Frusemide in Heart Failure of Infancy

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Richardson, Heather (1971). *Archives of Disease in Childhood*, 46, 520. **Frusemide in heart failure of infancy.** Twelve infants with heart failure and one with perinatal oedema were treated with intramuscular frusemide (1.0–1.25 mg/kg). Frusemide was found to be a safe effective diuretic in infants with heart failure, resulting in clinical improvement, marked excretion of water, sodium, and chloride, with a lesser and more variable effect on potassium excretion. Complications were uncommon with this dose. The drug is most effective in acute pulmonary oedema or acute worsening of heart failure, but day-to-day control of persistent heart failure is more easily obtained by using repeated doses of oral or intramuscular frusemide plus, if needed, aldactone A or triamterene.

There is little quantitative information on the use of frusemide in infancy. Reimold (1964) reports on its administration to 3 infants with perinatal oedema but observed little improvement; however, one infant aged 6 weeks, with heart failure due to myocarditis, responded well to a dose of 0.4–1 mg/kg of frusemide.

Thieffry, Joly, and Ferchiou (1969) reported a significant diuresis and natriuresis in 8 infants with congenital heart disease, and 5 infants with other causes of fluid retention. In one infant, circulatory collapse was provoked, but they concluded that frusemide was a safe effective diuretic in a dose of 0.7–1.25 mg/kg. Therefore it was decided to carry out a further study to assess the usefulness of frusemide as a diuretic in a series of infants admitted with fluid retention predominantly due to heart failure.

Short-term Studies

Eleven infants aged 3 days to 6 months were studied. Details of diagnosis, sex, age on admission, and mode of presentation are given in Table I. The usual criteria for a diagnosis of heart failure were used (Lees, 1969); however, tachypnoea of more than 60 respirations per minute and cardiac enlargement on x-ray in patients with congenital heart disease were considered to be sufficient to make the diagnosis. Of the 11 infants, 9 were moderately to critically ill, their most striking clinical features being tachypnoea and exhaustion (Table II). Frusemide in a dose of 1.0–1.25 mg/kg was given intramuscularly under the following conditions.

(a) Initially, when a diagnosis of heart failure was made; (b) when deterioration in an infant's condition occurred, usually associated with increasing tachypnoea, and clinically attributed to increasing heart failure; and

(c) when an increase in weight of 2% total body weight occurred in a 12-hour period.

At the time of initial examination, 8 of the children had been digitalized and one had received one dose of mersalyl. During the period of the study no other diuretic therapy other than frusemide was given.

Control urines (24-hour) were obtained from all the infants on admission, and twice a week thereafter. This was relatively easy in male infants using Paul's tubing. In female infants urine collecting bags (Down Bros.) were employed with less successful results. Accordingly, accurately timed specimens without leakage were accepted, particularly in female infants, when 24 specimens were incomplete. Ward sisters, experienced in collecting urine from infants, supervised. The volumes of urine were measured, and concentrations of electrolytes, urea, creatinine, and osmolality were estimated. Post-frusemide urine collections were started at the time of injection of frusemide and continued for 4 hours precisely. Hourly excretion rates before and after frusemide were calculated for all parameters. Blood samples were obtained during the control periods, before the 10 a.m. feed, and also just before the injection of frusemide. The values of serum electrolytes, urea, osmolality, and occasionally creatinine were obtained. Creatinine clearances were estimated at least once during admission. The clinical state before and after administration of frusemide was noted, with particular reference to respiratory rate and weight.

Long-term Study

A long-term study was carried out on 2 infants, with heart failure, aged 21 days and 35 days. A 12-hour urine collection was started at the time of frusemide injection, followed, if possible, by a further three consecutive 12-hour urines to act as controls and minimize the effect of any diurnal variation in excretory patterns (Hellbrügge, 1960; Wesson, 1964; Dodge,

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TABLE I
Some Details of Infants in Study

Case No.	Sex	Age on Admission (dy)	Age of Onset of Symptoms (dy)	Mode of Onset	Diagnosis	Results
1	M	2	From birth	Peripheral cyanosis; tachypnoea	Perinatal oedema	Discharged
2	M	3	From birth	Tachypnoea	PDA, coarctation, VSD, mod. PS	Dead
3	F	10	9	Feeding difficulties	ASD, VSD	Dead
4	F	14	3-4	Tachypnoea; oedema	PTA	Discharged
5	F	14	4	Murmur; cyanosis tachypnoea	VSD	Dead
6	M	30	7	Tachypnoea; dusky	Pulm. atresia, ASD, VSD	Discharged
7	F	43	11	Feeding difficulties; tachypnoea	Coarctation	Discharged
8	M	47	10	Feeding difficulties; tachypnoea; irritability	ASD (large)	Dead
9	M	77	42	Vomiting; tachypnoea	PDA, ASD, common ventricle	Dead
10	F	178	From birth	Failure to thrive	PDA	Discharged
11	M	182	From birth	Feeding difficulties	Aorta-pulmonary window; anomalous LCA	Dead

PDA, persistent ductus arteriosus; VSD, ventricular septal defect; PS, pulmonary stenosis; PTA, persistent truncus arteriosus; ASD, atrial septal defect (secundum); LCA, left coronary artery.

