Summary

1. Acebutolol, a \( \beta_1 \)-receptor blocker, has, at a daily dose of 800 mg, a mild but significant anti-hypertensive effect in moderate sustained essential hypertension with normal or low plasma renin activity.

2. Prediction of its anti-hypertensive effect is better based on the evaluation of the sympathetic nervous system responsiveness to head-up tilt than on the evaluation of plasma renin activity or dopamine-\( \beta \)-hydroxylase.

3. The anti-hypertensive effect of acebutolol is better explained on the basis of inhibition of the sympathetic nervous system activity than on the basis of suppression of plasma renin activity.

4. A positive correlation between plasma renin activity and dopamine-\( \beta \)-hydroxylase in patients on diuretics suggests the common dependence of these two variables on sympathetic overactivity.

Key words: acebutolol, dopamine-\( \beta \)-hydroxylase, hypertension, plasma renin activity, urinary catecholamine response to tilt.

Introduction

The reduction in arterial pressure produced by \( \beta \)-receptor blockers has no consistent relationship to alteration in PRA. This has been demonstrated not only with practolol, a selective blocker (Esler & Nestel, 1973a), but also with propranolol, especially when this latter agent is combined with diuretics (Bravo, Tarazi, Dustan & Lewis, 1974). Furthermore, renin suppression by \( \beta \)-receptor blockers occurs immediately and with low doses whereas blood pressure reduction occurs only after some delay and sometimes only with high doses of the drug (Shand & Hollifield, 1975). Therefore, a dual mechanism for the anti-hypertensive action of \( \beta \)-receptor blockers has been suggested (Buhler, Burkart, Lutold, Kung, Marbet & Pfisterer, 1975): acute blockade of renin-angiotensin-mediated vasoconstriction, augmented by a delayed central nervous system effect.

To test this hypothesis, we examined the relationship between the anti-hypertensive effect of acebutolol, a new \( \beta_1 \)-receptor selective blocker, not only with PRA, but also with two indices of sympathetic nervous system activity. We have therefore studied the response before and after acebutolol of urinary catecholamine excretion to 25° head-up tilt and the activity of plasma dopamine-\( \beta \)-hydroxylase, an enzyme which has been used as an index of sympathetic tone (Geffen, Rush, Louis & Doyle, 1973; Alexandre, London, Chevillard, Lemaire, Safar & Weiss, 1975).

Methods

Patients

Eighteen patients (nine men, nine women; mean age 47 \( \pm 14 \) years) were studied. Before treatment with acebutolol, all had a diastolic blood pressure \( \geq 90 \) mmHg on three occasions, in spite of diuretic therapy in seven. The diagnosis of essential hypertension was reasonably established by routine screening tests. Hypertension was well tolerated and renal insufficiency (serum creatinine between 2 and 4 mg/100 ml) was present in only three cases.
Drug trial design

The anti-hypertensive effect of acebutolol was evaluated in a single blind cross-over trial in which a placebo was first given for 4 weeks, and then a fixed dose of acebutolol (200 mg, four times a day) for 6 weeks, and then again a placebo for 4 weeks. The patients were seen every 2 weeks and their blood pressure was measured after 5 min in the lying position and after 1 min standing; pulse rate and body weight were also measured. During the study, the patients were on a mildly restricted salt diet (120 ± 30 mmol/24 h) and the diuretic therapy previously given in seven patients was continued unchanged.

Laboratory investigations

The 25° head-up tilt procedure was performed according to the protocol of Esler & Nestel (1973b). This procedure was performed in all patients during the first placebo period and repeated only in eight while they were receiving acebutolol for 4-6 weeks.

At the last visit in each of the three periods, the patients brought a 24 h urine sample for creatinine and sodium determination and had a blood sample taken for determination of electrolytes, glucose, creatinine, PRA and DBH activity.

Analytical methods

Total urinary catecholamine were measured after hydrolysis at pH 1 according to the method of Ehrilen (1949). Creatinine was measured by the method of Bosnes & Tauskky (1945). PRA was measured by radioimmunoassay of angiotensin I, according to the method of Menard, Corvol, Allegrini & Breminer (1972). Normal values after ambulation for 1 h on a sodium diet (120 mmol/day) range from 0·7 to 3·0 ng h⁻¹ ml⁻¹. DBH was measured by the spectrophotometric method of Nagatsu & Udenfriend (1972). The mean value ± SEM in a normotensive group is 41·2 ± 3 (Alexandre et al., 1975).

Results

The clinical and biological effects of acebutolol are summarized in Table 1.

Correlation between the anti-hypertensive effect and other variables

The anti-hypertensive effect was taken as the difference in mean arterial pressure between week 6 on acebutolol and week 4 on placebo. There was no correlation with initial heart rate or with heart-rate decrease.

