Plasma Renin Concentration and the Control of Blood Pressure in Patients with Chronic Renal Failure: the Effect of Haemodialysis

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INTRODUCTION

Hypertension commonly occurs in chronic renal failure, and although usually controlled with ease by regular haemodialysis, occasional patients may require bilateral nephrectomy before the blood pressure can be reduced to acceptable levels (Schupak et al, 1963; Kolff et al, 1964; Toussaint et al, 1966; Brown et al, 1969).

The purpose of this study is to examine more fully the interrelationships between severe hypertension, sodium balance, plasma renin and plasma aldosterone concentrations in patients receiving regular haemodialysis. Some of these results have been reported previously (Brown et al, 1969).

METHODS

The study involved 21 patients with chronic renal failure, each maintained by regular haemodialysis therapy, using either Kid machines for 12 hours twice a week, or coils with a 100 litre bath and recirculating pump, for 8 hours twice a week. Dietary sodium intake was restricted to approximately 50 mEq/day, with more severe restriction in those patients with poorly controlled blood pressure, or those with large weight gains between dialyses.

The patients were divided into 3 groups on the basis of the ease with which blood pressure was controlled. There were 13 patients in Group 1, in whom blood pressure was easy to control by regular haemodialysis, together with moderate salt and water restriction. Group 2 (3 patients) were those in whom blood pressure was only moderately controlled by these measures plus the use of hypotensive drugs. Group 3 (5 patients) consisted of
patients whose blood pressure was not controlled by the measures used in Group 2, but was lowered satisfactorily after bilateral nephrectomy.

The blood pressure was measured by sphygmomanometer with the patient in the recumbent position prior to haemodialysis. Electrolyte estimations were made on a Technicon Autoanalyser. Plasma renin concentrations were measured by the technique of Brown et al (1964); normal range 4-20 units/l. Plasma aldosterone levels were measured by a modification of the double isotope derivative technique (Fraser & James, 1968), normal values <18 μg/100 ml.

Blood samples were taken from the arterial cannula in each patient, both before the start of the dialysis, with the patient recumbent, and at the end of dialysis before the blood was washed back from the kidney machine into the patient.

Renin concentration in the dialysis bath fluid was measured by extracting renin-like material in 20 litre aliquots of dialysis bath fluid by absorption on to DEAE cellulose after counter-current dialysis. The concentrated eluate was then assayed in the same way as a plasma extract (Brown et al, 1964).

Some of the results in cases 2-4, 7 and 8 and 11-21, shown at the bottom of Figure 3, have been reported in a previous paper (Brown et al, 1969).

RESULTS

BLOOD PRESSURE CONTROL
Generally blood pressure was well controlled in the 13 patients in Group 1. Bilateral nephrectomy was undertaken in 2 of these patients in preparation for renal transplantation. This produced no significant change in the blood pressure. Group 2 comprised 3 patients in whom the blood pressure was only moderately controlled, even with the addition of hypotensive drugs. Bilateral nephrectomy in one of the patients in Group 2 enabled the hypotensive drugs to be withdrawn. In Group 3, however, bilateral nephrectomy was undertaken in all 5 patients and thereafter the blood pressure was controlled without difficulty.

PLASMA SODIUM CONCENTRATION AND BLOOD PRESSURE CONTROL
Generally plasma sodium levels were inversely related to the ease with which blood pressure was controlled (Figure 1), although hyponatraemia was not an invariable finding in patients with poor control of blood pressure. In the 4 patients in Group 3 for whom adequate plasma sodium data are available, bilateral nephrectomy produced a marked rise in plasma sodium levels.

PLASMA RENIN CONCENTRATIONS AND BLOOD PRESSURE CONTROL
Figure 2 shows the plasma renin values plotted for individual patients, grouped by ease of blood pressure control. As can be seen, plasma renin concentrations were highest in the patients whose blood pressure was the most difficult to control.
Figure 1. Plasma sodium concentrations, pre- and post-nephrectomy, in patients grouped according to control of blood pressure. Mean ± 1 S.E.M.

Figure 2. Plasma renin concentrations, plotted on log. scale, in patients grouped according to control of blood pressure. Normal range indicated by horizontal dotted lines.
THIRST
Three patients in Group 3 complained of severe thirst after maintenance haemodialysis was begun. Each of these patients exceeded their daily fluid allowance by surreptitious drinking, and in each hyponatraemia (mean plasma sodium of the 3 patients was 129.5 mEq/l) accompanied very high plasma renin levels (Figure 1). One patient, however, in the group (case No. 5) had a similar increase in plasma renin concentration, but without thirst. The average plasma sodium level in this patient, 136.2 mEq/l, was the highest in the group. Bilateral nephrectomy abolished the thirst in each of these 3 patients and was accompanied by a return of the plasma sodium levels to normal.

