SODIUM CONSERVATION IN CHRONIC RENAL FAILURE: STUDIES USING ORAL DIAZOXIDE

J. D. SWALES, H. THURSTON AND J. E. F. POHL

University Department of Medicine, Royal Infirmary, Manchester

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SUMMARY

1. The defect in sodium conservation shown by patients with advanced chronic renal failure has been studied during the administration of diazoxide.
2. All nine patients showed a reduction in urinary sodium concentration to levels substantially lower than those which can normally be produced in such patients even with prolonged sodium depletion. Seven patients produced a nearly sodium-free urine. In all patients this effect could be reversed by the administration of high doses of frusemide. The fall in urinary sodium concentration was associated with a sustained fall in creatinine clearance in only two cases.
3. One patient with salt-losing renal disease showed a more modest fall in sodium concentration on treatment with diazoxide.
4. It is concluded that since the defect in sodium conservation shown by patients with chronic renal failure can be corrected without diminishing the osmotic load, it cannot be solely due to the effect of the osmotic diuresis upon residual functioning nephrons. It is suggested that the distal tubular transport mechanism for sodium is saturated by the increased delivery of sodium from the proximal tubule.

Key words: sodium, renal failure, creatinine clearance, sodium-losing renal disease.

Patients with chronic renal failure are unable to conserve sodium during severe salt restriction. This defect, which was initially demonstrated in terms of chloride balance (Peters, Wakeman & Lee, 1929), is due to the inability of such patients to reduce the urinary sodium concentration below a fixed minimum (Coleman, Arias, Carter, Rector & Seldin, 1966; Kleeman, Okun & Heller, 1966). Coleman et al. (1966) have suggested that this ‘threshold’ effect is due to an osmotic diuresis through residual functioning nephrons: this is known to impair tubular sodium reabsorption (Mudge, Foulks & Gilman, 1949). An alternative view, rejected by Coleman et al. (1966), is that distal tubular sodium transport is saturated secondary to the increased

Correspondence: Dr J. D. Swales, University Department of Medicine, Royal Infirmary, Manchester M13 9WL.
proximal tubular sodium rejection which probably occurs in renal failure (Platt, 1950). Merrill & Hampers (1971) suggest a third mechanism, i.e. impairment of sodium reabsorption secondary to structural tubular changes.

The mechanism of salt conservation in renal failure cannot be adequately investigated by salt depletion as this decreases the glomerular filtration rate (Landis, Elsom, Bott & Shiels, 1935; Nickel, Lowrance, Leifer & Bradley, 1953; Levin & Cade, 1965) which lowers both the osmotic and sodium load upon the nephron. Diazoxide causes sodium retention by stimulating proximal tubular sodium reabsorption, probably as an indirect effect of its peripheral vascular action (Pohl, Thurston & Swales, 1972). Since this effect is independent of changes in glomerular filtration or osmolar excretion, it provides a unique tool for investigating renal sodium conservation in renal failure. We have accordingly studied sodium excretion in a group of patients with chronic renal failure who were undergoing treatment with oral diazoxide.

METHODS

Nine patients with advanced chronic renal failure (Table 1) were studied for 7–14 days during treatment of hypertension with oral diazoxide (200–600 mg/day). Seven cases had been receiving a 20 mmol sodium per day diet for a minimum of 2 weeks before study: cases 7 and 8 had been receiving a 50 mmol sodium per day diet for a similar period. Patients with a creatinine clearance of less than 3 ml/min were receiving an 18 g/day protein diet and the remaining patients a 50 g/day diet, except for case 9 who ate an unrestricted protein diet.

One non-hypertensive patient with salt-losing renal disease was studied (case 10). This patient presented with Addisonian pigmentation, dehydration and uraemia. She required intravenous infusions of sodium chloride followed by a 100 mmol salt supplement daily. During the period of study her sodium intake was reduced to 50 mmol daily and after 4 days 300 mg of diazoxide was given daily for 5 days. After a further 6 days 9α-fluorohydrocortisone was given orally in doses of 0-3 mg daily for 3 days.

Daily 24 h urine and blood samples were collected from all patients. Creatinine was measured on a Technicon AutoAnalyser; sodium and potassium by flame photometer; urinary
osmolality was measured on fresh specimens from six patients cryoscopically (Advanced Instruments).

