Hypotensive Effects of Sodium Volume Depletion and 1-Sar-8-Ala-Angiotensin II in Relation to Plasma Renin in Hypertensive Patients

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Summary. The hypotensive effect of acute sodium volume depletion, produced by chlorthalidone and a low sodium diet, was inversely related to the plasma renin concentration (PRC) in 13 hypertensive patients of varying aetiology (r = 0.61; p<0.05); weight reduction induced by this therapy was not related to PRC (r = 0.12; p>0.1). The angiotensin II antagonist 1-sar-8-ala-angiotensin II failed to reduce arterial pressure when the patients ingested 130 mEq sodium per day, but pressure fell when it was infused during sodium volume depletion, except when PRC remained low; the changes in pressure were related to the plasma renin level (r = 0.78; p<0.005). The combined hypotensive response to acute sodium volume depletion and to angiotensin II blockade during sodium volume depletion was not related to PRC (r = 0.15; p>0.1). The results demonstrate that acute sodium volume depletion caused similar weight loss in patients with high and low PRC values, and it would have had similar hypotensive effects but for angiotensin-induced vasoconstriction in the high renin patients. Since 1-sar-8-ala-angiotensin II also reduced arterial pressure in 6 patients during chronic diuretic therapy, angiotensin II must still induce vasoconstriction in these circumstances.

Key words: Hypertension, low sodium diet, angiotensin antagonist, plasma renin, chlorthalidone, hypotensive effect, sodium depletion.

The hypotensive effects of spironolactone (Crane et al., 1970; Spark et al., 1971; Adlin et al., 1972; Carey et al. 1972; Vaughan et al., 1973), of thiazides (Adlin et al., 1972; Fagard et al., 1976b) and of chlorthalidone (Vaughan et al., 1973; Woods et al., 1976) have been shown to be more pronounced in hypertensive patients with a low plasma renin level, and the drugs have been less effective if the renin level has been high. These observations have contributed to the vasoconstriction-volume concept of hypertension, in which low renin hypertension is considered largely to be volume sustained, whilst arteriolar vasoconstriction is the predominant factor in high renin hypertension, irrespective of the basic aetiology (Laragh, 1973). The better hypotensive response to diuretics in low renin patients has also been explained by an impaired response of the renin-angiotensin system to sodium volume depletion, while the lesser response in high renin patients has been related to renin-induced peripheral vasoconstriction (Lancet, Editorial, 1975). Study of the hypotensive effect of angiotensin II-antagonists during diuretic therapy may help to distinguish between the hypotheses.

Patients and Methods

Nineteen patients with hypertension of various aetiologies were studied. The diagnosis was based on history, physical examination, appropriate laboratory tests and intravenous pyelography; a renal arteriogram had been performed in 18 subjects and cineangiography had demonstrated coarctation of the aorta in the remaining patient. The severity of hypertension was assessed by the criteria of the World Health Organisation. All patients were admitted to hospital. Six continued the therapy they had taken for 7 to 16 months which consisted of chlorthalidone 50 mg daily and low sodium diet. Their 24 h urinary sodium excretion averaged 30 mEq on the first day in hospital. The other 13, in whom all treatment had been interrupted at least
3 weeks before admission to hospital, received a diet containing sodium 130 mEq per day, which was checked by the analysis of 24 h urine specimens. None of the female patients were taking oral contraceptive drugs.

1-Sar-8-ala-angiotensin II (saralasin; Norwich Pharmacal Company) was infused in 12 of the 13 high sodium volume patients and intra-arterial pressure measurements were obtained in the other member of this group. In all 13 patients the drug was infused after they had been on chlorthalidone 50 mg/d and a diet containing sodium 20 mEq/d for 3–5 days (acute sodium volume depletion). Saralasin was infused in 6 patients during chronic sodium volume depletion. The saralasin infusion was given in the morning after a light breakfast, with the patient recumbent, in a laboratory at 18 to 22 °C, and humidity 40 to 60 °. In 27 of the total of 31 tests a catheter in the brachial artery was used to record intra-arterial pressure; in 2 patients an Arteriosonde® was used before and during acute sodium volume depletion. A control period of 45–60 min was observed during which glucose 5% was infused intravenously. Arterial (or venous; n = 4) blood was sampled at the end of the control period for determination of plasma renin concentration (PRC), using the method of Skinner (Skinner, 1967) modified for radioimmunoassay (Lijnen et al., 1976); normal range, sodium replete: 8–25 log ng/ml/h. Then the intravenous infusion of saralasin was started at a rate of 10 μg/kg/min and continued for 30 min (n = 7), or 60 min (n = 24). Patients were observed for 30 min (n = 8) or 60 min (n = 23) after the end of infusion.

