Archives of Disease in Childhood, 1984, **59**, 414–422

Hyponatraemia in the first week of life in preterm infants

Part I Arginine vasopressin secretion

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SUMMARY Continuous sequential urinary arginine vasopressin measurements in 14 preterm, ventilated infants suggest that both osmoreceptor and volume receptor systems are able to stimulate the prolonged secretion of arginine vasopressin from 26 weeks' gestation. The kidney is able to respond to arginine vasopressin stimulation from the first day of life and from 26 weeks' gestation. A maximum urine osmolality not exceeding 550 mOsm/kg was reached which varied with hydration of the infant. Excretion of arginine vasopressin and urine osmolality increased during deterioration of respiratory illness, mask ventilation, bilateral pneumothoraces, and severe intraventricular haemorrhage. The data show that inappropriate arginine vasopressin secretion is common during illness in the first week of life in preterm infants and that strict attention must be paid to water balance during this time.

Though disturbances in water balance are common in preterm, low birthweight infants during the first week of life, there have been few studies of the part played by arginine vasopressin in these disorders.[1–4] Consequently the factors affecting secretion and the renal response to the hormone are poorly understood.

In the human fetal pituitary there is a progressive increase in arginine vasopressin content up to 28 weeks' gestation with relatively little increase thereafter.[5] During the last third of pregnancy release mechanisms are functioning because very high arginine vasopressin concentrations are found in umbilical cord blood after normal vaginal delivery in both term and preterm labours,[6] the highest occurring during difficult births.[7]

An increase in plasma concentrations has also been shown in human neonates in response to pain[1] and surgery,[2] and raised concentrations have been found during ventilation for hyaline membrane disease[3] and in association with pneumothorax.[4]

The syndrome of inappropriate secretion of arginine vasopressin in preterm infants has been recognised for several years[8 9] and has been associated with hypoxic-ischaemic events,[10] intracranial haemorrhage,[11] pneumothorax,[4 9] ligation of patent ductus arteriosus,[8] and hyaline membrane disease.[12] Plasma arginine vasopressin measurements have been made in only three cases, however.[8 10] Since urinary arginine vasopressin has been shown to reflect plasma values closely[13] we have attempted to monitor secretion continuously by measuring the amounts excreted in sequential, four hourly urine collection and have thus been able to evaluate the response of the neonatal pituitary to physiological and pathological events that commonly occur in sick, preterm infants. From measurements of urine osmolality we have also been able to determine the response of the newborn kidney to the hormone. The relation between arginine vasopressin concentrations and changes in sodium and water balance will be discussed in Part II.[14]

Patients and methods

Patients. Fourteen preterm boys admitted to the neonatal intensive care unit at University College Hospital were studied for a mean of 5·4 days (range 1 to 10 days). Seven infants were delivered by caesarean section and 7 by normal vaginal delivery. All the infants were being ventilated because of hyaline membrane disease; their mean gestational age was 29·6 weeks (range 26 to 35 weeks) and mean birthweight was 1294 g (range 800 to 2290 g).

Methods. Urine bags measuring approximately 3 × 10 cm and pointed at the lower end were fashioned out of thin polythylene food freezer bags. They were applied as soon after birth as possible using Dow Corning Medical adhesive B (Dow Corning Corp, USA). Urine was continuously aspirated by a diaphragm pump (Charles Austin Ltd, UK) into a preweighed 50 ml glass Eherlenmeyer flask placed on ice, using a closed circuit system.[15] The urine flask was changed four hourly and the urine volume was determined by weighing. The portion used for urinary arginine vasopressin measurement was acidified with M hydrochloric acid in the ratio of 1 ml acid to 5 ml urine and frozen at −20°C until assay.

Arginine vasopressin was extracted using bentonite and measured by radioimmunoassay.[13] Osmolality of the remaining urine was measured by depression of freezing point on a Precision Instruments osmometer (Schuco International, UK). Hydrogen ion concentration, Pao_2, $Paco_2$, and base excess were measured on an Instrumentation Laboratory System 1303 pH/blood gas analyser and plasma sodium was measured by an Instrumentation Laboratory Flame Photometer 343 (Analytical Instrument Division, USA).

