LACK OF EFFECT OF BUMETANIDE ON BODY POTASSIUM CONTENT IN HYPERTENSION

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- 1 Twelve patients with mild hypertension were treated with bumetanide for a six-month period. No evidence was found of hypokalaemia or decreased total exchangeable potassium in subjects with or without additional potassium supplements.
- 2 Bumetanide was well tolerated by all patients. It caused hyperuricaemia but no episodes of gout occurred. Minor abnormalities of liver function were noted.
- 3 Bumetanide did not have a sustained antihypertensive action.

Introduction

Bumetanide (3-*n*-butylamino-4-phenoxy-5-sulphamoyl benzoic acid) is a potent new diuretic compound derived from metanilamide, in contrast to frusemide and the thiazides, which are derived from sulphanilamide. It has been shown to be equipotent with frusemide at one-fortieth the molar dosage, and is an effective natriuretic agent in oedematous subjects, both in those with adequate and in those with poor renal function (Asbury, Gatenby, O'Sullivan & Bourke, 1972). The present study is an investigation of the effect of long term administration of bumetanide on potassium metabolism in non-oedematous patients with essential hypertension.

Methods

The subjects were twelve mildly hypertensive patients aged 29 to 61 years (mean age 46 years) of whom seven were males. All were non-obese and free from oedema, uraemia, and clinical evidence of liver disease. They had received no diuretics for three months prior to the trial. Two patients were already taking antihypertensive drugs (methyldopa and practolol respectively), and these were continued in reduced dosage throughout the trial. The study was approved by the local ethical committee.

All subjects were given bumetanide (0.5 mg tablets) twice daily for six months. Six of the subjects received, by random allocation, slow-release potassium (16 mEq) twice daily, and six received inert tablets. All were admitted to

hospital for 48 h prior to commencement of the trial, and again three months and six months later, for estimation of total exchangeable potassium using ^{42}K (Blaht, 1965). During each admission a dietary history was obtained by recall to assess daily potassium intake. The patients were reviewed at an outpatient clinic two and four weeks after commencing treatment, and thereafter at monthly intervals. At each visit a standard symptom questionnaire was completed and a tablet count was carried out. The blood pressure was measured and an ECG performed. A blood sample was obtained at each visit for the estimation of urea and electrolytes, magnesium, uric acid, liver function tests, and full blood count, all performed by standard laboratory techniques.

Results

No significant changes were seen throughout the six-month period in serum potassium concentrations (Table 1), and levels were similar in potassium and placebo-treated groups. Similarly, no changes occurred in total exchangeable potassium during treatment with potassium, and there were no significant differences between potassium and placebo groups (Table 2).

Individual dietary potassium intakes ranged from 54 to 128 mEq/24 h (mean 77.9 ± 3.8 mEq/24 h), but appeared fairly constant over the six-month period, and did not differ significantly in the two groups. At no time was there electrocardiographic evidence of hypokalaemia.

Table 1 Serum biochemical values in all subjects (mean $\pm$ s.e. mean) before and at times after bumetanide (0.5 mg) twice daily