These observations suggest that severe and uncontrollable hypertension in patients on a maintenance haemodialysis programme is likely to be associated with raised plasma renin concentrations and, in some instances, with thirst and hyponatraemia. The following case report suggests that each of these abnormalities may develop during the attempt to control blood pressure by dialysis.

CASE REPORT (Case No. 1)
L.C., a 24-year old female patient (Figure 3) was admitted in November

![Figure 3. Case 1. Plasma renin and sodium concentrations, and blood pressure and their response to peritoneal dialysis, haemodialysis and bilateral nephrectomy. Plasma renin (log. scale), normal range indicated by horizontal dotted lines. P.D. = peritoneal dialysis. H.D. = haemodialysis.](image-url)
1968 with poorly controlled blood pressure, terminal renal failure and oedema. Plasma renin concentrations at this time were only slightly raised at 21.0 and 19.0 units/l. In spite of large doses of hypotensive drugs, the patient's blood pressure remained uncontrolled. Peritoneal dialysis was undertaken using both hypertonic dialysis solutions, and also solutions with a sodium concentration varying from 70 - 140 mEq/l, some of which were slightly hypotonic with respect to the patient’s plasma, in an attempt to remove both water and salt. After 10 days intermittent peritoneal dialysis, and with a weight loss of 8 kg, the blood pressure was controlled temporarily. The plasma sodium level at this time was 128 mEq/l and the plasma renin concentration had risen to 175 units/l. Because of the rising blood urea level and recurrence of severe hypertension, regular maintenance haemodialysis was begun. In spite of a further weight loss of 5 kg over the following 5 weeks, the patient remained hypertensive. Plasma renin concentrations remained elevated throughout this period, with values up to 750 units/l, and were accompanied by increased plasma aldosterone concentrations (Figure 4). At this time and during the period of peritoneal dialysis, she complained of severe thirst, which was so marked that she exceeded her restricted fluid allowance by surreptitious drinking. In an attempt to control the blood pressure, bilateral nephrectomy was undertaken. This led to prompt fall of both the plasma renin and plasma aldosterone levels to low and normal levels respectively (Figure 4). Thereafter blood pressure was controlled easily without the use of hypotensive
drugs. The patient commented spontaneously on waking from the anaesthetic that her severe thirst had disappeared.

CHANGES OF PLASMA RENIN CONCENTRATIONS FOLLOWING NEPHRECTOMY
As in the earlier study (Brown et al, 1969), plasma renin concentration was reduced to low but detectable levels in 3 patients following bilateral nephrectomy.

CHANGES OF PLASMA RENIN CONCENTRATIONS DURING DIALYSIS
In the previous study (Brown et al, 1969), it was shown that the loss of weight across dialysis was related directly to the percentage change in plasma renin concentration \( r = +0.687, p = <0.001 \). However, when the weight loss was small, plasma renin concentration tended to fall. This observation prompted us to investigate the possibility of renin crossing the dialysis membrane. This was tested in two ways. Firstly, in six experiments, renin could not be detected in dialysis bath fluid after extraction and 10,000 fold concentration. Secondly, no significant difference in plasma renin concentration was found in blood entering and leaving the kidney machine. (In 10 pairs of observations mean difference \( +8% \pm S.E. 36\% \)).

PLASMA ALDOSTERONE LEVELS
The plasma levels of aldosterone and renin were measured in three patients (cases Nos.1, 6 & 10), one from each of the three groups of blood pressure control. Before bilateral nephrectomy plasma renin and aldosterone concentrations changed in parallel in each patient, although the ratio of renin to aldosterone differed considerably (Figure 4). Bilateral nephrectomy reduced plasma renin and aldosterone values in each case. However, the magnitude of the fall of the plasma renin concentration was clearly related to its level before operation, whilst plasma aldosterone decreased markedly in each instance, independently of the magnitude of the change in plasma renin concentration.

