Haemodynamic actions of a novel sino-atrial node function modulator, ZENECA ZD7288, in the anaesthetized dog: a comparison with zatebradine, atenolol and nitrendipine

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1 ZENECA ZD7288 (4-(*N*-ethyl-*N*-phenylamino)-1,2-dimethyl-6-(methylamino) pyrimidinium chloride, formerly ICI D7288) is a novel sino-atrial node function modulator which selectively slows sinus node rate. Its effects on haemodynamic function have been studied in pentobarbitone anaesthetized dogs, in comparison with zatebradine, atenolol and nitrendipine.

2 ZD7288 lowered heart rate in the dose-range 0.02 to 1.0 mg kg⁻¹ i.v. from 152 to 77 beats min⁻¹. Myocardial contractile function (measured as both dP_{LV}/dt_{max} and right ventricular free wall developed force) decreased along with rate. Stroke volume increased as rate decreased. Cardiac output decreased at doses in excess of 0.2 mg kg⁻¹, i.v.

3 These haemodynamic changes were reversed when heart rate reduction was reversed by atrial pacing and are, therefore, considered to be indirect consequences of heart rate changes induced by ZD7288.

4 The effects of zatebradine paralleled those of ZD7288 (heart rate reduced from 149 to 60.5 beats min⁻¹ over the dose-range 0.02 to 1.0 mg kg⁻¹, i.v.), except that dP_{LV}/dt_{max} did not decrease with heart rate and increased during atrial pacing.

5 Neither ZD7288 nor zatebradine had significant effects on atrio-ventricular conduction at intrinsic heart rates, but both significantly and dose-dependently prolonged the atrio-ventricular conduction interval during atrial pacing at 180 beats min⁻¹.

6 The observed effects of atenolol were commensurate with removal of β -sympathetic cardiac drive. Atrial pacing was found not to restore the pre-atenolol haemodynamic state completely.

7 Nitrendipine up to 0.2 mg kg⁻¹ i.v. induced changes indicative of direct vasodilatation accompanied by reflex compensation, followed by cardiac depression at higher doses. Atrial pacing failed to compensate for the effects of vasodilatation, but caused atrio-ventricular conduction block at doses above 0.5 mg kg⁻¹, i.v.

8 The data show ZD7288 has marked heart rate slowing properties and that accompanying haemodynamic changes appear to be secondary to the rate changes, being reversed by atrial pacing even in the continued presence of the drug. Heart rate slowing without depression of contractile function should prove to be of benefit in the treatment of myocardial ischaemia, particularly in the presence of myocardial dysfunction.

Keywords: Haemodynamics; anaesthetized dog; heart rate; sino-atrial node; specific bradycardic agent; ZD7288; zatebradine; atenolol; nitrendipine

Introduction

Angina pectoris in patients suffering from myocardial ischaemia is a consequence of the imbalance between myocardial oxygen demand and supply. Supply adequacy can become supply deficit if heart work requirement outstrips coronary blood flow and oxygen supply. Heart work, in turn, is determined by pressure development, wall stress and heart rate. Under emotional stress or during exercise, heart rate and blood pressure will increase, contributing to myocardial ischaemia. Of the determinants of cardiac work load, rate is the most crucial; not only does it influence myocardial work (demand), but by affecting diastolic interval, it influences myocardial blood supply, particularly influencing that to the endocardium (Gross & Dämmgen, 1987). Drugs employed to treat angina pectoris include those which are aimed at influencing myocardial blood supply, such as nitrates and calcium channel blockers; and those which cause reduction in heart rate, such as β -adrenoceptor antagonists and some calcium channel blockers. Calcium channel blockers and β -adrenoceptor antagonists also influence contractile function, the former being directly depressant and the latter antagoniz-

ing sympathetically-mediated positive inotropic drive, and in certain instances, also being directly depressant.

In recent years, a class of compounds generally referred to as 'specific bradycardic agents' or 'sinus node inhibitors', has been introduced (Kobinger & Lillie, 1984; 1987; Lillie, 1991). These compounds have been found to affect the sino-atrial node pacemaking current, I_f (BoSmith *et al.*, 1993) and therefore can reduce heart rate without necessarily affecting contractile function.

In this paper we present results from investigations in anaesthetized dogs to elucidate haemodynamic effects of a novel sino-atrial node function modulating compound, ZD7288 (4-(*N*-ethyl-*N*-phenylamino)-1,2-dimethyl-6-(methylamino) pyrimidinium chloride, known as ICI D7288 in previous publications) (Hargreaves *et al.*, 1992; Marshall *et al.*, 1993) with sinus node I_f blocking activity (BoSmith *et al.*, 1993). The results are compared with results from comparable experiments into the effects of an example of a recently-developed 'specific bradycardic agent' zatebradine (UL-FS 49) which, currently under clinical trial, has been shown to have clinical efficacy (Baiker *et al.*, 1991); and with the β -adrenoceptor antagonist atenolol (Tenormin) and the calcium channel blocker, nitrendipine.

