Frusemide in respiratory distress syndrome

M. O. SAVAGE,* A. R. WILKINSON,† J. D. BAUM, and N. R. C. ROBERTON‡

From the Department of Paediatrics, University of Oxford, John Radcliffe Hospital

Savage, M. O., Wilkinson, A. R., Baum, J. D., Robertson, N. R. C. (1975). *Archives of Disease in Childhood*, 50, 709. **Frusemide in respiratory distress syndrome.** The effect of frusemide on urinary volume, urinary sodium excretion, and urinary calcium excretion in 7 premature infants with severe respiratory distress syndrome (RDS) has been studied. The results are compared with similar measurements on 13 infants of comparable gestational age and birthweight with less severe RDS who did not receive frusemide. The effect of frusemide on P_{aO_2} and P_{aCO_2} tensions in 5 infants with RDS was also investigated.

Frusemide produced a fourfold increase in urinary volume and a tenfold increase in urinary sodium and urinary calcium excretion compared with the untreated group. It caused no improvement in blood gas tensions. The use of this diuretic for the routine management of RDS cannot be recommended.

Severe interstitial oedema is found on histological examination of the lungs of infants dying from the respiratory distress syndrome (RDS) during the first few hours of life (Gandy, Jacobson, and Gairdner, 1970). In pulmonary oedema developing in other clinical situations in the neonatal period, frusemide has been shown to be an effective diuretic (Richardson, 1971). It was therefore decided to study the effect of frusemide on blood gas tensions and fluid and electrolyte balance during the first 24 hours of life in infants suffering from severe RDS.

Material and methods

Two groups of infants were studied. 7 infants received frusemide and 13 infants received no diuretic and constituted an untreated group. Patients were randomly allocated to the 2 groups but were not matched for the severity of RDS. All infants had RDS according to classical criteria (Davies *et al.*, 1972). The infants in the treated group had more severe RDS than those in the untreated group (Tables I and II). The management of the infants was that in current use in the unit, which includes umbilical arterial and venous catheterization (Davies *et al.*, 1972).

Frusemide was given in 3 doses each of 1.5 mg/kg body weight intravenously through the umbilical venous catheter at 2, 6, and 12 hours of age. For the 60 minutes after each dose, the infant was kept in a

constant inspired oxygen concentration. Blood gases were measured (using the IL 313 Blood Gas Analyser) immediately before, 20 minutes after, and 60 minutes after each dose of diuretic. They were also routinely measured 4-hourly during the first 24 hours of life.

The fluid, calcium, and sodium intake of all infants was measured during the first 24 hours of life. All urine passed during this period was collected, the volume noted, and the calcium and sodium concentrations measured. Measurements were also made of plasma sodium (by flame photometry), calcium (by titrimetric method using EDTA), osmolality (Advanced osmometer), albumin (Bromocresol green colorimetry), and colloid osmotic pressure (using a pressure transducer osmometer as described by Baum *et al.* (1971) on cord blood and blood samples taken at 24 hours of age.

The data from the 7 infants who received frusemide were compared with data derived from the 13 infants in the untreated group.

Results

Urine volume and composition. The fluid intake and output for both groups of infants are shown in Table III. Fluid intake in the 2 groups was similar; the mean urine output in the frusemide group was significantly greater (63 ml/kg per 24 h against 16 ml/kg 24 h; $P < 0.001$). The mean urinary sodium excretion in the frusemide group was significantly greater than in the untreated group (7.1 mEq/24 h against 0.5 mEq/24 h; $P < 0.001$).

The sodium intake was, however, significantly greater in the frusemide treated group ($P < 0.025$). This was due to sodium bicarbonate used to correct

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Present addresses: *Department of Paediatrics, Guy's Hospital, London.

†Nuffield Institute for Medical Research, Oxford.

‡Addenbrooke's Hospital, Cambridge.