Travis, and Daeschner, 1967). Urine samples were analysed as above. Serum samples were obtained during the first 12-hour collection period and analysed as above.

TABLE II
Incidence of Symptoms and Clinical Findings

Symptoms	No. of Infants Affected (11)
Cyanosis	5
Feeding difficulties	9
Breathlessness	11
Increased sweating	3
Diminished urine volume	0
<i>Findings</i>	
Respirations >60/min	11
Pulse rate >180/min	0
Hepatomegaly >3 cm in anterior axillary line	5
Oedema	5
Gallop rhythm	2
Rhonchi	0
Rales	0
Systemic arterial O ₂ saturation <85%	5
Cardiac enlargement on x-ray	10
Pulmonary plethora on x-ray	10

Results

Short-term results. Results are calculated from 36 control collections and 22 post-frusemide collections for urine volume and osmolality, and from 15 control collections and 16 post-frusemide collections for sodium, potassium, and chloride, the urines having been selected from patients who were comparable for clinical state, electrolyte, and fluid intake (Table III).

Results from the two infants with persistent heart failure are discussed later.

Urine volumes. The onset of diuresis occurred at 20 to 40 minutes after the administration of frusemide. Mean hourly urine volumes increased from 8.9 ± 4.1 before frusemide to 31.6 ± 13.9 ml per hour after frusemide ($P < 0.001$).

Sodium excretion. Mean hourly sodium excretion increased from 203 ± 139 μ Eq/hour before frusemide to 2132 ± 1769 μ Eq/hour after frusemide ($P < 0.001$).

Potassium excretion. Mean hourly potassium excretion increased from 347 ± 231 μ Eq/hour before frusemide to 795 ± 741 μ Eq after frusemide

TABLE III
Mean Changes in Urinary Constituents Before and After Frusemide

	Mean Urine Vol. (ml/hr)	Mean Na Excretion (μ Eq/hr)	Mean K Excretion (μ Eq/hr)	Mean Na/K Ratios	Mean Cl Excretion (μ Eq/hr)	Mean Osmolality (mOsm/l.)	Mean Osmolar Clearance (ml/hr)	Mean Free Water Clearance (ml/hr)
Prefrusemide values	8.9 ± 4.1	203 ± 139	347 ± 231	0.5 ± 0.2	229 ± 164	345 ± 202	8.4 ± 5.6	-0.8 ± 4.4
Postfrusemide values	31.6 ± 13.9	2132 ± 1769	795 ± 741	4.1 ± 2.1	2875 ± 2173	229 ± 79	23.0 ± 15.7	5.2 ± 8.6
P	< 0.001	< 0.001	N.S.	< 0.001	< 0.001	< 0.01	< 0.001	< 0.001

($P > 0.05$). Potassium loss tended to increase with increasing urine volumes. There was no correlation between excessive potassium loss and age, and excessive potassium loss might or might not occur in the same patient.

Sodium potassium ratios (Na/K). Mean Na/K ratio increased from 0.5 ± 0.2 before frusemide to 4.1 ± 2.1 after frusemide ($P < 0.001$), indicating that the urinary loss of sodium is much greater than that for potassium.

Chloride excretion. Mean chloride excretion increased from 229 ± 164 $\mu\text{Eq/hour}$ before frusemide to 2875 ± 2173 $\mu\text{Eq/hour}$ after frusemide ($P < 0.001$).

Urine osmolality. Mean urine osmolality decreased from 345 ± 202 mOsm/l. before frusemide to 229 ± 79 mOsm/l. after frusemide ($P < 0.01$).

Osmolar clearance. Mean osmolar clearance increased from 8.4 ± 5.6 ml/hour before frusemide administration to 23.0 ± 15.7 ml/hour after frusemide ($P < 0.001$).

Free water clearance. Mean free water clearance increased from -0.8 ± 4.4 ml per hour before frusemide to 5.2 ± 8.6 after frusemide ($P < 0.001$).

Creatinine clearances. Creatinine clearances ranged from 5.2 – 33 ml/min per 1.73 m².

Clinical. Oedema, which was present in 5 infants, cleared rapidly. The 2 infants (Cases 7 and 10) with excessive weight gain and tachypnoea responded well to intramuscular frusemide. Thereafter heart failure was controlled by digoxin and restricted fluid and sodium intake until corrective surgery was undertaken. One infant (Case 4) with persistent truncus arteriosus also responded well to one injection of frusemide and was discharged home well controlled on digoxin and restricted fluid and sodium intake. The remaining 8 infants improved slightly or their condition did not deteriorate further; however in 12 to 24 hours they lost all benefit from the diuretic, as judged by their clinical state, particularly respiratory rate and weight.