	Mean basal/ levels	2 weeks	1 month	2 months	3 months	4 months	5 months	6 months
Potassium (mEq/l)	4.3 ± 0.1	4.3 ± 0.2	4.4 ± 0.2	4.2 ± 0.1	4.3 ± 0.1	4.4 ± 0.1	4.3 ± 0.1	4.4 ± 0.1
Sodium (mEq/l)	141 ± 0.6	141 ± 0.9	140* ± 0.8	142 ± 0.5	141 ± 0.3	142 ± 0.6	141 ± 0.4	143 ± 0.5
Chloride (mEq/l)	99 ± 1.1	94* ± 1.9	98 ± 1.6	95 ± 1.8	98 ± 1.1	95 ± 1.9	98 ± 2.2	101 ± 1.3
Bicarbonate (mEq/l)	26.8 ± 0.4	27.6 ± 0.8	27.8 ± 0.5	28.3 ± 0.5	27.4 ± 0.4	29.3* ± 1.0	28.1 ± 0.6	27.8 ± 0.5
Urea (mg/100 ml)	33.8 ± 2.7	39.7* ± 2.8	36.3 ± 2.4	37.5 ± 2.9	36.9 ± 2.9	39.3 ± 3.7	37.2 ± 1.9	36.5 ± 2.1
Uric acid (mg/100 ml)	5.5 ± 0.4	6.4*** ± 0.4	6.5*** ± 0.5	6.5*** ± 0.5	6.4*** ± 0.5	6.6*** ± 0.6	6.4** ± 0.5	6.5** ± 0.5
Alkaline phosphatase (KA units)	9.6 ± 0.8	10.6* ± 0.8	10.0 ± 0.6	10.8 ± 1.1	10.5 ± 0.7	10.8 ± 0.8	11.4*** ± 0.7	10.8 ± 0.8
Leucine aminopeptidase (units/100 ml)	13.0 ± 0.6	17.9** ± 1.2	16.8* ± 1.2	16.4** ± 1.1	15.9 ± 0.9	14.8 ± 1.2	18.1 ± 2.4	15.8 ± 1.3

Significant differences from mean basal value * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Table 2 Total exchangeable potassium in potassium and placebo groups (mean $\pm$ s.e. mean) before and 3 and 6 months after bumetanide (0.5 mg) twice daily

	Mean basal levels		3 months		6 months	
	Potassium group	Placebo group	Potassium group	Placebo group	Potassium group	Placebo group
Total exchangeable potassium (mEq)	2240 $\pm$ 334	2947 $\pm$ 275	2570 $\pm$ 333	3162 $\pm$ 364	2471 $\pm$ 253	3089 $\pm$ 297
Total exchangeable potassium (mEq/kg)	39.5 $\pm$ 2.7	41.5 $\pm$ 2.7	40.6 $\pm$ 1.7	45.6 $\pm$ 3.5	39.3 $\pm$ 0.9	44.5 $\pm$ 2.8

Table 3 Blood pressure levels in ten subjects before and at times after taking diuretic (bumetanide 0.5 mg, twice daily) only (mean $\pm$ s.e. mean)

	Mean basal levels		2 weeks	1 month	2 months	3 months	4 months	5 months	6 months
BP supine (mmHg)	146 ± 5 93 ± 2	142 ± 3 92 ± 1	141 ± 4 90 ± 3	141 ± 5 89 ± 3	142 ± 6 89 ± 3	142 ± 4 92 ± 3	144 ± 4 89 ± 2	146 ± 6 93 ± 2	
BP erect (mmHg)	147 ± 6 93 ± 3	$134^* \pm 3$ 95 ± 2	$132^* \pm 3$ 91 ± 4	$132^* \pm 6$ 94 ± 3	136 ± 5 89 ± 4	$128^* \pm 3$ 88 ± 3	135 ± 2 91 ± 2	140 ± 5 93 ± 2	

Significant differences from mean basal value * $P < 0.05$

Only minor changes were noted in serum sodium, chloride and bicarbonate levels (Table 1), with no change in serum magnesium from the mean pre-treatment concentration of 1.7 ± 0.04 mEq/litre. There was a transient rise in blood urea two weeks following commencement of bumetanide therapy, with levels thereafter tending to return to basal values. Serum uric acid concentrations, on the other hand, rose in all subjects and remained elevated throughout the whole treatment period, exceeding the upper limit of normal in eight of the twelve subjects.

In the two patients receiving other anti-hypertensive drugs, the dosage of these drugs was reduced before starting bumetanide in anticipation of a fall in blood pressure. In the remaining ten subjects there was no significant change in the blood pressure recorded in the supine position (Table 3). The blood pressure in the erect position, however, showed a significant fall in the systolic pressure of approximately 15 mmHg for four months after starting bumetanide, but thereafter tended to return to pretreatment levels. The diastolic pressure did not alter significantly.