DISCUSSION
BLOOD PRESSURE CONTROL: THIRST, HYponatraemia AND RENIN
In both this and the previous study (Brown et al, 1969) we have noted the relationship between the ease of blood pressure control and the height of the plasma renin concentration. Similar findings have recently been reported by Safar et al (1969). Before starting on regular dialysis therapy, patients with poorly controlled blood pressure are often salt and water overloaded on clinical grounds, as assessed by being overweight, with puffy faces and pitting or non-pitting oedema. Accordingly they are subjected to large weight losing dialyses in an attempt to remove the presumed salt and water excess and control the hypertension. Each dialysis, involving the removal
of up to 4 litres of sodium containing fluid is probably a strong stimulus to renin release, in contrast to the less vigorous dialyses in the majority of patients in whom renin usually falls. The elevation of plasma renin concentration may have several effects. Firstly it may perpetuate the hypertension via the vaso-constrictor effect of angiotensin, although there is no direct evidence that the plasma renin concentrations obtained are in the pressor range in man (Bianchi et al, 1968). Secondly renin may stimulate thirst which leads to re-expansion of the extracellular fluid compartment through excess fluid intake. A large weight gain between dialyses, will necessitate a further large weight removal across dialysis, so that a vicious circle may be perpetuated. This vicious circle has proved difficult to control except by bilateral nephrectomy which removes the major source of renin production.

Increasing difficulty in control of the blood pressure appears to be related, in the patients studied, to hyponatraemia. One possible explanation for the hyponatraemia is severe thirst which leads to excessive fluid intake and dilutional hyponatraemia. Three of the 5 patients in Group 3, each with the lowest plasma sodium values, and the highest plasma renin levels, were also the most thirsty. There is suggestive evidence that renin may stimulate thirst in some way (Fitzsimons, 1966; Fitzsimons & Simons, 1968; Brown et al, 1969).

The case report (Figure 3) indicates that the decreased plasma sodium and elevated renin values, and the marked thirst were not present before regular haemodialysis treatment was started. It is therefore probable that dialysis was responsible for producing these abnormalities. The appearance of hyponatraemia, high plasma renin concentration and marked thirst in a patient with poorly controlled blood pressure during regular haemodialysis, may be an indication to avoid large weight losing dialyses or to consider bilateral nephrectomy as a therapeutic measure.

REDUCTION OF PLASMA RENIN LEVELS BY DIALYSIS
A fall in plasma renin concentration across dialysis (Brown et al, 1969) may have several explanations. The work of Houssay et al (1942) suggests that some substances present in uraemic tissues may inhibit the normal metabolic clearance of renin. We have, however, no evidence that dialysis removes any such substances. Moreover, whilst dialysis could remove a stimulus to renin production, we have no evidence on this point.

The third possibility is that renin might cross the dialysis membrane. This was investigated in two ways, and both suggest that renin does not cross the dialysis membrane in sufficient quantities to cause the fall in plasma renin levels.

PLASMA RENIN LEVELS FOLLOWING BILATERAL NEPHRECTOMY
As in earlier studies (Lever & Robertson, 1964; Touissaint et al, 1968; Lundgren et al, 1966; Capelli et al, 1968) renin (or a renin-like enzyme)
was detected in the plasma of three patients (2 females and 1 male) following bilateral nephrectomy. We have previously discussed the significance of this finding (Brown et al, 1969).

PLASMA RENIN AND ALDOSTERONE LEVELS
Before bilateral nephrectomy the plasma levels of renin and aldosterone changed in parallel (Figure 4). However, the ratio of plasma renin concentration to plasma aldosterone concentration differed markedly in the three patients. With the proviso that the number of observations is small, this suggests that the extent to which renin can stimulate aldosterone production may vary considerably. This might result from differences of renin substrate present in the three patients. Alternatively, differences of electrolyte balance may have influenced the ability of renin and angiotensin to stimulate aldosterone production (Blair-West et al, 1965).

Following bilateral nephrectomy both the plasma renin and the plasma aldosterone values fell to the low part of the normal range in all three patients, although in one patient (case 10) a large change of aldosterone occurred with only a minor change of renin.

SUMMARY
1. In a group of 22 patients with chronic renal failure, undergoing maintenance haemodialysis, plasma renin concentration was related to the ease of blood pressure control.
2. Severe hypertension, was often associated with thirst, hyponatraemia and raised plasma renin concentrations. Bilateral nephrectomy corrected these abnormalities.
3. Several features of this syndrome may develop during regular haemodialysis treatment, possibly as a result of the comparatively greater removal of salt and water during dialysis in patients whose blood pressure is difficult to control.
4. In some instances plasma renin levels fell during dialysis. This was not due to renin crossing the dialysis membrane.
5. In three patients plasma renin and aldosterone levels changed in parallel before bilateral nephrectomy. Following operation both the plasma renin and aldosterone levels fell, and in one patient the reduction of the plasma aldosterone level was considerably greater than the fall in plasma renin concentration.

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139