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Some of the data presented here have previously been published in abstract form (Rouse & Johnson, 1992).

Methods

Beagles of the Alderley Park strain in the weight range 14 to 18 kg, were anaesthetized with pentobarbitone ('Sagatal'), 40 mg kg⁻¹, i.v.. The trachea was intubated with a cuffed endotracheal tube. A double lumen catheter was inserted into the left jugular vein: one lumen was used for compound administration, the other for infusion of anaesthetic maintenance dose throughout the experiment ('Sagatal', 4 mg kg⁻¹ min⁻¹, i.v.). Caution was used throughout preparation to limit bleeding.

Respiration by intermittent positive pressure was commenced (Harvard pump), and a right fourth intercostal space thoracotomy was performed. Arterial blood PO₂, PCO₂ and pH were monitored at intervals (Corning 178 pH/Blood Gas Analyser), and the respiration pump was altered to keep values within physiological limits. Lead II electrocardiogram was monitored from needle electrodes inserted subcutaneously.

The heart was suspended in a pericardial cradle, and the aortic root was cleared of fat just sufficiently to allow a close-fitting electromagnetic flow probe ('Skalar', Delft, The Netherlands) to be placed around the ascending aorta.

Platinum electrodes, embedded 1.5 mm apart in acrylic plaques, were sutured to the right atrial appendage and the interventricular sulcus to permit atrial pacing and to record atrial and ventricular epicardiograms.

A Walton-Brodie type strain gauge arch was attached to the free wall of the right ventricle by sutures which passed completely through the thickness of the ventricular wall. Stretch was applied to the myocardium between the sutures sufficient to prevent slackening of the arch during an experiment.

Left ventricular pressure was recorded with Millar 'Mikrotip' catheter tip transducers: either a Type SPC 470 introduced before thoracotomy via the right carotid artery and aortic valve, or a Type MPC 500 introduced after thoracotomy, directly via the left ventricular apical dimple. In the former case, aortic arch pressure was recorded through a 2 mm internal diameter, 600 mm long Teflon tube inserted (before thoracotomy) via a femoral artery; in the latter case, using a similar 200 mm long tube inserted via the right carotid artery. In either case, Transamerican Instruments type 4-422-0001, or Spectramed disposable strain gauge pressure transducers were employed to measure aortic arch pressure.

Signal conditioning employed pressure bridge and electrocardiogram amplifiers which were part of an analogue computing system constructed by the first author. The system was reset every heart beat by a logic pulse triggered by the ventricular epicardial ECG. Haemodynamic variables computed by the system were delivered as analogue peak-read outputs for recording on a 16-channel Gould TA4000 thermal-array recorder. The peak voltage levels were also sampled via an 8-channel analogue-to-digital converter, clocked by the ventricular-driven logic pulse, for data-logging into an IBM PC286 digital computer. The ADC was multiplexed to read up to 16 channels of information as two groups of eight for each heart beat.

From the transducer inputs the following variables were derived by the analogue computing system: systolic, diastolic and true mean aortic pressures; dP_{LV}/dt_{max} and cardiac contractile force developed during systole as indices of contractile function; instantaneous heart rate from the epicardial ventricular electrocardiogram; atrio-ventricular conduction interval; and stroke volume, by integration of the ascending aortic arch flow velocity with respect to time. Cardiac output and total peripheral resistance were calculated after data transfer to the digital computer by dedicated software written

by the second author. The programme enabled on-line display of drug induced responses of any recorded variable against either time of dosing or logarithm of dose administered. The programme also permitted changes in any two chosen recorded variable to be plotted against one another, as well as enabling acquired data to be filed on magnetic discs.

Protocol

After stabilization of the preparation over a period of at least 30 min, data samples of 10 s duration were acquired on the PC at 10 min intervals, firstly at intrinsic heart rate then directly afterwards when stable conditions had been attained during atrial pacing at 180 beats min⁻¹ (this usually took about 30 s). Pacing at 180 beats min⁻¹ enabled the intrinsic heart rates of all dogs used in the study to be over-ridden and permitted paced results to be compared directly one with another. In retrospect, a second pacing interval at the control rate of each individual animal would have been useful for comparative purposes. After each paced data sample, the compound under study was administered cumulatively by the intravenous route. Data samples were accepted only if no irregular events occurred during sampling. Otherwise, the sample was replaced by a further sample.

