The effects of ICI 118,587 and atenolol on the responses to exercise and on breathlessness in healthy subjects

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1 The effects of ICI 118,587 and atenolol on the responses to submaximal exercise and on breathlessness were studied in six healthy subjects. Atenolol reduced heart rate at rest and during exercise whereas ICI 118,587 increased resting heart rate but caused a small reduction in the highest heart rate achieved during exercise.

2 Neither ICI 118,587 nor atenolol significantly changed minute ventilation or oxygen uptake either at rest or during exercise. There were no effects on bronchomotor tone.

3 The assessment of breathlessness was validated for the subjects participating in the study. Atenolol increased the intensity of breathlessness in relation either to ventilation or to oxygen uptake. This effect was not secondary to a change in bronchomotor tone but was possibly related to changes in pulmonary haemodynamics. On the other hand, the relationships of breathlessness to ventilation or to oxygen uptake were unchanged by ICI 118,587. The effects of ICI 118,587 on exercise tolerance and dyspnoea in patients with impaired cardiac function should now be determined.

Keywords ICI 118,587 atenolol breathlessness

Introduction

Doubt remains about the role of β -adrenoceptors in the control of breathing. Butland *et al.* (1982) demonstrated an increase in resting ventilation when noradrenaline or isoprenaline was infused into normal volunteers. These responses were reduced by various β -adrenoceptor antagonists and it was suggested that the peripheral chemoreceptors were involved through β_1 -receptors. Mustchin *et al.* (1976) demonstrated a reduction in the ventilatory response to carbon dioxide after ($\pm$)-propranolol but not after (+)-propranolol and suggested a central role for β -receptors in this response. Conflicting findings from Patrick *et al.* (1978) showed no effect of propranolol on the ventilatory response to CO₂ or to hypoxia.

The aim of the present study was to alter the responses to sympathetic activity during exercise to examine the cardiorespiratory responses as well as the sensation of breathlessness. The latter was assessed using methods we have described and validated (Stark *et al.*, 1981, 1983a).

Preliminary findings have been presented previously (Stark *et al.*, 1983b).

The pharmacological agents used to change the responses to sympathetic activity were atenolol, a β_1 -adrenoceptor antagonist which is devoid of intrinsic sympathomimetic activity (ISA), and ICI 118,587, a β_1 -adrenoceptor partial agonist which possesses considerable ISA (i.e., in the dog its maximum agonist effect is 43% of the maximum effect of the full agonist, isoprenaline). Thus, when sympathetic activity was low ICI 118,587 increased heart rate and when sympathetic tone was high, it acted as an antagonist (Nuttall & Snow, 1982).

Methods

Subjects

Six 'naive' subjects volunteered to take part in the study and gave informed consent. None had

evidence of disease from the history or on clinical examination, and in all subjects the ECG was within normal limits. Smoking was prohibited for 2 h, and consumption of beverages containing caffeine or alcohol for 10 h prior to the exercise tests. Environmental factors were similar on the two study days and these were separated by an interval of at least 7 days. Subjects became familiar with the procedures and measurements before entering the treatment section of the study. PEFR was measured with a Wright's peak flow meter at rest, before and after treatment, and after exercise.

Exercise test

The test was similar to that described in detail previously (Stark *et al.*, 1981). Sub-maximal exercise was undertaken by walking on an inclined treadmill at three speeds (2 kph for 2 min, 4 kph for 2 min and 6 kph for 2 min) to achieve a range of values for ventilation rather than a steady state. Measurements were made during a rest period for baseline values, during 6 min of exercise and during a 5 min period of recovery with the subject wearing a tight fitting face mask to permit collection of expired gases. Ventilation and tidal volume (BTPS), oxygen uptake and carbon dioxide production (STP) and respiratory and cardiac frequencies were measured continuously. Data from the pneumotachograph, oxygen and carbon dioxide analysers and the cardiac frequency were processed by a MINC II computer and presented at intervals of 1 min. Calibration preceded every study.

Assessment of breathlessness and validation

Breathlessness was assessed with visual analogue scales (VAS) presented by a PET Commodore computer at intervals of 1 min during the test. The maximum point of the VAS ('very breathless') was set before administration of the treatment by a short period of strenuous exercise on the treadmill which increased heart rate to approximately 85% of the maximum predicted rate. It was necessary to establish that this group of subjects could use the VAS in a reliable and consistent way. Each volunteer received placebo on two occasions in single-blind fashion, and this always preceded treatment with active drug. The relationships of breathlessness score to ventilation were compared from the two placebo runs as a measure of reproducibility.

