Effects of the β_2 -adrenoceptor antagonist ICI 118,551 on exercise tachycardia and isoprenaline-induced β -adrenoceptor responses in man

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1 ICI 118,551, 5 to 80 mg orally, did not significantly alter resting heart rate or blood pressure. In doses less than 40 mg the reduction in exercise tachycardia was under 10 beats/min.

2 ICI 118,551, 10 to 40 mg, did not appear to reduce the maximum rise in systolic pressure with isoprenaline but did attenuate the changes in diastolic pressure, forearm blood flow and finger tremor. It also attenuated the isoprenaline-induced changes in serum glucose, insulin and potassium. On these observed changes, the effect of ICI 118,551 20 mg was similar to that of 40 mg and of propranolol 10 mg, but greater than that of atenolol 25 mg.

3 An isoprenaline tachycardia was attenuated by all doses of ICI 118,551 studied. After atropine (0.04 mg/kg) ICI 118,551 20 mg still significantly reduced the effects of isoprenaline suggesting that functional β_2 -adrenoceptors may be present in the human heart.

4 In doses less than 40 mg, ICI 118,551 appears to be a selective and competitive antagonist of β_2 -adrenoceptors in man.

Keywords ICI 118,551 β_2 -adrenoceptor antagonist

Introduction

The widespread use of β -adrenoceptor antagonists has focused attention on the relative importance of drugs which are selective at β_1 -adrenoceptors in clinical practice (Kendall, 1981; McDevitt, 1983). In contrast β_2 -selective adrenoceptor antagonists have lacked either selectivity or potency (O'Donnell & Wanstall, 1980) and have received little attention. ICI 118,551 (erythro-($\pm$)-1-(7-methylindan-4-yloxy)-3-isopropylamino-butan-2-ol) is a new drug which has been shown to be highly selective at β_2 -adrenoceptors in animals (O'Donnell &

Wanstall, 1980; Cheah *et al.*, 1982; Bilski *et al.*, 1983). In man, doses of 20 and 50 mg cause significant displacement of the bronchial airway dose-response curve to salbutamol, confirming β_2 -adrenoceptor antagonism (Tattersfield & Cragg, 1983). However, the larger dose also significantly reduced an exercise tachycardia, suggesting some antagonism of β_1 -adrenoceptors.

The present studies, using graded intravenous isoprenaline infusions and severe exercise, were designed to investigate in greater detail the ex-

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tent to which ICI 118,551 selectively antagonises β_2 -adrenoceptors in man. The effects of ICI 118,551 have been compared with atenolol and propranolol: in addition, the influence of vagal reflexes on the response to isoprenaline after ICI 118,551 has been assessed.

Methods

Approval for the studies was obtained from the University Ethics Committee. All subjects were non-smoking males who gave written informed consent and showed no abnormality on routine medical examination, twelve lead electrocardiogram and standard laboratory tests.

Study 1

Six subjects (aged 23.2 ± 0.98 years; weighing 66.5 ± 2.8 kg; mean $\pm$ s.e. mean) completed a randomised double-blind study of the effects of ICI 118,551 on heart rate and blood pressure at rest and during exercise. At weekly intervals, following a light breakfast containing no caffeine, the subjects received either ICI 118,551, 5, 10, 20, 40, 80 mg (ICI 5, 10, 20, 40, 80 mg) or placebo as identical oral syrup preparations. Two hours later, heart rate and blood pressure were measured at the end of 15 min supine rest and 3 min erect position. Heart rate was measured from limb lead II of an electrocardiogram, as the shortest time between six consecutive R waves. Blood pressure was measured using a semi-automated sphygmomanometer (Crijikon Exercise Monitor, Model 1165). Each subject then completed 3 min of a standard exercise step test (46 cm step, 32 steps/min); blood pressure was measured during the last 45 s, and heart rate within 5 s of completion of exercise. Statistical comparisons of the results were made using a general linear model for analysis of variance, with contrasts assessed by Duncan's multiple range test.

