Plasma renin in long-term diuretic treatment of hypertension: effect of discontinuation and restarting therapy

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Summary

1. Plasma renin activity, body weight and blood pressure were measured before and after 7 days' treatment with bendrofluazide in ten hypertensive subjects. They were then treated with bendrofluazide alone (5 mg daily) for a minimum of 3 years. The diuretic was then discontinued and the measurements were repeated before and again after 7 days with bendrofluazide. The results were compared with those obtained before chronic treatment with the diuretic.

2. Chronic diuretic treatment was associated with a persistent and progressive rise in plasma renin activity, that fell promptly to pretreatment levels when diuretics were discontinued. This was associated with significant weight gain but no immediate significant rise in blood pressure.

3. When acutely challenged with bendrofluazide the patients showed a greater increase in plasma renin activity on the second occasion than on the first. Three out of five patients with an initially subnormal response had normal responses after chronic diuretic treatment.

4. Chronic diuretic treatment increased the responsiveness of the juxtaglomerular apparatus in some hypertensive patients.

5. Classification of hypertensive patients into renin subgroups may be influenced by previous therapy, even when that therapy has been discontinued for 4 weeks. In particular 'low renin hypertension' may be masked by recent use of diuretics, as shown by three of the five patients in this subgroup in the present study.

Key words: diuretics, extracellular fluid, hypertension, juxtaglomerular apparatus, plasma renin activity.

Introduction

There are differences in the short- and long-term effects of thiazide diuretics in the treatment of hypertension. Initially plasma volume is reduced [1-3] and cardiac output falls with a rise in peripheral resistance [1, 4]. The renin-angiotensin system is stimulated and plasma renin rises [5, 6]. In the long term cardiac output returns to normal and peripheral resistance falls [4, 7, 8]. Early studies suggested that the initial negative fluid balance was corrected [8-10] and plasma renin returned to pretreatment levels [5]. However, the majority of studies now show that fluid and sodium depletion persist [3, 8, 11-13] and plasma renin remains raised [8, 14, 15].

We have reported a progressive rise in plasma renin activity over a 2 year period in hypertensive patients treated with thiazide diuretics alone, in the absence of a consistent change in sodium intake [16]. This might be due to a progressive increase in the stimulus to renin secretion or enhanced responsiveness of the juxtaglomerular apparatus in response to prolonged stimulation. To study this further we have compared the initial response to thiazide diuretics with the response obtained 4 weeks after stopping prolonged diuretic treatment, in order to determine whether there has been a sustained change in the control of renin secretion.

Methods

Ten patients with mild essential hypertension were studied: six men, four women; mean age
was 52 ± 3.6 SEM years. Nine had not previously been treated when first seen; one patient had received a short course of methyldopa (250 mg twice daily) that had been discontinued 2 weeks before referral. No patient had cardiac or renal failure (serum creatinine 91 ± 9 μmol/l) or other systemic disease. Plasma renin activity was measured in all hypertensive patients untreated and after 7 days' treatment with bendrofluazide (5 mg daily) to assess renin status (see below). In the ten patients studied bendrofluazide alone was sufficient to control blood pressure and had been continued for a minimum of 3 years (mean 49, range 39–69 months) before the present study was undertaken. These patients had not received any other drug on a regular basis during this time. Informed consent was obtained and the study had been approved by the ethical committee of the Leicestershire Area Health Authority.

The study consisted of two parts.

(1) Withdrawal of long-term diuretic therapy.

Plasma renin activity (PRA), body weight and blood pressure, lying and standing (Bosomat automatic blood pressure recorder) were measured and bendrofluazide was then discontinued. These measurements were repeated at 4, 7, 14, 21 and 28 days after the diuretic was stopped.

(2) Rechallenge with diuretic. When the above measurements had been made bendrofluazide (5 mg daily) was restarted and PRA, body weight and blood were measured 7 days later. Thus both the initial responses to 7 days' bendrofluazide treatment and responses after a period of continuous diuretic therapy could be compared in these patients.

