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Electrolytes sodium
hyponatremia very low birthweight infants

Electrolyte Abnormalities in Very Low Birthweight Infants

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Extract

In 30 very low birth weight (VLBW) infants, fed a commercial formula at 200 ml/kg/24 hr to provide 160 cal/kg/24 hr, hyponatremia (plasma Na^+ < 130 mEq/liter) occurred in 23 patients (14 appropriate for gestational age (AGA), 9 small for gestational age (SGA)) between the ages of 2 and 6 weeks. In five infants the hyponatremia recurred even after adequate correction of the deficit. Calcium supplementation given to 14 of the infants did not affect the incidence or severity of hyponatremia. In AGA infants, the hyponatremia was more severe than in SGA babies.

Hyperkalemia (plasma K^+ > 5.5 mEq/liter) was more common in AGA than in SGA infants (16/17 AGA, 7/13 SGA). Decrease in mean plasma chloride concentrations was proportionate to the decrease in mean Na^+.

Urinary Na^+ averaged 1.0 mEq/kg/24 hr and was equal between groups during the first balance at a mean age of 18 days. In subsequent balances it appeared to decrease more rapidly in noncalcium-supplemented than in calcium-supplemented infants, but the difference was not significant ($P < 0.1$). Fecal excretion of Na^+ did not differ between groups.

Symptoms were unrelated to the degree of hyponatremia or hyperkalemia and were nonspecific.

Hyponatremia in AGA infants occurred in 50% of instances when growth was ≤ 0.75 cm/week, whereas it occurred in only 13.5% of infants when growth exceeded 1 cm/week ($P < 0.01$). A similar trend in SGA infants was not statistically significant ($P < 0.2$).

Speculation

The hyponatremia in VLBW infants between weeks 2 and 6 of postnatal age is due to a combination of high urinary losses relative to plasma levels, insufficient intake due to the relatively low Na^+ content of certain infant formulas and coprecipitation of Na^+ in

bone when length growth is rapid. Renal compensatory mechanisms for increased Na^+ retention develop after prolonged feeding of low Na^+ formula to VLBW infants.

There are few reports of plasma Na^+ concentrations in "healthy" VLBW infants after the immediate neonatal period (19–21), moreover these refer to few infants of birthweight <1.3 kg (8).

We have shown previously that VLBW infants fed with standard formula develop marked calcium deficiency within a few weeks of birth (6). An incidental and disturbing finding in many of these infants was that of hyponatremia and hyperkalemia, usually between the second and sixth week of life.

We wish to report the electrolyte changes in these infants and discuss possible contributory factors.

PATIENTS AND METHODS

PATIENTS AND PROCEDURES

For the purposes of this study hyponatremia and hyperkalemia were defined arbitrarily as plasma $[Na^+] < 130$ mEq/liter and as plasma $[K^+] > 5.5$ mEq/liter.

Thirty VLBW infants were studied, none of them seriously ill during the study period. The infants were assessed for gestational age (7) and assigned to pairs within birthweight categories as described in a previous paper (6). The infants were admitted to the study when they were able to consume at least 80% of the desired formula intake (200 ml/kg/24 hr), which was achieved at an average age of 18 days. The study terminated when infants reached 1.8 kg body weight. All infants were fed SMA (27), 200 ml/kg/24 hr to provide 160 cal/kg/24 hr and were given 0.3 ml of a multivitamin preparation (28) daily.

One member of each pair, assigned to *group B*, received supplemental calcium (147 mg/kg/24 hr) as calcium lactate in addition to the 110 mg Ca/kg/24 hr contained in the formula. Acid-base status was maintained within 1 SD of normal mean for infants of this age (2) by oral $NaHCO_3$ as necessary (6).

Venous or arterialized heel-prick blood was obtained twice weekly for determination of plasma electrolytes. Blood for K^+ determination was processed and analyzed promptly and was not hemolyzed.