Results

Physiological causes of arginine vasopressin release and the renal response.

(1) Effect of plasma osmolality on urinary arginine vasopressin excretion.

Fig. 1 shows the relation between plasma osmolality and four hourly urinary arginine vasopressin excretion in two infants who developed hypernatraemic dehydration from birth due to very high insensible water losses.[15] Only values obtained when there were no events shown to precipitate inappropriate release of arginine vasopressin (see below) were used.

There was a significant linear relation between urinary arginine vasopressin excretion and plasma osmolality ($r = 0{\cdot}82$, $P<0{\cdot}01$); a finding compatible with the presence of functioning osmoreceptors. The intercept in adult subjects using plasma arginine vasopressin values but calculated in the same way is shown for comparison.[16]

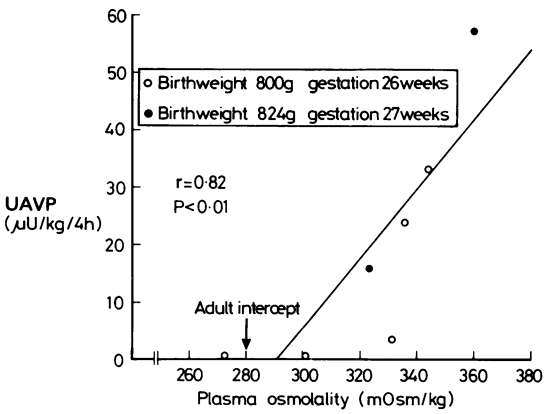

Fig. 1 *Relation between plasma osmolality and urinary arginine vasopressin (UAVP) excretion in two infants during the development of hypernatraemic dehydration. The adult intercept is taken from the data of Robertson et al.*[16]

(2) Urinary arginine vasopressin excretion during acute blood loss

Fig. 2 shows changes in urinary arginine vasopressin concentrations during an episode of acute blood loss that occurred after the removal of an umbilical arterial catheter. The haemorrhage, which was estimated to be 10% of the infant's blood volume, was associated with a twofold increase in the urinary arginine vasopressin excretion. As this event occurred at a time when no other complicating factors could be identified it was probably due to a functioning volume receptor response.

(3) Response of the kidney to increasing arginine vasopressin excretion and the effect of body hydration

Fig. 3 shows the relation between urinary arginine

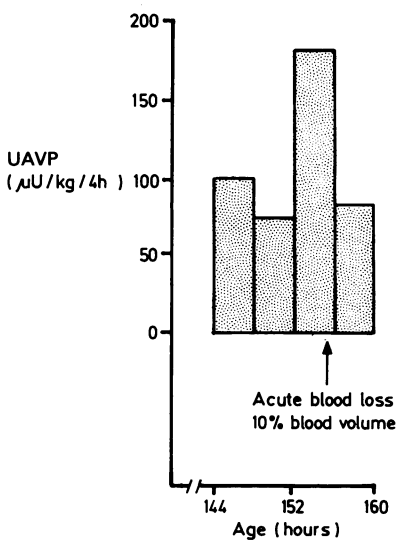

Fig. 2 *Urinary arginine vasopressin (UAVP) excretion during acute blood loss in an infant of birthweight 800 g and gestational age 26 weeks.*

