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CLINICAL SYNDROMES ASSOCIATED WITH DISORDERS OF RENAL TUBULAR CHLORIDE TRANSPORT : EXCESS AND DEFICIENCY OF A CIRCULATING FACTOR?

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ABSTRACT

Two contrasting patients are described, one with pseudo-Bartter's syndrome induced by frusemide abuse and the other a case of hyporeninaemic hypoaldosteronism.

The clinical and biochemical features of these two conditions are the opposite of each other and, in the first patient, the effects of frusemide were antagonised by treatment with indomethacin while in the second frusemide itself corrected the syndrome.

The decreased pressor sensitivity to infused angiotensin II seen in the patient with pseudo-Bartter's syndrome was corrected with indomethacin and the enhanced pressor sensitivity seen in hyporeninaemic hypoaldosteronism was reversed with frusemide.

Frusemide, an agent which blocks chloride transport at the ascending limb of Henle's loop, was respectively thus the cause and the cure of these conditions. On the basis of this the suggestion is made that Bartter's syndrome and hyporeninaemic hypoaldosteronism represent respectively an excess and a deficiency of a circulating factor similar to frusemide capable of blocking renal tubular chloride transport.

INTRODUCTION

Bartter's syndrome (1) and hyporeninaemic hypoaldosteronism (2) are two uncommon conditions whose aetiologies are unknown. The features of Bartter's syndrome can be closely mimicked in patients who abuse diuretics, particularly loop diuretics (3-7), and there is evidence to suggest that the biochemical defects of hyporeninaemic hypoaldosteronism can

be corrected or improved by the long-term administration of diuretics (8-11). Many of the biochemical features of these two conditions are the exact opposite of each other and we have recently suggested (12) that they may represent opposite abnormalities of chloride reabsorption at the thick ascending limb of Henle's loop. We further argued (12) that rather than there being a structural renal abnormality in these conditions they represented an excess (Bartter's syndrome) and a deficiency (hyporeninaemic hypoaldosteronism) of a circulating factor capable of inhibiting chloride transport. This current report describes studies in two patients which provide circumstantial evidence for the validity of this hypothesis.

CASE REPORTS

Case 1

A 53 year old hypertensive Caucasian female was first seen at the University of Michigan Hospital in January 1979 when she was reportedly taking methyldopa 1500 mg/d together with spironolactone 200 mg/d and potassium supplements 200 mmol/d because of previous hypokalaemia. Physical examination was unremarkable, blood pressure 150/92 mmHg and serum potassium 2.6 mmol/l. After discontinuation of all therapy for one month, the patient was admitted to the Clinical Research Center for a three week period during which sodium and potassium intakes were fixed at 130 and 150 mmol/d respectively. In addition to investigations outlined in Figure 1, on three occasions (days 5, 16 and 22), after overnight fast and recumbency, the patient underwent incremental infusions of angiotensin II (Hypertensin - CIBA) to assess pressor sensitivity (13).

Serum sodium remained essentially unchanged throughout the period of study (Fig 1). Serum potassium was normal (3.7 mmol/l) on admission but fell rapidly during the period before institution of indomethacin (2.5 mmol/l). During treatment with indomethacin, serum potassium increased progressively to a maximum of 3.6 mmol/l but fell again on withdrawal of the drug (2.7 mmol/l). Sodium balance did not appear to be achieved prior to indomethacin treatment and was progressively positive thereafter (Fig 1). Potassium balance also appeared persistently positive (see Discussion).

Despite the observed sodium balance data, changes in weight closely paralleled serum potassium, there being an initial fall followed by an increase during indomethacin therapy (Fig 1). The fall in weight seen between the third and seventh day of indomethacin therapy prompted the increase in the dose from 150 to 200 mg/d which was immediately followed by further weight gain. There was a rapid fall in weight after stopping treatment. Blood pressure rose during treatment with indomethacin (132/86 to 164/98 mmHg) and fell to control levels on stopping therapy (142/90 mmHg).