Study 2

One hour after a standard light breakfast (two slices of lightly buttered brown toast, one glass of milk) six subjects (aged 19.7 ± 0.4 years; weighing 75.5 ± 4.3 kg) reported to a temperature controlled laboratory (23–24°C) and received single-blind, in a randomised order at weekly intervals, either ICI 118,551, 10, 20, or 40 mg (ICI 10, 20, 40 mg) or placebo as an oral syrup. One hour later, an intravenous cannula (Butterfly 19G) was inserted into a dorsal foot vein. Heart rate was monitored continuously from chest electrocardiograph leads, through an instantaneous ratemeter (Devices 4522) and pen

recorder (Devices MX4). Changes in heart rate were calculated from the shortest three consecutive R-R intervals on limb lead II of an electrocardiogram (Minigraph, Cardiac Recorders Ltd). Blood pressure measurements were taken from the left arm with a random zero sphygmomanometer (Hawksley-Gelman) and the mean of two observations calculated. Diastolic pressure was recorded at the fourth Korotkoff point. Mean arterial pressure was calculated as diastolic pressure plus one third of the pulse pressure. Blood flow was measured in the right forearm by venous occlusion plethysmography (Greenfield, 1960) with a mercury in rubber strain gauge. The venous cuff was inflated to 60 mm Hg for 10 s, then deflated for five seconds. Ten flows were recorded and the mean calculated by an observer who was blind to the treatment used. Finger tremor was measured with a piezo-resistive accelerometer (Devices Trem 1) lightly taped to the dorsum of the middle finger of the left hand. The fingers and hand were outstretched horizontally in the same plane as the left forearm, which was comfortably supported to the wrist on a wooden rest. The output of the accelerometer was displayed directly by a pen recorder (Devices MX4) and was integrated and displayed by the same recorder (Arnold & McDevitt, 1984a). Tremor was measured as the summated integrator ramp heights over the third minute of recording.

On each study day, after 30 min supine rest, an 8 min intravenous infusion of saline 0.9% was followed by four graded sequential 8 min infusions of isoprenaline sulphate, freshly prepared with sodium metabisulphite 0.1% as preservative. For each drug treatment, every subject received the same four isoprenaline infusion rates, the largest of which was chosen so that heart rate did not increase by more than 50 beats/min, and systolic pressure did not rise more than 50 mm Hg or exceed an absolute pressure of 160 mm Hg. During each 8 min infusion, measurements of individual parameters were taken as follows: heart rate between 3.0–3.5 min; blood pressure between 3.5–5.0 min; forearm blood flow and finger tremor between 5–8 min. Changes are expressed with reference to the control values obtained during saline infusion. Finger tremor is calculated as percentage change from control (Arnold & McDevitt, 1984a).

Venous blood samples were taken before the saline infusion and immediately after the last isoprenaline infusion. Aliquots (10 ml) were placed on ice immediately and assayed colorimetrically for free fatty acids (Duncombe, 1964). Samples (3 ml) were centrifuged, the serum stored at -40°C and serum insulin subsequently

assayed by radioimmunoassay using a double antibody separation system, with an international reference preparation 66/304 as standard (Hales & Randle, 1963). Serum potassium and plasma glucose were measured routinely in the hospital laboratory. Thirty minutes after the end of the isoprenaline infusion an exercise test was performed with measurement of heart rate and blood pressure as described for Study 1.

Subsequently, under identical conditions separated by 1 week, each subject received propranolol 10 mg and atenolol 25 mg orally, single-blind, in a randomised order, and the same measurements were made with isoprenaline and exercise. On one further occasion, after a light lunch, each subject received ICI 118,551 20 mg (ICI 20 mg) orally. Ninety minutes later, intravenous isoprenaline infusions were given and measurements of heart rate, blood pressure, forearm blood flow and finger tremor were made as before. Thirty minutes after the last isoprenaline infusion, atropine sulphate 0.04 mg/kg was administered by slow intravenous injection and, when heart rate had restabilised, the whole procedure was repeated.

