Br. J. Pharmac. (1982), **77**, 381–388

THE CARDIOVASCULAR EFFECTS OF ICI 118,587: A β_1-ADRENOCEPTOR PARTIAL AGONIST

A. NUTTALL & H.M. SNOW

Imperial Chemical Industries PLC, Pharmaceuticals Division, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG

1 In a preparation in which cardiovascular reflexes were prevented from occurring, ICI 118,587 (1-(*p*-hydroxyphenoxy)-3-β-(morpholinocarbonamido) ethylamino-2-propranol fumarate) caused dose-dependent positive chronotropic and inotropic effects upon the dog heart.

2 The increase in heart rate brought about by ICI 118,587 was about 43% of the maximum increase produced by isoprenaline.

3 For a given chronotropic effect produced by either ICI 118,587 or isoprenaline, each compound produced a similar inotropic effect as indicated by an increase in LV d*p*/d*t max.*

4 In contrast to the direct stimulant action of ICI 118,587 on the heart no direct effects on vascular smooth muscle were observed.

5 ICI 118,587 was shown to be a competitive antagonist of the chronotropic and vasodilator effects of isoprenaline on the heart and blood vessels and of the chronotropic effects of noradrenaline on the heart.

6 It is concluded that ICI 118,587 is a selective β_1-adrenoceptor partial agonist.

Introduction

ICI 118,587 (1-(*p*-hydroxyphenoxy)-3-β-(morpholino carbonamido) ethylamino-2-propranol fumarate) is currently being evaluated in the clinic as a cardiac stimulant and may be of use in the chronic treatment of heart failure. In man at rest, preliminary results have shown that the compound has a positive inotropic effect upon the heart as indicated by a shortening of the systolic time intervals, an increase in systolic blood pressure with no significant change in diastolic blood pressure and a small increase in heart rate (Marlow, Harry & Shields, 1980).

In a previous series of experiments (Barlow, Main & Snow, 1979), the structure-activity relationship of a series of aryloxypropanolamines and arylethanolamines, known to interact with cardiac (β_1) and vascular (β_2) adrenoceptors, was studied in the anaesthetized dog. ICI 118,587 was selected from the above series of compounds for further study because of its cardioselective stimulant action. The object of the present study was to define in a quantitative manner the direct action of the compound on the heart and circulation of the dog. Therefore, experiments were carried out in an anaesthetized dog preparation in which cardiovascular reflexes were prevented from occurring. A preliminary account of some of the results obtained has been given (Barlow, Main, Nuttall, Moors & Snow, 1979).

Methods

General methods

Beagle dogs of either sex weighing between 10–16.5 kg were treated with syrosingopine (dose 5 mg kg^{-1} s.c. daily for two days) before the experiment in order to deplete catecholamines. The dogs were anaesthetized with pentobarbitone (20 mg kg^{-1} i.v.) through a cannula inserted, under local anaesthesia, via a saphenous vein into the inferior vena cava and maintained on a dose of 2 mg kg^{-1} every 30 min. The cannula was also used for the intravenous injection and infusion of drugs. The animals were ventilated through a tracheotomy with a mixture of 40% oxygen in room air supplied by a Starling Ideal pump. When the chest was opened a resistance to expiration was produced by placing the expiratory output of the pump under 3 cm of water. Samples of arterial blood were withdrawn at intervals throughtout each experiment and pH, P_{O_2} and P_{CO_2} were measured with a Corning EEL blood gas analyser. End tidal P_{CO_2} was continuously measured by aspirating expired air from the trachea into an infrared carbon dioxide analyser (P.K. Morgan Ltd). The arterial P_{CO_2} was kept within the limits of 34–42 mmHg and the arterial pH between 7.35 and

0007-1188/82/100381–08 $01.00

7.43 by either the adjustment of respiration of the intravenous injection of 1.0 M $NaHCO_3$ solution. Oesophageal temperature was recorded from a thermister probe (Yellow Springs Inst. Co. Inc.) and maintained at 37° ± 1°C by heating lamps above and below the animal. The ECG lead II was recorded and the signal used to drive a cardiotachometer (Devices Model 4521). Systemic arterial pressure was recorded through a cannula inserted into the right carotid artery. All pressures were recorded using strain gauge manometers (Hewlett Packard 4-442-001), attached to a d.c. bridge amplifier (Devices N3552) the output of which was recorded using a u.v. light recorder (S.E. Laboratories Model 6008). In all experiments the vagal nerves were divided in the neck. (±)-Isoprenaline sulphate and (−)-noradrenaline bitartrate were dissolved in a solution of 0.9% w/v NaCl (saline) and 0.02% w/v $Na_2S_2O_5$. ICI 118,587 (molecular weight of base 339.5) was dissolved in saline. All drug concentrations are expressed as weight of base.

