Electrophysiological effects of Org 7797 in the closed-chest anaesthetized dog

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1 The intravenous electrophysiological effects of a new antifibrillatory agent, Org 7797, were studied in closed chest anaesthetized dogs. Effects of fast sodium and slow calcium-mediated action potentials were also examined in guinea-pig isolated papillary muscle.

2 The major effects of a known antifibrillatory dose of Org 7797 (0.5 mg kg⁻¹) were a protracted slowing of AV nodal conduction (for at least 20 min) and prolongation of the AV nodal functional refractory period. Conduction in the atria and His-Purkinje system (reflected by the St-A and HV intervals) were not significantly modified whilst ventricular conduction (reflected by the QRS interval) and the ventricular functional refractory period were only transiently prolonged. No other electrophysiological changes were seen.

3 A higher dose of Org 7797 (1.5 mg kg⁻¹) slowed conduction at all levels of the myocardium (as evidenced by increases in the St-A, AH, HV and QRS intervals), slightly shortened cardiac repolarization (as assessed from JTc) and decreased Wenckebach rate. Atrial refractory periods were increased whereas effects on ventricular refractory periods were modest.

4 Neither heart rate nor sinus node recovery time were modified by either dose of Org 7797.

5 Org 7797, at a concentration (20 µM) which reduced V_{max} of fast sodium-mediated action potentials in isolated papillary muscle by 83%, did not modify V_{max} of slow calcium-mediated action potentials. It prolonged duration of the latter but did not modify that of the former. However, the plateau phase of both the 'fast' and especially the 'slow' action potentials was prolonged.

6 It is concluded that the main electrophysiological effects of a known antifibrillatory dose of Org 7797 in dogs with normal cardiac function are seen at the level of the AV node, actions which are unlikely to be explained by calcium channel block. Higher doses display a class Ic profile. This preferential action on the AV node may contribute to the control of ventricular rate during atrial fibrillation in the absence of infra-nodal conduction disturbances.

7 These results contrast with those previously obtained in infarcted dogs and might further suggest that myocardial infarction enhances the Class I action of Org 7797.

Keywords: Org 7797; electrophysiology; anaesthetized dog; normal ventricular function

Introduction

Org 7797 ((16α, 17β)-17-methylamino-estra-1,3,5(10-triene-3,16-diol(z)-2 butenedioate) is a new antifibrillatory agent (Janse *et al.*, 1990; Kirchhof *et al.*, 1991) currently undergoing clinical evaluation. Previous electrophysiological studies *in vitro* characterized Org 7797 as a class I drug with a profile more similar to that of the Ic agent propafenone than that of Ia or Ib drugs (Winslow *et al.*, 1989), results which were confirmed *in vivo* using a known antifibrillatory dose (0.5 mg kg⁻¹) (Winslow *et al.*, 1991) in dogs with 5 to 6 day-old myocardial infarcts (Campbell *et al.*, 1991). However, the consistent and potent antifibrillatory actions of Org 7797 observed in rat, canine and porcine models of myocardial ischaemia (Janse *et al.*, 1990; Winslow *et al.*, 1991) are difficult to reconcile with a Ic sodium channel blocking action since agents of this class, which, whilst having proven antiarrhythmic effects, do not appear to prevent, and indeed may exacerbate, ventricular fibrillation during ischaemia both in animals (e.g. Lynch *et al.*, 1987; Timour *et al.*, 1991) and man (The Cardiac Arrhythmia Suppression Trial Investigators, 1989). In addition, although qualitatively similar electrophysiological actions (slowed conduction at all levels of the myocardium) to those induced by propafenone are seen in infarcted dogs (Campbell *et al.*, 1991), Org 7797, whilst being about 4 times more potent than propafenone in these respects, is only equipotent with this agent in controlling 'late' ischaemia-induced tachyarrhythmias in conscious dogs, despite the dependency of these arrhythmias on sodium

channel block for their suppression (Marshall & Winslow, 1982). Further discrepancies arise from clinical studies in which intravenous Org 7797 administered to healthy volunteers in a dose (36 mg) similar to that used in the study of Campbell *et al.* (1991) (0.5 mg kg⁻¹) failed to modify QRS duration (Morrison, unpublished). Taken together, these results suggest that the electrophysiological actions of Org 7797 may be different in normal and infarcted hearts. The aim of the present study was, therefore, to evaluate the electrophysiological effects of Org 7797 in dogs with normal cardiac function since no detailed experimental or clinical electrophysiological study has yet been performed in subjects with normal ventricular function. Part of this work has been published in abstract form (Leboeuf *et al.*, 1992).

