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Bumetanide in heart failure in infancy

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SUMMARY The effect of bumetanide in infants with congenital heart disease presenting with cardiac failure was studied. The study was divided into acute (3 days) and long-term (mean 10·5 weeks) cases. A total of 12 male infants was included in the acute study and 13 cases were evaluated in the long-term study. The dose used in the acute study (0·015 mg/kg) was suboptimal; notwithstanding, it was found to cause significant natriuresis and chloruresis. Bumetanide in doses varying in different infants from as little as 0·015 mg/kg on alternate days to as much as 0·10 mg/kg daily was shown to be an effective diuretic for long-term use. No side effects were observed in either study.

Bumetanide (Burinex) is a potent loop diuretic. Although it bears some structural resemblance to frusemide, unlike the latter which is derived from sulphanilamide, bumetanide is a metanilamide derivative (Feit, 1971). In dogs it is weight for weight 40 to 60 times more active than frusemide when given intravenously and 100 times more active when given orally (Ostergaard *et al.*, 1972). In rats, bumetanide is practically ineffective. In human studies 1 mg bumetanide was equipotent to 40 mg frusemide with regard to urinary excretion of sodium, chloride, potassium, and water (Asbury *et al.*, 1972). In healthy volunteers the major action of bumetanide has been shown to be on the ascending limb of Henle's loop with an additional effect on the proximal tubule but no significant effect on the distal tubule (Bourke *et al.*, 1973). In this study we evaluated the effect of bumetanide in infants with congenital heart disease presenting with cardiac failure. The usual criteria for diagnosis of cardiac failure were used (Lees, 1969). The study is divided into acute cases and long-term cases.

Acute cases

Twelve male infants with ages ranging from 2 weeks to 7 months were studied. Details of age, diagnosis, and mode of presentation are given in Table 1. The diagnoses were confirmed by cardiac catheterization and at necropsy in those infants who later succumbed to their cardiac malformation. Of the 12 infants, 11 had complex congenital heart disease and had moderate to severe cardiac failure. All the infants were on digoxin before entering into the study and digoxin was continued during the trial. On study day 1 no diuretic was given but a preliminary 24-hour collection of urine was obtained. Only male infants were studied in order to facilitate accurate collection of urine samples. The 24-hour urine on day 1 was used as a control and was analysed for volume, sodium, potassium chloride, calcium, magnesium, phosphate, urate, glucose, and osmolality. On day 2 the infant was weighed and a blood sample was obtained and analysed for urea, sodium, potassium, chloride, calcium, magnesium, phosphate, liver function tests (serum proteins, SGOT, SGPT, alkaline phosphatase, bilirubin), haemoglobin, white cell count, and glucose. Immediately after blood sampling bumetanide 0·015 mg/kg (prepared by dilution of the injectable form in sterile water) was administered orally. Urine was then collected at hourly intervals for 6 hours, followed by a further 18-hour collection to complete the 24-hour urine collection for day 2. On day 3 the infant's weight was recorded again and all the haematological and biochemical tests listed above were repeated.

Biochemical methods. Na and K were measured by flame photometry (EEL 227), Cl by Corning 920 chloride meter; Ca and Mg by atomic absorption spectrophotometry (Pye—Unicam SP 90), phosphate by Fiske and Subbarrow method (modified), urea by urease/Berthelot reaction, plasma glucose by glucose oxidase (Trinder—modified), and osmolality by Advanced osmometer using freezing point depression technique.

Results of acute study

Urinary volume and electrolytes.