Stimulation of the sympathetic nerves to the heart

In these experiments the dogs were not depleted of catecholamines. The right and left stellate ganglia were approached through thoracotomies in the second rib space and crushed. The right ansa subclavia was stimulated via platinum bi-polar electrodes attached to a Grass S88 stimulator at supramaximal voltages in the frequency range 0.2 Hz to 20 Hz.

Perfusion of the left hind limb

To perfuse the left hind limb the abdominal aorta was exposed through a flank incision and all branches below the renal arteries tied off. Blood was drawn through a cannula in the aorta and returned to the animal via a roller pump (Watson Marlow), and a cannula inserted into the left femoral artery. Mean perfusion pressure in the hind limb was recorded through a cannula within the bore of the perfusion cannula. Coagulation of blood was prevented by an intravenous injection of heparin (dose 500 iu/kg). The pump was primed with 150 ml of Dextran 150 injection BP in 5% w/v dextrose. The blood vessels of the hind limb were denervated by division of the left femoral, left spinal nerves and the sympathetic chain at the level of L7.

Measurement of pressure in the left ventricle

The chest was opened in the mid line, an adjustable snare placed around the thoracic aorta and the heart suspended in a pericardial cradle. The left ventricle was cannulated though the apex using a short wide bore metal cannula. The cannula was attached to a strain gauge manometer and the pressure recorded as described above. The frequency response of the ventricular pressure recording system was flat (± 5%) to 80 Hz. The rate of change of pressure in the left ventricle was obtained by an analogue differentiator (Model BEU 210, ICI Pharmaceuticals Division).

Experimental protocols

Intrinsic sympathomimetic activity (ISA) of ICI 118,587 on heart rate and hind limb perfusion pressure (HLPP) In these experiments, heart rate was used as an index of the cardiac action and hind limb perfusion pressure as an index of the vascular action of the compound. Dose-response curves relating intravenous injections of isoprenaline in the range 0.05 $\mu g\,kg^{-1}$ to 10 $\mu g\,kg^{-1}$ to the peak changes in heart rate and hind limb perfusion pressure were obtained. After each injection, heart rate and hind limb perfusion pressure were allowed to return to within 10% of the original control value before administration of the next higher dose. When heart rate and hind limb perfusion pressure had returned to control values, about 45 min after the final dose of isoprenaline, cumulative dose-response curves relating ICI 118,587 to heart rate and hind limb perfusion pressure were obtained in the dose range 1 $\mu g\,kg^{-1}$ to 3 $mg\,kg^{-1}$. The ISA of ICI 118,587 on heart rate and hind limb perfusion pressure was calculated as the maximum change brought about by ICI 118,587 as a percentage of the maximum change brought about by isoprenaline.

Relative effects of ICI 118,587 on heart rate and force of contraction After obtaining control records of heart rate, LV $dp/dt\,max$ and arterial blood pressure, isoprenaline was infused at rates ranging from 0.5 $\mu g\,min^{-1}$ to 5 $\mu g\,min^{-1}$. To obtain a steady state response of heart rate and LV $dp/dt\,max$ each infusion rate was maintained for 3 min. Records were obtained at the same aortic diastolic pressure by partial occlusion of the aorta when necessary. When heart rate and LV $dp/dt\,max$ had returned to control values, usually about 45 min after stopping the infusion of isoprenaline, ICI 118,587 was given as intravenous injections in the following cumulative doses, 1, 2, 5, 10, 20, 50, 100, 200, 500, and 1000 $\mu g\,kg^{-1}$. The time between each dose was 3–5 min and records taken when a steady state response to the compound had been obtained, usually in the third minute.

Antagonistic effects of ICI 118,587 Three series of experiments were performed:(1) The antagonism of the actions of isoprenaline on heart rate and hind limb perfusion pressure. (2) The antagonism of the actions of noradrenaline on the heart. (3) The an-

tagonism of the effects of sympathetic nerve stimulation on the heart.

Dose-response curves relating changes in heart rate and hind limb perfusion pressure to doses of isoprenaline were obtained in the absence and in the presence of increasing doses of ICI 118,587. In each experiment a minimum of three dose-response curves to isoprenaline in the presence of ICI 118,587 were obtained. In the second series of experiments noradrenaline was used as the agonist and dose-response curves to heart rate only obtained and in the third series heart rate was increased by stimulating the right ansa subclavia.

