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Physiological Approach to Sodium Supplementation in Preterm Infants

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Abstract

Objective—To implement and evaluate a clinical practice algorithm to identify preterm infants with sodium deficiency and guide sodium supplementation based on urine sodium concentrations.

Study Design—Urine sodium concentration was measured in infants born at 26^{0/7} to 29^{6/7} weeks' gestation at 2-week intervals. Sodium supplementation was based on the urine sodium algorithm. Growth and respiratory outcomes in this cohort were compared with a matched cohort cared for in our neonatal intensive care unit prior to algorithm implementation (2014–2015 cohort).

Results—Data were compared for 50 infants in the 2014–2015 cohort and 40 infants in the 2016 cohort. Urine sodium concentration met criteria for supplementation in 75% of the 2016 cohort infants within the first 4 weeks after birth. Average daily sodium intake was greater in the 2016 cohort compared with the 2014–2015 cohort ($p < 0.05$). Caloric, protein, and total fluid intakes were similar between cohorts. The change in weight Z-score between 2 and 8 weeks of age was significantly greater in the 2016 versus 2014–2015 cohort (0.32 ± 0.05 vs. -0.01 ± 0.08 ; $p < 0.01$). No impact on respiratory status at 28 days of age or 36 weeks of postmenstrual age was identified.

Conclusion—Institution of a clinical practice algorithm to instruct clinicians on sodium supplementation in preterm infants may improve growth outcomes.

Keywords

sodium; kidney; growth; premature infant; urine sodium

Sodium is the major cation of extracellular fluid, which includes blood plasma and interstitial fluid. Responsibility for maintaining the composition of extracellular fluid with respect to constituents other than oxygen and carbon dioxide resides largely with the kidneys. Preterm birth poses a unique challenge to this process as the immature kidney lacks fully functional regulatory systems, including those involved in sodium homeostasis.

Beyond the immediate postnatal period, preterm infants have higher sodium requirements (mEq/kg) than term infants and older children, primarily related to the inability of the preterm kidney to retain salt.^{1,2} The issue of determining the quantity of sodium that preterm infants require is significant given the impact of total body sodium status on somatic growth and the well-described link between postnatal growth failure and adverse neurodevelopmental outcome.^{3–6}

An underappreciated though convenient approach to the assessment of sodium homeostasis is the use of urine sodium concentration measured from a spot urine sample.⁷ In the mature kidney, a low urine sodium concentration often reflects active renal conservation of sodium in response to a decrease in total body sodium. However, in the preterm population, an approach using urine sodium concentrations as an indicator of total body sodium status is confounded by renal tubular immaturity and higher obligatory urine sodium losses, as well as ongoing maturation of renal function with postnatal age.^{2,8} Using published measures of glomerular and tubular function in preterm infants, we modeled expected urine sodium losses and urine sodium concentrations with advancing gestational and postnatal ages. Using the model, we developed, implemented, and evaluated a clinical practice algorithm based on projected urine sodium concentrations over a range of gestational and postnatal ages to identify sodium deficient preterm infants and guide sodium supplementation on an individual basis.

Study Design

Description of Sodium Supplementation Algorithm

Published measures of glomerular and tubular function were used to calculate expected daily urinary sodium losses and urine sodium concentrations at advancing gestational and postnatal ages.^{2,8,9} Calculations were based on the following equations:

1. $\text{GFR (mL/minute)} = \text{BSA} \times \text{GFR (mL/minute/1.73 m}^2\text{)}$, where GFR is glomerular filtration rate and BSA is body surface area.
2. $\text{Daily GFR (mL/day)} = \text{GFR (mL/minute)} \times 60 \text{ minute/hour} \times 24 \text{ hour/day}$
3. $\text{Daily filtered sodium} = \text{Daily GFR} \times \text{serum sodium concentration (138 mEq/L)}$
4. $\text{Total urine sodium (U}_{\text{Na}}, \text{ per day)} = \text{Daily filtered sodium} \times \text{fractional excretion of sodium (FE}_{\text{Na}}\text{)}$
5. $\text{Urine sodium concentration} = \text{U}_{\text{Na}}/\text{urine volume (per day)}$.

