DEVELOPMENTAL STUDY OF THE RENAL RESPONSE TO AN ORAL SALT LOAD IN PRETERM INFANTS

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ABSTRACT. Aperia, A., Broberger, O., Thodenius, K. and Zetterstrom, R. (Department of Paediatrics, Karolinska Institutet, S:t Göran's Children's Hospital, Stockholm, Sweden). Developmental study of the renal response to an oral salt load in preterm infants. Acta Paediatr Scand 63: 517, 1974.—An evaluation of sodium homeostasis in 44 preterm infants with gestational ages between 29 and 37 weeks has been carried out during the first week after birth and until time of expected term. The natriuretic response to an oral sodium load has been studied in all infants and the GFR (single injection technique of inulin) in 17 infants. The results are compared with those previously found in full-term infants. The natriuretic response was highest and the GFR was lowest in the very preterm neonates. In the very preterm infants the values for sodium excretion and GFR was just about the same at the time of expected term as in full-term newborns. Various explanations for the difference between the very preterm neonates and full-term neonates are discussed. One factor of importance might be the anatomical development. The immature kidney has in comparison to the adult kidney relatively larger glomerular than tubular mass. Extra-uterine life seems to have little influence on the development of GFR as well as on the development of the response to the oral salt load. Thus in the very preterm infants, the postmenstrual rather than the postnatal age should be considered when prescribing fluid, electrolytes and drugs.

KEY WORDS: Newborn, preterm, renal function, glomerular filtration rate, sodium excretion, water diuresis

The renal response to an oral sodium load has previously been reported to be low in newborn full-term infants (3). In preterm infants glomerular filtration rate (GFR) is lower than in full-term infants and older children (4, 36). One might therefore speculate that the ability to excrete sodium is even lower in preterm infants than in infants born at term.

In the present report the renal response to an oral salt load has been studied in newborn preterm infants of various gestational ages. The results have been compared with those previously found in full-term infants (3) and in older children (15). The postnatal development of the renal sodium elimination and glomerular filtration rate (GFR) has been followed until 40 weeks of postmenstrual age.

MATERIAL AND METHODS

Forty-nine studies have been performed in 44 healthy preterm infants of gestational ages varying between 29 and 37 weeks. One infant was studied 3 times and 3 were studied twice. In addition, 3 full-term infants have been investigated. Gestational age was calculated from the first day of the mother's last menstrual period until the day of birth. In order to confirm the gestational
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Fig. 1. Hourly natriuretic response to an oral salt load of 0.12 g/kg body weight in three different preterm infants. All studies during first week after birth. ---, natriuretic response to the same load in a representative study in the older children.

Fig. 2. Mean values of average hourly urine sodium excretion, following an oral salt load of 0.12 g/kg body weight, glomerular filtration rate and hematocrit in preterm infants of various gestational ages. All studies performed 1–7 days after birth. The figure also shows the value found in full-term infants. Range bars represent standard error of mean (S.E.M.).

kg body weight was given as a single intravenous injection in a scalp vein. Capillary blood was taken every 5 minutes during the first 20 minutes after the injection, then every 10–15 minutes during the following 55 minutes.

The sodium concentration in serum and urine was analyzed by a flame photometer (Eppendorf). Inulin in blood was determined according to Heyrovsky (16). Osmolality in blood and urine was determined cryoscopically with the aid of a Knauer osmometer. Serum albumin was determined by a refractometric method. Hematocrit in capillary blood was estimated in glass capillaries which were centrifuged at 10000 rpm for 5 minutes.

Students t-test has been used in statistical analyses.

RESULTS

All infants studied responded to the oral sodium load with an increased urinary sodium excretion. In the newborn full-term infants the pattern of the responses was rather consistent. The hourly sodium excretion increased during the first hour after the load had been given and was then fairly constant. The pattern of the response in older children (15) was similar to that observed in full-term infants. The magnitude of the response was, however, much larger in the older children. In the very preterm infants, the response to the oral sodium load was more variable. Dif-
Renal response to an oral salt load in preterm infants

Different patterns of response are demonstrated in Fig. 1. In some infants there was one short, but intense period of natriuresis, in others there was one or several short periods of higher sodium excretion. Between these periods the excretion was low. This might be due to greater variations in the time between each voiding and incomplete emptying of the bladder. Errors of this type can be expected to be less if more collecting periods are included. It therefore seems correct to represent the urinary sodium excretion for each infant as the average hourly sodium excretion calculated from all urinary samples obtained between 1 and 5 hours after the sodium load had been given.

First week after birth

Fig. 2 shows the average urinary sodium excretion, the GFR and the hematocrit in infants of different gestational ages 1–7 days after birth. The hematocrit was the same in the 4 different groups. GFR was higher in infants with a gestational age above 36 weeks than in those with a gestational age of 29–35 weeks. The difference was of border-line significance \( (p=0.1) \). The natriuretic response was significantly higher in infants of 29–35 weeks gestation than in infants of 36–37 weeks gestation and full-term infants \( (0.005>p>0.001) \). The natriuretic response in the preterm infants is, however, still five to ten-fold lower than the natriuretic response observed in children 8–14 years old \( (5) \).

