Abnormalities of sodium excretion and other disorders of renal function in fulminant hepatic failure

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SUMMARY Renal function was evaluated in 40 patients with fulminant hepatic failure. They were divided into two groups on the basis of glomerular filtration rates greater than 40 ml/min or less than 25 ml/min. A number of patients in group 1 had markedly abnormal renal retention of sodium together with a reduced free water clearance and low potassium excretion which could be explained by increased proximal tubular reabsorption of sodium. The patients in group 2 had evidence that renal tubular integrity was maintained when the glomerular filtration rate was ≥ 3 ml/min (functional renal failure), but evidence of tubular damage was present when this was < 3 ml/min (acute tubular necrosis).

A previous study of 48 patients with fulminant hepatic failure showed that 38 had evidence of renal impairment associated with a particularly poor prognosis (Wilkinson *et al.*, 1974a). A number of patients from that study whose renal function otherwise appeared to be normal showed marked renal retention of sodium. In the present series we studied an additional consecutive group of 40 patients to establish more precisely the functional changes occurring within the kidney, particularly the renal handling of sodium when the glomerular filtration rate is relatively well maintained.

Methods

Fulminant hepatic failure was caused by viral hepatitis in 10 patients (two being HBsAg positive), multiple anaesthetic exposures to halothane in nine, self-induced overdose with paracetamol (16), acute Budd-Chiari syndrome (one), hypersensitivity to pyrazinamide (one), acute fatty liver of pregnancy (two), and poisoning with *Amanita phalloides* (one). The patients, 29 female and 11 male, were aged between 15 and 66 years and all 40 had severe hepatic encephalopathy. The patients were all well hydrated and none had previously received diuretics or had a history of renal or cardiac disease. No fluids containing sodium were given for one hour

before the study. Arterial blood pressure, central venous pressure, and respiratory rate had been constant in all cases for at least six hours and no patient was bleeding.

Renal function was evaluated by inulin clearance (glomerular filtration rate), para-aminohippurate clearance (effective renal plasma flow), free water clearance (a measure of the patient's ability to excrete a water load), urinary sodium and potassium excretion, and microscopy of the sediment of a fresh urine specimen. Each patient was given a water load of 20 ml/kg body weight intravenously as 5% dextrose, over one hour. This procedure never reduced plasma sodium concentration by more than 3 mmol/l. Inulin and para-aminohippurate were then immediately infused intravenously, initially as a loading dose followed by a constant infusion. Urine collections were made from a three-way indwelling Foley bladder catheter every 30 minutes, ensuring by air displacement that the bladder was empty. Free water clearance was calculated as the difference between maximum urinary flow and osmolar clearance (Smith, 1956) for the 30 minute period of maximal diuresis after the water load was given. Values for inulin and para-aminohippurate clearance, corrected to a body surface of 1.73 sq.m were calculated from the mean of three consecutive 30 minute clearances—the first beginning 30 minutes after the loading doses of inulin and para-aminohippurate. Blood samples for osmolality, inulin, and para-aminohippurate concentrations were taken at the midpoint of each clearance period. Inulin and para-

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Fig. 1 Relationship between sodium excretion and glomerular filtration rate in the complete series.

aminohippurate concentrations were determined by standard biochemical methods (Varley, 1967), osmolality by depression of the freezing point, and sodium and potassium by flame photometry. The water load was not given to patients with urine volumes of less than 25 ml/h, and in severely oliguric patients (urine volume less than 12 ml/h) glomerular filtration rate was determined from the endogenous creatinine clearance based on 12 or 24 hour urine collections. In the latter group of patients para-aminohippurate clearance was not measured.

In all, 52 studies were carried out in the 40 patients.

Results

Glomerular filtration rate and urinary sodium

excretion ranged widely with values from less than 1 to 176 ml/min and from less than 1 to 295 mmol/24 hours respectively. Statistical analysis showed a highly significant correlation between these two measurements ($r = 0.49$, $p < 0.001$). However, the series was heavily weighted by the large number of patients with a markedly reduced glomerular filtration rate of less than 25 ml/min, all of whom had values for urinary sodium excretion of less than 25 mmol/24 hours. None of the patients had glomerular filtration rates between 25 and 40 ml/min, and in the 18 patients whose values were greater than 40 there was no correlation between the two variables (Fig. 1). The patients have therefore been grouped into those with a glomerular filtration rate of greater than 40 ml/min (group 1) and those in whom this was reduced to less than 25 ml/min (group 2).

