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The effects of the novel anti-anginal compound RS 43285 on myocardial conduction in the anaesthetized dog

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1 A pentobarbitone-anaesthetized canine model of myocardial conduction was developed to evaluate drug effects on intra-atrial (I-A), intra-ventricular (I-V) and atrioventricular (A-V) conduction parameters, both at rest and during electrical pacing of the right atrium or ventricle. Drug effects on the ability of the sino-atrial (SA) node to re-establish sinus rhythm on switching off electrical pacing were also considered. The effects of the novel anti-anginal compound RS 43285-193 ((±)-N-(2,6-dimethylphenyl)-4[2-hydroxy-3-(2-methoxyphenoxy)propyl]-1-piperazine acetamide dihydrochloride) were compared to those of the standard anti-anginal compounds nicardipine, nifedipine and verapamil.

2 In the dose range 15–7000 $\mu g\,kg^{-1}$, RS 43285 had no significant effects on I-A, I-V or A-V conduction either at rest or during electrical pacing and did not affect the re-establishment of sinus rhythm.

3 Nicardipine had no effects on conduction parameters at resting heart rate. There were no effects on I-A or I-V conduction on electrical pacing but A-V conduction was increased at 200–500 $\mu g\,kg^{-1}$ (with a 2:1 A-V conduction block in two out of six dogs); this was accompanied by a prolongation of the interval to reversion of sinus rhythm.

4 Nifedipine had no significant effects on I-A or I-V conduction but significantly prolonged A-V conduction at 1000 $\mu g\,kg^{-1}$ and this dose also increased the interval to SA node recovery.

5 Verapamil did not effect I-A or I-V conduction. However, A-V conduction was affected with a significant prolongation occurring at resting heart rate at 100–400 $\mu g\,kg^{-1}$ and a 2:1 A-V block in one dog at rest. During right atrial pacing verapamil significantly increased A-V conduction at 50–400 $\mu g\,kg^{-1}$. All dogs exhibited a 2:1 A-V conduction block at the highest frequency at 400 $\mu g\,kg^{-1}$.

Introduction

In the management of ischaemic heart disease, the drug of choice is often combined with a β-blocker. However, β-adrenoceptor blockade may (by reducing myocardial oxygen requirements) reduce sympathetic drive to the heart and thus unmask any cardiodepressant effects of the combinant drug such as a reduction of heart rate, contractility and atrioventricular (A-V) conduction. This would be of special significance in the treatment of angina where the drugs would be employed both during periods of transient myocardial ischaemia and in episodes of normal coronary flow. Electrophysiological experiments in ischaemic myocardium have shown that delayed conduction is an important contributory factor to the genesis of re-entrant arrhythmias early following coronary ligation (Elharar & Zipes, 1977; Lazzara *et al.*, 1978). A drug of choice in the treatment of ischaemic heart disease which was devoid of cardiodepressant activity would therefore be desirable. We have previously shown that RS 43285 (Figure 1) protects against the electrophysiological, haemodynamic (unpublished observations) and biochemical (Allely *et al.*, 1987) consequences of transient myocardial ischaemia in the pentobarbitone-anaesthetized dog without the acompaniment of overt haemodynamic effects. In the present study we examined the effects of RS 43285 on canine myocardial conduction and compared them with those of three standard anti-anginal drugs which are employed alone and in combination with β-blockers both clinically and experimentally (nicardipine: Rousseau *et al.*, 1984; 1986; nifedipine, Fujimoto *et al.*, 1981; Braun *et al.*, 1985; verapamil, Winniford *et al.*, 1982; Braun *et al.*, 1985).

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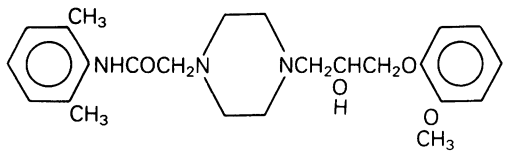

Figure 1 Structural formula of (±)-RS 43285-193.

