Immediate haemodynamic effects of a novel partial agonist, β_1 -adrenoceptor blocking drug ICI 141 292 after intravenous administration to healthy young volunteers and patients with ischaemic heart disease

J. BONDE, T. L. SVENDSEN, K. LYNGBORG, J. MEHLSSEN & J. TRAP-JENSEN

Department of Clinical Physiology and Internal Medicine M, Frederiksberg Hospital, 2000 Frederiksberg, Denmark

1 ICI 141 292 is a new β_1 -adrenoceptor blocking drug. The β_1 -adrenoceptor antagonistic effect of ICI 141 292 was examined in a double-blind, randomised crossover study in eight healthy young volunteers and compared with atenolol. Three doses of ICI 141 292 (1, 2 and 4 mg) and atenolol 5 mg were administered intravenously. The attenuation in exercise induced tachycardia varied between 16.0 and 21.2% ($P < 0.01$). A significant reduction in blood pressure could be demonstrated following all three doses of ICI 141 292 and atenolol during exercise.

2 At rest in the sitting position HR decreased approximately 8% following all three doses of ICI 141 292 and 14.9% after atenolol 5 mg. No changes in blood pressure were observed under resting conditions after any of the drugs.

3 In six patients with ischaemic heart disease the intrinsic sympathomimetic activity following intravenous administration of four sequential doses (0.5, 0.5, 1.0 and 2.0 mg) of ICI 141 292 was examined. HR decreased 7% ($P < 0.05$) following ICI 141 292 1 mg with no further decrease following the succeeding doses. Cardiac output decreased 5.2% ($P < 0.05$) following a cumulative dose of 4 mg.

4 No significant changes were observed in mean arterial blood pressure, stroke volume or total peripheral resistance whereas an increase in supine resting mean pulmonary arterial pressure of 3.4 mm Hg ($P < 0.05$) could be demonstrated.

5 ICI 141 292 seems to be a potent (at least five times as potent as atenolol) β_1 -adrenoceptor blocking agent possessing moderate intrinsic sympathomimetic activity.

Keywords β_1 -adrenoceptor blockade haemodynamics intrinsic sympathomimetic activity

Introduction

ICI 141 292 (N(2-(3-*O*-cyanophenoxy-2-hydroxy-propylamino) ethyl)-4-hydroxyphenylacetamide) is a new selective β_1 -adrenoceptor antagonistic agent (Harry *et al.*, 1984; Norris *et al.*, 1984).

Animal experiments have indicated that ICI 141 292 seems to possess intrinsic sympathomimetic activity (ISA) (Smith *et al.*, 1983). From animal experiments the degree of ISA of ICI 141 292

Correspondence: Dr J. Bonde, Department of Anaesthesiology, Københavns Amts Sygehus i Herlev, Herlev Ringvej, 2730 Herlev, Copenhagen, Denmark

is estimated to be between that of practolol and pindolol (laboratory data) i.e. approximately 20% of that of isoprenaline. In young healthy volunteers Harry *et al.* (1984) and Norris *et al.* (1984) have demonstrated that ICI 141 292 is a selective β_1 -adrenoceptor antagonist. Studies being performed in patients with hypertension and angina pectoris indicate that ICI 141 292 offers control of angina (Akhras *et al.*, 1985) and possesses mild antihypertensive effects (Leonetti *et al.*, 1985). The purpose of this study was: Part 1: to assess the β_1 -adrenoceptor blocking potency of ICI 141 292, and part 2: to evaluate the acute haemodynamic effects after increasing intravenous doses of ICI 141 292 in order to estimate the ISA (evaluated by changes in cardiac output and heart rates) in patients with ischaemic heart disease, and to compare the observed haemodynamic effects with earlier results obtained in similar studies with acebutolol, atenolol, pindolol, practolol and propranolol.

Methods

Subjects

Part 1 Eight healthy young men with a mean weight and height of 72.4 kg (range: 64–86 kg) and 180.1 cm (range: 173–190 cm), respectively entered the study. The age varied from 29 to 36 years (mean 32.0 years).

