

Sodium homeostasis in term and preterm neonates

III Effect of salt supplementation

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SUMMARY Clinical and biochemical effects of supplementing dietary sodium intake to 4 to 5 mmol(mEq)/kg/day from days 4 to 14 of life were studied in 22 infants of gestational age 27 to 34 weeks. These infants were compared with a group of 24 unsupplemented babies. Supplemented infants lost less weight postnatally and regained birthweight more quickly: their improved weight gain continued after supplementation was stopped. Sodium balance was positive at age 5 to 11 days in supplemented babies but slightly negative in controls. Potassium balance was more strongly positive in the supplemented group. Plasma sodium concentration was higher in supplemented infants during weeks 3 and 4. Hyponatraemia was significantly more common in unsupplemented (37.5%) than supplemented (13.6%) infants. No infant became oedematous, hypernatraemic, or showed evidence of circulatory overload. The incidence of patent ductus arteriosus and necrotising enterocolitis was not increased; no intracranial haemorrhages occurred. Urinary potassium:sodium ratio was lower in supplemented babies than controls suggesting responsiveness of the distal tubule to mineralocorticoids. Providing 4 to 5 mmol(mEq)/kg/day of sodium to infants born before 34 weeks' gestation for the first two postnatal weeks improves growth and biochemical status and causes no undesirable side effects.

We have previously shown that preterm babies of less than 35 weeks' gestation have high renal and intestinal sodium losses during the first two weeks of life, leading to negative sodium balance and hyponatraemia (plasma sodium less than 130 mmol(mEq)/l) in many.^{1,2} We concluded that increasing dietary sodium intake to 4 mmol(mEq)/kg/day for infants of gestational age 31 to 34 weeks and 5 mmol(mEq)/kg/day for infants of less than 31 weeks' gestation from age 4 to 14 days only, should be sufficient to allow the babies to maintain positive sodium balance and to prevent hyponatraemia. The present study was designed to test this hypothesis and to determine whether salt supplementation was associated with any undesirable side effects.

Patients and methods

Twenty two newborn infants of gestational age 27 to 34 weeks who were given sodium supplements (group A) were compared with a control group (B) of 24 unsupplemented infants; details of the two groups are presented in Table 1. Gestational age was estimated according to the mother's menstrual

history and the clinical criteria of Dubowitz *et al*³ and this was confirmed by ultrasound examination in most cases. The study protocol was approved by the ethical committee of Guy's Hospital and Medical School. Informed consent was obtained from

Table 1 Comparison between sodium supplemented (group A) and unsupplemented (group B) infants for gestational age, birthweight, and ages at which the three studies were performed. Values expressed as mean (SD)

	Group A (n=22)	Group B (n=24)	
Gestational age (weeks)	30.75 (1.88)	30.38 (1.82)	NS
Birthweight (g)	1423.18 (317.6)	1381.67 (203.9)	NS
No with respiratory distress syndrome	6 (27%)	6 (25%)	NS
Aminophylline treatment	8 (36%)	9 (37.5%)	NS
Age (days) at:			
Study 1	3.27 (0.98) (n=22)	3.23 (0.75) (n=17)	NS
Study 2	8.36 (2.25) (n=22)	7.44 (2.22) (n=18)	NS
Study 3	17.2 (3.55) (n=15)	17.7 (4.1) (n=14)	NS

NS=not significant.

parents of all subjects before entry into the study. The infants were cared for in the Special Care Baby Unit at Guy's Hospital. Only healthy infants were accepted for the study; babies were excluded if there was a history of asphyxia, severe respiratory distress, or sepsis and none received artificial ventilation. Six infants in each group had mild respiratory distress syndrome; eight infants in group A and nine in group B received aminophylline. There was no difference in fluid intake between groups (Table 2). Infants in group A were given additional sodium chloride by mouth from age 4 to 14 days in a quantity sufficient to increase total sodium intake to 4 mmol(mEq)/kg/day (gestational age 31 to 34 weeks) or 5 mmol(mEq)/kg/day (gestational age less than 31 weeks), allowance being made for the sodium content of concurrently administered milk, intravenous fluids, and drugs. The supplement was given as molar sodium chloride solution, administered in three or four doses daily after feeds. Babies in both groups were fed either on pooled, mature human milk or SMA Gold Cap according to the previously published current feeding policy of the unit.¹

Twenty four hour balance studies were performed according to methods described elsewhere.^{1,2} Each infant was studied three times—before, during, and after the period of supplementation. Study 1 was performed on day two or three of life, study 2 between days five and 11, and study 3 between days 14 and 25.

