The cardiovascular pharmacology of ICI 170777 ((6RS)-6-methyl-5-(pyrid-4-yl)-3H,6H-1,3,4-thiadiazin-2-one) a novel compound with positive inotropic and vasodilator effects

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1 This paper describes the cardiovascular effects of ICI 170777, a novel compound which enhances cardiac contractility and causes arterial and venous dilatation.

2 The positive inotropic effects of ICI 170777 on the heart were demonstrated by an increase in left ventricular dP/dt_{max} in the anaesthetized and conscious dog, and by an increase in tension development in isolated papillary muscles from the cat.

3 In the anaesthetized dog, the positive inotropic effects of ICI 170777 and of isoprenaline were attenuated by atenolol (5 mg kg^{-1} , i.v.). Atenolol displaced the dose-response curve to ICI 170777 to the right by 4 fold but displaced the isoprenaline dose-response curve to the right by 247 fold. *In vitro*, however, atenolol ($10 \mu\text{M}$) had no significant effect on the positive inotropic response to ICI 170777. In the ganglion-blocked anaesthetized dog, infusion of a low dose of ICI 170777 which had no effect on the basal left ventricular dP/dt_{max} , selectively potentiated the positive inotropic effects of isoprenaline. These results indicate that ICI 170777 has both a non-adrenoceptor-mediated positive inotropic effect on the heart and also facilitates the β -adrenoceptor-mediated control of contractility.

4 In the denervated and perfused hind-limb of the dog, ICI 170777 reduced arterial perfusion pressure and increased limb circumference at a constant arterial flow and venous pressure. This indicates that ICI 170777 has direct dilator actions on both arterial and venous vessels. In this preparation, diazoxide exerted an arterial selective vasodilator effect and sodium nitroprusside was a relatively selective venous dilator. ICI 170777 exhibited a balanced arterial and venous dilator effect which was intermediate in profile between that of diazoxide and that of sodium nitroprusside.

5 In the conscious dog, low doses ($2\text{--}5 \text{ mg kg}^{-1}$, orally) of ICI 170777 evoked an increase in left ventricular dP/dt_{max} with no significant effect on heart rate or blood pressure. At a higher dose (10 mg kg^{-1} , orally) it also reduced blood pressure and caused a significant increase in heart rate. The duration of the positive inotropic effect of 5 mg kg^{-1} (orally) of ICI 170777 was 10–12 hours. This response did not diminish following repeated administration of the compound.

6 The positive inotropic action and balanced arterial and venous dilator effect of ICI 170777 indicate that the compound may be useful in the treatment of congestive heart failure, a disorder that is characterized by decreased cardiac contractility and enhanced arterial and venous constrictor tone.

Introduction

Congestive heart failure is characterized by a depression in ventricular contractility and by an inappropriate increase in arterial and venous constrictor tone (Harris, 1982; Vanhoutte, 1983). It therefore appears

logical to treat the disorder with agents that reduce or reverse these haemodynamic abnormalities. The orally active positive inotropic agents that are currently available, the cardiac glycosides, are not ideal since they have the ability to provoke life threatening arrhythmias (Mason *et al.*, 1971). Arterial and

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Figure 1 Structure of ICI 170777 ((6*RS*)-6-methyl-5-(pyrid-4-yl)-3*H*,6*H*-1,3,4-thiadiazin-2-one).

venous vasodilatation can be achieved by co-administration of hydralazine and isosorbide dinitrate; however, a high incidence of side-effects is observed with this combination (Cohn *et al.*, 1986). Recent clinical results suggest that novel β_1 -adrenoceptor partial agonists and angiotensin converting enzyme inhibitors exert clinically useful positive inotropic and vasodilator effects, respectively, with a low incidence of side effects (Pouleur *et al.*, 1982a; Lipkin & Poole-Wilson, 1985; The German and Austrian Xamoterol Study Group, 1988).

The development of novel pharmacological agents which combine arterial and venous dilatation with positive inotropic effects on the heart seems logical on haemodynamic grounds and could yield drugs with a high degree of efficacy in treating congestive heart failure (Cohn & Franciosa, 1978). The present paper describes the cardiovascular pharmacology of ICI 170777 (Figure 1), a novel, orally active compound which evokes these therapeutically advantageous haemodynamic effects.