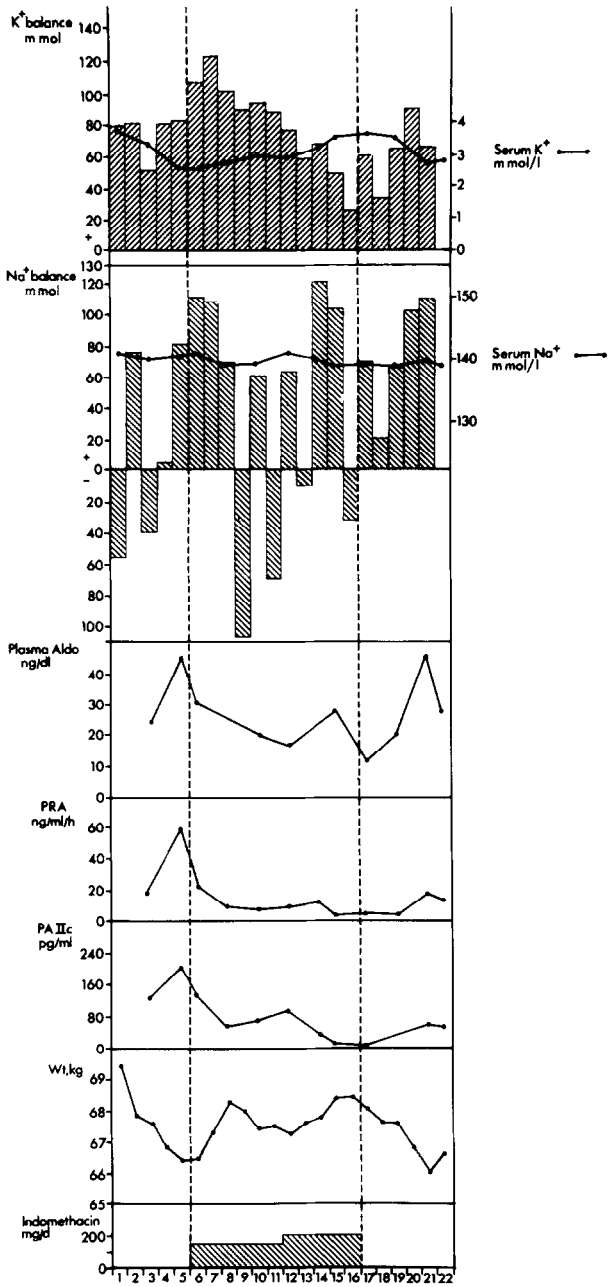

Figure 1 Case I: Changes in body weight, PRA, angiotensin II and aldosterone together with sodium and potassium balance. Indomethacin was administered between day 6 and 16.
PAIIc = plasma angiotensin II concentration.

Changes in PRA (14), angiotensin II (15) and aldosterone (16) can be seen to closely parallel each other and to occur in opposite directions to change in weight, blood pressure and serum potassium (Fig 1). Indomethacin therapy returned PRA, angiotensin II and aldosterone levels to normal. Plasma volume (Evans Blue dilution) increased from 1982 ml to 2277 ml over the period of indomethacin therapy.

The dose response curve relating changes in circulating venous angiotensin II to changes in mean blood pressure was displaced far to the right of that seen in normal human volunteers on similar sodium intakes (13), i.e. the blood pressure response was diminished. Treatment with indomethacin caused a shift to the left of the dose response curve which approximated to that seen in normal subjects on a normal sodium intake; after stopping indomethacin the dose response curve returned towards that seen in the basal state (Fig 2).