Part 2 Six male patients, with a mean age of 56 years (range 38–68 years), who all had had an uncomplicated myocardial infarction at least 6 months prior to the investigation. The weight and height of the patients varied from 73 to 93 kg (mean 83.0 kg) and 169 to 188 cm (mean 174.6 cm), respectively. The patients underwent a physical examination, an X-ray of the chest and an ECG at rest and during exercise was performed before entering the trial. The patients received no medicine apart from nitroglycerin. None of the patients had objective or subjective signs of heart failure, all were normotensive and without symptoms of obstructive lung disease.

Informed consent to the study was obtained from all of the subjects after careful explanation of the risks and inconveniences to be expected. The protocol was approved by the local ethics committee.

All of the subjects had normal values of serum creatinine, liver enzymes and electrolytes. Two of the persons were smokers (> 10 cigarettes/day), and none had an alcohol consumption of more than 25 g/day.

Procedure

Part 1 This part of the study was conducted as a double-blind randomised crossover trial in which three doses of ICI 141 292 (1, 2 and 4 mg) and 1 dose of atenolol (5 mg) was given intravenously on four different days interspaced by at least 1 week. Before entering the study all volunteers performed an exercise test on an electrically braked cycle ergometer (Elema Schonander) to determine an individual work load eliciting a heart rate (HR) of 140–150 beats min^{-1} . At each occasion a sphygmomanometer cuff was placed on the right upper arm and three ECG-electrodes were attached to the thorax. After 10 min upright rest in the sitting position on the cycle ergometer blood pressure (BP) and HR were recorded. The volunteers then exercised 5 min at the work load determined earlier. BP was recorded every min and HR was continuously registered from a precordial lead. After at least 45 min rest in the supine position an intravenous dose of either ICI 141 292 or atenolol was given over a 3 min period. The exercise test was repeated as described above 15 min after the drug administration.

Part 2 This study was conducted as an open study evaluating the haemodynamic effects at supine rest of four sequential doses of ICI 141 292 administered intravenously to each individual. On the day of the haemodynamic study the patients came to the laboratory having fasted overnight. With the patients in the supine position a flow-directed balloon tipped catheter for thermodilution (Swan-Ganz thermodilution catheter 93–112–7F) was inserted in a cubital vein. Under fluoroscopic guidance the tip of the catheter was placed in the pulmonary artery. The patients rested recumbent for 1 h in a quiet room with a constant temperature of 22 °C. Talking was not permitted during the study. The patients were instructed to rest but not to sleep.

After determination of cardiac output (CO), HR, BP and pulmonary artery pressure (PAP) 0.5 mg ICI 141 292 was injected intravenously. The above mentioned parameters were determined 15 min following the injection and another 0.5 mg was injected intravenously. The measurements were repeated after 15 min and again twice 15 min after injections of 1.0 and 2.0 mg (giving a total dose of 4 mg).

Techniques

Cardiac output was determined by the thermodilution technique (Forrester *et al.*, 1972) using an Edwards Laboratory computer model 9510. The CO was calculated as the mean of five

determinations made in the course of 3–5 min. Pulmonary artery pressure was registered continuously by means of an Elema Schonander pressure transducer (EMT 35). Blood pressure was measured with a mercury sphygmomanometer and diastolic BP was read at phase V. Heart rate was read from a continuously recorded ECG from a precordial lead. Total peripheral resistance (TPR) was calculated as the mean systemic arterial blood pressure (MAP) divided with CO. Stroke volume was calculated by dividing CO with HR.

Statistical evaluation was made by means of the Wilcoxon test for paired observations and the Mann-Whitney test for unpaired observations. A P value < 0.05 was considered significant.

Results

Part 1 The detailed results are given in Table 1. In the sitting position HR decreased 14.9% ($P < 0.01$), 8.4% ($P < 0.05$), 9.0% ($P < 0.05$) and 8.2% ($P < 0.05$) following atenolol 5 mg and ICI 141 292 1, 2 and 4 mg, respectively. The reduction was significantly greater ($P < 0.05$) following atenolol compared to any of the ICI 141 292 doses.

