Sodium intake and preterm babies

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How much sodium do preterm babies need and when should sodium supplementation start? Sodium is required to maintain extracellular tonicity and positive sodium balance is a prerequisite of growth. However, for most preterm babies, growth is unlikely during the first days after birth, as overall nutritional intake is limited. The primary aim of nutritional management, during this time, should be to provide an energy intake sufficient to minimise tissue breakdown. Total energy expenditure in stable, non-growing preterm babies in the first few days after birth varies widely around 84–168 kJ (20–40 kcal)/kg/day.1 Many infants do not even receive such a minimum intake in this time.

In addition, during the first days after birth, several adaptive processes must take place if the newborn baby is to negotiate successfully the transition from the intrauterine environment. Failure of adaptation of the cardio-pulmonary system is the commonest cause of perinatal death. Less attention has been paid to the adaptive changes that occur in body water distribution, though failure of, or delay in, achieving this aspect of postnatal adaptation is also a cause of significant morbidity.2–7

Postnatal alterations in body water
What are the normal changes in body water distribution after birth and how do they occur? After birth, a contraction of the extracellular compartment takes place due to loss of interstitial fluid8–12 and accounts, at least in part, for early postnatal weight loss. A contraction in the percentage of total body weight that is extracellular water takes place steadily throughout life. Extracellular water decreases from around 65% at 28 weeks' gestation to 40% at term and 20% by the age of 10 years.13 Superimposed on this gradual change with time, there is a more abrupt contraction in the extracellular compartment that occurs shortly after birth. This change appears to be closely interrelated with cardiopulmonary adaptation. Several studies now suggest that the postnatal natriuresis/diuresis and extracellular volume contraction is triggered by a surge in atrial natriuretic peptide release brought about by increased atrial stretch as pulmonary vascular resistance falls.14–16 The intravascular compartment may also be acutely expanded during birth because of reabsorption of lung liquid and a variable placental transfusion. It has been suggested that there is movement of water from the intracellular to the extracellular compartment immediately after birth, though the evidence for this is not conclusive as the study in question drew conclusions from cross sectional data from dehydrated subjects.19

If isotonic contraction of the extracellular compartment is to occur, net water and sodium balance in the first days after birth must be negative and should be regarded as physiological. That early negative sodium balance is physiological is borne out by the observation that, in healthy newborn babies, an increase in early sodium intake leads to an increase in sodium excretion.12 20 21 However all preterm babies have a limited (but variable) capacity to excrete a sodium load so that, despite increasing excretion in response to an increase in intake, sodium retention readily occurs.22 Shaffer and Meade studied sodium balance and extracellular volume regulation in a group of babies between 25–31 weeks' gestation in the first 10 days after birth.12 In the group given a sodium intake of 3 mmol/kg/day, 50% became hypernatraemic, as did 20% in the group given 1 mmol/kg/day. In this study, water intake began at 75 ml/kg/day on the first day, increasing by 10 ml/kg/day until day 5. If a more liberal water intake is allowed in conjunction with sodium intake, extracellular tonicity is maintained by expansion of the extracellular compartment. This is a common occurrence in neonatal intensive care units; many babies gain weight in the first days after birth, when nutritional intake is clearly insufficient to sustain growth and have a positive sodium balance with a normal serum sodium concentration.22 23 In the majority of babies this cumulative positive balance is subsequently lost; in other words, the normal postnatal changes in body water distribution occur, but are delayed.22 23 The well recognised diuresis that accompanies improving respiratory function in babies with respiratory distress syndrome is in fact a natriuresis14 and is an example of delayed postnatal adaptation. Costarino et al confirmed some of these observations in a blind trial comparing sodium restriction in the first five days after birth with sodium supplementation of 3–4 mmol/kg/day from birth.2 Water intake was administered independently. Unfortunately extracellular volume was not measured in this study, nor were the babies weighed. However, sodium balance was positive in the sodium supplemented group on the first day after birth and this group had a significantly higher incidence of bronchopulmonary dysplasia.
Developmental changes in sodium transport

How are the age dependent alterations in the regulation of sodium balance brought about? Immediately after birth there is a net stimulus to excrete sodium, followed later by a net stimulus to retain sodium as the demands of growth become paramount. In preterm babies both abilities are limited. The low glomerular filtration rate is not a limiting factor for sodium excretion. Circulating levels of natriuretic agents are variable and are influenced by the stage of cardiopulmonary adaptation. The renin-angiotensin-aldosterone system cannot be fully inhibited in preterm babies during intravascular volume expansion, further limiting sodium excretory capacity. The hypothesis that natriuresis may be induced by redistribution of blood flow to nephrons that are more immature and therefore more salt losing, remains unproved. The role of prolactin and the kinins in the regulation of perinatal body water distribution is unclear. Of most importance appears to be that both sodium transporting and regulating systems undergo postnatal maturation in a complex and exquisitely controlled manner.

