Is $\beta_1$-Antagonism Essential for the Antihypertensive Action of $\beta$-Blockers?

Hieronymus H. Vincent, Arie J. Man in't Veld, Frans Boomsma, Frans H. M. Derkx, and Maarten A. D. H. Schalekamp

SUMMARY Both nonselective $\beta$-blockers and $\beta_1$-selective blockers are effective antihypertensive agents. $\beta_1$-Blockade generally is considered to be responsible for their antihypertensive action, whereas $\beta_2$-blockade is regarded as undesirable. These common assumptions notwithstanding, the mechanism by which $\beta$-blockers lower blood pressure remains unknown. To examine the possibility that $\beta_2$-blockade may contribute to the antihypertensive action of $\beta$-blocker therapy, we studied the cardiovascular effects of compound ICI 118551, a $\beta_2$-selective blocker. First, we showed that 50 mg t.i.d. orally is a $\beta_2$-selective dose. In contrast to propranolol, 80 mg t.i.d., or atenolol, 100 mg once a day, 50 mg of ICI 118551 t.i.d. failed to block $\beta_2$-mediated inotropic stimulation and stimulation of renin by isoproterenol. We then performed a double-blind, placebo-controlled trial in patients with mild essential hypertension to compare this compound with propranolol, 80 mg t.i.d., and showed that ICI 118551 significantly decreased systolic and diastolic blood pressure. This antihypertensive effect was demonstrated by direct as well as by indirect blood pressure measurements. Thus, contrary to prevailing thought, $\beta_2$-blockade has an antihypertensive effect independent of, and distinct from, $\beta_1$-blockade. (Hypertension 9: 198-203, 1987)

KEY WORDS $\beta_1$-adrenergic receptors $\beta_2$-adrenergic receptors presynaptic $\beta$-adrenergic receptors $\beta$-adrenergic receptor antagonists hypertension isoproterenol norepinephrine renin

Nonselective $\beta$-blockers and $\beta_1$-selective blockers are both effective in lowering blood pressure. $\beta_2$-Adrenergic receptor blockade generally is thought to be essential for this effect, and $\beta_2$-blockade is often regarded as an undesirable property that increases the chance of unfavorable side effects. On the other hand, the mechanism by which $\beta$-blockers lower blood pressure is not known, and $\beta_1$-selective blockers also have their drawbacks. A $\beta$-blocker that is highly selective for $\beta_2$-adrenergic receptors, ICI 118551 (DL-erythro-3-isopropylamine-1-[7-methyl-4-indanyloxy]-2-butanol hydrochloride), is now available for clinical use. In the present study we found that this compound has an antihypertensive action in a dose that blocks the $\beta_2$-adrenergic receptor-mediated responses to isoproterenol but has no detectable effect on $\beta_1$-adrenergic receptor-mediated responses.

Patients and Methods

Nineteen men (mean age, 36 years; age range, 21-50 years) were studied. Their blood pressure in the outpatient clinic was 140 to 160 mm Hg systolic and 90 to 105 mm Hg diastolic. Routine clinical investigations revealed no cause for their hypertension. There were no signs of cardiac or renal disease. After the purpose and the procedures of the study had been explained, the patients gave their consent to participate. The study was approved by the hospital ethical review committee. Drug treatment, if any, was withdrawn 3 weeks before the study. Nine patients (mean age, 35 years) were enrolled in a double-blind, placebo-controlled crossover trial comparing the $\beta_2$-selective antagonist ICI 118551 with propranolol. Four of them had never been treated before. Patients were randomized to receive placebo, followed by ICI 118551, placebo, and propranolol or placebo, followed by propranolol, placebo, and ICI 118551. Each treatment period lasted 1 week. ICI 118551 (50 mg t.i.d.) was given as a syrup, and propranolol (80 mg t.i.d.) was given as tablets. Either placebo tablets or placebo syrup was added to active treatment, and both were given in the placebo periods.
The times at which the various measurements were made are shown in Figure 1. The patients rested in the supine position for 15 minutes, and then three blood pressure measurements were made with a blind sphygmomanometer (London School of Hygiene). Then a series of blood pressure measurements was made every 5 minutes for 1 hour using an automatic oscillometric device (Accutorr, Datascite, Paramus, NJ, USA). At the end of each week of placebo or active treatment, blood pressure was also measured intra-arterially. All blood pressure measurements were made 2 to 4 hours after the last dose of placebo or active drug. Blood samples were drawn from the arterial line, collected in chilled, heparinized tubes, and immediately centrifuged. Plasma was stored at −20°C before assay of active renin. Plasma was deproteinized by 10% (vol/vol) of 3 M trichloroacetic acid and stored at −20°C for a maximum of 2 weeks before assay of norepinephrine.

