Renal Handling of Sodium in Premature and Full-Term Neonates: a Study Using Clearance Methods during Water Diuresis

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Summary

A study using fractional clearances during orally induced water diuresis was designed to delineate the mechanism underlying defective tubular reabsorption of sodium in very low-birth-weight neonates. The use of clearance methodology during maximal water diuresis may give an indirect estimate of distal sodium delivery [urine volume (V), $C_{H_2O} + C_{Na+K}$], sodium reabsorption at the diluting segments (C_{H_2O}), and proportion of the distal load reabsorbed distally ($C_{H_2O}/C_{H_2O} + C_{Na+K}$), when all values are corrected to 100 ml glomerular filtration rate.

The study was carried out in 28 healthy newborn infants who were grouped according to conceptual age (CA): 13 infants with mean birth weight of 1370 ± 330 g and mean CA of 31.8 wk (range, 28–34 wk), and 15 infants with mean birth weight of 2330 ± 550 g and mean CA of 37.9 wk (range, 35–41 wk). All studies were performed at 6–7 days of age. It was demonstrated that higher urinary osmolality (67.5 ± 23.2 versus 52.9 ± 9.4 mOsm/kg, $P < 0.0025$) and higher fractional sodium excretion (2.3 ± 1.8 versus 0.9 ± 0.5 ml/dl glomerular filtration, $P < 0.01$) observed in the group of very preterm infants resulted from significantly decreased proximal (V: 18.7 ± 6.0 versus 13.3 ± 3.6 ml/dl glomerular filtration, $P < 0.005$; $C_{H_2O} + C_{Na+K}$: 17.1 ± 5.2 versus 11.9 ± 3.3 ml/dl glomerular filtration, $P < 0.005$) and distal ($C_{H_2O}/C_{H_2O} + C_{Na+K} \times 100$: 81.9 ± 8.2 versus $88.2 \pm 4.5\%$, $P < 0.01$) tubular sodium reabsorption. Distal sodium delivery correlated significantly and inversely with CA when all subjects were considered, but when correlations were assessed separately in each group, only in the group of very preterm infants were significant correlations present between CA and urinary osmolality, sodium and chloride clearances, and percentage of distal sodium reabsorption.

These results suggest that the urinary sodium loss observed in very preterm infants depends on the incapacity of the distal tubule to cope with the arrival of an increased fractional load of sodium. A modest defect in urinary dilution is observed as an obligatory consequence.

Abbreviations

CA, conceptual age
GFR, glomerular filtration rate
V, urine volume

One of the important recent advances in neonatal renal physiology has been the demonstration that very low-birth-weight infants are unable to maintain sodium balance on a standard salt intake (13, 15, 19, 26, 31). This phenomenon is due to a

greater basal excretion of sodium that improves significantly with increasing gestational (2, 5, 15, 27) or postnatal age (2, 7, 19, 25, 31, 32). The mechanism for such impaired sodium conservation in very preterm infants has not been completely elucidated but inability of either the proximal or distal parts of the nephron, or of both, to reabsorb sodium efficiently might be responsible (8, 32, 34).

Clearance methodology during water diuresis, although limited by the necessity for invoking a variety of assumptions, is a well accepted means to approach *in vivo* tubular handling of glomerular filtrate (12). In the present study such methodology has been used to assess maturation of tubular handling of sodium in newborn infants. Our results confirm the previous suggestion (32, 34) that the urinary sodium loss observed in very preterm infants depends not only on increased distal sodium delivery but also, and principally, on a distal tubular defect in sodium reabsorption.

MATERIALS AND METHODS

The study was performed in 28 healthy newborn infants who were grouped according to CA: 13 infants with mean birth weight of 1370 ± 330 g and mean CA of 31.8 wk (range, 28–34 wk), and 15 infants with mean birth weight of 2330 ± 550 g and mean CA of 37.9 wk (range, 35–41 wk). This distribution was based on current concepts of developmental renal physiology (16). The CA was calculated adding the postnatal age to the gestational age, judged from the menstrual history of the mother and confirmed by physical examination of the infants. All studies were performed at 6–7 days of age. The perinatal course remained uneventful, that is, was not complicated by hypoxia, respiratory distress, exchange transfusions, or serious infections. All infants were fed on breast milk. The mothers had been on normal diets and had not received diuretic therapy. In every case a parental informed consent was obtained.

