Plasma renin concentration and the hypotensive effect of bendrofluazide and of atenolol

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Summary

1. The anti-hypertensive effect of atenolol was greater than that of bendrofluazide.

2. The change in systolic blood pressure caused by bendrofluazide showed a significant inverse correlation with the plasma renin concentration ($r = -0.47; P < 0.01$).

3. The correlation between the change in systolic blood pressure caused by atenolol and the plasma renin concentration was not significant ($r = 0.28; 0.1 > P > 0.05$).

4. Plasma renin concentration was unaffected by atenolol.

Key words: atenolol, bendrofluazide, hypertension, plasma renin concentration, $\beta$-receptor blockade.

Introduction

The hypotensive effect of diuretics has been shown to be more pronounced in patients with low plasma renin values (Crane & Harris, 1970; Spark & Melby, 1971; Adlin, Marks & Channick, 1972; Carey, Douglas, Schweikert & Liddle, 1972; Vaughan, Laragh, Gavras, Bühler, Gavras, Brunner & Baer, 1973). On the other hand, the $\beta$-receptor blocker propranolol is most effective in lowering blood pressure in patients with high plasma renin (Bühler, Laragh, Baer, Vaughan & Brunner, 1972; Bühler, Laragh, Vaughan, Brunner, Gavras & Baer, 1973). The present paper reports on a double-blind crossover trial involving treatment periods with placebo, the thiazide bendrofluazide and the $\beta$-receptor-blocker atenolol. Atenolol (Tenormin, ICI 66082) is a cardioselective $\beta$-adrenoreceptor-blocking agent with no intrinsic sympathomimetic or membrane-stabilizing effects. Plasma renin measurements were made in forty-one of the fifty-five patients who entered the study. This paper reports on these forty-one subjects.

Methods

Thirty patients with essential hypertension, six with renovascular hypertension and five patients with nephritis were studied as out-patients for six consecutive periods of 3 weeks' duration. In each period they took six tablets daily, identical in taste, shape and colour. After the first two periods on placebo, when their diastolic blood pressure exceeded 90 mmHg, they received either atenolol (200 mg three times daily) or bendrofluazide (5 mg three times daily) for 3 weeks. At the end of each 3 weeks period blood pressure was measured in the recumbent and in the standing position, at the afternoon out-patient clinic. Blood samples for the determination of plasma renin concentration, by the method of Skinner (1967), were taken in the sitting position. A 24 h urine sample was analysed for creatinine and sodium.

Results

The recumbent control blood pressure averaged $189.9 \pm 3.3$ (SEM) and $117.5 \pm 1.9$ mmHg and dropped to $166.0 \pm 4.1/101.3 \pm 2.2$ ($P < 0.001$) on the $\beta$-receptor blocker and to $172.8 \pm 3.7/111.4 \pm 2.0$ mmHg on the thiazide ($P < 0.001$). The fall in pressure was significantly greater with the $\beta$-receptor blocker than with the diuretic ($P < 0.05$). During thiazide administration body weight decreased from $68.4 \pm 1.6$ to $66.8 \pm 1.6$ kg ($P < 0.001$). The change in body weight did not correlate with the fall in blood pressure...
(r = 0.05; P < 0.1), nor with the initial plasma renin concentration (r = 0.07; P > 0.1). During treatment with the β-receptor blocker a small increase of 0.4 ± 0.6 kg (P < 0.01) was observed. Heart rate fell from 84 ± 2 to 61 ± 1 beats/min (P < 0.001) with the β-receptor-blocking agent and did not change with the thiazide.

Urinary sodium excretion of the patients ranged from 85 to 304 mmol/l when they were on placebo. Eighty-two determinations of the afternoon plasma renin concentration in sixty-five normal volunteer subjects, with urine sodium excretions ranging from 5 to 330 mmol 24 h⁻¹ l⁻¹, showed no correlation between plasma renin and urine sodium excretions when the latter was greater than 85 mmol 24 h⁻¹ l⁻¹ (r = 0.07; P > 0.1); only at lower urine sodium excretions did plasma renin increase (unpublished data). This observation justifies the analysis of the plasma renin results without correcting the plasma renin value for the sodium intake: the relation between plasma renin and the hypotensive effect of the drugs was analysed by using correlation calculations. Fig. 1(a) shows the inverse correlation between the changes in systolic blood pressure caused by bendrofluazide and the initial plasma renin (r = -0.47; P < 0.01). The lower-renin patients respond better than the higher-renin patients. Fig. 1(b) shows that the correlation between plasma renin and the fall in blood pressure on atenolol did not reach an acceptable level of significance (r = 0.28; 0.1 > P > 0.05). For the thirty patients with essential hypertension, however, the correlation was significant (r = 0.39; P < 0.05).

Plasma renin concentration was not reduced after 3 weeks' administration of atenolol (15.6 ± 1.4 vs control value 14.3 ± 1.1 units/ml; P > 0.1) and increased 2.3-fold with the thiazide (P < 0.001).

Discussion

The present study confirms earlier findings that hypertensive patients with low plasma renin values have a greater blood pressure response to diuretic therapy (Crane & Harris, 1970; Spark & Melby, 1971; Adlin et al., 1972; Carey et al., 1972; Vaughan et al., 1973). In addition we found a significant correlation between the initial plasma renin concentration and the hypotensive effects of bendrofluazide (Fig. 1a). However, the correlation between the changes in pressure and the initial plasma renin
Bendrofluazide, atenolol and plasma renin was not a close one, suggesting that the predictive power of the renin determinations is small.

Bühler et al. (1972, 1973) reported that high-renin patients responded well to the non-cardio-selective β-receptor-blocker propranolol, and the blood pressure response of low-renin patients to this drug was minimal. Moreover the decrease in blood pressure was related to changes in plasma renin activity. In the present study we used atenolol, a more cardio-selective β-receptor blocker with a more prominent effect on the β1-receptors. Because the renin release in the kidneys is probably mediated through β2-adrenoreceptors it can be expected that the effects of atenolol on renal renin release are minimal. We observed no change in plasma renin when the drug was administered for 3 weeks and in the cat atenolol was found to be about one-fifth as effective as propranolol in inhibiting the release of renin from the kidney resulting from renal nerve stimulation (Johns & Singer, 1974). Although atenolol did not affect plasma renin it lowered the recumbent blood pressure from 190/117 to 166/101 mmHg.

The initial plasma renin had some value in predicting the blood pressure response to the drug. The correlation between the initial plasma renin and the hypotensive effect of atenolol did, however, not reach an acceptable level of significance (Fig. 1b), except when patients with renal hypertension were excluded. The data suggest that one has to distinguish between the predictive value of plasma renin for the hypotensive response to the β-receptor blocker and the role of changes in plasma renin in the hypotensive response. However, the low correlation coefficient \( r = 0.28 \) between the initial plasma renin and the hypotensive response to atenolol indicates that the usefulness of basing the therapeutic regimen for individual patients only on plasma renin determinations remains questionable.

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References

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