In order to obtain a quantitative index of the potency of ICI 118,587 as an antagonist, the agonist dose or frequency-response curves obtained in the above series of experiments were analysed in the manner described by Bilski, Robertson & Wale (1979). Firstly, the curves were normalized by expressing the response as a fraction of the maximum possible response for that particular curve. From the resulting set of parallel curves, dose-ratios (DR) at a response equal to 0.5 of the maximum were calculated, and log (DR−1) plotted against the logarithm of the corresponding dose of ICI 118,587. The value of the dose of ICI 118,587 when the dose-ratio is 2 is an index of the antagonist potency and has been named the apparent dissociation constant ('K_B').

Results

When recording began about 2 h after the induction of anaesthesia, heart rate, systolic and diastolic blood pressure in 11 dogs depleted of catecholamines were respectively: 120.2 beats min^{-1} mean (range 99–141), 152.3 mmHg mean (range 190–126), 112.5 mmHg mean (range 144–78), and in three dogs not depleted of catecholamines: 144.3 beats min^{-1} mean (range 149–140), 153.3 mmHg mean (range 160–145), 96.6 mmHg mean (range 100–90).

Direct effects of ICI 118,587 on heart rate and hind limb perfusion pressure

The effects of ICI 118,587 and isoprenaline on heart rate and hind limb perfusion pressure were determined in seven dogs. The maximum increase in heart rate brought about by isoprenaline was 184.9 ± 10.0 beats min^{-1} (mean ± s.e.mean) and the ED_{50} was 0.376 ± 0.055 $\mu g\,kg^{-1}$ i.v. The mean maximum increase in heart rate brought about by ICI 118,587 was 79.4 ± 3.0 beats min^{-1} and the ED_{50} was 3.2 ± 0.41 $\mu g\,kg^{-1}$ i.v. The effects of ICI 118,587 on heart rate and hind limb perfusion pressure in one dog are shown in Figures 1 and 2. It will be seen that isoprenaline caused both an increase in heart rate and

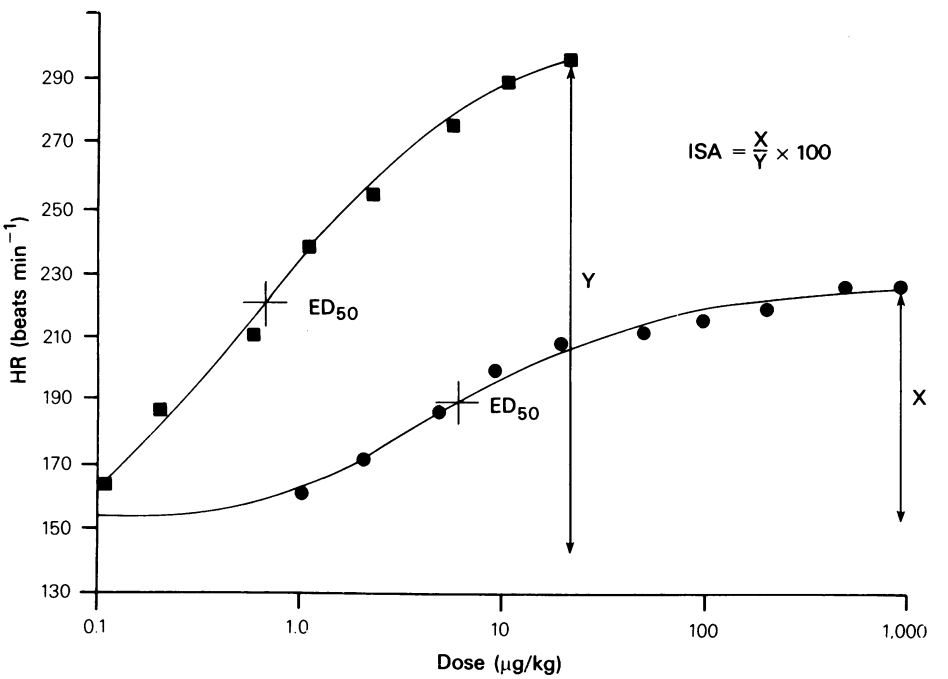

Figure 1 Dose-response curves in a single dog relating heart rate to the dose of isoprenaline (■) and ICI 118,587 (●). The sympathomimetic activity (ISA) of ICI 118,587 is calculated as the maximum change in heart rate caused by ICI 118,587 as a percentage of the maximum caused by isoprenaline.

