Effects of the β_2 -adrenoceptor antagonist ICI 118,551 on blood pressure in hypertensive patients known to respond to β_1 -adrenoceptor antagonists

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- 1 The selective β_2 -adrenoceptor antagonist ICI 118,551, 50 mg orally given thrice daily, did not lower blood pressure in hypertensive patients known to respond to therapy with atenolol or propranolol.
- 2 This dosage regimen resulted in a small decrease in supine heart rate which might represent partial β_1 -adrenoceptor antagonism by ICI 118,551.
- 3 The results suggest that β_2 -selective antagonism does not play a role in the hypotensive action of β -adrenoceptor antagonists.

Keywords ICI 118,551 β_2 -adrenoceptor antagonist hypertension atenolol propranolol

Introduction

The mechanisms by which β -adrenoceptor antagonist drugs influence blood pressure in animals and man appear to be complex. Both non-selective and β_1 -selective agents have been used in clinical practice to reduce blood pressure in patients with hypertension, suggesting a relative importance of blockade of β_1 -adrenoceptors. The effects of predominant blockade of β_2 -adrenoceptors on the blood pressure of hypertensive patients appear negligible (Dahlof *et al.*, 1983), although previously available β_2 -adrenoceptor antagonists may have lacked selectivity (O'Donnell & Walduck, 1981).

ICI 118,551 ($\pm$ -erythro-3-isopropylamino-1-(7-methyl-4-indanyloxy)-2-butanol hydrochloride) is a selective β_2 -adrenoceptor blocking drug which has been shown in animal models to have a selectivity ratio of β_2 over β_1 of at least 200 (Bilski *et al.*, 1983). Selectivity has also been demonstrated in normal man (Fitzgerald *et al.*, 1982; Tattersfield & Cragg, 1983; Arnold *et al.*, 1985).

Observations on the effect of ICI 118,551 in hypertensive patients known to respond to cardio-selective or non-cardioselective β -adrenoceptor

blocking drugs should give information about the relative contribution of blockade of β_2 -adrenoceptors to the antihypertensive effect of β -adrenoceptor blocking agents.

Methods

Subjects

Ten patients (six male, four female, mean age 46 years) with essential hypertension successfully treated with atenolol (8) or propranolol (2) alone were studied. Mean pre-treatment sustained supine blood pressure was 167/104 mm Hg (s.d. 21/8) and on treatment 128/81 mm Hg (s.d. 21/10). The duration of previous therapy with β -adrenoceptor blockers ranged from 3–101 (mean 25.4) months. None of the patients had a history of asthma or peripheral vascular disease. The study was approved by the Joint Ethics Committee of Grampian Health Board and the University of Aberdeen. All patients gave informed written consent.

Design

All usual therapy was withdrawn and the β -adrenoceptor blocker replaced by a matching placebo for an initial washout period. Patients remained on placebo for up to 1 month until the supine diastolic blood pressure (Phase 5) had risen to more than 95 mm Hg. During this washout period the treadmill exercise load required to produce a target heart rate of 140 beats min^{-1} at the end of 3 min was determined.

On entering the active treatment period ICI 118, 551 50 mg as an oral syrup, or matching placebo were given thrice daily for 1 week according to a double-blind randomised cross-over design with washout placebo matching the original β -adrenoceptor blocker therapy prescribed for the intervening week. After 1 further week of this placebo, patients returned to their pre-study therapy. The patients were studied on 6 separate days: Day 1 and Day 8 of the two randomised treatment periods and on Day 1 and Day 8 following re-institution of pre-study β -adrenoceptor blocker therapy. Supine, standing end-exercise and post-exercise heart rates and blood pressures were measured before the first (Day 1) and last (Day 8) dose and at 2, 4 and 6 h post dose on each of these days.

Methods of measurement

Blood pressure was measured on each of the study days using the previously described Remler semi-automated recording system (Scott & Petrie, 1982). The mean of two readings was recorded in the supine and standing positions and one reading for end-exercise and 15–30 s post-exercise. Heart rate was measured from an ECG trace.

Statistical analysis

Changes from baseline (Day 1 before first treatment in the double-blind treatment phase (time 0)) for any one treatment were analysed for all results. In the comparison of ICI 118,551 and placebo ANOVA preceded a Student's *t*-test. Comparison of placebo and ICI 118,551 with results following re-introduction of usual therapy after a further week on placebo was by a paired Student's *t*-test. Confidence intervals (95%) for mean differences from baseline were calculated for supine systolic and diastolic blood pressure and exercise heart rate (Gardner & Altman, 1986).

Results

All 10 subjects received placebo, ICI 118,551

and their usual therapy. No untoward effects were recorded in the study.

