which is much less than for self-poisoning in general (Matthew et al., 1969). An appreciable number of patients refused further psychiatric help and many of those given outpatient appointments failed to attend. Only 11 (6%) were thought to be suffering from a psychiatric illness. Of those regarded as having a personality disorder most were psychopaths. Each patient was seen by a medical social worker but it was found impossible to evaluate the help offered.

This study shows that drug abusers place a significant work load on the police and hospital services. Most admissions occurred after 10 p.m., the patients were often abusive, demanding, and disruptive, thus placing great strain on junior medical and nursing staff. Rather less than half the admissions required resuscitation, gastric aspiration and lavage, or sedation. Few needed or accepted psychiatric or social support. The study supports the view that, like alcoholic intoxication, and unlike self-poisoning in general (Greer and Bagley, 1971; Kennedy, 1972) there is often little to be gained from the psychiatric point of view from admitting drug abusers to hospital, and admission should be mainly based on the patient's medical condition when examined in the casualty department. This knowledge should prove of value in areas where medical hospital beds are at a premium.

We are indebted to Dr. Henry Matthew for encouragement and helpful advice, to the psychiatrists who co-operated in the study, and to the nursing staff and resident medical officers. We are also indebted to Miss A. S. Bell for expert secretarial help.

References

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Interdependence of Exchangeable Sodium and Plasma Renin Concentration in Determining Blood Pressure in Patients Treated by Maintenance Dialysis

S. M. ROSEN, P. J. A. ROBINSON

British Medical Journal, 1973, 4, 139–143

Summary
Plasma renin concentration and exchangeable sodium were measured in 13 patients with terminal renal failure maintained by dialysis therapy. Blood pressure in seven “responsive” patients was controlled by ultrafiltration but was not controlled in six “resistant” patients. Plasma renin concentration was inversely related to exchangeable sodium in the responsive group but was inappropriately high for the level of exchangeable sodium in the resistant group. There was a better correlation between mean blood pressure and the product of plasma renin concentration and exchangeable sodium than with renin concentration alone.

These results indicate that a severely diseased kidney can respond to changes in exchangeable sodium by alterations in renin secretion and they also support the concept that the potential pressor effect of renin is modified by exchangeable sodium. The product of the two factors might be used to determine the “effective” plasma renin concentration in respect of blood pressure.

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Introduction
The role of renin as a pressor agent in patients with terminal renal failure maintained by dialysis therapy is the subject of continuing speculation. Evidence in favour of a part played by renin in the maintenance of hypertension stems largely from the fact that patients with severe uncontrolled hypertension have a very high plasma renin concentration, and bilateral nephrectomy reduces the plasma renin with a concomitant reduction in blood pressure (Onesti et al., 1968; Brown et al., 1969). Kidneys from such patients with severe hypertension have a higher content of renin than those with controlled blood pressure (Vertes et al., 1969).

However, the correlation between plasma renin concentration and blood pressure is not close, owing to a wide scatter of values (Brown et al., 1969; Wilkinson et al., 1970). Furthermore, plasma renin concentration may rise during a dialysis treatment, though a reduction in blood pressure may be effected (Bianchi et al., 1972).

During ultrafiltration with dialysis therapy there is usually a reduction in blood pressure associated with the removal of salt and water (Shaldon et al., 1963). Loss of sodium in a normal person causes a rise in plasma renin concentration (Brown et al., 1963; Veyrat et al., 1964; Bull et al., 1970), but evidence from dogs indicates that the potential pressor effect of this increase in plasma renin is offset by the reduction of body sodium (Bianchi et al., 1968).

This suggests that a relation between renin and blood pressure may be found only if the effective pressor potential of the renin is calculated by taking into account other factors which may alter the capacity of blood vessels to respond to the biological products of renin.

This paper studies the inter-relation of renin and sodium and blood pressure in terminal renal failure.
Subjects

Thirteen patients were studied. They were all receiving thrice-weekly maintenance dialysis therapy for terminal renal failure using a single pass, double-layer KiiI dialyser for 30 hours a week. None of the patients had received hypotensive drugs within one week of the study and none had restricted intake of protein or salt. They were advised to restrict fluid intake so that weight gain between dialyses was less than 1.5 kg, but this was not always achieved. Less than two litres of fluid were removed at each dialysis.