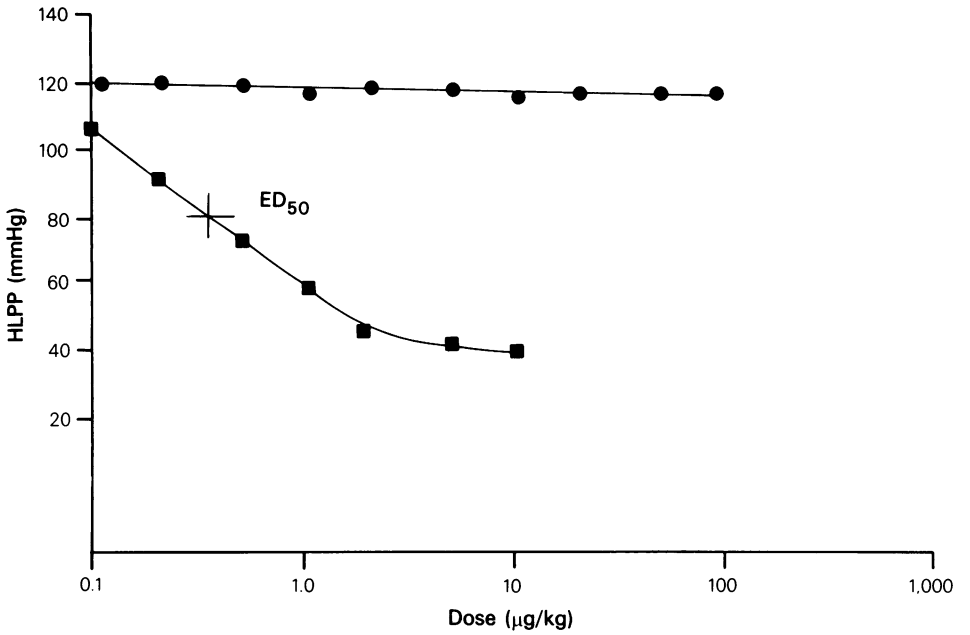

Figure 2 Dose-response curves in a single dog relating the hind limb perfusion pressure (HLPP) to the dose of isoprenaline (■) and ICI 118,587 (●). ICI 118,587 caused no significant changes in hind limb perfusion pressure.

a fall in hind limb perfusion pressure, whereas ICI 118,587 caused only an increase in heart rate which is less than that brought about by isoprenaline. The half life of the response to a dose of 200 $\mu g\,kg^{-1}$ i.v. of ICI 118,587 was found to be in excess of 4 h. It may be concluded that ICI 118,587 has an ISA equal to about 43% of that of isoprenaline on the heart but unlike isoprenaline has no direct vasodilator activity.

Relative effects of ICI 118,587 on heart rate and force of contraction

The effects of both isoprenaline and ICI 118,587 on heart rate and force of contraction were determined in two dogs. Results obtained in one dog are shown in Figure 3 where the increases in both heart rate and LV d*p/dt max* brought about by either increasing the infusion rate of isoprenaline or the amount of ICI 118,587 injected intravenously are plotted against each other. The slopes of the two relationships, 77 $mmHg\,S^{-1}\,HR^{-1}$ for ICI 118,587 and 70 $mmHg\,S^{-1}\,HR^{-1}$ for isoprenaline are not significantly different from each other. Similar results were obtained in the second experiment where the slopes were respectively 55 $mmHg\,S^{-1}\,HR^{-1}$ for ICI 118,587 and 68 $mmHg\,S^{-1}\,HR^{-1}$ for isoprenaline. The ED_{50} values for ICI 118,587 in the two

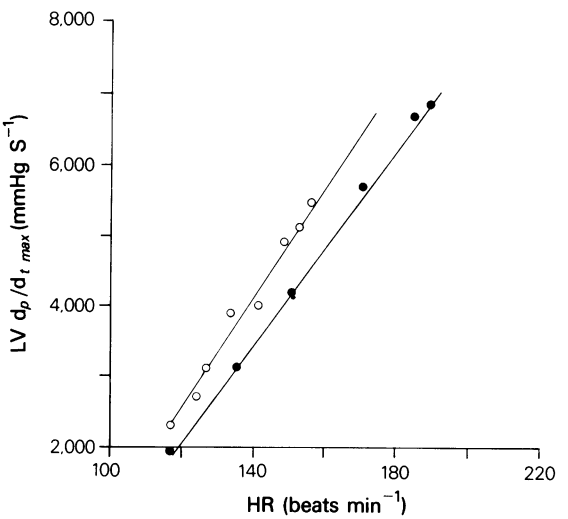

Figure 3 Effects of increasing doses of isoprenaline (●) and ICI 118,587 (○) on heart rate and LV d*p/dt max* in an anaesthetized dog depleted of catecholamines and in which the vagal nerves were sectioned in the neck. The lowest point on each curve is the control point, successive points show the effects of increasing doses of isoprenaline and ICI 118,587 on both heart rate and LV d*p/dt max*. It may be seen that for a given increase in heart rate both isoprenaline and ICI 118,587 cause similar increases in LV d*p/dt max*.