Methods

Electrophysiological studies in vivo

Beagle dogs of either sex (12–16 kg) were given sodium pentobarbitone (5 mg kg⁻¹, i.v.) to avoid chloralose-induced tremors and alpha-chloralose (100 mg kg⁻¹, i.v.) used for induction and maintenance of the anaesthesia. The trachea was cannulated and the animal artificially respired with room air to maintain arterial blood gases and pH within the physiological range (P_O₂, 80–100 mmHg; P_{CO}₂, 35–40 mmHg and pH 7.4 ± 0.5). Three endocavitary electrodes (Plastimed 6F) were positioned with the aid of an image intensifier as described previously (Leboeuf *et al.*, 1989) for

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recording of the His-bundle and atrial electrograms and to allow pacing of either atrium or the right ventricle. A limb (Lead II) electrocardiogram (ECG) was recorded from subcutaneous electrodes and arterial blood pressure recorded from the right femoral artery. Records were displayed on a Gould ES 1000 recorder.

Intraventricular conduction time (QRS) and ventricular repolarization time (QT) were measured during normal sinus rhythm. The St-A, AH, and HV intervals (the time between the start of the stimulus artefact and the first deflection of the atrial electrogram, the interval from the first deflection of the atrial electrogram to the start of the largest His deflection and the time between the start of the largest His deflection to the start of the ventricular electrogram, respectively) were measured during atrial pacing at a rate 20% above the spontaneous sinus rate. Atrial, AV nodal and ventricular refractory periods were determined by interpolating an extra stimulus (S2) after every 8th paced stimulus (S1) (pulse width 2 ms; $2 \times$ threshold voltage). The effective refractory period (ERP) was defined as the greatest S1–S2 interval which failed to elicit a propagated response (R2). The functional refractory period (FRP) was taken as the smallest value of R1–R2 (R1 being the propagated response to S1) for any S1–S2. For assessment of the AV junctional refractory periods the reference was the atrial R1–R2 interval rather than the S1–S2 interval.

Anterograde and retrograde Wenckebach rates were determined by progressively increasing the rate of atrial and ventricular pacing respectively until AV conduction block appeared.

Sinus node recovery time (SRT) was defined as the interval between the start of the last atrial complex during pacing and the beginning of the first atrial complex when normal sinus rhythm recommenced. The corrected SRT (cSRT) was measured according to the method of Narula *et al.* (1972) as the difference between the sinus pause duration and the spontaneous cycle length.

The QT and JT (QT–QRS) intervals were corrected for heart rate using the Bazett formula (1920) to give values of QTc (QT/ $\sqrt{RR}$) and Jtc (JT/ $\sqrt{RR}$).

Org 7797 (0.5 mg kg^{-1} followed 35 min later by 1.5 mg kg^{-1}) was administered as intravenous bolus injections in 10 ml saline given over 1 min. Control dogs received two 20 ml injections of saline. Electrophysiological determinations were made prior to drug or vehicle administration and at various times up to 35 min following administration.

Absolute changes from pretreatment values in both the Org 7797 and control groups were determined and compared by Student's *t* test for independent series. A *P* value of ≤ 0.05 was considered significant.