Volume. On day 2 urinary volume rose from a control value of 7·6 ml/h in 24 hours to a mean

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Table 1 *Clinical details of the 12 acute cases*

Case no.	*Age (w)*	*Weight (kg)*	*Diagnosis*	*Mode of presentation of failure*
1	8	3·50	VSD, PH	Tachpynoea, cyanosis, hepatomegaly
2	3	3·44	Coarctation, VSD	Tachypnoea, hepatomegaly, cardiomegaly
3	16	2·73	Preductal coarctation	Feeding difficulty, hypertension, cardiomegaly, hepatomegaly
4	6	3·78	VSD	Tachypnoea, cardiomegaly
5	4	3·47	Coarctation, VSD	Tachypnoea, hypertension, cardiomegaly
6	8	4·18	TGA, VSD, PS	Tachypnoea, cyanosis, hepatomegaly
7	8	3·20	TAPVD	Feeding difficulty, tachypnoea, cardiomegaly, rales
8	2	3·24	VSD, ASD, PDA	Oedema, tachypnoea, cardiomegaly, feeding difficulty, sweating
9	12	4·10	Double outlet RV, VSD	Oedema, tachypnoea, hepatomegaly, cyanosis, cardiomegaly
10	5	2·47	TGA & pneumonitis	Cyanosis, hepatomegaly, rales
11	28		Double outlet RV, VSD	Cyanosis, tachypnoea, hepatomegaly
12	8	3·25	Congenital heart block AS	Cardiomegaly, tachypnoea, rales, oedema

AS = aortic stenosis; ASD = atrial septal defect; PDA = patent ductus arteriosus; PH = pulmonary hypertension; PS = pulmonary stenosis; RV = right ventricle; TAPVD = total anomalous pulmonary venous drainage; TGA = transposition of great arteries; VSD = ventricular septal defect.

value of 9·8 ml/h. The increase occurred mainly in the first 6 hours when the mean volume was 17·9 ml/h. There was a significant increase in the 24-hour urinary volume ($P<0·05$; Student's *t* test) (see Table 3).

Na excretion. Mean hourly urinary Na rose from 128·0 μmol/h in the control to 451·9 μmol/h on day 2. The peak urinary Na excretion occurred in the first 3 hours after bumetanide. There was a significant increase in 24-hour urinary Na ($P<0·001$; Student's *t* test).

K excretion. Mean urinary excretion in the control period was 248 μmol/h. After bumetanide the mean K rose to 285·4 μmol/h over the 24 hours of day 2. This rise was not significant.

Cl excretion. The pattern of Cl excretion closely followed that of Na excretion (see Fig.). Again, the maximum effect was seen in the first 3 hours after administration.

Ca excretion. Ca was estimated in the control 24-hour urine, and on day 2 urinary Ca was estimated on the pooled 6-hour urine after the administration of bumetanide and in the pooled urine for the following 18 hours. The results are shown in Table 2. An increase in urinary Ca occurred on day 2. This increase is most marked in the 0- to 6-hour period. Mean urinary Ca concentration in the control period was 3·3 mg/100 ml (0·83 mmol/l) and this rose to 5·5 mg/100 ml (1·38 mmol/l) and 4·6 mg/100 ml (1·15 mmol/l) in the 0- to 6-hour and 7- to 24-hour periods of day 2 respectively. The change in 24-hour Ca excretion was significant ($P<0·01$).