The subject's ability to use the scales in a sensitive manner was assessed by performance of two periods of exercise in the presence and absence of an inspiratory resistance (0.67 cm H₂O) in random sequence. The ratios of the breathlessness score to minute ventilation at the

end of these exercise periods were compared. In accordance with the protocol, one subject who did not demonstrate sensitivity was excluded from the study.

Treatment and design

The study was a double-blind within-subject comparison of ICI 118,587 (200 mg) and atenolol (100 mg) with the order of treatment randomised. In addition, placebo treatment was administered single-blind to all subjects before the active treatments. Treatments were given 2 h before exercise. The double-blind nature of the study was achieved by a double placebo technique.

Statistical analysis

The heart rate, ventilation and oxygen uptake at rest and at the maximum exercise load together with the PEFR data were analysed by paired Student's *t*-tests.

Alterations in the relationship of breathlessness to ventilation were tested by plotting the graphs generated by each of the volunteers after the active and the placebo treatments. Thus, each volunteer contributed four graphs and there were 24 in total from the six subjects. The point representing the lowest ventilation achieved during the final minute of exercise for all 24 plots was determined. A line was drawn through this point perpendicular to the ventilation axis and cutting all the plots. This procedure defined 24 breathlessness points all relating to a single common value of ventilation. In addition, the penultimate point was similarly chosen and the procedure repeated.

The differences in breathlessness between the active treatments and also their corresponding placebos could thus be calculated for each of the subjects and averaged between the two ventilation sampling points. These mean differences were then tested by paired *t*-tests.

The procedure was also adopted for the relationship of breathlessness to oxygen uptake.

Results

General

The six male volunteers admitted to the study had a mean age of 29.3 years (range 22–42 years), a mean weight of 80.5 kg (76–89.2 kg) and a mean height of 1.81 m (1.73–1.91 m). There were five non-smokers and one smoker (10/day) in the group. The drugs were well tolerated apart from one subject who had a decrease in his exercise tolerance and a raised ventilation after receiving atenolol.

The PEFR of the group as a whole did not show any significant change after atenolol (mean before 600 ± 59 l/min and mean after 592 ± 56 l/min) or ICI 118,587 (mean before 598 ± 62 l/min and mean after 588 ± 66 l/min). Neither drug induced significant bronchoconstriction during exercise (atenolol: mean immediately after exercise 584 ± 65 l/min; ICI 118,587: 588 ± 58 l/min).

Objective responses to exercise

After ICI 118,587 heart rate at the mid-point of the rest period increased by 9.7 beats/min ($P < 0.06$) and there was a decrease in heart rate of 7.2 beats/min ($P < 0.03$) at the highest work load. Atenolol, on the other hand, reduced heart rate both at rest and during exercise (Figure 1 and Table 1).

The oxygen uptakes after all treatments were similar at rest and during exercise (Figure 1 and Table 1). Neither atenolol nor ICI 118,587 caused any overall change in ventilation at rest or during exercise when compared with placebo (Table 1).

Breathlessness

The tests of validation showed a high level of reproducibility for the relationship between

breathlessness score and ventilation similar to results presented previously (Stark *et al.*, 1981, 1983a). In the six subjects admitted to the study a greater sensation of breathlessness occurred at the higher levels of ventilation in the presence of the inspiratory resistance. This suggested that they could use the VAS in a way which was capable of indicating a drug-induced effect.

The relationship between breathlessness and ventilation did not differ before and after ICI 118,587 (Figure 2). Thus, breathlessness at a given level of ventilation was neither increased nor decreased by ICI 118,587 in normal subjects. A similar situation occurred when breathlessness was related to oxygen uptake (Figure 2).

On the other hand, breathlessness during exercise was significantly greater after atenolol both in relation to ventilation ($P < 0.03$; Figure 2) and especially to oxygen uptake ($P < 0.04$; Figure 2).

Discussion

In the present study, resting heart rate in the standing position after ICI 118,587 was increased while at the highest workload, heart rate was reduced. Such findings are consistent with the fact that ICI 118,587 has high partial agonist activity. In dogs the effects of ICI 118,587 on heart rate were studied during varying levels of cardiac sympathetic stimulation. At low frequencies of stimulation, ICI 118,587 increased heart rate and at high frequencies antagonism occurred with a reduction in heart rate in comparison with controls (Nuttall & Snow, 1982). An earlier study of the effects of intravenously administered ICI 118,587 on heart rate during exercise on a bicycle ergometer showed a reduction in heart rate at high workloads but the effects at rest were less clear (Harry *et al.*, 1981) although a positive inotropic effect has been demonstrated in this situation (Marlow *et al.*, 1982).