The studies were carried out in the morning, without altering the ordinary feeding pattern. Each infant received a continuous gastric drip of 0.33% saline at a rate of $4 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ over a period of 90 min. The spontaneously voided urine was collected in plastic bags during a period of 2 h. No bladder catheterization was necessary because results are factored by GFR so that accurately timed urine collections are not mandatory. GFR was determined by endogenous creatinine clearance and, to obviate the inaccuracy of individual periods, only the average value for all collecting periods was considered. Two capillary blood samples were taken at the beginning and at the end of the study and estimated serum values at the midpoint of each urine collection were used for clearance calculations.

Creatinine was analyzed in serum and urine using a kinetic

Table 1. Summary of biochemical data in serum during water diuresis (mean $\pm$ S.D.)¹

	Infants <35 wk CA (n = 13)	Infants ≥35 wk CA (n = 15)	P
Na (mmole/liter)	137.5 $\pm$ 6.0	140.3 $\pm$ 4.2	NS
K (mmole/liter)	5.08 $\pm$ 0.75	4.91 $\pm$ 0.46	NS
Cl (mmole/liter)	110.1 $\pm$ 11.8	112.3 $\pm$ 5.3	NS
Osmolality (mOsm/kg)	282.2 $\pm$ 8.5	280.5 $\pm$ 7.6	NS

¹ Abbreviations: CA, conceptual age and NS, not significant.

approach to the Jaffé reaction (Beckman creatinine analyzer). With this method, serum creatinine represents a valid marker of renal function in newborn infants older than 4–5 days (17, 36). Serum and urine osmolality were determined by freezing-point depression using an Advanced Osmometer. Sodium and potassium concentration were measured by flame photometry and chloride concentration by potentiometric titration using a Radiometer chloridometer.

Clearance methodology used for study of tubular function was in accord with current knowledge (12). Osmolar (C_{osm}), sodium (C_{Na}), chloride (C_{Cl}), and potassium (C_{K}) clearances were calculated by standard formula. Free water clearance ($C_{\text{H}_2\text{O}}$) was derived from: $C_{\text{H}_2\text{O}} = V - C_{\text{osm}}$, where V stands for diuresis. During maximal water diuresis, $C_{\text{H}_2\text{O}}$ approximates the reabsorption of NaCl at the distal diluting segments of the nephron, V represents the fraction of filtrate that reaches the ascending loop of Henle, and the calculations $C_{\text{H}_2\text{O}} + C_{\text{Na}}$, $C_{\text{H}_2\text{O}} + C_{\text{Cl}}$ and $C_{\text{H}_2\text{O}} + C_{\text{Na}+\text{K}}$ provide an estimation of distal NaCl delivery. The % of distal NaCl reabsorption is assessed relating distal reabsorption to distal load: $C_{\text{H}_2\text{O}}/C_{\text{H}_2\text{O}} + C_{\text{Na}}$, $C_{\text{H}_2\text{O}}/C_{\text{H}_2\text{O}} + C_{\text{Cl}}$ and $C_{\text{H}_2\text{O}}/C_{\text{H}_2\text{O}} + C_{\text{Na}+\text{K}}$.

Statistics were calculated by Student's *t* test for unpaired data. Correlation coefficients were determined with the least-square formula. *P* values less than 0.05 were considered significant. All values are given as mean $\pm$ standard deviation (S.D.).

RESULTS

In Table 1 the biochemical data in serum during water diuresis are given. No statistical differences were found in osmolality and concentrations of sodium, potassium, and chloride. The values after water loading were not statistically different from the baseline values. Although no overall correlation was present between serum values and CA, the lowest values for serum sodium tended to be observed in the more premature infants.

