

# Use of bumetanide in the treatment of ascites due to liver disease

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**SUMMARY** Bumetanide is an effective diuretic for the treatment of ascites. Fifteen out of 17 patients with chronic liver disease responded satisfactorily and the incidence of hepatic encephalopathy and electrolyte disturbances was similar to that previously observed with frusemide. Colicky abdominal pain was reported in three patients but no other adverse effects were noted. An unexpected response was obtained in two patients who had diuresis without natriuresis.

Bumetanide (3-n-butylamino-4-phenoxy-5-sulphamoyl benzoic acid) is a new diuretic agent. In normal subjects free water clearance is reduced during water diuresis, and the maximum tubular reabsorption of free water is reduced during hydropenia. The drug has proved an effective diuretic for the treatment of cardiac oedema, even with creatinine clearance as low as 10 ml/minute (Asbury, Gatenby, O'Sullivan, and Bourke, 1972; Olesen, Sigurd, Steiness, and Leth, 1973).

The use of potent diuretics in the treatment of hepatic ascites is associated with a high incidence of electrolyte disturbances and hepatic encephalopathy, especially in patients with poor hepatocellular function (Sherlock, Senewiratne, Scott, and Walker, 1966). The purpose of the present study is to evaluate bumetanide in the treatment of ascites in patients with chronic liver disease and in particular to assess the incidence of such complications.

## Method

Seventeen patients with chronic liver disease and moderate to severe ascites were treated (table). Ten patients had been receiving other diuretic drugs and these were discontinued on admission to hospital. All were put to bed with dietary sodium intake restricted to 22 m-equiv and fluid intake to 1 litre daily. Dietary potassium intake was estimated at 50 m-equiv daily.

When body weight had remained stable for three days (the basal period) bumetanide was commenced at a dose of 1 mg daily. This was subsequently varied (in the range of  $\frac{1}{2}$ -4 mg daily) according to the

response, which included weight loss, urine output, and sodium excretion. Ideal weight loss was judged to be 0.5 kg daily, and the dose was increased if less than 2 kg was lost in four days.

If plasma potassium levels were normal on admission no supplements were given until plasma potassium was less than 3.1 m-equiv/l. Slow-release or effervescent potassium chloride was then given in divided doses up to 100 m-equiv daily. Potassium-sparing diuretics (amiloride or spironolactone) were added later in six of the 17 patients because potassium levels could not be maintained even with 100 m-equiv daily of potassium supplements, or because diuresis was poorly sustained with bumetanide 2 mg daily.

Frequent clinical observations were made and patients were examined daily for hepatic encephalopathy. They were weighed at the same time each day and urine was collected for estimation of 24-hour volume and electrolytes. Plasma electrolytes, urea, and postprandial blood sugar were estimated at least three times weekly. Serum bilirubin, aspartate transaminase, alkaline phosphatase, calcium, phosphate, uric acid and creatinine, with haemoglobin, leucocytes, platelet count, and Thrombotest were measured weekly.

## Results

During the prediuretic period six patients neither lost nor gained more than 0.5 kg in weight. Two patients gained weight, and the remaining nine experienced a spontaneous diuresis which in two was considerable (weight loss of 3.9 and 4.8 kg). Of these nine patients, two had recently been taking spironolactone, a long-acting diuretic. However, in

