THE ADDITION OF PRAZOSIN TO STANDARD TRIPLE THERAPY IN THE TREATMENT OF SEVERE HYPERTENSION

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- 1 A small dose of prazosin was added to the treatment regime of sixteen hypertensive patients poorly controlled on a combination of bendrofluazide, hydralazine and propranolol.
- 2 There was a significant improvement in blood pressure control in all patients at 1 month ($P < 0.01$) and this was maintained at 9 months ($P < 0.02$). Tolerance to prazosin was not a problem.
- 3 The addition of prazosin to conventional triple drug therapy produces a further useful fall in blood pressure.

Introduction

The treatment of hypertension often requires the use of multiple drug therapy. A widely advocated step-care approach employs a progressive combination of thiazide diuretic, β -adrenoceptor blocker and a vasodilator such as hydralazine (Moser *et al.*, 1977). However, in some patients blood pressure is not controlled even using maximal safe doses of these agents. Alternative therapy such as minoxidil, diazoxide or captopril is associated with a relatively high incidence of toxic side-effects (Pettinger, 1980; Atkinson & Robertson, 1979). Clearly if a patient has severe target organ damage as a result of uncontrolled hypertension, such risks are outweighed by the need to control the blood pressure promptly. However, there are a number of asymptomatic hypertensive patients whose blood pressure is inadequately controlled on the above regime, and who consequently have a poorer prognosis (Taguchi & Freis, 1975).

Prazosin, an α_1 -adrenoceptor blocking agent, acts on the peripheral vasculature at a different site from hydralazine. Apart from an excessive 'first dose' hypotensive effect (Graham *et al.*, 1976) it is well tolerated and has few side-effects. Accordingly, we have studied prospectively, patients in whom maximal doses of thiazide diuretic, β -adrenoceptor blocker and hydralazine were already being employed with poor blood pressure control.

Methods

Sixteen hypertensive patients (13 male), aged 40–65 (mean 55) years, were studied. Previous investigations had established that thirteen had essential

hypertension with normal renal function, and three had hypertension associated with mild diabetes of whom two had chronic renal failure (serum creatinine values of 860 and 215 $\mu\text{mol/l}$). All patients were receiving optimum daily doses of thiazide diuretic (bendrofluazide 5 mg), β -adrenoceptor blocker (propranolol 320 mg) and hydralazine (200 mg), but remained poorly controlled, with lying and standing diastolic blood pressures in excess of 100 mmHg, measured at weekly intervals for 3 weeks.

Before entering the study, an electrocardiogram (ECG) and chest X-ray were performed, a blood sample was taken for urea, electrolytes (U and E) and creatinine, and a mid-stream specimen of urine (MSU) was collected. Patients were given prazosin orally 1–3 mg daily in divided doses. The first tablet was given at night to avoid the first dose postural drop, and the drug continued daily afterwards. Blood pressure (BP) was measured in both lying and standing positions with a standard mercury sphygmomanometer, using Korotkov sounds I and V at 0, 1, 3, 6 and 9 months. The dose of prazosin was increased until blood pressure control was obtained (standing diastolic BP ≤ 95 mm Hg). The chest X-ray, ECG, blood and urine tests were repeated after at least 3 months on this quadruple therapy.

All values are quoted as mean $\pm$ s.e. mean, and statistical analysis was performed using paired Student's *t*-test.

Results

Mean blood pressure before starting prazosin was $197 \pm 11.0/108 \pm 4.8$ mm Hg lying and $191 \pm 9.4/114 \pm$

Figure 1 Effect on blood pressure (lying, open columns; standing, hatched columns) before and during the addition of prazosin to triple therapy comprising diuretic, β -adrenoceptor blocker and hydralazine. All blood pressures on prazosin are significantly lower than on triple therapy alone ($P < 0.02$).

3.0 mm Hg standing. There was a significant reduction in both systolic and diastolic blood pressures in the lying and standing positions in all 16 patients studied at 1 month (Figure 1, $P < 0.01$). This fall was maintained in the 11 patients who have been followed to 9 months (Figure 1, $P < 0.02$). This was achieved with a low dose of prazosin (median dose at 1 month was 1.5 mg daily, range 1–3 mg, and at 9 months was 3 mg, range 1.5–18 mg). Only one patient required a daily dose in excess of 8 mg, and in the others, the dose remained constant after blood pressure control was obtained. No patient experienced any side effects attributable to prazosin.

There was no change in chest X-ray appearance or renal function during treatment with prazosin. The two patients with impaired renal function showed no deterioration, their serum creatinine levels being 756 and 230 $\mu\text{mol/l}$ on quadruple therapy. Ten patients had normal ECG findings before starting prazosin and showed no change: six patients showed left ventricular hypertrophy on voltage criteria before prazosin and this improved in five.

One patient complained of arthralgia after 9 months and developed a positive serum antinuclear factor. Hydralazine sensitivity was diagnosed, the drug was withdrawn, and the symptoms resolved. She was the only patient to be withdrawn from the study.

Discussion

These results clearly demonstrate that when prazosin is given to patients already on optimal doses of a thiazide diuretic, β -adrenoceptor blocker and hydralazine, a further useful fall in blood pressure can be achieved. All subjects in the study were adequately controlled on this quadruple therapy, the majority requiring only a low dose of prazosin which was well tolerated. There was no deterioration in either cardiac or renal function, and indeed the ECG improved in five cases.

The reason for the further decrease in blood pressure with prazosin is not known, but three possibilities exist. First, the maximum daily dose of hydralazine (200 mg) used is not the highest at which a full effect on blood pressure could be expected, but higher doses particularly in slow acetylators increase the incidence of toxic side effects (Anon, 1977; Bing *et al.*, 1980). Secondly, prazosin lowers blood pressure by peripheral α_1 -adrenoceptor blockade and unlike hydralazine has an effect upon capacitance vessels as well as resistance vessels (Awan *et al.*, 1978a). Third, although the β -adrenergic receptor effects of reflex sympathetic stimulation induced by hydralazine are controlled by β -adrenoceptor blockade, the α -adrenergic receptor effects are not.

A further possible clinical problem is pharmacological tolerance to the regime. Studies have demonstrated that the effects of prazosin in the treatment of heart failure diminish with time (Packer *et al.*, 1979; Awan *et al.*, 1978b). However, this has not been the case with prazosin in hypertension and we did not encounter it in our study, although one patient did require an increase in dosage to 18 mg daily at 9 months to maintain blood pressure control.

Many observers have demonstrated that prazosin is an effective anti-hypertensive agent when given alone or in combination with a diuretic and β -adrenoceptor blockade (Marshall *et al.*, 1977). In cross-over studies it appears to be as effective as hydralazine in combination therapy (Hua *et al.*, 1977). Consequently

one must question whether good blood pressure control could have been obtained merely by substituting prazosin completely for hydralazine. This is unlikely as prazosin is the weaker agent. Certainly the one patient who had hydralazine withdrawn because of sensitivity, developed uncontrolled hypertension, despite increasing prazosin to the maximum recommended level (24 mg/day).

For patients with blood pressure which is difficult to control on conventional triple therapy, we feel that before resorting to the more potent and toxic anti-hypertensive agents, a small dose of prazosin may be a useful adjunct to treatment improving control with the minimum of side effects.

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