Effects of Aldosterone and Atrial Natriuretic Peptide on Water and Electrolyte Homeostasis of Sick Neonates

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ABSTRACT. To clarify fluid homeostasis in neonates, 27 sick neonates (51 had respiratory distress syndrome, 12 had hyperbilirubinemia, and nine were low birth wt infants) were studied on 13 to 15 days of age. The infants were stabilized and required neither ventilation nor intravenous fluids at the time of study. All infants were breast fed, and their sodium intake ranged from 1.7 to 2.9 (2.2 ± 0.3) mEq/kg/d. Gestational age ranged from 30 to 39 (34 ± 3.4) wk and birth wt ranged from 1080 to 3280 ($2,070 \pm 672$) g. Creatinine clearance (Ccr), fractional excretion of sodium (FENa), fluid and electrolyte balance, plasma aldosterone and human atrial natriuretic peptide (ANP) concentrations were determined and analyzed according to conceptional age (CA) to clarify their maturational changes. None of the infants had a negative sodium balance or hyponatremia. Ccr remained almost constant until the 36th wk of CA, after which an abrupt increase occurred. FENa and plasma aldosterone level of infants less than the 32nd wk of CA were high ($0.75 \pm 0.33\%$, 2868 ± 1153 pg/ml, respectively) when compared with those in infants of the 33 to 34th wk of CA ($0.47 \pm 0.12\%$, $1,663 \pm 488$ pg/ml, respectively). There was a negative correlation between FENa and plasma aldosterone level in all cases ($p < 0.01$). Plasma ANP level of all infants were higher than those of healthy adults (40 ± 20 pg/ml). A good correlation was observed between Ccr and plasma ANP level in infants less than 36th wk of CA. These results show that the high plasma aldosterone concentrations possibly act to enhance the reabsorptive capacity of the distal nephron for sodium during development under conditions of low sodium intake and suggest that ANP may be released to control the extracellular space in premature infants with a limited Ccr. (*Pediatr Res* 25: 591–594, 1989)

Abbreviations

ANP, α -human atrial natriuretic peptide
CA, conceptional age
Ccr, creatinine clearance
ECV, extracellular fluid volume
FENa, fractional excretion of sodium
GFR, glomerular filtration rate
LBW, low birth wt
RAAS, renin-angiotensin-aldosterone system
RDS, respiratory distress syndrome

Plasma aldosterone concentration is relatively high in human newborn infants (1, 2). The cause of increased activity of the RAAS during the neonatal period is not clear. In the newborn the homeostatic function of the kidney may be limited (3). Although full-term infants are able to maintain the volume of body fluids within a narrow range, the physiologic limitations of the renal control of salt and water balance in low birth wt infants are not well established. In addition, recent reports demonstrated that ANP may play an important part in regulating water balance in the newborn period (4, 5). The purpose of this study was to clarify the roles of RAAS and ANP in neonatal fluid homeostasis.

MATERIALS AND METHODS

Study protocol. A total of 27 hospitalized sick neonates (15 boys and 12 girls; six had RDS, 12 had hyperbilirubinemia, and nine were LBW infants) were the subjects of this study. Informed consent was obtained from each patient's parents. Gestational age ranged from 30 to 39 (34 ± 3.4) wk and birth wt ranged from 1080 to 3280 ($2,070 \pm 672$) g. These 27 infants were divided into five groups according to the CA: group A, 5 infants of 30 to 32 wk; group B, 6 infants of 33 to 34 wks; group C, 6 infants of 35 to 36 wk; group D, 5 infants of 37 to 38 wk; group E, 5 infants of 39 to 41 wk of CA, respectively. The CA was calculated by adding the postnatal age to the gestational age, judged from the mother's menstrual history and physical examination of the infants. Apgar scores of 1 and 5 min were 8.4 ± 0.9 (range 7–10) and 9.6 ± 0.6 (range 8–10), respectively. Six infants with RDS were ventilated with the Bourns BP 2001 respirator. Duration of mechanical ventilation was 4.8 ± 2.9 (range 2–10) days. All infants had intravenous infusion therapy, which averaged 6.5 ± 1.5 (range 5–9) d in length. The infusion fluid consisted of 10% glucose supplemented with calcium (100 mg/kg/d) within the first 3 days of life, after which sodium chloride (35 mEq/liter) and potassium chloride (20 mEq/liter) were added. Total water intake (ml/kg/day) during the 1st wk of life in the premature infants was determined by our study protocol: 50 to 60 on day 1, 60 to 70 on day 2, 70 to 80 on day 3, and 100 to 120 on day 7, respectively. The mean volume of fluid administered (ml/kg/day) was 65 ± 18 on day 1, 69 ± 20 on day 2, 82 ± 23 on day 3, and 120 ± 26 on day 7, respectively. The sequential changes of body wt in infants of these five groups were shown in Table 1. None had bradycardia, hypotension, intracranial hemorrhage, or apnea in the early stages of life and clinical stability of the infants during the study period was good. All studies were performed at 13 to 15 days of life. All infants were breast fed. Sodium intake was determined by sodium analysis of the human milk sodium content (concentration ranged from 7–26 mEq/liter: which averaged 15.4 ± 2.2 mEq/liter in premature and 13 ± 2.4 mEq/liter in mature infants).

