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Antiarrhythmic and Electrophysiological Effects In-vivo of the Major Metabolite of Org 7797 Found in Canine and Rodent Liver Homogenate Preparations

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Abstract

Org 20781, the major metabolite of Org 7797 found in in-vitro experiments was examined for antiarrhythmic and electrophysiological effects in-vivo.

Org 20781 (0·5–2·0 mg kg^{-1}, i.v.) inhibited the development of early ischaemia-induced arrhythmias in rats, suppressed spontaneous ventricular tachycardia (VT) in conscious dogs with 24-h old infarcts, and prevented electrical induction of VT in dogs with 5–6-day old infarcts, actions associated with slowing of conduction at all levels of the myocardium. Cardiac refractory periods were only modestly prolonged whilst repolarization was unchanged. Peak plasma levels of the parent compound (infused to total doses of 2–4 mg kg^{-1}) associated with suppression of late arrhythmias were 6–18 μM, whilst the mean plasma elimination half-life (in normal dogs) was 107 min.

It was concluded that the major metabolite has a similar antiarrhythmic and electrophysiological profile to the parent compound, is at least half as potent and may contribute to the therapeutic effects of Org 7797 administration.

Org 7797 is a new steroidal antifibrillatory agent currently undergoing clinical evaluation. Previous studies have shown that Org 7797 protects against the development of early ischaemia-induced ventricular fibrillation (VF) in rodent, canine and porcine models (Janse et al 1990; Winslow et al 1991), and reduces the incidence and duration of electrically-induced supraventricular fibrillation in conscious dogs (Kirchhof et al 1991) via a mechanism which is not yet clearly understood. Higher doses are required to suppress late ischaemia-induced ventricular tachycardia in conscious animals, an action attributed to class IC properties (Winslow et al 1989; Campbell et al 1991).

Liver homogenates metabolize Org 7797 almost exclusively by C2 hydroxylation to Org 20781 (Fig. 1) and only 28% of unmetabolized Org 7797 remains after incubation of Org 7797 with dog liver homogenates for 1 h (Delbressine unpublished). The major metabolite was therefore tested for antiarrhythmic and electrophysiological actions in whole animals. Since one of the main aims of this study was to determine whether the major metabolite was likely to contribute to the therapeutic effects of the parent compound, therapeutic plasma levels of Org 7797 were determined in dog with spontaneous arrhythmias seen 24 h after coronary artery occlusion. The pharmacokinetics of Org 7797 in normal dogs were also studied.

Materials and Methods

Pharmacokinetics in dogs

Beagle dogs, 10·7–13 kg, were given a single intravenous bolus injection of 2 mg kg^{-1} Org 7797 via a hind-limb vein. The drug was dissolved in PEG 200 and diluted with an equal volume of dog plasma. At fixed times after dosing, 10-mL blood samples were taken from a jugular vein using evacuated blood-collecting tubes containing 150 USP units lithium heparin. Plasma was prepared by centrifugation at 15 000 N kg^{-1} and room temperature (21°C) for 15 min. The plasma was aspirated, mixed with 0·38% trisodium citrate and stored at −20°C before assay. Plasma concentrations of Org 7797 were measured using electrochemical detection SPE C18 cartridges were pretreated with one column volume of methanol and one volume of 1 mM EDTA (pH = 3, phosphoric acid). Subsequently, approximately 1 mL dog plasma was mixed with an internal standard, added to the column and washed with one volume 1 mM EDTA, one volume 10 M ammonium acetate (pH 4·2) : acetonitrile (20 : 1, v/v) and one volume diethylether. Finally, the cartridge was washed with ethanol, the eluate containing Org 7797 and the internal standard. After evaporation of the ethanol, the residue was redissolved

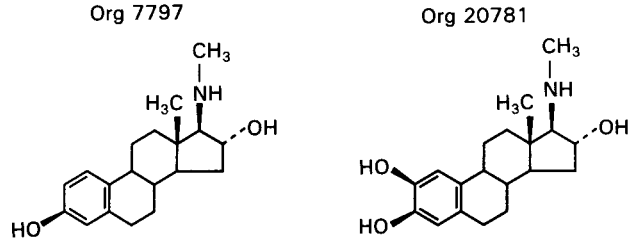

FIG. 1. The molecular structures of Org 7797 and its major metabolite Org 20781.