Values for weight and length at various postmenstrual ages were obtained using an online calculator (<http://peditools.org/fenton2013/>) based on the revised Fenton growth curves, using the 50th percentile for girls.¹⁰ Body surface area was calculated according to a standardized Eq. ($\text{BSA} = 0.024265 \times \text{W}^{0.5378} \times \text{H}^{0.3954}$).¹¹ Glomerular filtration rate at each gestational and postnatal age was extrapolated from the literature.⁸ Filtered sodium was calculated using an ideal estimated serum sodium concentration of 138 mEq/L. Fractional excretion of sodium was based on the interpolation and extrapolation of published longitudinal data on FE_{Na} in preterm infants born in less than 28 weeks' and 29 to 31 weeks'

gestation.⁵ The value chosen for urine volume (100 mL/kg/day) was based on values reported in the literature and verified in our own patient population.¹²

Using the calculated urine sodium concentrations (Fig. 1A), we developed a novel clinical practice guideline algorithm using urine and serum sodium concentrations to guide sodium supplementation. To address the concern that our calculations may overestimate sodium losses and risk adverse outcome with oversupplementation, we approached the development of the algorithm conservatively, choosing values reflecting the need for sodium supplementation purposefully less than the calculated urine sodium concentration values at each gestational and postnatal age. The algorithm (Table 1) allows for an increased amount of supplementation based on subsequent urine sodium concentration.

Application of Sodium Algorithm

Use of the algorithm was instituted in the University of Iowa Stead Family Children's Hospital neonatal intensive care unit (NICU) in January 2016. When indicated by a urine sodium concentration less than the calculated (expected) value or gestational and postnatal ages, supplementation of 4 mEq/kg/day above the current sodium intake was initiated. Existing data in older infants and children suggest that this degree of supplementation overcomes sodium depletion and improves growth without the development of hypernatremia.^{11,13} According to the algorithm, supplementation was increased by an additional 2 mEq/kg/day if urine sodium remained below goal on subsequent urine sodium concentration measurements.

Urine sodium concentration was determined every 2 weeks, beginning at 2 weeks of age. Urine was collected by placing cotton balls in a disposable diaper. Cotton balls without fecal contamination were placed in a 20-mL syringe and urine mechanically transferred into a sterile specimen container. The urine sodium concentration was determined by our hospital laboratory using an ion selective electrode. No patient received diuretics before the initial urine sodium concentration determination (2 weeks of age), and no patient received chronic diuretic therapy over the time period reviewed. Two patients received a single dose of diuretics, though not within 48 hours of urine collection. Infants with underlying renal and cardiac disease, or with ostomies, were excluded from adherence to the algorithm.

Data Analysis and Use of Historical Controls

To assess the effects of implementation of the algorithm and provide comparative data, we identified a random cohort of 50 infants of similar gestational age and birthweight cared for during 2014 and 2015, prior to the use of the algorithm. To our knowledge, no significant changes in our nursery's approach to neonatal nutrition occurred over this period of time. Data regarding weight, sodium intake, and respiratory outcomes were collected. Forty infants (gestational age: 26^{0/7}–29^{6/7} weeks) born between January 1 and September, 2016, were managed using the algorithm identified previously. Statistical comparisons were made by nonpaired *t*-test. Data are expressed as mean (standard error) unless otherwise noted. Parental consent and the University of Iowa Institutional Review Board approval was obtained.

Results

Values for projected urine sodium concentrations for infants born at 23 to 29 weeks' gestation and at postnatal ages of 2 to 8 weeks are shown in Fig. 1A. There is a wide variation in the calculated urine sodium concentration over the ranges of gestational age, though all exceed the 30 mEq/L value used in children with mature renal function to signify a sodium replete state. Total calculated urine sodium losses ranged from 5.4 to 7 mEq/day at 2 weeks of age down to 3.5 to 4 mEq/kg/day at 8 weeks of age (Fig. 1B). Losses were inversely correlated with advancing gestational and postnatal ages.

