Early neonatal hypocalcaemia

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Roberton, N. R. C., and Smith, M. A. (1975). *Archives of Disease in Childhood*, 50, 604. **Early neonatal hypocalcaemia.** In our hospital early neonatal hypocalcaemia is now the major cause of low serum calcium in the neonatal period. Over a 2-year period, only 2 cases of hypocalcaemic convulsions were seen in a total of 8700 deliveries, though 51 infants had early neonatal hypocalcaemia. All sick low birth-weight infants should have daily serum calcium estimations carried out. Calcium supplements should be considered if symptoms of hypocalcaemia are present.

There are two occasions when hypocalcaemia is frequently found during the neonatal period. In the first 48-72 hours it has been described in association with low birthweight, birth asphyxia, and maternal diabetes (Tsang and Oh, 1970; Tsang *et al.*, 1972; Tsang *et al.*, 1973a; Tsang *et al.*, 1974). At the end of the first week hypocalcaemia occurs in association with hyperphosphataemia due to the high phosphate intake when cow's milk feeds are given to infants. These infants develop multifocal fits which have a good long-term prognosis (Cockburn *et al.*, 1973). This late hypocalcaemia has received considerable attention in recent years, but the realization that both the fits and biochemical abnormality could be prevented by the use of low phosphate milks has resulted in the reduction of such cases to an acceptable minimum in most units.

The finding of extremely low serum calcium values during the first few days of life in sick, low birthweight babies receiving intermittent positive pressure ventilation (IPPV), who were extremely jittery and difficult to ventilate, led us to carry out a prospective study of the incidence of the early type of hypocalcaemia.

Material and methods

The study was carried out during 1972 and 1973. All low birthweight infants admitted to the Special Care Baby Unit and considered to be ill enough to require umbilical arterial catheterization as part of routine management of their illness were studied. Serum calcium values were estimated every 24 hours, or more frequently if indicated. Any other infant showing signs or symptoms of hypocalcaemia in the

neonatal period also had serum calcium estimations carried out.

For the purpose of this study, hypocalcaemia was defined as a serum calcium level of 3 mEq/l or less, which represents the lower normal limit of most surveys of serum calcium carried out in preterm infants during the first few days of life (Jukarainen, 1971; Tsang *et al.*, 1973a).

Asphyxia neonatorum was diagnosed when the infant required intubation and positive pressure ventilation to establish spontaneous respiration after birth. Hyaline membrane disease was diagnosed according to the usual criteria (Roberton, 1975). The exposure to high inspired oxygen concentrations and IPPV, the duration of hypoxaemia of ≤ 60 torr and ≤ 40 torr, and the duration of acidemia of $\text{pH} \leq 7.25$ and ≤ 7.10 was assessed in hours during the first 48 hours of life, since 45 of the 51 infants who developed hypocalcaemia did so by this time. The dose of base administered was calculated in mEq bicarbonate ion received; for infants receiving THAM it was assumed that 1 mol THAM is equivalent to 0.5 mEq bicarbonate (Heird *et al.*, 1972). Calcium intake was calculated from the amount of milk ingested between 0 and 24 hours, and 24 and 48 hours of life, using the data for calcium content of Shaw, Jones, and Gunther (1973).

Results

Incidence of hypocalcaemia. 131 ill newborn infants with indwelling umbilical artery catheters were studied during the 2-year period. 51 infants (15 deaths) developed hypocalcaemia before 96 hours of age, and 45 of these were hypocalcaemic before 48 hours of age. None of the remaining 80 infants (18 deaths) developed hypocalcaemia of less than 3 mEq/l. The diagnoses in these infants are given in Table I. Most of them were suffering from hyaline membrane disease (HMD).

