowed following administration of 0.5 mg kg^{-1} whereas 2.0 mg kg^{-1} flecainide was required to induce qualitatively similar changes in these parameters. Electrophysiologically, propafenone appeared the least potent of the 3 drugs and indeed QRS lengthening was not statistically significant at the higher dose (2.0 mg kg^{-1}).

Despite the apparently greater potency of Org 7797 compared to propafenone, 0.5 mg kg^{-1} of the latter drug appeared at least as effective as Org 7797 against inducible arrhythmias in dogs with established infarcts whilst, if anything, the higher dose was more effective than Org 7797 (or flecainide). This discrepancy might be explained by the known β -adrenoceptor blocking actions of propafenone (Brown *et al.*, 1986; Burnett *et al.*, 1988) since β -blockers e.g. (propranolol, timolol or atenolol) suppress inducible arrhythmias in canine models similar to that employed in our laboratory (Gang & Bigger, 1984; Uprichard & Harron, 1989). In contrast, selective sodium channel block by Ic (or Ib) agents generally only prevents inducible VT/VF in 10 to 30 percent of animals (e.g. Sullivan *et al.*, 1990) a success rate similar to that found in the present study with Org 7797 (33%). Flecainide (1 or 2 mg kg^{-1}) did not prevent induction of VT in any animal but at both doses reduced the VT rate, an action expected when

Table 3 Haemodynamic changes induced by Org 7797 (0.5 mg kg⁻¹, i.v.) 10 min after administration to anaesthetized greyhounds

	Pre Org 7797	10 min after Org 7797	% change
Systolic blood pressure (mmHg)	163 ± 7	177 ± 6**	+8.6
Diastolic blood pressure (mmHg)	118 ± 6	127 ± 7	+7.6
Heart rate (beats min ⁻¹)	148 ± 4	144 ± 3*	-2.7
Cardiac output (litres min ⁻¹)	3.09 ± 0.32	2.96 ± 0.29	-4.2
Stroke volume (ml beat ⁻¹)	21.0 ± 2.1	20.7 ± 2.0	-1.4
Left ventricular pressure (mmHg)	158 ± 6	163 ± 7	+3.2
Left ventricular end diastolic pressure (mmHg)	9.1 ± 0.91	10.9 ± 1.1**	+19.8
Left ventricular dP/dt P ⁻¹ (s ⁻¹)	54.4 ± 4.8	48.9 ± 4.1	-10.1
External cardiac work (kgm min ⁻¹)	5.72 ± 0.60	5.72 ± 0.48	0
Peripheral vascular resistance (dynes s cm ⁻³)	37.3 ± 3.8	40.9 ± 4.2**	+9.7
Coronary blood flow (ml min ⁻¹)	43.4 ± 5.4	45.3 ± 7.1	+4.4

Each result is the mean ± s.e.mean of 7 observations.

* $P < 0.05$ and ** $P < 0.01$ denote significant differences between pre- and post-drug values.

drug-induced slowing of conduction in the presence of anatomical block exceeds prolongation of refractoriness (Wellens *et al.*, 1984). Slowing of the VT rate was also seen following the higher doses of Org 7797 and propafenone but not following the lower doses (0.5 mg kg⁻¹) even though inducible arrhythmias were prevented in 20–33% of the animals. These differences between the three drugs may indicate differences in their mechanism(s) of action.

Org 7797 (and propafenone) also differed from flecainide with regard to effects on sinus rate relative to antifibrillatory potency. Whereas, in the rat, significant bradycardia was induced by subthreshold antifibrillatory doses of flecainide and therapeutic doses of propafenone, therapeutic doses of Org 7797 (0.5 mg kg⁻¹) failed to alter sinus rate. This difference between Org 7797 and flecainide was also observed in the beagle.