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in 50 μL methanol : acetonitrile : 0·01 M ammonium acetate (pH 4·2) (25 : 25 : 50 by volume). The HPLC system consisted of a Novapak C18 column and a LC-8-DB guard column with 11% acetonitrile in 0·1 M ammonium acetate (pH 4·2) as the mobile phase in conjunction with electromechanical detection (+800 mV). The flow was 1·2 mL min^{-1} and the column was maintained at 40°C. The detection limit was approximately 10 ng. Simultaneously with the plasma samples a standard calibration curve for Org 7797 and internal standard was processed. Accuracy and precision were judged from standard plasma samples analysed concomitantly. Org 7797 concentrations were calculated using simultaneously processed calibration samples. Curve fitting was performed on a VAX computer using a two-compartmental model to determine the elimination half-life ($t_{\frac{1}{2}}$), the area under the curve (AUC) and clearance (CL).

Early ischaemia-induced arrhythmias in rats

Male Wistar rats 260–330 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. Org 20781 or an equivalent volume of saline (0·1 mL/100 g) was 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 ± 0·5°C. A Chi square test was used to determine the significance of differences between incidences of VF and mortalities. Arrhythmias were analysed using an unpaired *t*-test.

Late ischaemia-induced arrhythmias in beagle dogs

Male or female beagle dogs, 10–14 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. Myocardial infarction was produced by inflating the catheter balloon 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. Org 20781 or Org 7797 were then infused over 10- and 20-min periods, respectively, 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 drug was given. Each dog received only one drug. The number of sinus beats (SB) 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, using a paired *t*-test with the mean %SB obtained during the control period. A drug-induced increase in %SB reflects an increase in the number of normal sinus beats compared with premature beats and denotes antiarrhythmic activity. Blood samples were also taken during and post-infusion from the Org 7797-treated animals and analysed for Org 7797 content as described above.

Electrophysiological recording and programmed electrical stimulation

Five or six days after myocardial infarction, dogs 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 to obtain a clear electrical signal from the His bundle. Electrophysiological measurements were made during normal sinus rhythm (NSR). 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 RR, PR, QRS and QT intervals were measured from the lead II ECG. Atrial and ventricular effective refractory periods (ERPs) were determined during atrial pacing and during simultaneous atrial and ventricular pacing, respectively, at a basic cycle length of 300 ms. 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 ST-A interval, determined from the start of the stimulus artefact to the earliest atrial deflection, was also measured. Refractor periods were determined immediately before and at 5 and 10 min after Org 20781 administration. All other measurements were additionally made at 2 min after drug administration.

Programmed electrical stimulation (PES) was performed as described by Winslow et al (1990). A BBC microcomputer, specially designed software and a Grass S88 stimulator were used to deliver up to three premature stimuli during NSR, during simultaneous atrial and ventricular pacing at a basic cycle length of 250 ms and, if necessary, during burst pacing. 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, defined as VT lasting for at least 20 s) or VF was induced or until the protocol was exhausted. Termination of SVT sometimes required overdrive pacing or direct current

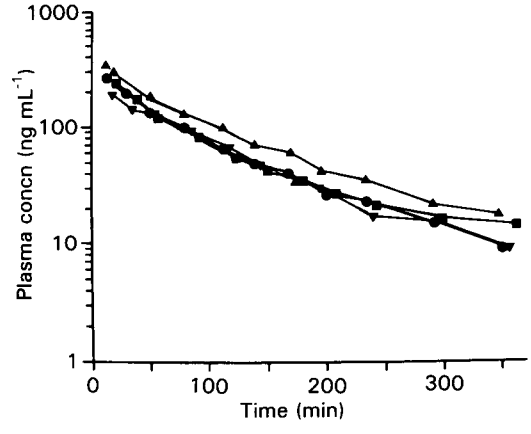

FIG. 2. Time course of Org 7797 plasma levels in four dogs following intravenous administration of 2 mg kg^{-1}.

