Diuretic-induced renal impairment without volume depletion in cirrhosis: changes in the renin-angiotensin system and the effect of β -adrenergic blockade

S. P. WILKINSON
M.D., M.R.C.P.*

P. G. WHEELER
D.M., M.R.C.P.

M. BERNARDI
M.D.

I. K. SMITH
Ph.D.

R. WILLIAMS
M.D., F.R.C.P.

Liver Unit and Department of Biochemical Pharmacology, King's College Hospital and Medical School, Denmark Hill, London, S.E.5

Summary

In 4 patients with cirrhosis and ascites, diuretic therapy resulted in an impairment of renal function that was associated with a rise in plasma renin activity (PRA). In 3, this occurred in the absence of volume depletion. When diuretics were discontinued, renal function returned to normal. β -adrenergic blocking drugs were then given to suppress renin secretion and diuretics restarted. On this occasion, impairment of renal function did not occur. In 2 further patients, administration of β -adrenergic blockers during a period of diuretic-induced renal impairment resulted in an improvement in renal function. Although these findings may indicate that diuretic-induced renal impairment in cirrhosis is at least partly due to activation of the renin-angiotensin system, in another group of patients a diuretic-induced rise in PRA was not associated with a deterioration in renal function.

Introduction

Ascites due to cirrhosis can usually be treated successfully with a combination of dietary sodium restriction and diuretics. The latter, however, may cause impairment of renal function, the frequency in one series amounting to 26% of 85 patients (Rodés, Bosch and Arroyo, 1975). In such cases the withdrawal of diuretics usually results in a prompt improvement in renal function, but if continued the situation may become irreversible, often with the precipitation of hepatic encephalopathy.

The underlying mechanism may, in part, be depletion of the plasma or extracellular fluid volumes.

*Present address: Gloucestershire Royal Hospital, Gloucester, Gloucestershire.

The maximum rate at which ascites can be mobilized has been reported to be less than 11/day (Shear, Ching and Gabuzda, 1970) and a negative fluid balance in excess of this would be expected to lead to a contraction in the extracellular fluid volumes with consequent reduction in renal blood flow. Lieberman and Reynolds (1966) showed that the fall in creatinine clearance due to diuretics in 5 patients was related to the contraction of the plasma volume, but in a later study infusions of plasma did not prevent the fall in creatinine clearance although saline infusions were effective (Lieberman, Ito and Reynolds, 1969). If extracellular volume depletion were the only factor involved, one would expect to find a raised blood haematocrit, yet this has only rarely been observed. Another possible mechanism may be related to the renin-angiotensin system, since diuretics almost invariably increase renin secretion and angiotensin II is a powerful renal vasoconstrictor. It has been shown that β -adrenergic blocking drugs such as propranolol may prevent the diuretic-induced increased renin secretion (Winer *et al.*, 1969; Leonetti *et al.*, 1975), and in the study reported here the effect is evaluated of these drugs on the development of diuretic-induced renal impairment in 6 patients with cirrhosis and ascites. The effect of diuretics on plasma renin activity and creatinine clearance in 8 further patients who did not develop overt renal impairment was also investigated.

Patients and methods

The 6 patients who developed renal impairment whilst receiving diuretics all had histologically proved cirrhosis attributed to excess alcohol intake. Three were male and ages ranged from 36 to 53 years. All

FIG. 1. Illustrating the relationships between treatment, renal function and plasma renin activity in 4 patients who developed renal impairment whilst receiving diuretics (values given are the mean $\pm$ s.e. mean)

had marked ascites. None of the patients had a history of hepatic encephalopathy or recent gastrointestinal haemorrhage and liver function tests showed marked abnormalities with the prothrombin time ranging from 5 to 14 sec prolonged, the serum albumin concentration from 19 to 39 g/l (normal 35 to 50) and the serum bilirubin from 19 to 390 μ mol/l (normal 3 to 20).

The causes of the cirrhosis in the other 8 patients were alcohol (6 cases), chronic active hepatitis (one), and cryptogenic (one). All were male with an age range of 35 to 64 years. All patients were similar both clinically and with respect to liver function tests.

All 14 patients were maintained on a 20–30 mmol daily sodium intake throughout their hospital stay.

Blood samples for plasma renin activity (PRA) were taken after the patients had been supine for at least one hr. PRA was determined by radioimmunoassay for angiotensin I generation, this being linear with time, as described by Wilkinson *et al.* (1977b).