A continuous infusion of isoproterenol was given at the end of Week 1 on placebo and at the end of Weeks 2 and 4 on active drug. The dose of isoproterenol was increased every 15 minutes. Before infusion and at the end of each dose step, intra-arterial pressure, heart rate, and duration of electromechanical systole were measured and blood samples were drawn for determination of plasma renin, norepinephrine, and potassium concentrations.

The effects of the first 2 hours of active drug on blood pressure, heart rate, renin, and norepinephrine were assessed at the beginning of Weeks 2 and 4. The first dose of active drug was given 30 to 45 minutes after the isoproterenol infusion had been stopped. In 10 patients isoproterenol was infused while they were untreated, after 1 week of propranolol, 80 mg t.i.d., and after 1 week of atenolol, 100 mg once daily. These data are presented in order to compare the shifts of the isoproterenol dose-response curves caused by β₂-adrenergic receptor blockade with those caused by β₁-adrenergic receptor blockade.

Data are presented as means ± SEM. Student's paired t test was used for comparison. A p value of less than 0.05 was considered significant.

Results

Short-term Effects of ICI 118551 and Propranolol
Intra-arterial pressure after the first dose of either ICI 118551 or propranolol did not change in the 2 hours that it was measured (Table 1). In contrast, heart rate was lowered by the two drugs. Plasma renin was significantly lowered by propranolol but not by ICI 118551. Plasma norepinephrine rose after propranolol and was unchanged after ICI 118551 (Figure 2).

Effects of a 1-Week Treatment with ICI 118551 or Propranolol
After 1 week of treatment systolic and diastolic pressures, measured both directly and indirectly, were significantly reduced by ICI 118551 as well as by propranolol (Table 1, Figures 3 and 4). Heart rate and plasma renin were also reduced by both drugs after 1

| TABLE 1. Short-Term and Long-Term Effects of ICI 118551 and Propranolol |

<table>
<thead>
<tr>
<th></th>
<th>ICI 118551 (n = 9)</th>
<th>Propranolol (n = 9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before 2 hr 1 wk</td>
<td>Before 2 hr 1 wk</td>
</tr>
<tr>
<td>Intra-arterial blood pressure (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>157 ± 2</td>
<td>160 ± 5</td>
</tr>
<tr>
<td>Diastolic</td>
<td>86 ± 3</td>
<td>90 ± 2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68 ± 3</td>
<td>61 ± 3*</td>
</tr>
<tr>
<td>Norepinephrine (nmol/L)</td>
<td>1.78 ± 0.20</td>
<td>1.65 ± 0.20</td>
</tr>
<tr>
<td>Active renin (μU/ml)</td>
<td>21 ± 7</td>
<td>13 ± 4</td>
</tr>
</tbody>
</table>

Values are means ± SEM. Blood pressure, norepinephrine, and renin measured before and 2 hours after the first dose and after 1 week of treatment. Data after 1 week were compared with corresponding data after placebo.

*p < 0.05, †p < 0.01, compared with pretreatment values.
FIGURE 2. Change in norepinephrine levels after short-term administration and after 1 week of treatment with ICI 118551 or propranolol. Asterisk indicates significant difference (p < 0.05) compared with placebo values.

week of treatment. Plasma norepinephrine rose after propranolol but did not change after ICI 118551 (see Figure 2).

Isoproterenol Infusion Tests

As described in Methods, the effects of β₂-selective blockade on the responses to isoproterenol infusion were compared with the effects of β₁-selective blockade by studying two groups of patients. One group received ICI 118551 and propranolol, the other received atenolol and propranolol. In the first group intra-arterial pressure before isoproterenol infusion was 160 ± 4/87 ± 2 mm Hg without β-blocker treatment, 150 ± 3/80 ± 2 mm Hg after 1 week of ICI 118551, and 139 ± 6/72 ± 3 mm Hg after 1 week of propranolol. In the second group the pressure was 152 ± 4/77 ± 3 mm Hg without treatment, 130 ± 5/62 ± 2 mm Hg after 1 week of atenolol, and 130 ± 5/66 ± 2 mm Hg after 1 week of propranolol. Thus, the blood pressure values before isoproterenol infusion were comparable in the two groups.

ICI 118551 did not alter the inotropic effects of isoproterenol (i.e., shortening of electromechanical systole [QS₁ₑ₆] and rise in systolic pressure; Figure 5). Neither did it alter the effect of isoproterenol on plasma renin (Figure 6). In contrast, these responses were shifted by a dose factor of eight or more by both atenolol and propranolol. The heart rate response was shifted by a dose factor of about two after ICI 118551, by a factor of four after atenolol, and by a factor of 16 after propranolol. The effects of isoproterenol on diastolic pressure, plasma norepinephrine, and plasma potassium were abolished by ICI 118551 and propranolol. After atenolol treatment these effects were shifted by a dose factor of two.