The results were compared statistically by analysis of variance. Contrasts between groups were assessed by Duncan's multiple range technique (Duncan, 1955) for the isoprenaline induced changes in finger tremor and haemodynamic variables, and by the *t* method for the other variables. A log transformation of the data was used in the analysis of the isoprenaline-enhanced changes in tremor and forearm blood flow. As some values were negative the value 50 was added to the tremor measurements and the value 0.4 to the blood flow measurements before the log_e transformation was performed. Student's paired *t*-test was also used to compare paired data. Results are expressed as the arithmetic or geometric mean where appropriate.

Results

The subjects did not complain of side-effects due to ICI 118,551 and none was observed during the study.

Study 1

After placebo, heart rate and diastolic blood pressure were significantly greater in the standing than in the supine position but systolic pressure was not altered: exercise significantly increased systolic blood pressure and heart rate. There were no significant differences in systolic or diastolic pressure in the supine or standing positions, and during the last 45 s of exercise following treatment with any doses of ICI 118,551 in comparison to placebo (Table 1). Standing systolic pressure following ICI 80 mg (100.0 mm Hg) was significantly lower than after ICI 10 mg (108.5 mm Hg; $P < 0.05$) and ICI 5 mg (112.0 mm Hg; $P < 0.01$). Supine heart rate was significantly decreased after ICI 5, 40 and 80 mg compared with placebo. Supine heart rate after ICI 40 mg was significantly decreased compared to ICI 5, 10 and 20 mg. No significant changes were observed on standing heart rate between drug treatments and placebo, or between drug treatments. Exercise heart rate was significantly reduced compared with placebo by ICI 40 and 80 mg. Lower doses of ICI 118,551 had no significant effects. Exercise heart rates after ICI 5 and 20 mg were significantly greater than after ICI 80 mg.

Study 2

Although performed within the same six subjects, the studies with atenolol and propranolol were conducted after the randomised administration of ICI 118,551. Thus, a possible order

Table 1 Mean results from six subjects in Study 1 for heart rate (HR, beats/min), systolic and diastolic blood pressure (mm Hg) measured 2 h after oral placebo or ICI 118,551 5, 10, 20, 40 and 80 mg.

	Supine			Standing			Exercise		
	Blood pressure systolic	diastolic	HR	Blood pressure systolic	diastolic	HR	Blood pressure systolic	diastolic	HR
Placebo	106.8	57.5	59.8	106.2	71.3	83.5	151.3	64.3	155.7
ICI 118,551 5 mg	106.0	54.3	53.5*	112.0	78.0	77.8	158.8	78.5	153.3
ICI 118,551 10 mg	105.7	62.8	55.7	108.5	76.8	81.3	158.3	76.5	149.0
ICI 118,551 20 mg	101.8	65.5	56.3	105.7	80.7	80.8	138.5	70.0	152.3
ICI 118,551 40 mg	99.5	60.5	48.3**	104.5	75.0	74.0	145.3	62.0	145.0**
ICI 118,551 80 mg	100.5	56.0	52.0**	100.0	79.7	80.8	156.5	80.2	141.00**
Standard error of population mean	2.2	4.4	1.6	2.7	3.1	2.9	7.6	7.4	3.2

* $P < 0.05$, ** $P < 0.01$ compared with placebo

effect exists which is probably minimised, both by the nature of the observations, and by the fact that these single drug doses were given at weekly intervals. Nevertheless, to simplify the tables and figures, and to illustrate possible differences between β_2 -selective, β_1 -selective and non-selective adrenoceptor antagonists, the results for all drugs are presented and analysed together.