Patient	Age	Sex	Diagnosis <sup>1</sup>	Other Diuretics Given with Bumetanide		Spontaneous Weight Change before Bumetanide (kg)	On Bumetanide			Complications during Therapy
				Name	From day		Days	Weight Loss (kg)	Mean Daily Weight Loss (kg)	
HS	55	M	Cryptogenic cirrhosis	Amiloride	13	+ 2.9	33	7.9	0.24	Hypokalaemia, colic
GM	56	F	Cryptogenic cirrhosis	—	—	- 0.9	8	5.0	0.63	—
PP	54	M	Cryptogenic cirrhosis	Spironolactone	6	- 0.5	7	3.6	0.51	—
ED	16	F	Chronic active hepatitis	Amiloride	18	- 1.1	34	15.7	0.46	Encephalopathy, haematemesis, colic
YK	16	F	Chronic active hepatitis	—	—	- 1.7	18	2.6	0.14	Hypokalaemia
DR	38	M	Chronic active hepatitis	Amiloride	12	+ 1.3	12	2.6	0.22	Fatal variceal haemorrhage
IM	58	F	Primary biliary cirrhosis	—	—	- 4.8	18	4.8	0.27	Infected ascites
DM	63	F	Primary biliary cirrhosis	Amiloride	11	- 0.3	17	6.6	0.39	Hypokalaemia
MP	49	F	Primary biliary cirrhosis	—	—	- 0.8	51	10.2	0.20	Encephalopathy, hypokalaemia
FA	40	M	Hepatitis B antigen and cirrhosis	—	—	- 0.7	12	5.7	0.47	—
DK	68	F	Hepatitis B antigen and cirrhosis	—	—	+ 0.2	6	0.2	0.03	Fatal variceal haemorrhage
DA	35	M	Alcoholic cirrhosis	—	—	- 0.8	28	10.9	0.39	Hypokalaemia, epistaxes
EM	58	F	Alcoholic cirrhosis	—	—	- 0.5	17	7.7	0.45	Hypokalaemia
WO	32	M	Alcoholic cirrhosis	—	—	- 0.3	17	4.5	0.26	—
WS	48	M	Alcoholic cirrhosis	—	—	- 3.9	3	1.1	0.37	—
PW	62	F	Alcoholic cirrhosis	Amiloride	15	- 0.6	63 <sup>1</sup>	7.2 15.7	0.36	Encephalopathy, hypokalaemia, abdominal pain
PS	29	F	Budd Chiari	—	—	- 0.5	6	2.8	0.47	Hypokalaemia
Mean	46	—	—	—	—	—	21	6.4	0.35	—

Table Summary of clinical details of present series

<sup>1</sup>Two admissions, 16 and 47 days respectively

each case this drug had been discontinued six days before the start of the basal period.

Sodium excretion in the basal period, after spontaneous diuresis, was generally less than 10 m-equiv daily.

Thirteen out of the 17 patients responded to the initial 1 mg dose, with weight loss averaging 0.58 kg/day, increased urine volume, and natriuresis between 49 and 131 m-equiv/day (fig 1). In four patients natriuresis did not occur. One (D.K.) died of bleeding oesophageal varices seven days after starting bumetanide. Another (E.D.) responded to a larger dose (2 mg).

The remaining two patients (D.R. and D.A.) responded with diuresis, losing 3.9 and 3.2 kg respectively, over the first nine days of bumetanide, but sodium excretion during this period remained less than dietary intake. Relevant data on D.R. are shown in figure 2. For comparison a typical response is shown in figure 3. D.A. subsequently showed natriuresis on 2 mg bumetanide daily, but D.R. developed variceal haemorrhage and died.

Bumetanide was given for an average of 21 days (table) and weight loss ranged from 0 to 15.7 kg (mean 6.4 kg). Six of the patients also received

potassium-sparing diuretics during part of the same period.

In the 10 patients for whom comparable data are available urinary potassium excretion rose from the basal level of  $42.3 \pm 15.5$  m-equiv per 24 hours to  $67.9 \pm 15.1$  m-equiv per 24 hours during the first four days on bumetanide, an increase of  $25.6 \pm 19.6$  m-equiv per 24 hours which is highly significant ( $p < 0.01$ ). Three patients were hypokalaemic (less than 3.1 m-equiv/l) before bumetanide (one related to previous frusemide administration; two spontaneously). Eight of the remaining 14 patients developed hypokalaemia within a few days of starting therapy.

Initially hepatic encephalopathy was present in six of the 17 patients. This was treated and was not aggravated by the diuretic. Two of the remaining 11 patients developed encephalopathy during bumetanide treatment. In both cases this was associated with hypokalaemia (2.8 m-equiv/l), and in one of them followed an excessive diuresis. However, when all 17 patients were considered together no association could be found between hypokalaemia and encephalopathy either before or during bumetanide treatment.