A further 6 infants who did not have indwelling

TABLE I

Diagnosis in infants with indwelling catheters studied for hypocalcaemia. (Number of deaths in parentheses)

Diagnosis	Hypocalcaemic <3.0	Normocalcaemic >3.0
Hyaline membrane disease	41 (11)	61 (6)
Septicaemia	4 (1)	2 (2)
Birth asphyxia	3 (1)	5 (5)
Haemolytic disease of the newborn	1	7 (1)
Congenital malformations	1 (1)	4 (4)
Extreme prematurity (<1.0 kg and <28 w)	1 (1)	1(-)
Total	51 (15)	80 (18)

catheters were found to be hypocalcaemic within 96 hours of birth. Their blood was taken for analysis because symptoms suggesting hypocalcaemia were present. 4 were preterm infants who became very jittery, and 2 were term infants with severe birth asphyxia and enterocolitis, respectively. None of them had fits. During the 2-year period only 4 infants out of approximately 8700 births were known to have developed hypocalcaemia after 96 hours of age. 3 of these were probably due to high phosphate feeds, and 2 of these developed fits. The fourth infant, whose mother had been on large doses of opiates for metastatic malignant disease, became hypocalcaemic concurrently with symptoms suggesting a withdrawal syndrome. The overall incidence of convulsions in our hospital during this period was 5.3/1000 live births.

Cause of hypocalcaemia. Data from the 131 infants in the prospective study were analysed. Many of the infants were of short gestation and low

birthweight, which reflects the selection of infants with severe illness, usually HMD, for the study group. There was no difference in birthweight and gestational age between the hypocalcaemic and normocalcaemic infants in the group, and it was therefore felt justifiable to compare the various other factors in these infants in an attempt to elucidate further the causes of hypocalcaemia (Table II).

Serum calcium levels in infants exposed to various stress factors were significantly lower than levels in infants not so exposed (Table III). Infants with serum calcium levels of >3 mEq/l, however, were often those less seriously ill who never received bicarbonate or frusemide, or were exposed to hypoxaemia, acidaemia, or IPPV. When infants exposed to stress factors are considered alone, the only difference between hypocalcaemic infants and normocalcaemic infants is a lower calcium intake and a longer duration of exposure to high inspired oxygen concentration (Table IV). This difference was still significant when the most severely ill infants, i.e. those who received IPPV, were analysed alone (Table V). This excess exposure to high inspired oxygen concentrations or low calcium intake was not due to an excess of very low birthweight babies among infants so exposed; Table VI shows a longer exposure to oxygen in hypocalcaemic infants at all birthweights, though the number of infants involved at each weight is too small for statistical analysis.

Symptoms due to hypocalcaemia.

Jitteriness and irritability. 9 of the 51 hypocalcaemic infants developed symptoms of marked jitteriness compared with 7 out of 80 normocalcaemic infants ($\chi^2 = 1.549$, $P > 0.2$, not significant). 6 of the latter had serum calcium values between 3.1 and 3.5 mEq/l, and in these as well as in those

TABLE II

Birthweight and gestational age of infants in prospective study who were hypocalcaemic or normocalcaemic

	Birthweight (kg)					
	<1.0	1.0-1.5	1.5-2.0	2.0-2.5	>2.5	
Hypocalcaemic	2	12	10	16	11	
Normocalcaemic	3	14	14	13	36	
					$\chi^2 = 2.79, P < 0.6$	
	Gestational age (w)					
	26/27	28/29	30/31	32/33	34/35	>36
Hypocalcaemic	2	6	8	8	11	16
Normocalcaemic	4	8	7	9	16	38
					$\chi^2 = 3.88, P < 0.6$	

TABLE III

Mean serum calcium levels compared between those infants exposed to a given stress and those not exposed