Methods

Cat isolated papillary muscle

Cat right ventricular papillary muscles were mounted for isometric tension recording in organ baths containing Krebs solution (37°C) bubbled with 95% O₂, 5% CO₂. The composition of the Krebs solution was (mM): NaCl 118.3, KCl 4.7, MgSO₄ 1.2, KH₂PO₄ 1.2, CaCl₂ 2.5, disodium edetate 0.026, glucose 5.5. An initial tension of 1 g was applied to the tissues which were stimulated electrically via punctate electrodes (5 ms, 20% supra-threshold voltage, 1 Hz). A 1 h equilibration period was allowed before the addition of drugs. Dose-response curves were made to ICI 170777 and to isoprenaline before and after incubation of the tissue with atenolol (10 μ M, 30 min incubation time). ICI 170777 was prepared at 10 mM in 20% polyethylene glycol 400, 80% distilled water. This vehicle had no effect on force development by the papillary muscle.

Anaesthetized dog preparations

Alderley Park beagle dogs of either sex (10–15 kg) were anaesthetized with either sodium pentobarbitone (30–40 mg kg⁻¹, i.v.) or α -chloralose (100 mg kg⁻¹, i.v. after pre-medication with morphine sulphate, 1 mg kg⁻¹, s.c.). The trachea was intubated and the dogs were artificially ventilated (18–24 cycles min⁻¹, tidal volume 10–15 ml kg⁻¹) with a mixture of room air and oxygen. In those dogs in which the thorax was opened, expiration was against a fixed resistance (3–5 cmH₂O) to prevent collapse of the lungs. The pH, PCO₂ and PO₂ of arterial blood were measured with a Corning 175 pH and blood gas system. These parameters were maintained within the normal range by adjustment of the ventilator and by i.v. injection of sodium bicarbonate. Body temperature was monitored via a rectal probe and maintained at 37°C by a heating blanket.

A femoral vein was cannulated for drug administration. A femoral artery was cannulated and systemic blood pressure was measured with a Bell and Howell L221 pressure transducer. Heart rate was derived from the blood pressure signal. Lead 2 electrocardiogram was recorded. In most animals, the left carotid artery was exposed and a Millar Mikro-tip pressure transducer (model PC470) was passed down the artery, across the aortic valves and into the left ventricle. The Mikro-tip transducer was calibrated *in situ* from the pressure recorded from the saline-filled lumen of the catheter for comparison. The first differential of left ventricular pressure (dP/dt) was derived electronically.

In animal preparations in which ICI 170777 was likely to cause a decrease in systemic blood pressure, the chest was opened and a snare was placed around the descending aorta. This was tightened for short periods (10–20 s) when necessary, in order to compensate for a decrease in diastolic pressure of greater than 10% evoked by ICI 170777. In this way the effects of ICI 170777 on dP/dt_{max} could be measured without interference from changes in afterload evoked by the compound (Furnival *et al.*, 1970).

In some animals, a hind-limb was surgically denervated and perfused via the femoral artery by use of a constant flow roller pump (Watson-Marlow HRE200). The circulation to the paw was occluded by a ligature and the perfusion pressure of the limb was monitored and matched to the systemic pressure by adjustment of the pump output. In certain animals, hind-limb circumference was also measured by use of a mercury in rubber strain gauge (Whitney, 1953). In these animals, femoral vein pressure was measured. Changes in limb circumference which occurred in the absence of changes in venous pressure were taken as indicative of changes in venous compliance. In order to standardize this measure-

ment between different dogs, the increase in circumference evoked by vasodilators was expressed as a percentage of the maximum increase evoked by sodium nitroprusside (6–8 μg) in that limb.

ICI 170777 was prepared for use in *in vivo* by dissolving it in 100% polyethylene glycol 400 at 10 mg ml^{-1} and subsequent dilution in 0.9% saline. In most experiments, ICI 170777 was administered i.v. on a cumulative dosing cycle: 5 min was allowed between doses as this allowed a maximum expression of the haemodynamic response. The vehicle used had no effect on haemodynamic parameters measured 5 min after administration. ICI 170777 was also administered by infusion in some experiments. In experiments where the effects of ICI 170777 on hind-limb perfusion pressure and limb circumference were evaluated simultaneously in the same animal, the compound was administered by injection into the extracorporeal arterial circuit that passed through the perfusion pump.