**RESULTS**

All nine patients exhibited a major fall in urinary sodium concentration to values which were near zero in seven cases (Table 2, Figs. 1–3). Small doses of frusemide or ethacrynic acid

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Initial values</th>
<th>Final values</th>
<th>High-dose frusemide values</th>
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<tr>
<td></td>
<td>C&lt;sub&gt;Cr&lt;/sub&gt; (ml/min)</td>
<td>U&lt;sub&gt;Na&lt;/sub&gt; (mM)</td>
<td>UV&lt;sub&gt;Na&lt;/sub&gt; (mmol)</td>
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<tr>
<td>1</td>
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<td>3</td>
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<td>23·0</td>
<td>18·4</td>
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<tr>
<td>6</td>
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<td>36·8</td>
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<tr>
<td>9</td>
<td>16·0</td>
<td>28·0</td>
<td>30·8</td>
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(<200 mg/day) had no influence upon the degree of sodium retention. The reduction in urinary sodium concentration coincided with an increase in potassium concentration (Table 3), although the change in concentration of these two ions was not equimolar. Net osmolar excretion (urine osmolality × urine volume) did not change significantly in the six patients in whom it was measured (Table 3). Mean serum sodium concentration was unchanged (Table 3). A sustained fall in creatinine clearance occurred in two patients (cases 1 and 3: Table 1). In these there was a close relationship between the changes in creatinine clearance and urinary sodium concentration although the decrease in urinary sodium concentration was disproportionately greater (Fig. 2). In the other seven patients there was no association between urinary sodium concentration and change in creatinine clearance (Fig. 1).

Large doses of frusemide (500 mg to 1 g daily) were administered to correct the sodium retention. A rise in urinary sodium concentration occurred. This was associated with a slight rise in creatinine clearance in five out of nine patients and a fall in the remaining four (Table 2).

The patient with salt-losing renal disease showed a steady initial urinary sodium concentration of 40–45 mM. The administration of diazoxide resulted in a substantial fall in sodium concentration, which was reversed when the drug was stopped (Fig. 3). No change in urine concentration was produced by 9α-fluorohydrocortisone. A slight increase in creatinine clearance during the course of the study was paralleled by a rise in urinary sodium concentration (Fig. 3).
DISCUSSION

Patients with chronic renal failure differ from normal individuals in being unable to produce a near sodium-free urine (Coleman et al., 1966; Kleeman et al., 1966). Although this has been described as a 'gradient defect' (Coleman et al., 1966), there is no close analogy between this phenomenon and that seen in 'distal' renal tubular acidosis, where distal tubular hydrogen ion concentration cannot be increased above a fixed maximum however much the mechanism is stressed by ammonium chloride loading (Wrong & Davies, 1959). In chronic renal failure reduction of the sodium load by reducing glomerular filtration enables the urinary sodium concentration to fall (Coleman et al., 1966). The present studies show conclusively that urinary sodium concentration in patients with chronic renal failure can be reduced to the very low values seen in salt-depleted normal subjects. The values obtained in our patients were well below those obtained by Coleman et al. (1966) and Kleeman et al. (1966) in patients subjected to prolonged sodium depletion. Since neither creatinine clearance nor the serum sodium concentration changed consistently in the majority of patients there is no evidence that the tubular load of sodium is the limiting factor in urinary sodium conservation. Neither can the defect be one which imposes a fixed limitation upon the ability of the distal tubule to maintain a gradient of sodium concentration between the blood and tubular fluid. Likewise, our results do not support the contention that the osmotic diuresis through residual nephrons produces a defect in sodium conservation (Stanbury & Mahler, 1959; Bricker, Klahr & Rieselbach, 1964; Coleman et al., 1966). Diazoxide tends to produce an increase in urinary osmolality.

Fig. 1. Creatinine clearance and urinary sodium concentration in a patient treated with oral diazoxide who showed no consistent change in glomerular filtration (case 6).
through its effect upon free water clearance (Pohl et al., 1972) and osmolar excretion was not altered in the current experiments.

It is probable that diazoxide causes increased proximal tubular sodium reabsorption (Pohl et al., 1972) and therefore a decreased sodium load upon the distal tubule. If sodium transport at this site was normally saturated in these patients, the unique efficacy of diazoxide could be explained.

![Graph](image_url)

**FIG. 2.** Creatinine clearance and urinary sodium concentration in a patient treated with oral diazoxide who showed a fall in glomerular filtration during study (case 1).