Concentrations of sodium and potassium in plasma, urine, stool, and milk were measured by flame photometry. Creatinine was estimated in plasma and urine by the method of Cook.⁴ Weight was recorded daily during the first two weeks and thereafter twice weekly.

Results

Sequential changes in sodium and potassium balances are shown in Figs. 1 and 2. Sodium *intake* was significantly higher in group A than in group B in all three studies, the difference being greater in study 2. Sodium *output* (the sum of urinary and faecal losses) was significantly greater in group A than in group B in studies 2 and 3 ($P<0.025$), but was not different in study 1. Sodium *balance* was not different between groups in studies 1 and 3, but was strongly positive in group A in study 2, while slightly negative in group B. Potassium *intake* was higher in group A in studies 1 and 2 ($P<0.0025$). Potassium *output* was higher in group A infants in study 3 ($P<0.05$) but not in the first two studies. Potassium *balance* was significantly more positive in group A than in group B in study 2 only. The urinary potassium:sodium ratio (Fig. 3) was less in supplemented infants than in controls in study 2 only ($P<0.025$). Stool sodium loss was less in group A than group B in study 2 ($P<0.01$) only. Mean plasma sodium and potassium concentrations, fractional sodium excretion, and creatinine clearances are compared in Table 2. The

Table 2 Comparison between supplemented (group A) and unsupplemented (group B) infants. Values expressed as mean (SD)

	Study No	Group A	Group B	P value
Fluid intake (ml/kg/day)	1	129 (37)	115 (25)	NS
	2	182 (33)	170 (33)	NS
	3	192 (24)	200 (20)	NS
Creatinine clearance (ml/min)	1	0.71 (0.31)	1.1 (0.52)	<0.005
	2	1.12 (0.70)	1.09 (0.87)	NS
	3	1.70 (0.62)	1.10 (0.5)	<0.01
Fractional sodium excretion (%)	1	2.26 (1.08)	1.93 (0.67)	NS
	2	1.71 (0.77)	1.45 (0.81)	NS
	3	0.66 (0.32)	0.84 (0.05)	NS
Plasma sodium concentration (mmol(mEq)/l)	1	141.5 (4.3)	141.1 (5.1)	NS
	2	136.9 (4.6)	136.3 (7.1)	NS
	3	135.6 (3.4)	132.5 (5.3)	<0.025
Plasma potassium concentration mmol(mEq)/l)	1	4.8 (0.96)	5.3 (0.46)	<0.025
	2	4.9 (0.92)	5.3 (0.65)	<0.05
	3	5.1 (0.74)	4.9 (0.50)	NS
Stool sodium (mmol(mEq)/kg/day)	1	0.09 (0.07)	0.08 (0.05)	NS
	2	0.06 (0.05)	0.11 (0.07)	<0.01
	3	0.05 (0.05)	0.06 (0.05)	NS

NS=not significant.

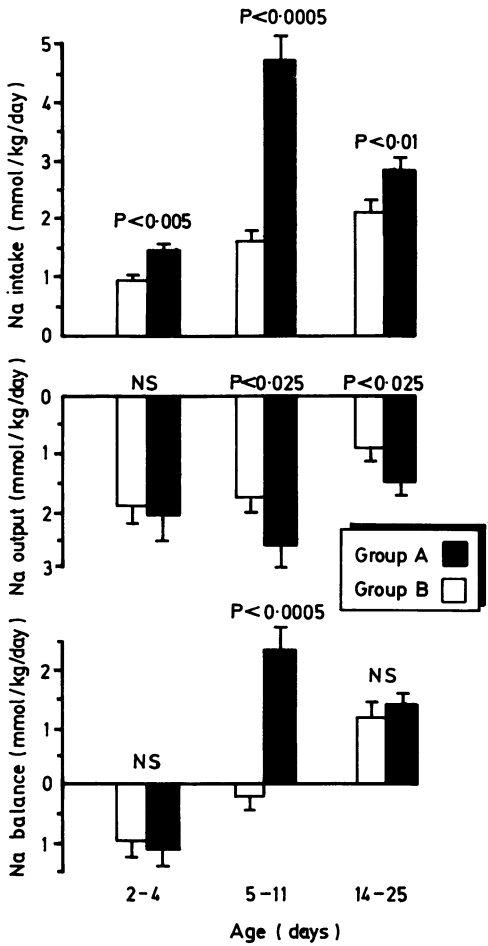


Fig. 1 Sodium intake, output, and net external balance in three studies in sodium supplemented (group A) and unsupplemented (group B) infants.

