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Relationship between the postnatal development of the renin–angiotensin–aldosterone system and the electrolyte and acid–base status in the sodium chloride supplemented premature infant

By

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To investigate the relationship between the renin–angiotensin–aldosterone system (RAAS) and the electrolyte and acid–base status during early postnatal life, plasma renin activity (PRA), plasma aldosterone concentration (PAldo) and urinary aldosterone exretion (UAE) were measured using RIA, along with simultaneous determination of plasma Na, K and Cl levels, Na and K balance as well as acid–base parameters in 7 low birth weight premature infants supplemented with NaCl (group S).

The study was performed on the 7th day and at weekly intervals thereafter until the 6th week of life. The results were compared with those obtained in infants of similar birth weight and gestational age without NaCl supplementation (group NS). NaCl supplementation was given in a dose of 3—5 mEq/kg/day and 1.5—2.5 mEq/kg/day for 8—21 days and 22—35 days, respectively.

NaCl supplementation resulted in positive Na balance and restored the plasma Na level to 140.3 $\pm$ 0.36 (mean $\pm$SE) mEq/l by the second week of life. The plasma Na ($p < 0.01$) and plasma Cl ($p < 0.05$) concentrations were significantly higher in group S than in group NS in the 3rd week. In group S, urinary Na excretion ($p < 0.01$) and urinary Na/K ratio ($p < 0.05$) were also higher than in group NS in weeks 2nd to 4th and 3rd to 4th, respectively.

In response to NaCl supplementation, neither PRA, PAldo nor UAE rose above the initial values. Instead, PRA fell significantly from 14.5 $\pm$ 1.3 to 5.8 $\pm$ 2.8 ng/ml/hr ($p < 0.05$) and PAldo showed no consistent change during the course of the study. UAE fell at first from 4.2 $\pm$ 0.08 to 2.1 $\pm$ 0.2 μg/day by the 3rd week ($p < 0.05$) followed by a rise to 7.1 $\pm$ 2.3 μg/day ($p < 0.01$). PRA in weeks 2nd to 4th ($p < 0.01$), PAldo in week 3rd ($p < 0.05$) and UAE in weeks 2nd to 4th ($p < 0.01$) were significantly lower in group S than in group NS.

After NaCl supplementation, no late metabolic acidosis developed and significantly higher total CO_2 ($p < 0.01$) and lower base deficit ($p < 0.01$) values could be observed in the 2nd and 3rd weeks.

It is concluded that renal salt wasting and the negative salt balance in the first two weeks of life might be of prime importance in the profound postnatal increase in RAAS activity and also in the development of late metabolic acidosis frequently seen in low birth weight premature infants.

In a series of recent publications it has been reported that the activity of the renin–angiotensin–aldosterone system (RAAS) is markedly elevated in the early neonatal period [7, 8, 13, 16, 17, 19, 20, 22, 24, 26, 28, 32, 34, 35].

It has also been shown that the pattern of its postnatal development in preterm infants [21, 39] is very different from that found in full-term newborn infants [13, 17, 20, 28, 34, 35].

In full-term neonates plasma renin activity (PRA) [13, 17, 20, 34], plasma angiotensin [9] and plasma aldosterone concentration (PAldo) [7, 13, 17, 28, 34, 35] have been shown to fall progressively with increasing postnatal age, whereas in preterm infants these parameters increased dramatically within a few weeks of birth and reached their peak value by the end of the 3rd—4th week, followed thereafter by a slight and gradual decline [21, 39]. Moreover, it has been suggested that the postnatal increase and the sustained high activity of RAAS are closely related to the increased urinary sodium loss, the subsequent negative sodium balance and late hyponatraemia occurring in low birth weight preterm infants [21, 39, 40]. At the same time, the forced stimulation by the excessively activated RAAS results in rapid improvement of distal tubular reabsorption of sodium, consequently it is of great importance in restoring to normal the sodium balance and the rising plasma sodium concentration [41].

Since these observations clearly demonstrate the essential role of RAAS in the control of sodium homeostasis in preterm infants, it seemed worthwhile to explore this relationship. The present study was undertaken to compare the postnatal change of PRA, PAldo and UAE in relation to electrolyte balance in NaCl-supplemented preterm infants during the first six weeks of life with those previously found in a comparable group of preterm infants without NaCl supplementation [39]. In addition, the acid–base parameters of the blood were determined to study the influence of NaCl supplementation on the development of late metabolic acidosis.