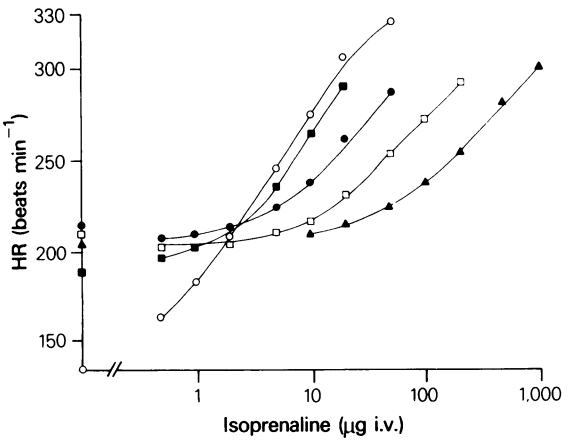

Figure 4 Dose-response curves obtained in a single dog relating the increase in heart rate to the dose of isoprenaline. The control curve (○) was obtained in the absence of ICI 118,587 and the other curves in the presence of increasing doses of ICI 118,587: (■) 10 μg/kg; (●) 50 μg/kg; (□) 200 μg/kg; (▲) 1000 μg/kg.

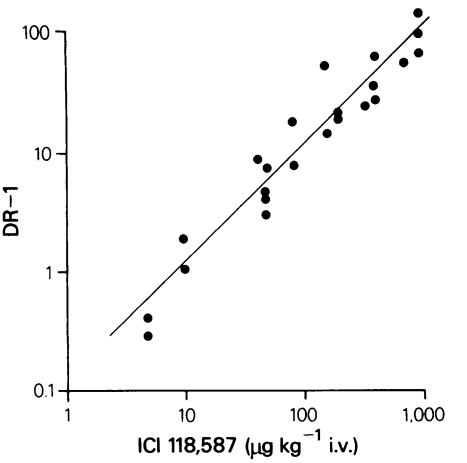

Figure 5 Schild plot showing all dose-ratios of isoprenaline (log DR − 1) obtained in six dogs plotted against the dose of ICI 118,587. The apparent dissociation constant ('K_B') of ICI 118,587 is $8.89 \pm 0.96\,\mu g\,kg^{-1}$ (s.e. mean) and the slope of the regression line is 0.96 (s.e. mean ± 0.06).

dogs were for heart rate 3.7 and $3.5\,\mu g\,kg^{-1}$ i.v. and for LV $dp/dt\,max$ 4.0 and $2.9\,\mu g\,kg^{-1}$ i.v.

Antagonistic effects of ICI 118,587

The ability of ICI 118,587 to antagonize the cardiac stimulating and arterial vasodilator effects of isoprenaline were measured in six dogs. Results obtained in one dog (Figure 4) show the effects of increasing doses of isoprenaline upon heart rate in the absence and presence of increasing doses of ICI 118,587. The isoprenaline dose-response curves are altered in two ways by ICI 118,587: firstly the initial heart rate is increased and secondly the curves are displaced to the right, changes typical of the effects of a partial agonist upon the action of a full agonist. Results from all six dogs are shown in Figure 5, where the dose ratio (DR) shifts of the isoprenaline dose-response curves expressed as (DR − 1) are plotted against the doses of ICI 118,587. Regression analysis of these data showed that the slope of log (DR − 1) plot against log dose of ICI 118,587 was 0.96 ± 0.06. The mean value of the apparent dissociation constant 'K_B' for ICI 118,587 against isoprenaline was found to be $8.89 \pm 0.96\,\mu g\,kg^{-1}$. In four of the above dogs the antagonism of the effects of isoprenaline on hind limb perfusion pressure was also determined in a similar manner and 'K_B' found to be $116 \pm 40\,\mu g\,kg^{-1}$. Thus, as an antagonist of the effects of isoprenaline ICI 118,587 is about 13 times more potent for β_1- than β_2-adrenoceptors.

In three dogs noradrenaline was used as the agonist and the 'K_B' of ICI 118,587 against noradrenaline on the heart found to be $3.1\,\mu g\,kg^{-1}$ i.v. (range 2.7 to 3.7). An example of the effects of ICI 118,587 on the response of the heart to noradrenaline released from the sympathetic nerves is shown in Figure 6. At rates of stimulation below about 1 Hz, heart rate is increased by ICI 118,587 and at rates above 1 Hz decreased, in particular the maximum response to sympathetic nerve stimulation is decreased and at high doses of ICI 118,587 sympathetic nerve stimulation has only a small effect upon heart rate. The above change in the slope of the frequency-response curves means that only the lower part of the curves may be used for analysis of 'K_B' and in the two dogs in which noradrenaline was released by stimulation of the right ansa subclavia the value of 'K_B' were respectively, 5.7 and $2.0\,\mu g\,kg^{-1}$. Regression analysis of the relationship between log (DR − 1) and log dose ICI 118,587 for noradrenaline as the agonist gave a slope of 0.93 ± 0.09 and a value for 'K_B' of $3.22 \pm 0.6\,\mu g\,kg^{-1}$.