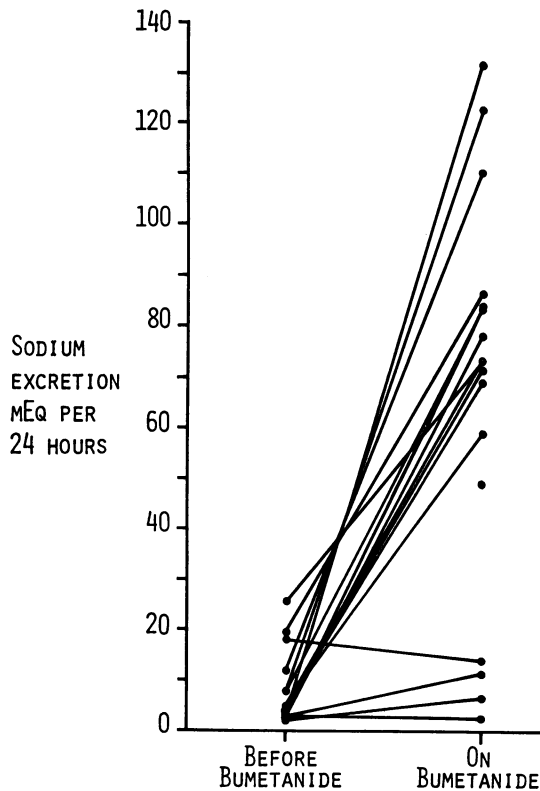


Fig 1 Mean sodium excretion before and during the first four days of bumetanide 1 mg daily. A satisfactory natriuretic response was obtained in 13 of the 17 patients. Data are not available for the basal sodium excretion in patient W.S.

Initial plasma sodium levels were below normal (< 136 m-equiv/l) in 13 of the 17 patients and below 130 m-equiv/l in three of those. Mean values on bumetanide therapy were significantly lower (paired t test;  $P < 0.05$ ), and a further seven patients had values recorded which were below 130 m-equiv/l. In each of these patients the drop occurred during the first week of therapy. There was no correlation between the changes in plasma sodium concentration and either the duration of treatment or the diuresis obtained.

In four patients the blood urea level was elevated (> 40 mg/100 ml) during the basal period (up to 144 mg/100 ml) but uraemia was not aggravated by treatment. In three patients with previously normal levels blood urea rose on treatment. Gastrointestinal haemorrhage could have accounted for the rise in one of these, but the other two (53 and 55 mg/100 ml) were attributed to diuretic therapy.

No significant change was found in blood glucose

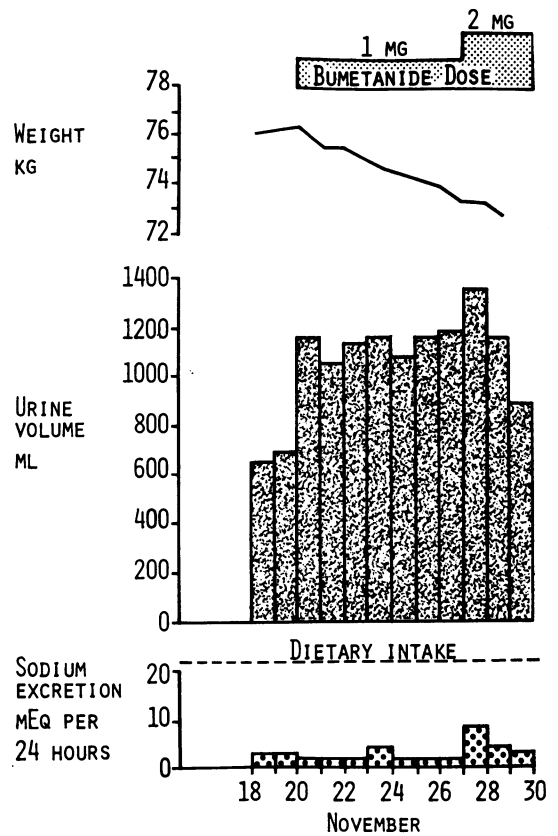


Fig 2 Patient D.R. Bumetanide caused weight loss and increased urine output, but urinary sodium excretion remained less than dietary intake. Patient died on the fourteenth day of treatment.

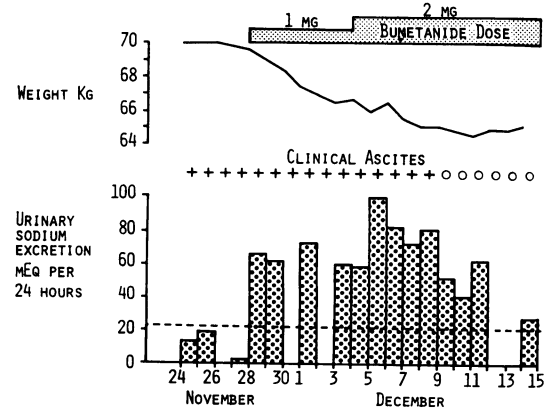


Fig 3 Patient W.O. Satisfactory response to bumetanide with weight loss, increased sodium excretion, and loss of ascites.

or serum uric acid levels during the short period of inpatient treatment. There was no consistent change in serum creatinine, calcium, phosphate, bilirubin, aspartate transaminase, or alkaline phosphatase, nor in haematological indices (particularly the white cell count).