Material and Methods

Two groups of healthy male preterm infants were selected for the study. Group I consisted of 7 infants with a birth weight of 1080—1740 g (mean, 1480 g) and gestational age of 28—33 weeks (mean, 30.8 weeks). The members of this group were given NaCl supplementation. Group II included 14 non-supplemented infants; 7 of these served as control for the hormone, electrolyte and acid–base balance studies. Their mean birth weight and mean gestational age was 1580 g (range, 1160—1850 g) and 31 weeks (range, 30—32 weeks), respectively. The results obtained in these 7 infants have already been reported [39]. Group II was completed with 7 further preterm infants ranging in birth weight and gestational age from 1100 to 1820 g (mean, 1610 g) and from 28 to 32 weeks (mean, 30.5 weeks), respectively. Their plasma electrolyte levels were measured serially and compared to those supplemented with NaCl.

Gestational age was calculated from the mother's menstrual history and was later confirmed by physical examination of the infants. Birth weight of the infants was within the 10th and 90th percentiles according to our local standard.

The infants were born after uncomplicated pregnancy and normal vaginal delivery with Apgar score of 7 or more at one minute of age. Maternal history did not reveal a salt-restricted diet or diuretic treatment. The immediate neonatal period

was uneventful and initial respiratory difficulties were not severe enough to warrant positive pressure ventilation. Having overcome the difficulties of respiratory adaptation all infants remained well during the whole period of study.

The infants were kept in incubators to provide controlled thermal environment until their weight had reached 2 kg. All were fed at 2-hourly intervals until the body weight of 1500 g had been attained and at 3-hourly intervals thereafter, in an amount to ensure a daily calorie and fluid intake of 120—140 cal/kg and 180—200 ml/kg, respectively, by the end of the second week of life.

Sodium supplementation was introduced on the 8th day, in the form of 5% NaCl solution, irrespective of the base deficit. The required amount of NaCl was added to the formula and distributed in equal quantities throughout the day. Infants with a birth weight less than 1500 g received 5 mEq/kg/day NaCl, while to those with a birth weight of 1500—1750 g, 3 mEq/kg/day NaCl was given for a period of two weeks. Then the supplemental NaCl intake was halved and administered further in this reduced dose for another period of two weeks. The supplementation was terminated at the end of the fifth week of life.

Sodium and potassium balances, acid-base status and hormone levels were determined on the 7th day of life and in weekly intervals thereafter up to the 6th week of life. The first determinations in the NaCl supplemented group were performed just before starting supplementation.

For measurements of sodium, potassium, PRA and PAldo, blood was taken from a scalp vein. For the acid–base studies arterialized capillary blood was used.

Urine was collected fractionally for a period of 24 hours. The specimens were refrigerated, pooled and stored at −20 °C until analysed for urinary sodium and potassium excretion as well as for UAE. Electrolyte balances were calculated as the difference between dietary intake and urinary excretion, losses in the stool and sweat were not considered.

Sodium and potassium concentrations in plasma, urine and formula were determined by flame photometry. Acid–base parameters of the blood were measured by the method of Astrup et al [6]. PRA was measured by the radioimmunoassay of generated angiotensin I according to the method of Haber et al [18]. PAldo and urinary aldosterone concentration measurements were made by radioimmunoassay (42) using commercial kits as reported previously [39, 40].

Informed parental consent was obtained for blood sampling and urine collection.

The results were expressed as mean ± SE and statistical evaluation was done by using Student's t test.

Results

Electrolyte balance

Sequential changes in sodium and potassium balances are shown in Fig. 1. It can be seen that the sodium

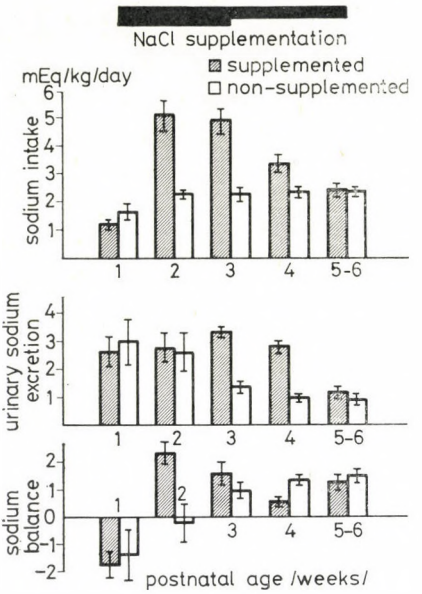

FIG. 1. Postnatal development of sodium intake, urinary sodium excretion and sodium balance in preterm infants with and without NaCl supplementation during the first six weeks of life. The vertical bars represent SEM in each Figure