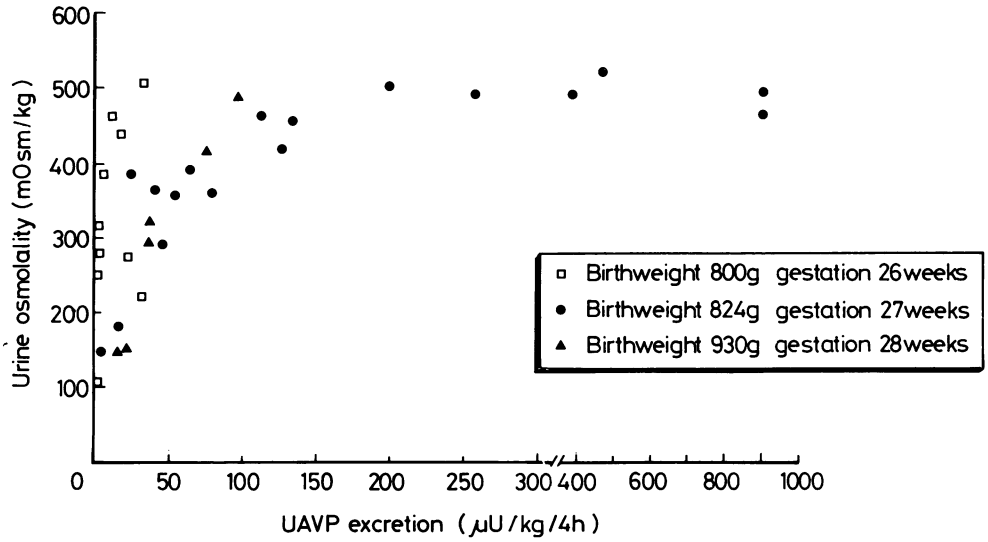

Fig. 3 *Response of the kidney to increasing urinary arginine vasopressin (UAVP) excretion in three infants with hypernatraemic dehydration.*

vasopressin and urine osmolality in three infants who developed hypernatraemic dehydration due to excessive insensible water losses.[14] As the urinary arginine vasopressin rose, so did the urine osmolality and in one infant with very high excretion rates of arginine vasopressin, urine osmolality reached a plateau averaging 494 mOsm/kg (range 468 to 521 mOsm/kg).

Fig. 4 shows the relation between urinary arginine vasopressin excretion and urine osmolality in two of the infants after recovery from hypernatraemia. In spite of a very similar range in arginine vasopressin excretion, the urine osmolality response was less steep and the plateau lower (mean 355 mOsm/kg, range 302 to 462 mOsm/kg) suggesting that the renal concentrating ability was dependent on the infants' state of hydration.

Pathological causes of increased urinary arginine vasopressin excretion. The continuous measurements showed large, short duration increases in urinary arginine vasopressin excretion, evident as

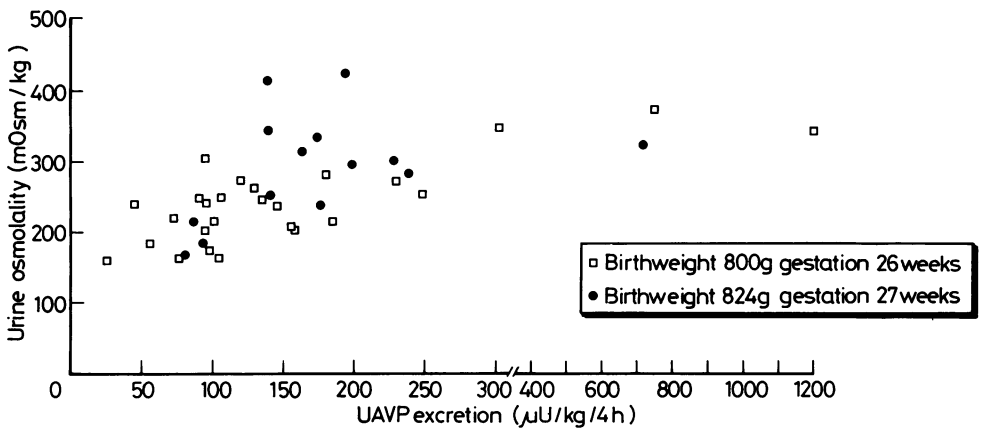

Fig. 4 *Response of the kidney to increasing urinary arginine vasopressin (UAVP) excretion in two infants after correction of the hypernatraemic dehydration.*

peaks in the ensuing Figs. Eight of 14 infants experienced 16 peaks of greater than 250 μU/kg/4 hours, capable of producing a maximally concentrated urine (Fig. 3). In some[14] and possibly all these patients the increase in arginine vasopressin secretion was inappropriate to the demands of water balance. There were also several smaller peaks causing parallel changes in urine osmolality that again had the potential to alter water balance unfavourably. As all the babies were very sick and many events that might have caused arginine vasopressin release occurred simultaneously it was not always possible to identify the precise cause of each peak and peaks sometimes occurred without any reason being evident. The Table lists the clinical events associated with the 16 largest peaks.