A summary of data for all studies are presented in Table 2. In this table and in all figures, only one value, that corresponding to the period of maximal free water clearance, is considered in each subject except for values of creatinine clearance, which correspond to the average value of all collection periods. Very preterm infants (CA less than 35 wk) presented significantly higher values for urinary osmolality and for osmolar, sodium, potassium, and chloride clearances. Fractional urine volume and fractional distal NaCl delivery ($C_{\text{H}_2\text{O}} + C_{\text{Na}}$, $C_{\text{H}_2\text{O}} + C_{\text{Cl}}$, $C_{\text{H}_2\text{O}} + C_{\text{Na}+\text{K}}$) were also significantly higher in the group of more immature newborns. Although the three terms used to express distal NaCl delivery were almost identical, only the value of $C_{\text{H}_2\text{O}} + C_{\text{Na}+\text{K}}$ will be used for correlations. The mean value of creatinine clearance in very preterm infants was $26.4 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$, significantly lower than the value found in more mature newborns of $46.4 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$. A negative correlation was present between fractional distal sodium delivery and creatinine clearance when all subjects were considered: $C_{\text{H}_2\text{O}} + C_{\text{Na}+\text{K}} \text{ (ml/dl GF)} = 21.3 - 0.18 \text{ Ccr (ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2})$, $r = -0.54$, $P < 0.01$.

Sodium chloride reabsorption at the diluting segments, esti-

Table 2. Summary of data from period of maximal free water clearance (mean $\pm$ S.D.)¹

	Infants <35 wk CA (n = 13)	Infants ≥35 wk CA (n = 15)	P
Uosm (mOsm/kg)	67.5 $\pm$ 23.2	52.9 $\pm$ 9.4	<0.0025
V (ml/100 ml GF)	18.7 $\pm$ 6.0	13.3 $\pm$ 3.6	<0.005
Cosm (ml/100 ml GF)	4.8 $\pm$ 2.7	2.9 $\pm$ 1.5	<0.025
$C_{\text{H}_2\text{O}}$ (ml/100 ml GF)	13.9 $\pm$ 4.4	10.9 $\pm$ 3.1	<0.025
C_{Na} (ml/100 ml GF)	2.3 $\pm$ 1.8	0.9 $\pm$ 0.5	<0.01
C_{K} (ml/100 ml GF)	23.1 $\pm$ 17.3	13.6 $\pm$ 7.4	<0.05
C_{Cl} (ml/100 ml GF)	3.2 $\pm$ 2.3	1.0 $\pm$ 0.4	<0.0025
$C_{\text{H}_2\text{O}} + C_{\text{Na}}$ (ml/100 ml GF)	16.2 $\pm$ 5.7	11.8 $\pm$ 3.3	<0.01
$C_{\text{H}_2\text{O}} + C_{\text{Cl}}$ (ml/100 ml GF)	17.1 $\pm$ 5.2	11.9 $\pm$ 3.3	<0.0025
$C_{\text{H}_2\text{O}} + C_{\text{Na}+\text{K}}$ (ml/100 ml GF)	17.1 $\pm$ 5.5	12.2 $\pm$ 3.3	<0.005
$C_{\text{H}_2\text{O}}/C_{\text{H}_2\text{O}} + C_{\text{Na}} \times 100$ (%)	86.6 $\pm$ 8.7	92.0 $\pm$ 3.1	<0.025
$C_{\text{H}_2\text{O}}/C_{\text{H}_2\text{O}} + C_{\text{Cl}} \times 100$ (%)	81.9 $\pm$ 10.7	91.6 $\pm$ 2.8	<0.0025
$C_{\text{H}_2\text{O}}/C_{\text{H}_2\text{O}} + C_{\text{Na}+\text{K}} \times 100$ (%)	81.9 $\pm$ 8.2	88.2 $\pm$ 4.5	<0.01
C_{cr} (ml $\cdot$ min ⁻¹ $\cdot$ 1.73 m ⁻²)	26.4 $\pm$ 10.5	46.4 $\pm$ 11.1	<0.0005

¹ Abbreviations: Uosm, urine osmolality; V, urine volume; Cosm, osmolar clearance; $C_{\text{H}_2\text{O}}$, free water clearance; C_{Na} , C_{K} , C_{Cl} , sodium, potassium, and chloride clearances, respectively; $C_{\text{H}_2\text{O}} + C_{\text{Na}}$, $C_{\text{H}_2\text{O}} + C_{\text{Cl}}$, $C_{\text{H}_2\text{O}} + C_{\text{Na}+\text{K}}$, distal sodium delivery; $C_{\text{H}_2\text{O}}/C_{\text{H}_2\text{O}} + C_{\text{Na}}$, $C_{\text{H}_2\text{O}}/C_{\text{H}_2\text{O}} + C_{\text{Cl}}$, $C_{\text{H}_2\text{O}}/C_{\text{H}_2\text{O}} + C_{\text{Na}+\text{K}}$, % of distal sodium reabsorption; and C_{cr} , creatinine clearance.