Heart rates

ICI 118, 551 vs placebo In the supine position comparison of the differences from baseline (time 0, Day 1) 2, 4 and 6 h after dosing on Day 1 and before the last dose and 2, 4 and 6 h after dosing on Day 8 showed a significant reduction in heart rate after ICI 118,551 (Table 1). This did not occur in the standing position, at end-exercise nor post-exercise (except, 2 h post dosing on Day 1).

ICI 118, 551 vs usual therapy Comparison of the reductions from baseline after dosing on Days 1 and 8 showed these to be significantly greater at all times after usual therapy in the standing position, at end-exercise, and post-exercise (Table 1). No statistically significant difference was shown in the supine position (except 2 h post-dosing on Day 8) but the heart rates on usual treatment were lower than on ICI 118, 551.

The changes in post-exercise heart rate follow-placebo, ICI 118,551 and usual therapy are shown in Figure 1 and show that apart from 2 h after the first dose of placebo or ICI 118,551, there was no difference from baseline with these treatments whilst with usual treatment there clearly was.

Systolic blood pressure

Comparison of the difference from baseline after dosing on Days 1 and 8 showed no significant reduction after placebo or ICI 118,551 in supine, standing, end-exercise or post-exercise pressures. A statistically significant increase over baseline was noted after ICI 118,551 in the supine position on Day 8, 2 h post dosing and in the standing position on three occasions—Day 1 at 2 and 6 h and Day 8 at 0 h. These effects were small and of the order of 2 mm Hg supine and 3–8 mm Hg standing.

Comparison of the differences from baseline showed these to be significantly greater after usual therapy compared with ICI 118,551 at all times on Days 1 and 8 in the supine (except Day 1, 2 h) and standing positions and at end-exercise (except Day 8, 0 h).

The effects of placebo, ICI 118,551 and usual therapy on supine systolic blood pressure on Days 1 and 8 are summarised in Figure 2. Clearly there is little difference between ICI 118,551 and placebo and no hint of a reduction in systolic pressure following ICI 118,551.

Table 1 Mean (s.e. mean) heart rate (beats min⁻¹) in the supine, standing and post exercise positions after dosing with placebo, ICI 118,551 and usual therapy on Day 1 and Day 8.

Time post-dosing	Day 1			Day 8		
	0 h	2 h	4 h	0 h	2 h	4 h
<i>Supine</i>						
Placebo	77 (3.4)	75 (3.6)	79 (3.5)	77 (2.9)	75 (3.5)	77 (3.1)
ICI 118,551	77 (3.6)	65 (1.8)**	69 (3.0)**	69 (3.4)**	66 (3.2)*	66 (2.1)*
Usual therapy	78 (3.3)	63 (2.3)	64 (2.0)	66 (2.5)	60 (2.3)†	63 (3.1)
<i>Standing</i>						
Placebo	86 (4.8)	87 (3.9)	90 (3.8)	86 (3.8)	83 (3.8)	86 (4.1)
ICI 118,551	82 (3.3)	74 (2.7)*	80 (3.8)	81 (4.3)	74 (3.7)	81 (3.8)
Usual therapy	86 (3.7)	67 (2.7)†	69 (2.7)†	72 (3.3)††	64 (3.6)††	68 (3.0)††
<i>End exercise</i>						
Placebo	143 (4.6)	141 (4.5)	144 (4.5)	140 (3.8)	135 (3.0)	138 (2.5)
ICI 118,551	134 (3.9)	125 (3.8)**	129 (4.4)	129 (3.4)	124 (3.9)	128 (4.1)
Usual therapy	132 (3.3)	106 (1.7)††	108 (1.9)††	116 (3.3)†	104 (2.8)††	105 (2.2)††
<i>Post exercise</i>						
Placebo	134 (6.5)	129 (6.1)	135 (6.1)	130 (4.6)	126 (3.7)	128 (3.4)
ICI 118,551	123 (5.1)	107 (4.1)*	118 (4.6)	118 (5.4)	109 (5.9)	119 (4.5)
Usual therapy	122 (3.6)	95 (2.0)†	99 (2.1)†††	106 (3.9)†	93 (3.1)†	96 (2.6)†††

Indicators of statistical significance refer to the differences from baseline [Predose (time 0) Day 1]. Comparison of ICI 118,551 with placebo—* $P < 0.05$, ** $P < 0.01$. Comparison of ICI 118,551 with usual therapy—† $P < 0.05$, †† $P < 0.01$, ††† $P < 0.001$.

Figure 1 Mean change (beats min^{-1}) from baseline (Day 1, time 0) for post exercise heart rate on Days 1 and 8 following placebo (Δ), ICI 118, 551 ($\bullet$) and usual therapy ($\blacktriangle$) showing 95% CI, $t = 2.262$.