(1) Severe hyaline membrane disease

Fig. 5 gives an example of arginine vasopressin excretion during severe hyaline membrane disease. This infant was ventilated soon after hospital admission and was treated with tolazoline and pancuronium. Between 12 and 24 hours of age his blood gases deteriorated and between 28 and 34 hours his systolic blood pressure fell to 35 mmHg. During the first 32 hours he passed only 2·3 ml of urine and gained 75 g in weight. At 25 hours his plasma arginine vasopressin concentration was inappropriately raised at 19·2 μU/ml (normal range up to 2·5 μU/ml. After 32 hours he began to pass small volumes of concentrated urine with a high urinary arginine vasopressin excretion rate and his plasma sodium fell to 127 mmol/l. From 52 hours blood gases began to improve, urine output increased, and his urinary arginine vasopressin excretion and urine osmolality fell. Examples of urinary arginine vasopressin excretion during severe deterioration of respiratory illness (baby 2, Fig. 8) and during accidental extubation (baby 3, Fig. 8) were also seen and will be discussed below.

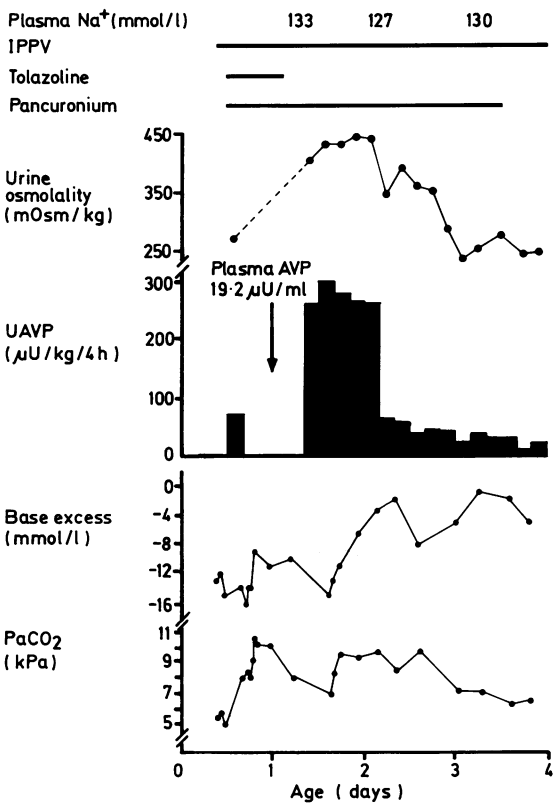

Fig. 5 *Urinary arginine vasopressin (UAVP) excretion and urine osmolality during severe hyaline membrane disease in an infant of gestational age 30 weeks and birthweight 1620 g.*

IPPV = intermittent positive pressure ventilation.

Table *Clinical events associated with urinary arginine vasopressin excretion (UAVP) greater than 250 μU/kg/4 hours*

Events	*No of episodes*	*No of peaks of UAVP > 250 μU/kg/4 hrs*
Deterioration of hyaline membrane disease alone. ($Paco_2$ > 8·0 kPa and pH < 7·1)	9	4
Mask ventilation. (associated with $Paco_2$ > 8·0 kPa and pH < 7·1)	3	2
Mask ventilation ($Paco_2$ < 7·2 kPa and pH > 7·17)	4	1
Bilateral pneumothoraces ($Paco_2$ < 8·27 kPa and pH > 7·09)	1	1
IVH > bilateral grade II (associated with $Paco_2$ > 8·0 kPa and pH < 7·1)	4	3
Cause uncertain	—	5

IVH = intraventricular haemorrhage.