GROUP 1 (PATIENTS WITH GLOMERULAR FILTRATION RATE GREATER THAN 40 ML/MIN) (Table 1)

All 18 patients in this group were receiving at least 100 mmol sodium daily (range 100-300 mmol) given in the form of fresh frozen plasma as treatment for their coagulation disturbance. A comparison of urinary sodium excretion and sodium intake showed that in 10 patients (sodium retainers) renal retention of sodium was marked, with a positive balance of at least 100 mmol on the day of investigation. Four of these patients were admitted to this unit within one day of the onset of fulminant hepatic failure and none of them had a negative sodium balance before their renal function was investigated. In the other six a previous negative sodium balance was most unlikely as they had not received diuretics or lost sodium by vomiting. A later test of sodium excretion in two of the sodium retainers and the remaining eight in group 1 showed that they had a normal sodium excretion or only moderate sodium retention (sodium

Table 1 Renal function in patients with glomerular filtration rate > 40 ml/min

Glomerular filtration rate (ml/min)	Renal plasma flow (ml/min)	Free water clearance (ml/min)	Plasma sodium concentration (mmol/l)	Sodium intake (mmol/24 h)	Total sodium loss* (mmol/24 h)	Urinary sodium excretion (mmol/24 h)	Plasma potassium concentration (mmol/l)	Potassium intake (mmol/24 h)	Urinary potassium excretion (mmol/24 h)	Arterial pH
Sodium excretors										
Mean										
113	730	6.5	133	175	128	123	3.6	70	53	7.49
± SD										
37	337	3.7	5	57	72	69	0.5	39	22	0.04
Sodium retainers										
Mean										
87	559	0.8	131	193	31	9	3.7	60	50	7.49
± SD										
40	271	1.9	7	67	44	8	0.5	53	50	0.05

*Includes urinary loss and gastric aspirate. Does not include stool and insensible losses.

Fig. 2 Comparison of glomerular filtration rate, free water clearance, and potassium excretion in patients with glomerular filtration rate > 40 ml/min. Values for potassium excretion in patients with arterial pH > 7.50 are not included (SE—sodium excretors, SR—sodium retainers; mean values with standard deviations shown)

excretors). In most cases excretion matched intake, and no positive balance exceeded 100 mmol/day.

A comparison of other renal function tests of the sodium retainers and sodium excretors showed a similar range of values for glomerular filtration rate (Fig. 2), renal plasma flow, plasma sodium concentration, and filtered load of sodium (the product of glomerular filtration rate and plasma sodium concentration). In all cases systolic arterial blood pressure exceeded 105 mmHg, with a central venous pressure ranging from 1 to 6 cm H₂O. There were differences, however, in the measurements of free water clearance, the mean value in the sodium excretors being significantly higher than that found in the sodium retainers (mean 6.5 ml/min ± 3.7 SD, mean 0.8 ml/min ± 1.9 respectively, $P < 0.001$) (Fig. 2).

There was a statistically significant relationship between free water clearance and filtered load of sodium ($r = 0.60$, $P < 0.005$) in the complete group, although four patients who could not excrete free water had relatively high values for the latter (greater than 11 mmol/min).

The sodium excretors and sodium retainers had similar mean values for urinary potassium excretion, but when patients with a severe alkalosis (arterial pH greater than 7.50) were excluded, significantly lower values for potassium excretion were found in those with severe sodium retention ($P < 0.005$) (Fig. 2). Urinary losses of potassium in excess of intake were seen only in patients with severe alkalosis. Mean values for plasma potassium, calculated potassium intake, and arterial pH were similar in the two groups and plasma potassium was unrelated to urinary potassium excretion ($r = -0.21$, NS).

Subsequent course Five of the 10 patients with severe sodium retention died, three of these developing renal failure before death. One of the five survivors regained her ability to excrete sodium normally while still in deep coma, but the remainder recovered consciousness before this occurred.