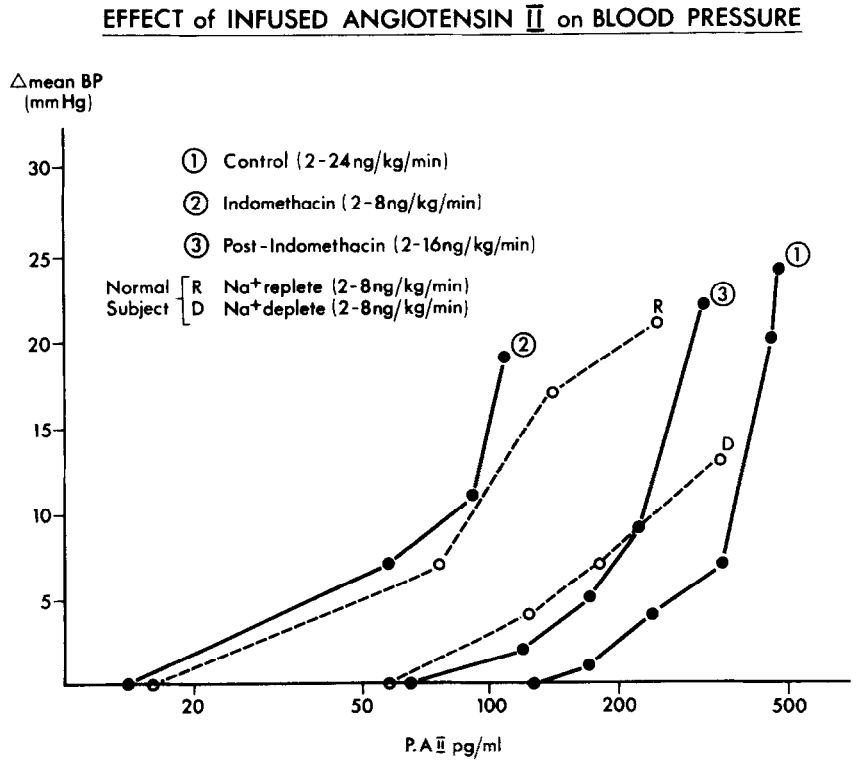

Figure 2 Case I: The relationship of change of mean blood pressure (diastolic + one third of pulse pressure) to venous plasma levels of angiotensin II during angiotensin II infusion. Lines R and D represent the mean responsiveness of normal subjects studied in an identical fashion on sodium replete and deplete intakes respectively (13).

Aliquots of urine from days 3, 9 and 11 of the study (chosen because of increased sodium content - see Fig 1) were analysed qualitatively for frusemide. This was found in all samples of urine and a quantitative assessment from the urine on day 3 revealed 6.3 µg/ml.

Case 2

A 54 year old diabetic hypertensive black male had been noted to be hyperkalaemic (7.3 mmol/l) during an episode of deterioration of diabetic control. Serum potassium had fallen with lowering of the blood sugar and plasma aldosterone was low at 2.2 ng/dl together with a low urinary aldosterone excretion (1.1 µg/24 h (normal 2-20)). A provisional diagnosis of hyporeninaemic hypoaldosteronism was made and after discontinuing methyldopa for four weeks the patient was admitted to the Clinical Research Center. Insulin therapy was continued unchanged throughout all studies.

Apart from hypertension and diminished foot pulses, the only significant abnormality was the presence of mild background diabetic retinopathy. Serum creatinine varied between 180 and 250 mmol/l. Blood sugar was well controlled throughout admission (<6.5 mmol/l). Possibly because of the absence of hyperglycaemia the patient was never frankly hyperkalaemic (4.2-5.6 mmol/l). Sodium (130 mmol/d) and potassium (90 mmol/d) were kept constant during the first four days of admission and thereafter sodium intake was decreased to 10 mmol/d preceded by an intravenous bolus of 40 mg frusemide to enhance sodium depletion. On the fourth day of normal sodium intake, pressor sensitivity to infused angiotensin II was assessed.

The patient was discharged on oral frusemide, the dose of which was increased as an outpatient till a repeat admission three months later for an identical study, although oral frusemide was continued throughout.

During the first admission basal levels of PRA, angiotensin II and aldosterone were low on a normal sodium intake, with only a sluggish response to three days of salt restriction (Fig 3). Sodium balance was not quite achieved during this period, urine sodium falling to 16 mmol/d after three days.

During the second admission, after the patient had increased his frusemide (on his own volition) to 480 mg/d, serum potassium (4.3-4.9 mmol/l) was not significantly different from the earlier admission. PRA, angiotensin II and aldosterone were all increased to levels seen during salt depletion in normal subjects (Fig 3). Acute salt depletion produced a brisk increase in all indices (Fig 3), urine sodium decreasing only to 55 mmol/d.