Three-day stool and 24-hr urine collections for electrolyte measurement were obtained as described previously (6). From these data net balances (excluding losses in sweat) were calculated for Na^+ and K^+.

CHEMICAL METHODS

Na^+ and K^+ concentrations were determined in plasma, urine, feces, and formula with standard flame spectrophotometric techniques (29). Plasma Cl^- was determined by amperometric-coulometric titration (5).

RESULTS

PLASMA ELECTROLYTES

Because no statistically significant differences were observed between nonsupplemented (*group A*) and calcium-supplemented groups (*group B*), the plasma values were pooled. Values obtained within 48 hr of Na^+ supplementation in any form were excluded.

Plasma Na^+, K^+, and Cl^- concentrations on admission to the hospital, at the start of the study, and at weekly intervals thereafter are shown in Figure 1. Mean plasma Na^+ and K^+ concentrations were normal (Na^+ 135–145 mEq/liter; K^+ 3.5–5.0 mEq/liter) (1) on admission, usually on the first day of life. When the infants entered the study the plasma Na^+ had already decreased significantly in all instances; mean values declined further, the lowest occurring between *week 1* and *week 3* of the study (postnatal age 3–5 weeks). During the study, hyponatremia occurred in 23 of the 30 patients. Table 1 shows the number of infants in each gestational age and treatment category and the severity of episodes of electrolyte abnormalities. There was no difference in the frequency and severity of hyponatremia between *groups A* and *B*, but lowest values were observed in AGA infants. In five of the infants the hyponatremia recurred despite apparently adequate therapy for the deficit.

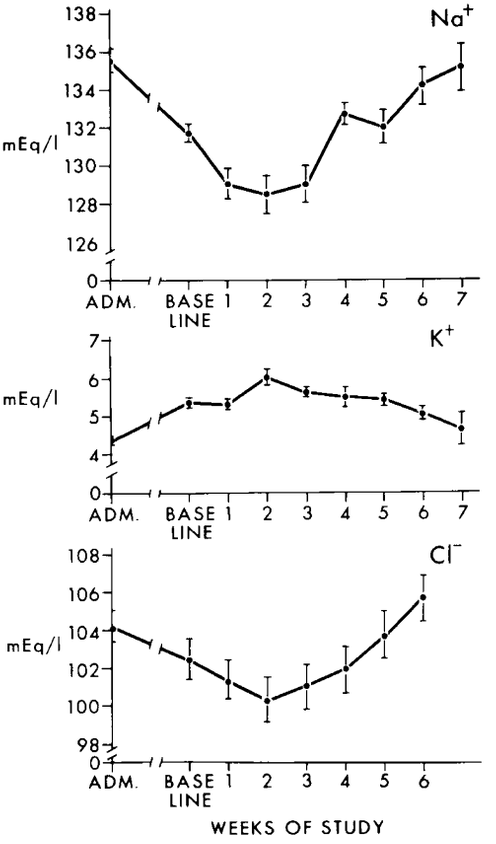

Fig. 1. Plasma Na^+, K^+, and Cl^- concentrations. *Adm:* admission specimen; baseline specimen at a mean age of 18 days. Results from individual patients have been averaged each week and from these total means ± 1 SEM have been calculated.

The mean plasma K^+ concentration was significantly higher at the beginning of the study at 18 days of age than on admission to hospital (Fig. 1) ($P < 0.01$). Hyperkalemia occurred in 23 patients (16 AGA, 7 SGA). The incidence of hyperkalemic episodes was similar in *Groups A* and *B*. Individual values were as high as 8.5 mEq/liter.

Despite the apparent inverse relationship of mean plasma Na^+ and K^+ concentrations (Fig. 1), no significant correlation was found on analysis of results for individual patients. The predominant electrolyte pattern in AGA infants was hyperkalemia with normal plasma $[Na^+]$. In the 10 of 13 SGA infants with electrolyte abnormalities, hyponatremia with or without hyperkalemia predominated.