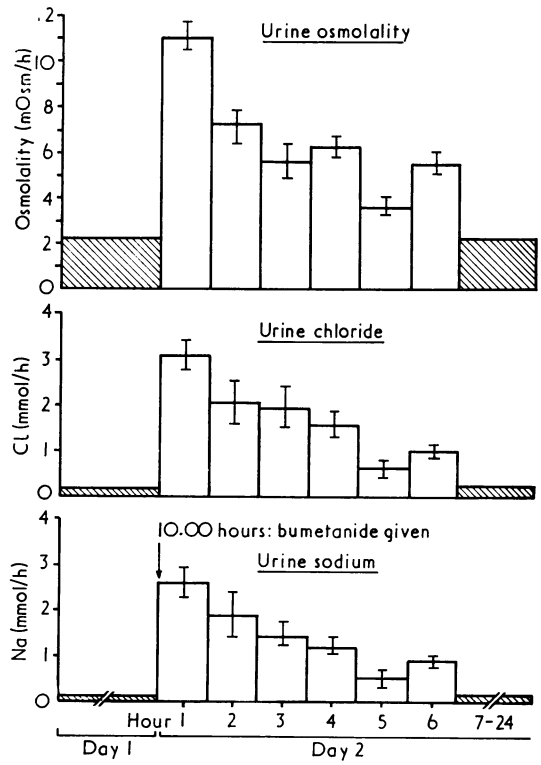

Fig. *On study day 1, during which no diuretic was given, a 24-hour urine sample was collected. On day 2, after oral administration of bumetanide at a dose of 0·015 mg/kg, urine was collected at hourly intervals for 6 hours. A further 18-hour urine collection was obtained for day 2. Urine samples were analysed for sodium, chloride, and osmolality.*

Table 2 *Mean levels of urinary volume and electrolytes in the 12 acute cases*

	Day 1	*Day 2*								
	Control	1 h	2 h	3 h	4 h	5 h	6 h	0–6 h	7–24 h	0–24 h
Volume (ml)	182	32	27	20	25	14	20	138	128	236
Na (mmol/l)	17	80	70	77	51	36	47	59	27	46
K (mmol/l)	33	38	27	24	17	19	18	22	37	29
Cl (mmol/l)	21	97	76	98	63	45	57	74	25	46
Ca (mg/100 ml)	3·3							5·4	4·6	5·2
Mg (mg/100 ml)	1·1							0·9	1·6	1·3
PO_4 (mg/100 ml)	37							26	49	38
Urate (mg/100 ml)	22							1·2	23	17

Note: On study day 1, when no diuretic was given, the preliminary 24-hour urine was used as a control. After bumetanide administration, urine was collected at hourly intervals for 6 hours followed by a further 18-hour collection. Ions, e.g. calcium, magnesium, phosphate, and urate were not estimated for the hourly samples on day 2.
Conversion: Traditional units to SI—Na, K, Cl: 1 mEq/l = 1 mmol/l. Ca: 1 mg/100 ml≈0·250 mmol/l. Mg: 1 mg/100 ml≈0·411 mmol/l. PO_4: 1 mg/100 ml≈0·323 mmol/l. Urate: 1 mg/100 ml≈59·5 μmol/l.

Table 3 *Urinary excretion 0-24 hours in the 12 acute cases*

	Control (day 1)		*Bumetanide (day 2)*		*Bu/Co*	
Variable	*Mean**	*SD†*	*Mean**	*SD†*	*Mean**	*SD†*
Volume (ml/24 h)	159	15·4	213	14·6	1·34 (P<0·05)	11·4
Na (mmol/24 h)	2·08	28·1	8·69	24·7	4·17 (P<0·001)	31·3
K (mmol/24 h)	4·64	21·7	5·56	19·8	1·20	16·9
Na/K	0·45	25·7	1·56	16·3	3·48 (P<0·001)	24·4
Cl (mmol/24 h)	2·77	27·3	9·09	20·6	8·95 (P<0·05)	91·8
Ca (mg/24 h)	4·19	27·8	9·65	23·9	2·37 (P<0·01)	25·4
Mg (mg/24 h)	2·34	37·5	1·89	32·0	0·97	30·0
PO_4 (mg/24 h)	43·9	38·2	52·6	35·5	1·20	16·7
Urate (mg/24 h)	29·3	26·4	33·9	35·2	1·16	28·1

*Geometric mean. Values were converted to logarithms, means and standard deviations computed and converted back to the original units.
†Standard deviations of means, expressed in % of the means. P values determined by Student's *t* test.
Conversion: Traditional units to SI—Ca: 1 mg/24 h≈0·0250 mmol/24 h. Mg: 1 mg/24 h≈0·0411 mmol/24 h. PO_4: 1 g/24 h≈32·3 mmol/24 h. Urate: 1 mg/24 h≈5·95 μmol/24 h.