Doses

Doses of drugs were used which, from previous experimental experience, were expected to produce significant changes in heart rate (in the case of ZD7288, zatebradine and atenolol) or atrio-ventricular conduction time (nitrendipine). Thus, the cumulative intravenous doses used were as follows: ZD7288 and nitrendipine; 0.02, 0.05, 0.1, 0.2, 0.5 and 1.0 mg kg⁻¹; zatebradine, 0.01, 0.02, 0.05, 0.1, 0.2, 0.5, and 1.0 mg kg⁻¹; and atenolol, 0.01, 0.02, 0.05, 0.1, 0.2 and 0.5 mg kg⁻¹.

Results

Experiments described here were of approximately 2 h duration. For comparison, in saline-dosed control experiments of 2 h duration in similar preparations (unpublished data), mean heart rate over the 2 h period was 185, ranging between 178 and 190. Similarly, mean values (and ranges) for other variables were as follows: dP_{LV}/dt , 3209 (3120–3339); mean aortic pressure, 129 (123–134); stroke volume, 9.0 (7.9–9.9); cardiac output, 1.66 (1.47–1.75); and systemic vascular resistance, 6107 (5640–6980).

Haemodynamic measurements appertaining to ZD7288 are illustrated in Figures 1 and 2, and are listed in full in Table 1. Results at selected dose levels from experiments on other compounds are shown in Table 2.

ZD7288

Intrinsic heart rate showed statistically significant dose-dependent decreases at all dose levels in excess of 0.02 mg kg⁻¹ ZD7288 i.v.; 0.2 mg kg⁻¹ caused a mean decrease in heart rate of 57.3 beats min⁻¹. There was a concomitant rate-related increase in stroke volume, but, statistically, cardiac output was not maintained constant at doses greater than 0.2 mg kg⁻¹. Contractile function as indexed by dP_{LV}/dt_{max} was also depressed above 0.5 mg kg⁻¹, though directly measured right ventricular contractile force decreased rate-dependently above 0.05 mg kg⁻¹. Systolic blood pressure remained constant, but diastolic pressure decreased with heart rate, even though systemic resistance increased.

Despite the presence of ZD7288, atrial pacing restored all variables to control-pacing levels with the exception of atrio-ventricular conduction interval, which increased significantly in a dose-dependent manner.

Zatebradine

Heart rate decreased significantly at doses greater than 0.1 mg kg^{-1} i.v. (by $47.3 \text{ beats min}^{-1}$ after 0.2 mg kg^{-1} zatebradine). Stroke volume increased significantly at doses above 0.05 mg kg^{-1} i.v., and systemic vascular resistance tended to increase whilst cardiac output decreased (significantly at doses in excess of 0.5 mg kg^{-1} i.v.) as heart rate was reduced.

During right atrial pacing there was a dose related increase in dP_{LV}/dt_{max} , with a tendency for stroke volume, cardiac output and aortic pressures to increase. Pacing induced atrio-ventricular conduction interval increases at dose levels above

0.5 mg kg^{-1} i.v.; the magnitudes of these changes were similar to those seen after ZD7288.

Atenolol

Atenolol reduced heart rate significantly at all but the lowest dose studied (0.01 mg kg^{-1} i.v.). At 0.2 mg kg^{-1} i.v., heart rate was decreased by $40.4 \text{ beats min}^{-1}$ on average. There was a significant depression of contractile function by 24% and 22% for dP_{LV}/dt_{max} and right ventricular contractile force respectively. Atrio-ventricular conduction was significantly depressed at doses above 0.05 mg kg^{-1} i.v.

Whereas atrial pacing to $180 \text{ beats min}^{-1}$ maintained con-

Figure 1 Dose-response relationship between ZD7288 and measured and calculated haemodynamic variables at intrinsic sinus rates in pentobarbitone anaesthetized beagles. Means $\pm$ s.e. mean, $n = 6$. (P_{Ao} : systolic and diastolic aortic pressures; TPR: total peripheral resistance; CO: cardiac output; SV: stroke volume; CT_{AV} : atrio-ventricular conduction interval; CCF_{RV} : right ventricular free-wall developed cardiac contractile force; dP_{LV}/dt : maximal rate of left ventricular isovolumic pressure development; HR: heart rate).

tractile function at constant levels in the presence of ZD7288, both dP_{LV}/dt_{max} and right ventricular contractile force during pacing decreased in the presence of increasing dose levels of atenolol. Cardiac output decreased significantly, and atrio-ventricular conduction interval was significantly prolonged during pacing.