The reduction in exercise induced tachycardia after atenolol 5 mg and ICI 141 292 1, 2 and 4 mg was 16%, 20.0% 21.2% and 20.2% ($P < 0.01$), respectively, with no significant difference in the relative reduction in HR between any of the four groups.

The blood pressure in the sitting position was not modified by either atenolol or ICI 141 292. The reduction in BP during exercise compared with the predrug exercise test was 5.5% ($P < 0.05$), 11.2% ($P < 0.01$), 8.5% ($P < 0.01$) and 11.7% ($P < 0.01$) after atenolol 5 mg, ICI 141 292 1, 2 and 4 mg, respectively. No significant differences in the BP measured during exercise were observed between the groups studied.

Part 2 CO decreased 5.3% ($P < 0.05$) following the administration of 0.5 mg ICI 141 292. No further decrease in CO was observed following the last three doses of ICI 141 292. Cardiovascular variables are given in Table 2. A significant decrease (7.4%, $P < 0.05$) in HR was observed following a cumulative dose of 1 mg whereas no additional reduction could be demonstrated following the succeeding doses. No significant changes in SV, MAP or TPR were observed. MPAP increased from 18.5 ± 1.8 to 20.8 ± 2.0 mm Hg ($P < 0.05$) following 0.5 mg ICI 141 292 increasing further to 21.9 ± 2.1 mm Hg ($P < 0.05$) at a cumulative dose of 4.0 mg. Figure 1 shows the dose-response curve for CO in per-

centage change from control value of ICI 141 292 compared with the changes observed following the administration of pindolol, practolol, acebutolol, atenolol and propranolol (data derived from experiments carried out in earlier studies in the same laboratory (Svensen *et al.*, 1985)).

The drugs were well tolerated and no adverse reactions were observed.

Discussion

The first part of the study has demonstrated that ICI 141 292 administered intravenously to healthy young volunteers in doses of 1, 2 and 4 mg decreased HR during exercise significantly. This is suggestive of ICI 141 292 possessing β_1 -adrenoceptor blocking properties. The attenuation in exercise induced tachycardia was not significantly different between the doses given, 1, 2 and 4 mg. This might reflect that the dose-response curve levels off before 1 mg with respect to the decrease in exercise induced tachycardia. The reduction in exercise induced tachycardia following ICI 141 292 and atenolol was not significantly different, indicating that ICI 141 292 is at least five times as potent as atenolol.

At rest in the sitting position 5 mg atenolol caused a pronounced reduction in HR (14.9%) whereas the reduction following any of the ICI 141 292 doses only amounted to approximately 8%. This difference may be caused by the ISA possessed by ICI 141 292. The findings that ISA is demonstrable at rest and difficult to demonstrate during exercise or other conditions with increased sympathetic tone is in accordance with the observations of Svendsen *et al.*, 1980. In contrast, McDevitt *et al.* (1977), Jennings *et al.* (1981) and Tomlinson *et al.* (1984) have been able to demonstrate a slight difference in the reduction in exercise induced tachycardia between β -adrenoceptor blockers with and without ISA. A more pronounced reduction in exercise induced tachycardia would probably have been achieved by increasing the *iv* dose of atenolol (Shanks *et al.*, 1977).

During exercise MAP was equally reduced after the three doses of ICI 141 292 and atenolol. No significant reduction could be demonstrated at rest in the sitting position consistent with the results of Svendsen *et al.* (1979).

The second part of the study has demonstrated that ICI 141 292 0.5 mg decreased CO with 5.3% ($P < 0.05$) in the resting supine position in patients with ischaemic heart disease. The succeeding doses induced no further reduction in CO. The reduction in HR following ICI 141 292 1 mg was 7.4% ($P < 0.05$) and no additional

Table 1 HR and mean arterial BP during exercise before and after atenolol and three doses of ICI 141 292 in eight young healthy volunteers. Resting HR and BP are recorded in the sitting position.