Electrophysiological studies in vitro

Right papillary muscles were removed from male guinea-pigs (Dunkin-Hartley) and pinned to the base of a recording chamber. The preparations were superfused with physiological salt solution containing (mM): NaCl 119, KCl 4.7, MgCl_2 0.56, NaH_2PO_4 1.0, NaHCO_3 25, CaCl_2 2.5 and glucose 22, gassed with carbogen and maintained at a temperature of $37 \pm 0.5^\circ\text{C}$. The tissues were electrically stimulated at a frequency of 0.5 Hz (2 ms duration, $2\text{--}3 \times$ threshold voltage). After a 90 min equilibration period, nor-

mal 'fast' transmembrane action potentials were recorded using 3 M KCl-filled glass microelectrodes. 'Slow' calcium-mediated action potentials were then elicited by superfusion with salt solution containing 26 mM potassium and $1 \mu\text{M}$ isoprenaline and after 30 min action potentials again recorded. The tissues were subsequently superfused for 30 min with depolarizing medium containing $20 \mu\text{M}$ Org 7797 followed by normal medium also containing $20 \mu\text{M}$ Org 7797 and action potentials recorded at the end of the 30 min drug exposure periods. Action potentials were displayed on an oscilloscope and the signals fed into a Hewlett-Packard 85 microcomputer for measurement and data analysis (using an unpaired *t* test). The parameters measured were resting membrane potential (RMP), action potential amplitude (APH) and the times taken to reach 50 and 90% repolarization (APD_{50} and APD_{90}). The maximum rate of depolarization (V_{max}) was obtained by electronic differentiation. Effective refractory periods were determined by the paired stimulus technique.

Results

The electrophysiological effects of Org 7797 were investigated in 7 dogs and compared to those of its solvent given to 5 dogs (control group). Two of these dogs were unable to follow the pacing stimulus after administration of the higher dose, thereby precluding electrophysiological measurement. These two dogs have therefore been excluded from the study to allow a properly controlled comparison of the effects of the two different doses of Org 7797 used. Table 1 shows mean baseline values of the various parameters obtained prior to drug or saline administration.

Effects of Org 7797 on sinus function

Pretreatment spontaneous rates were 140 ± 8 and 145 ± 11 beats min^{-1} in the Org 7797 and control groups respectively ($n = 5$). Org 7797 did not significantly modify heart rate, sinus node recovery time or corrected sinus node recovery time (Figure 1).

Effects of Org 7797 at the level of the atrium

As shown in Figure 2, 0.5 mg kg^{-1} Org 7797 failed to modify either atrial conduction time or the atrial effective (AERP) or functional (AFRP) refractory periods. In contrast, the higher dose (1.5 mg kg^{-1}) markedly increased St-A (from 30 ± 3 to 52 ± 4 ms) and prolonged both AERP (from 108 ± 4 to 156 ± 12 ms) and AFRP (from 155 ± 8 to 188 ± 15 ms). The effects on the refractory periods appeared shorter lived than the effect on conduction which was still significantly slowed 20 min after administration. Effects on the refractory periods failed to maintain significance at this time.

Effects of Org 7797 on the AV node

Intranodal conduction (AH) was increased by Org 7797 in a dose-dependent manner (Figure 3a) from 56 ± 6 ms pretreatment to 75 ± 3 and 98 ± 8 ms after administration of 0.5 and 1.5 mg kg^{-1} , respectively. These actions were accompanied by lengthening of the functional refractory period from 217 ± 16

Table 1 Baseline values of the electrophysiological parameters in the two groups of animals

	HR	SRT	cSRT	QRS	St-A	AH	HV	QT	JT	QTc	Jtc	AERP	AFRP	AVFRP	VERP	VFRP	AWCK	RWCK
Control	145 ± 11	580 ± 43	156 ± 26	71 ± 2	34 ± 3	56 ± 6	22 ± 1	244 ± 10	173 ± 11	376 ± 8	266 ± 7	118 ± 7	149 ± 6	244 ± 12	164 ± 7	199 ± 10	301 ± 10	263 ± 35
Org 7797	140 ± 8	660 ± 83	138 ± 34	62 ± 2	27 ± 2	56 ± 6	23 ± 2	231 ± 7	168 ± 6	351 ± 7	256 ± 6	104 ± 2	148 ± 9	217 ± 16	138 ± 6	180 ± 5	327 ± 19	220 ± 6

Parameters are expressed as mean $\pm$ s.e.mean of 5 experiments.