(2) Mask ventilation

Fig. 6 shows urinary arginine vasopressin excretion in an infant who underwent three periods of mask ventilation. The first was associated with a large increase in urinary arginine vasopressin excretion and concentration of the urine and a small rise in the arterial carbon dioxide tension. During the second and third periods of mask ventilation the two associated peaks in urinary arginine vasopressin excretion were smaller in spite of a rise in $Paco_2$ to

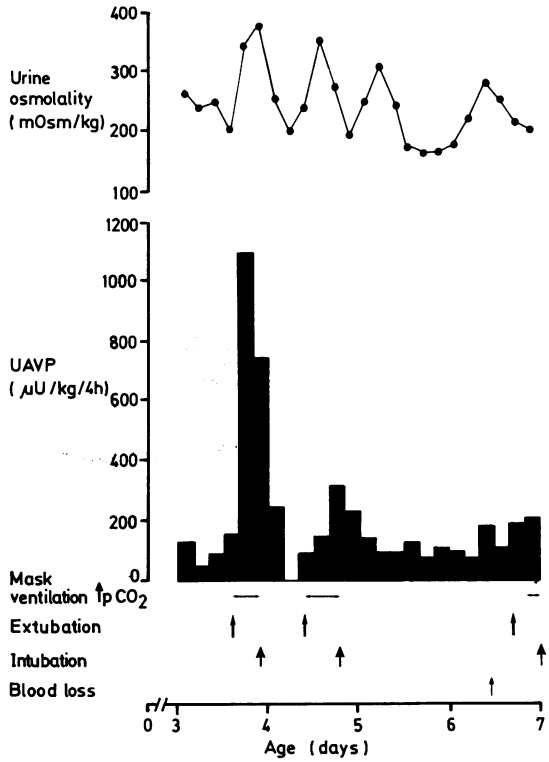

Fig. 6 *Urinary arginine vasopressin (UAVP) excretion and urine osmolality during mask ventilation in an infant of gestational age 26 weeks and birthweight 800 g.*

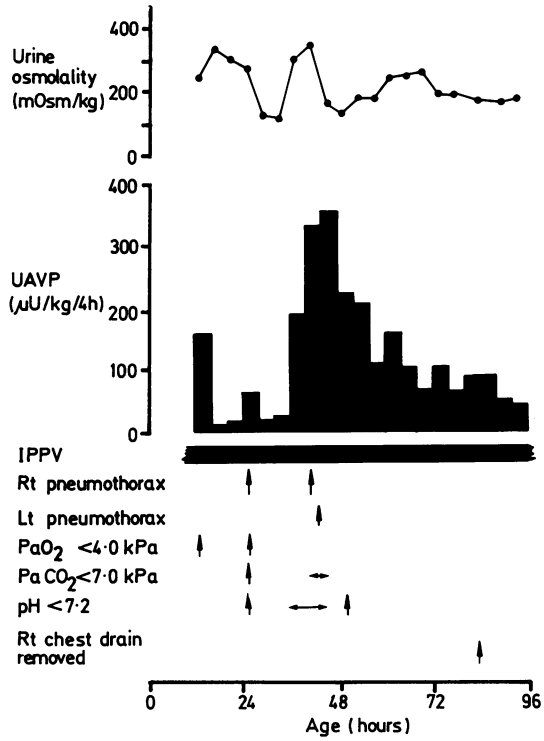

Fig. 7 *Urinary arginine vasopressin (UAVP) excretion and urine osmolality during pneumothorax in an infant of gestational age 31 weeks and birthweight 1475 g.*

IPPV=intermittent positive pressure ventilation.

over 8·0 kPa and a fall in pH to less than 7·1, suggesting that mask ventilation had had an effect on arginine vasopressin secretion by a mechanism other than deterioration in blood gases.

(3) Pneumothorax

Fig. 7 shows urinary arginine vasopressin excretion during pneumothorax. In this infant an initial rise in the excretion rate at 12 hours of age was associated with an episode of hypoxia. The small peak at 24 to 28 hours occurred at the time of diagnosis of a right pneumothorax and fell subsequent to its drainage. A second, larger increase occurred during the development of bilateral tension pneumothoraces at 42 hours of age and was associated with a concentrated urine. The urinary arginine vasopressin excretion fell slowly over the succeeding two days. A germinal layer haemorrhage was diagnosed by ultrasound examination at 73 hours of age.