Stress factor	All infants in prospective study				Infants with HMD only			
	Serum Ca in infants exposed (mEq/l)	Serum Ca in infants not exposed (mEq/l)	t	P	Serum Ca in infants exposed (mEq/l)	Serum Ca in infants not exposed (mEq/l)	t	P
Intravenous base	3.15	3.58	3.638	<0.001	3.05	3.62	4.748	<0.001
Frusemide therapy	3.12	3.49	3.117	<0.001	3.02	3.51	4.015	<0.001
Pao ₂ ≤60 torr	2.31	3.54	2.710	<0.01	3.18	3.56	2.903	<0.005
Pao ₂ ≤40 torr	3.11	3.41	2.220	<0.025	3.09	3.40	2.176	<0.025
pH ≤7.25	3.20	3.48	2.307	<0.025	3.09	3.52	3.495	<0.001
pH ≤7.10	3.13	3.38	1.610	NS	2.85	3.39	2.918	<0.005
Fio ₂ ≥0.6	3.18	3.64	3.759	<0.001	3.13	3.69	4.340	<0.001
Fio ₂ ≥0.8	3.08	3.52	3.417	<0.001	2.81	3.52	4.688	<0.001
IPPV	3.24	3.40	1.665	NS	3.01	3.47	3.671	<0.001
Birth asphyxia	3.36	3.35	0.137	NS	3.26	3.39	1.009	NS
	Dead 3.36	Alive 3.33	0.205	NS	Dead 2.97	Alive 3.38	2.348	<0.02

TABLE IV

Stress factors in hypocalcaemic and normocalcaemic infants during first 48 hours of life

Stress factors	All infants in prospective study				Infants with HMD only			
	Hypo-calcaemic	Normo-calcaemic	t	P	Hypo-calcaemic	Normo-calcaemic	t	P
Base (mEq/kg)	7.65	6.97	0.551	NS	7.21	6.82	0.338	NS
Frusemide (mg/kg)	1.97	1.83	0.392	NS	2.04	1.79	0.563	NS
Hours pH ≤7.25	5.29	7.24	1.248	NS	4.34	5.99	0.258	NS
Hours pH ≤7.10	1.50	3.84	2.63	<0.02	Insufficient for statistical analysis			
Hours Po ₂ ≤60 torr	12.02	10.49	0.741	NS				
Hours Po ₂ ≤40 torr	5.56	4.90	0.432	NS	12.15	9.92	1.048	NS
Hours ≥Fio ₂ 0.6	26.7	14.75	3.656	<0.001	4.97	5.31	0.234	NS
Hours ≥Fio ₂ 0.8	20.94	11.25	3.268	<0.005	26.63	15.82	2.655	<0.01
Hours of IPPV	21.65	15.45	1.554	NS	21.36	10.56	2.916	<0.005
Ca intake 0-24 h (mg/kg)	4.09	8.06	3.116	<0.005	20.61	15.56	0.924	NS
Ca intake 24-48 h (mg/kg)	4.40	11.81	3.196	<0.005	4.04	7.77	2.746	<0.01
					3.92	12.07	4.122	<0.001

TABLE V

Stress factors in ventilated hypocalcaemic and ventilated normocalcaemic infants during first 48 hours of life

Stress factors	All infants in prospective study				Infants with HMD only			
	Hypo-calcaemic	Normo-calcaemic	t	P	Hypo-calcaemic	Normo-calcaemic	t	P
Base (mEq/kg)	8.35	7.27	0.4	NS	7.90	7.96	0.04	NS
Frusemide (mg/kg)	1.78	2.34	1.2	NS	1.71	2.17	1.02	NS
Hours pH ≤7.25	4.6	7.78	1.75	NS	4.55	6.70	1.24	NS
Hours pH ≤7.10	0.6	1.48	1.68	NS	0.58	1.24	0.21	NS
Hours Po ₂ ≤60	13.02	10.06	0.87	NS	14.56	10.29	1.39	NS
Hours Po ₂ ≤40	3.28	2.88	0.33	NS	2.99	3.48	0.36	NS
Hours Fio ₂ ≥0.6	31.2	19.6	2.790	<0.01	37.3	26.4	2.63	<0.02
Hours Fio ₂ ≥0.8	20.8	11.7	2.630	<0.02	24.5	11.6	3.32	<0.001
Duration IPPV	19.8	14.9	1.23	NS	18.6	13.0	1.09	NS
Ca intake 0-24 h (mg/kg)	3.56	3.64	0.05	NS	4.74	6.45	0.93	NS
Ca intake 24-40 h (mg/kg)	2.91	7.12	1.51	NS	2.13	5.06	2.309	<0.025