Blood for PRA was taken from ambulant patients whose sodium intake was unrestricted. Samples were collected in precooled tubes containing EDTA, and plasma was separated and stored at −20°C until assayed. PRA was measured by radioimmunoassay of generated angiotensin I (ANG I). Patients were designated as high (basal PRA > 3.4 pmol of ANG I h⁻¹ ml⁻¹, upper limit for normal subjects), low (stimulated PRA < 3.1, lower limit for normal subjects) or normal (basal PRA < 3.4, stimulated PRA > 3.1) renin hypertension according to the measurements made when first seen, as previously published from this laboratory [17, 18].

Statistical analysis was by paired Student's t-tests. PRA values were converted into square root values before analysis as PRA is not normally distributed [18].

Results

Blood pressure rose slightly during the 4 weeks off diuretic therapy, but this was not significant (147 ± 4/97 ± 3 lying, 144 ± 5/97 ± 4 mmHg standing to 151 ± 4/102 ± 4 and 151 ± 3/102 ± 2 mmHg at 4 weeks respectively, mean ± SEM, P > 0·1). Reintroduction of therapy produced no change in blood pressure (151 ± 3/92 ± 3 lying and 153 ± 4/100 ± 3 mmHg standing), whereas when diuretics were first given blood pressure had fallen significantly (166 ± 8/94 ± 2 and 167 ± 6/100 ± 2 to 152 ± 4/86 ± 2 and 143 ± 5/89 ± 2 mmHg respectively, P < 0·05). Changes in mean blood pressure (diastolic + pulse pressure) are shown in Fig. 1.

PRA fell promptly on discontinuing diuretics and had returned to pretreatment levels by 4 days (Fig. 1). At the same time body weight increased significantly by a mean of 3 kg (P < 0·01). During the remainder of the time off treatment there was no further significant change in either PRA or body weight.

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**Fig. 1.** Changes in plasma renin (pmol of ANG I h⁻¹ ml⁻¹), body weight (kg) and mean blood pressure (mmHg) during initial treatment with bendrofluazide (BF, 5 mg daily), after withdrawal of diuretics after a minimum of 3 years' therapy and on rechallenging with diuretics. Results are expressed as means ± SEM for the ten patients studied.
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FIG. 2. Plasma renin activity responses (a) at presentation and (b) when rechallenged after a minimum of 3 years' treatment with bendrofluazide (5 mg daily) in patients initially designated as having 'low renin hypertension'. Lower limit of responses in normal subjects similarly treated is 3.1 pmol of ANG I h⁻¹ ml⁻¹ (---).

Seven days after starting bendrofluazide PRA had risen significantly \((P < 0.01)\) both initially and when patients were rechallenged after a period of prolonged diuretic treatment (Fig. 1). However, the rise in PRA was greater on the second occasion \((5.2 \pm 2.1 \text{ pmol of ANG I h}^{-1} \text{ ml}^{-1})\) compared with the original challenge \((2.8 \pm 0.6)\), although the baseline values were not significantly different \((1.9 \pm 0.5 \text{ at presentation, } 1.8 \pm 0.4 \text{ pmol of ANG I h}^{-1} \text{ ml}^{-1} \text{ on the second occasion, } P > 0.7)\). This difference in the PRA response, however, was not significant for the group as a whole \((0.3 > P > 0.2)\). At presentation five patients met our criteria for 'low renin hypertension', two had 'normal' and three 'high renin hypertension'. On rechallenging with bendrofluazide the PRA response of four patients with 'low renin hypertension' had increased and the response of the other patient was unchanged, so that only two still had subnormal responses after prolonged diuretic treatment (Fig. 2). In this group of patients the PRA response on presentation and on rechallenging were significantly different \((+1.3 \pm 0.5 \text{ and } +2.7 \pm 1.1 \text{ pmol of ANG I h}^{-1} \text{ ml}^{-1} \text{ respectively, } P < 0.02)\). The other five patients with 'normal or high renin hypertension' showed a more variable change in PRA responses: in three it was greater and in two reduced on the second occasion (at presentation +4.4 \pm 0.5, on rechallenge +7.7 \pm 4.0 \text{ pmol of ANG I h}^{-1} \text{ ml}^{-1}, 0.4 > P > 0.3). None, however, had developed a subnormal response when rechallenged.

Neither the initial nor the final fall in body weight when diuretics were started was significant \((P > 0.05)\).