Surgical preparation

The study was carried out on male beagles (E.G. Crowley, Malvern, Worcs) weighing between 10.5 and 20 kg and which had been fasted overnight. Premedication was by 0.2 mg kg^{-1} acepromazine i.m. (Berk Pharmaceuticals Ltd.). General anaesthesia was induced with sodium pentobarbitone (Sagatal, May & Baker; 25 mg kg^{-1} i.v.) and maintained with this agent throughout the experiment as required. The trachea was intubated and the dogs respired with room air on a Harvard ventilator at a rate of 10–12 min^{-1}, tidal volume 300 ml. Body temperature was maintained at 38 ± 1°C by means of a rectal probe thermometer attached to a homeothermic blanket control unit (CFP 8185). The left femoral vein was cannulated for drug administration. The left femoral artery was catheterised for phasic aortic blood pressure recordings made from a Siemens 746 pressure transducer and recorded on a Mingograf 8-channel recorder (Siemens, 804, inkspray oscillograph). Five hundred ml Ringer-lactate solution was infused during surgery as fluid replacement therapy. Thoracotomy was performed via a mid-sternal split. The pericardial sac was incised and drawn up to 'cradle' the heart. Six close pairs of bipolar epicardial electrodes were sutured onto the heart as shown in Figure 2: one pair of stimulating and two pairs of recording electrodes were attached to the right atrium (RA) and the right ventricle (RV). This permitted alternate direct electrical stimulation of the RA or RV and the timing of arrival of spontaneous or electrically-induced impulses between fixed points on the RA and RV or between the RA and RV.

Experimental protocol

Epicardial electrograms (ECGs) were recorded from RA1, RA2, RV1 and RV2 electrodes on a Siemens 850 ECG amplifier attached to a Mingograf 8-channel recorder (Siemens, 804, inkspray oscillograph) made at a sensitivity of 1 cm = 1 mV; paper speed during sample recordings was 1000 mm s^{-1} to allow accurate measurement of intra-atrial (I-A), intra-ventricular (I-V) and atrioventricular (A-V) conduction times. A sample of spontaneous heart rate (HR) ECG was made, followed by a sample with RA pacing at each of 4 fixed pacing frequencies, with the stimulator switched off between samples. The paper was left running over this switch-off period in order that the interval between the last stimulus-evoked atrial depolarization and the first spontaneously-occurring atrial wave could be measured. This provides an index of the ability of the sino-atrial (SA) node to re-establish sinus rhythm following what is essentially an episode of atrial tachycardia. Direct RV stimulation using pulses of 5V and 1 ms duration at each of the 4 fixed frequencies was then performed. The pacing rates and frequencies used were:

Frequency (beat min^{-1})	187	214	240	260
Stimulus cycle length (ms)	320	280	250	230

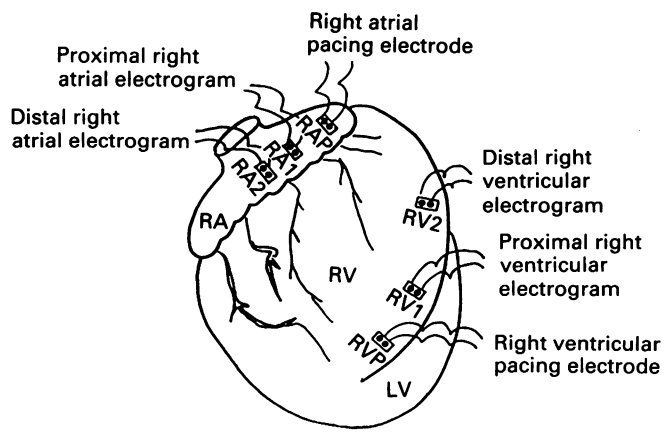

Figure 2 Placement of electrodes for alternate pacing of the right atrium or ventricle and recording of epicardial electograms in an anaesthetized canine model of myocardial conduction.

Two control series of recordings were made and the first drug dose was administered immediately following the final stimulus. The next samples were taken 10 min following drug injection, thus providing a test cycle of 13 min.

Drugs

RS 43285-193, nicardipine HCl (Syntex); nifedipine (Bayer) and verapamil HCl (Sigma).

Statistical analysis

All values given in the text are presented as mean ± s.e.mean. The s.e. bars are omitted from the figures for the sake of clarity. Student's two-tailed t test (Robson, 1973) was employed for the comparison of pre- and post-drug cardiac conduction times. Post-drug conduction times were considered to be statistically significantly different from pre-drug control values at $P < 0.05$.