Saline 'control' observations

Resting heart rate was not altered from placebo (67.5 ± 3.6 beats/min) by any drug treatment. Systolic pressure was reduced from placebo (115.7 ± 3.2 mm Hg) by ICI 40 mg (109.7 ± 4.1 mm Hg; $P < 0.05$), propranolol (108.7 ± 3.5 mm Hg; $P < 0.05$) and atenolol (104.2 ± 3.8 mm Hg; $P < 0.01$). Diastolic pressure was reduced from placebo (77.2 ± 1.5 mm Hg) by propranolol (71.8 ± 2.5 mm Hg; $P < 0.05$) and atenolol (68.0 ± 2.5 mm Hg; $P < 0.01$). Fore-arm blood flow (2.72 ± 0.37 ml 100 ml $^{-1}$ min $^{-1}$) was not altered by any active drug. Finger tremor was not altered by propranolol or atenolol but tended to be progressively reduced by increasing

doses of ICI 118,551, but the changes were not significant (placebo 113.3 ± 22.3 mm; ICI 40 mg 83.7 ± 8.0 mm; NS).

Effects of active treatments on isoprenaline-induced cardiovascular and tremor changes

The overall changes are illustrated in Figures 1, 2, 3 and 4. Mean results and significant differences for each of the parameters are given in Table 2 for isoprenaline infusion rates of 2 and 4 μ g/min, as these two doses were the only ones given with placebo and all active treatments.

Heart rate (Figure 1 and Table 2) Compared to placebo, each of the active treatments shifted the dose-response curve to the right. Atenolol appeared to be least effective, the three doses of ICI 118,551 showed increasing dose-related effects with ICI 40 mg similar to propranolol.

Blood pressure (Figures 2 and 3 and Table 2) The fall in diastolic pressure was attenuated by ICI 10 mg, but more so by ICI 20 and 40 mg, which were comparable to propranolol (Figure 2).

Figure 1 Isoprenaline-induced changes in heart rate with placebo (■), ICI 118,551 10 (●), 20 (▲), 40 mg (○), propranolol 10 mg (□) and atenolol 25 mg (◆). Points are shown as mean $\pm$ s.e. mean ($n = 6$).

Figure 2 Isoprenaline-induced changes in diastolic blood pressure with placebo (■), ICI 118,551 10 (●), 20 (▲), 40 mg (○), propranolol 10 mg (□) and atenolol 25 mg (◆). Points are shown as mean $\pm$ s.e. mean ($n = 6$).

Atenolol shifted the dose-response curve to the right. The rise in systolic pressure did not appear to be prevented by ICI 10, 20 or 40 mg but was significantly reduced by propranolol at 4 $\mu\text{g}/\text{min}$ (Figure 3). Mean pressure was reduced with placebo and atenolol but increased by propranolol and all doses of ICI 118,551.

Forearm blood flow (Figure 4 and Table 2) All three doses of ICI 118,551 reduced the isoprenaline-induced increases in forearm blood flow. Although atenolol also attenuated the response, the effect was less marked than with ICI 118,551, which was comparable to propranolol.

Finger tremor (Figure 5 and Table 2) All doses of ICI 118,551 and propranolol practically abolished the finger tremor increase at the isoprenaline infusion rates given, which were restricted by the heart rate and systolic pressure responses. Atenolol appeared to shift the dose-response curve for isoprenaline-induced increases in finger tremor to the right, though the

variability with both placebo and atenolol was large.

Effects of active treatments on isoprenaline-induced metabolic changes

The control values of the metabolic variables did not vary significantly on the different treatment days. With placebo, isoprenaline produced increases in free fatty acids (0.50 ± 0.06 to 1.03 ± 0.24 mmol/l; $P < 0.05$), glucose (4.1 ± 0.3 to 4.7 ± 0.2 mmol/l; $P < 0.05$) and insulin (11.8 ± 2.2 to 23.4 ± 4.3 $\mu\text{U}/\text{l}$; $P < 0.05$) but a fall in serum potassium (3.8 ± 0.2 to 3.5 ± 0.2 mmol/l; $P < 0.05$). The effects of the active treatments on these isoprenaline-induced changes are shown in Table 3. The increase in free fatty acids was not altered by any drug: the increase in glucose was reduced by both ICI 20 and 40 mg and by propranolol: the increase in insulin was reduced by all doses of ICI 118,551 and by propranolol: the fall in serum potassium was prevented by all doses of ICI 118,551 and by propranolol.