No symptoms attributable to adverse reaction to bumetanide were reported by any subject, and the haemoglobin, white cell counts and platelet counts remained normal. Serum bilirubin, albumin, total protein and aspartate aminotransferase (SGOT) levels were unaltered in all subjects. The mean serum alkaline phosphatase concentrations (Table 1) showed small increases from the pretreatment level at two weeks and five months, although levels remained within the normal range in all subjects with the exception of one whose initial alkaline phosphatase was at the upper limit of normal (16 King-Armstrong (KA) units, rising to a maximum of 19 KA units at two months). Serum leucine aminopeptidase levels also rose at two weeks and at one and two months, but the individual levels were all within the normal range of 8-22 units/100 ml. Thereafter the levels tended to return to pretreatment values except in two patients who had peak levels of 34 units and 29 units at five months, the latter being the patient who had transient elevation of the serum alkaline phosphatase.

Discussion

In this study, treatment of hypertensive patients with bumetanide over a six-month period produced no evidence of potassium depletion as measured by serum potassium or total exchangeable potassium levels. Short-term investigations have shown small increases in urinary potassium excretion for approximately six hours after oral bumetanide administration (Henning & Lundvall,

1973). Previous long-term studies on changes in body potassium content in hypertensive patients taking diuretics have shown variable effects. Healy, McKenna, Canning, Brien, Duffy & Muldowney (1970) demonstrated that chlorthalidone and frusemide both caused significant potassium depletion, whereas Leemhuis, van Damme & Struyvenberg (1972) using chlorthalidone, and Anderson, Godfrey, Hill, Munro-Faure & Sheldon (1971) using frusemide and hydrochlorothiazide demonstrated hypokalaemia but no significant decrease in total body potassium. On the other hand, Graybiel & Sode (1971) showed no evidence of negative potassium balance in subjects taking hydrochlorothiazide for several months. These contradictory findings may be due in part to the limitations of the methods available for measuring deficits in body potassium (Jones, 1970). Very few studies have taken into account differences in dietary potassium intakes, which might also be responsible for some of these discrepancies. It has been estimated that a good mixed diet provides some 50 to 70 mEq potassium/day (Flear, 1972). The dietary potassium intake in our subjects appeared to be satisfactory, both in those with and those without potassium supplements. Low potassium intakes have been found in patients with cardiac disease requiring long-term treatment with potent diuretics (Davidson, 1972). In those patients, potassium deficiency is common and often severe (Olesen, 1968), and may be related more closely to the cardiac disease than to diuretic-induced potassium loss (Edmondson, Hilton, Thomas, Patrick & Jones, 1974).

The finding of a consistent rise in the serum uric acid during bumetanide therapy is in keeping with those in other recently-reported studies of this drug (Bourke, Asbury, O'Sullivan & Gatenby, 1973; Olesen, Sigurd, Steiness & Leth, 1973), and is also known to occur with the thiazide diuretics, frusemide and ethacrynic acid (Laurence, 1973). Bumetanide has been shown to cause a decreased renal clearance of urate (Davies, Lant, Millard, Smith, Ward & Wilson, 1974). As in previous studies of bumetanide, no case of gouty arthritis occurred in our series. There was no evidence of bone marrow depression during bumetanide therapy. Although Davies, Lant, Millard, Smith, Ward & Wilson (1974) reported elevated serum aminotransferase levels in one patient during bumetanide therapy, no such effect was seen in this study. The small increases in serum concentrations of leucine aminopeptidase, a sensitive indicator of liver cell function, and alkaline phosphatase, are difficult to interpret, and may be of little clinical significance. Nevertheless, future studies of this drug should include monitoring of liver cell function.

This study has shown that bumetanide causes only a small temporary decrease in systolic blood pressure in the erect position, possibly related to the temporary decrease in extracellular fluid and plasma volumes that occurs during diuretic therapy (Wilson & Freis, 1959). It is therefore similar to frusemide in its lack of antihypertensive action (Healy *et al.*, 1970), and differs from the thiazide diuretics and chlorthalidone, which have a

sustained antihypertensive effect (Beevers, Hamilton & Harpur, 1971).

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