Initial clinical experience with ICI 141,292 (Visacor®), a new selective β_1 -adrenoceptor blocker with ISA—a multicentre trial in 59 patients

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1 The objective of this placebo controlled double-blind multicentre (six centres) trial was to investigate the safety and efficacy of ICI 141,292 (Visacor), a new selective β_1 -adrenoceptor antagonist with modest intrinsic sympathomimetic activity (ISA), in hypertensive patients.

2 Fifty-nine patients with mild essential hypertension were randomized to two of five treatment alternatives (placebo, 50 mg, 100 mg 200 mg or 300 mg of ICI 141,292) each given once daily for 2 weeks with a 4 week placebo period before (run in) and in between (wash out) active periods. Thus, each of the five treatments was evaluated in 20–24 patients.

3 After 2 weeks (24 h after last dose) the reduction in recumbent blood pressure for all doses except 50 mg of ICI 141,292 was statistically significant and in the order of 6/4 mm Hg.

4 Standing systolic blood pressure was reduced in a dose-dependent way but only significant for 200 mg of ICI 141,292 (8 mm Hg).

5 Heart rate changes (Δ) < 4 beats/min) were not statistically significant for any dose.

6 It is concluded that ICI 141,292 was well tolerated and had a significant but weak antihypertensive effect which might be explained by too much β_1 -adrenoceptor ISA.

Keywords ICI 141,292 Visacor β_1 -adrenoceptor antagonist hypertension

Introduction

Treatment of hypertension with β -adrenoceptor blocking drugs is well established and has become the therapy of first choice in many centres during the last 10–15 years (Hansson, 1983). All clinically used β -adrenoceptor antagonists appear to be equally effective in lowering blood pressure regardless of differences in pharmacodynamic or pharmacokinetic properties (Hansson, 1983). It is also

well known that β -adrenoceptor antagonists with β_1 -selectivity offer certain advantages in comparison to non-selective agents as regards side effects (Hansson, 1983).

Compounds with intrinsic sympathomimetic activity (ISA) e.g. pindolol appear to reduce blood pressure mainly through vasodilatation as opposed to the reduction in cardiac output seen with β -adrenoceptor antagonists devoid of ISA

Figure 1 Chemical structure of ICI 141,292 *N*-[2-(3-*o*-cyanophenoxy-2-hydroxypropylamino)ethyl-4-hydroxyphenylacetamide].

(Svensson *et al.*, 1982; Man in't Veld & Schalekamp, 1983). β -adrenoceptor blockers with ISA also reduce resting heart rate less than β -adrenoceptor blockers devoid of ISA (Svensson *et al.*, 1982) which should minimize the risk of bradycardia.

Against this background a selective- β_1 adrenoceptor antagonist with ISA would appear to offer an ideal combination of properties for the treatment of hypertension. Previously one such drug, practolol, was available. It had a useful antihypertensive effect (Prichard *et al.*, 1971) but due to serious unwanted effects (not related to ISA or β -adrenoceptor blockade) this drug was withdrawn (Brown *et al.*, 1974; Felix *et al.*, 1974).

The new β_1 -selective adrenoceptor blocking agent ICI 141,292 (Figure 1) possesses these theoretically appealing characteristics, i.e. β_1 -adrenoceptor selectivity and ISA (Smith *et al.*, 1983). Furthermore, ICI 141,292 has a low partition coefficient octanol: water (log *P* 0.87), lacks membrane stabilizing activity, is marginally more β_1 -selective than atenolol, has long duration and the ISA seems to be slightly higher than for practolol (Smith *et al.*, 1983;

Smith, personal communication). It has been shown to reduce blood pressure both in animals and in healthy volunteers. ICI 141,292's partial agonist activity has been shown to be β_1 -selective for the cardiovascular receptors (Smith *et al.*, 1983).

The present study, which is the first attempt to use ICI 141,292 in hypertension, was designed as a multicentre, double-blind placebo controlled trial. Its purpose was to assess the safety and efficacy of the drug given once daily in doses between 50 and 300 mg.