Figure 3 Isoprenaline-induced changes in systolic blood pressure, with placebo (■), ICI 118,551 10 (●), 20 (▲), 40 mg (○) propranolol 10 mg (□) and atenolol 25 mg (◆). Points are shown as mean $\pm$ s.e. mean ($n = 6$).

Atenolol had no significant effects on any of these metabolic changes.

Effects of active treatments on exercise heart rate and blood pressure

With placebo, exercise heart rate was 170.0 ± 7.0 beats/min. Small reductions occurred with ICI 10 mg (163.2 ± 6.9 beats/min; $P < 0.05$), ICI 20 mg (162.0 ± 6.6 beats/min; $P < 0.05$) and ICI 40 mg (158.5 ± 5.0 beats/min; $P < 0.001$). Propranolol and atenolol produced larger reductions in exercise tachycardia (147.7 ± 6.1 and 133.3 ± 5.8 beats/min respectively; $P < 0.001$). Systolic (159.8 ± 2.1 mm Hg) and diastolic pressure (64.7 ± 11.3 mm Hg) with placebo were not altered by any active drug.

Effects of atropine on the changes produced by isoprenaline in the presence of ICI 118,551 20 mg

Following ICI 20 mg the changes were similar to those seen previously in the same subjects. The increase in heart rate was decreased, the fall in diastolic pressure was less and the increase in

systolic pressure was unaffected (Figure 6 and Table 4). At $4 \mu\text{g/min}$, although mean pressure was increased compared to placebo ($+5.7 \pm 3.2$ and -8.4 ± 4.2 mm Hg respectively; $P < 0.01$), the rise in pulse pressure was less (32.3 ± 4.0 and 52.8 ± 3.8 mm Hg respectively; $P < 0.001$). Atropine enhanced the heart rate increases, although the changes remained significantly less than with placebo. The fall in diastolic pressure tended to be enhanced as the dose of isoprenaline increased, so at $6 \mu\text{g/min}$, the fall was 8.8 ± 2.6 mm Hg with ICI 20 mg, but 19.2 ± 1.4 mm Hg with drug plus atropine ($P < 0.01$). Similarly the previous rise in systolic pressure was reduced (ICI 20 mg, 40.9 ± 4.3 mm Hg; ICI + atropine, 10.7 ± 5.6 mm Hg; $P < 0.02$). Forearm blood flow and finger tremor responses were unchanged after atropine.

Discussion

The results of this study demonstrate that ICI 118,551 selectively and competitively antagonises β_2 -adrenoceptors in man. The tachycardia pro-

Figure 4 Isoprenaline-induced changes in forearm blood flow with placebo (■) ICI 118,551 10 (●), 20 (▲), 40 mg (○), propranolol 10 mg (□) and atenolol 25 mg (◆). Points are shown as mean $\pm$ s.e. mean ($n = 6$).

duced by strenuous exercise is regarded as an indicator of β_1 -adrenoceptor function (McDevitt, 1977), but it was reduced less than 10 beats/min by ICI 118,551 20 mg or less. The rise in systolic pressure is also interpreted as reflecting a β_1 -adrenoceptor mediated inotropic response. It was unaffected by any dose of ICI 118,551, and this is compatible with the observation that the drug does not attenuate the increase in cardiac contractility seen with dobutamine (Harry *et al.*, 1983). In contrast, small doses of propranolol and atenolol decreased the exercise tachycardia two–three times more than the larger doses of ICI 118,551, and attenuated the isoprenaline-induced rise in systolic pressure. Thus, at doses of 40 mg or below, ICI 118,551 appears to have little effect on β_1 -adrenoceptors.