TABLE VI

Mean duration of exposure to high inspired oxygen concentration at different birthweights in infants with HMD

Birthweight (kg)	Fio ₂ > 0.6		Fio ₂ > 0.8	
	Hypocalcaemic	Normocalcaemic	Hypocalcaemic	Normocalcaemic
1.0-1.5	27.6	14.7	23.3	10.4
1.5-2.0	29.7	32.5	29.5	15.5
2.0-2.5	23.3	9.4	14.2	-
2.5-3.0	40.7	16.1	23.0	10.5
> 3.0	38.0	16.0	15.0	8.0

infants with serum calcium levels of <3.0 mEq/l the symptoms improved when the hypocalcaemia was treated. However, the majority of infants with serum calcium values of <3 mEq/l showed no evidence of neuromuscular irritability.

Apnoea. No attempt was made to quantitate short apnoeic episodes in this study. However, only 5 infants had problems with prolonged recurrent apnoeic attacks. 3 had serum calcium values of <3 mEq/l and the other 2 had values of 3.3 and 3.6 mEq/l.

Convulsions. 12 of the 131 infants studied had convulsions; 8 were hypocalcaemic (Table VII). In 9 cases severe birth asphyxia, intraventricular haemorrhage, or protracted hypoglycaemia was more likely the cause of convulsions. In 2 cases

fits and hypocalcaemia were coincident and no other cause of convulsions was identified. These 2 infants and a baby who developed fits 24 hours after a low serum calcium was found are among the 4 who survived and they are making normal progress.

Persistent ductus arteriosus. 11 infants in this series had congestive failure attributed to persistent ductus arteriosus developing at the end of the first week of life when they were recovering from HMD. All were treated with digoxin and diuretics. 3 of these had serum calcium values of >3.0 mEq/l (3.3, 3.5, and 3.5), but the other 8 had serum calcium values of <3 mEq/l. This difference is significant ($\chi^2 = 5.311$, $P < 0.05$). A further 3 in the hypocalcaemic group, and 2 with normal serum calcium values, had a loud murmur suggestive of persistent ductus arteriosus, but did not go into

TABLE VII

Infants with fits

Case no.	Birthweight (g)	Serum Ca (mEq/l)	Type of fit	Likely aetiology	Outcome
1	1265	1.7	Tonic/clonic	IVH	Died; massive IVH at necropsy
2	1310	3.0	Tonic	IVH	Died; massive IVH at necropsy
3	1470	2.7	Tonic	Severe asphyxia, IVH	Died; IVH, subcapsular haematoma in liver; fracture clavicle and humerus
4	1870	3.0	Tonic/clonic	Severe asphyxia, morphinized	Alive and well; normal progress
5	2030	2.9	Clonic	↓ Ca ⁺⁺ coincident	Alive and well; normal progress
6	2810	2.9	Tonic/clonic	Severe asphyxia + hypotension after fetal bleeding	Alive; severe brain damage
7	3280	1.9	Tonic/clonic	Severe asphyxia	Died; severe hypoxia, brain damage at necropsy
8	3450	2.5	Clonic	↓ Ca ⁺⁺ coincident	Alive and well; <i>Proteus</i> septicaemia
9	1810	4.7	Tonic	IVH	Died; severe Rh hydrops; IVH at necropsy
10	2370	3.1	Clonic	? ↓ Ca ⁺⁺ fits 24 h later	Alive and well; normal progress
11	2790	3.9	Tonic/clonic	Severe asphyxia	Died; Apgar score 0
12	3270	3.2	Clonic	? ↓ Ca ⁺⁺ also hypoglycaemic	Alive; severe Rh hydrops; Apgar score 0; L. hemiplegia; retarded

IVH, intraventricular haemorrhage.

heart failure and received no treatment. No infant other than those with signs of persistent ductus arteriosus developed heart failure.