Nitrendipine

Heart rate reductions were minimal for doses of nitrendipine up to 0.2 mg kg^{-1} , i.v., there being a fall of only $3.5 \text{ beats min}^{-1}$ on average and both stroke volume and cardiac output increased. At the highest dose administered, 1.0 mg kg^{-1} , i.v., heart rate was approximately halved to $64.7 \pm 11.3 \text{ beats min}^{-1}$, comparable to heart rates following

ZD7288 or zatebradine at the same dose. Stroke volume decreased to near-control value, while cardiac output decreased to 60% of control. Contractile function decreased to 69% (dP_{LV}/dt_{max}) and 80.7% (CCF_{RV}) of control. Both systolic and diastolic aortic pressures were reduced, despite a marked peripheral vasoconstriction, as indicated by systemic peripheral resistance increase. Atrio-ventricular conduction interval increased markedly in three of the four experiments with nitrendipine (to a mean of $728 \pm 210 \text{ ms}$, $n = 4$).

It was not possible to pace the heart rate to $180 \text{ beats min}^{-1}$ at doses greater than 0.5 mg kg^{-1} i.v. without inducing complete atrio-ventricular block. Maximum attainable paced rates were 132.5 and 59.5 at 0.5 and 1.0 mg kg^{-1} i.v., respectively. Diastolic aortic pressure decreased significantly by 72.4%.

Figure 2 Dose-response relationships between ZD7288 and measured and calculated haemodynamic variables during right atrial pacing at $180 \text{ beats min}^{-1}$ in pentobarbitone anaesthetized beagles. Means $\pm$ s.e. mean; same experiments as shown in Figure 1.

Discussion

The results presented in this paper confirm that ZD7288 had a dose-dependent action in reducing heart rate in the anaesthetized dog. Despite the considerable difference in chemical structure, its haemodynamic effects were comparable to the effects of zatebradine at doses up to those resulting in approximately 30% reduction in heart rate (0.1 mg kg^{-1} for ZD7288 and 0.2 mg kg^{-1} in the case of zatebradine). In essence, neither compound caused any significant perturbation of haemodynamics apart from a reduction in heart rate and an accompanying compensatory stroke volume increase at those doses, so that cardiac output was maintained constant.

At higher doses, dP_{LV}/dt_{max} fell with decreasing heart rate in the case of ZD7288, but did not in the case of zatebradine. Reports of the effects of zatebradine on contractile function are somewhat varied; zatebradine has been reported to have either some positive inotropic effect (Raberger *et al.*, 1987a) or no effect on the inotropic state of the heart (van Woerkens *et al.*, 1992; Raberger *et al.*, 1987b; Johnston *et al.*, 1991), depending on conditions and species. In our experiments, zatebradine appears to have had a positive inotropic action, in that, though it was not statistically significant, there was a tendency for dP_{LV}/dt_{max} to increase in comparison to initial control dP_{LV}/dt_{max} as heart rate decreased. A rate related decrease in dP_{LV}/dt_{max} might have been expected (Furnival *et al.*, 1970).

However, the second contractile function index employed, the force developed by a segment of right ventricular free-wall (Falotico *et al.*, 1989), indicated that higher doses of either ZD7288 or zatebradine induced cardiac function decreases of remarkably similar magnitudes at intrinsic heart rates. Restoration of rate by atrial pacing indicated that changes in contractile function were rate-related in the case

of ZD7288, whether judged by dP_{LV}/dt_{max} measurements or by right ventricular contractile force, and the compound had little or no contractile depressant action.

During constant rate atrial pacing after zatebradine there was more evidence of positive inotropism as both dP_{LV}/dt_{max} and right ventricular free wall developed force increased with increasing dose levels, although only the observed increases in dP_{LV}/dt_{max} reached statistical significance.

It is debatable whether it is desirable to impose inotropic stimulation upon the myocardium in patients with angina of effort. It could be argued that such an action would be likely partially to offset any advantage gained in reducing myocardial oxygen consumption by decreasing heart rate. In addition, neither of the sino-atrial node function modulators used in these experiments has been shown to antagonize the influence of the sympathetic nervous system on myocardial contractile function (unpublished observations in the anaesthetized dog), so that the heart should still respond to altered sympathetic drive, and could rely upon sympathetic drive to support the myocardium. This would be in contrast to the situation where β -adrenoceptor antagonists are used to treat angina pectoris.

In experiments with atenolol, decreases in heart rate, myocardial contractile function, cardiac output and atrio-ventricular conduction velocity tended to plateau at about 0.1 mg kg^{-1} , i.v., as β -sympathetic drive was removed from the heart. There was seemingly little direct myocardial depression above 0.1 mg kg^{-1} , i.v., but atrial pacing failed to restore contractile function to pre-atenolol levels. Heart rate reduction was limited to that attained by removal of β -sympathetic drive and rates comparable to those seen after either ZD7288 or zatebradine could not be reached.