intake of about 5 mEq/kg/day in the 2nd and 3rd weeks and of 3.4 mEq/kg/day in the 4th week was significantly higher in the supplemented (S) than in the non-supplemented (NS) group ($p < 0.01$). Urinary sodium excretion in the NS group was highest (3 mEq/kg/day) in the first week; it decreased significantly in the next two weeks ($p < 0.01$) and remained at about the same level thereafter. When supplemental sodium was given, urinary sodium excretion showed no decline and mean values as high as 2.8 to 3.4 mEq/kg/day could be observed in the 2nd to 4th weeks; the differences between the two groups were significant ($p < 0.01$). As a result, in group S a positive sodium balance was found by the 2nd week compared with the negative balance at this age in group NS ($p < 0.01$). Later in life the retention rate of sodium did not differ significantly between NS and S infants (Fig. 1).

Intake, urinary excretion and retention rate of potassium were similar in both groups. Potassium excretion in urine increased steadily at a low rate during the whole observation period. Sodium supplementation had no apparent influence on its developmental pattern (Fig. 2).

The urinary sodium/potassium ratio (Fig. 3) decreased progressively with increasing age in both groups from the initial mean values of 5,8 and 4,5 in the NS and S groups, respectively. Due to the increased urinary sodium excretion, however, sodium supplementation

resulted in a significantly higher sodium/potassium ratio in group S during the 3rd and 4th weeks of life ($p < 0.05$).

Postnatal changes of plasma sodium, potassium and chloride concentration are shown in Fig. 4. At the beginning of the study, mean plasma sodium concentration was similar in the NS and S groups. Thereafter in the NS group its value decreased to the minimum level of 130 mEq/l by the end of the 3rd week ($p < 0.01$) followed by a stepwise increase until the end of the study. In contrast, the increased dietary sodium intake in

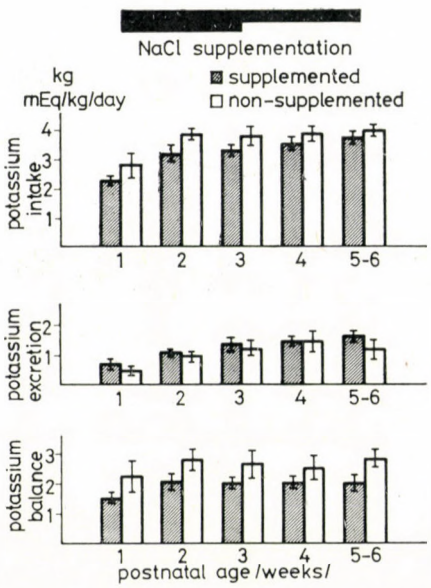

FIG. 2. Postnatal development of potassium intake, urinary potassium excretion and potassium balance in preterm infants with and without NaCl supplementation during the first six weeks of life

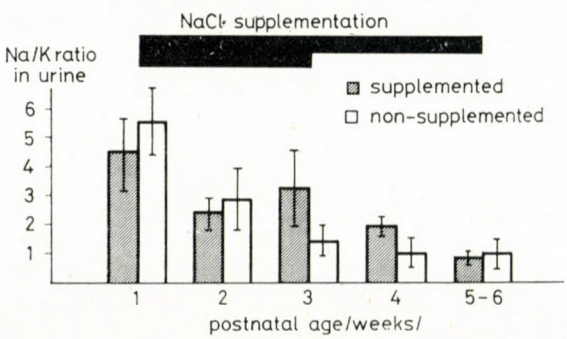

FIG. 3. Postnatal development of the urinary Na/K ratio in preterm infants with and without NaCl supplementation during the first six weeks of life