The demographics of the two cohorts are displayed in Table 2. No differences in gestational age, birthweight, or sex distribution were identified. In the 2016 cohort, there was little relationship between the initial urine sodium concentration obtained at 2 weeks of postnatal age and serum sodium (Fig. 2A). Based on the algorithm, 75% of infants in the 2016 cohort received sodium supplementation above that in their normal diet. Twenty-three (58%) of infants in the 2016 cohort had initial (2-week measurement) urine sodium concentrations warranting supplementation, while another 7 (18%) of infants had low urine sodium concentrations at 4 weeks of postnatal age warranting supplementation. As expected, fewer infants had urine sodium values < 40 mEq/L with advancing postnatal age, though the apparent lack of relationship between serum and urine sodium values persisted (Fig. 2). Daily sodium intake was similar at 2 weeks in both cohorts, but significantly greater ($p < 0.05$) at 4, 6, and 8 weeks in the 2016 versus 2014–2015 cohort (Table 3). Caloric, protein, and total fluid intakes, as well as daily urine output were similar between cohorts at each measured time point (Table 3). Mean weight was greater at 2 and 8 weeks of age in the 2016 versus 2014–2015 cohort (Table 2). Most importantly, weight gain, determined as change in weight Z-score between 2 and 8 weeks of age, was significantly greater in the 2016 versus 2014–2015 cohort (0.32 ± 0.05 vs. -0.01 ± 0.08 ; $p < 0.01$).

Use of the algorithm did not negatively impact respiratory morbidity at either 28 days of postnatal age (Fig. 3) or at 36 weeks of postmenstrual age (2014–2015 cohort: 60% receiving supplemental oxygen; 2016 cohort: 48% receiving supplemental oxygen). No infant required sodium supplementation to be discontinued due to hypernatremia (serum sodium concentration > 144 mEq/L).

Discussion

We assessed the development and use of a clinical practice algorithm based on expected urine sodium concentrations to identify preterm infants with sodium deficiency and guide sodium supplementation. Implementation of the algorithm resulted in increased dietary sodium intake and improved postnatal weight gain over the period of study. The improvement in weight gain was not a result of increased caloric, protein, or total fluid intake or decreased urine output, and no negative impact on respiratory status resulting from the use of the algorithm and additional sodium intake was identified in infants at 28 days of age or 36 weeks of postmenstrual age. To our knowledge, this is the first published use of urine sodium concentrations to guide sodium supplementation in this population. Our

findings suggest that optimizing sodium balance in premature infants may result in improved postnatal growth.

Postnatal growth failure remains a significant morbidity in very low birthweight (VLBW) infants. Efforts to promote growth in this population have included earlier initiation of parenteral nutrition and increased caloric and protein administration.¹⁴ While these advances in nutritional practices have resulted in improved growth velocity, up to 50% of VLBW infants continue to experience postnatal growth failure.^{15,16} Strong associations have been identified between in-hospital growth failure and impaired short-term (18–22 months) and long-term (up to 25 years) neurodevelopment.^{3–6} Thus, it is imperative that evidenced-based initiatives be designed to address this crucial issue impacting the care of preterm infants.

The need for adequate sodium intake and the maintenance of a sodium replete state to optimize growth is apparent from studies in animals and humans.^{13,17–19} Mitchell and Carman identified more than 90 years ago that rats and chicks demonstrated greater weight gain and nitrogen retention when provided rations with added NaCl.²⁰ In young, growing rats, a sodium deficient diet impairs weight and length growth, diminishes nitrogen retention, and decreases muscle protein synthesis and ribonucleic acid (RNA) concentrations.¹⁹ Weanling rats fed low sodium diets for 5 weeks displayed impaired bone growth, fat-free dry weight, and total body fat and nitrogen accretion compared with sodium replete animals.¹⁷ Despite a broad range of sodium intake (0.1–3 times the minimal daily requirement of sodium), study animals displayed similar body water content (percentage of body weight) and serum sodium values.

Limited attention has been given to identifying sodium requirements in preterm infants and the provision thereof.¹⁴ Current recommendations for preterm infants from the American Academy of Pediatrics (AAP) include enteral or parenteral intake of sodium of 3 to 5 mEq/kg/day and are based on a factorial approach calculated from fetal accretion of body components.^{21,22} This recommendation has not been updated since 1985 and fails to take into account the degree of renal immaturity present in extremely preterm infants who are surviving far earlier in gestation now than 30 years ago. Infants born at 23 to 31 weeks' gestation and receiving the AAP recommended sodium intake do not consistently achieve a state of positive sodium balance (intake > urine sodium losses) until after 32 weeks of postmenstrual age.²³ Considering that these calculations did not account for nonrenal sodium losses or sodium accretion associated with growth (~1.4 mEq/kg/day at these gestational ages), it is unlikely that sufficient sodium was provided at any time point.²²