The two-tailed Student’s t-test for paired data and regression analysis were used for statistical analysis.

**Results**

Details of the patients, who had mild to moderate hypertension, are given in Table 1.

**Sodium Volume Replete Patients**

Mean brachial artery pressure in the 13 patients with repletion of the sodium volume averaged 132.5 ± 22.5 (S.D.) mm Hg. Although PRC ranged from 4.0 to 72.4 ng/ml/h, saralasin did not cause a significant change in mean arterial pressure; after 30 min (n = 12) the average change was +1.0 ± 4.4 mm Hg (p > 0.1), after 60 min (n = 11) this value was −1.1 ± 3.5 mm Hg (p > 0.1) (Fig. 1).

**Acute Sodium Volume Depletion**

Chlorthalidone 50 mg daily and a low sodium diet for 3–5 days reduced mean arterial pressure to 120.9 ± 13.0 mm Hg (n = 13; p < 0.05). The change in arterial pressure was more pronounced in low renin patients (Fig. 2A) and was related to the (sodium replete) plasma renin concentration (y = −50.14 + 29.12 log x; r = +0.61; p < 0.05). Δ MAP was not related to change in body weight (r = 0.02; p > 0.1).

Plasma renin concentration rose from 1.32 ± 0.39 log ng/ml/h (antilog = 21.0 ng/ml/h) to 1.85 ± 0.51 log ng/ml/h (antilog = 70.3 ng/ml/h; p < 0.001) in response to chlorthalidone and diet. The increase in PRC was related to the (sodium replete) PRC (log Δ PRC = 0.35 + 0.95 log x; r = 0.59; p < 0.05), but not to the change in body weight (r = 0.22; p > 0.1). Body weight decreased by an average of 2.01 ± 1.4 kg; the change was not related to the (sodium replete) plasma renin level (r = +0.12; p > 0.1).

During acute sodium volume depletion saralasin reduced brachial artery pressure in 11 patients, whose PRC ranged from 45 to 408 ng/ml/h under these circumstances, whilst pressure increased slightly in the 2 patients in whom PRC had remained low (Fig. 1). The change in mean arterial pressure, 30 min after commencement of the infusion, was significantly related to the (sodium deplete) PRC (n = 13; y = 20.95 − 22.71 log x; r = −0.78; p < 0.005; Fig. 1), as were the changes after 60 min (n = 8; r = −0.93; p < 0.001).

The relationship between the (sodium replete) PRC and the combined hypotensive effect of sodium volume depletion and of saralasin, which averaged 32.6 ± 16.9 mm Hg is shown in Fig. 2B, i.e. the mean sodium replete brachial artery pressure minus the mean arterial pressure after 30 min of saralasin infusion during sodium volume depletion. No correlation was observed between the variables (r = +0.15; p > 0.1).

**Chronic sodium volume depletion (Table 2)**

Plasma renin concentration before the infusion of saralasin ranged from 56 to 380 ng/ml/h (mean: 2.17 ± 0.29 log ng/ml/h; = 146.3 ng/ml/h). Mean brachial artery pressure averaged 128.0 ± 20.4 mm Hg before the infusion of the drug and 103.2 ± 23.9 mm Hg after 30 min (p < 0.01). Changes in pressure were closely related to log PRC (r = −0.85; p < 0.05). For the average PRC level of 146.3 ng/ml/h a pressure decrease of 28.3 mm Hg would have been anticipated according to the regression equation obtained during acute sodium vol-