Each study was performed at least 12 hours after the termination of a dialysis period. Mean blood pressure was measured in the brachial artery using a 19- or 25-gauge needle connected to a Statham pressure transducer. Though the patients showed a continuous spectrum with regard to their level of mean blood pressure, they were recognized clinically as two distinct groups according to the response of their blood pressure to ultrafiltration.

Group A consisted of seven patients with a wide range of mean blood pressure before dialysis, but they all responded to ultrafiltration by a decrease in mean blood pressure to 110 mm Hg or below without the production of side effects.

Group B consisted of six patients whose mean blood pressure before dialysis was always above 110 mm Hg. They developed severe muscle cramps or severe postural hypotension or occasionally increases in blood pressure when ultrafiltration was continued in an attempt to decrease mean blood pressure below 117 mm Hg. These patients complained of excessive thirst and were unable to limit fluid intake as instructed. Methyldopa would result in a variable decrease in blood pressure and usually a decrease in thirst within one month. The preponderance of males in this group is typical of our experience of more than 100 patients on maintenance dialysis therapy. Clinical details of the patients at the time of study are shown in the table.

Clinical Details of Subjects

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Duration of Disease (Years)</th>
<th>Duration of Dialysis (Months)</th>
<th>Mean B.P. (mm Hg)</th>
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<tr>
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<td></td>
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<tr>
<td>1*</td>
<td>43</td>
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<td>Group B:</td>
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<tr>
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<tr>
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<tr>
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<td>45</td>
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</tbody>
</table>

*Patients had accelerated hypertension at the onset of the dialysis programme.

Methods

Plasma Renin Concentration was measured by the method of Brown et al. (1964) in blood drawn from a forearm vein at 09.00 hours with the patient fasting and having been recumbent for one hour.

Plasma Sodium was measured by flame photometry.

Exchangeable Sodium was measured by the isotope dilution technique using $^{24}$Na (Radiochemical Centre, Amersham). About 40 μCi of $^{24}$Na was weighed in a syringe and injected intravenously, the barrel of the syringe being withdrawn several times to ensure complete injection of the dose into the subject. Standard solutions were prepared by diluting a weighed amount of the original solution to a known volume with saline. Subjects took their normal diet and activity during the subsequent 24-hour equilibration period but avoided strenuous physical exertion. Urine was collected during the 24-hour period. Duplicate blood samples were taken in heparinized tubes at the end of the equilibration period. Polyethylene containers were used for all specimens. Aliquots of the 24-hour urine collection, plasma, and standard solutions were assayed for radioactivity. The activity of plasma samples was usually four to five times background, and counting errors were less than $\pm 2\%$. Corrections for decay during the counting period were made.

Total exchangeable sodium (mEq) =

$^{24}$Na space (l) $\times$ plasma sodium concentration (mEq/l.)

where

$^{24}$Na space (l) = dose injected—dose excreted in urine plasma concentration of $^{24}$Na

Lean Body Mass was determined by the formula of Edwards and White (1959) from height, body weight, and measurements of skin fold thickness using spring calipers at 5 cm to the left of the umbilicus, at the inferior angle of the scapula, and at the middle of the posterior surface of the left upper arm.

Results

Single values for plasma renin concentration are shown in fig. 1. Normal values are between 4 and 20 U/l. The mean value for group A is lower than that of group B and the difference between them is significant ($P < 0.05$). However, there is an overlap of values between the two groups.

Plasma renin concentration plotted against mean blood pressure is shown in fig. 2. Plasma renin concentration is plotted on a logarithmic scale since any effect of renin on blood pressure would be in the form of a log-dose response. There was a tendency for the higher mean blood pressure to be associated with a higher renin level, but this did not reach statistical significance ($0.05 < P < 0.1$).

Single values for exchangeable sodium/kg lean body mass are shown in fig. 3. The mean value for group B was marginally but
not significantly lower than group A (P < 0.9). All the measurements for group B were within the range found for group A.