Drug		Before drugs			After drugs		
		Resting HR (beats min ⁻¹)	Exercise HR (beats min ⁻¹)	Mean BP (mm Hg)	Resting HR (beats min ⁻¹)	Exercise HR (beats min ⁻¹)	Mean BP (mm Hg)
Atenolol	5 mg	81.1 ± 13.0	151.5 ± 11.4	115.4 ± 12.5	69.0 ± 15.5	127.3 ± 7.1	109.0 ± 11.9
ICI 141 292	1 mg	83.6 ± 8.7	149.0 ± 8.5	113.6 ± 13.0	76.6 ± 8.2	119.8 ± 6.1	100.9 ± 10.0
ICI 141 292	2 mg	76.8 ± 15.4	145.5 ± 13.6	116.9 ± 13.2	69.9 ± 12.3	114.6 ± 8.4	107.0 ± 12.7
ICI 141 292	4 mg	77.8 ± 12.1	147.3 ± 12.4	114.1 ± 12.0	71.4 ± 8.4	117.6 ± 8.1	100.8 ± 9.6

Table 2 Haemodynamic variables at rest before and after increasing doses of ICI 141 292. (Mean ± s.e. mean, *n* = 6) in patients with ischaemic heart disease.

Parameter	Control value	Cumulative dose (mg)				
		0.5	1.0	2.0	4.0	
Cardiac output (l min ⁻¹)	5.61 ± 0.52	5.31 ± 0.50	5.31 ± 0.51	5.27 ± 0.55	5.32 ± 0.53	
Heart rate (beats min ⁻¹)	64.8 ± 2.2	62.2 ± 2.5	60.0 ± 2.5	60.7 ± 2.4	60.8 ± 2.9	
Stroke volume (ml min ⁻¹)	87.0 ± 8.1	85.0 ± 5.8	84.5 ± 7.3	86.9 ± 8.0	87.9 ± 7.8	
Mean blood pressure (mm Hg)	110.0 ± 3.1	109.5 ± 3.5	110.4 ± 3.80	113.3 ± 4.9	112.8 ± 3.9	
Total peripheral resistance (units)	20.5 ± 2.0	21.6 ± 2.1	21.9 ± 2.4	22.8 ± 2.6	22.1 ± 2.1	
Mean pulmonary artery pressure (mm Hg)	18.5 ± 1.8	20.8 ± 2.0	20.6 ± 1.7	21.0 ± 2.4	21.9 ± 2.1	

reduction in HR could be demonstrated following the last two doses of ICI 141 292. The changes in haemodynamic variables after increasing doses are strongly suggestive of ICI 141 292 possessing ISA. In other studies it has been demonstrated that this protocol (i.e. using increasing doses of a β_1 -adrenoceptor blocker) is suitable for demonstrating differences in ISA (Svendsen *et al.*, 1979, 1981, 1985).

In earlier studies (Svendsen *et al.*, 1979, 1981, 1985) it has been possible to divide β_1 -adrenoceptor blockers in three groups according to the reduction in CO in the resting supine position. 1: No ISA (atenolol and propranolol) inducing a decrease in CO of about 25%. 2: Moderate ISA (acebutolol and practolol) reducing CO with approximately 10%. 3: Strong ISA (pindolol) with no demonstrable effect on CO (Figure 1).

Comparing the data of earlier studies with the present results it can be concluded that ICI 141

292 possesses moderate to strong ISA and is from a haemodynamic point of view comparable to acebutolol and practolol.

Our findings of only a moderate decrease in CO following ICI 141 292 are in contrast to the observation of Lund-Johansen *et al.* (1984), who found a decrease in CO of 23% following 200 mg ICI 141 292 given orally to patients with hypertension. This discrepancy may be explained by the dose difference and by the different experimental design. Another contributive factor may be an increased sympathetic tone in patients with hypertension, which might accentuate the decrease in CO.

In conclusion ICI 141 292 seems to be a potent β_1 -adrenoceptor blocking drug with an ISA of a magnitude between that of pindolol and acebutolol, when compared with results from earlier studies carried out in the same laboratory.

Figure 1 Reduction in cardiac output at rest after intravenous administration of increasing doses of β -adrenoceptor blocking drugs. Reductions are expressed as percent change from control. Abscissa shows the cumulative doses of the drugs. ICI 141 292 was in contrast to the other β -adrenoceptor blockers only administered in four doses.

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