Results

In the absence of drug, A-V conduction increased proportionally with decreasing stimulus cycle length (increasing HR) in all dogs as a consequence of compensatory inhibition, whereas I-A and I-V conduction were independent of pacing frequency. I-V conduction as stimulated by direct ventricular pacing was consistently longer than that measured during atrial pacing. This is because the former does not involve such a high proportion of the specialised ventricular conduction system, since it is produced in an abnormal sequence and is therefore more representative of direct myocardial conduction. The figures which follow represent only direct right ventricular pacing-induced I-V measurements, since in no instance were direct or indirect I-V conduction times differently affected by a drug.

RS 43285

The effects of RS 43285 on I-A, I-V and A-V conduction ($n = 6$) are shown in Figure 3. RS 43285 had no effects on I-A or I-V conduction up to a dose of 7 mg kg^{-1} (the doses given in all figures represent cumulative levels). Spontaneous A-V conduction was unaffected by RS 43285 (from a pre-drug time of 91.4 ± 4.3 ms to 95.7 ± 6.6 ms at 7 mg kg^{-1}). At the highest pacing frequency at the top two doses there was a tendency for A-V conduction to begin to increase but this was not significant. RS 43285 had no effects whatever on the interval between switching off atrial pacing and the re-establishment of sinus rhythm as shown in Figure 7. HR was decreased by 6% at 7 mg kg^{-1} which was not statistically significant and no effects on blood pressure (BP) were noted at any dose.

Nicardipine

The effects of nicardipine on I-A, I-V and A-V conduction are shown in Figure 4 ($n = 6$). Nicardipine produced no significant effects on I-A or I-V conduc-

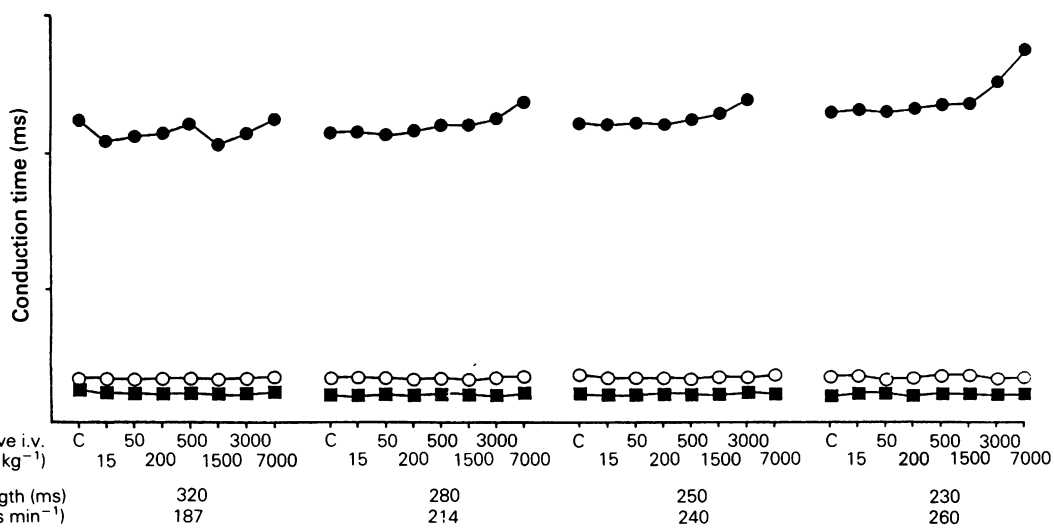

Figure 3 The effects of i.v. RS 43285 on intra-atrial (■), intra-ventricular (○) and atrioventricular (●) conduction at 4 pacing frequencies in the pentobarbitone-anaesthetized dog. Each value represents a mean ($n = 6$).