mated by the value of $C_{\text{H}_2\text{O}}$, was significantly higher in the group of very preterm infants (Table 2), implying a compensatory reabsorption of the proportionally higher amount of filtrate escaping proximal reabsorption. This compensation, however, was not sufficient to reabsorb distally the same proportion of the load, and the ratios $C_{\text{H}_2\text{O}}/C_{\text{H}_2\text{O}} + C_{\text{Na}}$, $C_{\text{H}_2\text{O}}/C_{\text{H}_2\text{O}} + C_{\text{Cl}}$ and $C_{\text{H}_2\text{O}}/C_{\text{H}_2\text{O}} + C_{\text{Na}+\text{K}}$ were significantly lower in the more immature subjects. This relationship is better analyzed in Figure 1, which expresses distal sodium reabsorption ($C_{\text{H}_2\text{O}}$) as a function of distal sodium load ($C_{\text{H}_2\text{O}} + C_{\text{Na}+\text{K}}$). It can be observed that the very preterm infants presented higher values of distal sodium delivery and higher values of free water formation, but the ratio between both variables remained below that found in more mature subjects.

When values for urinary osmolality and fractional clearances were related to CA, no correlations were present when CA was at or above 35 wk, but significant correlations were present for urinary osmolality, sodium, and chloride clearances, and % of distal sodium reabsorption when CA was less than 35 wk (Table

Fig. 1. Relationship between free water clearance ($C_{\text{H}_2\text{O}}$) and simultaneous fractional distal sodium delivery ($C_{\text{H}_2\text{O}} + C_{\text{Na}+\text{K}}$).

Table 3. Correlations between conceptual age (CA) and fractional clearances

	Infants <35 wk CA (n = 13)		Infants ≥35 wk CA (n = 15)	
	r	P	r	P
V	-0.33	NS	0.05	NS
Uosm	-0.76	<0.001	-0.23	NS
C _{H₂O}	-0.02	NS	-0.07	NS
C _{Na}	-0.56	<0.05	-0.15	NS
C _K	-0.12	NS	-0.24	NS
C _{Cl}	-0.59	<0.05	-0.04	NS
C _{H₂O} + C _{Na+K}	-0.23	NS	0.02	NS
C _{H₂O} /C _{H₂O} + C _{Na+K}	-0.70	<0.01	0.23	NS

Fig. 2. Fractional distal sodium delivery ($C_{H_2O} + C_{Na+K}$) plotted as a function of conceptual age.

3). Distal sodium delivery correlated, however, significantly with CA when all subjects were considered; that is, the more immature the subject the higher the proportion of the filtered load not reabsorbed proximally: $C_{H_2O} + C_{Na+K}$ (ml/dl GF) = $36.9 - 0.64$ CA (wk), $r = -0.48$, $P < 0.01$ (Fig. 2). Figure 3 expresses graphically the relation between the % of distal sodium reabsorption and CA: no correlation is present in the more mature subjects, but when CA is less than 35 wk, a positive correlation is present: $C_{H_2O}/C_{H_2O} + C_{Na+K}$ (%) = $3.85 + 2.45$ CA (wk), $r = 0.70$, $P < 0.01$.

DISCUSSION

This study using clearance methods during maximal water diuresis demonstrates the significant decrease of both proximal and distal tubular reabsorption of sodium in preterm infants born before the 34th gestational wk when compared to more mature or full-term neonates. Values for distal sodium delivery decreased significantly with advancing CA when all subjects were considered, whereas the % of distal sodium reabsorption only correlated significantly with CA in the group of very preterm infants. Incapacity of the distal tubule to cope with the arrival of an increased fractional load of sodium could explain the known inability of very immature infants to maintain sodium balance on a standard sodium intake (13, 15, 19, 26, 31).