Figure 1 Time course of the effects of Org 7797 on sinus function: (a,b and c) depict changes from pretreatment values in spontaneous heart rate, sinus node recovery time (SRT) and corrected sinus node recovery time respectively. The arrows denote administration of Org 7797 (0.5 followed by 1.5 mg kg⁻¹) (—) or saline (-----). Each point is the mean $\pm$ s.e.mean of 5 experiments. * $P \leq 0.05$ denotes a significant difference from saline-treated animals.

Figure 2 Time course of the effects of Org 7797 at the atrial level: (a,b and c) depict changes from pretreatment values in intraatrial conduction time (St-A), effective (AERP) and functional (AFRP) refractory periods respectively. The arrows denote administration of Org 7797 (0.5 followed by 1.5 mg kg⁻¹) (—) or saline (-----). Each point is the mean $\pm$ s.e.mean of 5 experiments. * $P \leq 0.05$ denotes a significant difference from saline-treated animals.

Figure 3 Time course of the effects of Org 7797 on AV nodal function: (a,b and c) depict changes from pretreatment values in AV conduction time (AH), anterograde (A-Wck) and retrograde (R-Wck) Wenckebach rates respectively. The arrows denote administration of Org 7797 (0.5 followed by 1.5 mg kg⁻¹) (—) or saline (-----). Each point is the mean $\pm$ s.e.mean of 5 experiments. * $P \leq 0.05$ denotes a significant difference from saline-treated animals.

Figure 4 Time course of the effects of Org 7797 on ventricular refractory periods: (a and b) depict changes from pretreatment values in the effective (VERP) and functional (VFRP) refractory periods respectively. The arrows denote administration of Org 7797 (0.5 followed by 1.5 mg kg⁻¹) (—) or saline (-----). Each point is the mean $\pm$ s.e.mean of 5 experiments. * $P \leq 0.05$ denotes a significant difference from saline-treated animals.

Figure 5 Time course of the effects of Org 7797 at the ventricular level: (a and b) depict changes from pretreatment values in interventricular (QRS) and His-Purkinje (HV) conduction times respectively. The arrows denote administration of Org 7797 (0.5 followed by 1.5 mg kg⁻¹) (—) or saline (-----). Each point is the mean $\pm$ s.e.mean of 5 experiments. * $P \leq 0.05$ denotes a significant difference from saline-treated animals.

to 248 ± 16 and 262 ± 10 ms respectively (not shown) and were still significant 20 min after administration at the lower dose. However, anterograde and retrograde Wenckebach rates were only decreased at the higher dose (Figure 3b and c).

Effects of Org 7797 at the ventricular level

Org 7797 induced dose-dependent increases in QRS (Figure 4a) and in both the effective (VERP) and functional (VFRP) refractory periods (Figure 5). With the exception of the prolongation in QRS induced by the higher dose, these effects were relatively short-lived. HV was unaltered by the lower dose of Org 7797 but prolonged by the higher dose (Figure 4b).

Figure 6 Time course of the effects of Org 7797 at the ventricular repolarization: (a and b) depict changes from pretreatment values in the QTc and JTc intervals respectively. The arrows denote administration of Org 7797 (0.5 followed by 1.5 mg kg⁻¹) (—) or saline (-----). Each point is the mean $\pm$ s.e.mean of 5 experiments. * $P \leq 0.05$ denotes a significant difference from saline-treated animals.

Table 2 Comparative electrophysiological actions of Org 7797 on 'fast' and 'slow' action potentials in guinea-pig papillary muscle driven at 0.5 Hz

Fast action potentials							
[] μ M	n	RMP	APH	APD ₅₀	APD ₉₀	V _{max}	ERP
0	24	-83.6 ± 0.7	121 ± 2	170 ± 4	202 ± 3	310 ± 21	203 ± 17
20	24	-82.5 ± 0.4	117 ± 2	183 ± 4 *	204 ± 4	53 ± 3 ***	>250 ***
Slow action potentials							
[] μ M	n	RMP	APH	APD ₅₀	APD ₉₀	V _{max}	
0	24	-46 ± 0.4	78 ± 0.9	112 ± 4	131 ± 3	19.8 ± 1	
20	24	-45 ± 0.5	71 ± 0.9 ***	146 ± 3 ***	168 ± 3 ***	19.6 ± 0.8	

For abbreviations, see text.