Oxygen uptake before and during exercise was not significantly affected by atenolol or by ICI 118,587. Opioids are known to decrease oxygen uptake (Santiago *et al.*, 1979) and the reduced oxygen requirement has been suggested as the mechanism of dihydrocodeine's beneficial effect on dyspnoea in 'pink puffers' (Johnson *et al.*, 1983). The present study has shown that breathlessness does not have a constant relationship to oxygen uptake and that it was possible to dissociate the two with atenolol (Figure 2).

Using methods which have been validated previously as well as in the subjects in this study, we found no change in the relationships between

Figure 1 Oxygen uptake and heart rate during rest, exercise and recovery. Values are shown before (open symbols) and after (closed symbols) ICI 118,587 Δ $\blacktriangle$ or atenolol $\circ$, $\bullet$, $n = 6$.

Table 1 Heart rate, oxygen uptake and minute ventilation at rest and at maximum exercise load before and after ICI 118,587 and atenolol (mean $\pm$ s.e. mean).

	Drug	Resting	Maximum exercise load
HR (beats/min)	Before atenolol	67.1 $\pm$ 7.1	133.0 $\pm$ 19.6
	After atenolol	54.8 $\pm$ 8.3	100.5 $\pm$ 6.9
	Before ICI 118,587	67.0 $\pm$ 15.7	131.2 $\pm$ 10.0
	After ICI 118,587	75.1 $\pm$ 13.3	124.0 $\pm$ 8.9
$\dot{V}O_2$ (ml/min)	Before atenolol	338 $\pm$ 65.9	2277 $\pm$ 249
	After atenolol	380 $\pm$ 55.0	2152 $\pm$ 447
	Before ICI 118,587	374 $\pm$ 64.9	2181 $\pm$ 238
	After ICI 118,587	405 $\pm$ 57.7	2270 $\pm$ 298
$\dot{V}$ (l/min)	Before atenolol	9.8 $\pm$ 1.0	45.6 $\pm$ 5.2
	After atenolol	10.7 $\pm$ 2.2	50.6 $\pm$ 11.6
	Before ICI 118,587	10.2 $\pm$ 0.9	45.3 $\pm$ 4.5
	After ICI 118,587	10.7 $\pm$ 1.5	43.9 $\pm$ 3.9

breathlessness and ventilation or between breathlessness and oxygen uptake after ICI 118,587. This compound is currently undergoing clinical evaluation in the treatment of cardiac failure and there have been reports of reduced breathlessness and increased exercise tolerance in such patients. Perhaps due to their different haemodynamic status, normal subjects provided no evidence of parallel benefits and it remains of interest to determine whether our methodology would detect a reduction of dyspnoea in patients with impaired cardiac function.

Atenolol, which is devoid of ISA, caused a mild increase of breathlessness in relation to ventilation in normal subjects. The mechanism

of this effect is of some interest. No change in bronchomotor tone was found in these normal subjects after atenolol and no bronchoconstriction occurred during exercise. It is known that atenolol reduces cardiac output (Lund-Johansen, 1977) and in the presence of an unchanged oxygen consumption, greater arterio-venous differences in oxygen and carbon dioxide would be expected. Since the physiological mechanisms for detecting such changes have not been established in the venous circulation, we are reluctant to attribute the increased breathlessness to this cause. Paintal (1977) has shown that type J-receptors may be stimulated by alterations in pulmonary haemodynamics and has suggested a role for such

Figure 2 In the panel on the left, breathlessness, assessed by the VAS, has been related to minute ventilation. The mean values are shown for the six subjects before (open symbols) and after (closed symbols) ICI 118,587 (Δ , $\bullet$) or atenolol ($\circ$, $\odot$). The panel on the right shows the effects of these treatments on the relationship between breathlessness and oxygen uptake.

receptors in the mediation of breathlessness. Changes in pulmonary haemodynamics after atenolol, particularly a rise in pulmonary capillary pressure, might operate in this way. However, there was no change in the accompanying pattern of breathing.

The effects on breathlessness of altering β -adrenoceptor activity in dyspnoeic patients has received little attention. Butland *et al.* (1980) studied metoprolol in 'pink puffers' and dem-

onstrated a significant reduction in ventilation at rest and during exercise but this was not accompanied by an increase in exercise tolerance. The ISA associated with ICI 118,587 and its possible effects in patients with cardiac impairment is clearly worthy of further study.

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