Changes in mean plasma chloride values paralleled plasma sodium values. Although individual values were lower during hyponatremic episodes, the lowest plasma Na^+ value was not necessarily associated with the lowest plasma chloride concentration. Episodes of hypochloremia (plasma $Cl^- < 95$ mEq/liter were infrequent. The lowest value observed was 92 mEq/liter.

ELECTROLYTE INTAKE AND OUTPUT

The results of Na^+ and K^+ intake and output measurements are shown in Figures 2 and 3. Urinary Na^+ excretion was initially similar in *groups A* and *B* and averaged 1 mEq/kg/24 hr at 2–3

Table 1. *Incidence and severity of hyponatremia and hyperkalemia*[1]

	No. patients	No. patients with hyponatremia	Episodes of hyponatremia (plasma Na^+, mEq/liter) Total	125–129	120–124	<120
Group A						
AGA	9	7	17	11	4	2
SGA	7	6	11	10	1	
Group B						
AGA	8	7	13	7	3	3
SGA	6	3	14	11	1	2
Total	30	23	55	39	9	7

	No. patients	No. patients with hyperkalemia	Episodes of hyperkalemia (plasma K^+, mEq/liter) Total	5.6–6.0	6.1–6.5	>6.5
Group A						
AGA	9	9	28	13	6	9
SGA	7	3	9	2	4	3
Group B						
AGA	8	7	19	9	5	5
SGA	6	4	10	5	1	4
Total	30	23	66	29	16	21

[1] AGA: appropriate for gestational age; SGA: small for gestational age.

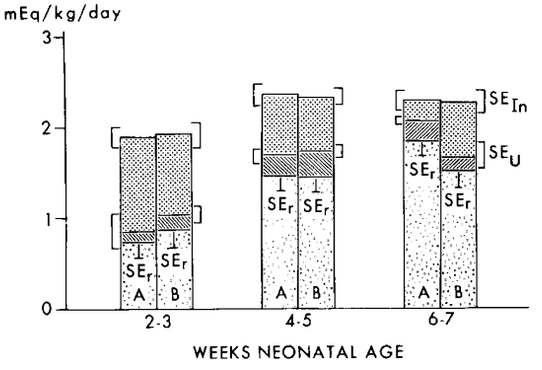

Fig. 2. Sodium intake and output, excluding losses in sweat (in milliequivalents per kg per 24 hr). Intake is plotted upwards from baseline; SE_{In}: ± SE of intake. ⬚ : urinary Na^+ excretion; SE_U: ± SE of urinary excretion. ▨ : fecal Na^+ excretion. ▩ : net Na^+ retention; SE_r: – standard error of net retention. None of the differences between groups is statistically significant.

weeks postnatal age. Subsequently, it decreased more rapidly in nonsupplemented than in calcium-supplemented infants, but the difference just failed to reach significance ($P < 0.1$). Fecal excretion of Na^+ did not differ between *groups A* and *B*, and there was an insignificant decrease with increasing age. Fecal excretion of Na^+ did not exceed 20% of intake, the mean being <10% during the second and third balance. Mean net Na^+ retention increased with age, more so in SGA than in AGA infants, but equally in calcium-supplemented and in nonsupplemented babies. Mean net retention rate of Na^+ in *group B* babies reached 1 mEq/kg/24 hr during the second balance but declined thereafter, whereas it rose steadily in *group A* babies.

There was no significant change in urinary K^+ output with age and excretion rates were similar in *groups A* and *B*. Fecal K^+ excretion was also similar in AGA and SGA babies (average 15% of intake). Net retention of K^+ did not change with age and did not differ between *groups A* and *B*.