Parameters are expressed as mean $\pm$ s.e.mean.

8 action potentials were recorded from each of 3 preparations.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

Baseline values of QT and JT intervals were in the same range in the control and Org 7797-treated groups (see Table 1). Org 7797, 0.5 mg kg⁻¹, did not significantly modify either the QT or JT intervals (increased by 11 ± 3 and $13 \pm 4\%$ respectively compared to 10 ± 8 and $14 \pm 11\%$ in the control group). A dose of 1.5 mg kg⁻¹ only significantly increased the QT interval at the 5 min time point (by $13 \pm 1.5\%$ vs $6 \pm 3\%$ in the control group) while the maximum JT interval in the Org 7797-treated group was shorter than that reached in the control group (201 ± 11 vs 229 ± 11 ms). Figure 6a and b illustrates the effects of Org 7797 on QTc and JTc. The lower dose was without effect whilst the higher dose induced a sustained shortening of JTc. QTc was unchanged except for a very transient increase seen immediately following administration of the higher dose.

Electrophysiological effects

The effects of Org 7797 were similar in all 3 preparations studied and the results are summarized in Table 2. Org 7797 (20 μ M) slightly prolonged APD₅₀ and markedly reduced V_{max} of normal 'fast' action potentials. These effects were accompanied by a small decrease in action potential amplitude and a prolongation of the effective refractory period beyond the limit of measurement. In contrast, V_{max} of 'slow' action potentials was unchanged although a significant decrease in action potential amplitude was observed. In addition marked prolongation of action potential duration (both at the 50 and 90% levels) was observed.

Discussion

In the present study, Org 7797 was given at a dose (0.5 mg kg⁻¹) known to exert marked antifibrillatory actions in both rats and greyhound dogs (Winslow *et al.*, 1991) and subsequently at three times this dose.

The results of this study indicate that the electrophysiological profile of high dose Org 7797 *in vivo* in dogs with normal cardiac function is similar to that reported for other known class Ic sodium channel blocking agents (Harrison, 1985; Karagueuzian *et al.*, 1984; 1985; Schlepper, 1987; Vaughan Williams, 1989). At a dose of 1.5 mg kg⁻¹, Org 7797 rendered 2 out of 7 dogs unable to follow an atrial pacing stimulus of approximately 170 beats min⁻¹. In the remaining dogs, conduction was slowed at all levels of the

myocardium as shown by prolongation of the St-A, AH, HV and QRS intervals, reflecting slowing of conduction in the atria, AV node, His-Purkinje system and ventricular myocardium, respectively. These effects were accompanied by only modest and transient increases in ventricular and atrial refractory periods and by a slight but definite shortening of cardiac repolarization as assessed from JTc. QTc was, however, essentially unaltered apart from a very transient increase which can be adequately explained by the marked prolongation of the QRS interval seen at this time. The slight shortening of JTc and the inactivity of Org 7797 on the duration of fast action potential *in vitro* seen in the present study are more reminiscent of the effects of class Ib agents such as mexilitine which either have no effect or shorten repolarization *in vivo* (Costard-Jackle & Franz, 1989) and *in vitro* (Vaughan Williams, 1989). The marked decrease of $V_{\max}$ (83%) of the fast action potential by Org 7797 in isolated papillary muscle and its lengthening of QRS (52%) *in vivo* suggest pronounced blockade of sodium channels in ventricular tissue following high dose administration.