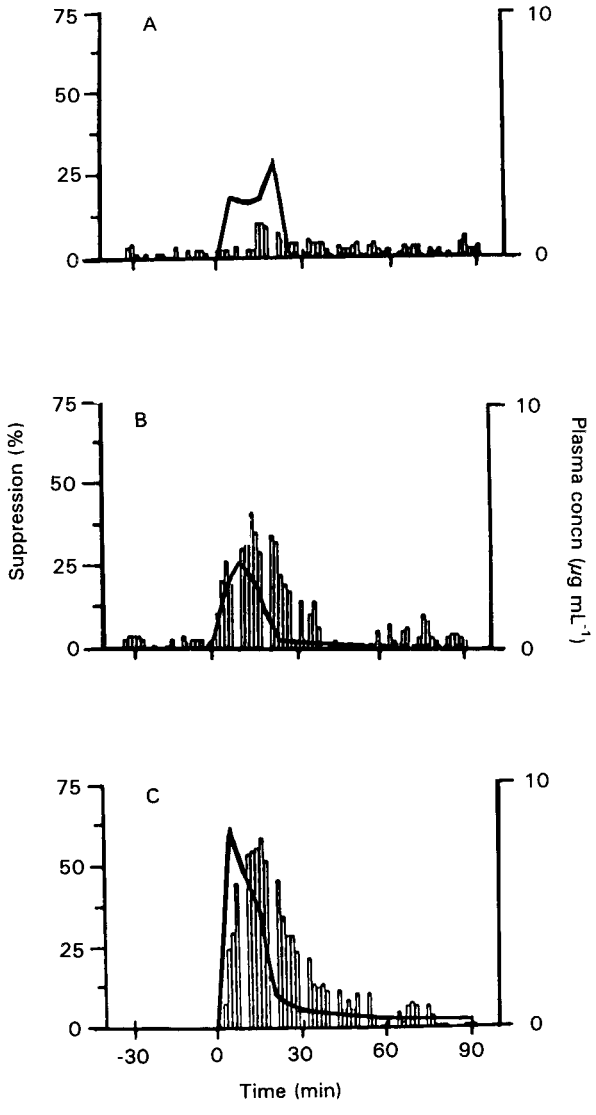

FIG. 3. Relationship between Org 7797 plasma levels and suppression of spontaneous arrhythmias in conscious beagle dogs with 24-h-old infarcts. The infusion rates were (A) 0·05 (n = 4), (B) 0·1 (n = 5) and (C) 0·2 mg kg^{-1} min^{-1} (n = 6).

(d.c.) conversion. If this was required, dogs were allowed to recover for at least 1 h before further challenge. Arrhythmia inducibility was assessed at least twice before drug administration to ensure reproducibility and PES again commenced 10 min after Org 20781 administration.

A paired *t*-test corrected for multiple comparisons (Bonferroni) was used to compare pre- and post-drug electrophysiological measurements.

Results

Pharmacokinetics of Org 7797, plasma levels and effects on late arrhythmias in dogs

The concentrations of Org 7797 in plasma samples taken from four normal dogs following a bolus injection of 2 mg kg^{-1} are shown in Fig. 2 and relevant pharmacokinetic parameters given in Table 1. The mean plasma elimination half-life was 107 min and clearance was 4·5 L h^{-1} kg^{-1}. Fig. 3 shows the effects of Org 7797 (0·05, 0·1 and 0·2 mg kg^{-1} min^{-1} for 20 min) on spontaneous late arrhythmias together with Org 7797 plasma levels determined at 5 min intervals both during and after cessation of the infusion. Peak antiarrhythmic activity was associated with peak plasma levels of 2640 ± 673 and 6179 ± 2415 ng mL^{-1} (mean ± s.d.) at the two higher infusion levels. The mean peak plasma level in the low dose group was 1836 ± 1483 ng mL^{-1} but there was no overall arrhythmia suppression in this group. Thirty minutes after cessation of infusion of 0·1 and 0·2 mg kg^{-1} min^{-1}, at a time when antiarrhythmic activity had completely subsided, plasma levels of Org 7797 were 149 ± 22 and 335 ± 48 ng mL^{-1}, respectively. The antiarrhythmic effects of Org 7797 were accompanied by decreases in ventricular rate (data not shown).

Table 1. Derived pharmacokinetic parameters in each of four dogs given an intravenous bolus injection of 2 mg kg^{-1} Org 7797.

Dog number	$t_{\frac{1}{2}}$ (min)	$AUC_{0-\infty}$ (μg mL^{-1} min)	C_0 (ng mL^{-1})	CL (L h^{-1} kg^{-1})
1	137	26·7	330	4·5
2	108	22·7	230	5·3
3	82	24·7	330	4·8
4	99	34·8	380	3·5
mean ± s.d.	107 ± 23	27·2 ± 5·3	317 ± 63	4·5 ± 0·8

Early ischaemia-induced arrhythmias in rats

The results are summarized in Table 2. Org 20781 (0·5 mg kg^{-1}) markedly reduced the occurrence of ventricular tachycardia and salvos compared with controls. Higher doses (1 and 2 mg kg^{-1}) additionally prevented the development of VF and prevented electrical deaths.