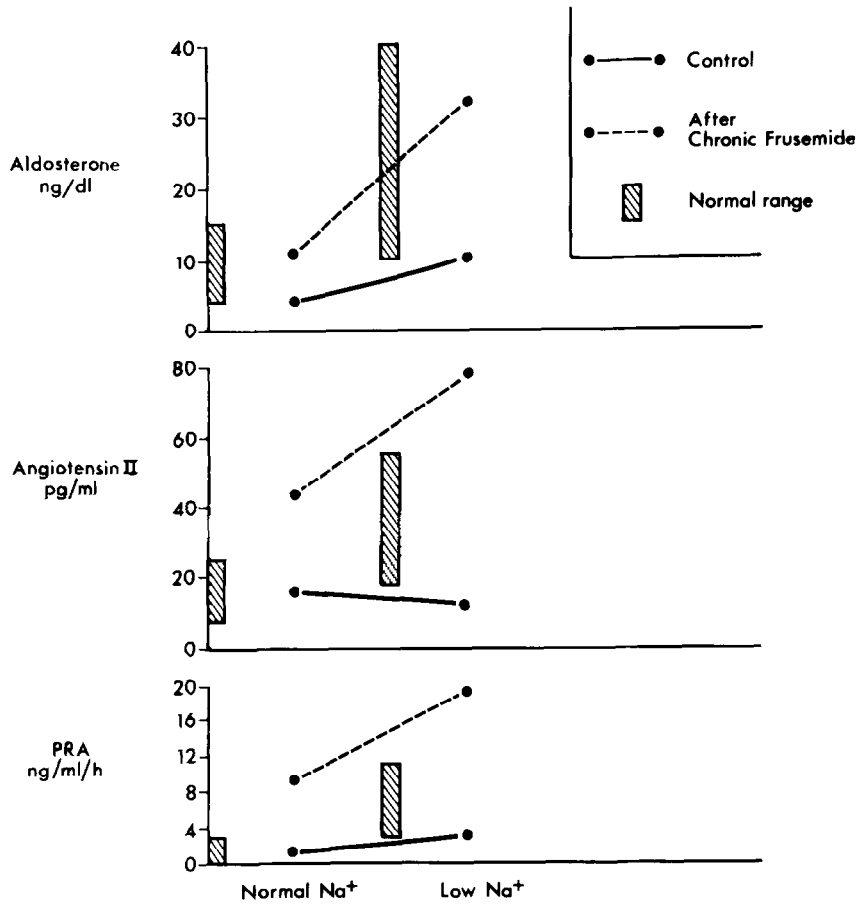

Figure 3 Case II; The effect of acute sodium depletion of PRA, angiotensin II and aldosterone before (o——o) and during long term frusemide administration (o---o). Normal ranges shown in cross hatching.

Basal blood pressure on the morning of the angiotensin II infusion during the first admission was 152/100 mmHg. Infusion of 2 mg/kg/min of angiotensin II produced a marked rise of blood pressure to 170/116 mmHg (Fig 4). While increasing the infusion rate to 4 mg/kg/min, blood pressure rose to 198/134 mmHg within five minutes and the infusion was terminated without further blood sampling. In comparison with normal subjects (Fig 4) this represents a markedly increased pressor response. During the second admission, following long term frusemide therapy, basal blood pressure was lower at 132/88 mmHg. The blood pressure response to infused angiotensin II was much reduced, the dose response curve of venous angiotensin II

against changes in mean blood pressure was shifted to the right and approximated to that seen in sodium replete normal subjects (Fig 4).