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milk, (range 7–26 mEq/liter). No infants were placed on aminoglycosides or diuretics during the study period. None of the subjects had renal dysfunction. Mean serum creatinine concentration on the 7th day of life was 0.76 ± 0.13 mg/dl (range 0.5 to 1.0). Urine was collected in a collecting bag every 6 h, once or twice during the study period. Blood sampling was done at the midpoint of urine collection.

Plasma and urine assay. Blood samples were collected between 0900 and 1200 h by puncture of the radial artery on the study day. Each specimen was collected in a syringe with sodium citrate as an anti-coagulant. Samples were centrifuged at 2000 rpm for 10 min at 4°C . Plasma was decanted to determine aldosterone, ANP, creatinine, and electrolytes. Each 6-h urine sample was pooled for the determination of sodium, potassium, and creatinine concentrations to calculate Ccr, FENa. Ccr and FENa were determined using standard formulas shown below:

$$\text{CCr (ml/min/kg)} = \frac{\text{Ucr} \times \text{V}}{\text{Scr}}, \quad \text{FENa (\%)} = \frac{\text{UNa} \times \text{SNa}}{\text{Ucr} \times \text{Scr}} \times 100,$$

where SNa indicates serum sodium concentration (mEq/liter); V, urine flow (ml/min/kg); UNa, urinary sodium concentration (mEq/liter); Scr, serum creatinine (mg/dl); Ucr, urinary creatinine (mg/dl). Aldosterone was measured by RIA (17) and ANP was measured as described in our previous report (5). Creatinine and electrolytes in serum and urine were determined using an autoanalyzer (Beckman Astra-8). Data are presented according to CA to clarify the maturational changes of Ccr, FENa, and plasma aldosterone and ANP concentrations. Results are expressed as mean $\pm$ SD and analysis of variance was used to determine significant differences between various age groups; $p < 0.05$ was considered significant.

RESULTS

Body wt, serum sodium concentration, and water and sodium balance in the subjects during the study period are shown in Table 2. There was no difference in serum sodium concentration

Table 1. Sequential changes of body wt in infants of five study groups*

Group	Birth wt (g)	Nadir wt (age in d)	Wt at 1 wk	Wt at study
A	1295 $\pm$ 278	1166 $\pm$ 290 (5.2 $\pm$ 1.5)	1197 $\pm$ 291	1368 $\pm$ 298
B	1508 $\pm$ 327	1354 $\pm$ 321 (5.0 $\pm$ 1.1)	1386 $\pm$ 323	1515 $\pm$ 310
C	1792 $\pm$ 244	1646 $\pm$ 237 (4.0 $\pm$ 0.9)	1726 $\pm$ 203	1848 $\pm$ 180
D	2006 $\pm$ 325	1848 $\pm$ 361 (4.8 $\pm$ 1.5)	1886 $\pm$ 384	2000 $\pm$ 438
E	3082 $\pm$ 115	2856 $\pm$ 133 (3.6 $\pm$ 0.8)	3006 $\pm$ 253	3153 $\pm$ 152

* Data was presented as mean $\pm$ SD.

Table 2. Changes of clinical and laboratory parameters in five study groups*

Group	Serum sodium concentrations (mEq/liter)	Water intake/output ratio	Sodium intake/output ratio
A	135.6 $\pm$ 1.9	1.38 $\pm$ 0.16	4.1 $\pm$ 4.9
B	136.8 $\pm$ 1.6	1.50 $\pm$ 0.13	5.9 $\pm$ 4.5
C	136.9 $\pm$ 2.6	1.40 $\pm$ 0.17	7.2 $\pm$ 5.7
D	137.0 $\pm$ 1.9	1.30 $\pm$ 0.20	4.6 $\pm$ 3.2
E	137.4 $\pm$ 1.7	1.40 $\pm$ 0.16	4.2 $\pm$ 2.5

* Data was presented as mean $\pm$ SD.

in each group. None had a hyponatremia less than 130 mEq/liter. Each group had the same water and sodium intake/output ratio. Although sodium intake of all groups was low, ranging between 1.7 and 2.9 mEq/kg/d, none had a negative sodium balance. There was no difference in these parameters between infants with RDS and LBW infants. Ccr, FENa, plasma aldosterone, and ANP concentrations in each group are shown in Figure 1. Ccr of infants less than 36th wk of CA (group A, 0.92 ± 0.26 , group B, 0.83 ± 0.19 , group C, 0.86 ± 0.31 ml/min/kg, respectively) was low when compared with the Ccr of infants more than 37th wk of CA (group D, 1.24 ± 0.08 , group E, 1.87 ± 0.66 ml/min/kg, respectively). FENa of group A ($0.73 \pm 0.41\%$) was significantly elevated more than that in group B ($0.25 \pm 0.15\%$). Plasma aldosterone concentration of group A (2868 ± 1153 pg/ml) was significantly higher than aldosterone levels in groups D and E (group D, 828 ± 395 , group E, 1004 ± 373 pg/ml, respectively). Plasma ANP concentration was constant in each group, although it was elevated compared with values found in healthy adults (40 ± 20 pg/ml). The relationship between FENa and plasma aldosterone levels in all cases is shown