Studies in preterm infants suggest that sodium supplementation above that provided in the diet may optimize weight gain. Vanpée et al provided 4 mEq/kg/day of supplemental sodium chloride to infants with 29 to 34 weeks' gestational age from 4 to 14 days of life.¹³ At 2 weeks of age, supplemented infants weighed approximately 6% above birthweight, while nonsupplemented infants were approximately 2% below birthweight (<0.01); fluid intake and urine output were similar between groups. Iseman et al randomized infants <32 weeks' gestation to receive 4 mEq/kg/day of sodium or placebo from 7 to 35 days of life, with an average daily sodium intake of 6.3 mEq/kg in the supplemented group and 2.9 mEq/kg in the placebo group.²⁴ At 6 weeks of age, 79% of supplemented infants maintained their birth-

weight percentile compared with only 13% in the placebo group. The average daily sodium intake between 2 and 8 weeks of postnatal age differed in our two cohorts by 1.5 to 1.9 mEq/kg/day, significantly less than that in Isemann's study. This difference resulted from the increased daily intake in the reference groups (Isemann placebo group and our 2014–2015 cohort) and the fact that only 75% of infants in our 2016 cohort required supplementation.

A primary issue in preterm infants failing to receive adequate sodium intake is the lack of a clinical measure of total body sodium status. Most neonatologists base the decision to provide supplemental sodium on serum sodium concentrations (J. L. Segar, personal communication); however, the physiological basis for this practice is limited, given the poor relationship between serum sodium concentration and total body sodium content.^{11,25,26} Though far from ideal, measurement of urine sodium concentration allows assessment of total body sodium content.⁷ There is general agreement that in patients with normal and mature renal function, urine sodium > 30 mEq/L is reflective of positive sodium balance, measurements < 30 mEq/L represent total body sodium depletion, and measurements < 10 mEq/L indicate a severe deficit. Studies in term and older infants at a risk of sodium depletion support that appropriate sodium supplementation enhances growth. Several groups identified that infants with short bowel syndrome at a risk of sodium depletion due to intestinal losses displayed improved growth with sodium supplementation and sodium repletion, evidenced by increased urine sodium concentrations, typically >30 mEq/L.^{18,27}

We recognize several limitations with this report. First, our goal was the development of a clinical practice algorithm to identify infants at a risk of sodium depletion and guide sodium supplementation; this is not a randomized controlled trial. The algorithm cannot be used in infants with underlying renal disease or those receiving chronic diuretics. The form of sodium provided as supplementation (sodium chloride vs. sodium acetate vs. sodium citrate) was at the discretion of the provider. Our primary outcome was weight gain; unfortunately, changes in length and head circumference over this 6-week period were not consistently recorded in the medical record. Additionally, we cannot address whether the increase in weight was lean body mass. No attempts were made to monitor adherence to the guideline, though our NICU dietician team tracked the data and alerted the care teams to laboratory results and algorithm recommendations. Finally, spot urine sodium concentration is dependent on circadian cycle, urine flow rate, and dietary and fluid consumption and thus may not reflect a continuous pattern of renal sodium excretion.²⁸ However, in contrast to older children and adults, there is typically a consistent pattern of provision of diet and fluid to preterm infants, ameliorating some of this concern.

While sodium deficiency may contribute to postnatal growth failure, increasing the sodium intake of all premature infants likely results in providing sodium to infants not depleted and unlikely to benefit from supplementation. A targeted approach that identifies preterm infants with sodium deficiency and guides sodium supplementation is preferable. We demonstrated that the use of a physiologically based algorithm, which allows identification of the individual preterm infant's need for supplementation, resulted in increased sodium intake and growth. Given the potential benefits of the urine sodium concentration algorithm on growth and, in turn, neurodevelopmental outcome, a randomized controlled trial to evaluate the efficacy of this approach, including changes body composition, is planned.

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Fig. 1.

(A) Estimated urine sodium concentration in infants 23 to 29 weeks of gestational age at postnatal ages of 2 to 8 weeks. Estimates based on the methodology outlined in text. (B) Estimated total urine sodium losses in infants 23 to 29 weeks of gestational age at postnatal ages of 2 to 8 weeks. Estimates based on the methodology outlined in text.