(4) Intraventricular haemorrhage

All the infants had cerebral ultrasound examinations at least once daily and 8 of 14 had evidence of intraventricular haemorrhage. Four infants had germinal layer or unilateral grade II intraventricular haemorrhage only, and in these no definitely associated peaks in urinary arginine vasopressin excretion were found. Two infants, however, had bilateral grade II intraventricular haemorrhages and two had grade IV intraventricular haemorrhages, and in three of these infants peaks in urinary arginine vasopressin excretion of greater than 900 μU/kg/4 hours had a clear, temporal association with the haemorrhage. Details of these three infants are shown in Fig. 8.

Initially baby 1 (Fig. 8) had a low urinary arginine vasopressin excretion and a normal ultrasound scan. At 38 hours of age he became unwell with blood in the cerebrospinal fluid and this was associated with a steep rise in urinary arginine vasopressin excretion. At 46 hours his arterial carbon dioxide tension rose to greater than 10 kPa and his pH fell to less than 7·0. A bilateral grade II intraventricular haemorrhage was diagnosed at 51 hours.

In baby 2 (Fig. 8) the early increase in urinary arginine vasopressin excretion was associated with deterioration of his hyaline membrane disease ($Paco_2$> 9kPa, pH<7·1) and fell after ventilatory support began. Ultrasound scans at one and 11 hours were normal. At 15 hours a possible right germinal layer haemorrhage was seen and this was confirmed at 18 hours. Although the urinary arginine vasopressin excretion peak between 20 and 28 hours followed a grade I haemorrhage, there was no associated event other than a short episode of acidosis (pH<7·2, base excess > −12) at 22 hours of age. Between 48 and 66 hours the infant developed a right grade IV intraventricular haemorrhage and a left germinal layer haemorrhage and during this time there was a massive release of arginine vasopressin in amounts beyond the limit of the assay. Although the deterioration in his blood gases might have contributed to this peak, the most likely cause was the grade IV haemorrhage.

Baby 3 (Fig. 8) had severe hyaline membrane disease. Very high arginine vasopressin excretion occurred during an episode of severe asphyxia after accidental extubation at a time when no intraventricular haemorrhage was detectable on ultrasound. A second outpouring of arginine vasopressin between 56 and 72 hours of age was associated with a second episode of asphyxia and the development of a right grade IV intraventricular haemorrhage and a left germinal layer haemorrhage. In all three infants the peaks in urinary arginine vasopressin excretion were accompanied by concentration of the urine.

Discussion

Our results suggest that from the first day of life and from a gestational age of 26 weeks in the absence of complicating factors, neonatal arginine vasopressin secretion occurs appropriately in response to varia-