Nitrendipine induced positive inotropic actions both without and with pacing of heart rate, as well as marked increase in stroke volume even though heart rate did not decrease

Table 1 Haemodynamic effects of ZD7288 at intrinsic heart rates and when paced at $180 \text{ beats min}^{-1}$

Drug	Dose (mg kg^{-1} , i.v.)	HR (min^{-1})	dP_{LV}/dt (mmHg s^{-1})	CCF_{RV} (%)	SV (ml)	CO (l min^{-1})	P_{Aos} (mmHg)	P_{Aod} (mmHg)	SVR (dyn s cm^{-5})	CT_{AV} (ms)
ZD7288										
Unpaced: $n = 6$	Pre-dose	151.7 ± 9.1	2572 ± 151	100.0 ± 0.0	13.0 ± 1.5	1.90 ± 0.11	128.5 ± 3.5	85.8 ± 4.3	4288 ± 324	104.8 ± 5.4
	0.02	137.3 ¹ ± 5.8	2617 ± 105	92.1 ± 6.1	14.2 ¹ ± 1.6	1.90 ± 0.14	129.9 ± 2.8	83.8 ± 4.6	4312 ± 373	96.5 ± 5.1
	0.05	119.1 ² ± 5.6	2570 ± 114	82.5 ¹ ± 6.3	15.5 ³ ± 1.4	1.81 ± 0.11	132.3 ± 3.7	83.6 ± 3.6	4495 ± 342	99.9 ± 3.6
	0.1	105.1 ³ ± 5.2	2484 ± 103	72.6 ¹ ± 7.7	16.8 ³ ± 1.3	1.73 ± 0.08	133.3 ± 4.5	79.5 ¹ ± 4.0	4550 ± 307	105.1 ± 3.8
	0.2	94.4 ³ ± 4.7	2350 ± 100	65.5 ² ± 7.6	17.7 ³ ± 1.1	1.65 ¹ ± 0.05	131.7 ± 5.3	75.5 ¹ ± 4.3	4589 ± 263	107.7 ± 4.1
	0.5	83.9 ³ ± 4.8	2084 ¹ ± 84	56.8 ¹ ± 10.7	18.4 ² ± 1.4	1.51 ¹ ± 0.06	131.2 ± 5.5	72.6 ¹ ± 4.0	4907 ± 334	107.6 ± 6.5
	1	77.2 ³ ± 4.5	1901 ² ± 75	54.0 ² ± 7.8	18.3 ² ± 1.3	1.39 ² ± 0.07	126.1 ± 5.1	67.4 ² ± 4.8	5093 ± 438	111.6 ± 6.4
	Pre-dose	180.9 ± 1.1	2915 ± 163	111.9 ± 5.2	11.3 ± 1.0	2.04 ± 0.18	130.9 ± 4.2	93.0 ± 3.2	4296 ± 377	122.5 ± 7.7
	0.02	180.3 ± 0.5	3145 ± 203	109.1 ± 8.5	12.0 ± 1.0	2.16 ± 0.19	133.9 ± 3.4	92.5 ± 3.6	4089 ± 342	121.8 ± 7.0
	0.05	180.1 ± 0.6	3248 ¹ ± 175	105.3 ± 9.4	12.1 ¹ ± 1.0	2.17 ± 0.18	134.6 ± 3.4	92.7 ± 2.5	4084 ± 394	127.5 ² ± 7.9
	0.1	180.2 ± 0.5	3194 ± 122	104.3 ± 12.7	12.1 ¹ ± 0.9	2.17 ¹ ± 0.16	135.7 ± 3.8	93.8 ± 2.3	4080 ± 317	137.1 ² ± 7.8
	0.2	180.4 ± 0.5	3233 ± 101	98.7 ± 14.4	12.1 ± 0.7	2.19 ± 0.14	137.7 ± 4.1	95.7 ± 2.0	4092 ± 272	143.6 ³ ± 8.7
	0.5	180.2 ± 0.5	3089 ± 104	96.2 ± 15.8	12.1 ± 0.6	2.18 ± 0.12	141.0 ± 5.2	98.5 ± 2.7	4210 ± 318	156.6 ³ ± 8.8
	1	180.2 ± 0.6	2922 ± 161	91.3 ± 16.3	11.9 ± 0.7	2.14 ± 0.14	133.5 ± 4.1	94.5 ± 2.9	4095 ± 308	160.5 ³ ± 9.0

Means $\pm$ s.e. mean shown beneath values; ¹ $P < 0.05$; ² $P < 0.01$; ³ $P < 0.001$; Student's paired *t* test with respect to pre-drug controls. (HR, heart rate; dP_{LV}/dt_{max} , maximum rate of isovolumic left ventricular pressure change; CCF_{RV} , right ventricular free wall contractile force; SV, stroke volume; CO, cardiac output; P_{Ao} , aortic pressure, systolic and diastolic; SVR, systemic vascular resistance; CT_{AV} , atrioventricular conduction interval).