All the doses of ICI 118,551 studied had a significant effect on β_2 -adrenoceptor mediated responses, which included changes in diastolic blood pressure, forearm blood flow, finger tremor and several metabolic parameters. In general, ICI 118,551 attenuated the isoprenaline-induced fall in diastolic blood pressure and reduced the increase in forearm blood flow in a manner comparable to the non-selective drug,

propranolol. Atenolol, the β_1 -selective adrenoceptor antagonist, had a smaller but nevertheless significant effect on both of these parameters even at a dose of 25 mg; such an effect on diastolic pressure has been reported previously (Conway *et al.*, 1976). Forearm blood flow has been used previously in the assessment of β -adrenoceptor antagonists, with either intra-arterial isoprenaline (Brick *et al.*, 1968; Briant *et al.*, 1973), or intravenous bolus injections (Mougeot *et al.*, 1981; Arnold *et al.*, 1983). During intravenous administration, changes in forearm blood flow may be influenced by proximal cardiovascular changes, for example, in perfusion pressure. In the present study, mean blood pressure showed a small increase with ICI 118,551. This would tend to increase blood flow, and hence the observed reductions by ICI 118,551 in the increases in forearm blood flow produced by isoprenaline may have been underestimated.

Enhancement of physiological finger tremor by isoprenaline infusions has been shown to provide a means for distinguishing between the effects of selective and non-selective β -adrenoceptor antagonists (Arnold & McDevitt, 1984a).

Table 2 Changes in β -adrenoceptor mediated responses to intravenous isoprenaline sulphate. Each value is mean $\pm$ s.e. mean ($n = 6$)

a Isoprenaline sulphate 2 μg/min						
	Placebo	10 mg	ICI 118,551 20 mg	40 mg	Propranolol 10 mg	Atenolol 25 mg
Heart rate increase (beats/min)	26.2 $\pm$ 2.6	6.0 $\pm$ 1.9**	1.7 $\pm$ 1.9**	4.2 $\pm$ 1.6**	2.2 $\pm$ 1.7**	8.3 $\pm$ 1.2**
Systolic pressure increase (mm Hg)	21.3 $\pm$ 4.2	14.8 $\pm$ 3.2	9.3 $\pm$ 1.9**	12.5 $\pm$ 2.0*	4.7 $\pm$ 1.8**	5.2 $\pm$ 1.3**
Diastolic pressure decrease (mm Hg)	18.3 $\pm$ 3.4	2.6 $\pm$ 2.1**	0.3 $\pm$ 2.2**	+1.8 $\pm$ 2.1**	1.5 $\pm$ 1.7**	5.8 $\pm$ 2.4**
Forearm blood flow increase (ml 100 ml ⁻¹ min ⁻¹)	1.7 $\pm$ 0.5	0.4 $\pm$ 0.2**	0.5 $\pm$ 0.2**	0.5 $\pm$ 0.1**	0.3 $\pm$ 0.2**	0.9 $\pm$ 0.2
Finger tremor increase (% change)	354 $\pm$ 129	16 $\pm$ 11**	2 $\pm$ 3**	23 $\pm$ 10**	1 $\pm$ 13**	131 $\pm$ 31*
b Isoprenaline sulphate 4 μg/min						
Heart rate increase (beats/min)	43.0 $\pm$ 3.3	14.0 $\pm$ 2.0**	9.3 $\pm$ 3.2**	8.0 $\pm$ 1.6**	8.5 $\pm$ 2.5**	21.8 $\pm$ 1.6**
Systolic pressure increase (mm Hg)	26.8 $\pm$ 4.4	30.2 $\pm$ 3.5	28.1 $\pm$ 3.8	24.2 $\pm$ 2.1	12.7 $\pm$ 2.7**	19.6 $\pm$ 6.3
Diastolic pressure decrease (mm Hg)	26.1 $\pm$ 4.7	10.1 $\pm$ 1.6**	3.3 $\pm$ 3.3**	0.5 $\pm$ 2.2**	3.3 $\pm$ 3.4**	15.0 $\pm$ 3.9**
Forearm blood flow increase (ml 100 ml ⁻¹ min ⁻¹)	3.7 $\pm$ 1.0	0.8 $\pm$ 0.3**	0.6 $\pm$ 0.2**	0.9 $\pm$ 0.3**	0.8 $\pm$ 0.4**	1.5 $\pm$ 0.5**
Finger tremor increase (% change)	472 $\pm$ 191	46 $\pm$ 27**	-3 $\pm$ 4**	16 $\pm$ 8**	18 $\pm$ 11**	277 $\pm$ 69