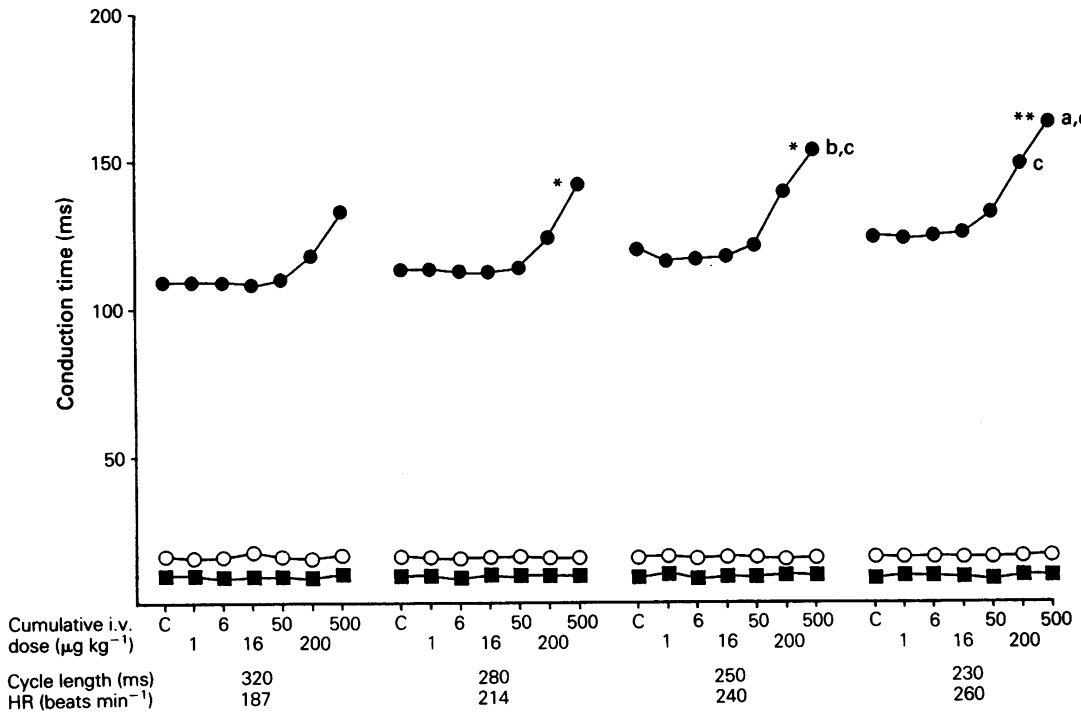

Figure 4 The effects of i.v. nicardipine on intra-atrial (■), intra-ventricular (○) and atrioventricular (●) conduction at 4 pacing frequencies in the pentobarbitone-anaesthetized dog. Each value represents a mean ($n = 6$). A 2:1 atrioventricular conduction block occurred as follows: (a) (2 dogs), (b) (1 dog), with waveform disruption at (c) (1 dog). Significant increases from control baseline values were assessed by Student's two-tailed t test: $^*P < 0.05$; $^{**}P < 0.01$.

tion at doses up to 500 μg kg^{-1}. Spontaneous A-V conduction was unaffected by nicardipine (pre-drug time of 91.1 ± 3.7 ms to 95.2 ± 7.3 ms at 500 μg kg^{-1}). A-V conduction during atrial pacing was increased by 200 and 500 μg kg^{-1}, becoming significant at 500 μg kg^{-1} at the higher three frequencies. Two out of six dogs exhibited a 2:1 A-V block at 500 μg kg^{-1} at a HR of 260 and one of these dogs also showed it at 240 beat min^{-1}. A further A-V disruption was noted as shown in the figure in one dog with an intermittent A-V block (3:2, 4:3 etc). Three animals showed no disruptions whatever. Since at the points where A-V block occurred A-V conduction could only be measured at those beats where ventricular waves appeared, these A-V conduction average values are artificially low. At 50–500 μg kg^{-1} nicardipine produced a dose-dependent increase in the interval between atrial pacing and the return of sinus rhythm ($n = 3$; Figure 7). The prolongation of this parameter was significant at 200 and 500 μg kg^{-1} at all pacing frequencies (except in one instance due to a large standard error) and at 50 μg kg^{-1} at the top frequency. In the range 200–500 μg kg^{-1} nicardipine produced a reduction in HR (5 and 15% respectively) the latter only being significant. Both of these doses produced a similar significant reduction in systolic and diastolic BP (approximately 25% systolic and 50% diastolic).