Table 2 Haemodynamic effects of zatebradine, atenolol and nitrendipine at intrinsic heart rates and during pacing at 180 beats per min

Drug	Dose (mg kg ⁻¹ , i.v.)	HR (min ⁻¹)	dP _{LV} /dt (mmHg s ⁻¹)	CCF _{RV} (%)	SV (ml)	CO (l min ⁻¹)	P _{Aos} (mmHg)	P _{Aod} (mmHg)	SVR (dyn s cm ⁻⁵)	CT _{AV} (ms)
Zatebradine										
Unpaced: <i>n</i> = 4	Pre-dose	148.8 ± 9.6	3221 ± 73	100.0 ± 0.0	18.9 ± 1.65	2.77 ± 0.10	124.8 ± 6.6	94.4 ± 5.6	3045 ± 284	115.7 ± 6.2
	0.02	140.5 ± 6.3	3254 ± 23	97.6 ± 1.4	19.5 ± 1.4	2.72 ± 0.13	123.6 ± 7.2	91.8 ± 4.9	3035 ± 334	116.3 ± 4.4
	0.1	119.1 ¹ ± 5.3	3317 ± 57	89.0 ¹ ± 2.8	22.5 ² ± 1.4	2.67 ± 0.16	124.5 ± 7.8	87.2 ± 5.7	3045 ± 383	114.0 ± 3.8
	0.5	75.9 ² ± 3.6	3464 ± 223	61.5 ² ± 3.3	29.3 ³ ± 1.8	2.23 ¹ ± 0.20	132.4 ± 11.4	75.0 ¹ ± 8.1	3493 ± 593	116.9 ± 3.6
	Pre-dose	179.5 ± 0.8	3387 ± 34	110.3 ± 4.2	15.9 ± 0.7	2.85 ± 0.13	124.1 ± 5.4	96.2 ± 4.8	2989 ± 269	125.4 ± 1.9
	0.02	180.0 ± 0.7	3563 ± 48	112.5 ± 3.5	16.0 ± 0.7	2.89 ± 0.13	123.1 ± 5.6	94.4 ± 5.0	2911 ± 283	127.0 ± 2.0
	0.1	180.1 ± 0.8	3719 ± 41	113.7 ± 2.9	16.4 ± 0.8	2.96 ± 0.15	125.1 ± 7.1	95.9 ± 6.9	2897 ± 349	130.6 ± 0.7
	0.5	180.2 ± 0.9	4283 ¹ ± 226	116.0 ± 1.8	17.2 ± 1.1	3.10 ± 0.21	133.1 ± 9.4	100.4 ± 9.0	2940 ± 440	148.2 ¹ ± 3.2
	Pre-dose	167.2 ± 1.6	2687 ± 308	100.0 ± 0.0	13.7 ± 1.0	2.29 ± 0.14	123.0 ± 5.0	92.7 ± 4.5	3629 ± 300	100.4 ± 2.7
	0.02	143.7 ¹ ± 4.6	2664 ¹ ± 350	85.2 ± 3.6	15.4 ± 1.1	2.20 ± 0.11	123.8 ± 7.8	94.4 ± 7.3	3794 ± 278	109.9 ± 4.5
	0.1	128.0 ³ ± 3.9	2221 ¹ ± 253	83.4 ² ± 1.8	16.7 ± 1.3	2.13 ± 0.13	112.1 ¹ ± 4.7	81.4 ¹ ± 5.1	3483 ± 298	120.6 ¹ ± 5.5
	0.5	123.3 ³ ± 4.3	2052 ¹ ± 181	75.4 ² ± 2.8	15.7 ± 1.5	1.93 ¹ ± 0.14	111.3 ± 6.4	83.0 ± 6.9	4158 ± 454	121.6 ¹ ± 6.5
Paced	Pre-dose	178.7 ± 0.4	2698 ± 260	108.4 ± 3.1	12.8 ± 0.6	2.29 ± 0.11	121.6 ± 4.7	92.9 ± 4.7	3605 ± 261	121.5 ± 10.4
	0.02	178.3 ± 0.2	2784 ± 313	99.8 ± 3.3	13.0 ± 0.7	2.32 ± 0.13	120.8 ± 6.1	95.5 ± 3.5	3595 ± 208	142.2 ± 10.2
	0.1	177.1 ± 1.9	2425 ± 224	100.8 ¹ ± 4.5	13.0 ± 0.6	2.30 ± 0.13	113.0 ± 3.5	86.5 ± 5.1	3352 ± 276	142.6 ¹ ± 10.4
	0.5	176.9 ± 2.0	2279 ± 148	95.4 ² ± 5.4	12.0 ¹ ± 0.7	2.13 ¹ ± 0.14	110.4 ± 5.1	86.3 ± 6.8	3790 ± 423	147.0 ¹ ± 10.5
	Pre-dose	122.7 ± 4.2	2087 ± 296	100.0 ± 0.0	11.1 ± 1.1	1.36 ± 0.12	94.5 ± 7.4	62.3 ± 5.9	4315 ± 289	134.0 ± 10.1
Unpaced: <i>n</i> = 4	0.02	124.4 ± 5.7	2546 ± 383	106.4 ± 5.4	12.5 ± 1.7	1.55 ± 0.22	94.4 ± 11.6	57.2 ± 4.9	3649 ± 212	128.0 ± 10.9
	0.1	122.0 ± 4.7	3163 ± 582	110.9 ¹ ± 2.8	15.3 ± 2.5	1.88 ± 0.36	106.0 ± 13.3	49.8 ± 8.5	2974 ± 193	120.7 ± 10.5