Conscious animal experiments

Alderley Park Beagle dogs of either sex, (12–15 kg) were trained to sit in a shallow box; they were otherwise unrestrained. When they had been adequately trained the dogs were anaesthetized (thiopentone 25 mg kg^{-1} i.v. for induction, and after tracheal intubation, maintenance with halothane in oxygen). All subsequent surgical procedures were performed under sterile conditions. The chest was opened in the fourth intercostal space. An electromagnetic flow probe was placed around the root of the aorta and a miniature pressure transducer was implanted through the apex of the left ventricle into the ventricular cavity. A tripolar recording electrode was implanted in the lower part of the interventricular sulcus. The thorax was closed in layers, and the leads from the transducers were tunnelled to the dorsal surface of the neck, where they were brought out via transcutaneous button sockets. Analgesia (as required) and antibiotics were given throughout recovery. When the animals had recovered from this procedure and showed normal heart rate and sinus arrhythmia they were anaesthetized again and 1 mm bore polyethylene catheters were implanted in the aortic arch via the right carotid artery, and in the right atrium via a branch of the jugular vein. These catheters were also exteriorized on the dorsal surface of the neck.

From the implanted probes the following parameters were derived by analogue techniques: beat by beat stroke volume; systolic, diastolic and mean aortic pressures; peak of the first differential of left ventricular pressure with respect to time (dP/dt_{max}) and instantaneous heart rate. Over each 1 min period, the following were derived by integration: mean systolic and diastolic aortic pressures; mean

aortic pressure, heart rate and dP/dt_{max} . Mean stroke volume and cardiac output (as minute integrated aortic flow) and total peripheral resistance were determined as percentages of control values as the aortic flow probe was not calibrated.

The protocol of the experiments was as follows. The animals sat quietly in boxes to which they had become accustomed. At least 30 min of control recording was taken for each experiment. During this period it was required that the heart rate was stable and not in excess of $120\text{ beats min}^{-1}$. The animals were then dosed with ICI 170777 given orally in a gelatine capsule followed by 20 ml of water. Recording of haemodynamic parameters was then continued for the duration of the experiment.

Drugs and compounds used

ICI 170777: (6RS)-6-methyl-5-(pyrid-4-yl)-3H,6H-1,3,4-thiadiazin-2-one was prepared in the Chemistry department at ICI by Drs R. Hargreaves, S.D. Mills and B.J. McLoughlin (European Patent Specification No. 85227) and used as a free base. Because ICI 170777 (in aqueous solution) slowly decomposes in normal light conditions all solutions of the compound were protected from light. Atenolol (ICI), sodium nitroprusside (Sigma), diazoxide (Allen and Hanburys) and mecamlamine (M.S.D.) were also used.

Statistical analysis of the results was by Student's *t* test. A *P* value of <0.05 was regarded as significant. Data are expressed as mean $\pm$ s.e.mean except in the case of mean doses when geometric mean with 95% confidence limits, in parentheses, are given.

Results

Direct inotropic and vasodilator effects of ICI 170777 in the anaesthetized dog in which cardiovascular reflexes had been prevented

Dogs were anaesthetized and prepared for the measurement of cardiovascular parameters. Atenolol (5 mg kg^{-1} , i.v.) was administered and both vagi were cut. (The effectiveness of the β -blockade was assessed by repeating dose-response curves to isoprenaline before and after administration of atenolol, this gave a dose-ratio in excess of 100). In this preparation the effects of ICI 170777 on cardiac function and hind-limb vascular tone could be examined in the absence of autonomic reflexes. ICI 170777 ($50\text{--}10,000\text{ }\mu\text{g kg}^{-1}$) evoked dose-related increases in heart rate, dP/dt_{max} and decreased hind-limb perfusion pressure (Figure 2). These changes occurred over similar dose-ranges. A decrease in systemic blood pressure also occurred at the higher doses of the compound (data not shown) and was compensated for during short periods for the measurement

Figure 2 The effects of ICI 170777 on left-ventricular dp/dt_{max} , heart rate and hind-limb perfusion pressure in the anaesthetized areflexic dog: (■) control value; (●) value in presence of ICI 170777. All three parameters were significantly different ($P < 0.05$) from control after administration of 100–10,000 $\mu\text{g kg}^{-1}$ of ICI 170777 ($n = 5$).

of dp/dt_{max} by tightening of the aortic snare. A 50% increase in dp/dt_{max} was evoked by a mean dose of $0.81 (0.44\text{--}1.40) \text{ mg kg}^{-1}$.