There is evidence that, as the glomerular filtration rate falls, proximal tubular sodium reabsorption is decreased (Platt, 1950) although some workers would place the site of this homeostatic adjustment at a more distal level (Hayslett, Kashgarian & Epstein, 1969). The factors responsible for the adjustment have not been fully elucidated. They probably include, however, urea diuresis through residual nephrons (Bricker et al., 1964; Hayslett et al., 1969), hyperfiltration imposing an increased solute load (Bricker et al., 1964) and possibly a hormonal natriuretic factor (Slatopolsky, Elkan, Weerts & Bricker, 1968) identical to that postulated by De Wardener, Mills, Clapham & Hayter (1961). Whichever of these mechanisms predominates, we believe that the increased sodium load determines the limitation on sodium reabsorption, distally. This view is supported by studies with hypo-osmotic saline loading in dogs, which indicate a saline-induced limit upon distal tubular sodium transport which cannot be mimicked by
mannitol infusions (Stein, Abramson, Kahn & Levitt, 1967). In those few patients in whom diazoxide was associated with a fall in glomerular filtration rate, a double effect would occur since both actions relieve the distal tubular sodium load. It is noteworthy that, where a fall in the glomerular filtration rate did occur, the resultant fall in urinary sodium concentration was considerably greater than that produced by Coleman et al. (1966) when the glomerular filtration rate of sodium depleted chronic renal failure patients was reduced with Trimethaphan. In these latter experiments, urinary sodium concentration remained at an abnormally high

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\text{\textbf{FIG. 3. Creatinine clearance and urinary sodium concentration in a patient with salt-losing renal disease treated with 300 mg of diazoxide daily and then with 0.3 mg of 9α-fluorohydrocortisone daily (case 10).}}
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<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>Final</th>
<th>(P) value</th>
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<tbody>
<tr>
<td>Mean (U_{Na}) (mM)</td>
<td>28.0 (9.6)</td>
<td>2.1 (0.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean (U_K) (mM)</td>
<td>37.4 (15.9)</td>
<td>44.0 (15.2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean (U_{osm}) (mosmol/24 h)*</td>
<td>263.8 (46.3)</td>
<td>256.5 (58.1)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Mean (S_{Na})</td>
<td>129.1 (5.5)</td>
<td>129.6 (6.3)</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

* Observations on six patients only (cases 1, 2, 3, 5, 6 and 7).
value for salt depleted subjects. Thus, when these workers reduced creatinine clearance in a patient from 13.9 ml/min to 5.9 ml/min, mean urinary sodium concentration only fell from 8.7 mM to 6.8 mM. Our results cannot, therefore, be explained on the basis of small changes in glomerular filtration rate which were undetected because of inaccuracies involved in measuring this variable by means of endogenous creatinine clearance.

One finding of Coleman et al. (1966) is apparently inconsistent with our conclusion that the increased sodium load determines the limitation upon distal sodium reabsorption. An increase in urine volume induced by water diuresis is associated with a proportionate increase in sodium excretion, since urinary sodium concentration remains approximately constant. This is interpreted as indicating that the distal tubule cannot decrease urinary sodium concentration below a fixed value against an osmotic gradient, and is regarded as evidence against saturation of the sodium transport mechanism at this site. The natriuresis observed by these workers may, however, have represented diminished proximal rather than distal tubular sodium reabsorption. This is a distinct possibility in patients subjected to haemodilution since a reduction in haematocrit or plasma protein concentration may impair proximal tubular sodium reabsorption (Schrier & de Wardener, 1971).

The patient with salt-losing renal disease (Fig. 3) also showed a fall in urinary sodium concentration, although the final sodium concentration was not as low as in the other patients studied. Clearly the sodium retaining action of diazoxide upon the renal tubule is preserved in the more florid salt-losing states, as well as in other forms of chronic renal disease. The resistance to mineralocorticoids is well documented (e.g. Rosenheim, 1956) and supports the contention that diazoxide and mineralocorticoids act at different sites. Our observations on this patient indicate that even in this situation the defect is not a true ‘gradient defect’ since the blood–tubular fluid sodium gradient can be increased.

Our results do not enable us to discriminate between the possibility that a structural defect imposes a maximum rate upon distal tubular transport as postulated by Franklin & Merrill (1960) and a high sodium load resulting in saturation of a normally functioning distal tubular transport mechanism. However, the fact that the distal mechanism is normally of limited capacity by comparison with the more proximal mechanisms (Giebisch & Windhager, 1964) suggests that it is unnecessary to postulate an additional pathological impairment of distal function in chronic renal failure.

ACKNOWLEDGMENTS

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REFERENCES