	0.5	96.5 ± 15.8	2640 ± 612	103.4 ± 11.6	16.3 ¹ ± 1.5	1.57 ± 0.30	104.9 ± 12.0	41.2 ¹ ± 8.0	3276 ± 196	294.7 ± 146.6
	Pre-dose	178.3 ± 0.9	2066 ± 402	106.1 ± 4.4	7.5 ± 1.0	1.33 ± 0.18	91.0 ± 9.6	64.6 ± 7.0	4528 ± 448	167.5 ± 14.3
	0.02	178.2 ± 0.9	2455 ± 569	115.6 ± 9.6	8.1 ± 1.5	1.45 ± 0.27	88.5 ± 14.1	58.6 ± 6.1	3961 ± 372	165.1 ± 12.7
	0.1	178.2 ± 0.8	3168 ± 751	135.9 ¹ ± 8.5	10.5 ± 2.1	1.87 ± 0.38	99.5 ± 15.8	52.0 ² ± 7.9	2984 ± 222	166.2 ± 12.5
	0.5	132.0 ± 27.4	2427 ± 637	111.8 ± 11.1	12.8 ± 3.0	1.50 ± 0.3	91.6 ± 16.2	43.5 ² ± 7.0	3238 ± 259	A-V BLOCK
	Pre-dose	122.7 ± 4.2	2087 ± 296	100.0 ± 0.0	11.1 ± 1.1	1.36 ± 0.12	94.5 ± 7.4	62.3 ± 5.9	4315 ± 289	134.0 ± 10.1
	0.02	124.4 ± 5.7	2546 ± 383	106.4 ± 5.4	12.5 ± 1.7	1.55 ± 0.22	94.4 ± 11.6	57.2 ± 4.9	3649 ± 212	128.0 ± 10.9
	0.1	122.0 ± 4.7	3163 ± 582	110.9 ¹ ± 2.8	15.3 ± 2.5	1.88 ± 0.36	106.0 ± 13.3	49.8 ± 8.5	2974 ± 193	120.7 ± 10.5
	0.5	96.5 ± 15.8	2640 ± 612	103.4 ± 11.6	16.3 ¹ ± 1.5	1.57 ± 0.30	104.9 ± 12.0	41.2 ¹ ± 8.0	3276 ± 196	294.7 ± 146.6
	Pre-dose	178.3 ± 0.9	2066 ± 402	106.1 ± 4.4	7.5 ± 1.0	1.33 ± 0.18	91.0 ± 9.6	64.6 ± 7.0	4528 ± 448	167.5 ± 14.3
	0.02	178.2 ± 0.9	2455 ± 569	115.6 ± 9.6	8.1 ± 1.5	1.45 ± 0.27	88.5 ± 14.1	58.6 ± 6.1	3961 ± 372	165.1 ± 12.7
	0.1	178.2 ± 0.8	3168 ± 751	135.9 ¹ ± 8.5	10.5 ± 2.1	1.87 ± 0.38	99.5 ± 15.8	52.0 ² ± 7.9	2984 ± 222	166.2 ± 12.5
	0.5	132.0 ± 27.4	2427 ± 637	111.8 ± 11.1	12.8 ± 3.0	1.50 ± 0.3	91.6 ± 16.2	43.5 ² ± 7.0	3238 ± 259	A-V BLOCK
Nitrendipine										
Unpaced: <i>n</i> = 4	Pre-dose	122.7 ± 4.2	2087 ± 296	100.0 ± 0.0	11.1 ± 1.1	1.36 ± 0.12	94.5 ± 7.4	62.3 ± 5.9	4315 ± 289	134.0 ± 10.1
	0.02	124.4 ± 5.7	2546 ± 383	106.4 ± 5.4	12.5 ± 1.7	1.55 ± 0.22	94.4 ± 11.6	57.2 ± 4.9	3649 ± 212	128.0 ± 10.9
	0.1	122.0 ± 4.7	3163 ± 582	110.9 ¹ ± 2.8	15.3 ± 2.5	1.88 ± 0.36	106.0 ± 13.3	49.8 ± 8.5	2974 ± 193	120.7 ± 10.5
	0.5	96.5 ± 15.8	2640 ± 612	103.4 ± 11.6	16.3 ¹ ± 1.5	1.57 ± 0.30	104.9 ± 12.0	41.2 ¹ ± 8.0	3276 ± 196	294.7 ± 146.6
	Pre-dose	178.3 ± 0.9	2066 ± 402	106.1 ± 4.4	7.5 ± 1.0	1.33 ± 0.18	91.0 ± 9.6	64.6 ± 7.0	4528 ± 448	167.5 ± 14.3
Paced	0.02	178.2 ± 0.9	2455 ± 569	115.6 ± 9.6	8.1 ± 1.5	1.45 ± 0.27	88.5 ± 14.1	58.6 ± 6.1	3961 ± 372	165.1 ± 12.7
	0.1	178.2 ± 0.8	3168 ± 751	135.9 ¹ ± 8.5	10.5 ± 2.1	1.87 ± 0.38	99.5 ± 15.8	52.0 ² ± 7.9	2984 ± 222	166.2 ± 12.5
	0.5	132.0 ± 27.4	2427 ± 637	111.8 ± 11.1	12.8 ± 3.0	1.50 ± 0.3	91.6 ± 16.2	43.5 ² ± 7.0	3238 ± 259	A-V BLOCK
	Pre-dose	122.7 ± 4.2	2087 ± 296	100.0 ± 0.0	11.1 ± 1.1	1.36 ± 0.12	94.5 ± 7.4	62.3 ± 5.9	4315 ± 289	134.0 ± 10.1
	0.02	124.4 ± 5.7	2546 ± 383	106.4 ± 5.4	12.5 ± 1.7	1.55 ± 0.22	94.4 ± 11.6	57.2 ± 4.9	3649 ± 212	128.0 ± 10.9