Effects of Org 20781 on late arrhythmias in conscious beagle dogs

Org 20781 (10 min infusions of 0·05 followed by 0·2 mg kg^{-1} min^{-1}) significantly increased the number of sinus

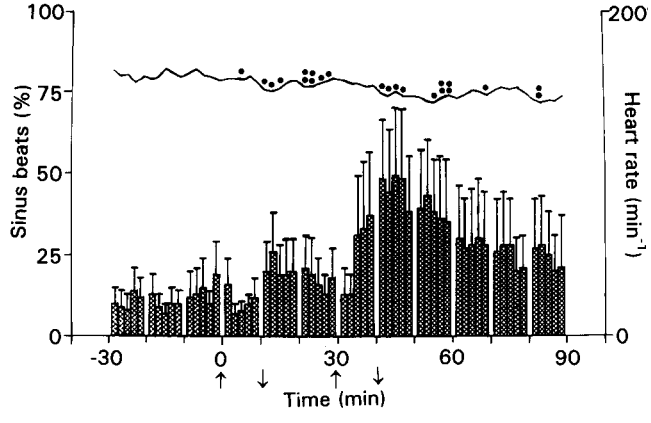

FIG. 4. Effects of intravenous infusion of Org 20781 on the percentage sinus beats (columns with standard error bars) assessed over successive 2-min intervals in conscious beagles 1–2 days after myocardial infarction. Heart rate is shown by the horizontal line. The arrows denote the periods during which 0·5 followed by 2·0 mg kg^{-1} was infused. Each result is the mean of six observations. $*P < 0.05$, $**P < 0.01$ denote significant differences from pretreatment values.

Table 2. Intravenous antiarrhythmic activity of the metabolite of Org 7797 in the anaesthetized rat.

Treatment (mg kg^{-1})	n	VPBs					
		Single	Salvo	VT	Total	%VF	%M
Saline	12	152 ± 45	66 ± 20	560 ± 215	778 ± 274	50	42
Org 20781 (0·5)	10	169 ± 154	8 ± 6*	21 ± 21*	198 ± 180	40	40
(1·0	10	67 ± 27	14 ± 6*	148 ± 112	229 ± 137	0*	0†
(2·0)	10	110 ± 35	10 ± 7*	8 ± 7*	128 ± 43*	0*	0†

*$P < 0.05$ denotes a significant difference from the appropriate control group. †$P = 0.07$.

beats compared with pretreatment values (Fig. 4). Ventricular rate remained significantly reduced for at least 50 min after cessation of infusion.

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

Before Org 20781 administration, three of five dogs fibrillated and two developed sustained VT in response to PES. Two of the dogs which fibrillated did so in response to burst pacing. After 0·5 mg kg^{-1} Org 20781, arrhythmias were still inducible in four of the five dogs (Table 3), although VF was prevented in two animals. Arrhythmias could not be induced in three of the four dogs given an additional 2 mg kg^{-1} Org 20781 ($P = 0.09$). The induced VT rate was 452 ± 17 and 440 ± 21 beats min^{-1} before and after 0·5 mg kg^{-1} Org 20781, and in the one animal in which VT rate could be measured following 2 mg kg^{-1} there was again no apparent reduction (417 vs 410 beats min^{-1}).

Electrophysiological effects

Mean baseline values for each parameter analysed are given in Table 4. Maximum electrophysiological changes in response to Org 20781 (0·2–2·0 mg kg^{-1}) were seen within 2–5 min of administration and were sustained for at least 10 min (Fig. 5). Org 20781 dose-dependently lengthened PR, QRS, AH, HV and St-A intervals whilst RR, QTc, QT (during pacing) and SNRT were unchanged. Atrial and ventricular refractory periods were unchanged by the lower doses used. The highest dose increased both the ventricular and atrial ERPs, although only the latter attained statistical significance.

In these experiments arterial blood pressure remained unchanged by Org 20781.

Table 3. Responses to programmed electrical stimulation before and after administration of 0·5 mg kg^{-1} followed by 2 mg kg^{-1} Org 20781 to each of five anaesthetized beagle dogs.