Mg excretion. Urinary Mg was 2·0 mg/24 h (0·08 mmol/24 h) on day 1 and in the 0- to 6-hour period on day 2 the urinary concentration fell to 0·92 mg/100 ml (0·378 mmol/l) but rose to 1·60 mg/100 ml (0·658 mmol/l) in the 7- to 24-hour period with a concentration of 3·07 mg/24 h (0·13 mmol/24 h) on day 2.

P excretion. P excretion closely followed that of Mg.

Urate excretion. Urate excretion fell during the first 6 hours of day 2, but returned to baseline values over the succeeding 18 hours. This was not significant (see Table 2).

Glucose excretion. No glucose was detected in any of the urine samples tested by Clinistix (Ames).

Osmolality. Urinary osmolality was markedly increased throughout the first 6 hours of drug administration, returning towards baseline values over the succeeding 18-hour period of observation (Fig.).

Haematological status. All results of full blood counts were normal after the single dose of bumetanide.

Biochemistry. Liver function tests and serum K, Cl, Ca, Mg, P, uric acid, and glucose estimations were normal after the single dose of bumetanide.

Table 4 *Long-term cases of bumetanide therapy*

Case no.	At start of treatment: Weight (kg)	Age (w)	Diagnosis	Concomitant therapy	Duration of therapy (w)	Dose of bumetanide (mg)	Result of therapy	Side effects	Comments
13	3·44	3	Coarctation + VSD	Digitalis, potassium suppl	20	0·06 alt days	Cardiac failure controlled	No clinical or biochemical abnormality noted	
14	5·10	32	VSD with pulmonary hypertension	,,	12	0·07–0·1 alt days	,,	Nil	Had successful open heart surgery
15	4·10	3	Double outlet RV, VSD	,,	40	0·05–0·1 daily	,,	,,	
16	3·2	8	Congenital heart block, AS coarctation	,,	5	0·5 daily	,,	,,	Permanent pace-maker inserted
17	1·83	3	VSD + PDA severe pneumonitis	Digitalis, cephalexin	2	0·025–0·05 daily	Cardiac failure difficult to control	,,	Baby died shortly after PDA operation
18	2·73	16	Preductal coarctation	Digitalis, potassium suppl	5	0·05 daily	,,	,,	Necropsy confirmed diagnosis; lungs showed patchy atelectasis, congestion, oedema, and haemorrhage
19	4·95	32	Down's syndrome, ostium primum defect	,,	8	0·075 daily	Cardiac failure well controlled	,,	Collapsed at home with temperature of 107°; died shortly after admission; permission for necropsy refused.
20	2·47	5	TGA pneumonitis	,,	4	0·05–0·075 daily	Cardiac failure controlled	,,	Poor septostomy; died as a result
21	3·50	8	VSD with PH pneumonitis	Digitalis, potassium suppl, ampicillin	12	0·05–0·1 daily	Cardiac failure not controlled	,,	Died in spite of all treatment
22	3·95	12	VSD with 4·1 shunt	Digitalis, potassium suppl	10	0·1–0·2 daily	Cardiac failure well controlled	,,	Discharged home
23	3·60	15	VSD with 5:1 shunt	Digitalis, potassium	6	0·1–0·2 daily	,,	,,	,, ,,
24	3·15	3	Ostium primum defect	,,	13	0·1 daily	,,	,,	,, ,,
25	3·20	1	TGA	Digitalis	2	0·05	,,	,,	,, ,,

Long-term study

Since we were satisfied with the results of the acute study and felt confident about diuresis in long-term use, we considered it important to monitor various parameters with a view to further evaluation of the safety of the compound for long-term diuretic treatment. A total of 13 cases was studied (Table 4). The dose of bumetanide given varied in different infants from as little as 0·015 mg/kg on alternate days to as much as 0·10 mg/kg daily. Potassium supplement (Sando K, one half tablet bd) was also given. In the acute study, the K urinary concentration was higher in the control period than in the period after bumetanide administration (see Table 2). However, if the volume of urine is taken into account, it will be seen that the total urinary excretion of K was higher after bumetanide administration, though this was not significant. We were not sure if a higher dose of bumetanide would in fact cause even greater urinary excretion of K and hence K supplement was given as a precaution.