Methods

Fifty-nine patients with uncomplicated mild essential hypertension, who had given their written consent, were recruited for the trial. There were 32 males aged 50.0 ± 1.8 (mean $\pm$ s.e. mean) and 27 females aged 46.4 ± 2.2 years. All patients had been evaluated in a routine diagnostic workup in order to exclude secondary forms of hypertension (Andersson *et al.*, 1978). Their prestudy treatment consisted of: selective β -adrenoceptor blockade (mostly atenolol), $n = 32$; diuretics, $n = 5$; combined treatment, $n = 7$. Fifteen patients were untreated before the study. The study design is shown in Figure 2. All patients were given placebo during the first 4 weeks of the study (single blind). At the end of this run in period the average recumbent blood pressure for all patients was 154/98 mm Hg and the average standing blood pressure was 150/104 mm Hg. After this first placebo period the patients were randomly allocated to two 2 week treatment periods with either placebo or ICI 141,292 50 mg, 100 mg, 200 mg or 300 mg once daily. Between treatment periods there was a 4 week

Figure 2 Study design. Patients were not randomized to the same treatment twice. Blood pressure (BP) was also measured 2 h after drug intake at week 4, 6, 10 and 12.

placebo wash out period. In other words, during this 12 week study each of the patients received two of the five treatment alternatives and each dose including placebo was evaluated in 20–24 patients. The study had been approved by the Ethical Committee of the University of Göteborg.

Blood pressure was assessed, before and 2 h after drug intake every second week throughout the study, indirectly with a mercury sphygmomanometer and a regular arm cuff (rubber balloon = 12 × 35 cm) after 5 min rest in the supine position and after 1 min of standing. The disappearance of the Korotkoff sounds (phase V) was taken as the diastolic blood pressure. Heart rate was assessed by palpation of the radial pulse for 30 s in connection with the blood pressure recordings. The blood pressure values obtained after the placebo periods were used for comparisons with the blood pressures obtained, before and 2 h after taking the drug, on the last day of the 2 week active treatment periods.

Analysis of blood haemoglobin, WBC, platelet count, blood glucose, serum sodium, potassium, creatinine, protein, alkaline phosphatase, alanine transaminase, bilirubin, urine protein and erythrocytes were performed repeatedly during the trial.

Statistics

In the statistical evaluation conventional

methods were used for calculating the mean value and standard error. A two tailed paired *t*-test was used for comparing the patients' placebo and active treatment values. Differences were regarded as significant if $P < 0.05$.

Results

Blood pressure

Fifty-five patients completed the trial. The systolic and diastolic blood pressures, recumbent and standing, are shown in Tables 1 and 2.

Recumbent blood pressure Before drug intake (24 h after the last dose) there was no significant diastolic difference between placebo and 50 mg of ICI 141,292. However, the 100, 200 and 300 mg doses all caused significant (both compared to baseline and the placebo group) reductions in blood pressure in the order of 6/4 mm Hg. The reductions in blood pressure were somewhat greater 2 h after drug intake for the three higher doses.

Standing blood pressure Before drug intake (24 h after the last dose) only 300 mg of ICI 141,292 had significant blood pressure lowering effect, both diastolic and systolic compared to baseline. All doses caused significantly greater blood pressure fall than placebo. Two hours after drug intake the reductions in blood

Table 1 ICI 141,292, recumbent blood pressure (mean ± s.e. mean)

	Recumbent blood pressure (mm Hg)				
	Placebo	50 mg	100 mg	200 mg	300 mg
	<i>n</i> = 21	<i>n</i> = 21	<i>n</i> = 24	<i>n</i> = 23	<i>n</i> = 22
Control	151.9 ± 4.3 98.9 ± 1.4	150.2 ± 3.9 98.7 ± 1.6	155.9 ± 2.7 100.5 ± 1.6	153.2 ± 3.6 96.7 ± 1.6	155.1 ± 3.7 98.7 ± 1.6
	<i>n</i> = 21	<i>n</i> = 21	<i>n</i> = 24	<i>n</i> = 23	<i>n</i> = 22
24 h	149.2 ± 3.7 96.5 ± 1.8	147.4 ± 3.9 95.4 ± 1.9	149.8 ± 2.9 96.6 ± 1.6	147.0 ± 3.2 92.5 ± 1.5	149.9 ± 3.0 94.1 ± 1.8
Δ 24 h	2.7 ± 2.3 2.4 ± 1.5	2.8 ± 2.4 3.3 ± 1.5*	6.1 ± 2.8* 3.8 ± 1.0***	6.2 ± 2.3* 4.2 ± 1.3**	5.3 ± 2.4* 4.5 ± 1.4**
	<i>n</i> = 19	<i>n</i> = 18	<i>n</i> = 21	<i>n</i> = 20	<i>n</i> = 20
2h	148.5 ± 3.4 95.9 ± 1.3	144.3 ± 4.3 94.9 ± 1.8	148.0 ± 2.7 94.6 ± 1.9	144.8 ± 3.6 92.0 ± 1.8	147.1 ± 2.8 91.3 ± 1.6
Δ 2 h	3.1 ± 2.3 3.0 ± 1.6	6.2 ± 2.9* 4.1 ± 1.5*	7.1 ± 2.0** 6.2 ± 1.4***	9.5 ± 2.9** 5.2 ± 1.4**	8.1 ± 3.1* 6.7 ± 1.8**