The vertical bars represent mean (SEM). Significance values obtained by Student's *t* test. NS=not significant.

plasma sodium concentration was significantly lower in group B than in group A infants in study 3. Although the mean values lay within the normal range in both groups, nine unsupplemented infants had plasma sodium concentrations below 130 mmol(mEq)/l compared with only three in the supplemented group. Postnatal weight changes are summarised in Table 3 and Figs. 4 and 5. Supplemented babies lost significantly less weight, both in absolute terms and as a proportion of birthweight (Table 3). Rate of weight gain was significantly greater in group A than in group B in all postnatal age ranges except between days 17 to 20 (Fig. 4). In

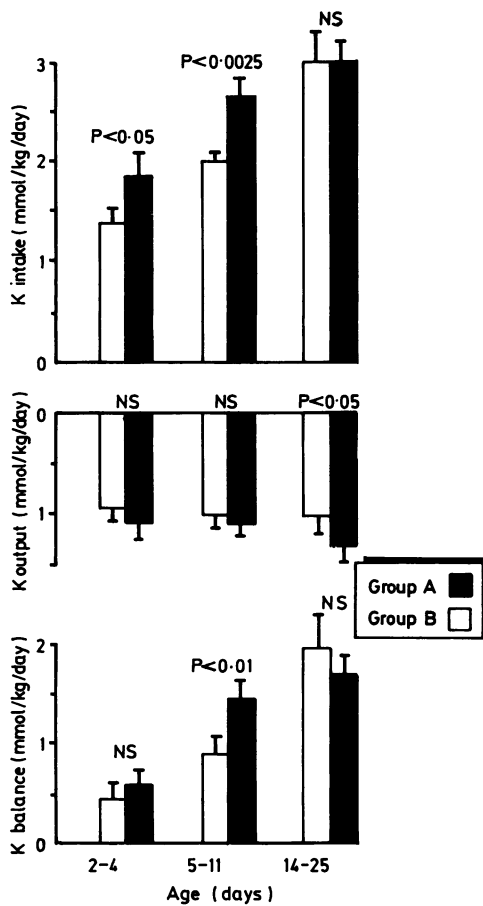


Fig. 2 Potassium intake, output, and balance in sodium supplemented (group A) and unsupplemented (group B) infants.

Vertical bars represent mean (SEM). Significance values obtained by Student's *t* test. NS=not significant.

consequence, cumulative weight gain was greater in group A from the eighth postnatal day and the difference remained significant after supplementation was stopped on day 14 (Fig. 5).

Table 3 Summary of weight changes in sodium supplemented (group A) and unsupplemented (group B) infants up to the time of regaining birthweight (BW). Values expressed as mean (SD)

	Group A	Group B	P value
Maximum weight loss (g)	124 (56)	174.5 (43)	<0.005
Maximum weight loss (% BW)	9.78 (4.3)	12.5 (3.2)	<0.05
Days to regain BW	10.5 (2.9)	16.5 (2.4)	<0.0005

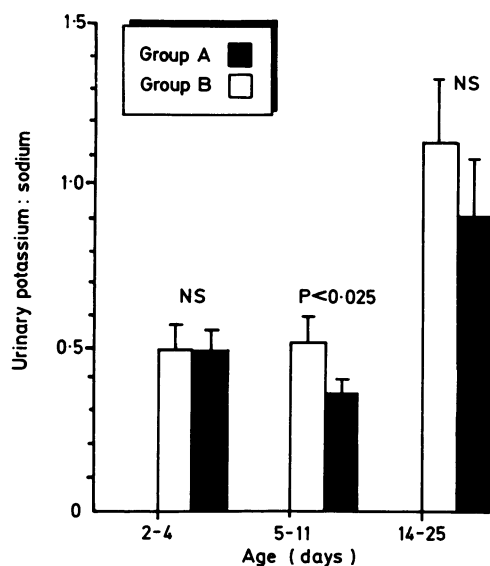


Fig. 3 Urinary potassium: sodium ratio in the three studies in sodium supplemented (group A) and unsupplemented (group B) infants.