Comparison of the effects of ICI 170777 with those of isoprenaline on heart rate and dp/dt_{max} was made by regression analysis of the two parameters. This analysis demonstrated that ICI 170777 evoked an increase of $119.5 \pm 28.6 \text{ mmHg s}^{-1}$ in dp/dt_{max} for a unit increase in heart rate ($n = 5$), which was significantly greater than the increase of $46.1 \pm 7.0 \text{ mmHg s}^{-1}$ per unit increase in heart rate for isoprenaline ($n = 9$, $P < 0.05$).

Haemodynamic effects in the chloralose-anaesthetized dog

Dogs were anaesthetized with chloralose and prepared for measurement of dp/dt_{max} (closed chest). ICI

Figure 3 The effects of ICI 170777 on left-ventricular dp/dt_{max} , heart rate, systolic and diastolic blood pressure in dogs anaesthetized with chloralose: (□) control value; (○) value in presence of ICI 170777. Open symbols indicate value in the absence of atenolol ($n = 5$); closed symbols indicate value in presence of atenolol (5 mg kg^{-1} , $n = 3$). *Indicates significant difference from control ($P < 0.05$).

170777 ($10\text{--}500 \mu\text{g kg}^{-1}$) evoked a dose-related increase in dp/dt_{max} . In 5 dogs a 50% increase occurred at a mean dose of $0.46 (0.31\text{--}0.64) \text{ mg kg}^{-1}$. Heart rate and diastolic blood pressure were not significantly affected, systolic pressure showed a small

Figure 4 The effect of ICI 170777 on isometric force development in cat isolated papillary muscles in the absence (O, $n = 5$) and presence (●, $n = 5$) of atenolol ($1 \mu\text{M}$). Control tension development was $0.60 \pm 0.16 \text{ g}$ in the absence of atenolol, and $0.5 \pm 0.16 \text{ g}$ in the presence of atenolol ($P > 0.05$). Atenolol had no significant effect on the positive inotropic effect of ICI 170777.

increase (Figure 3). In a further 3 dogs, the effects of ICI 170777 and isoprenaline were examined in the presence of atenolol (5 mg kg^{-1}). The mean doses of isoprenaline required to increase dP/dt_{max} by 50% before and after administration of 5 mg kg^{-1} atenolol were 0.0134 and $3.31 \mu\text{g kg}^{-1}$ respectively (a dose-ratio of 247). In animals which had been treated with atenolol, the effect of ICI 170777 on dP/dt_{max} was attenuated but not abolished (Figure 3) when compared to the effects of the compound in the absence of atenolol. In atenolol-treated animals, a mean dose of $1.82(1.32\text{--}2.41) \text{ mg kg}^{-1}$ of ICI 170777 was required to evoke a 50% increase in dP/dt_{max} (a dose-ratio of 4 compared to control). In atenolol-treated dogs, doses of ICI 170777 in excess of 0.5 mg kg^{-1} increased heart rate but had little effect on diastolic blood pressure. Systolic pressure tended to decrease at the highest doses of ICI 170777 (Figure 3).

Effect of ICI 170777 on isolated papillary muscles

Since the positive inotropic effect of ICI 170777 was attenuated by β -adrenoceptor blockade in the chloralose-anaesthetized dog, the interaction of the compound with atenolol was examined in isolated papillary muscles. ICI 170777 (0.3 to $100 \mu\text{M}$, $n = 5$) evoked an increase in the tension development of papillary muscles. This positive inotropic response was repeatable but was not significantly altered in the presence of atenolol ($1 \mu\text{M}$, $n = 5$, Figure 4).