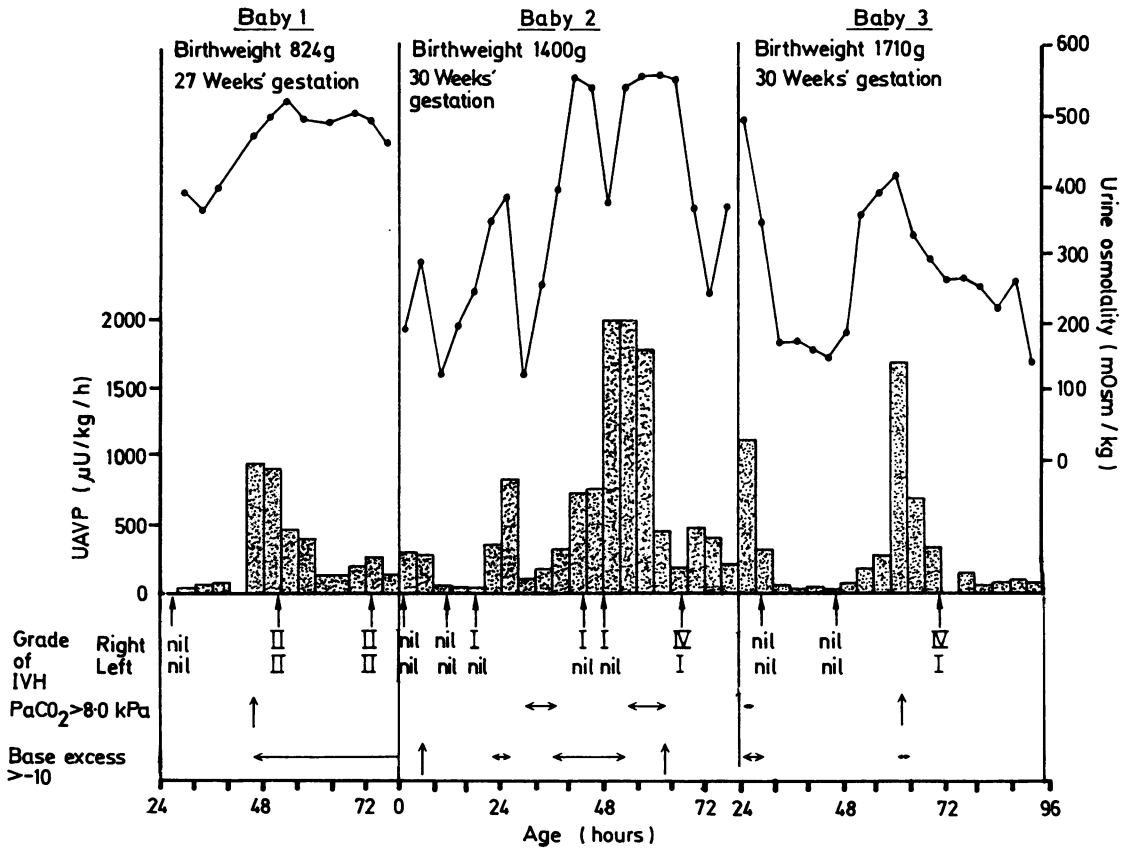

Fig. 8 *Urinary arginine vasopressin (UAVP) excretion and urine osmolality during the evolution of severe intraventricular haemorrhage (IVH) in three infants.*

tions in plasma osmolality. Furthermore, the observation of a rise in arginine vasopressin excretion after haemorrhage in one infant (Fig. 2) is compatible with the presence of functioning volume receptors. Our data are therefore consistent with the finding of functioning osmoreceptors and volume receptors in fetal animals in the last third of gestation.[17 18] In addition, the neonatal pituitary is also capable of maintaining a high, prolonged secretion rate. We claim no great precision for our estimated threshold for arginine vasopressin secretion at a plasma osmolality of 291 mOsm/kg. Nevertheless it is comparable with the value of 280 mOsm/kg established in adults using a similar method.[16] It is possible that stimulation of volume receptors[19] may have affected the relation shown in Fig. 1. Hypovolaemia would not, however, be expected to alter the slope of the regression line but rather to shift it to the left.[20]

In this study the kidney was able to respond to increasing arginine vasopressin secretion by concentrating the urine to a maximum that did not exceed 550 mOsm/kg. The renal response to the hormone is known to be diminished in neonates compared with adults.[21] One contributing factor may be the incomplete development of the renal solute gradient which is affected by the shortness of the loop of Henle, the low availability of urea, and the relatively high blood flow through the vasa recta.[22] In addition, high renal prostaglandin E production in the newborn is thought to attenuate the cellular action of arginine vasopressin through an interference with cyclic adenosine monophosphate production.[23] The observation that the maximum osmolality was higher during hypernatraemic dehydration may be due to an increase in renal medullary hypertonicity made possible by the delivery of a glomerular filtrate high in sodium and urea to the loop of Henle. It therefore seems likely that the renal solute gradient is the most important factor limiting the renal response to arginine vasopressin.[21]

In 8 of 14 infants studied arginine vasopressin peaks occurred in response to non-osmotic stimuli and resulted in an inappropriately concentrated urine. The frequency of these stimuli and associated changes in arginine vasopressin secretion during the course of severe hyaline membrane disease show the precarious nature of water balance during this illness. Assigning causes to the increases in arginine vasopressin excretion was difficult because numerous events that have been shown to stimulate release in experimental animals occurred simultaneously in our patients. It is likely therefore that a number of stimuli contributed to each peak.