There was no relation between exchangeable sodium/kg lean body mass and blood pressure in either group alone or in the combined groups (fig. 4).

Paired data for plasma renin and exchangeable sodium/kg lean body mass are shown in figs. 5 and 6 for groups A and B respectively. An inverse relation was found for group A (r = 0.77, P < 0.05), but not for group B (r = 0.16, P > 0.1). In the latter group the values for plasma renin concentration were higher for the level of exchangeable sodium than in group A.

The product of plasma renin concentration and exchangeable sodium/kg lean body mass ("effective" plasma renin concentration) is shown in fig. 7. There is a significant difference between the means of the two groups (P < 0.01) with no overlap of values.
The regression line for the combined groups of "effective" plasma renin concentration against mean blood pressure is significant, as shown in fig. 8 (P < 0.05).

![Graph showing the correlation between effective plasma renin and mean blood pressure](image)

There was no significant difference in plasma sodium between groups A and B (0.7 > P > 0.6) and plasma sodium showed no correlation with plasma renin concentration in either group A (P > 0.1) or group B (P > 0.1) or in both groups combined (P > 0.1).

Discussion

In the early stages of development of maintenance dialysis therapy it was recognized that hypertension which was even severe enough to cause blindness could be controlled and vision restored by ultrafiltration with removal of salt and water (Shaldon et al., 1963). It was concluded by some workers that hypertension could be controlled in all such patients by adequate removal of salt and water (Comty, 1968).

It was later recognized, however, that hypertension in other patients was resistant to removal of salt and water but did respond to bilateral nephrectomy (Onesti et al., 1968). There were fewer "resistant" patients than "responsive" patients and they had high levels of plasma renin concentration (Brown et al., 1969). Thus it was assumed that hypertension in the smaller resistant group was caused by too much renin, whereas blood pressure in the responsive group was caused by too much sodium and water.

Goss et al. (1967) and Reubi et al. (1970) described a reduction in cardiac index associated with the ultrafiltration of dialysis. These data were interpreted by other workers (Brown et al., 1971; Craswell et al., 1972) as indicating that control of blood pressure by ultrafiltration in the responsive group was due to decreased cardiac output. However, mean blood pressure in the series of Goss et al. (1967) did not change despite the reduction in cardiac index.

The evidence produced from this study supports a unifying concept that associates both renin and exchangeable sodium in determining the level of blood pressure in all patients of both groups. Exchangeable sodium alone could not be responsible for the difference between the two groups, since mean values were similar in both groups and all values for the resistant group were within the range of the responsive group. Wilkinson et al. (1970) also described similar values to this study with a large overlap of values for patients in similar clinical groupings. Lack of sensitivity of the technique cannot account for the failure to detect differences in exchangeable sodium/kg lean body mass since Blumberg et al. (1967) found a narrow range of 59.5 ± 1.1 S.D. mEq/kg lean body mass for a control series of 10 subjects.

Nor could plasma renin concentration be the sole difference between the two groups. Though higher mean blood pressure was associated with higher values for plasma renin concentration, the correlation was not significant and there was an overlap of values for plasma renin concentration between the resistant and the responsive groups. These findings have also been found by other workers (Brown et al., 1969). Wilkinson et al. (1970) found a statistical correlation between plasma renin concentration and both systolic and diastolic blood pressures but also commented on the gross overlap of values. They described similar values of plasma renin concentration in patients who had systolic and diastolic pressures differing by as much as 100 and 60 mm Hg respectively.

The unifying concept pursued in this study is that renin has a pressor potential in both groups of patients but its effect is modified by the level of exchangeable sodium. Bianchi et al. (1968) showed that a decrease in sodium diet in dogs decreases the pressor effect of infused renin. The "effective" plasma renin concentration must therefore be calculated from the measured plasma renin concentration by introducing a factor linked to exchangeable sodium.

Our studies in the responsive group showed an inverse relation between exchangeable sodium and plasma renin concentration. This supports the observations of Bianchi et al. (1972) that the kidney with terminal disease is still capable of secreting renin in response to decrease in exchangeable sodium. We postulate that the pressor effect of this increased secretion of renin is reduced by the lowered level of exchangeable sodium and that blood pressure remains normal because the product of the two factors tends to decrease slightly as a result of dialysis. Analysis of the data of Bianchi et al. (1972) provides support for this thesis.