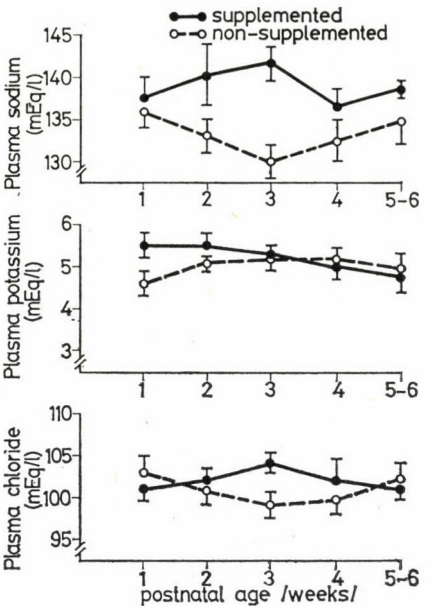

FIG. 4. Postnatal development of plasma sodium, potassium and chloride concentration in preterm infants with and without NaCl supplementation during the first six weeks of life

group S prevented any fall in the plasma sodium level and resulted in an immediate restoration of plasma sodium concentration to about 140 mEq/l which could be maintained throughout the study. In the 3rd week the difference in plasma sodium concentration between the two groups was significant ($p < 0.01$).

The trend of plasma potassium concentration in the NS group was opposite to that of sodium. Its mean value of 4.6 mEq/l in the first week increased significantly during the period of hyponatraemia ($p < 0.05$), then a gradual decline followed. At the same time the plasma potassium level in group S showed a tendency to fall during the whole study, but the fall failed to reach statistical significance (Fig. 4/b).

Plasma chloride concentration roughly corresponded to the plasma sodium concentration in the NS group, showing a significant fall until the 3rd week ($p < 0.05$) followed by a moderate increase later in the study. In S infants no similar changes in plasma chloride concentration could be seen; the mean was highest in the 3rd week and then remained relatively constant throughout the observation period. NaCl supplementation resulted in significantly higher plasma chloride levels only in the 3rd week of life ($p < < 0.05$) (Fig. 4/c).

Hormonal changes

As shown in Fig. 5, PRA, PAldo and UAE in NS infants increased from the initially high values of 18.2±

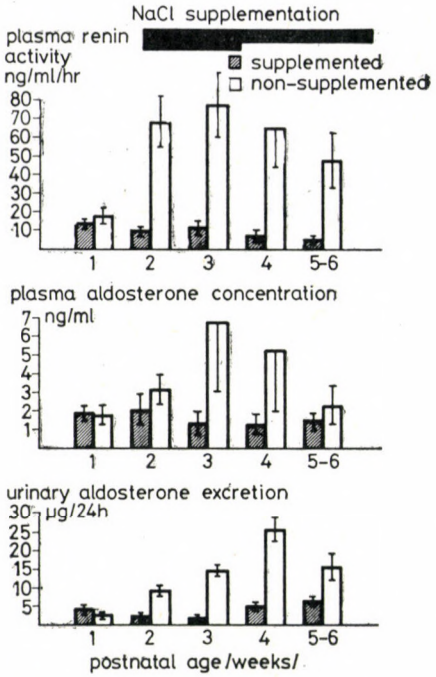

FIG. 5. Postnatal development of plasma renin activity, plasma aldosterone concentration and urinary aldosterone excretion in preterm infants with and without NaCl supplementation during the first six weeks of life

$\pm$ 4.1 ng/ml/hr, 1.77 $\pm$ 0.5 ng/ml and 2.6 $\pm$ 0,4 μg/day in the first week to a maximum of 78,6 $\pm$ 18.1 ng/ml/hr ($p < 0.01$), 6.8 $\pm$ 3.7 ng/ml ($p < 0.05$) and 26.4 $\pm$ 2.9 μg/day ($p < 0.01$) in the 3rd week, respectively. Later gradual declines occurred, but PRA, PAldo and UAE remained markedly elevated even at the end of the study. By contrast, in response to NaCl supplementation neither PRA, PAldo, nor UAE rose above the initial values of 14.5 $\pm$ 1.3 ng/ml/hr, 2.0 $\pm$ 0.4 ng/ml and 4.2 $\pm$ 0.8 μg/day, respectively. Instead, PRA fell to 5.8 $\pm$ 2.8 ng/ml/hr ($p < 0.05$) and PAldo showed no consistent change during of the study. UAE fell to 2.1 $\pm$ 0.2 μg/day by the 3rd week ($p < 0.05$) to rise significantly afterwards ($p < 0.01$). Comparing the hormone levels in the two groups, PRA in weeks 2nd to 4th ($p < 0.01$), PAldo in week 3rd ($p < 0.05$) and UAE in weeks 2nd to 4th ($p < 0.01$) proved to be significantly lower in the S group than in the NS group.