TABLE 3
Clinical details of infants

Case no.	Birthweight (g)	Gestational age (w)	Sex	Pao ₂ (torr)* in Fio ₂ 1.0	Ventilation
1	1330	31	F	120	CDP
2	1280	29	M	132	CDP/IPPV
3	1260	29	F	230	CDP/IPPV
4	1300	28	M	65	CDP
5	1850	36	M	216	CDP
6†	4020	36	F	135	—
7	1770	33	M	240	—

*Within 6 h of birth: used as indication of severity of RDS.

†Twins. No necropsy.

‡Infant of diabetic mother.

CDP, continuous distending pressure; IPPV, intermittent positive pressure ventilation; RDS, respiratory distress syndrome; HMD, hyaline membrane disease; IVH, intraventricular haemorrhage; Pn, pneumothorax.

TABLE 4
Clinical details of infants who

Case no.	Birthweight (g)	Gestational age (w)	Sex	Pao ₂ (torr)* in Fio ₂ 1.0	Ventilation
8	2430	35	M	150	—
9	1530	32	M	—	—
10	1610	29	F	—	—
11	1930	31	F	180	—
12	1070	33	M	280	—
13	1180	30	F	278	—
14	1640	33	M	220	—
15	1760	35	M	280	—
16	1290	28	F	115	CDP/IPPV
17	1270	32	M	242	CDP/IPPV
18	2320	36	M	230	—
19	1700	32	F	185	—
20	1280	28	M	202	IPPV

*Within 6 h of birth: used as indication of severity of RDS.

acidosis in 5 of the 7 infants in this group. However, in the remaining 2 frusemide-treated patients who did not receive sodium bicarbonate, and who had similar intakes to the untreated group, the sodium output was greatly increased after frusemide (10.9 and 3.3 mEq/24 h against a mean of 0.5 mEq/24 h; Table IV).

The mean urinary calcium excretion was significantly greater in the frusemide-treated group of infants (2.8 mEq/24 h against 0.2 mEq/24 h; $P < 0.001$). 2 of the treated infants received supplementary intravenous 10% calcium gluconate during the first 24 hours of life, and as a result the

mean calcium intake for the frusemide-treated group was significantly higher than in the untreated group (53.3 mEq/24 h against 12.8 mEq/24 h; $P < 0.05$).

However, when the 5 infants who did not receive calcium supplements are considered (Table IV) their mean calcium intake was significantly lower than the 13 infants who did not receive frusemide (4.8 mEq/24 h against 12.8 mEq/24 h; $P < 0.05$); even so, their urinary calcium excretion was significantly greater than the calcium excretion in the 13 infants who did not receive frusemide. Furthermore the calcium excretion within the frusemide-treated group was not increased in the 2 infants

I.
receiving frusemide

Cause of death	Time of death (h)	Weight at 24 h (g)	Systolic blood pressure (mmHg)		Blood transfusion
			Birth	24 h	
IVH	168	—	35	—	+
RDS (Pn)†	27	—	55	60	+
RDS (Pn)†	45	—	—	—	—
—	—	—	45	—	—
IVH/HMD	62	—	—	80	+
—	—	3480	—	—	—
—	—	1570	—	—	—

II
did not receive frusemide

Cause of death	Time of death (h)	Weight at 24 h (g)	Systolic blood pressure (mmHg)		Blood transfusion
			(Birth)	(24 h)	
—	—	—	75	—	—
—	—	—	—	—	—
—	—	—	—	—	—
—	—	1070	—	—	—
—	—	—	—	—	—
—	—	—	—	—	—
—	—	—	—	—	—
—	—	—	23	34	+
Peritonitis	73 d	—	47	53	+
—	—	2300	—	—	—
—	—	—	—	—	—
IVH	52	1200	—	—	+

TABLE III
Mean 24-hour fluid, sodium, and calcium intake and output in two groups

	Frusemide treated	No frusemide	t	P
Fluid intake (ml/kg per 24 h)	51 (29-79)	48 (35-61)	0.653	0.5
Urinary output (ml/kg per 24 h)	63 (37-106)	16 (43-8)	5.36	<0.001
Sodium intake (mEq/kg per 24 h)	5.1 (0.9-12.6)	0.8 (0-1.3)	3.77	<0.0025
Output (mEq/kg per 24 h)	7.1 (3.3-10.9)	0.5 (0.1-1.2)	7.62	<0.001
Calcium intake (mg/kg per 24 h)	53.3 (0-192)	12.8 (0-25.2)	1.78	<0.05
Output (mg/kg per 24 h)	2.8 (0.8-6.7)	0.2 (0.1-1.2)	4.31	<0.001

Range in parentheses.