Control = blood pressure recorded at end of run-in/washout

24 h = blood pressure prior to last tablet in 2 week period

Δ 24 h = difference control–24 h

2 h = blood pressure 2 h after final tablet

Δ 2 h = difference control–2 h

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

Table 2 ICI 141,292, standing blood pressure (mean $\pm$ s.e. mean)

	Standing blood pressure (mm Hg)				
	Placebo	50 mg	100 mg	200 mg	300 mg
Control	<i>n</i> = 21 148.0 $\pm$ 4.2 104.4 $\pm$ 1.7	<i>n</i> = 21 148.1 $\pm$ 4.0 104.6 $\pm$ 1.9	<i>n</i> = 24 151.0 $\pm$ 3.8 105.7 $\pm$ 1.7	<i>n</i> = 23 152.2 $\pm$ 3.0 101.9 $\pm$ 1.7	<i>n</i> = 22 150.9 $\pm$ 3.4 104.7 $\pm$ 2.0
24 h	<i>n</i> = 21 147.7 $\pm$ 3.5 104.1 $\pm$ 1.7	<i>n</i> = 21 144.4 $\pm$ 4.1 101.5 $\pm$ 2.3	<i>n</i> = 24 146.5 $\pm$ 4.1 101.1 $\pm$ 1.8	<i>n</i> = 23 144.0 $\pm$ 3.5 98 $\pm$ 1.5	<i>n</i> = 22 144.0 $\pm$ 2.9 100.3 $\pm$ 1.8
Δ 24 h	0.3 $\pm$ 2.1 0.3 $\pm$ 1.6	3.8 $\pm$ 2.5 3.0 $\pm$ 1.9	4.5 $\pm$ 3.0 4.5 $\pm$ 1.7*	8.2 $\pm$ 2.4** 3.0 $\pm$ 1.5	6.9 $\pm$ 2.4** 4.4 $\pm$ 1.6*
2 h	<i>n</i> = 19 146.1 $\pm$ 3.9 101.6 $\pm$ 1.5	<i>n</i> = 18 140.2 $\pm$ 4.6 100.4 $\pm$ 2.0	<i>n</i> = 21 140.8 $\pm$ 3.6 99.4 $\pm$ 2.0	<i>n</i> = 20 135.2 $\pm$ 3.4 97.8 $\pm$ 2.1	<i>n</i> = 20 134.8 $\pm$ 3.8 97.5 $\pm$ 1.8
Δ 2 h	1.5 $\pm$ 2.6 1.6 $\pm$ 1.9	8.2 $\pm$ 2.9* 4.6 $\pm$ 1.5**	9.1 $\pm$ 2.8** 6.7 $\pm$ 1.8**	18.1 $\pm$ 2.4*** 4.1 $\pm$ 1.7*	15.7 $\pm$ 3.3*** 6.6 $\pm$ 1.8**

Control = blood pressure recorded at end of run-in/washout

24 h = blood pressure prior to last tablet in 2 week period

Δ 24 h = difference control–24 h

2 h = blood pressure 2 h after final tablet

Δ 2 h = difference control–2 h

* P < 0.05; ** P < 0.01; *** P < 0.001

pressure for all doses were significant. The systolic blood pressure seemed to be reduced in a dose-dependent way with 50–200 mg of ICI 141,292.