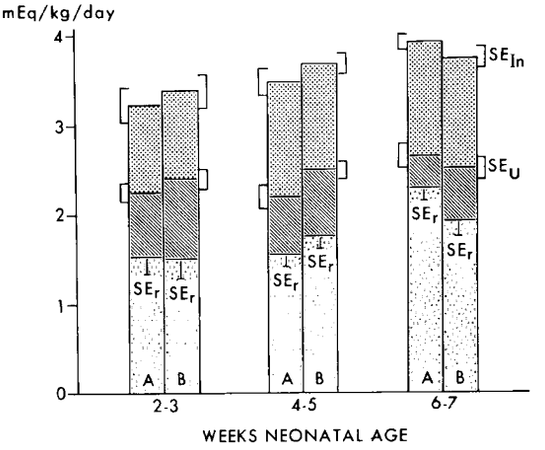

Fig. 3. Potassium intake and output (in milliequivalents per kg per 24 hr). ⬚ intake is plotted upwards from baseline; SE_{In}: ± standard error of intake. : urinary K^+ excretion, SE_U: ± SE of urine. ▨ : fecal K^+ excretion. ▩ : net K^+ retention, SE_r: – SE of net retention. None of the differences is statistically significant between groups.

CLINICAL FEATURES

All but 1 of the 39 episodes of mild hyponatremia developed while the infants were clinically well. Two infants, one normonatremic and one mildly hyponatremic, had severe apneic spells. Of the seven patients with plasma Na^+ values between 120 and 124 mEq/liter, five were asymptomatic and well, one had apneic spells, and another one had pulmonary edema due to a patent ductus arteriosus. One infant convulsed while moderately hyponatremic, but she had previously had several generalized convulsions when her plasma Na^+ was normal. Of the four patients with severe hyponatremia (plasma Na^+ <120 mEq/liter), two were asymptomatic, two were lethargic, and one also had severe apneic spells. There was no clinical evidence of extracellular fluid volume contraction or expansion.

When AGA infants were hyponatremic they showed a higher incidence of reduced growth in length (<1.0 cm/week) than when plasma Na^+ was above 130 mEq/liter (50% *vs* 13.5%; $P < 0.01$). There was a similar trend of reduced growth in length in SGA infants during hyponatremia, but the relationship was not significant (64% *vs* 40%; $P < 0.20$).

DISCUSSION

Severe hyponatremia (plasma Na^+ <120 mEq/liter) developed in 4 of 17 AGA and 1 of 13 SGA infants; mild episodes of hyponatremia (plasma Na^+ 125–129 mEq/liter) occurred in almost all other AGA babies, usually at 2–6 weeks of age. Most of the patients remained clinically well, but length gain ceased temporarily in some.

Occasional instances of significant hyponatremia in the VLBW occurring after the immediate neonatal period have been reported by Sulyok (20) and Honour *et al.* (8). Others who reported sequential plasma electrolyte concentrations in prematures did not observe any abnormalities (19, 21), but plasma sodium concentrations before 14 days of age were higher than between 15 and 28 days. These reports included only a few infants in the birthweight range examined in our study.

Contributory factors to hyponatremia investigated in this study include inadequate intake, increased losses of Na, and water retention.

Insufficient intake of sodium as a result of low Na^+ concentrations in the formula could have contributed to the hyponatremia. According to the findings of Shaw (16) and Widdowson (25), the intrauterine Na^+ acquisition rate between weeks 31 and 38 is approximately 1.2 mEq/kg/24 hr. This was the postconceptional age of the infants discussed in the present study who received 1.6 mEq/kg/24 hr. A continuing deficit developed, inasmuch as urinary excretion rates were high relative to plasma values. The mean net retention rates at 4–5 weeks of postnatal age were slightly higher than the intrauterine Na^+ acquisition rate, and this was followed by a gradual return of plasma Na^+ values to normal. Decreased absorption was not a factor.

With continuing growth, increased amounts of Na^+ are required not only for maintaining the extracellular Na^+ concentration but also for coprecipitation with calcium in bone (18). Although calcium-supplemented infants showed better mineralized bones on radiographs (6), the frequency and degree of hyponatremia did not differ between the groups. Sodium precipitation in bone was therefore not a major factor in the development of hyponatremia.