Results

Effect of β -adrenergic blockade on diuretic-induced renal impairment

In 4 patients the plasma urea and creatinine concentrations were initially within normal limits (< 6.7 mmol/l, < 0.13 mmol/l respectively) and became elevated within 2 days of starting diuretic therapy (maximum rise of up to 19.2 mmol/l and 0.30 mmol/l). The diuretics were then discontinued and the urea and creatinine concentrations returned

to normal within one week (Fig. 1). The drugs and daily dosage in 3 of these patients were as follows: spironolactone 50 mg (first patient), spironolactone 200 mg (second patient), and spironolactone 200 mg with frusemide 40 mg (third patient). In the fourth patient (Fig. 2) renal impairment occurred on 3 separate occasions when given diuretics, comprising spironolactone 100 mg initially, then spironolactone 50 mg with frusemide 20 mg, and finally amiloride 10–30 mg. The plasma urea and creatinine concentrations fell to normal between treatments.

The development of renal impairment in 3 of the patients was *not* associated with weight loss or a negative sodium balance, the renal excretion of sodium remaining at < 10 mmol/day. In case 2, however, the sodium excretion increased from 8 to 102 mmol/day and she lost 4 kg in weight in 5 days. Haematocrit values did not change by more than 3% in any patient.

When the plasma urea and creatinine concentrations had returned to normal, either propranolol (up to 160 mg/day) or practolol* (up to 600 mg/day) were given alone for 3 days. During this time, effective β -blockade was achieved as shown by a fall in the resting pulse rate of at least 15%. This had no effect on sodium excretion or the plasma urea concentration. Diuretics were then reinstituted, the β -blocker being continued, and in each case there was a satisfactory diuresis, with a steady weight loss of at

*Practolol has now been withdrawn from use in the U.K.

FIG. 2. Serial study in one patient developing diuretic-induced renal impairment. PRA, plasma renin activity.

least 0.5 kg/day until the patient was rendered free of ascites and able to leave hospital. The greatest loss (21 kg in 35 days) occurred in case 4 (Fig. 2). The dose of diuretics used on the second occasion in cases 2 and 3 was identical to that previously used, in case 1 the dose of spironolactone was initially identical but later doubled to 100 mg daily, and in case 4 frusemide (40 mg daily) was added to the amiloride. The plasma urea and creatinine concentration remained normal throughout the period of successful diuresis (Fig. 1).

Before diuretic therapy, the PRA was normal in 2 of the patients (< 3.80 nmol/litre/hr), but increased up to 7.96 nmol/litre/hr in the others (Fig. 1). There was a substantial rise in association with development of renal impairment (maximum value 16.92 nmol/litre/hr), but a return to values similar to those initially found when the diuretics were discontinued. During the period of treatment with propranolol or practolol alone, there was a further fall in PRA although this did not achieve statistical significance (from 4.18 nmol/litre/hr $\pm$ s.e. 1.43 to 2.18 nmol/litre/hr $\pm$ 0.40, $P < 0.3$). When the diuretics were added to the β -blocker there was no further change.

The rise in PRA following diuretics was associated with a fall in plasma sodium concentration (from 132 mmol/l $\pm$ s.e. 2, to 126 mmol/l $\pm$ s.e. 2, $P < 0.05$) and an increase in plasma potassium (from 4.2 mmol/l $\pm$ s.e. 0.2, to 5.3 mmol/l $\pm$ s.e. 0.3, $P < 0.005$), but daily urea, creatinine and electrolyte estimations showed that renal function had deteriorated before these changes occurred.

In 2 further patients who also had initially normal plasma urea and creatinine concentrations, β -blockers were added to the diuretic regime during the period of diuretic-induced renal impairment. In one, increasing doses of diuretics were used over 4 weeks so that he was eventually receiving spironolactone 800 mg and frusemide 60 mg daily (Fig. 3). Despite these high doses the daily renal sodium excretion never exceeded 8 mmol and the plasma urea concentration rose from 5.3 to 15.2 mmol/l (plasma creatinine from 0.10 to 0.26 mmol/l). Practolol, starting with a dose of 200 mg daily but increasing until there was evidence of effective β -blockade with a dose of 600 mg daily after 3 days, was added to the same dose of diuretics. He then had a natriuresis and lost 21 kg in weight before leaving hospital 4 weeks later, the plasma urea progressively falling to a normal value of 5 mmol/l (creatinine to 0.10 mmol/l) 2 weeks after effective β -blockade had been achieved. In the other patient the plasma urea concentration rose from 3.7 to 9.0 mmol/l (creatinine from 0.06 to 0.12 mmol/l) within 3 days of receiving spironolactone 1000 mg daily with frusemide 40 mg daily. Weight loss during this period was 2.6 kg. Propranolol 80 mg daily was added to the diuretics and the plasma urea fell to 6.4 mmol/l (creatinine, to 0.09 mmol/l). This patient, who had a severe alcoholic hepatitis, became encephalopathic at this stage and diuretic treatment was discontinued. He later developed renal failure spontaneously and died in hepatic coma. There was no change in haematocrit in either of these patients with

development of renal impairment, and PRA was not determined.