Acid–base balance

In Fig. 6 it is seen that prior to NaCl supplementation a moderate and nearly identical metabolic acidosis appeared in both groups. During the next two weeks the base deficit tended to increase and total CO_2 tended to

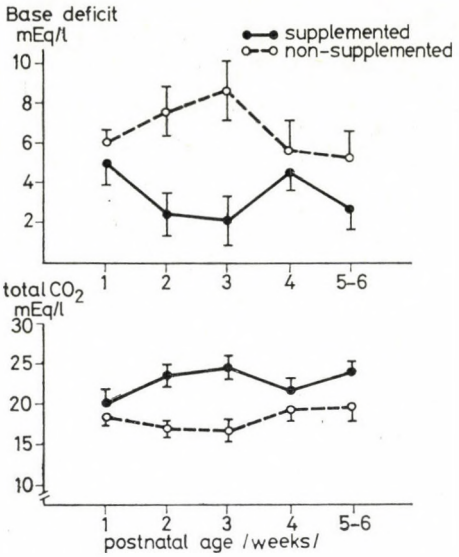

FIG. 6. Postnatal development of base deficit and total CO_2 content of the blood in preterm infants with and without NaCl supplementation during the first six weeks of life

decrease at a similar rate in group NS indicating the increasing acidosis. Subsequently both parameters approached gradually the normal level. In contrast, metabolic acidosis rapidly improved in S infants and the mean base deficit and mean total CO_2 remained within the ranges of 2.1 to 4.6 mEq/l and 21.7 to 24.8 mEq/l, respectively, after the 2nd week of life. In the 2nd and 3rd weeks the difference in the degree of metabolic acidosis between the two groups was significant ($p < 0{,}01$).

Weight gain

In every infant, body weight increased with age at a similar rate irrespective of sodium intake. The rate of growth was slightly higher in infants on the high than in those on the low sodium diet in the second week of life (Table I).

TABLE I

Effect of NaCl supplementation on weight gain (g/kg/day) of preterm infants

Age (weeks)	Supplemented	Non-supplemented
1	$-6{,}7 \pm 2.5$	-7.5 ± 2.8
2	11.2 ± 2.7	6.8 ± 2.1
3	13.5 ± 1.8	11.2 ± 1.6
4	14.8 ± 1.9	14.2 ± 1.8
5—6	14.9 ± 1.5	13.7 ± 1.3

DISCUSSION

There is a considerable controversy concerning sodium requirements of low birth weight preterm infants. Experimental studies in rats and epidemiological studies in humans have

shown that a high dietary sodium intake early in life may result in hypertension in adult life. The Committee on Nutrition of the American Academy of Pediatrics recommended that the salt intake of infants should be kept low [1]. This recommendation did not take into account the differences between preterm and term infants.

In the last decade, however, it became apparent that the rate of urinary sodium excretion, and in particular the rate of fractional sodium excretion [3, 4, 14, 21, 23, 30, 33, 36, 37] and the natriuretic response to salt challange [3] is much higher in preterm than in full-term infants. It has also been shown that renal salt wasting resulted in a negative sodium balance and hyponatraemia in low birth weight infants which were fed breast milk or a formula with a sodium level similar to that in human milk [12, 14, 21, 25, 31, 36, 43].

These observations clearly indicate that human milk and low sodium formulas fail to provide the maintainance requirements of sodium and therefore additional sodium should be given to keep up with the high sodium needs of these infants. In contrast with the more recent recommendation of the Committee on Nutrition [2], it is now generally accepted that an increased sodium intake should be provided for preterm infants. Recent data, however, suggest that the amount of sodium to be administered varies to a great extent with birth weight, postnatal age and clinical condition of the infant [14, 21, 25, 31, 43].

Based on detailed balance studies in very low birth weight (1300 g) infants, Roy et al. recommended a sodium supplementation of 3 mEq/kg/ /day until the body weight of 1500 g had been reached [31]. The value agrees well with that estimated by Fomon et al. for hypothetic growing premature infants with a body weight of 1200 g, a weight gain of 20 g/day and an energy intake of 120 kcal/kg/ /day, when they assumed that intestinal absorption reached 87% and urinary sodium excretion, 1 mEq/kg/day [15].