Nifedipine

Figure 5 shows the effects of nifedipine ($n = 6$) on I-A, I-V and A-V conduction. No effects on I-A or I-V conduction were noted. Spontaneous A-V conduction was unaffected by nifedipine (pre-drug time of 79.8 ± 1.4 ms to 80.6 ± 2.1 ms in the presence of 1 mg kg^{-1}). At 1 mg kg^{-1} nifedipine significantly increased A-V conduction at the higher three pacing frequencies with no incidences of A-V block. The effects of nifedipine on the interval to the re-establishment of sinus rhythm are shown in Figure 7 ($n = 6$). This parameter was significantly prolonged by 1 mg kg^{-1} at the higher three frequencies and by 200 μg kg^{-1} at a HR of 260. Nifedipine had no effects on resting HR and produced an 8% fall in systolic BP with a 25% fall in diastolic at 1 mg kg^{-1} which was not significant.

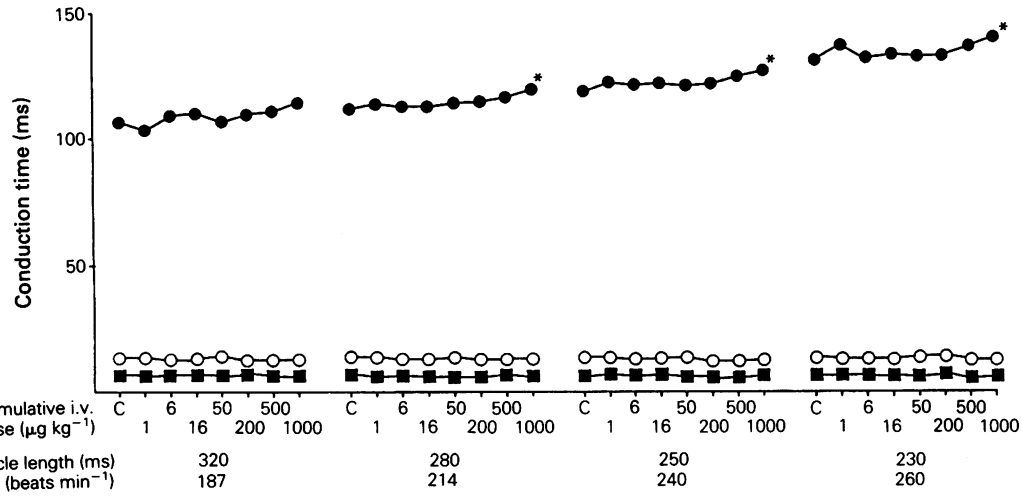

Figure 5 The effects of i.v. nifedipine on intra-atrial (■), intra-ventricular (○) and atrioventricular (●) conduction at 4 pacing frequencies in the pentobarbitone-anaesthetized dog. Each value represents a mean ($n = 6$). Significant increases from control baseline values were assessed by Student's two-tailed t test: $^*P < 0.05$.

Verapamil

Verapamil had no effects on I-A or I-V conduction ($n = 6$) as shown in Figure 6. Spontaneous A-V conduction was dose-dependently increased by verapamil and this prolongation became statistically significant in the dose range 100–400 $\mu g\,kg^{-1}$ as follows: 89.8 ± 2.6 ms pre-drug; 101.7 ± 3.6 ms at 100 $\mu g\,kg^{-1}$ ($P < 0.05$); 112.2 ± 3.6 ms at 200 $\mu g\,kg^{-1}$ ($P < 0.01$); 134.7 ± 9.6 ms at 400 $\mu g\,kg^{-1}$ ($P < 0.001$). At 400 $\mu g\,kg^{-1}$ a 2:1 A-V block occurred in one dog at spontaneous HR. During episodes of RA pacing, A-V conduction was dose-dependently increased by verapamil in the range of 50–400 $\mu g\,kg^{-1}$, most of these points reaching statistical significance as shown. At 200–400 $\mu g\,kg^{-1}$ verapamil produced some degree of A-V disruption or block in all animals and the varying instances are shown. Figure 7 shows the effects of verapamil ($n = 3$) on the SA node's ability to re-establish sinus rhythm. Although verapamil increased this index at doses of 100–400 $\mu g\,kg^{-1}$, the effects were not statistically significant. Verapamil reduced HR by 8% at 100 $\mu g\,kg^{-1}$, 13% at 200 $\mu g\,kg^{-1}$ and 17% at 400 $\mu g\,kg^{-1}$, but the effect was not significant and there was no effect on systolic or diastolic BP.