Fig. 1. Creatinine clearance, fractional excretion of sodium, plasma aldosterone, and atrial natriuretic peptide concentrations during the 30 to 41 wk of conceptional age. Data were shown as mean $\pm$ SD.

in Figure 2. There was a good negative correlation between these two parameters ($r = -0.515$, $p < 0.01$). The relationship between Ccr and plasma ANP level in infants less than the 36th wk of CA is shown in Figure 3. Good correlation was observed between Ccr and plasma ANP level ($r = 0.522$, $p < 0.05$).

DISCUSSION

This study showed that plasma aldosterone level and FENa in more immature neonates were higher than those in mature neonates. Recent studies have shown that FENa is greater in premature infants than in mature ones and is inversely proportional to the maturity of a neonate (6, 15). Premature infants of less than 35 wk of gestation have an obligatory sodium loss, which is believed to be physiologic, resulting from isotonic contraction of body fluid compartments and the disposal of intra- and extracellular fluid solute through the kidney (9). Other studies have indicated that the increased urinary sodium loss in premature infants resulted from deficient proximal and distal tubular reabsorption of sodium (8, 16). Although our data on Ccr, FENa, and plasma aldosterone level in infants of the 30th to 32nd wk of life were nearly the same as those published previously, FENa and plasma aldosterone levels in infants of more than the 33rd wk of life were lower than those in other reports (15, 16). In this study, we found that FENa was correlated with plasma aldosterone level and that there was no case of negative sodium balance or hyponatremia. Although these results show that positive sodium balance could be maintained even in the premature infants, our results contradict the current practice. Sulyok and Varga (6) have found that in low birth wt infants renal salt wasting, subsequent negative sodium balance, and the fall in plasma sodium level induce marked elevation of the

activity of the RAAS. In our study, there was no case of negative sodium balance or hyponatremia. We do not know why those premature infants are able to establish positive sodium balance so easily. The characteristics of our nursery protocol may be that sodium and water intakes of premature infants are significantly lower than those found in other nurseries (14), especially during the 1st wk of life. Recent reports have also described that the challenge of salt and water loading leads to a marked natriuretic response and a decrease in the plasma sodium level in premature infants (7). Rodriguez-Soriano *et al.* (8) demonstrated that the urinary sodium loss observed in very low birthweight infants depends on the incapacity of the distal tubule to cope with the arrival of an increased fractional load of sodium (9). Based on the above observations, we speculate that renal salt wasting in the premature infant may be one of the stimuli for increased aldosterone secretion but that he or she can easily achieve a positive sodium balance under conditions of low sodium intake. For these reasons, we suggest that low dietary sodium may be effective in regulating sodium balance in premature infants.

It is generally considered that GFR does not change appreciably until about the 34th wk of CA, which corresponds to completion of nephrogenesis in the human kidney (10). Although our results were compatible with the above observation, we found that Ccr in premature infants may be partly regulated by plasma ANP level because creatinine clearance and ANP were related prior to 36 wk CA (Fig. 3). ANP has multiple effects, including inhibition of aldosterone, renin, and vasopressin release, reduction in systolic blood pressure and enhancement of GFR (11). We reported previously that hypersecretion of ANP may play an important part in initiating spontaneous diuresis in sick neonates (5). Tikkanen *et al.* (12) reported that ANP is released in response to volume distention of the atria in adults. Collectively, these results suggest that ANP may be released in response to volume distention of the extracellular space in premature infants who have a limited GFR. Recently, Shaffer *et al.* (13) demonstrated that ECV in very low birth wt infants is regulated within a range similar to that in older infants. However, the mechanism of regulation of ECV in premature infants has not yet been well established. The fall in plasma renin concentrations after saline loading in puppies was greater as they got older, suggesting that the mechanism responsible for the maintenance of plasma renin concentration may be less responsive in the immediate neonatal period (6). In conclusion, we speculate that positive sodium balance established in response to a highly activated RAAS in the premature infant may change ECV and that ANP may compensate for these effects. Further studies are required to clarify the mechanism of water balance in a developing neonate.

Fig. 2. Relationship between plasma aldosterone concentrations and FENa in all cases ($r = -0.515$, $p < 0.01$).

Fig. 3. Relationship between plasma ANP concentrations and Ccr in the infants of less than 36 wk of conceptional age ($r = 0.522$, $p < 0.05$).

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