Colicky abdominal pain was reported by three of the 17 patients during therapy. In one patient this had occurred previously on frusemide; another had a duodenal ulcer.

Two patients died during the initial period of bumetanide treatment, and a further four have since died of their liver disease (mean follow up eight months). Eleven patients in all were discharged taking bumetanide, and 10 of these have been followed in the outpatient clinic, on the drug, for between 65 and 308 days (mean 154 days). Six patients have remained well controlled on the same dose, but two required an increased dose to control recurrence of ascites, and in one of these hypokalaemia was a persistent problem. The remaining two patients reaccumulated fluid despite treatment and died.

## Discussion

Fifteen of our 17 patients responded satisfactorily to bumetanide and were discharged from hospital with little or no ascites. In six of these patients, however, a potassium-sparing diuretic was necessary to achieve control. Treatment failed in two patients, both of whom died within two weeks.

One mg of bumetanide was found to be a suitable initial dose. This may be increased every two to four days in  $\frac{1}{2}$ -1 mg steps until a satisfactory rate of diuresis is just achieved. Severe dietary sodium restriction is essential. Studies in two of our patients agree with earlier reports, that the diuretic action of bumetanide lasts for about four hours after an oral dose.

Total exchangeable potassium is low in cirrhotic patients (Casey, Summerskill, and Orvis, 1965) and bumetanide increased urinary potassium loss in our patients by an average of 25.6 m-equiv daily. Therefore all cirrhotics treated with bumetanide should receive potassium chloride supplements or potassium-sparing diuretics from the start.

The main complications of diuretic therapy in liver diseases are the development of encephalopathy, electrolyte disturbances such as hyponatraemia or hypokalaemia, and uraemia. All these complications were found among our patients on bumetanide, and the number developing each of these effects was very similar to those observed in a trial of frusemide by Sherlock *et al* (1966) also involving 17 patients. No direct comparison has been made with other

diuretic agents because of the difficulties in maintaining a large number of patients in a steady state over the necessary period of time.

The response of D.R. and the initial response of D.A. deserve comment. Bumetanide increased urine volume, with weight loss, but no increase in urinary sodium excretion (fig 2). Bumetanide increases sodium and water delivery to the distal tubule leading to increased urine flow and potassium exchange in the distal tubule. A critical dose of the drug might be sufficient to stimulate potassium exchange in this way but insufficient to overwhelm the potassium exchange mechanism (Lowenthal and Shear, 1973), so that diuresis and kaliuresis occur, but not natriuresis. The urinary potassium excretion of D.A. did indeed increase from 31, 50, 43 m-equiv daily in the basal period to 65 and 63 m-equiv in the first two days on bumetanide. Unfortunately, potassium excretion data on D.R. are unreliable as his diet had included large and variable amounts of salt substitute (92% potassium chloride). In addition, the basal urine osmolality of D.R. was high (840 mOsm/kg), despite low plasma osmolality (269 mOsm/kg). This suggests inappropriate levels of antidiuretic hormone, though increased water reabsorption due to low flow rate in the collecting tubule may play a part (Harrington and Cohen, 1973). Bumetanide reduces urinary concentrating power (Olesen *et al*, 1973), and this combined with increased flow in the distal nephron, reduces urine osmolality. Despite antidiuretic hormone, urine flow must increase to excrete the same solute load.

The conclusion from these two patients is that a suboptimal dose of bumetanide may induce loss of potassium, water, or both, without the desired natriuresis, although free water loss may in itself be desirable. Frusemide and other agents with actions similar to bumetanide might do the same. Measurement of urinary electrolytes is of value in selected patients.

For an equivalent effect, bumetanide is at present somewhat cheaper than other potent diuretics. This advantage must be weighed against the clinical experience already gained in the use of other agents and their established safety or otherwise.

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