It is generally accepted that the diluting capacity is a function of distal tubular sodium re-absorption \( (21, 31) \). The diluting capacity is most often measured as free water clearance. A characteristic relationship normally exists between the diluting capacity and the distal tubular sodium delivery, which can be given as the sum of free water clearance \( (C_{\text{H}_2\text{O}}) \) and sodium clearance \( (C_{\text{Na}}) \). In Fig. 3 the relationship between free water clearance \( (C_{\text{H}_2\text{O}}) \) and distal tubular delivery \( (C_{\text{H}_2\text{O}}+C_{\text{Na}}) \) is demonstrated and compared with that found in full-term infants. The relationship is just about the same in both groups of infants, though the diluting capacity seems to be somewhat better in the preterm infants.

Postnatal development

Fig. 4 shows the postnatal changes of hematocrit and the serum concentrations of albumin.
Fig. 5. Postnatal development of the natriuretic response to an oral salt load of 0.12 g/kg body weight represented as mean values of the average hourly urinary sodium excretion. Mean values of glomerular filtration rate during postnatal development are also represented. Range bars represent standard error of mean (S.E.M.).

There was, as expected, a general fall in the hematocrit (15) which was most pronounced in the most preterm group. The well known fall in serum albumin concentration (33) was observed. The serum sodium concentration remained constant.

The postnatal development of the urinary sodium excretion and GFR in infants of varying gestational ages is demonstrated in Fig. 5. The GFR increased in all groups. In the very preterm infants the GFR increased from 22 ml/min to 32 ml/min/1.73 m² body surface. In infants with gestational ages of 34–35 and 36–37 weeks the GFR increased to 48 ml/min and 58 ml/min/1.73 m² body surface, respectively. In preterm infants the GFR was consistently higher at a postmenstrual age of 40 weeks than in newborn full-term infants. The difference was found to be most pronounced in infants born after 34–37 weeks gestation. The determinations of GFR were however too few to allow statistical analysis.

The response to an oral salt load develops in a characteristic way during the postnatal period. In the very preterm newborn infants the urinary sodium excretion following a salt load was comparatively high. During the postnatal period, the natriuretic response was reduced to the same level as in newborn full-

Table 1. The diuretic response in infants of different postmenstrual age

<table>
<thead>
<tr>
<th>Gestational age (weeks)</th>
<th>Postnatal age</th>
<th>Postnatal age</th>
<th>At expected term</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–1 week</td>
<td>2–3 weeks</td>
<td></td>
</tr>
<tr>
<td>Group I</td>
<td>157.4±13.0</td>
<td>149.1±39.6</td>
<td>189.9±49.8</td>
</tr>
<tr>
<td>29–33</td>
<td>n=5</td>
<td>n=6</td>
<td>n=7</td>
</tr>
<tr>
<td>Group II</td>
<td>159.0±27.9</td>
<td>164.8±35.1</td>
<td>210.8±43.5</td>
</tr>
<tr>
<td>34–35</td>
<td>n=7</td>
<td>n=6</td>
<td>n=4</td>
</tr>
<tr>
<td>Group III</td>
<td>133.6±37.2</td>
<td>180.3±56.7</td>
<td>188.6±71.8</td>
</tr>
<tr>
<td>36–37</td>
<td>n=6</td>
<td>n=3</td>
<td>n=5</td>
</tr>
<tr>
<td>Group IV</td>
<td></td>
<td></td>
<td>168.1±53.3</td>
</tr>
<tr>
<td>38–42</td>
<td></td>
<td></td>
<td>n=23</td>
</tr>
</tbody>
</table>

*The values represent mean ± 1 S.D. and are expressed in ml/1.73 m²/hour.

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term infants. In infants born after more than 36 weeks gestation, the response was about the same as in newborn full-term infants.

The postnatal changes in the relationship between sodium excretion and GFR are demonstrated in Fig. 6. The urinary sodium excretion in percentage of filtered sodium (\(C_{Na}/C_{in}\)), the so-called fractional sodium excretion, is given and related to postmenstrual and postnatal ages. The sodium excretion in relationship to the GFR is highest in the infants with the lowest postmenstrual age. With longer gestation as well as with increasing postnatal age the fractional sodium excretion decreases.

The diuretic response following the salt load is shown in Table I. No statistically significant difference could be found between the different groups, except in Group II where an almost significant difference exists between first week and at expected term.