The clearance methodology used in the present study could be a matter of criticism because there is no experimental demonstration that such fractional clearances are also valid indexes of tubular function in the very immature kidney. The study, however, fulfilled all necessary requirements to assure a correct interpretation of the results. Urinary osmolality reached values as low as 67.5 and 52.9 mOsm/kg in very preterm and term

infants, respectively, implying complete endogenous antidiuretic hormone suppression. This maximal water diuresis was not accomplished in two similar studies previously reported by Sulyok *et al.* (32, 34): minimal urinary osmolality did not reach mean values below 160 and 130 mOsm/kg in premature and term infants, respectively, under a different oral hydrating protocol. Their results should be interpreted with caution because values for C_{H_2O} were extremely low and the physiologic interpretation of the test was therefore erroneous. Even under ideal experimental conditions, a possible error in using C_{H_2O} as an index of NaCl reabsorption in the distal nephron must be assumed because there is evidence that the distal nephron is not completely watertight even in absence of antidiuretic hormone (20). Although a lower rate of back-diffusion of water from the collecting duct in very preterm infants could theoretically account for the higher values of C_{H_2O} , we think that improbable because the higher C_{H_2O} was accompanied by higher, rather than lower, values of urinary osmolality. The finding of a significant negative correlation between minimal urinary osmolality and CA in infants of less than 35 wk of CA has not been previously recognized because it is accepted knowledge that urinary diluting capacity is fully developed in premature infants (22). Our data indicate, however, that very preterm infants present a small defect in urinary dilution secondary to the impairment in NaCl reabsorption in the distal diluting segments.

A second important requirement of this type of study is that an adequate volume of fluid must be filtered and escape proximal reabsorption to allow for maximal water diuresis (12). This is best accomplished by some degree of extracellular fluid volume expansion. Although such expansion was probably small in our protocol because it was induced by ingestion, and not by infusion, of hypotonic saline, the results are not quantitatively comparable to those previously reported by us in infants and children (24). Additional factors such as serum sodium concentration could also influence free water formation but they are not relevant to the interpretation of our results because significant hyponatremic expansion was not present (11).

The first and quantitatively most important step in the process of sodium reabsorption occurs in the proximal tubule. The present results confirm the hypothesis that in the preterm infant there is an imbalance between glomerular and tubular function with regard to the capacity to handle sodium (8). A similar imbalance has also been shown to exist for β_2 -microglobulin, a low molecular weight protein which is constantly produced by the body, freely filtered and exclusively reabsorbed in the proximal tubule (6, 7). Experimental studies have demonstrated that in the immature nephron the sodium reabsorptive capacity is relatively low in the proximal tubule (19). Aperia and associates (4) have studied ultrastructural and enzymatic development of superficial proximal tubular cells of the rat nephron and have found that development of sodium reabsorptive capacity parallels

Fig. 3. Percent of distal sodium reabsorption ($C_{H_2O}/C_{H_2O} + C_{Na+K} \times 100$) plotted as a function of conceptual age.

both the ultrastructural maturation and the increase in Na-K-ATPase (10).

Although the existence in the immature kidney of a glomerulo-tubular imbalance is not accepted by all authors (30), Elinder *et al.* (14) have suggested that active renal vasoconstriction maintains GFR at low level in the perinatal period to protect the proximal tubules from overload. If an important sodium loss does not occur not only depends on that adaptative phenomenon but also, and fundamentally, because the distal tubules are able to cope with the fractional load delivered to them. There is strong evidence, both in man (3, 24) and in experimental animals (9, 21), that there is an enhanced reabsorptive capacity of the distal nephron for sodium during development. The enhanced distal reabsorption will also explain the blunted response to saline loading characteristic of the neonatal kidney (1, 18). This adaptative phenomenon appears to be absolutely necessary to maintain sodium balance (30), and may be partly induced by the observed increase in neonates of plasma renin activity and aldosterone concentration (23). The inability of very low-birth-weight infants to keep the equilibrium of sodium balance could be due to inefficiency of that distal compensatory mechanism of sodium reabsorption. Although the incorrect methodology of the studies reported by Sulyok *et al.* (32, 34) have been already commented upon, these authors arrived at a similar conclusion. Whether the distal abnormality depends on an insufficient rise in aldosterone secretion or is due to a limited tubular response to aldosterone stimulation is a matter of speculation (30). The studies in the fetal lamb showing that the adrenal cortex cannot be adequately stimulated during the last trimester (28, 29) will favor the first possibility, but the alternative or concurrent existence of a partial unresponsiveness of the distal nephron to aldosterone is strongly suggested by the studies of Sulyok and coworkers, showing that negative sodium balance in premature infants is accompanied by high plasma renin activity and aldosterone concentration and decreased K/Na quotient in the urine (33), and that all these abnormalities are completely reverted after NaCl supplementation (35).

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