Renal response to arginine vasopressin in premature infants with late hyponatraemia

L KOVÁCS, E SULYOK, B LICHARDUS, N MIHAJLOVSKIJ, AND J BIRCAK

Department of Pediatrics, Comenius University, and Institute of Experimental Endocrinology, CPR Sci of Slovak Academy of Sciences, Bratislava, Czechoslovakia, and County Children's Hospital, Pécs, Hungary

SUMMARY   To assess the influence of late hyponatraemia on the renal responsiveness to endogenous arginine vasopressin (AVP), urinary excretion and plasma concentration of sodium, plasma and urine osmolality, free water clearance, and urinary AVP concentration and excretion were measured in 11 healthy premature infants with a mean birth weight of 1360 g and mean gestational age of 31 weeks. Studies were performed on days 1, 5, and 19.

The development of late hyponatraemia was associated with a pronounced decline in urine osmolality, whereas urine flow rate and free water clearance increased significantly. Mean (SEM) urine AVP concentration and excretion also rose significantly from 2·15 (0·31) pg/ml and 0·36 (0·55) pg/min/m^2 on the first day to 6·5 (0·96) pg/ml and 3·85 (0·63) pg/min/m^2 on the 19th day, respectively.

When renal response to AVP was compared at different ages the highest urine osmolality and steepest response curve was observed on the first day. With development of hyponatraemia the renal response became blunted.

It is concluded that the limited tubular sodium transport and hyponatraemia hinders the establishment of intrarenal osmotic gradient, impairs renal response to AVP, and prevents excessive water retention and further fall of plasma sodium.

In a recent study on the role of arginine vasopressin (AVP) in development of late hyponatraemia in premature infants we showed a steady rise in urinary AVP excretion with age in spite of the pronounced decline in plasma sodium concentration and osmolality.[1] This finding was interpreted as indicating that the protracted volume contraction due to renal salt wasting stimulates AVP release, which, in turn, enhances free water reabsorption and contributes towards restoring the volume of body fluid compartments to normal. Interestingly, however, the rising AVP excretion was not associated with the expected rise in urine osmolality; what is more, the lowest mean value for urine osmolality was observed in the third week when hyponatraemia was already established.

On the basis of these observations it could be assumed that contrary to the general view[2] either no postnatal increase in renal responsiveness to endogenous AVP occurs over the age period studied or the renal response to AVP is blunted by late hyponatraemia.

In the present study we attempted to determine whether the impaired renal sodium conservation and hyponatraemia might limit the ability of the kidneys of premature infants to concentrate urine independent of AVP.

Patients and methods

Eleven healthy male premature infants with a mean birth weight of 1360 g (range 1020–1620 g) and mean gestational age of 31 weeks (range 29–33 weeks) were studied. All infants were delivered vaginally after uncomplicated pregnancy and labour. There were no pathological events known to increase AVP secretion during the perinatal period—that is, perinatal asphyxia, cardiopulmonary distress, or perinatal infection. They were nursed in a thermally controlled environment and fed pooled human milk. On the first day 5% glucose infusion was also given to provide daily fluid intake of 70–80 ml/kg.

Urinary excretion and plasma concentration of sodium, plasma and urine osmolality, endogenous

Table *Postnatal values (mean (SEM)) of plasma sodium concentration and osmolality, urine osmolality and flow rate, arginine vasopressin (AVP) concentration and excretion in urine, free water clearance, and fractional sodium excretion in 11 healthy premature infants*

Age (days)	Plasma sodium (mmol/l)	Osmolality (mOsm/kg H₂O)		Urine flow rate (ml/min/1·73 m²)	Free water clearance (ml/min/1·73 m²)	Fractional sodium excretion (%)	Urine AVP	
		Plasma	Urine				Concentration (pg/ml)	Excretion (pg/min/m²)
1	138·0 (2·5)	288·0 (1·6)	159·0 (16·2)	0·26 (0·02)	0·10 (0·03)	1·79 (0·27)	2·15 (0·31)	0·36 (0·05)
5	139·6 (1·8)	290·0 (4·0)	146·0 (14·7)	0·57 (0·05)*	0·27 (0·06)*	2·02 (0·41)	4·70 (0·57)*	1·80 (0·25)*
19	130·8 (1·4)**	281·0 (1·6)*	93·0 (11·5)*	0·98 (0·09)**	0·72 (0·14)**	0·51 (0·09)**	6·50 (0·96)*	3·85 (0·63)**

*p<0·05 v day 1.
**p<0·01 v day 1.

creatinine clearance, and urinary AVP excretion were measured on the first, fifth, and 19th days of life.

Plasma and urine sodium concentrations were determined by flame photometry. Osmolality was measured by freezing point depression, using a Knauer osmometer.[3] Creatinine concentration was determined according to the method of Jaffe with some modification.[4] Urinary AVP was measured by radioimmunoassay as described by Sramkova *et al.*[5]

Informed parental consent and approval of a local ethics committee was obtained for blood sampling and urine collection.

Statistical analysis was by the unpaired Student's *t* test and log-linear correlation.