Deterioration of respiratory function. Increased arginine vasopressin secretion associated with deterioration in respiratory illness may have been due to stimulation of volume receptors[19] by alterations in intrathoracic pressures and blood flow or accompanying changes in blood gas tensions. Experimental hypercapnia of 7·9 kPa increases the plasma arginine vasopressin concentration twofold in ventilated dogs[24] and chronic obstructive airways disease with hypoxia and hypercapnia is associated with a raised plasma arginine vasopressin concentration and fluid retention.[25]

Hypoxia is a potent stimulus for arginine vasopressin release in the fetal and newborn lamb. There is an enhanced response in the fetus approaching parturition and in the neonatal lamb compared with the younger fetus or the adult ewe.[26] Whether this is so in the human is not known.

It is clear that the factors stimulating arginine vasopressin release during severe hyaline membrane disease are multiple, and in this study they cannot be separated.

Mask ventilation. The association between arginine vasopressin peaks and periods of mask ventilation strongly suggests a causal relation. Again there are several possible stimuli for these peaks. If the mask slips it may obstruct the airway and if there are leaks ventilation will be impaired. It is also possible that compression of the head during fixing of the mask may play a role. Both short and long term increases in intracranial pressure have been shown to increase arginine vasopressin secretion in cats and monkeys.[27 28]

Pneumothorax. Arginine vasopressin excretion peaked in one infant at the time of occurrence of bilateral pneumothoraces, confirming the findings of a previous study.[4] Although it is likely that mediastinal compression and decreased venous return, by stimulating left atrial baroreceptors,[19] played a large part in the arginine vasopressin release seen in this infant (Fig. 7), the associated deterioration in blood gas tensions may also have contributed.

Intraventricular haemorrhage. The syndrome of inappropriate secretion of arginine vasopressin after intraventricular haemorrhage has been reported previously but arginine vasopressin measurements were not made.[11] The use of sequential estimates of urinary arginine vasopressin excretion has enabled us to document the temporal relation between inappropriate secretion of arginine vasopressin and the evolution of intraventricular haemorrhage.

Minor grades of haemorrhage, which are associated with a good prognosis, had no definite associa-

tion with arginine vasopressin release. However, haemorrhages greater than bilateral grade II, which are associated with a worse prognosis, were accompanied by peak concentrations lasting between 16 and 30 hours that were the largest seen in this study. These large increases in arginine vasopressin excretion are probably caused by the intraventricular haemorrhage and may be stimulated by a sudden reduction in blood volume,[19] by an acute rise in intracranial pressure,[27 28] or by the accompanying anoxia and hypercapnia.[24–26] It has been postulated that arginine vasopressin release plays a role in the development or extension of intraventricular haemorrhage.[29] Pneumothorax and deteriorating hyaline membrane disease are both highly significant antecedents of intraventricular haemorrhage[30 31] and it is possible that they exert their effect through arginine vasopressin release. The combination of the pressor effect of arginine vasopressin[32–34] and its action in reducing cerebrospinal fluid production[35] may, by increasing the transmural pressure in the germinal layer capillaries, create conditions that are favourable to the development of vessel rupture and intraventricular haemorrhage.

Several unexplained peaks in urinary arginine vasopressin excretion occurred during the study. Arginine vasopressin is released in response to stress[1] so it may be that traumatic venepunctures, insertion of arterial catheters and feeding lines, and even routine procedures contribute to these unexplained peaks.

We have shown that inappropriate secretion of arginine vasopressin is common in sick, preterm infants in the first week of life and is an important cause of hyponatraemia during this time. The changes in sodium and water balance will be presented in Part II.[14]

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Received 1 February 1984