Renal conservation of Na^+ was inefficient, particularly early in the study when most infants were hyponatremic. The electrolyte pattern in plasma (hyponatremia and hyperkalemia) and urine was similar to that reported by Sulyok (20). Hyponatremia and hyperkalemia may occur secondary to hypoaldosteronism, due either to immaturity of the renal tubular Na^+ reabsorptive mechanism in the VLBW related to immaturity of the renin-angiotensin-aldosterone system or to renal tubular unresponsiveness to aldosterone (pseudohypoaldosteronism) (13, 14). During the first week of life in infants of any gestational age the size of the extracellular fluid compartment decreases and urinary excretion rates of Na^+ are high. This relatively high urinary sodium excretion rate seems to be protracted in premature infants as described by Kerpel-Fronius *et al.* (10) and Sulyok (20). These investigators found, as we did, a gradual reduction of urinary Na^+ excretion rates after the age of 4–5 weeks.

High serum and urinary aldosterone values have been reported both in premature and full term infants (3, 8, 11–13, 17, 24). Primary hypoaldosteronism, therefore, is unlikely to have been a major factor. Renal tubular unresponsiveness to aldosterone, producing a state of pseudohypoaldosteronism, may coexist with normal or elevated plasma aldosterone levels (13, 14) and cannot be excluded. We did not measure aldosterone secretion rates in these tiny infants, but in several babies plasma $[K^+]$ after treatment with Na^+ decreased significantly to normal values.

It is said that there is a direct relationship between renal tubular reabsorption of calcium and sodium; increased urinary calcium excretion is usually associated with increased losses of sodium in the urine and *vice versa* (23, 26). Thus, the increased calcium intake in infants of *group B* which might have resulted in hypercalciuria may have contributed to the high urinary losses of Na^+. However, Na^+ excretion was highest in the first balance before calcium supplementation had started and no significant differences occurred in urinary calcium excretion between groups.

Of the possible routes of Na^+ loss, emesis was not a problem nor was fecal loss excessive. Sweat Na^+ was not measured since very premature infants do not usually sweat (4). Furthermore, the babies included in the study were maintained in a strictly controlled thermal environment in a humidified atmosphere.

Hyperkalemia was particularly frequent in AGA infants. High mean plasma K^+ values have been observed in both premature and full term neonates (1, 9, 20, 22). In the premature infant with respiratory distress syndrome, Usher (22) attributed the hyperkalemia to acidosis resulting in altered distribution of K^+ between plasma and erythrocytes and other cells.

The majority of infants had no clinical edema and weight gain was relatively steady from *day 21* onwards. Measurement of total body water (antipyrine space) and extracellular fluid (bromide space) in a subsequent study has failed to show any expansion of these body spaces (15). Thus, there seems little evidence of dilutional hyponatremia.

SUMMARY

Hyponatremia (plasma $Na^+ < 130$ mEq/liter) occurred frequently in < 1.3 kg VLBW infants between the ages of 3 and 6 weeks, and was not affected by calcium supplementation. Hyperkalemia (plasma $K^+ > 5.5$ mEq/liter) also occurred commonly in these babies, particularly in AGA infants. Although there was no direct correlation between these two electrolyte abnormalities, elevated plasma K^+ values decreased when hyponatremia was corrected. It was found that high urinary losses of Na^+ relative to the plasma Na^+ concentration, as well as insufficient intake because of the relatively low Na^+ content of the diet, contributed to the development of hyponatremia. Coprecipitation of Na^+ in bone at times of rapid length growth also may have been an additional factor in the development of this electrolyte abnormality. The prolonged feeding of relatively low sodium formula initially exceeded the renal compensatory mechanisms for Na^+ retention. Balance measurements suggest that VLBW infants require approximately 3 mEq/kg/24 hr of sodium to achieve normonatremia between the ages of 2 and 5 weeks.

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28. ABDEC, Parke Davis & Co., Ltd., 350 Evans Avenue, Toronto 18, Ont.
29. Unicam SP 1900 Atomic absorption flame spectrophotometer, Pye Unicam, York St., Cambridge, CB1 2PX, England.