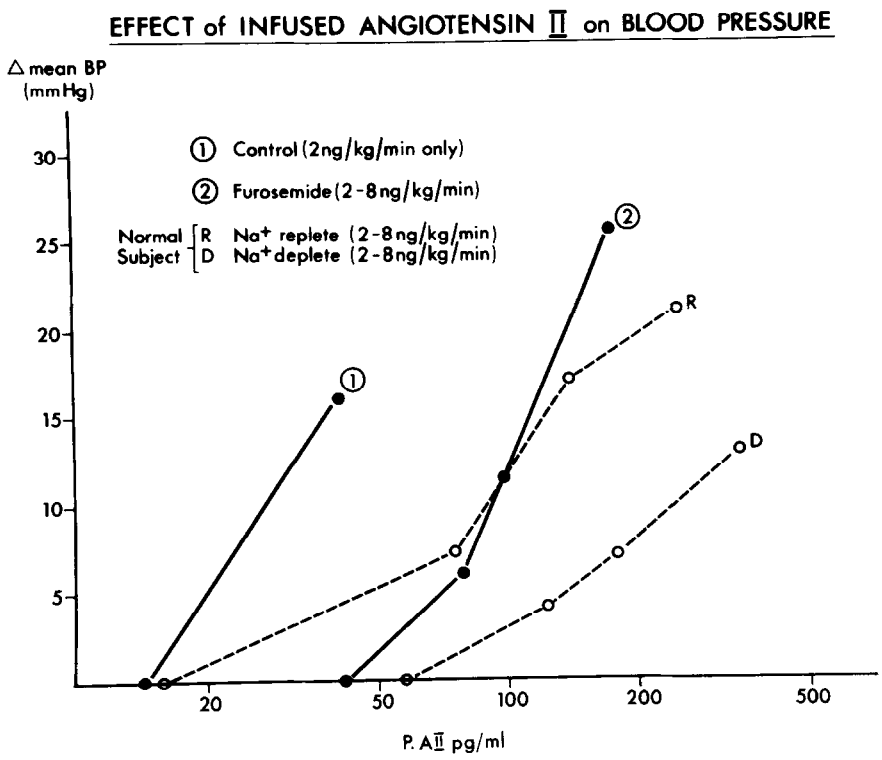

Figure 4 Case II; Relationship of changes in mean blood pressure to plasma levels of angiotensin II during angiotensin II infusions. Lines R and D represent normal subjects similarly infused on low and normal salt intakes respectively.

DISCUSSION

Our first patient caused some initial confusion because of the discrepant urinary electrolyte results seen throughout her studies. In view of the subsequent discovery that she was taking frusemide it seems likely that she was not consuming the whole of her dietary intake to explain an apparent positive potassium balance.

The two patients described have biochemical defects which are opposite to one another: the first patient (although supposedly being treated for hypertension) had a near

normal blood pressure and a persistent hypokalaemic alkalosis. She had markedly increased circulating levels of PRA, angiotensin II and aldosterone with a diminished pressor sensitivity to infused angiotensin II. The second patient (a diabetic with mildly impaired renal function) had elevated blood pressure and intermittent hyperkalaemia with mild acidosis. Plasma renin activity, angiotensin II and aldosterone were all low and relatively unresponsive to acute stimulatory manoeuvres. The pressor sensitivity to infused angiotensin II was dramatically increased. In the first case the abnormalities described were caused by the surreptitious abuse of frusemide. In the second, therapeutic use of the same drug corrected opposite abnormalities.

Bartter's syndrome has as its essential characteristics hypokalaemic alkalosis, increased plasma levels of renin, angiotensin II and often aldosterone, together with juxtaglomerular cell hyperplasia of the kidney. Patients are normotensive but display a marked insensitivity to the pressor effects of infused angiotensin II (17). The proximal cause for this constellation of biochemical features remains uncertain. The demonstration of increased production of renal prostaglandins (18-22) together with the correction of many of the features of this syndrome with the use of prostaglandin synthetase inhibitors (18-21, 23-25) led many to suppose that excessive prostaglandin production was the cause of the condition. However, long term therapy with indomethacin, while correcting the hypereninaemia and the hyporesponsiveness to the pressor effects of infused angiotensin II, does not fully correct the renal loss of potassium or the hypokalaemia (24) suggesting that potassium loss might be the cause rather than the effect of excessive prostaglandin production (26, 27). The suggestion that chloride reabsorption at the ascending limb of Henle's loop (3) might be defective in this condition was confirmed by Gill and Bartter (28) and a defect at this site in the renal tubule appears at the moment to be the most likely cause of Bartter's syndrome. Chloride is known to be actively transported at the ascending limb of Henle's loop (29,30) which is the site at which loop diuretics act to block chloride transport (31). Self administration of diuretics can indice a clinical state virtually indistinguishable from Bartter's syndrome (3,7) including juxtaglomerular cell hyperplasia (4,7). Frusemide administration is also known to increase urinary prostaglandin E_2 (32,33). The marked similarity between Bartter's syndrome and the effects of frusemide as demonstrated in our patient, together with the normalising of all biochemical abnormalities with indomethacin therapy, allow us to suggest the possibility that an excess of a circulating factor similar to frusemide might be responsible for Bartter's syndrome. There is in fact