Although Org 7797 was potent against early ischaemia-induced VF, it was surprisingly less potent against spontaneous tachyarrhythmias arising 24–48 h after myocardial infarction and indeed was only equipotent with flecainide and propafenone. Since these arrhythmias result mainly from enhanced automaticity of surviving but 'electrically-depressed' sub-endocardial Purkinje fibres (Scherlag *et al.*, 1970; Lazzara *et al.*, 1974) and are sensitive to sodium channel blocking agents (reviewed by Marshall & Winslow, 1982), these observations would suggest that arrhythmias of automatic origin are less sensitive to Org 7797 than those arising from reentry, the major mechanism underlying early ischaemia-induced fibrillation (Janse & Wit, 1989). On the other hand, although all three drugs have class Ic actions, as shown in the present study by slowing of intracardiac conduction, unchanged repolarization and only small increases in refractory periods (Harrison, 1985), it is possible that different or additional drug properties are responsible for the marked antifibrillatory actions of Org 7797 seen at lower doses in both rats and dogs. In this context it may be relevant that the Ic agents, lorcaïnide and flecainide (and also a number of Ib agents) have often been found to increase, rather than decrease, susceptibility to early ischaemia-induced VF in large animals (Gerin & Kulbertus, 1978; Zipes & Troup, 1978; Lederman *et al.*, 1989). These pro-arrhythmogenic effects can be attributed to further slowing of conduction during reentry with a consequent decrease in wavelength (the distance an impulse travels during its own refractory period) thereby facilitating reentry (Wellens *et al.*, 1984). In contrast, Kirchhof *et al.* (1991) have shown that supraventricular antifibrillatory doses of Org 7797 in conscious dogs diminish physiological rate-dependent shortening of refractoriness resulting in a prolongation of wavelength during maximal heart rates. In addition, Janse *et al.* (1990) using pig isolated perfused hearts found that in concentrations required to prevent ischaemia-induced VF, Org 7797

substantially prolonged both the shortest possible pacing interval and the corresponding refractory period, attenuated or prevented shortening of the refractory period during subsequent application of premature stimuli and prolonged the average interval between depolarizations during electrically induced VF in non-ischaemic hearts (from 87 to 150 ms). An equimolar concentration of flecainide had little, if any, effect on the shortest pacing interval, induced significantly less lengthening of the VF interval and unlike Org 7797, failed to prevent VF induced by direct current during ischaemia.

Taken together, the results from the above studies strongly suggest that the antifibrillatory action of Org 7797 can be explained by prolongation of wavelength at very short cycle lengths due to prolongation of refractoriness outweighing slowing of conduction. This action could involve blockade of potassium channels as has recently been demonstrated for flecainide (Follmer & Colatsky, 1990).

However in comparison to flecainide, and perhaps other class Ic drugs, this property of Org 7797 might become manifest at low doses which have relatively less effect on sodium channels. This could explain the 4 fold difference between the dose required to prevent VF (due to reentry) and the dose required to suppress VT arising from abnormal sodium currents in depressed Purkinje tissue.

In an antifibrillatory dose, Org 7797 exerted minimal haemodynamic effects in anaesthetized greyhound dogs. The only significant effects were an almost negligible decrease in heart rate (3%), a 10% increase in peripheral vascular resistance together with a 9% increase in systolic blood pressure and a 20% increase in LVEDP accompanied by a 10% decrease in LV dP/dt P⁻¹. However, these effects on cardiac contractility were not sufficient to reduce either stroke volume or cardiac output. Coronary blood flow was preserved. Both propafenone and flecainide are known to be cardiodepressant (reflected by a reduced left ventricular ejection fraction) in antiarrhythmic doses (reviewed by Nestico *et al.*, 1988) whilst PVR is either unchanged by either drug, decreased by propafenone or increased by flecainide.

In conclusion, Org 7797 is a potent antifibrillatory agent which, in higher doses, suppresses late ischaemia-induced arrhythmias of automatic origin. Unlike flecainide and propafenone, therapeutic doses of Org 7797 exert minimal negative inotropic effects. In antifibrillatory doses its major haemodynamic effect is to increase modestly systemic vascular resistance whilst coronary blood flow is preserved. Although suppression of tachyarrhythmias arising from abnormal automaticity can be attributed to a class Ic action, the mechanism underlying its antifibrillatory action is not clearly understood but may be a consequence of attenuation (or indeed lengthening) of refractory periods at fast frequencies resulting in a prolongation of wavelength.

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