Results

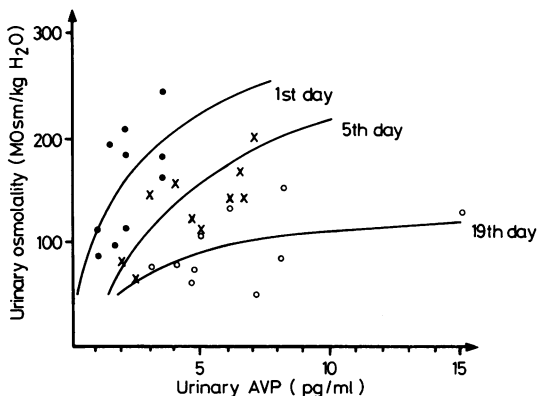Postnatal changes in plasma sodium and osmolality,

Figure *Renal osmotic response to endogenous arginine vasopressin (AVP) in premature infants on the first (●), fifth (X), and 19th (○) days of life.*

For first day, y=112·95+70·01, r=0·65, p<0·01.
For fifth day, y=12·31+91·62, r=0·84, p<0·01.
For 19th day, y=27·99+36·71, r=0·45, p<0·05.

urine volume, urine osmolality, free water clearance, fractional sodium excretion, and urinary excretion and concentration of AVP are summarised in the Table. There was a significant decrease of plasma sodium (p<0·05) and plasma osmolality (p<0·05) by the 19th day.

The development of late hyponatraemia was associated with a pronounced decline in urine osmolality, whereas urine flow rate and free water clearance increased significantly over this period. In spite of the falling plasma sodium and osmolality, mean (SEM) urine AVP concentration and excretion rose steadily from 2·15 (0·31) pg/ml and 0·36 (0·05) pg/min/m², respectively, on the first day to 6·5 (0·96) pg/ml and 3·85 (0·63) pg/min/m², respectively, on 19th day (p<0·01).

The postnatal alterations in renal concentrating performance were assessed by comparing the AVP response curves at different ages (Figure). The highest urine osmolality and steepest curve were observed on the first day. With advancing age and development of late hyponatraemia, the renal response became paradoxically blunted as indicated by the lower urine osmolality and the less steep slope of the response curve.

Discussion

The results of the present study on renal responsiveness to endogenous AVP suggest that renal salt wasting and development of late hyponatraemia interferes with the postnatal maturation of renal concentrating mechanisms.

It has been postulated that an interstitial osmotic gradient from renal cortex to papilla should be generated and maintained for elaboration of concentrated urine.[6 7] The generation of a hypertonic renal interstitium involves several factors, including passive medullary urea recycling[8] and active sodium chloride transport in the ascending limb of Henle's loop.[9]

Moore *et al* have shown that the fetal lamb could

establish a steep intrarenal osmolar gradient already at mid-gestation and infusion of hypertonic urea induced a significant increase in intrarenal urea concentration from cortex to papilla, whereas after hypertonic administration of sodium chloride the corticopapillary sodium gradient remained unaltered.[10] These experimental data are consistent with the clinical observations of Edelmann et al, showing that in preterm and full term neonates the concentrating performance can be enhanced by providing high protein diet or urea supplement, but sodium chloride supplementation proved to be inefficient.[11] These findings lend support to the concept that urea as a urinary solute is of prime importance in the renal concentrating mechanism.

In newborn rats urea accounts for only 25% of papillary solute and the adult value of about 50% is only reached by 21 days.[12] In agreement with these observations Zink and Horster found that in the early distal tubular fluid of 12–15 day old rats sodium chloride comprised most of the solute but that its relative contribution to the total solute concentration markedly decreased with age.[13] It can be assumed, therefore, that in the early period of life sodium chloride plays a major role in the build up of corticopapillary osmotic gradient, whereby the intact renal tubular sodium transport is an important prerequisite of efficient renal concentration.

Rees et al recently showed that urine osmolality response to AVP was more pronounced in premature infants with hypertonic dehydration than in those recovering from hyponatraemia.[14] This observation has been thought to indicate that in hypernatraemia the delivery of glomerular filtrate high in sodium and the medullary hypertonicity are important factors in enhancing renal response to AVP. With this suggestion in mind it is reasonable to speculate that hyponatraemia, the lower rate of sodium delivery to the distal nephron, and the subsequent decrease of renal solute gradient may limit the production of concentrated urine.

In addition to the diminished renal osmotic gradient, the increased renal prostaglandin production may also be considered as a factor contributing to the impaired renal response to AVP. In a group of healthy premature infants a progressive increase in urinary prostaglandin E excretion has been shown during the first three weeks of life when hyponatraemia and decreased renal responsiveness to AVP developed.[15]

In conclusion, our findings indicate that renal salt loss and volume stimulated increased AVP secretion may both be involved in the development of late hyponatraemia of prematurity. On the other hand, the limited renal tubular sodium reabsorption and the hyponatraemic state may hinder the establishment of intrarenal osmotic gradient and impairs renal response to AVP, thus preventing excessive water retention and further worsening of hyponatraemia.

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Correspondence to Dr E Sulyok, County Children's Hospital, H-7601 Pécs, Box 76, Hungary.