Figure 2 Mean change (mm Hg) from baseline (Day 1, time 0) for supine systolic blood pressure on Days 1 and 8 following placebo (Δ), ICI 118, 551 ($\bullet$) and usual therapy ($\blacktriangle$) showing 95% CI, $t = 2.262$.

Diastolic blood pressure

Similar comparisons showed no significant reduction of diastolic blood pressure after ICI 118, 551 compared to placebo in the lying, standing, end-exercise or post-exercise measurements. A significant increase was shown after ICI 118, 551 in the supine position on Day 8 at 0 and 2 h compared to baseline. The increase was modest and of the order of 4–7 mm Hg. This effect is summarised in Figure 3 which also shows the

tendency of ICI 118, 551 to raise supine diastolic pressure compared to placebo and usual therapy at other time points.

Discussion

The results of this study show that the selective β_2 -adrenoceptor antagonist ICI 118,551 given orally in a dose of 50 mg three times daily for 1 week did not reduce to any clinically important

Figure 3 Mean change (mm Hg) from baseline (Day 1, time 0) for supine diastolic blood pressure on Days 1 and 8 following placebo (Δ), ICI 118,551 ($\bullet$) and usual therapy ($\blacktriangle$) showing 95% CI, $t = 2.262$.

degree the systolic or diastolic blood pressures of patients with hypertension known previously to respond to β -adrenoceptor antagonists. This suggests that blockade of β_2 -adrenoceptors does not contribute to the control of blood pressure when β -adrenoceptors are used in the treatment of patients with hypertension.

The results on resting blood pressures are in agreement with those reported by Dahlof *et al.* (1983) who used rather higher doses than used in our study (50 or 100 mg three times daily) and a less stringent design. In both studies the investigations were performed in patients who were known to be responsive to either β_1 -selective or non-selective β -adrenoceptor blocking drugs. The evidence to support the findings in our study resides in the observations that blood pressure rose after withdrawal of usual therapy with the β -adrenoceptor blocking drugs and fell again when that therapy was re-introduced. The effects of the original therapy on blood pressure were clearly different to those of ICI 118,551 thus making the lack of effect of ICI 118,551 a positive observation.

Four points should be made in respect of the design of our study. Firstly we have previously shown that a 1 week washout period of pre-existing β -adrenoceptor blocker therapy is sufficient (Webster *et al.*, 1982) but a longer interval might have been preferable. Secondly the requirement to demonstrate the effectiveness of pre-existing β -adrenoceptor blocker therapy in individual patients following the double-blind

phase of the study led to a potential source of bias in that such therapy always followed the comparison of ICI 118, 551 with placebo. Observer bias in this non double-blind period of observation was reduced by use of the Remler semi-automated device which minimises involvement of observers (Scott & Petrie, 1982). Fourthly, examination of the results and 95% confidence intervals does not suggest that inclusion of a larger number of patients would have exposed significant differences between ICI 118, 551 and placebo in their effect in reducing blood pressure.

In view of the lack of effect of ICI 118, 551 in this study, at least on blood pressure, it is important to cite evidence that 50 mg does produce blockade of β_2 -adrenoceptors in man. Tattersfield & Cragg (1983) showed in normal volunteers a significant displacement of the bronchial airway dose-response curve to salbutamol comparing this β_2 -adrenoceptor antagonism at the bronchi with little (but some) effect on exercise tachycardia both 2 h after a 50 mg dose of ICI 118,551. Stimulation of β_2 -adrenoceptors by intravenous isoprenaline as shown by a fall in diastolic blood pressure, increase in physiological tremor or fall in serum potassium in man can be antagonised by doses of ICI 118, 551 as low as 5 mg oral dose 2 h after dosing (Fitzgerald *et al.*, 1982; Arnold *et al.*, 1985; Brown *et al.*, 1983). Some small effects are probably seen on β_1 -adrenoceptors at 40–50 mg single oral doses of ICI 118, 551 2 h after dosing (Arnold *et al.*, 1985; Harry *et al.*, 1984). However, in the present

study the lack of effect of ICI 118, 551 on end-exercise heart rate and systolic blood pressure would suggest that this was not occurring. If the doses used in our study had produced some small antagonism on β_1 -adrenoceptors some effect should have been evident on blood pressure at least 2 and 4 h after the last dose of drug on Day 8. The doses did not affect blood pressure and so even if some effect is occurring at β_1 -adrenoceptors this clearly was not sufficient to produce any fall in blood pressure in our patients with hypertension.