Two patients developed collapse of a lobe of a lung after diuretic therapy, possibly related to loss of intrapulmonary fluid.

Long-term studies. Results from only one of the patients are presented in detail, as they were similar in the two patients. Intermittent intramuscular frusemide was extremely effective in promoting increase in urine volume (from a mean of 5.9 ± 2.9 to 14.8 ± 1.8 ml/hour ($P < 0.001$)) and sodium excretion (from a mean of 105 ± 127 to 722 ± 263 $\mu\text{Eq/hour}$, $P < 0.001$). Frusemide had a lesser effect on promoting potassium excretion

(mean increase from 276 ± 115 $\mu\text{Eq/hour}$ to 319 ± 83 $\mu\text{Eq/hour}$ $P < 0.001$). Urea and creatinine excretion were not significantly affected. Urine osmolality decreased from 395 ± 197 mOsm/l. to 206 ± 73 mOsm/l. ($P < 0.005$). Osmolar clearance increased from 1.3 ± 0.9 to 1.6 ± 0.5 ml/hr ($P > 0.05$) and free water clearances increased from -0.40 ± 0.85 to 0.64 ± 0.65 ($P < 0.001$). The falls that occurred in weight and respiratory rate are shown in the Fig. and correlated well with the observed clinical improvement.

Mild hyponatraemia, moderate hypochloraemia, occasional hypokalaemia, and very occasionally a rise in blood urea were noted and attributed to frusemide therapy. Serious dehydration and extracellular alkalosis did not occur.

Discussion and Comment

In structure, frusemide is a saturated benzene ring with attached sulphamyl and chlorine groups. In human adults peak plasma levels of sulphur-35 labelled frusemide were found at 30 minutes after intramuscular administration, and 60 minutes after oral administration; approximately 80% of the labelled dose being recovered in the urine after intravenous and intramuscular administration (Calesnick, Christensen, and Richter, 1966). It is rapidly excreted in adults by filtration and tubular secretion in the urine (Deetjen, 1966), and it is also excreted in the bile and faeces (Schirmeister and Willmann, 1964). Excretion of frusemide like other drugs may be slower in the newborn.

The diuretic action of frusemide may well be brought about by a lowering of the permeability of cell membranes for ions, thus reducing passage of ions from the lumen of the tubule (Nagel and Karger, 1964). Decreased permeability to ions has been shown by Lipson and Hays (1966) in the toad bladder; and Holzgreve *et al.* (1965) using a continuous micropfusion technique found that sodium efflux out of both proximal and distal tubules was inhibited by frusemide.

A fall in glomerular filtration rate (GFR) occurs in normal subjects with frusemide, probably accounted for by the accompanying fall in extracellular fluid (Stein and Kirkendall, 1967). However, frusemide is an effective diuretic even in the presence of greatly impaired renal function (Vorbuerger, 1964; Muth, 1966; Reubi, 1966), and Vorbuerger (1964) has observed increases in GFR in patients in renal failure, with frusemide. A marked rise in renal blood flow occurs with frusemide (Schirmeister and Willmann, 1964; Vorbuerger, 1964; and Hook *et al.*, 1966). Barger (1966) and

Barger and Herd 1967) found that, in dogs, frusemide increased cortical blood flow at the time of diuresis, and lowered renal vein resistance, thus reversing the situation that occurs in heart failure (Birtch *et al.*, 1967).

The predominant site of action in the renal tubule is probably the ascending loop of Henle, as shown by the drug's interference with the concentrating mechanism (Buchborn and Anastakis, 1964; Suzuki, Klütsch, and Heidland, 1964; Gayer, 1965; Lezotte *et al.*, 1966; Deetjen, 1966). Potassium loss occurs primarily because of increased distal tubular secretion of potassium, and this loss may be augmented in situations where there is increased aldosterone secretion (Cannon *et al.*, 1965; Stason *et al.*, 1966).

than control period samples, suggesting that interference with the medullary concentration gradient occurred and that frusemide acted on the ascending loop of Henle (Seldin *et al.*, 1966; Suki, Rector, and Seldin, 1965; Berliner, Dirks, and Cirkseña, 1966).

Intramuscular frusemide was shown to be a potent diuretic in infants with heart failure, and because of its ease of administration, speed of action, and lack of toxicity, is one of the diuretics of choice for the initial treatment of heart failure. However, as infants tend to lose all benefit from the drug in 12 to 24 hours, persistent heart failure is more easily controlled by twice daily administration of frusemide, and if heart failure is still uncontrolled drugs with a distal tubular site of action such as aldactone A or triamterene might be given in addition.

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