Means ± s.e.mean shown; ¹*P* < 0.05; ²*P* < 0.01; ³*P* < 0.001; Student's paired *t* test with respect to pre-drug controls. Abbreviations as in Table 1).

significantly until dose levels greater than 0.2 mg kg⁻¹, i.v. were achieved. These changes were most likely an indication of activation of sympathetic reflexes in response to the direct vasodilator effect of nitrendipine (as evidenced by decreased systemic vascular resistance), though no experimental steps were adopted to confirm this conjecture. At doses greater than 0.2 mg kg⁻¹, i.v., the depressant properties of nitrendipine became evident, and contractile function and cardiac output decreased. Above this dose, nitrendipine had most pronounced effects on atrioventricular conduction at intrinsic heart rates but because of the considerable variation in magnitude between experiments these effects did not reach statistical significance: depression of conduction prevented conduction during atrial pacing.

During atrial pacing at 180 beats min⁻¹, atrio-ventricular conduction interval showed significant dose-related changes after either ZD7288 or zatebradine, although neither compound had significant effects at intrinsic heart rates. The exact nature of these effects on atrio-ventricular conduction seen with these compounds are not yet clear, and further experimental investigations will be needed to elucidate the mechanisms concerned.

In summary, ZD7288 appears to have direct effects on heart rate in pentobarbitone anaesthetized dogs, similar in all respects to those seen with zatebradine. Concomitant haemodynamic effects appear to be direct consequences of lowering heart rate by atrial pacing. The profile of action of ZD7288, being devoid of direct contractile influences, sug-

gests that ZD7288 may be of benefit in the treatment of ischaemic heart disease, particularly in instances where myocardial dysfunction would preclude the use of β -adrenoceptor antagonists.

Haemodynamic effects in the absence of anaesthesia, when

autonomic reflexes are fully active, have been studied in conscious dogs trained to run on a motor-driven treadmill, and are described in the following paper (Rouse *et al.*, 1994).

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(Received January 31, 1994

Revised June 12, 1994

Accepted July 22, 1994)