Dog number	Pre	Post	
		0·5 mg kg^{-1}	2·0 mg kg^{-1}
1	Ventricular fibrillation	Non-inducible arrhythmias	Non-inducible arrhythmias
2	Ventricular fibrillation	Ventricular fibrillation	Non-inducible arrhythmias
3	Sustained ventricular tachycardia	Sustained ventricular tachycardia	Non-inducible arrhythmias
4	Ventricular fibrillation	Sustained ventricular tachycardia	Sustained ventricular tachycardia
5	Sustained ventricular tachycardia	Sustained ventricular tachycardia	

Discussion

The results of the present study show that the major metabolite of Org 7797 found in in-vitro experiments (the 2-ol derivative) has antifibrillatory and antiarrhythmic properties in animal models of myocardial infarction. A dose of 1 mg kg^{-1} completely prevented early ischaemia-induced VF in the rat whilst a lower dose (0·5 mg kg^{-1}) prevented inducible VF in two of three dogs with established infarcts. Although a dose of 0·5 mg kg^{-1} failed to prevent the development of VF in the rat model, the severity of VT and the number of salvos were markedly reduced. Org 20781 (2 mg kg^{-1}) also suppressed late spontaneous ventricular tachycardia in conscious dogs with 1–2-day old infarcts. These results are qualitatively similar to those previously

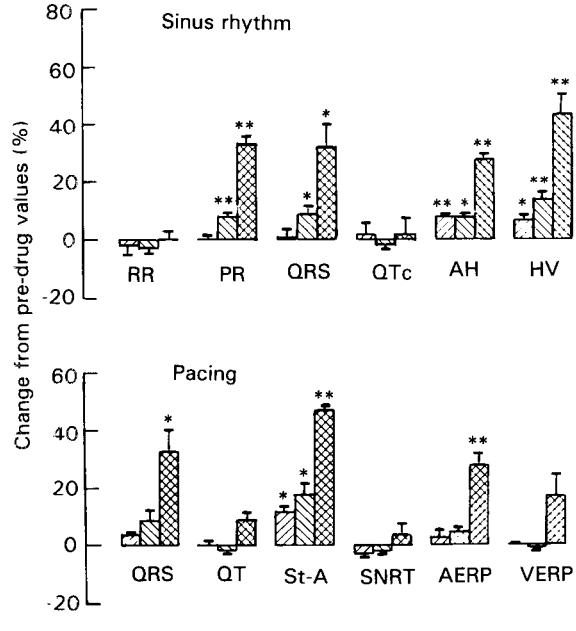

FIG. 5. Electrophysiological effects of 0·2 (▨), 0·5 (▩) and 2·0 (▩) mg kg^{-1} Org 20781 seen 10 min after administration to anaesthetized beagles. Each result is the mean % change from pre-drug values in six dogs; vertical bars show s.e. mean. *$P < 0.05$, **$P < 0.01$ denote significant changes from pretreatment values.

Table 4. Baseline values (ms) for electrophysiological parameters recorded from beagle dogs pre-drug administration.

Normal sinus rhythm						Pacing (BCL 300 ms)				
RR	PR	QRS	QTc	AH	HV	QT	St-A	SNRT	AERP	VERP
370 ± 30	82 ± 3	43 ± 2	357 ± 18	53 ± 6	29 ± 3	207 ± 8	29 ± 3	399 ± 21	114 ± 6	141 ± 5

Values are the mean ± s.e. mean of six observations.