Discussion

Propagation of cardiac action potentials varies in different areas of the myocardium. The model employed in the present study to evaluate drug effects on conduction parameters of the canine myocardium involves direct electrical stimulation, either of the right atrium or right ventricle, to simulate episodes of atrial or ventricular tachycardia. *In vivo* conduction measurements involving direct right atrial pacing are going to involve specialised myocardial conduction pathways between the atrium and ventricle reflecting the His-Purkinje system status (Rogel & Hasin, 1971). Transmission through the A-V node is proportional to the degree of sympathetic tone, unlike I-A or I-V conduction. Direct right ventricular stimulation sets up an essentially abnormal ventricular activation sequence and the validity of resultant information has long been questioned (Scherlag *et al.*, 1967; Damato *et al.*, 1969). Since our model involves both direct and indirect pacing methods at four frequencies, it should be susceptible to the effects of compounds affecting myocardial conduction systems, specialised or otherwise. The model requires only one stimulus generator and, without the technique of the introduction of extrasystoles, can give an indirect index of SA node status as affected by Ca^{2+}-entry block.

In a study to compare the anti-anginal effects of the four compounds studied here, (unpublished observations) a canine model of transient myocardial ischaemia was developed. An anti-anginal therapeutic profile in terms of electrophysiological improvement of the consequences of myocardial ischaemia was obtained. The 'anti-anginal therapeutic' dose ranges obtained were 50–200 $\mu g\,kg^{-1}$ (RS 43285 and verapamil) and 6–50 $\mu g\,kg^{-1}$ (nicardipine and nifedipine). In the treatment of coronary artery disease and angina it is likely that combinant therapy with other agents may be desirable. In humans at rest there

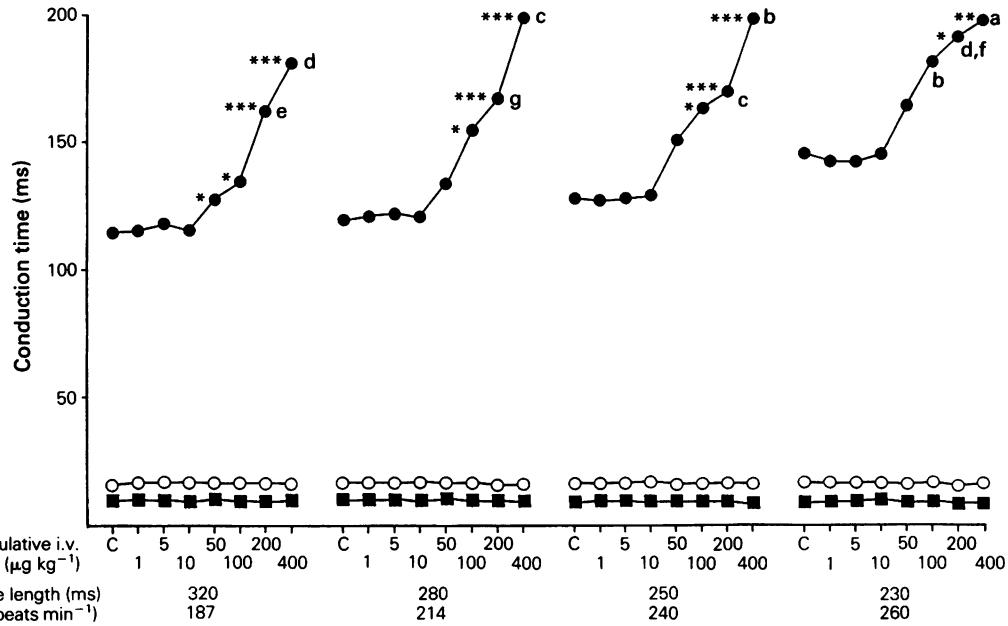

Figure 6 The effects of i.v. verapamil on intra-atrial (■), intra-ventricular (○) and atrioventricular (●) conduction at 4 pacing frequencies in the pentobarbitone-anaesthetized dog ($n = 6$). A 2:1 atrioventricular conduction block developed as follows: (a) (all dogs), (b) (4 dogs), (c) (3 dogs), (d) (2 dogs), (e) (1 dog), with incidences of ventricular waveform disruption at (f) (4 dogs) and (g) (2 dogs). Significant increases from baseline control values were assessed by Student's two-tailed t test: $*P<0.05$; $**P<0.01$; $***P<0.001$.