Discussion

Both early work (Bakwin, 1937; Bruck and Weintraub, 1955; Gittleman *et al.*, 1956) and that published more recently (Tsang and Oh, 1970; Tsang *et al.*, 1973a; Radde *et al.*, 1972) have shown that early neonatal hypocalcaemia is more common in infants of low birthweight. However, those studies included only a minority of seriously ill infants. In our series, in which only ill infants with indwelling catheters were studied, analyses of the data showed that the only factors associated with early hypocalcaemia other than low birthweight were duration of exposure to high inspired oxygen concentrations and low calcium intake. In current neonatal practice, acidaemia and hypoxaemia are avoidable. The duration of exposure to high inspired oxygen concentration is therefore probably a better guide to the severity of an infant's illness. Furthermore, a low calcium intake may also indicate severe illness, since the ileus in such infants (Dunn, 1963) would result in pooling of the milk in the stomach and feeding being discontinued. Our results therefore suggest that it is severity of illness which correlates best with hypocalcaemia in the first few days of life.

The total body calcium even of a preterm infant is very large in comparison with the small fluxes in serum calcium caused by variations in oral intake of expressed breast milk, calcium losses in the urine (even under the influence of calciuretic drugs), or transient changes in calcium homeostasis caused by short-lived acidaemia or infusions of base. Low serum calcium values in the early neonatal period have therefore always been attributed to hypoparathyroidism, and recently published data on parathormone levels in the immediate neonatal period have implicated diminished parathormone release rather than end-organ unresponsiveness. This hypoparathyroidism was more marked in low birthweight infants (Tsang *et al.* 1973b; Fairney, Jackson, and Clayton, 1973; Bergman, Kjellmer, and Selstam, 1974; David and Anast, 1974). In seriously ill newborn infants the hypoparathyroidism will be aggravated by raised levels of other hormones such as corticosteroids, calcitonin, and glucagon, which depress serum calcium (Reynolds, 1973; Bergman *et al.*, 1974).

Because we considered that the hypocalcaemia might be harmful to these infants and cause symptoms, it was treated in most cases. 35 of the

45 infants who were hypocalcaemic before 48 hours of age received small doses of oral or intravenous 10% calcium gluconate (maximum 9 ml/24 h). For the reasons stated above, this cannot contribute significantly to the total body calcium, yet it did seem to be associated with a rise in serum calcium in such infants.

The plasma calcium level had not risen when next checked in only 2 of the 35 who were treated. The 2 infants who developed clonic convulsions simultaneously with the hypocalcaemia did not develop further convulsions after oral calcium supplements had raised the serum calcium to normal.

Although we did not show a significant increase of jitteriness in infants who were hypocalcaemic, 6 of the other jittery infants had serum calcium levels of less than 3.5 mEq/l, a level considered by many people to be hypocalcaemic. David and Anast (1974) also found that most of their hypocalcaemic infants were jittery. The infants in our series who were jittery and difficult to ventilate undoubtedly improved clinically when calcium supplements were given and the serum calcium rose. We did not see any cases of hypocalcaemic heart failure (Troughton and Singh, 1972), but there was an increased incidence of infants with serious heart failure due to persistent ductus arteriosus in the hypocalcaemic group. This is probably because the more seriously ill infants with HMD developed persistent ductus arteriosus rather than that hypocalcaemia in some way prevented constriction of the ductus arteriosus, though this has been shown *in vitro* (Kovalčik, 1963). A trial of prevention of hypocalcaemia in critically ill infants, as suggested by Nervez *et al.* (1974), will be the only way of assessing the effect that normalizing serum calcium has on jitteriness, difficulty in ventilating the infant, and on the incidence of persistent ductus arteriosus.

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