In one of these 6 patients there was no change in arterial blood pressure during β -blockade. In the others the systolic pressure fell between 10 and 20 mmHg.

FIG. 3. Serial study in one patient given practolol during diuretic-induced renal impairment

Effect of spironolactone on creatinine clearance and plasma renin activity in patients not developing overt renal impairment

These 8 patients with ascites had never previously received diuretics. After 2 to 4 days of bed rest and a

20 mmol daily sodium intake, the endogenous 24-hr creatinine clearance was evaluated (values of 64 to 114 ml/min) and PRA determined (1.00 to 4.55 nmol/litre/hr). They were then given spironolactone, starting with a daily dose of 100 mg which was increased by 100 mg every 2 or 3 days until the renal sodium excretion exceeded 100 mmol/24 hr. The daily dose required ranged from 200 to 600 mg. Creatinine clearance and PRA were then determined again.

In all patients there was a rise in PRA, the mean increase being 141% ($\pm$ s.e. 46). Three of the patients showed little or no change ($<15\%$) in creatinine clearance, but in the other 5 it fell by at least 40%. In the latter group there was a rise in the plasma urea and creatinine concentrations, but these did not exceed the upper limit of normal. Apart from the differences in the change in creatinine clearance, the 2 groups were otherwise similar regarding the initial values for PRA and creatinine clearance, the rise in PRA, the renal sodium excretion, weight loss, and the dose of spironolactone (Table 1).

Discussion

The absence of a natriuresis or weight loss in 4 of 6 patients developing diuretic-induced renal impairment clearly indicates that mechanisms other than volume depletion were responsible. The finding of increased values for plasma renin activity (PRA) at the time of renal impairment, together with the failure of both PRA and the plasma urea concentration to rise when diuretics were given following effective β -adrenergic blockade may indicate that the renin-angiotensin system and the development of renal dysfunction were in some way pathogenically related. It is unlikely that the renal impairment was the stimulus to an increased renal secretion of renin since 3 of the second group of 8 patients also showed

TABLE 1. Effect of spironolactone on plasma renin activity and creatinine clearance before and after treatment

Case No.	Plasma renin activity (nmol/litre/hr)			Creatinine clearance (ml/min)			Renal sodium excretion (mmol/24 hr)	Weight loss (kg)	Dose spironolactone (mg/24 hr)
	Before	After	% change	Before	After	% change			
Group A. Minimal change in creatinine clearance									
7	2.32	4.88	+ 110	101	99	- 2	145	1.0	300
8	1.00	3.28	+ 258	111	126	+ 13	162	1.0	200
9	4.55	8.47	+ 86	69	61	- 12	110	0.7	300
Mean	2.62	5.64	+ 155	94	95	0	139	0.9	267
+ s.e. mean	1.03	1.46	54	13	19	7	15	0.1	33
Group B. Fall in creatinine clearance									
10	2.25	3.89	+ 73	85	45	- 47	104	0.7	400
11	1.05	5.40	+ 416	64	30	- 53	110	0.8	600
12	1.06	2.28	+ 114	114	67	- 41	101	0.8	200
13	2.28	3.03	+ 33	109	61	- 44	112	0.6	200
14	2.99	4.20	+ 40	79	38	- 52	171	1.1	200
Mean	1.92	3.76	+ 135	90	48	- 47	120	0.8	320
+ s.e. mean	0.37	0.53	72	9	7	2	13	0.1	80

a marked rise in PRA despite little or no change in creatinine clearance. PRA has been reported to be closely related to the plasma angiotensin II concentration in cirrhosis (Wernze, Spech and Müller, 1978) and the latter is a potent renal vasoconstrictor. It is therefore possible that the renal impairment was due to the effect of angiotensin II on the renal circulation consequent upon a stimulation of renin release. However, the lack of a fall in creatinine clearance for some patients showing a rise in PRA would argue against this unless the sensitivity of the renal circulation to angiotensin II differed in different patients. That this may be so in cirrhosis, has been shown by 2 groups (Laragh *et al.*, 1963; Gutman *et al.*, 1973). Of possible relevance to the present studies are the recent findings of Eliahou *et al.* (1977) who showed that propranolol reduced the severity of ischaemic renal failure in the rat and that this appeared to be independent of any effect on the renin-angiotensin system.