Discussion

This study confirms our previous observation that PRA remains elevated in hypertensive patients on chronic diuretic therapy [16]. However, in the present study the average follow-up (47 months) was nearly twice that of the original. These results are in agreement with several recent reports [3, 8, 14, 15]. During the first 2 years of diuretic therapy there was a progressive rise in PRA [16]. However, for the 10 patients in this study the latest PRA values were not significantly different from those at 2 years, suggesting that the response had reached a plateau. The elevation of PRA and the further progressive rise may limit the efficacy of diuretic therapy in hypertension [19, 20]. Despite prolonged elevation of PRA, discontinuing diuretics resulted in a prompt fall to pretreatment levels with no subsequent change while off therapy.

The changes in body weight were inversely related to those in PRA. Thus on stopping diuretics body weight rose and on restarting diuretics body weight fell. The rapid change in weight suggests that patients on chronic diuretic therapy remain in negative fluid balance. Direct studies of plasma and extracellular fluid volumes support such a view [3, 8, 11–13]. The increase in body weight observed when diuretics were discontinued was associated only with a small, non-significant rise in blood pressure. It is possible that this dissociation between fluid state and blood pressure is due to ‘resetting’ of peripheral resistance control mechanisms as a result of prolonged blood pressure control [21], although this effect may be reversed slowly after therapy is stopped [22].

The major aim of the present study was to assess the response of patients rechallenged with diuretics. In particular, we were interested in observing whether prolonged diuretic therapy modifies the juxtaglomerular response to stimulation, just as it appears to modify blood pressure control for a period of time. This is particularly important as in many studies diuretics have been withdrawn for a period of only 3–4 weeks. Lowder & Liddle [23] observed that four out of five patients with ‘low renin hypertension’ treated with spironolactone showed persistent elevation
of plasma renin for up to 36 weeks after withdrawal of the drug. Furthermore, the renin response to frusemide was enhanced by spironolactone in these patients. Our findings differ, in that plasma renin fell quickly to pretreatment levels after withdrawal of treatment in all patients including those with 'low renin hypertension'. Despite this, the renin response to diuretic stimulation was significantly increased in the patients with 'low renin hypertension', so that only two such patients had a subnormal response on the second occasion. Although the patient numbers were small in this study it suggests that suppressed juxtaglomerular apparatus responsiveness was corrected by chronic diuretic treatment.

Much importance has been attached to the renin subgroup classification of patients with essential hypertension [24–26], although the distinct identification of renin subgroups has been challenged [17, 27–29]. More recently patients with 'low renin hypertension' have been shown to have a more marked disturbance of leucocyte sodium transport than that shown by other patients with essential hypertension [30], and such observations might suggest a different pathogenesis for hypertension in such patients. The present study indicates that previous treatment, even if discontinued for as long as 4 weeks, can have a substantial effect upon the classification of patients into the 'low renin' subgroup.

The mechanism by which diuretics produce this persistent effect is uncertain and will probably remain so as long as the nature of 'low renin hypertension' is obscure. The early suggestion that plasma renin was suppressed by extracellular fluid volume expansion [31] has not been confirmed by later studies [32, 33]. It is difficult therefore to argue that diuretics act by correcting an underlying abnormality in fluid volume control. In our study the stimulation of plasma renin on the second occasion was associated with no blood pressure change so that an altered blood pressure response cannot easily be invoked. Other suggested explanations for the subnormal juxtaglomerular response in 'low renin hypertension' include juxtaglomerular baroreceptor rigidity induced by nephrosclerosis [34] and reduced efferent sympathetic activity [35]. It is difficult to see how diuretic therapy could result in a persistent modification of these factors. The most likely explanation seems to be enhanced juxtaglomerular function associated with hypertrophy as a result of longstanding stimulation. Such hypertrophy has been demonstrated as a result of prolonged stimulation by fluid depletion [36]. In addition there may be an analogy with the adrenal zona glomerulosa, which shows enhanced responsiveness to ANG II after several days' stimulation by salt depletion [37]. The present studies do not allow us to determine the mechanisms for the phenomenon demonstrated, but they do indicate a potentially important response to long-term diuretic treatment.

References

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