is a parasympathetic dominance of the SA node governing pacemaker activity and a disturbance of this delicate balance of sympathetic/parasympathetic drive by β-blocker therapy etc. may lead to a reduction in the rate of discharge of the SA node. Any cardiodepressant effects of compounds likely to be employed in combination therapy are therefore to be avoided.

In pre-drug control runs A-V conduction was seen to increase with a rise in the rate of atrial stimulation which represents episodes of supraventricular tachycardia. This itself never occurred to the point of preventing normal electrical activation since the A-V conduction system refractory period decreases as HR increases (Denes *et al.*, 1974; Bissett *et al.*, 1975). It is this electrophysiological property of the specialised cardiac conduction system that may lead to heart block in the presence of drugs affecting its refractory period or with cardiodepressant actions – especially during episodes of tachycardia.

Nifedipine had only marginal effects on conduction until a cumulative dose of 1 mg kg^{-1} was reached when A-V conduction was prolonged without incidence of A-V block. The A-V prolongation at this dose is probably due to Ca^{2+}-entry block of the A-V node. The combination of a reduction in resting BP and lack of effect on resting A-V transmission did not produce the expected reflex sympathetically-induced tachycardia, since this would be counteracted by direct SA node depression (exhibited in isolated heart tissue by all Ca^{2+}-entry blockers; Millard *et al.*, 1982), which was seen to be the case during pacing, as shown in Figure 7, resulting in no net change in HR. All of the conduction effects of nifedipine were well-separated from its anti-anginal effective dose range.

Nicardipine appeared to be more potent than nifedipine in terms of A-V node Ca^{2+}-block during pacing at 200–500 μg kg^{-1}. The SA node Ca^{2+} block seen during pacing is probably also responsible for the reduced HR at rest which accompanied the lower BP. The conduction effects of nicardipine are well-separated from the previously-established therapeutic range within which no conduction or haemodynamic effects occurred.

Verapamil, on the other hand, produced marked conduction effects in terms of A-V block well within the therapeutic dose range and was the only compound to produce an A-V block at resting HR in one dog. Depression of A-V node function by verapamil is well-documented (Mangiardi *et al.*, 1978; Singh *et al.*, 1978). The prolongation of the return to sinus rhythm is not significant even at the higher doses, though measurement of this parameter is complicated by the high incidence of A-V block. Since on switch-off the