Vertical bars represent mean (SEM). Significance values obtained by Student's *t* test. NS=not significant.

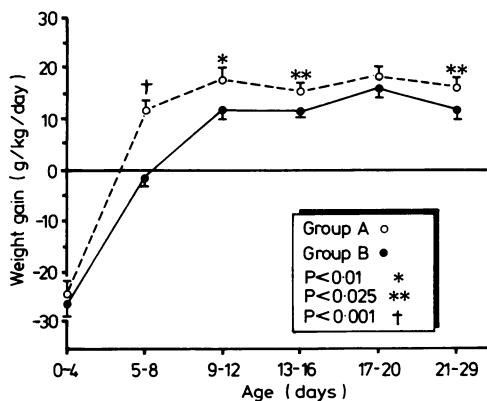


Fig. 4 Weight gain during the first month of life in sodium supplemented (group A) and unsupplemented (group B) infants.

Vertical bars represent mean (SEM). Significance values obtained by Student's *t* test. NS=not significant.

Discussion

It has been suggested that preterm infants, if given the same diet as mature infants, are at risk from nutritional deficiencies which may impair growth

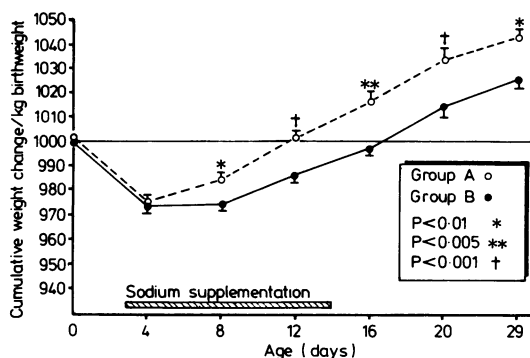


Fig. 5 Cumulative weight changes standardised for birthweight and plotted at 4 day intervals in sodium supplemented (group A) and unsupplemented (group B) infants.

Significance values by Student's *t* test.

and development of the skeleton and nervous system.^{5,6} Several groups have shown that low birthweight infants fed on low sodium milks frequently develop 'late hyponatraemia' after high urinary and faecal sodium losses during the first two weeks of life.^{1,2,7,8} Although the long term clinical importance of this is not clear, it is unlikely to be beneficial. Bursey and Watson⁹ recently showed that the offspring of rats fed a sodium deficient diet during pregnancy had decreased brain weight and reduced brain protein and RNA content compared with normal controls.

In the present study nine of 24 unsupplemented babies became hyponatraemic (plasma sodium less than 130 mmol(mEq)/l) during study 3, and we have observed plasma sodium concentrations as low as 107 mmol(mEq)/l in such infants.¹ In contrast, only three of the 22 supplemented infants were hyponatraemic and the lowest value seen in this group was 126 mmol(mEq)/l. Considerable evidence exists that hyponatraemia persisting for several days or more is associated with a significant loss of brain sodium¹⁰⁻¹² and potassium,^{12,13} and possibly amino acid¹⁴ content. The long term consequences of such changes are unknown, but their occurrence during a period of rapid brain growth is worrying and certainly in contrast to the rapid accretion of these substances into brain tissue which takes place in utero.

Aviv *et al*¹⁵ found that 3 to 7 week old rats fed 1.5 mmol(mEq)/kg/day sodium suffered severe growth retardation compared with others fed 3.1 or 8.9 mmol(mEq)/kg/day. Atkinson *et al*¹⁶ showed that infants of less than 1.3 kg birthweight fed their own

mothers' milk retained sodium at a rate similar to the intrauterine accretion rate, while those fed SMA did not unless the formula was supplemented with sodium bicarbonate. Similarly, in a study of infants of 1600 g or less, Gross¹⁷ showed superior growth in those fed either on milk from prematurely delivered mothers or on a high sodium (24.5 mmol(mEq)/l) formula compared with infants given mature human milk. It is well established that milk from mothers who have given birth to preterm infants has a higher sodium content than mature human milk.^{18, 19} Chance *et al.*,²⁰ studying the effects of selectively altering the dietary intake of sodium, calcium, phosphorus, and energy on the growth of infants of less than 1.3 kg, found that only the sodium intake influenced body weight significantly within the range of energy intake studied.