Figure 5 The effect of ICI 170777 on the positive inotropic and chronotropic effects of isoprenaline in the ganglion-blocked dog: (□) responses to isoprenaline in the absence of ICI 170777 ($n = 6$); (■) responses to isoprenaline in presence of an infusion of ICI 170777 ($20 \mu\text{g kg}^{-1} \text{ min}^{-1}$, $n = 6$). *Indicates a significant ($P < 0.05$) difference from the response in the absence of ICI 170777.

Responses evoked by isoprenaline in this preparation were significantly antagonized by atenolol with a log dose-ratio = 1.34 ± 0.16 ($n = 6$) but were not significantly altered by the β_2 -selective antagonist ICI 118551.

Effect of ICI 170777 on inotropic and chronotropic responses to isoprenaline in the anaesthetized ganglion-blocked dog

Dogs were anaesthetized with pentobarbitone and prepared for measurement of left ventricular

dP/dt_{max} . The ganglion blocking agent mecamlamine (5 mg kg^{-1} , i.v.) was administered. (This dose of mecamlamine abolished the tachycardia evoked by a 30 s carotid occlusion). Isoprenaline ($0.01\text{--}0.1 \mu\text{g kg}^{-1}$) was administered before and during infusion of ICI 170777 ($20 \mu\text{g kg}^{-1} \text{ min}^{-1}$ i.v., begun 10 min before the second dose-response curve to isoprenaline). In some dogs calcium chloride was administered (0.1 ml kg^{-1} , i.v., of a 1 M solution) before and during infusion of ICI 170777. In 6 dogs, isoprenaline evoked dose-related increases in heart rate and in dP/dt_{max} . Infusion of ICI 170777 at the low dose of $20 \mu\text{g kg}^{-1} \text{ min}^{-1}$ had no significant effect on dP/dt_{max} (control = 2158 ± 318 , ICI 170777 = $2250 \pm 304 \text{ mmHg s}^{-1}$) or on blood pressure but caused a small yet significant increase in heart rate (control = 112.7 ± 5.4 , ICI 170777 = 118.3 ± 6.6 $P < 0.05$). Infusion of ICI 170777 significantly enhanced the positive inotropic effects of isoprenaline but had no significant effect on the chronotropic response (Figure 5). The positive inotropic response evoked by calcium chloride was unaffected by ICI 170777 (control = 2544 ± 122 , ICI 170777 = $2755 \pm 235 \text{ mmHg s}^{-1}$).

Effects of ICI 170777 on arterial resistance and venous compliance in the dog perfused hind-limb

ICI 170777 ($10\text{--}100 \mu\text{g}$), diazoxide ($200\text{--}2000 \mu\text{g}$) and sodium nitroprusside ($1\text{--}8 \mu\text{g}$) were administered into the arterial perfusion circuit in random order. Diazoxide caused predominantly arterial dilatation decreasing arterial perfusion pressure whilst causing only small increases in venous compliance (Figure 6). Sodium nitroprusside caused large increases in venous compliance but evoked small decreases in arterial perfusion pressure. ICI 170777 had an intermediate profile having more effect in increasing venous compliance than diazoxide and more effect in decreasing arterial perfusion pressure than sodium nitroprusside (Figure 6).

Effect of ICI 170777 on haemodynamic parameters in the conscious dog

In 4 control animals, (dosed with an empty gelatine capsule) there was little significant alteration in haemodynamic parameters over a 5 h recording period. Heart rate tended to decrease with time, showing a $16 \pm 5\%$ decrease after 3 h, $P < 0.05$, but by 5 h this decrease was not significant ($-8 \pm 10\%$). Cardiac output also decreased slightly ($-14 \pm 4\%$ at 3 h, $P < 0.05$; $-7 \pm 11\%$ at 5 h).