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Feed volume sodium
hyponatremia urine
plasma very low birthweight infants

Late Hyponatremia in Very Low Birthweight Infants (<1.3 Kilograms)

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Extract

Late hyponatremia (plasma Na^+ <130 mEq/liter) occurred frequently (on 54 of 159 occasions) in 46 very low birthweight (VLBW) infants (<1.3 kg at birth) between 2 and 6 weeks of age while receiving a sodium intake of ≤2 mEq/kg/24 hr. To elucidate possible pathogenetic mechanisms five groups of such infants were studied while receiving a commercially available formula reconstituted to give two different volumes and two different Na^+ concentrations. Sodium intake in the nonsupplemented (NS) infants (n = 23) was less than 2 mEq/kg/24 hr. Supplemented (S) infants (n = 16) received approximately 3 mEq Na^+/kg/24 hr. A further group of seven infants given a high volume (200 ml/kg/24 hr), high caloric (100 cal/dl) formula and Na^+ supplementation (to 3 mEq/kg/24 hr) was also included. Infants were studied from age 14 days until they weighed 1.80 ± 0.05 kg at a mean age of 47 days.

At the time of start of the study, 6 of 20 NS and 6 of 19 S infants were hyponatremic. After supplementation only two episodes of hyponatremia occurred in S infants, both during the first study week, whereas the high incidence of hyponatremia in NS infants remained unchanged throughout the first 3 weeks of the study period.

During baseline urine collections all infants excreted between 80 and 100 ml/kg/24 hr urine, but those receiving 150 ml/kg/24 hr formula decreased their urinary output rapidly to 50 ml/kg/24 hr, whereas infants receiving high volume feeds (200 ml/kg/24 hr) did not decrease their urinary output until the third balance at an average age of 45 days. All infants excreted between 1.0 and 1.2 mEq/kg/24 hr of sodium in their urine during the initial collection. Nonsupplemented infants reduced their urinary Na^+ excretion more rapidly than supplemented babies (NS: from 1.03 to 0.55 mEq/kg/24 hr, first *vs* second balance; S: from 1.00 to 0.80 mEq/kg/24 hr, first *vs* third balance). Mean potassium excretion remained unchanged in NS and S infants during the study period and was not affected by the volume or caloric content of the formula.

Extracellular volume (ECV) and total body water (TBW) were measured serially, and there were no differences between S and NS infants in the distribution of body water. The percentage of TBW and ECV decreased in all groups with increasing postnatal age.

Speculation

VLBW infants are prone to hyponatremia in the first 6 weeks of life because of the combined influence of renal immaturity, which permits relatively high urinary sodium loss in the presence of low plasma [Na^+], and low intake of sodium (≤2 mEq/kg/24 hr), the amount provided by some current formulas based on breast milk. Dilutional factors are not involved, but the role of aldosterone remains unresolved. Supplementation of the formula to provide a daily total sodium intake of 3 mEq/kg/24 hr until a weight of 1.5 kg is reached is corrective.

Investigations into the nutritional requirements for the VLBW infant (<1.3 kg) are being carried out in several phases in the Hospital for Sick Children, Toronto. During earlier investigations of calcium supplementation (7), a frequent incidental finding was a low plasma sodium concentration at 2–7 weeks postnatal age (8). The present study was designed to determine in VLBW infants the appropriate Na^+ intake to prevent this hyponatremia and to investigate possible underlying factors. We examined the effect of differences in feed volume and Na^+ and caloric intakes on plasma and urinary electrolytes and on body fluid compartments.

PATIENTS, PROCEDURES, AND METHODS

PATIENTS

Forty-six infants of birthweight <1.3 kg were studied. Table 1 shows the study groups, their mean birthweight, and their gestational age. All infants <1.3 kg birthweight admitted to the Neonatal Unit of the Hospital for Sick Children, Toronto, were