The electrophysiological effects of the lower (antifibrillatory dose) of Org 7797 were almost exclusively confined to the AV node. At other levels of the myocardium, the only effects which were seen were modest and transient slowing of ventricular conduction (prolongation of QRS of 19%) together with very modest increases in the ventricular refractory periods. These results are in marked contrast to those reported in anaesthetized dogs with 5–6 day old myocardial infarcts (Campbell *et al.*, 1991) in which a similar dose of Org 7797 maximally increased St-A, QRS and HV by 81, 37 and 22% respectively, effects which were still significant 10 min after drug administration. Taken together these results suggest that the sodium channel blocking action of Org 7797 may be enhanced by myocardial infarction, as has been suggested for other class I drugs including propafenone (Seipel & Breithardt, 1978; Connolly *et al.*, 1983a,b) and disopyramide (Marrott *et al.*, 1976; Ross *et al.*, 1978). Despite the failure of low dose Org 7797 to influence conduction markedly in the fast conducting system or in atrial or ventricular muscle, a noticeable and sustained (at least 20 min) slowing of AV nodal conduction was observed (AH was increased by 34%) accompanied by a sustained prolongation (of 14%) of the AV nodal functional refractory period. These results might suggest a blockade of calcium ion channels (Fleckenstein, 1985). However, other calcium-dependent processes in large animals (Fleckenstein, 1985), such as heart rate in the present study and myocardial contractility in previous studies (Winslow *et al.*, 1991; Winslow & Mason, 1992), are not reduced by this dose of Org 7797. Also a concentration of Org 7797 which reduced $V_{\max}$ of fast sodium-mediated action potentials in isolated papillary muscle by 83% (at low stimulation frequency) failed to modify $V_{\max}$ of slow calcium-mediated action potentials (Table 2) suggesting that marked inhibition of sodium ion channels is

not accompanied by blockade of calcium ion channels. This would also be consistent with the observation that the FRP of the atrium changed more rapidly than the ERP. Although action potential amplitude was reduced, this may be explained by inhibition of residual sodium current in the depolarized tissues. These results are puzzling but the action of Org 7797 on AV nodal refractoriness might be explained by effects on currents involved in the plateau phase of the action potential (such as sodium-calcium exchange, sodium or calcium window or potassium currents; Noble, 1992; Hiraoka *et al.*, 1992; January & Moscucci, 1992) since in the present study, the duration of the fast action potential at the level of the plateau phase was lengthened as was the duration of the slow calcium-mediated action potential (see Table 2). Other Ic antiarrhythmic agents such as flecainide, which also prolong AV conduction and refractoriness (e.g. Hodess *et al.*, 1979), have been shown to influence potassium currents (Follmer & Colasky, 1990) whereas Ib drugs which do not slow conduction during normal sinus rhythm have no such effect at therapeutic concentrations (Campbell, 1987). These *in vitro* effects may explain the lengthening of the AV nodal refractory period observed in this study. Janse *et al.* (1990) and Kirchhof *et al.* (1991) have also provided evidence from porcine or canine preparations to suggest that the anti-fibrillatory effects of Org 7797 may be explained by prolongation of wavelength (the product of conduction velocity and refractory period) at fast frequencies. This preferential prolongation of refractory periods (compared to slowing of conduction) might at least be contributed to by rate-dependent prolongation of repolarization (Winslow & Campbell, 1991). However, explanation for the preferential electrophysiological effects of Org 7797 at the level of the AV node seen in the present study must remain speculative until the effects of Org 7797 on the various ion channels at different levels of the myocardium are elucidated. The picture is also complicated by the known frequency-dependent and concentration-dependent effects of Org 7797 on the inward sodium current (Winslow & Campbell, 1991) both of which would tend to oppose drug-induced prolongation of action potential duration. Nevertheless, the selective effect of this agent on the AV node in an antifibrillatory dose might contribute to the control of ventricular rate during atrial fibrillation in the absence of infra-nodal conduction disturbances.

In conclusion, the results of the present study suggest that the main electrophysiological effects of an antifibrillatory dose of Org 7797 in dogs with normal cardiac function are seen at the level of the AV node. Comparisons with previous studies also indicate that myocardial infarction may enhance the sodium channel blocking activity of this compound.

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