Initially the infants were clinically evaluated weekly and also had a full blood count, urea, electrolytes, and liver function tests weekly for the first month. Thereafter, they were checked at monthly intervals.

In one case abnormal liver function tests were recorded (SGOT, 308 IU/l (upper limit for SGOT, 40 IU/l); SGPT, 246 IU/l (upper limit for SGPT, 38 IU/l)) after 2 weeks on bumetanide. However, it was noted that the infant was also receiving cepha-

lexin for a chest infection, and when this was discontinued the liver function tests returned to normal. Bumetanide treatment was not interrupted.

The length of treatment with bumetanide in these long-term cases varied from 2 weeks to 40 weeks with a mean duration of 10·5 weeks. Since no undesirable side effects were observed, the use of bumetanide as a routine long-term diuretic in patients with congenital heart disease is being continued.

Discussion

The cases selected for the acute study were, in general, cases with moderate to severe cardiac failure. It can be seen from Table 1 that all except Case 4 suffered from complex congenital heart disease. It is likely that the dose of bumetanide 0·015 mg/kg was a suboptimal dose for such severe failure. In spite of that there is no doubt that bumetanide caused a significant natriuresis. Bumetanide is rapidly absorbed from the gut. After an oral dose a peak plasma concentration is achieved at one and a half hours, which corresponds to the peak period for both urinary sodium and bumetanide output (Davies *et al.*, 1974). The natriuresis was accompanied by a chloruresis.

There was no significant increase in potassium excretion. In the long-term cases there was no fall in plasma Na, K, or Cl. It is notable that the urinary Na in the control period is about half that of K. This may reflect the fact that these cases have severe cardiac failure and are therefore reabsorbing a great deal of Na. The fact that they had all been on diuretics before may also have contributed to the low urinary sodium in the control period when no diuretic was given. Richardson (1971) found a similar pattern in Na and K excretion in her study with frusemide in heart failure in infancy.

Ca excretion was increased during the 0- to 6-hour period, but fell slightly in the 7- to 24-hour period. Overall, it was still higher than in the control period. Excretion of Ca depends on the ratio of quantity filtered in the glomeruli to the amount absorbed. Under normal circumstances, 98% of the filtered load of calcium will be reabsorbed. In infants the excretion is also influenced by Ca intake. Feeding difficulties are common in infants with cardiac failure and this may account for low Ca excretion in some cases. Kleeman *et al.* (1964) showed that there was a positive correlation between clearances of Na and Ca in man. An increase in excretion of Ca was found after the administration of frusemide (Tambyah and Lim, 1969; Toft and Roin, 1971). Davies *et al.* (1974) found that with the administration of bumetanide in adults there was an increase in urinary Ca in the 0- to 6-hour period followed by retention in the subsequent 6 to 12 hours, so that over the whole 24 hours excretion was not significantly increased.

In our results, the 24-hour Ca loss after bumetanide was higher than our control values, though the excretion was most marked in the 0- to 6-hour period. The absence of significant long-term effect on body Ca can be inferred from the normal alkaline phosphatase observed. Mg excretion was not increased during bumetanide therapy and serum magnesium showed no significant change in the long-term follow-up. Similar observations have been made by other workers (Olesen *et al.*, 1973). Mg levels are not without significance in patients with heart failure, since depletion can predispose to ventricular extrasystoles, digitalis toxicity, muscular cramps, paraesthesias, nausea, and vomiting. Lim and Jacob (1972) found that 5 out of 10 patients who had been on long-term diuretic therapy for cardiac failure showed features of Mg deficiency which were corrected by replacement Mg therapy.

There is a need for a safe diuretic for the treatment of congestive heart failure in infants with congenital heart disease. Bumetanide has been shown to be effective as a durietic for both short- and long-term use in such infants and to be devoid of side effects under both conditions of administration.

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