obtained in response to Org 7797 in similar models using similar doses and indicate that the metabolite is at least half as potent as the parent compound as an antiarrhythmic agent (Winslow et al 1991). Electrophysiological studies in anaesthetized beagle dogs showed that the metabolite slows conduction in atrial, Purkinje and ventricular tissue (reflected by prolongation of the St-A, HV and QRS intervals), and modestly prolongs atrial and ventricular refractory periods whilst repolarization (assessed from QTc and QT during pacing) is unchanged. This electrophysiological profile is similar to that expected from a class IC agent (Harrison 1985) and is similar to that of Org 7797 (Campbell et al 1991). However, the parent compound appears to be about twice as potent as its metabolite in these respects; for example, in the study by Campbell et al, a dose of Org 7797 of 0·5 mg kg^{-1} in the same dog model prolonged HV, QRS, VERP and AERP by maxima of 25, 30, 4 and 8%, respectively within 2–5 min, whilst equivalent values following the same dose of Org 20781 were 14, 9, −1 and 5%. However, the immediate effects of the metabolite were sustained during the 10-min recording period whilst by 10 min after Org 7797, changes in electrophysiological parameters were similar to those seen following the metabolite (15, 14, 2 and 3%). In addition, 2 mg kg^{-1} Org 7797 rendered seven out of eight dogs unable to follow a pacing stimulus of BCL 322 ± 7 ms and prolonged the RR interval by 22%, effects which again declined within 10 min. Failure to follow the driving stimulus (300 ms BCL) was not seen following the same dose of the metabolite and the RR interval was unchanged. Thus although the intrinsic activity of Org 7797 appears higher than that of the metabolite, the longer duration of action of the latter would account for the apparent similarity in antiarrhythmic potency in-vivo. A dose of Org 20781 2 mg kg^{-1} prevented inducible tachyarrhythmias (VT/VF) in three out of four animals (75%), whilst 0·5 mg kg^{-1} prevented arrhythmia induction in one of five dogs (20%). This success rate is at least equivalent to that reported for other class I agents (10–30%) (e.g. Sullivan et al 1990) including Org 7797 (33% at both 0·5 and 2 mg kg^{-1}) (Winslow et al 1991) and suggests that the metabolite is at least equi-active with Org 7797 in this respect.

Suppression of late ischaemia-induced arrhythmias in the beagle by Org 7797 infused to total doses of 2 and 4 mg kg^{-1} over 20 min, paralleled plasma Org 7797 concentrations. Moreover, peak levels of Org 7797 (2·64 and 6·18 μg mL^{-1} = 6·33 and 14·82 μM) were similar to those required to reduce the maximum rate of depolarization of cardiac cells in-vitro (1–10 μM) (Winslow et al 1989; Winslow & Campbell 1991) indicating that arrhythmia suppression in this model is a direct consequence of sodium-channel block. This is consistent both with the mechanism underlying this type of arrhythmia and with its known dependency on sodium-channel block for its suppression (Lazzara et al 1974; Marshall & Winslow 1982). By 30 min after cessation of infusion of the highest dose, at a time when arrhythmia suppression had completely subsided, mean plasma levels were 0·335 μg mL^{-1} (0·8 μM), a concentration some 3–6 times that associated with marked antifibrillatory activity in rats (Delbressine et al 1992), suggesting that the antifibrillatory effects of Org 7797 are not a result of sodium-channel block. This would be consistent with results obtained by Janse et al (1990) and Kirchhof et al (1991) who concluded from phase mapping-activation studies in porcine and canine hearts that the mechanism underlying the antifibrillatory effect of Org 7797 was a prolongation of wavelength at fast frequencies resulting from a relatively greater effect to prolong refractoriness than to slow conduction. Such an action would be expected to reduce the likelihood of VF development from re-entrant mechanisms during ischaemia (Rensma et al 1988; Janse & Wit 1989). Since the metabolite also displayed antifibrillatory activity at doses (0·5–1·0 mg kg^{-1}) below those necessary to suppress late arrhythmias, it may be that the metabolite also shares this action. However, this remains to be tested.

Intravenous Org 7797 was rapidly eliminated from the plasma in non-infarcted beagles (mean $t_{\frac{1}{2}}$ = 107 min). Together with unpublished observations that dog-liver homogenates transform 72% of added Org 7797 to the major metabolite within 60 min (Delbressine unpublished) and the observed potency of the metabolite seen in the present studies, it seems likely that the metabolite does contribute to both the antiarrhythmic and antifibrillatory effects of the parent compound. However, since the studies performed by Janse et al (1990) described above were conducted in isolated perfused hearts of pig, it seems clear that the antifibrillatory effect of Org 7797 in-vivo is intrinsic to the parent compound and cannot be ascribed solely to the production of its major metabolite. The metabolite may, however, add to both the therapeutic effect and extend the duration of action of the parent compound. In conclusion, evidence has been provided to suggest that the major metabolite of Org 7797 has an antiarrhythmic and electrophysiological profile similar to that of the parent compound and may contribute to the therapeutic effect of Org 7797 observed in-vivo. Nevertheless, it must be kept in mind that in-vivo plasma measurements of both the parent compound (Org 7797) and the active metabolite (Org 20781) are necessary to establish a reliable correlation between observed effects and plasma concentrations.

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