Sodium transporters

Sodium, potassium (Na⁺,K⁺)-ATPase is the enzyme responsible for active sodium transport in all eukaryotic cells. It is a transmembrane protein, made up of two subunits, that maintains electrochemical sodium and potassium gradients across the cell membrane. The larger of the subunits, the α subunit, contains an intracellular ATP binding site and a phosphorylation site and extracellular binding sites for various hormones and drugs. There are many forms of Na⁺,K⁺-ATPase, each encoded by specific groups of Na⁺,K⁺-ATPase genes. In renal tubular cells Na⁺,K⁺-ATPase creates an electrochemical gradient that is the energy source for the cotransport, involving specific transporter proteins, of sodium ions and glucose and sodium ions and amino acids and the countertransport of sodium and hydrogen ions. These transporters are also transmembrane proteins. There is a postnatal, maturational increase in abundance of Na⁺,K⁺-ATPase and other transporter proteins. This postnatal increase is accompanied by an increase in Na⁺,K⁺-ATPase mRNA. There are tissue specific differences in the time scale of such maturational changes.

Regulators

Sodium balance is subject to both long and short term regulation. Changes in the abundance of sodium transporters are responsible for long term regulation. Glucocorticoids, for example, lead to an increased abundance of Na⁺,K⁺-ATPase and chronic incubation of renal tubular cells in an acid medium, to an increase in the protein responsible for the countertransport of sodium and hydrogen ions. Short term regulation of sodium balance is brought about by increases or decreases in the activity of sodium transporters. Down regulatory factors, which cause natriuresis, include atrial natriuretic peptide, dopamine, and diuretics. Noradrenaline is an up regulatory factor, which results in sodium retention. Dopamine inhibits and noradrenaline stimulates, Na⁺,K⁺-ATPase activity. The renal tubular sodium/hydrogen ion exchanger is amiloride sensitive.

Regulatory factors exert their effects via a cascade of intracellular messengers. These intracellular signal systems also undergo postnatal maturation. End organ responsiveness increases with postnatal maturation of cellular signal systems, and evidence of this at molecular and cellular levels, now substantiates clinical observations. Atrial natriuretic peptide stimulates membrane bound guanylate cyclase, which leads to an increase in the intracellular second messenger, cyclic guanosine monophosphate (cGMP), generated from endogenous guanosine triphosphate. cGMP interacts with specific protein kinases which in turn catalyse the phosphorylation of several protein substrates and finally leads to a biological effect such as inhibition of sodium reabsorption. Each step in such a cascade is subject to developmental regulation. In a study of preterm babies, the ratio of cGMP to atrial natriuretic peptide was found to increase exponentially in the first three days after birth, then reaching a plateau. The ratio of sodium excretion to cGMP continued to increase over the 10 days of the study. This suggests a postnatal increase in the atrial natriuretic peptide/cGMP/sodium excretion cascade and thus an increasing postnatal ability to excrete sodium.

Periods of sensitivity

In an elegant series of experiments, Celsi and others have shown age dependent differences in the ability of glucocorticoids to induce Na⁺,K⁺-ATPase. In rats, betamethasone will increase Na⁺,K⁺-ATPase mRNA in the kidney during infancy, but not during fetal life, nor in adults. In contrast, lung tissue Na⁺,K⁺-ATPase is maximally induced by glucocorticoids during the perinatal period. The inference is that glucocorticoids interact with other transcriptional factors, expressed in an age dependent fashion, to activate the genes for Na⁺,K⁺-ATPase so that different tissues have different periods of sensitivity to glucocorticoid regulation. In the future, the therapeutic activation of transcriptional factors determining tissue maturation may be possible. Conversely, a note of caution must be sounded, as activation of transcriptional factors during periods of sensitivity may lead to ‘imprinting’, an example of which may be the recent evidence that antenatal exposure to corticosteroids increases the risks of later hypertension.