Discussion

β₂-Selectivity of ICI 118551

ICI 118551 is a highly selective and specific β₂-adrenergic receptor antagonist in vitro. The present study shows that ICI 118551, given in a dosage of 50 mg t.i.d., is also β₂-selective in vivo. The drug antagonized the effects of isoproterenol on diastolic pressure, plasma norepinephrine, and plasma potassium, which are β₂-adrenergic responses. ICI 118551 did not antagonize the rise in systolic pressure or the shortening of electromechanical systole (QS₁ₑ₆) caused by isoproterenol, which are inotropic responses mediated by β₁-adrenergic receptors. Neither did it antagonize the effect of isoproterenol on plasma renin. This effect of isoproterenol also is regarded as a β₁-adrenergic response. The chronotropic effect of isoproterenol, which is a mixed β₁/β₂-adrenergic response, was antagonized by a factor of only two by ICI 118551, as compared with a factor of 16 by propranolol. When the shifts of the β₁-adrenergic responses (systolic pressure, QS₁ₑ₆, renin) and of the β₂-adrenergic responses (diastolic pressure, norepinephrine, potassium) caused by ICI 118551 were compared with the shifts caused by atenolol, the β₂-selectivity of ICI 118551 was even greater than the β₁-selectivity of atenolol, at least in the doses we have used.

Antihypertensive Effect of ICI 118551

The main finding of this study is that ICI 118551, in a β₂-selective dose, lowered blood pressure. This observation is at variance with earlier reports by Robb et al. and by Dahlof et al. who could not demonstrate
**FIGURE 4.** Average blood pressure before treatment (run in; A), after placebo (B), after placebo (wash out; C), after ICI 118551 (D), after propranolol (E). Single (p<0.05) and double (p<0.01) asterisks indicate significant difference compared with placebo.

**FIGURE 5.** Isoproterenol dose-response curves before treatment (○) and after treatment with ICI 118551 (▲), atenolol (◇), or propranolol (□).

**FIGURE 6.** Isoproterenol dose-response curves before treatment (○) and after treatment with ICI 118551 (▲), atenolol (◇), or propranolol (□).
an antihypertensive effect of ICI 118551. The mean age of the patients (48 and 46 years, respectively) in those two studies was higher than that in our study (35 years). Moreover, the patients in the two negative studies had all been treated previously, whereas four of our patients had never been treated before. This difference suggests that their patients had hypertension of longer duration. It could be that β2-blockade is more effective in an earlier stage of the disease. It may also be important that Dahlof et al.15 did not use placebo controls after the run-in phase. This omission might obscure the antihypertensive effect of ICI 118551 by a gradual return of hypertension, not only during the run-in phase but also during ICI 118551 treatment.

Mechanism of Action of ICI 118551

The mechanism by which β-blockers lower blood pressure remains a matter of debate.16-19 Cardiac, vascular, or hormonal changes and effects on body fluid volumes have been suggested to play a role.20,21 β-Blockers with different ancillary properties, such as partial agonist activity, β1-adrenergic receptor selectivity, or hydrophilicity, all lower blood pressure. β1-Adrenergic receptor blockade generally is considered the common denominator of this effect. The current study, however, shows that selective blockade of β2-adrenergic receptors also lowers blood pressure. Firm conclusions on the anatomical site of this β2-adrenergic receptor, centrally, presynaptically, or postsynaptically in the heart, kidneys, or blood vessels, cannot be drawn from our data.

Currently, there is little evidence that β2-adrenergic receptors in the central nervous system are involved in blood pressure regulation. We have no information on changes in cardiac output, vascular resistance, or body fluid volumes after ICI 118551 treatment. The drug did lower the basal levels of plasma renin, which might contribute to its antihypertensive effect. Plasma norepinephrine was higher with propranolol treatment but did not change with ICI 118551 treatment. This difference might be explained by different effects of the two drugs on the clearance of plasma norepinephrine. Heart rate (and therefore probably cardiac output) fell more during propranolol than during ICI 118551 treatment. Indeed, changes in plasma norepinephrine level during β-blockade seem to reflect changes in the clearance of this neurotransmitter rather than changes in its release.17,22-24

One of the theories explaining the antihypertensive effect of β-blockers implicates a role for presynaptic β2-adrenergic receptors, which serve to facilitate norepinephrine release from sympathetic nerves. Activation of these receptors by epinephrine might cause hypertension.25,26 Blockade of these receptors would decrease norepinephrine release and thereby lead to diminished activation of cardiac β2-adrenergic receptors and vascular α-adrenergic receptors. This mechanism might account for the antihypertensive effect of β2-blockade, although it does not provide an explanation for the antihypertensive action of β1-blockade. The rise in renin in response to isoproteoneron was not antagonized by ICI 118551, which confirms its β2-selectivity. Yet the drug lowered the basal level of renin. Again, this response may be explained by presynaptic inhibition of norepinephrine release, leading to diminished activation of postsynaptic β2-adrenergic receptors in the kidney.

Whatever the precise mechanism of the fall in blood pressure after β2-blockade, our data demonstrate that β2-blockade is no always essential for the antihypertensive effect of β-blocker therapy.

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