<table>
<thead>
<tr>
<th>Table 1. Effect of acebutolol on the mean arterial pressure (MAP), heart rate and other variables</th>
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<tbody>
<tr>
<td>Mean values ± SEM are shown. * P&lt;0·05; ** P&lt;0·01, for the comparison of acebutolol versus placebo values with the Wilcoxon test. MAP = mean arterial pressure.</td>
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<td>Lying MAP (mmHg)</td>
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<td>Standing MAP (mmHg)</td>
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<td>Heart rate (min⁻¹)</td>
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<td>Urinary sodium (mmol/l)</td>
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<td>Serum creatinine (mg/100 ml)</td>
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<td>Plasma potassium (mmol/l)</td>
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<td>Ambulatory PRA (ng h⁻¹ ml⁻¹)</td>
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<td>Ambulatory DBH (i.u.)</td>
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<td>Δ Urinary catecholamines to tilt (%)</td>
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<td>ΔPRA to tilt (ng h⁻¹ ml⁻¹)</td>
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<td>ΔDBH to tilt (i.u.)</td>
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</table>

(11) Ambulatory PRA was normal in five and low in six patients without diuretics and increased only in three out of the seven patients with diuretic.
No correlation was found between initial values of PRA and change in blood pressure either when the whole group was considered or when the two sub-groups were individualized according to the presence or absence of diuretic therapy. However, when the patients were classified into two groups according to the initial PRA values, it appears that decrease in mean arterial pressure was greater ($P < 0.10$) in the normal PRA group ($-22 \pm 14$ mmHg) than in the low PRA group ($-3 \pm 5$ mmHg).

Anti-hypertensive effect and renin suppression were not correlated ($r = 0.15$) when the whole group is considered. However, the correlation almost reached the level of significance ($P = 0.10$) when only the patients not receiving diuretics were considered ($r = 0.52; n = 10$).

No correlation was found between change in mean arterial pressure and initial values of ambulatory DBH activity. However, a borderline significant positive correlation ($P < 0.10, r = 0.33, n = 26$), by pooling changes between acebutolol and the two placebo periods, was found with changes in mean arterial pressure and DBH activity.

A highly significant ($P < 0.01$) negative correlation ($r = -0.65$) was found between change in mean arterial pressure and the response of catecholamine excretion to tilting during the first placebo period. The correlation between the changes in these two indices induced by acebutolol was, however, not significant ($r = 0.11$), mainly because of one patient.

**Correlation between PRA and sympathetic activity**

No correlation was found between change in urinary excretion of catecholamines and the changes of PRA and DBH activity by head-up tilting.

Absolute values of DBH and PRA were positively correlated in the patients receiving a diuretic ($r = 0.71; P < 0.01$), but not in the patients not receiving a diuretic. No correlation was found between the changes of PRA and the changes of DBH in either of the two groups.

**Discussion**

Acebutolol, a $\beta_1$-receptor selective blocker has, at a daily dose of 800 mg, a mild but significant anti-hypertensive effect in moderate sustained essential hypertension with normal or low PRA. This anti-hypertensive effect was associated with no obvious changes in the sodium balance since body weight and urinary sodium did not change. No clinical or biological side effect was observed. The slight increase in plasma potassium may be advantageous in patients on diuretics. Evaluation of the sympathetic nervous system responsiveness to head-up tilt was a better predictor of the anti-hypertensive effect of the drug than measurement of heart rate or evaluation of PRA or DBH before therapy.

Since there was no correlation between changes in heart rate and changes in blood pressure, it is suggested that the anti-hypertensive effect of acebutolol cannot be directly explained by the reduction of cardiac output, a mechanism already discarded for other $\beta$-receptor blockers (Esler & Nestel, 1973a). The role of PRA suppression in the anti-hypertensive effect of acebutolol is not obvious in our study but cannot be excluded, since there was a borderline significant correlation between change in mean arterial pressure and PRA in patients without diuretic.

However, our result favour another mechanism: the inhibition of sympathetic nervous activity. This hypothesis is based on two sets of facts: (1) acebutolol significantly decreases activity of DBH and there is a borderline significant correlation between change in mean arterial pressure and $\Delta$DBH; (2) acebutolol decreases the sympathetic nervous system response to head-up tilt and the anti-hypertensive effect is more pronounced in subjects in whom this response was greater before use of the drug.

Such a mechanism has already been proposed for practolol by Esler & Nestel (1973a), on similar evidence. This implies an action on the central nervous system which is quite compatible with the work of Daskalopoulos & Schmitt (1976) showing decreased activity of the splanchnic nerve after systemic or cerebroventricular injection of acebutolol.

Esler & Nestel (1973b) have suggested that PRA is a marker of sympathetic tone, since they found a correlation between APRA and change in excretion of catecholamines during head-up tilt in sustained hypertension, as well as a correlation between PRA and the anti-hypertensive effect of phentolamine in labile hypertension. Our results are not comparable with theirs, since we found no correlation between change in urinary catecholamines and APRA by tilting. This can be explained by the nature of our population which was composed mainly of subjects showing no response of diastolic pressure and PRA to tilt. However, in patients on diuretics we found a positive correlation between DBH and PRA. This
suggests that these two activities are dependent on a common causal factor, the sympathetic overactivity induced by sodium depletion.

Acknowledgments

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References