Discussion

Previous experiments have shown that at rest in both man and dog ICI 118,587 is an orally active cardiac stimulant and during exercise in man is able to cause reductions in heart rate (Snow, Nuttall, Moors & Rouse, 1980; Marlow *et al.*, 1981; Harry, Marlow, Wardleworth & Young, 1981). The pharmacological basis of this dual action of ICI 118,587 on the response of the heart to sympathetic stimulation is evaluated in the present paper in terms of the direct

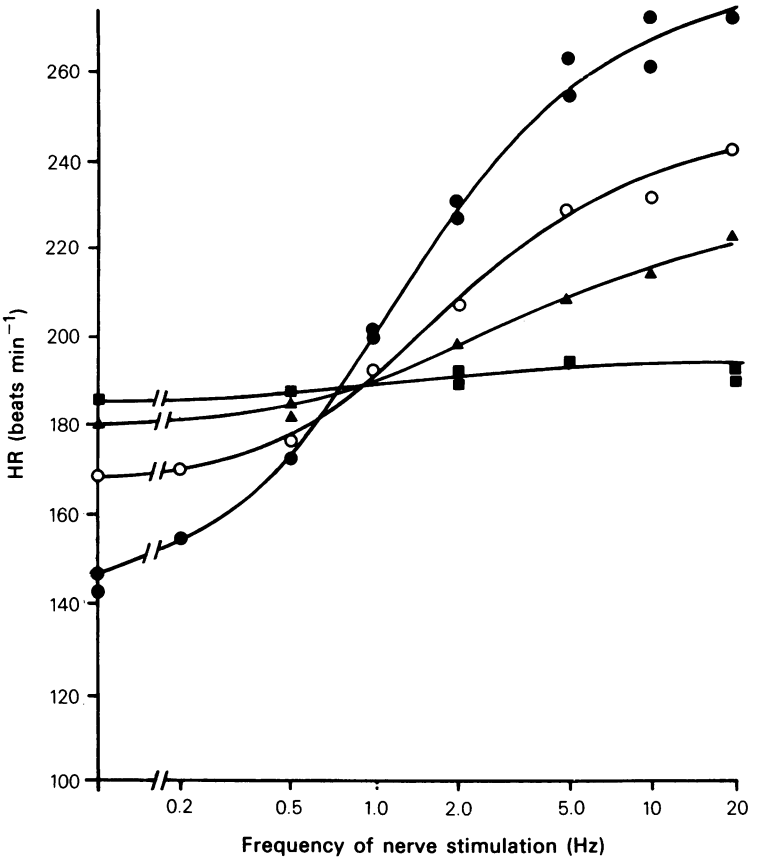

Figure 6 Frequency-response curves relating heart rate (HR) in beats min^{-1} to the frequency of stimulation of the sympathetic serves to the heart (Hz) in a single dog in the absence (●) and in the presence of 5 (○), 50 (▲) and 250 (■) μg kg^{-1} of ICI 118,587. The rotation of the curves about a fixed point with increasing doses of ICI 118,587 is characteristic of the action of a partial agonist and illustrates the stabilizing action of the compound on the response of the heart to sympathetic stimulation.

chronotropic and inotropic effects of the compound upon the dog heart and its ability to antagonize the effects of isoprenaline and noradrenaline.

Before discussing the results it is important to consider problems associated with the measurement of direct effects of compounds on the intact heart. Firstly, quantitative measurements of the inotropic effects of compounds on the heart are technically difficult and of doubtful reliability when obtained in the presence of the large changes in heart rate and blood pressure which may be caused by doses of isoprenaline and noradrenaline (Furnival *et al.*, 1970; Mason, Braunwald, Covell, Sonnenblick & Ross, 1971). However, previous experiments in carefully controlled preparations have shown that the same relative changes in force and rate are brought about by many compounds which act on the heart through the β-adrenoceptor (Furnival, Linden & Snow, 1971: Harry, Kappagoda, Linden & Snow, 1973; Robie, Nutter, Moody & McNay, 1974; Bolter & Ledsome, 1976). In the present series of experiments it was shown that ICI 118,587 produced the same relative changes in the force of contraction for a given change in heart rate as did isoprenaline (Figure 3). Therefore it was decided to use heart rate as the main measure of the effect of the compound, particularly as the maximum response of the heart to large doses of catecholamines was to be obtained. Secondly, the direct actions of compounds upon the heart and circulation may be modified by cardiovascular reflexes. For example, when the reflexes are prevented from occurring, noradrenaline and isoprenaline cause similar increases in both heart rate and force of contraction (Furnival *et al.*, 1971), whereas in the intact animal noradrenaline may even cause a decrease in heart rate and isoprenaline an even greater increase (Cobbold, Ginsburg & Paton, 1960). This dissociation of an effect on rate from that on force, in the intact animal probably results from the contrasting vasoconstrictor and vasodilator ac-