Two other interesting observations were seen in this study. Firstly the small reduction in heart rate seen in the patients with hypertension are in agreement with the results of Dahlof *et al.* (1983), but are at variance with results from normal volunteers where doses up to 100 mg do not seem to affect the resting heart rate (Arnold *et al.*, 1985; Harry *et al.*, 1984). This may reflect a greater sensitivity of the heart in hypertensive patients to β_1 -adrenoceptor blockade, or may reflect a relative importance of β_2 -adrenoceptors in hypertensive patients compared with normals. β_2 -adrenoceptors are present in the human atrium (Brodde *et al.*, 1983) but whether differences exist between hypertensives and normals is not known. In a study in normotensive volun-

teers (Daule *et al.*, 1986) ICI 118, 551 in a dose of 25 mg three times a day for 14 days inhibited isoprenaline-induced tachycardia and fall in diastolic blood pressure (mediated principally via β_2 -receptors) but had no effect on exercise induced tachycardia (mediated principally via β_1 -receptors). On vigorous exercise a difference appears to exist because β_2 -adrenoceptor blockade clearly does not affect the tachycardia or the systolic blood pressure response.

Secondly ICI 118, 551 may have produced a small rise in diastolic blood pressure in the hypertensive patients both at rest and on exercise (maximal effect about 6 mm Hg in the supine position). A similar trend has been seen in studies in normal volunteers (Arnold *et al.*, 1985; Harry *et al.*, 1984). The mechanism of this small rise in diastolic blood pressure may be related to the activity of circulating adrenaline. The latter can produce vasodilatation of blood vessels in skeletal muscle by stimulation of β -adrenoceptors. ICI 118,551 can block the effect of circulating adrenaline and so increase peripheral resistance.

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References

- Arnold, J. M. O., O'Connor, P. C., Riddell, J. G., Harron, D. W. G., Shanks, R. G. & McDevitt, D. G. (1985). Effects of the β_2 -adrenoceptor antagonists ICI 118, 551 on exercise tachycardia and isoprenaline induced β -adrenoceptor responses in man. *Br. J. clin. Pharmacol.*, **19**, 619-630.
- Bilski, A. J., Halliday, S. E., Fitzgerald, J. D. & Wale, J. L. (1983). The pharmacology of a β_2 -selective adrenoceptor antagonist (ICI 118, 551). *J. cardiovascular. Pharmacol.*, **5**, 430-437.
- Brodde, O. E., Karad, K., Zerkowski, H. R., Rohm, N. & Reidemeister, J. C. (1983). Coexistence of β_1 - β_2 adrenoceptors in human right atrium. Direct identification by I-(125) iodocyanopindolol binding. *Circ. Res.*, **53**, 752-758.
- Brown, M. J., Brown, D. C. & Murphy, M. B. (1983). Hypokalaemia from β_2 -receptor stimulation by circulating epinephrine. *New Engl. J. Med.*, **309**, 1414-1419.
- Dahlof, B., Andren, L., Svensson, A. & Hanssen, L. (1983). Antihypertensive mechanism of β -adrenoceptor antagonism—the role of β_2 -blockade. *J. Hypertension*, **1** (Suppl 2), 112-115.
- Daule, A., Johnston, T., Reher, M., Kruger, M. & Brodde, O-E. (1986). Abstracts of 11th Scientific Meeting of the International Society of Hypertension, 128P.
- Fitzgerald, D., Gumbrielle, J. & Harry, J. D. (1982). Effects in man of ICI 118, 551 (a selective β_2 -adrenoceptor blocking drug) on some cardiovascular responses induced by isoprenaline. *Br. J. clin. Pharmacol.*, **13**, 586P.
- Gardner, M. J. & Altman, D. G. (1986). Confidence intervals rather than p values: estimations rather than hypothesis testing. *Br. med. J.*, **292**, 746-750.
- Harry, J. D., Norris, S. C., Percival, P. G. & Young, J. (1984). Effects in man of ICI 118, 551 (a β_2 -adrenoceptor antagonist) on some cardiovascular actions of dobutamine. *Br. J. clin. Pharmacol.*, **17**, 187P-188P.
- O'Donnell, S. R. & Walduck, K. (1981). How β_2 -selective is the adrenoceptor antagonist drug IPS 339? *J. Pharm. Pharmacol.*, **33**, 223-225.
- Scott, A. K. & Petrie, J. C. (1982). Assessment of Remler blood pressure recording system. *Br. J. clin. Pharmacol.*, **13**, 289P-290P.
- Tattersfield, A. E. & Cragg, D. J. (1983). Effect of ICI 118, 551 on bronchial β -adrenoceptor function and exercise heart rate in normal man. *Br. J. clin. Pharmacol.*, **16**, 587-590.
- Webster, J., Hawksworth, G. M., Barber, H. E., Jeffers, T. A. & Petrie, J. C. (1982). Withdrawal of long-term atenolol in hypertensive patients. *Br. J. clin. Pharmacol.*, **12**, 211-214.

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