ICI 170777 ($2, 5$ and 10 mg kg^{-1} , orally) administered to groups of 4 dogs, caused a dose-dependent

Figure 6 The effect of ICI 170777 ($\bullet$, $10, 50, 100 \mu\text{g}$), diazoxide ($\blacksquare$, $200, 800, 2000 \mu\text{g}$) and sodium nitroprusside ($\blacktriangle$, $1, 2, 4, 6, 8 \mu\text{g}$) on arterial perfusion pressure and circumference of the dog perfused hind-limb preparation ($n = 3$). (Increases in limb circumference are indicative of an increase in venous capacitance. The initial arterial perfusion pressures in the hind-limb of the three dogs were 100, 100 and 105 mmHg).

increase in dP/dt_{max} which, at all doses, was significantly different from data in untreated animals for at least one time point (Figure 7). Heart rate was also increased but this effect was less pronounced than the effect on dP/dt_{max} and was only statistically significant at the highest dose (Figure 7). At 2 and 5 mg kg^{-1} systolic and diastolic blood pressure were not significantly altered; at 10 mg kg^{-1} both showed a significant reduction (Figure 7). Stroke volume was not significantly altered by ICI 170777, cardiac output showed a tendency to increase which was significant at some time points after the 10 mg kg^{-1} dose (Figure 7). Total peripheral resistance was decreased by 5 and 10 mg kg^{-1} doses of ICI 170777 (Figure 7).

In a different group of three dogs, 5 mg kg^{-1} of ICI 170777 was administered orally and intravenously on separate occasions. The peak increase in dP/dt_{max} evoked by ICI 170777 given by the oral route (control = $2747 \pm 297 \text{ mmHg s}^{-1}$, ICI 170777 = $5514 \pm 292 \text{ mmHg s}^{-1}$) was only slightly less than that evoked by the compound administered i.v. (control = $2744 \pm 316 \text{ mmHg s}^{-1}$, ICI 170777 = $6459 \pm 438 \text{ mmHg s}^{-1}$). Thus ICI 170777 appears to have a good bio-availability.

In order to assess the potential of ICI 170777 for induction of tachyphylaxis, a different group of four

Figure 7 The effects of ICI 170777 (2–10 mg kg⁻¹ p.o.) over a 5 h period on (a) left-ventricular $dP/dt_{\max}$ (LV dP/dt), (b) heart rate (HR), (c) systolic blood pressure, (d) diastolic blood pressure, (e) stroke volume (SV), (f) cardiac output (CO), and (g) calculated peripheral resistance (TPR), in a group of 4 conscious dogs.

*Indicates value is significantly different from that in a control group of 4 dogs.

Figure 8 The effect of repeated administration of ICI 170777 (5 mg kg^{-1} , orally) on left-ventricular dP/dt_{max} in a group of 4 conscious dogs for 5 days. ICI 170777 was administered at 12 h intervals and the effect on dP/dt_{max} was recorded between doses for one 12 h period each day.

dogs were given the compound twice daily for 5 days at 5 mg kg^{-1} . Haemodynamic parameters were recorded continuously for 12 h each day immediately following administration of the compound. ICI 170777 produced a marked increase in dP/dt_{max} on each day of dosing (Figure 8). There was no evidence for a diminution of the response with repeated doses and the duration of action ranged from 10 h to in excess of 12 h.

Discussion

The results of this study demonstrate that ICI 170777 is an orally active compound which has positive inotropic and vasodilator effects. The positive inotropic effect of ICI 170777 was demonstrated by an increase in dP/dt_{max} in both anaesthetized and conscious animals, and by an increase in force development in isolated ventricular muscle.

The precise mechanism by which ICI 170777 exerts its positive inotropic effect cannot be elucidated from the present results. The compound however, appears to interact with the β -adrenoceptor control of cardiac inotropic state but also has positive inotropic effects which are independent of the β -adrenoceptor system. This latter effect was demonstrated by the inotropic effects of the compound in the presence of β -adrenoceptor blockade both *in vivo* and *in vitro*. The former effect was deduced from the effects of the compound in the

chloralose anaesthetized dog. In this preparation the positive inotropic response curve to ICI 170777 was shifted to the right by β -blockade, but this displacement was of much smaller magnitude than that seen for isoprenaline. One possible explanation for these results is that part of the positive inotropic effect of ICI 170777 is due to an increase in sympathetic drive to the ventricle, as a reflex response to the effects of the compound on the peripheral circulation. Although the chloralose anaesthetized animal is known to have relatively intact cardiovascular reflexes (Greishmeir, 1965) a reflex component of the response is unlikely as ICI 170777 did not lower blood pressure and heart rate was not augmented. A localized release of catecholamines in ventricular tissue by the compound could also explain the results, however the absence of an effect of atenolol on responses to ICI 170777 in the isolated papillary muscle argues against this. The most feasible explanation of the results is that ICI 170777 selectively enhances the positive inotropic effects of β -adrenoceptor stimulation on the ventricle. This explanation is supported by experiments performed in ganglion-blocked dogs (to avoid reflex influences) which showed such a selective potentiating action. A similar selective potentiation of positive inotropic responses to β -adrenoceptor stimulation has been noted *in vitro* with the phosphodiesterase inhibitor SK&F 94120 (Blakemore *et al.*, 1985).