All the patients with a relatively good sodium excretion survived, though one case developed evidence of severe sodium retention before beginning to improve. This difference in mortality between the two groups is statistically significant ($P = 0.01$, Fisher's exact test), although they were otherwise similar in age, sex, aetiology of liver failure, grade of encephalopathy, and standard liver function tests.

Follow-up studies on four cases during recovery showed that glomerular filtration rate, renal plasma flow, and free water clearance returned to normal within two weeks.

GROUP 2 (PATIENTS WITH GLOMERULAR FILTRATION RATE LESS THAN 25 ML/MIN) (Table 2)

In addition to the three sodium retainers whose renal function subsequently deteriorated, there were 22 other patients in this group. Of these 25 only one survived.

Glomerular filtration rate varied from less than 1 to 24 ml/min. The 14 patients in whom this was ≥ 3 ml/min all had low urine sodium concentration values, the highest being 14 mmol/l with a mean of 5 mmol/l (± 4 , SD). These patients also had a hyperosmolar urine, the lowest value of the ratio between the urine and plasma osmolality being 1.09 with a mean of 1.17 (± 0.05 , SD). In contrast, when glomerular filtration rate was < 3 ml/min (13 cases, including two in whom it was previously ≥ 3 ml/min), values for urine sodium concentrations were relatively high (≥ 16 mmol/l in all but one case, mean 35 mmol/l, ± 18 SD) and the urine:plasma osmolality ratio low (≤ 1.09 , mean 1.02 ± 0.02 SD). In the patients in whom glomerular filtration rate fell from ≥ 3 to < 3 ml/min, the values for urine sodium concentration and urine:plasma osmolality changed accordingly.

Renal histology from necropsy examination was available in eight of the cases whose glomerular filtration rate was < 3 ml/min, and at least one of the following changes was present: tubular dilatation, tubular necrosis, interstitial oedema. In seven cases with a glomerular filtration rate of ≥ 3 ml/min renal histology was normal, but in three others changes similar to those occurring in the other group were found. However, these latter three patients all had terminal hypotension and anuria.

Examination of the urine sediment for granular and cellular casts did not necessarily distinguish

Table 2 Renal function in patients with glomerular filtration rate < 25 ml/min*

Glomerular filtration rate (ml/min)	Renal plasma flow (ml/min)	24 hour urine volume (ml)	Concentration				Urine: plasma osmolality
			Plasma urea (mmol/l)	Plasma creatinine (mmol/l)	Plasma sodium (mmol/l)	Urine sodium (mmol/l)	
Glomerular filtration rate ≥ 3 ml/min							
Mean	74	611	17	0.35	125	5	1.17
± SD							
8	66	512	14	0.35	10	4	0.05
Glomerular filtration rate <3 ml/min							
Mean	—	158	17	0.55	130	35	1.02
± SD							
1	—	91	11	0.39	7	18	0.02

* Full details relating to individual patients are available from the authors.

between these patients. Although casts were always found in those with a glomerular filtration rate of < 3 ml/min, these were also seen in the urine from seven of the other 14 patients.

Para-aminohippurate clearance was measured in nine of the patients with a glomerular filtration rate of ≥ 3 ml/min and values ranged from 9 to 201 ml/min.

Discussion

Renal retention of sodium, an impaired response to a water load and minor reductions in renal perfusion have all been described in infectious hepatitis (Cachera and Darnis, 1951; Wolf *et al.*, 1958; Dittrich, 1966). In the present study these changes were also found in patients with hepatic necrosis due to paracetamol overdose and multiple exposures to halothane. Thus it is likely that these changes are secondary to hepatocellular disease rather than a direct nephrotoxic effect of these agents, even though paracetamol has been described as a nephrotoxin (Matthew, 1972). As in our previous study (Wilkinson *et al.*, 1974a) the incidence of renal failure in this series was similar in the different aetiological groups.