evidence of a more generalised defect in Bartter's syndrome including altered membrane sodium transport (34,35) and a defect in platelet aggregation (36) implying that there is more than a single renal abnormality in this condition.

In terms of clinical and biochemical features the condition most directly opposite to that of Bartter's syndrome is that condition first described in 1964 by Paver and Pauline (37), sometimes referred to as Gordon's syndrome (38) and most recently described by Schambelan et al as type II pseudohypoaldosteronism (39). This condition has been shown to be associated with increased renal chloride reasborption in the distal tubule (39) and is a strong candidate for the mirror image of Bartter's syndrome.

Hyporeninaemic hypoaldosteronism is a condition with similar biochemical features including a hyperkalaemic acidosis, low and unresponsive plasma levels of renin and/or angiotensin II, together with low plasma or urinary aldosterone levels. The condition tends to occur typically in elderly patients with diabetes and mild renal insufficiency. The features of the condition have been extensively reviewed recently (40,41) and were apparent in our patient. The presence of hypertension rather than hypotension in the majority of cases (41) makes it unlikely that aldosterone deficiency consequent upon renin deficiency is the primary cause of this condition. The observation that supraphysiological doses of mineralocorticoid are often needed to normalise the elevated serum potassium (8,10,42-48) suggests that the aldosterone deficiency is not the whole cause of the hyperkalaemia, and indeed these large doses of mineralocorticoid replacement often correct serum potassium levels only at the expense of raising blood pressure still further (10,46).

The active reabsorption of chloride at the ascending limb of Henle's loop will result in the passive reabsorption of both sodium and potassium giving rise to a tendency to hyperkalaemia in an opposite fashion to that suggested as the cause of hypokalaemia in Bartter's syndrome (28). It is known that prolonged sodium depletion (45) or long term therapy with diuretics (8-11) are capable of stimulating the production of renin and/or aldosterone while acute sodium depletion is not. In addition, where measured, patients with this condition have been shown to exhibit expansion of extracellular fluid volume and exchangeable sodium (10). These data suggest that renin suppression might be consequent upon volume expansion.

Other abnormalities recently described in hyporeninaemic hypoaldosteronism are also biochemically opposite to those seen in Bartter's syndrome and tend to support our argument; urinary prostaglandins have been shown to be low

(49,50) and in susceptible individuals with renal insufficiency the use of indomethacin, a drug which blocks prostaglandin synthesis, has been associated with a hyperkalaemic syndrome similar to hyporeninaemic hypoaldosteronism (51,52).

A mildly increased pressor sensitivity to infused angiotensin II has been described in essential hypertension (53,54) but is not a universal finding (55). The dramatic pressor response seen in our second patient is more like that described in primary hyperaldosteronism (53,56), an undoubted volume expanded state. The low-normal levels of renin/angiotensin II and aldosterone observed in our patient were significantly increased with long term diuretic therapy after a blunted acute response had been demonstrated. This, together with the significant fall in blood pressure induced by frusemide and the correction of increased pressor sensitivity to infused angiotensin II, is further strong evidence that volume expansion is an integral part of this syndrome. Our observation that frusemide corrected this syndrome argues against a structural renal defect as the cause of hyporeninaemic hypoaldosteronism, and allows us to postulate that this syndrome might occur in the absence of such an endogenously produced substance.

Evidence presented by these patients is of necessity inferential and cannot prove or disprove the idea that there exists a circulating factor capable of affecting chloride transport. That there are humoral factors other than aldosterone which govern sodium transport by the kidney seems to us to be well established (57). We suggest that at least one of these factors might act on the ascending limb of Henle's loop as a "chloriuretic hormone".

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