DISCUSSION

As expected (4, 36) glomerular filtration rate (GFR) was found to be low in preterm infants even when correlated to body surface. The difference in GFR between preterm and full-term infants correlates well with the results of histopathological studies (22, 25) according to which the formation of new glomeruli is not complete until the 36th gestational week. Another factor that could contribute to the low GFR is the low hydrostatic pressure (30). In view of the low GFR in preterm infants the relatively high natriuretic response following a salt load might be somewhat surprising. It should, however, be noted that the urinary sodium excretion is not only a function of GFR, but also of tubular re-absorption. When rapid changes in salt balance occur—as for instance by extracellular volume expansion—the resulting diuresis is more an effect of inhibition of tubular sodium re-absorption than of an increase of the filtered load (11). Some of the factors that influence tubular sodium re-absorption are intrarenal physical forces, such as hydrostatic and oncotic pressure between peritubular capillary and renal interstitium (6, 20). Newborn infants have a low hydrostatic pressure and a high hematocrit which would both enhance sodium re-absorption (29). On the other hand, serum albumin concentration is low, which should depress sodium re-absorption. Presently there is nothing that indicates that a hormone acting on tubular sodium re-absorption would be responsible for the sodium retention in early infancy. The aldosterone secretion rate has been shown to be low during the first week after birth (35).

The developmental stage of renal function can be expected to be correlated to the anatomical development of the kidney (24). Micro-dissection studies from young stillborn fetuses and infants have revealed that the vascular supply develops from the inner medulla to the outer cortex (21). The glomeruli of the juxtamedullary zone are the first ones to develop. If one assumes that the functional and anatomical developments run parallel, the major part of renal function would be carried out in the juxtamedullary nephrons in very young infants. Since extracellular volume expansion inhibits sodium re-absorption in superficial nephrons but not in juxtamedullary nephrons (18), this centrifugate development of nephrons might be one factor that could explain sodium retention in very young infants. It does not, however, explain the difference between preterm and full-term infants.

Micro-dissection studies in infants (14) and newborn dogs (17) have revealed a glomerular-tubular imbalance with larger glomeruli and smaller tubular mass as compared with older children and adult dogs. It seems likely that, in preterm infants, the tubular mass is even smaller than in term infants and thus the glomerular-tubular imbalance even larger. The relatively high fractional sodium excretion in the very preterm infants might thus be due to the fact that the tubular surface area for re-absorption is inadequate.

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The free water clearance data strongly suggest that the sodium pump functions optimally even in very preterm infants. The lowest osmolalities observed in neonates, 25–35 mOsm/l are much lower than those observed in older children and adults in this laboratory. This indicates that sodium can be reabsorbed against a high transtubular concentration gradient. The function in each tubular unit in the very preterm neonates should thus be as good as in newborn full-term infants.

In addition some extra-renal factors may also account for the higher sodium excretion in preterm than in full-term infants. Preterm infants have a larger extracellular volume (10) and a higher relative total sodium content (23) than full-term infants. Both those conditions are known to enhance the urinary sodium excretion (7, 11, 12, 26, 36).

The results of the studies of GFR and urinary sodium excretion in preterm infants of various postnatal ages give some views on the influence of extra-uterine life on the development of renal function. At a postmenstrual age of 40 weeks GFR was found to be about the same in very preterm infants as in newborn full-term infants. In infants with 34–37 weeks' gestation the GFR was somewhat higher at expected term than in newborn full-term infants. Since the observations are very few, they do not allow of any definite conclusions on a postnatal acceleration of the GFR in those groups. In case an actual postnatal acceleration exists it seems unlikely that this postnatal acceleration of the development would be due to high protein intake or a high mineral load (9, 13) since in our studies the protein intake was only 2.2 g/100 Cal and the sodium intake was fairly low (1.0 mEq Na+/100 Cal).

The results from the present study are well compatible with the hypothesis that extra-uterine life has only minor influence on the development of the control of sodium homeostasis. The developmental changes in glomerular-tubular balance discussed above could explain the reduction in urinary sodium excretion during early postnatal development among preterms. It should be noticed, however, that also environmental factors may contribute to the reduction in the natriuretic response to an oral salt load. One such factor might be that breast-fed newborn infants have a very low sodium intake. So far, unpublished observations from this laboratory have demonstrated that when salt intake is restricted in older children, the natriuretic response to an oral salt load is drastically reduced or even abolished.

In newborn full-term infants an inverse relationship has been demonstrated between the hematocrit and the natriuretic response to the oral salt load (3). Since polyglobulia has been shown to accelerate the renal tubular sodium reabsorption by the influence of intrarenal physical forces (8, 29) a high hematocrit was supposed to be one of the factors contributing to salt retention in very young infants. In the present study it was found that in preterm infants the natriuretic response to an oral salt load was still low 4–10 weeks after birth, that is at an age when the hematocrit is at a minimum level. Thus, polyglobulia cannot be a major factor responsible for the salt retention in the early postnatal period.

Renal excretory capacity is extremely low in preterm and full-term infants compared with older children and adults. The fact that GFR is even lower in preterm neonates than in full-term newborns, has obvious clinical implications as regards the prescription of drugs which are excreted by the kidneys. In preterm neonates the basal sodium excretion seems to be set at a higher level than in full-term infants. The limits for salt tolerance are thereby still more narrow in the preterm infant since the risks of giving too small amounts of sodium will also have to be considered. In very preterm infants extra-uterine life seems to have little influence on the development of GFR as well as on the development of the response to an oral salt load.
When calculating the sodium tolerance in a preterm or full-term infant during early infancy, postmenstrual rather than postnatal age has to be considered.

REFERENCES


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