Water

Neonatal paediatricians have long been concerned about ‘excessive’ fluid intake.
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Associations have been described between high fluid intakes and increased risk of symptomatic patent ductus arteriosus, necrotising enterocolitis, and bronchopulmonary dysplasia. In the former condition an expanded intravascular compartment might exacerbate left to right shunting and in the latter conditions, interstitial oedema has been implicated in pathogenesis. Regrettably, these studies have, without exception, failed to standardise sodium intake, so that increased ‘fluid’ has meant an increased intake of both sodium and water. In contrast to the reduced but rapidly altering sodium excretory capacity, preterm babies have less of a reduced ability to excrete water and this is to some extent compensated for by high insensible water losses. Coulthard and Hey have shown that stable, preterm babies are able to tolerate intakes of 200 ml/kg from the third day after birth, sodium intake remaining constant. They calculated that healthy preterm babies can achieve a urine flow rate of up to 7 ml/kg/hour. Leake et al found a group of babies between 28–34 weeks’ gestation to increase urine flow rate to a mean of 12 ml/kg/hour during acute increases in infusion rate to 250 ml/kg/day.

The capacity to excrete a water load may however be impaired in sick neonates by high circulating levels of the antidiuretic hormone, arginine vasopressin. Babies born after fetal distress or after difficult delivery have higher circulating arginine vasopressin concentrations than those born uneventfully. Rees et al have shown peaks of arginine vasopressin occurring during acute clinical events such as the development of a pneumothorax and cite this as evidence for the frequent occurrence of inappropriate antidiuretic hormone secretion in preterm neonates. However, the secretion of antidiuretic hormone can only be said to be ‘inappropriate’ if it occurs in the absence of osmotic or volume stimuli. Effective hypovolaemia probably occurs more frequently than is recognised in neonates receiving intensive care and in the postoperative period. More attention should be paid to assessment of the circulation using invasive arterial blood pressure and central venous pressure monitoring and non-invasively, core-peripheral temperature gradient, aiming to maintain this below 1–1.5°C. The latter parameter is an extremely useful index of volume depletion as shown by its strong correlation with circulating arginine vasopressin. Failure to provide adequate volume support in the form of salt containing solutions, preferably colloid, will lead to an inappropriate stimulus to arginine vasopressin release, water retention, and hyponatraemia. Once this has occurred water restriction will be necessary to correct the hyponatraemia safely.

**Clinical assessment**

**Urinary sodium concentration**

The fraction of filtered sodium excreted (FeNa) and urinary sodium concentration rise transiently during the postnatal natriuresis and then fall with postnatal age. Values for babies between 25–34 weeks’ gestation in the first weeks after birth are around 5% and 90 mmol/l respectively. ‘Spot’ urinary sodium concentrations bear no relationship to daily sodium balance and are of little use in determining the cause of hyponatraemia. A low urinary sodium concentration may be dilutional because of water excess or indicative of avid sodium retention. A high urinary sodium concentration in the presence of hyponatraemia may be due to inappropriate antidiuretic hormone secretion, to expansion of the extracellular compartment as in heart failure, to diuretic treatment or to true renal salt wastage. It is not uncommon for chronic sodium depletion to coexist with extracellular volume expansion as in the baby with cor pulmonale secondary to bronchopulmonary dysplasia who has also been on long term diuretic treatment. Fractional sodium excretion is often used in the evaluation of the oliguric infant. A value below 2.5% is said to be suggestive of prerenal oliguria and the urgent need for volume replacement whereas a high FeNa suggests established renal failure and the equally urgent need for restriction of fluid intake. Unfortunately, an FeNa greater than 2.5% has poor sensitivity to distinguish intrinsic renal failure in the preterm baby.

**Serum sodium concentration**

Water balance, before the postnatal diuresis/natriuresis, is best assessed by the change in serum sodium concentration. A decrease in serum sodium suggests positive water balance and excessive water intake; a rise in serum sodium suggests negative water balance and possibly insufficient water intake. After the first few days after birth the serum sodium concentration may reflect either water or sodium balance.