tions of these two compounds. Thus the baroreceptor reflexes operate in such a manner as to oppose the direct action of noradrenaline and reinforce that of isoprenaline on heart rate. The efferent pathway for this effect is probably through the vagal nerves, accounting for the greater effect upon heart rate than force of contraction. In the present series of experiments cardiovascular reflexes were prevented from occurring by surgical denervation and when appropriate, depletion of catecholamines. Hence the direct effects of compounds on the rate and force of contraction of the heart, and pressure in a perfused hind limb were measured, uncomplicated by any secondary effects from the cardiovascular reflexes.

The results show that ICI 118,587 produces about 43% of the maximum increase in heart rate brought about by isoprenaline; whereas even comparatively large doses had no direct effects upon the resistance to blood flow in the perfused hind limb. This lack of an agonist effect upon arterial smooth muscle in a compound with a significant β_1-adrenoceptor stimulant effect upon the heart is unusual. In a series of 46 substituted aryloxypropanolamines and arylethanolamines, all other compounds with β_1-adrenoceptor ISA higher than 30% of that of isoprenaline also possessed β_2-adrenoceptor agonist activity (Barlow *et al.*, 1981). The exception was ICI 118,587, which is considered to be unique in terms of the cardiospecificity of its stimulant action.

If the stimulant action of ICI 118,587 is through the β_1-adrenoceptor then the compound would be expected to inhibit the agonist activity of other β_1-adrenoceptor compounds. That such competitive inhibition of the action of isoprenaline and noradrenaline on heart rate takes place is shown by the displacement of the agonist dose-response curves (Figure 4) and the slope of unity found in the Schild plot (Figure 5). However, two properties are worthy of note with respect to the antagonistic properties of the compound. Firstly, even though the compound has no measurable β_2-adrenoceptor agonist activity on arterial smooth muscle, it does antagonize the vasodilator action of isoprenaline at doses some thirteen times those required to show antagonism of the effects on heart rate. Secondly, ICI 118,587 is about twice as potent an antagonist of noradrenaline as of isoprenaline. The 'K_B' of ICI 118,587 against noradrenaline whether injected intravenously or released from nerve endings and the ED_{50} for the compound as an agonist are all similar. In contrast, the 'K_B' against isoprenaline is about twice as large. Thus, with respect to noradrenaline the results are as predicted by the theory of Ariens, Simonis & Van Rossum (1964) and it may be concluded that noradrenaline and ICI 118,587 are competing for the same population of receptors and in the case of ICI 118,587 receptor occupancy is probably linearly related to the increase in heart rate. The different value for 'K_B' against isoprenaline suggests that a different population of receptors is involved. Support for such a speculation is provided by the ability of ICI 118,587 to antagonize the actions of isoprenaline on blood vessels and by the results of Carlsson, Ablad, Brandstrom & Carlsson (1972) who demonstrated the existence of two different populations of β-adrenoceptors in the cat heart.

The effect of ICI 118,587 on the response of the heart to sympathetic nerve stimulation demonstrates not only the ability of the compound to antagonize the effects of noradrenaline, but also the failure of the sympathetic nerves, even at high rates of stimulation, to release sufficient noradrenaline to overcome the effects of ICI 118,587 and reproduce the control maximum increase in heart rate. This limitation on the supply of noradrenaline to the receptor site has an important consequence in that an apparently complete β-adrenoceptor blockade may be achieved with a sufficiently high dose of an antagonist. Consequently, as the dose of ICI 118,587 or any other partial agonist is increased, the range of the response of the heart to sympathetic nerve stimulation becomes increasingly narrowed. For example (Figure 6), at each succeeding dose of ICI 118,587 the control heart rate is increased by the agonist effect and the maximum increase obtainable by sympathetic nerve stimulation decreased by the antagonist effect. The overall effect of the compound is to stabilize the response of the heart about a value determined by the intrinsic activity of the compound. Therefore whether a β-adrenoceptor partial agonist, such as ICI 118,587, acts to increase or decrease the response of the heart to sympathetic stimulation depends upon the ongoing level of activity. If high, as indicated by a high heart rate during exercise, then the effect of the compound is to reduce exercise heart rate (Harry *et al.*, 1981). On the other hand, in man at rest the effect of the compound is to cause a positive inotropic effect resulting in an increase in pulse pressure and no significant change in either heart rate or diastolic blood pressure (Marlow *et al.*, 1981).