* $P < 0.05$, ** $P < 0.01$ compared with placebo

In the present study, all doses of ICI 118,551 markedly reduced the isoprenaline-induced increases in tremor. This is consistent with the finding that it competitively inhibits the isoprenaline-induced decrease in twitch tension in the cat soleus muscle (Smith *et al.*, 1983), an action which would predict a decreased tremor in human muscles (Marsden *et al.*, 1967; Marsden & Meadows, 1968). The effects of ICI 118,551 on finger tremor were similar to propranolol but different from atenolol which, nonetheless, resulted in some attenuation of tremor responses.

The metabolic tests used were chosen because they are influenced by stimulation of β_2 -adrenoceptors (Leitch *et al.*, 1976; Holgate *et al.*, 1980). Isoprenaline induced significant

changes in each metabolic parameter, though the effect on free fatty acid was not sensitive to the degree of antagonism studied, a finding which has been observed previously (Harms *et al.*, 1978). The changes in glucose, insulin and potassium were reduced by ICI 118,551 and propranolol but not by atenolol. This presumably indicates differential effects between β_2 - and β_1 -adrenoceptor blockade. Similar changes in glucose and insulin have been observed with higher doses of ICI 118,551 (Harry *et al.*, 1982). The hypokalaemia which occurs with adrenaline infusions is also antagonised by low doses of ICI 118,551 (2.5 and 5 mg) (Brown *et al.*, 1983), and by the non-selective antagonist, timolol, but not by atenolol (Struthers *et al.*, 1981).

Figure 5 Isoprenaline-induced changes in finger tremor with placebo (■), ICI 118,551 10 (●), 20 (▲), 40 (○), propranolol 10 mg (□) and atenolol 25 mg (◆). Points are shown as mean $\pm$ s.e. mean. ($n = 6$).

In general, ICI 118,551 20 mg appeared to be as effective in antagonising the isoprenaline-induced changes measured as the 40 mg dose; it was similar to propranolol but different from atenolol. As the dose of isoprenaline which could be administered was limited by the increases in heart rate and systolic pressure, it was not possible to construct full dose-response

curves for some of the parameters. Therefore, potency ratios at β_2 -adrenoceptors could not be calculated. The results, however, are in agreement with a study performed on bronchial β -adrenoceptor function in normal man (Tattersfield & Cragg, 1983), confirming that ICI 118,551, in a dose of less than 40 mg acts selectively at β_2 -adrenoceptors.

Table 3 Isoprenaline-induced changes in free fatty acid (FFA), glucose, insulin and potassium with placebo, ICI 118,551, atenolol and propranolol. The changes are shown as the difference between the means calculated for the six subjects

	Placebo	10 mg	ICI 118,551 20 mg	40 mg	Propranolol 10 mg	Atenolol 25 mg
FFA (mmol/l)	+0.53	+0.21	+0.42	+0.38	+0.51	+0.24
Glucose (mmol)	+0.53	+0.41	+0.15*	-0.09**	+0.10*	+0.70
Insulin (mU)	+11.60	+1.19*	-3.63**	-0.37**	-3.29**	+19.20
Potassium (mmol/l)	-0.29	+0.28**	+0.10*	+0.25**	+0.12**	-0.45

* $P < 0.05$, ** $P < 0.01$ compared with placebo

Figure 6 Isoprenaline-induced changes in heart rate with placebo (■), ICI 118,551 20 mg (▲) and ICI 118,551 20 mg + atropine (◆). Points are shown as mean $\pm$ s.e. mean ($n = 6$).