**Urine flow rate**

It is generally held that a urine output less than 1 ml/kg/hour is suggestive of impaired renal function. This is because in the presence of a renal solute load of 15 mosm/kg/day and an approximate maximum urinary concentration of 500–700 mosm/kg water, solute retention would occur if urine flow rate were less than 1 ml/kg/hour. Extremely immature infants have considerably smaller solute loads on the first day after birth, and in these infants it may be more appropriate to regard a urine flow rate of less than 0.5 ml/kg/hour on day 1 and 1 ml/kg/hour thereafter, as abnormal. It has been estimated that the most immature preterm infants might achieve a maximum urine flow rate of around 7 ml/kg/hour. As neonates do not empty their bladders completely on voiding and as 7% fail to void during the first 24 hours of life external urine collections of short duration may be inaccurate.

**Urine osmolality**

Well, preterm infants are able to achieve a minimum urine osmolality of around 45 mosm/kg and infants with respiratory distress
syndrome around 90 mosm/kg. Maximum osmolality is of the order of 800 mosm/kg though higher values exceeding 1000 mosm/kg are occasionally seen. Urine osmolality that lies between 200–400 mosm/kg usually suggests that fluid intake is satisfactory. However, as immature babies in the first days after birth may have even more limited concentrating abilities, these infants may become dehydrated while continuing to pass urine of low osmolality. Specific gravity is often measured in place of osmolality as it can easily be performed on the ward. The presence of glucose or protein (both often found in samples from sick preterm babies) will however falsely increase the specific gravity. In addition the relationship between specific gravity, as measured with a refractometer, and osmolality, differs between the newborn and older children so that in the newborn an osmolality of 400 mosm/kg is indicative of a specific gravity between 1020–1030.42

**WEIGHT**

Isotonic expansion of the extracellular compartment can, and frequently does, occur in the preterm neonate. This will be missed if changes in body weight are not considered in conjunction with serum electrolytes. Poor growth, in the face of an adequate energy intake, may reflect chronic sodium depletion and this may occur with a normal or low normal serum sodium concentration.

**IMPLICATIONS OF DEVELOPMENTAL CHANGES**

Weight loss in preterm babies in the first days after birth is associated with a reduced morbidity from symptomatic patent ductus arteriosis,7 7 necrotising enterocolitis1 and bronchopulmonary dysplasia.2 3 6 Early management should permit an isotonic contraction of the extracellular compartment. In order to allow the reduction in extracellular fluid volume which is the basis for weight loss, the primary necessity is to avoid an early intake of sodium. Early water intake should be sufficient to maintain glomerular filtration to allow the excretion of the relatively small renal solute load43 and to maintain tonicity in the face of high, but rapidly changing, transepidermal losses.44 A reasonable 'best guess' of the volume at which to start is therefore 30–60 ml/kg/ day plus estimated insensible water loss. Subsequently, the appropriate volume of intake will be determined by the nutritional content of the fluid used. Early physiological weight loss should be of the order of 7% of birth weight,8 9 but this is only an approximation as hydration at birth is variable and birth weight does not correlate closely with extracellular water volume.10

The principles of management of sodium balance during the period of postnatal adaptation should be clearly distinguished from those pertaining subsequently. An early intake of sodium is unnecessary and possibly harmful and therefore should be avoided or at least minimised until the physiological postnatal diuresis/natriuresis.14 If this point is indeter-

**minate, supplementation should be deferred until a steady weight loss of at least 7% of birth weight has occurred. Once the phase of immediate postnatal adaptation is over, growth becomes of paramount importance. Chronic limitation of sodium intake is associated with poor growth,45–47 and adverse neurodevelopmental outcome. There is increasing evidence that sodium is a permissive factor for growth.48 Sodium deficiency inhibits DNA synthesis in the most immature cells.49 Renal salt wasting is common in babies below 32 weeks' gestation and is due to impaired reabsorption at both proximal and distal tubule. Intestinal absorption is also limited.49 Rapid postnatal maturation occurs by an increase in Na+,K+-ATPase50 and by increasing responsiveness of distal tubule to aldosterone.50 51 It is possible that in sick babies persistent expansion of the extracellular space may be another cause of continued sodium loss. Sodium should be provided in an amount sufficient to allow the retention of 1 mmol/kg/day52 but may be higher in the most immature infants. For babies of less than 32 weeks' gestation sodium supplementation of this order should continue for around 2–4 weeks by which time postnatal maturation of sodium conservation should have occurred.46 52 A high sodium intake beyond this point is not necessary but whether it is harmful, for example in relation to the subsequent development of hypertension, is unknown.

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