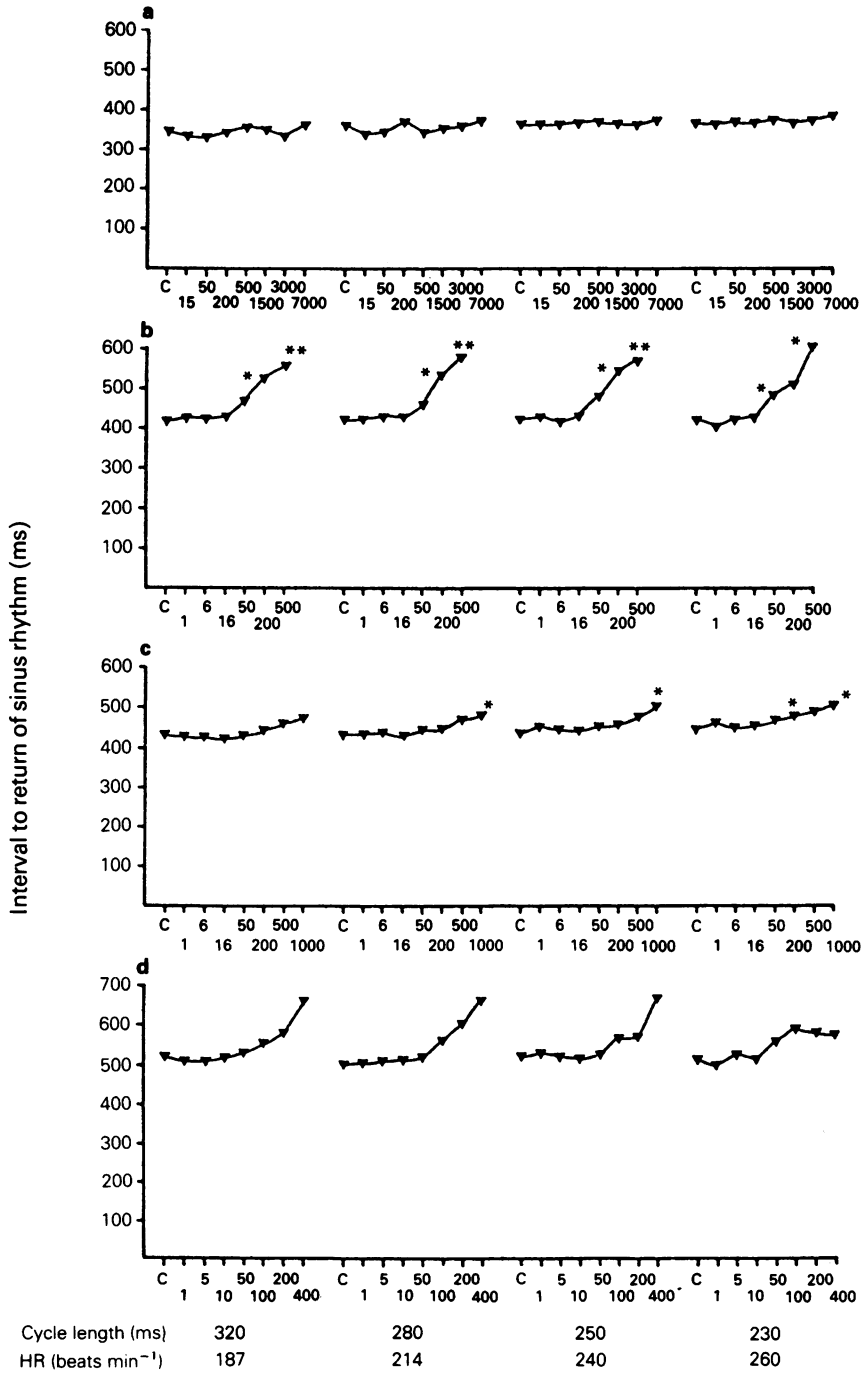

Figure 7 The effects of i.v. (a) RS 43285 ($n = 3$), (b) nicardipine ($n = 3$), (c) nifedipine ($n = 6$) and (d) verapamil ($n = 3$) on the interval between switching off electrical pacing of the right atrium (at 4 frequencies) and the re-establishment of sinus rhythm. Significant increases from baseline control values were assessed by Student's two-tailed t test: $^{*}P < 0.05$; $^{**}P < 0.01$.

last atrial wave was not necessarily followed by a ventricular depolarization, the resultant 'insult' is not as marked as it should be, thus resulting in an artificial value. The effects of verapamil therefore appear even more diverse – it increases the A-V conduction to the point of block, indicating an increase in the effective refractory period of the specialised conduction systems without apparently significantly depressing the SA node. The prolongation of SA and A-V conduction parameters disclosed during pacing was not accompanied by the expected decrease in resting BP and thus an overall reduction in HR resulted, an effect often noted with verapamil therapy (Frieshman *et al.*, 1986). The failure of verapamil to reduce BP in the present study is thought to be due to its underlying property of reducing vascular resistance; since this parameter is often the underlying factor in essential hypertension (Dargie *et al.*, 1986), verapamil might be expected to reduce that component of hypertension which would not be present in this study.

The novel anti-anginal compound RS 43285 exhibited no conduction effects, even in doses far in excess of its therapeutic range, and produced only a marginal reduction in HR. It would therefore appear from the present study that the compound could be used therapeutically without incidence of myocardial conduction disruption.

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