Evidence is accumulating to indicate that the rate of urinary sodium excretion often exceeds 1 mEq/kg/day [10, 21, 25, 39]. A sodium intake of 4—10 mEq/kg/day may meet the nutritional demands of some very low birth weight and sick neonates [14, 21, 25].

In our study, sodium supplementation was applied in a dose of 3—5 and 1.5—2.5 mEq/kg/day for 8—21 and 22—35 days, respectively. This high dose was chosen because in our practice a sodium intake of 2—3 mEq/kg/ /day was insufficient to prevent the fall of the plasma sodium level and to cope with the urinary sodium excretion of more than 1 mEq/kg/day. Interestingly, the study by Roy et al indicates the importance of a sodium intake greater than 3 mEq/kg/day. They showed that a sodium intake of 3 mEq/kg daily for as long as 4 weeks was necessary to raise the plasma sodium concentration to about 137 mEq/l, i.e. to the lower limit of the normal range [31]. It should, however, be kept in mind that the plasma so-

dium level in itself is only a rough estimate of the sodium requirement and other reliable indices should also be applied.

In a previous study we have shown that the RAAS of preterm infants is excessively activated during the first few weeks of life and we suggested that the profound postnatal increase in PRA, PAldo and UAE were related to the changes taking place in sodium balance [39]. It has also been shown that due to the forced stimulation by RAAS, fractional distal tubular sodium reabsorption rose rapidly and as a result, renal sodium concentration improved and the positive sodium balance was restored [41].

The present study provided further evidence as to the close relationship between the function of RAAS and electrolyte status in low birth weight preterm infants. By giving supplemental sodium, ensuring a positive sodium balance and maintaining a normal plasma sodium concentration, the postnatal increase in the activity of RAAS could be prevented and PRA, PAldo and UAE remained significantly lower than in preterm infants not supplemented with sodium, at a level similar to that of full-term infants of the same postnatal age [17, 20, 34, 35].

In view of these observations the following suggestions seem to be justified. 1) The excessive activation of the RAAS in preterm infants a few weeks after birth results from an inadequate sodium intake; 2) the RAAS of preterm infants even with very low birth weight and young age is readily responsive to the changes occurring in sodium balance, therefore the high values of PRA, PAldo and UAE should be regarded as indicating the extreme lability of their sodium homeostasis; 3) like in the salt-losing syndrome of congenital adrenal hyperplasia, when estimating the dietary sodium requirement of preterm infants, the activity of RAAS should also be determined [29]. The control of sodium homeostasis is assumed to be the best when PRA and PAldo are kept within the "normal" range. The term "normal" is used arbitrarily and refers to the values measured in healthy full-term infants of the same postnatal age.

A further point is the influence of NaCl supplementation on the acid–base balance. With respect to the progressive increase in renal Na^+ —H^+ exchange and the subsequent reciprocal changes in H^+ and sodium balance during development, as well as to the similar trend and time course of late metabolic acidosis and the plasma sodium level, it is assumed that the late metabolic acidosis seen in low birth weight infants might be related to the increased urinary sodium loss [23, 36]. Furthermore, a close negative correlation has been demonstrated between the renal threshold for bicarbonate reabsorption and urinary sodium excretion, indicating that the high urinary sodium excretion may account for the low renal bicarbonate threshold in preterm infants [38].

In agreement with these observations, it has been reported that on increasing the avidity of sodium reab-

sorption by pharmacological stimulation, the renal bicarbonate threshold will also increase in the salt-losing syndrome of congenital adrenal hyperplasia [27].

The finding that sodium supplementation in itself could be effective in maintaining a normal acid–base balance, provides further evidence as to the primary role of urinary sodium loss and sodium depletion in the development of late metabolic acidosis.

In conclusion, human milk and low sodium formulas do not meet the high daily sodium requirements of low birth weight preterm infants. Sodium supplementation is therefore recommended. When sodium intake is sufficient, the sodium balance becomes positive, the plasma level returns rapidly to normal and improvement occurs in late metabolic acidosis. Moreover, the activity of the RAAS remains within the range characteristic of full-term neonates. To estimate the optimum sodium requirement for healthy and sick preterm infants of different birth weight and gestational age, all these parameters should be monitored.

Considering the possible long-term effect of a high dietary sodium intake, follow-up studies of the growth rate [10], renal function [4] and blood pressure control [11] are to be conducted in all infants supplemented with NaCl.

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