TABLE IV

Mean sodium and calcium intake and output in frusemide-treated patients who did not receive sodium and calcium supplements compared with patients receiving no frusemide

	Frusemide treated	No frusemide	P
Sodium			
Intake (mEq/kg per 24 h)	1.0 (0.9-1.1) n = 2	0.8 (0-1.3) n = 13	<0.001
Output (mEq/kg per 24 h)	7.1 (3.3-10.9) n = 2	0.5 (0.1-1.2) n = 13	
Calcium			
Intake (mg/kg per 24 h)	4.8 (0-16) n = 5	12.8 (0-25.2) n = 13	<0.001
Output (mg/kg per 24 h)	2.9 (0.8-6.7) n = 5	0.2 (0.1-1.2) n = 13	

P values, using a 't' test, are significant; however, the numbers in the frusemide group are very small. Range in parentheses.

who received supplementary intravenous calcium compared with those who did not.

Plasma values. The mean plasma calcium in cord blood and in the sample drawn at 24 hours of age was no different in the frusemide-treated and the untreated groups of infants, though there was an identical and significant fall in the calcium values over this period of time in both groups. The mean cord levels for osmolality, albumin, and colloid osmotic pressure did not differ significantly between the two groups, and though at 24 hours these values were in each case greater in the frusemide-treated group than in the untreated group, these differences were not significantly different using the 't' test.

Blood gases. Results of blood gas estimations in 5 of the patients receiving frusemide are shown

in Table V. Arterial PO_2 and arterial PCO_2 after injection of frusemide showed no significant change by the paired 't' test.

Discussion

The present study has confirmed that frusemide is a powerful diuretic even in the critically ill infant with RDS. The mean increase in urinary output in the first 24 hours was fourfold, and the urine sodium and calcium excretion was increased tenfold in the treated group of infants compared with the less severely ill group who did not receive diuretics. This diuresis cannot be ascribed to the severity of the RDS since Cort (1962) showed that there was no increase in urine output or sodium excretion in preterm infants with RDS compared with normal preterm infants.

Despite the brisk diuresis we were only able to

TABLE V

Blood gas tensions before and after frusemide

Case no.	Time after birth (h)	PO_2 (mmHg)			PCO_2 (mmHg)		
		Before frusemide	After frusemide (min)		Before frusemide	After frusemide (min)	
			20	60		20	60
1	2	155	201	211	39	33	32
"	6	69	54	45	54	49	51
"	12	136	57	98	35	74	61
2	6	90	48	98	65	65	69
"	12	55	-	31	54	-	41
3	4	159	88	54	56	62	53
"	6	94	42	37	60	67	61
"	12	59	-	46	61	-	23
5	4	72	74	94	58	54	52
7	4	108	133	123	32	34	37
"	6	112	93	93	54	49	51
"	12	80	69	-	35	74	61
Mean		99	86	85	50	56	49

Using the paired 't' test there was no significant difference between the values for PO_2 or PCO_2 before or after frusemide.

show a trend towards haemoconcentration in terms of colloid osmotic pressure and albumin concentration. Normal measurements of blood pressure were obtained at 24 hours of age in 2 of the critically ill infants from the treated group. No clinical complications were observed in the treated group which could be attributed to diuretic therapy. The considerable increase in urine output in the treated infants might have been expected to result in a reduction in pulmonary oedema. In the 5 infants where blood gases were measured before and after frusemide, there was, however, no demonstrable improvement in arterial PO_2 or PCO_2 .

Since frusemide has a potential for causing serious dehydration with no associated improvement in blood gas tensions its use cannot be recommended for the routine management of infants with RDS.

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Correspondence to Dr. J. D. Baum, Department of Paediatrics, John Radcliffe Hospital, Headington, Oxford OX 3 9DU.