The resistant group shows a different pattern in these paired factors. There is an inappropriately high level of plasma renin concentration for the corresponding level of exchangeable sodium, a phenomenon also noted by Davies et al. (1973). A reduction in exchangeable sodium might thus cause an inappropriately large increase in plasma renin concentration. The product of these two factors—"effective" plasma renin concentration—is higher for every patient in this group than for any patient in the responsive group.

Our results show that effective plasma renin concentration provides a clear demarcation between the two groups, whereas...
plasma renin concentration alone provides an overlapping zone. Moreover, effective plasma renin correlates significantly with mean blood pressure, whereas plasma renin concentration alone does not.

The reason for the inappropriately high plasma renin concentration for the level of exchangeable sodium is probably due to other factors known to stimulate renin secretion. Included in these factors is ischaemia of the juxtaglomerular apparatus. Our experience that patients with resistant hypertension show more proliferation of the intima of the intrarenal arterioles supports this idea.

We wish to thank the staff of the M.R.C. High Blood Pressure Unit, Glasgow, for their helpful discussion, and Dr. M. Tree for performing the renin estimations.

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References


Single-dose, “Block-Replace” Drug Therapy in Hyperthyroidism

P. H. WISE, MILLICENT MARION, R. W. PAIN

*British Medical Journal*, 1973, 4, 143–145

Summary

In 30 consecutive hyperthyroid patients with diffuse goitre divided dose therapy with carbimazole 40 mg and triiodothyronine 80 μg daily was shown to produce total or subtotal block in thyroid hormonogenesis. Once produced, this block could be invariably maintained with an equivalent single daily dose for periods up to three years. Its notable acceptability to patients, a more stable degree of eutrophic control, ease of assessing suppressibility of trapping, and ability to treat patients in remote areas all support a wider use of this mode of therapy.

Introduction

In the drug treatment of hyperthyroidism it has been customary to use thiourea derivatives in a divided daily regimen, titrating dosage against clinical and biochemical thyroid status and only occasionally adding thyroid hormone replacement to prevent or correct iatrogenic hypothyroidism. This approach carries certain disadvantages—the need for periodic and sometimes frequent evaluation to prevent swings in thyroid status and the unreliability of clinical assessment of euthyroidism, especially when using propylthiouracil (Christensen et al., 1969) and in the early months of treatment where normal serum thyroxine (T-4) levels may not reflect euthyroid secretory pattern to disproportionately high triiodothyronine (T-3) concentrations (Bellarbarba et al., 1972). Furthermore, desired dose frequency is sometimes not adhered to, and the nuisance value of divided daily dosage can act as an incentive for subtotal thyroidectomy when on other grounds surgery may not be indicated.

The purpose of this study was to assess the efficacy of a regimen designed to block thyroid hormone synthesis as completely as possible using carbimazole while maintaining constant euthyroidism by replacement with triiodothyronine, both drugs being subsequently given in single daily dosage.

Subjects and Methods

After feasibility studies had been carried out in eight subjects with varying doses of carbimazole, 30 consecutive hyperthyroid patients aged 40 years or less with isotopically proved diffuse thyroid enlargement were studied. Clinical assessments were carried out by one observer (P.H.W.).

Total serum thyroxine was estimated by the method of Murphy (1965) (95% confidence limits for euthyroidism: 6-4-12-0 μg/100 ml), and thyrobinding index (T.B.I.) by the method of Oldfield and Pain (1969) (95% confidence limits for euthyroidism: 0-85-1-15); a free thyroxine index (F.T.I.) was derived from the ratio T-4/T.B.I. (95% confidence limits for euthyroidism: 6-3-12-3). Technetium (99mTc) uptake test and simultaneous scintiscanning were performed with a Nuclear Chicago gamma camera 40 minutes after an intravenous dose of 99mTc (Wise et al., 1973) (95% confidence limits for euthyroidism: 2.0-6-0% of dose).