Whether or not the renin-angiotensin system was responsible for the development of renal impairment, the increases of PRA in the first group of patients who did not go into negative fluid balance require explanation. Other mechanisms whereby diuretics may induce renin release include an altered load of sodium (or chloride) at the macula densa of the distal tubule, and an increased sympathetic nervous activity. The mechanism whereby an altered tubular fluid at the macula densa induces renin release from the adjacent juxtaglomerular cells may be a manifestation of a normal renal homeostatic feedback known as the 'tubuloglomerular feedback loop' which operates such that the glomerular filtration rate (GFR) is altered as a result of the stimulus at the macula densa. Recent evidence would suggest that the stimulus is likely to be an increased chloride load or concentration rather than sodium (Wright and Persson, 1974; Schnermann, Plath and Hermle, 1976), and there is considerable evidence pointing to an important role for the renin-angiotensin system in mediating the suppression of GFR although other factors are almost certainly involved (reviewed by Wright and Briggs, 1977). However, in none of these studies was amiloride or spironolactone investigated and both of these resulted in an increase in PRA in the absence of volume depletion in the present study. It is difficult to see how amiloride could stimulate renin *via* the macula densa since its action would appear to be distal to that site in the nephron (Duarte, Chomety and Giebisch, 1971), but spironolactone might increase the sodium delivery to the macula densa by inhibiting a proximally mediated aldosterone-dependent sodium reabsorption (Hierholzer and Stolte, 1969).

The importance of the sympathetic nervous system in mediating a diuretic-induced hyperreninaemia has

been shown by the effects of sympathectomy (Mogil *et al.*, 1969; Leonetti *et al.*, 1975). However, volume depletion, which itself activates the sympathetic nervous system, was not prevented in these studies and neither amiloride nor spironolactone were investigated. A possible interaction between the sympathetic nervous system and the macula densa-juxtaglomerular cells (juxtaglomerular apparatus) has been proposed by Slotkoff *et al.*, (1970). They found that the rise in PRA following chlorothiazide administration to normal subjects could be prevented if the activity of the sympathetic nervous system had been previously reduced by treatment with reserpine. They argued that if the macula densa was important in mediating the increased renin release, the sympathetic activity might play a permissive role through its innervation of the juxtaglomerular apparatus. This could explain the effect of propranolol or prazosin in preventing the rise of PRA in the present study. It is also of interest that propranolol has been shown to inhibit the tubuloglomerular feedback loop (Stowe and Schnermann, 1974). Others have shown that propranolol can inhibit the rise in PRA due to a variety of diuretics (Winer *et al.*, 1969; Leonetti *et al.*, 1975; Karlberg *et al.*, 1976) although in one study this was not so (Bravo, Tarazi and Dustan, 1975).

It was also of interest that β -adrenergic blockade appeared to be of value in preventing renal impairment in the 2 patients in whom this occurred in association with volume loss which agrees with the findings of Imbs *et al.* (1977) that propranolol can prevent the component of the rise in PRA due to volume depletion following frusemide.

Hyponatraemia also stimulates renin release. Although this occurred in association with a rise in PRA, the serial studies suggest that it was the result of the renal impairment rather than the cause of increased renin release. The associated hyperkalaemia would have been expected to suppress renin secretion (Davis and Freeman, 1976).

With regard to the clinical significance of the present findings there is no doubt that the simplest way of treating the majority of cases of diuretic-induced renal impairment is to withdraw therapy and, when the plasma urea concentration has returned to normal, reinstitute diuretics at a lower dosage. However, some patients such as case 4 in the present study, will become uraemic with each challenge, and in them the additional use of β -blockers may be particularly helpful. Two practical points need emphasizing. Firstly, if the renin-angiotensin system is involved in the pathogenesis of the renal impairment, adequate dosage of β -blocker is essential since in another study PRA has been shown not to be reduced unless there is also clinical evidence for effective β -blockade (Wilkinson *et al.* 1977a).

Secondly, some patients with cirrhosis and ascites appear to be dependent on angiotensin II for maintenance of their blood pressure in that the angiotensin II antagonist, saralasin, has been reported as causing severe hypotension (Schroeder *et al.*, 1976). It might therefore be predicted that β -blockers would have a similar effect in some patients although this was not seen in the present study.

The authors have also tried the effect of propranolol in patients with spontaneously occurring renal impairment, but without success. In such cases, the mechanism for the renal impairment may be quite different and several studies have now implicated endotoxaemia in its pathogenesis (Wilkinson *et al.*, 1976; Liehr *et al.*, 1976; Clemente *et al.*, 1977).

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