ICI 170777 had significantly less effect on heart rate than on indices of cardiac inotropic state. The most pronounced effect on heart rate was observed in the areflexic dog preparation. However, in this preparation ICI 170777 exhibited a significantly greater positive inotropic effect for a given increase in heart rate than isoprenaline. The relationship between positive inotropic and positive chronotropic effects for isoprenaline found in the present study is similar to that previously reported in the dog (Furnival *et al.*, 1971; Nuttall & Snow, 1982).

An effect of ICI 170777 on heart rate was much less pronounced in the chloralose-anaesthetized and conscious dog than in the areflexic preparation. It may be that the compound evokes an increase in vagal tone in the former preparations as the positive inotropic effects could increase the ejection velocity from the left ventricle and consequently the rate of change of pressure at the carotid sinus (Schmidt *et al.*, 1972). Another possibility is that venous dilatation evoked by ICI 170777, unloads cardiac mechanoreceptors with a resulting reduction in chronotropic drive to the heart (Ledsome & Linden, 1964; Donald & Shepherd, 1978). Whatever the explanation for the limited tachycardic effect of ICI 170777 in the reflexic animal, it allows an increase of approximately 50% in dP/dt_{max} to be achieved without a significant increase in heart rate. Such a

haemodynamic profile will have important consequences for a compound to be used in heart failure, as an increase in heart rate may be deleterious in terms of the concomitant increase in myocardial oxygen consumption and the reduced diastolic interval for perfusion of the coronary arteries (Evans *et al.*, 1982).

The vasodilator effect of ICI 170777 influenced both arterial and venous tone. The results do not allow speculation concerning the mode of action of the compound; however, it cannot be due to a reduction in sympathetic vasoconstrictor tone since it occurred in denervated preparations. The relative selectivity of the vasodilator effect of ICI 170777 for arterial and venous vessels was compared with that of sodium nitroprusside and diazoxide. Diazoxide and sodium nitroprusside are known respectively to be relatively arterial and venous selective in man (Robinson & Collier, 1979). The results of the present study confirm this relative selectivity, validating the model, and indicate an intermediate profile for ICI 170777. A balanced vasodilator effect on arterial and venous vessels should be advantageous in the treatment of heart failure as both arterial and venous vasoconstrictor tone is increased (Vanhoutte, 1983).

The effects of ICI 170777 in conscious dogs illustrate a number of its properties. The compound is absorbed orally and has an onset of action within 1–2 h of administration. The peak effects of the com-

pound are seen 2–5 h after dosing and the duration of action after a 5 mg kg⁻¹ oral dose is 10–12 h. There was no evidence of the development of tachyphylaxis after repeated administration.

The haemodynamic profile in the conscious dog (positive inotropy, decrease in peripheral resistance and only minor effects on blood pressure and heart rate, except at high doses) is consistent with its effects in anaesthetized preparations. However, stroke volume was not enhanced and cardiac output only increased at the highest dose level, concomitant with an increase in heart rate. This latter observation is in agreement with other studies which have shown that positive inotropic stimulation does not enhance stroke volume in the non-failing heart (Dage *et al.*, 1982; Pouleur *et al.*, 1982b). An additional factor contributing to the lack of increase in stroke volume in the case of ICI 170777 may have been its venodilator effect which could cause pooling of blood in the veins and a reduction in end-diastolic volume.

In conclusion, the results of this study indicate that ICI 170777 is an orally active compound with good bio-availability, which exerts positive inotropic effects on the heart and can dilate both arteries and veins. These properties suggest that the compound may be useful in the treatment of congestive heart failure in man since it should acutely reverse the major haemodynamic abnormalities associated with this disorder.

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