When assessing sodium and potassium excretion it is usual to base conclusions on the results of balance studies carried out for a minimum of three or four days. However, this is not possible in fulminant hepatic failure because of the unstable nature of the syndrome. The limitations of the value of the one day balances in the present study must therefore be borne in mind in the interpretation of the results. The separation of patients with a glomerular filtration rate greater than 40 ml/min into two groups on the basis of urinary sodium excretion is somewhat artificial in that a complete range of values was found. However, looking at the two ends of the spectrum might help in understanding the pathophysiology of sodium and water retention in this

condition. Since glomerular filtration and renal plasma flow were similar in those patients with and without sodium retention, it is unlikely that changes in these two factors were of major importance in the pathogenesis of sodium retention. Free water is normally generated in the kidney as a result of selective sodium (or chloride) absorption from the ascending limb of the loop of Henle so that early distal tubular fluid is hypotonic—that is, contains ‘free water’. This is therefore dependent on adequate delivery of sodium to the ascending limb and this depends on both the filtered load and proximal tubular reabsorption of sodium. Although there was a statistical relationship between free water clearance and filtered load of sodium a number of patients with relatively high values for the latter were unable to excrete free water, so again other factors must be involved. One explanation for both sodium and water retention is that the major site of abnormal sodium reabsorption is the proximal tubule since this would limit the amount of sodium delivered to the diluting segment for generation of free water. Hyperaldosteronism, even if present, would therefore not be of major importance in the abnormal sodium retention unless it has an action on the proximal in addition to the distal tubule of the nephron. Information on this latter point is conflicting (Hierholzer and Stolte, 1969; Lynch *et al.*, 1972). However, the low potassium excretion found in association with sodium retention is further evidence against hyperaldosteronism. Why excessive proximal sodium reabsorption should occur is therefore uncertain, but previous sodium depletion seems unlikely. Alternative explanations for the impaired free water clearance, such as inappropriately high circulating levels of antidiuretic hormone cannot, however, be excluded.

These findings differ from those described in cirrhosis, as retention of sodium in the latter condition is often accompanied by a well-maintained

capacity for free water clearance, indicating that in such patients excessive distal sodium reabsorption is important (Baldus *et al.*, 1964).

Free water clearance was determined in 24 investigations performed and, not surprisingly, a markedly reduced value (less than 1 ml/min) was related to the occurrence of hyponatraemia (plasma sodium concentration less than 130 mmol/l, $P = 0.03$, Fisher's exact test). Thus hyponatraemia is likely to be largely due to overhydration.

Although urinary loss of potassium is said to be high in fulminant hepatic failure (Trey and Davidson, 1970), we have not been able to confirm this, except in patients with a marked alkalosis. Some patients appeared to be in positive potassium balance yet values for plasma potassium concentration were often reduced or at the lower limit of normal. Other significant losses, such as gastric aspiration and diarrhoea, were not usually found.

Renal failure in fulminant hepatic failure and cirrhosis is often classified as being either 'functional' or 'acute tubular necrosis'. In the present study the patients with a glomerular filtration rate of between 3 and 25 ml/min had a low urine sodium concentration and a hyperosmolar urine, features suggestive of intact tubular function, though more specific tests for this (urinary acidification, excretion of amino-acids, and tubular proteins) were not carried out. However, since renal histology was normal in this group it is reasonable to refer to the renal failure as 'functional'. The reduced para-aminohippurate clearance in these patients suggests that the pathophysiology is of reduced renal perfusion, as has been described in cirrhosis (Baldus *et al.*, 1964; Epstein *et al.*, 1970). When the glomerular filtration rate was less than 3 ml/min the urine was virtually isomolar and the urine sodium concentration relatively high, findings that are usually considered to be indicative of acute tubular necrosis (Levinsky, 1966), and in these patients an abnormal renal histology was found. Granular or cellular casts in the urine sediment could not satisfactorily distinguish between the types of renal failure and, indeed, casts may be found in any jaundiced patient with otherwise good renal function (Eknayan, 1974). The difference between these two types of renal impairment may be quantitative rather than qualitative in that tubular function appears to be maintained until renal perfusion is so low that the glomerular filtration rate falls to less than 3 ml/min. Below that level tubular necrosis occurs. The progression of some patients from functional renal failure to acute tubular necrosis is additional evidence that these two types

of renal failure are part of a single spectrum. In other studies we have shown that there is a close correlation between the occurrence of both functional renal failure and acute tubular necrosis with endotoxaemia (Wilkinson *et al.*, 1974b). Endotoxin, a potent renal vasoconstrictor, is derived from gram negative organisms in the bowel, and presumably escapes into the systemic circulation because of impaired hepatic clearance.

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