Present feeding practices for preterm infants²¹ are based largely on recommendations drawn from observations of intrauterine growth rates, fetal nutrient accretion rates,^{22, 23} and anthropometric evaluation.²⁴ These recommendations take no account of the high renal¹ and intestinal² sodium losses characteristic of these babies and are, therefore, probably too low as regards sodium content (and possibly other minerals also). The results of the present study, like those of Sulyok,²⁵ support this contention: increasing the sodium intake to 4 to 5 mmol(mEq)/kg/day from the 4th to the 14th post-natal day was associated with an increase in early growth rate. This growth was sustained after the supplement was withdrawn (Figs. 4 and 5) arguing against fluid retention as the sole cause of the difference in rate of weight gain. The growth rate seen from day 4 in supplemented infants is comparable with the intrauterine growth rate reported by Usher²⁶ and with that achieved in the study of Chessex *et al.*²⁷ by feeding preterm infants on their own mothers' milk. In consequence, postnatal weight loss was less than that observed in unsupplemented infants while both birthweight and discharge weight were achieved earlier.

The more strongly positive potassium balance observed in supplemented infants, together with the lower plasma potassium concentrations, suggests that growth of the intracellular compartment may have been stimulated by sodium supplementation. If true, this interesting speculation is unexplained.

The quantity of supplementary salt given in our study was sufficient to produce positive sodium balance in all but two of the infants. Both of these were receiving aminophylline, which is known to be natriuretic in infants;²⁸ it is likely that babies being treated with methyl xanthines will require even larger amounts of sodium chloride than comparably immature patients not so treated, and we recom-

mend, therefore, that their plasma electrolyte concentrations be checked regularly during treatment.

The additional salt was well tolerated by all patients. No infant developed oedema or signs of circulatory overload, and none became hypernatraemic; indeed three became mildly hyponatraemic (plasma sodium 126 to 129 mmol(mEq)/l), including the two receiving aminophylline infusions. Withdrawal of the supplement on day 15 was not followed by weight loss or by slowing of the rate of weight gain, as would be expected if extracellular fluid volume had been inappropriately expanded. On the basis of these results, it seems more likely that the lag in weight gain seen in the unsupplemented patients is the consequence of volume contraction due to inadequate replacement of high obligate losses.

It is reassuring to note that the additional salt was efficiently absorbed from the intestine and was not lost in the urine; fractional sodium excretion was not higher in supplemented babies than in controls, while stool sodium losses were actually lower (Table 2). This finding is consistent with the suggestion that maturation of intestinal function is accelerated by increasing oral nutrient intake.²⁹ The lower urinary potassium:sodium ratio seen in the supplemented babies in study 2 suggests that salt supplements cause some suppression of aldosterone secretion, and also that the tubule is capable of responding to the hormone. The explanation for the lower values for glomerular filtration rate seen in group A in study 1 is not clear. The higher glomerular filtration rate seen in supplemented infants in study 3 may represent the effect of relative extracellular fluid volume expansion, or possibly the effect of improved renal growth as a consequence of avoiding sodium depletion. The slightly, but significantly, higher sodium and potassium intake seen in group A in study 1 is due to the fact that rather more infants in group A than group B received intravenous fluids at this time. The greater need for intravenous treatment suggests that group A infants were slightly less well than those in group B, a factor which would be expected to disadvantage this group with regard to early growth and development, whereas the results show that in fact they grew better than controls.

No side effects attributable to salt supplementation were observed in our study. In particular, the incidence of patent ductus was lower in supplemented (five of 22) than in control infants (nine of 24), although the difference was not significant ($\chi^2=1.184$, $P>0.2$). No difference was seen between groups in the incidence of necrotising enterocolitis (three affected babies in each group: $\chi^2=0.013$, $P>0.9$). Although cranial ultrasound

examinations were not routinely performed at the time of this study, no infant in either group showed evidence of symptomatic intracranial haemorrhage.

We conclude that mature human milk and conventional 'humanised' infant formulas fail to meet the nutritional sodium requirements of babies born before 34 weeks' gestation. They should either be fed on their own mothers' milk or be salt supplemented for the first few days of extrauterine life; the protocol described in this paper is sufficient to prevent hyponatraemia, to reduce postnatal weight loss, and to improve postnatal growth. It is not associated with any adverse effects. Supplementation is unnecessary after the second postnatal week.

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