In conclusion, the pharmacological properties of ICI 118,587, partial agonism and cardioselectivity, confer upon the compound a cardiac stabilizing activity which has been shown in man to provide moderate inotropic stimulation without increasing heart rate and to antagonize excessive sympathetic stimulation. The beneficial effects of these properties of ICI 118,587 are currently being investigated in patients suffering from heart failure.

The authors are indebted to Mrs J. Moors for expert technical assistance and to Dr W. Rouse and Mr B. G. Main for helpful discussions.

References

ARIENS, E.J., SIMONIS, A.M. & VAN ROSSUM, J.M. (1964). Drug receptor interaction: interaction of one or more drugs with one receptor system. In *Molecular Pharmacology*, Vol 1. ed. Ariens, E.J. London: Academic Press.

BARLOW, J.J., MAIN, B.G., NUTTALL, A., MOORS, J. & SNOW, H.M. (1979). The cardiovascular activity of ICI 118,587, a novel β_1-adrenoceptor partial agonist. *Br. J. Pharmac.*, **67,** 412P.

BARLOW, J.J., MAIN, B.G. & SNOW, H.M. (1981). β-Adrenoceptor stimulant properties of amidoalkaylamino-substituted 1-aryl-2-ethanols and 1-(aryloxy)-2-propanols. *J. med. Chem.*, **24,** 315–322.

BILSKI, A., ROBERTSON, H.K. & WALE, J.L. (1979). A study of the relationship between β-adrenoceptor blockade and intrinsic sympathomimetic activity in rats depleted of catecholamines. *Clin. exp. Pharmac. Physiol.*, **6,** 1–9.

BOLTER, C.P. & LEDSOME, J.R. Inotropic and chronotropic responses of the in vivo denervated dog myocardium to dobutamine. (1975). *Can. J. Physiol. Pharmac.*, **54,** 618–621.

CARLSSON, E., ABLAD, B., BRANDSTROM, A. & CARLSSON, B. (1972). Differential blockade of the chronotropic effects of various adrenergic stimuli in cat heart. *Life Sci.*, **11,** 953–958.

COBBOLD, A.F., GINSBURG, J. & PATON, A. (1960). Circulatory, respiratory, and metabolic responses to isopropylnoradrenaline in man. *J. Physiol.*, **151,** 539–550.

FURNIVAL, C.M., LINDEN, R.J. & SNOW, H.M. (1970). Inotropic changes in the left ventricle: the effect of changes in heart rate, aortic pressure and end-diastolic pressure. *J. Physiol.*, **211,** 359–387.

FURNIVAL, C.M., LINDEN, R.J. & SNOW, H.M. (1971). The inotropic and chronotropic effects of catecholamines on the dog heart. *J. Physiol.*, **214,** 15–28.

HARRY, J.D., KAPPAGODA, C.T., LINDEN, R.J. & SNOW, H.M. (1973). Action of propranolol on the dog heart. *Cardiovascular Res.*, **7,** 729–739.

HARRY, J.D., MARLOW, H.F., WARDLEWORTH, A.G. & YOUNG, J. (1981). The action of ICI 118,587 (a β_1-adrenoceptor partial agonist) on the heart rate response to exercise in man. *Br. J. clin. Pharmac.*, **12,** 266–267P.

MARLOW, H.F., HARRY, J.D. & SHIELDS, A.G. (1980). Duration of action of single intravenous doses of ICI 118,587, a cardiac β-stimulant. *World Conference on Clinical Pharmacology and Therapeutics*, Abstract No. 0772.

MASON, D.T., BRAUNWALD, E., COVELL, J.W., SONNENBLICK, E.H. & ROSS J. JR. (1971). Assessment of cardiac contractility; the relation between the rate of pressure rise and ventricular pressure during isovolumic systole. *Circulation*, **44,** 47–58.

ROBIE, N.W., NUTTER, D.O., MOODY, C. & McNAY, J.L. (1974). *In vivo* analysis of adrenergic receptor activity of dobutamine. *Circulation Res.*, **34,** 663–671.

SNOW H.M., NUTTALL, A., MOORS, J.A. & ROUSE, W. (1980). A β-adrenoceptor partial agonist for the treatment of heart failure. *Proc. VIII European Congress of Cardiology*, Abstract No. 0389.

(Received May 31, 1982.
Revised June 14, 1982.)