Heart rate The reductions in heart rate caused by ICI 141,292 or placebo were not significantly different and not more than 4 beats/min both before and after drug intake.

Laboratory tests No significant changes in the haematological or metabolic variables were recorded.

Side effects and withdrawals

Four patients dropped out of the trial, one because of reasons unrelated to the study, two did not reach the diastolic inclusion pressure and one patient was withdrawn because of headache, nausea and fatigue during placebo.

Apart from this there was no difference in the frequency of complaints and side effects during active treatment as compared to placebo. On the contrary several patients who were evaluated with a special questionnaire (one centre) were found to report a feeling of increased well being during active treatment as compared to placebo (Svensson, 1978).

Discussion

It can be argued that the ideal β -adrenoceptor

antagonist to be used in the treatment of hypertension should be β_1 -selective for the antagonistic activity and possess β_2 partial agonist activity (Hansson, 1983; Man In't Veld *et al.*, 1983). The rationale for β_1 -selectivity would be minimization of certain side effects such as bronchial constriction and also lack of negative effects on various metabolic variables such as blood glucose, plasma insulin and free fatty acids (Hansson, 1982). Moreover, β_1 -adrenoceptor blockade seems to be the necessary feature for the antihypertensive effect (Kaplan & Smith, 1981; Hansson, 1982; Dahlöf *et al.*, 1983). The reason for β_2 -partial agonist activity would be the achievement of a more favourable haemodynamic long term effect with vasodilatation and unaltered cardiac output (Svensson *et al.*, 1982).

Since ICI 141,292 possessed the desired properties of β_1 -selective antagonist activity and modest ISA, and in addition was remarkably well tolerated by the patients the modest antihypertensive effect observed in this trial is slightly disappointing. There may be several explanations for the comparatively weak antihypertensive effect.

One obvious reason is that all patients in the present trial were only mildly hypertensive (average recumbent placebo blood pressure 154/98 mm Hg) and it is a common clinical observation that the antihypertensive effect with any drug in absolute terms becomes less pronounced the lower the blood pressure is to begin with. If one considers the patients with

placebo diastolic blood pressure > 100 mm Hg who received 200 mg or 300 mg ($n = 10$) during the first active period there was a reduction of 11/10 mm Hg in recumbent blood pressure.

Another plausible explanation is that the ISA of ICI 141,292 is β_1 -selective and that may influence the blood pressure reduction. We have previously shown that β_1 -adrenoceptor blockade is the necessary feature for blood pressure reduction (Hansson, 1982; Dahlöf *et al.*, 1983). If a compound is both β_1 -selective blocking and also has β_1 -partial agonist activity (Smith *et al.*, 1983) one may obtain a situation of insufficient β_1 -adrenoceptor blockade at least under resting conditions. During higher sympathetic drive (standing) systolic blood pressure was reduced in a dose-dependent way up to 200 mg of ICI 141,292 which supports that concept. ICI 118,587, a β -adrenoceptor blocking agent with ISA that is at least twice as powerful as that of ICI 141,292 does not reduce blood pressure at all in preliminary investigations (Nuttall & Snow, 1982). Against the concept of too much ISA speaks the fact that all clinically used β -adrenoceptor blockers with

ISA (alprenolol, oxprenolol and pindolol) and practolol reduce blood pressure in hypertension effectively (Prichard & Owens, 1980). One explanation to the fact that these β -adrenoceptor antagonists with ISA are effective is that their ISA probably is not β_1 -selective.

The blood pressure reduction 2 h after drug intake was consistently greater than 24 h after drug intake, particularly as regards the higher doses (200 and 300 mg) and especially in the standing position. This may indicate inadequate 24 h duration of ICI 141,292. On the other hand, most β -adrenoceptor blockers are effective in hypertension when given once daily (Wilcox, 1978).

The possibilities of too small doses and/or too short treatment periods also have to be accounted for.

In conclusion, ICI 141,292 is well tolerated and in this first clinical trial has been shown to have a significant but modest antihypertensive effect. If the results of the present study are confirmed in future trials it appears unlikely that ICI 141,292 will play an important therapeutic role in hypertension.

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