Of particular interest was the observed reduction in isoprenaline-induced increases in heart rate by all doses of ICI 118,551 given. Similar changes have been described by Fitzgerald *et al.* (1982). The dose-response curves obtained were comparable to those with atenolol and propranolol (see Figure 1); the lower doses of ICI 118,551 appeared to be more effective than atenolol and the 40 mg dose similar to propranolol 10 mg. Exercise tachycardia was unaffected by low doses of ICI 118,551 and therefore it is unlikely that this reduction was due to β_1 -adrenoceptor antagonism. Since part of the drug's action is to prevent a fall in diastolic pressure and increase in forearm blood flow produced by isoprenaline, it is possible that the effect on heart rate might be influenced by indirect changes in cardiovascular reflexes, notably vagal tone. This was tested by comparing the effects of ICI 118,551 20 mg before and after atropine. The results indicate that atropine enhanced the heart rate response to isoprenaline in the presence of ICI 118,551, implying that vagal tone is increased rather than decreased. This is compatible with the observed increases in

mean blood pressure, even though the rise in pulse pressure was reduced. The increase in mean pressure would be expected to stimulate baroreceptors. It is also consistent with previous reports that cardiac vagal tone is increased during continuous isoprenaline infusions (Arnold & McDevitt, 1984b).

Even after atropine, ICI 118,551 significantly reduced the isoprenaline tachycardia as compared to placebo (see Figure 6). In fact, this difference is greater than it appears, since the placebo curve would also be shifted to the left by atropine (Arnold & McDevitt, 1984b). Thus ICI 118,551 appears to have a direct effect on the isoprenaline-induced changes in heart rate. In view of the other results from this study, it would appear that the β_2 -adrenoceptors in the heart are functionally active (Ablad *et al.*, 1974; Brodde *et al.*, 1983). This could explain the apparent differences in potency found between cardio-selective and non-selective β -adrenoceptor antagonists when the results with exercise techniques are compared to those from isoprenaline testing. These differences were initially attributed to isoprenaline-induced reflex vagal withdrawal

Table 4 Isoprenaline-induced changes in heart rate, systolic and diastolic blood pressure at infusion rates of 2 and 4 $\mu\text{g}/\text{min}$, in the presence of placebo, ICI 118,551 20 mg (ICI 118,551 20 mg plus atropine (0.04 mg/kg i.v.) (ICI 20 mg + ATR). Results are shown as mean $\pm$ s.e. mean ($n = 6$)

	Heart rate increase (beats/min)		Systolic blood pressure increase (mm Hg)		Diastolic blood pressure decrease (mm Hg)	
	2 $\mu\text{g}/\text{min}$	4 $\mu\text{g}/\text{min}$	2 $\mu\text{g}/\text{min}$	4 $\mu\text{g}/\text{min}$	2 $\mu\text{g}/\text{min}$	4 $\mu\text{g}/\text{min}$
Placebo	26.2 $\pm$ 2.6	43.0 $\pm$ 3.3	21.3 $\pm$ 4.2	26.8 $\pm$ 4.4	18.3 $\pm$ 3.4	26.1 $\pm$ 4.7
ICI 20 mg	3.8 $\pm$ 1.2***	11.8 $\pm$ 1.3***	13.2 $\pm$ 2.4	27.2 $\pm$ 3.9	4.1 $\pm$ 1.8***	5.1 $\pm$ 3.5***
ICI 20 mg + ATR	13.2 $\pm$ 1.6†††	30.3 $\pm$ 4.5†††	7.8 $\pm$ 4.9*	11.3 $\pm$ 6.4*†	3.9 $\pm$ 2.6***	9.8 $\pm$ 2.4***

* $P < 0.05$, *** $P < 0.001$ compared with placebo

† $P < 0.05$, †† $P < 0.01$, ††† $P < 0.001$ compared with ICI 20 mg

with cardioselective drugs (Dunlop & Shanks, 1968; McDevitt, 1977), but though the presence of such a reflex has been confirmed, it does not account for all of the observed differences between these two types of drugs (Arnold & McDevitt, 1983).

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