Fig. 2. Serum sodium versus urine sodium concentrations measured at 2 weeks (A), 4 weeks (B), 6 weeks (C), and 8 weeks (D) of postnatal age in infants born at 26^{0/7} to 29^{6/7} weeks' gestation.

Fig. 3.

Respiratory outcomes at 28 days of age for infants born at 26^{0/7} to 29 6/7 weeks' gestation in the 2014–2015 and 2016 cohorts. CPAP, continuous positive airway pressure; MV, mechanical ventilation; NC, nasal cannula; RA, room air.

Table 1

Algorithm for sodium supplementation based on urine sodium concentrations

Postnatal age (wk)	2	3	4	5	6	7	8	9	10	11	12	13	14
GA (birth)													
23–25 wk	50		50		40		40		40		30		30
26 ^{0/7} –29 ^{6/7} wk	40		40		40		40		30		30		

Abbreviation: GA, gestational age.

Notes: Values represent urine (Na), expressed as mEq/L, obtained every other week, being at approximately day 14 of life. If urine (Na) is below the threshold value, initiate supplementation at 4 mEq/kg/day above the current Na intake. Adjust supplementation weekly to account for weight gain. Increase by 2 mEq/kg at subsequent time points if less than the urine (Na) goal. Values should not be obtained within 48 hours of use of diuretic agent. Consider supplementation or determination of urine (Na) if serum (Na) is 132 mEq/L prior to the first scheduled urine (Na) determination. Provide supplementation if serum (Na) is 132 mEq/L, regardless of urine (Na), unless there is evidence of acute fluid overload (significant increase in weight). Hyponatremia in the presence of high urine (Na) likely represents a condition of pathological urinary sodium loss. Continue supplementation unless serum (Na) is >144 mEq/L. Consider discontinuation of supplementation at 38 weeks' postmenstrual age.

Table 2

Demographics of patient population

	2014–2015 cohort (<i>n</i> = 50)	2016 cohort (<i>n</i> = 40)
Gestational age (wk)	27.8 ± 0.15	28.2 ± 0.17
Birthweight (g)	1,090 ± 31	1,173 ± 36
Weight (g, 2 wk of age)	1,164 ± 33	1,289 ± 43 ^a
Weight (g, 8 wk of age)	2,340 ± 43	2,579 ± 80 ^a
Male sex (%)	50%	53%
Initial urine (Na) < 40 mEq/L	NA	58%
Any urine (Na) < 40 mEq/L ^b	NA	75%

^a $p < 0.05$ compared with the 2014–2015 cohort.^b Measured at 2, 4, 6, and 8 weeks of age.

Table 3

Sodium, caloric, and protein intakes at increasing postmenstrual ages

	Postmenstrual age			
	2 wk	4 wk	6 wk	8 wk
Sodium intake (mEq/kg/d)				
2014–2015 cohort	3.5 ± 0.2	3.8 ± 0.2	3.8 ± 0.2	3.2 ± 0.1
2016 cohort	3.7 ± 0.3	5.3 ± 0.2 ^a	5.7 ± 0.3 ^a	4.4 ± 0.2 ^a
Caloric intake (Kcal/kg/d)				
2014–2015 cohort	112 ± 3	119 ± 3	119 ± 3	125 ± 4
2016 cohort	115 ± 3	116 ± 2	121 ± 2	120 ± 2
Protein intake (g/kg/d)				
2014–2015 cohort	4.1 ± 0.1	3.9 ± 0.1	4.2 ± 0.1	4 ± 0.1
2016 cohort	4.2 ± 0.1	4 ± 0.1	4 ± 0.1	3.9 ± 0.1
Fluid intake (mL/kg/d)				
2014–2015 cohort	140 ± 2	147 ± 1	146 ± 1	148 ± 3
2016 cohort	139 ± 2	146 ± 2	147 ± 1	149 ± 2
Urine output (mL/kg/d)				
2014–2015 cohort	73 ± 3	83 ± 2	86 ± 3	93 ± 2
2016 cohort	75 ± 2	85 ± 2	85 ± 3	95 ± 3

^a*p* < 0.05 compared with the other cohort.