Serial measurement of plasma arginine vasopressin in the newborn

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SUMMARY Plasma arginine vasopressin was measured serially in 11 preterm infants and one asphyxiated, term infant. The samples were taken through umbilical arterial catheters placed at birth for blood gas measurements because ventilatory support was required. Plasma samples of 200 to 300 μ l were taken 4 to 12 hourly for up to 100 hours after birth. Plasma arginine vasopressin was measured by a cytochemical bioassay. A significant correlation between plasma arginine vasopressin and plasma osmolality was found in only two out of six infants. The normal 'resting' concentration was between 0.5 and 2 pg/ml. In five infants, apparent bursts of arginine vasopressin secretion were seen, and in one spontaneously breathing infant with respiratory distress, continuously high concentrations (12 to 25 pg/ml) were recorded over the first 100 hours.

In the healthy, term neonate, water homeostasis is maintained with reasonable efficiency, even though renal immaturity precludes a degree of control comparable with that of older children and adults.¹ The sick neonate, however, has problems retaining fluid at times of reduced water intake and of excreting excess if overloaded.¹ Fluid intake in the sick and preterm infant is likely to be regulated by the care giver, without much appreciation of the physiological control.

The posterior pituitary peptide hormone, arginine vasopressin, is the major antidiuretic hormone in man. Although concentrations in human umbilical cord blood have been extensively reported, there have been only isolated measurements of arginine vasopressin in the peripheral blood of term and preterm neonates.²⁻⁶ Consequently, little is known about the efficiency of the normal control that is exerted by the hypothalamo-neurohypophyseal axis on water homeostasis in the newborn.

The lack of data on plasma arginine vasopressin concentrations in neonates, stems from the apparently very low circulating concentrations of the hormone and the relative insensitivity of established assay systems. These together lead to the requirement for 2 to 5 ml of blood for extraction and measurement of the hormone. The aim of this study was to use a highly sensitive cytochemical bioassay to investigate the arginine vasopressin concentrations in serial plasma samples obtained from sick term and preterm infants, and to endeavour to

correlate the results with the clinical status of the child.

Materials and methods

Eleven preterm infants, with gestational ages of 26 to 34 weeks, and one term infant were studied in the neonatal unit at this hospital. All the clinical data relating to the condition of these infants are given in Table 1.

Approximately 0.5 ml blood samples were obtained via an umbilical catheter placed in the first few hours of life for blood gas and arterial blood pressure monitoring. After the dead space in the system had been discarded, the blood was drawn into a heparinised plastic syringe, quickly transferred to 1.5 ml polypropylene reaction tube, and immediately centrifuged at room temperature in a Beckman Microfuge at approximately $10^4 \times g$ for one minute. The plasma (approximately 300 μ l) was immediately snap frozen in liquid nitrogen and stored at -70°C until assayed.

The routine monitoring of these infants consisted of an indwelling umbilical arterial oxygen electrode, transcutaneous oxygen electrode, continuous heart rate monitoring, continuous blood pressure measurement with a transducer on the umbilical arterial catheter, and specific gravity of every urine sample passed (refractometer). The ventilated infants were managed on Bourne BP 200 ventilators. Peak airway pressure and expiratory pressure or

Table 1 Details of 11 preterm infants with respiratory distress syndrome and one term infant with birth asphyxia in whom plasma arginine vasopressin concentrations were measured

Case no	Sex	Birthweight (g)	Gestation (wks)	Time studied (after birth) (hrs)	Comments
1	M	960	28	3-41	IPPV, HMD, PDA, SR
2	F	1010	27	6-33	IPPV, HMD, hypernatraemia
3	F	2310	34	27-66	HMD, SR
4	F	1800	32	9-67	IPPV, HMD, pneumonia, hypocalcaemia
5	M	2320	34	22-60	IPPV
6	M	900	27	14-102	IPPV, HMD, pneumonia
7	F	1170	28	48 & 57	IPPV, HMD
8	F	1500	30	144-146	IPPV, SR
9	F	2280	39	27-33	SR, HMD
10	F	600	26	15 & 76	IPPV, HMD, PDA, hyperglycaemia
11	F	2700	40	72-95	Birth asphyxia, fits, SR, cerebral oedema
12	F	950	25	64	IPPV

IPPV=intermittent positive pressure ventilation; HMD=hyaline membrane disease; SR=spontaneous respiration; PDA=patent ductus arteriosus.

Figure Plasma arginine vasopressin (AVP) values (●—●) with corresponding plasma osmolality values (△---△) in six serially sampled sick neonates.

continuous positive airway pressure, ratio of inspiration to expiration, and ventilator rate were noted at hourly intervals, and a mean airway pressure was

Table 2 *Relation between plasma arginine vasopressin (AVP) concentrations and plasma osmolality and urine specific gravity (USG) with increasing age in preterm infants*

Case no	Age (hrs)	USG ($\times 1000$)	Plasma osmolality (mOsm/kg·H ₂ O)	Plasma AVP concentration (pg/ml)	r*
1	3	1005	276	2.8	r=0.92 (P=0.005)
	9	1005	276	1.2	
	15	1005	278	0.2	
	21	1005	286	5.0	
	28	1010	285	7.9	
	34	1009	295	9.4	
2	41	1012	300	20.0	r=0.82 (P>0.05)
	6	1005	278	0.2	
	10	1009	260	0.2	
	27	1008	291	3.0	
3	33	1008	272	0.4	r=0.54 (P>0.05)
	27	1010	240	14.5	
	37	1003	260	18.5	
	43	1006	230	17.5	
	53	1007	254	15.5	
	60	1006	258	18.0	
4	66	1006	263	26.6	r=0.67 (P>0.05)
	9	1006	—	0.9	
	14	1007	233	0.6	
	20	1007	268	4.9	
	35	1002	227	1.0	
	43	1002	253	2.4	
	49	1002	271	1.5	
	57	1002	274	3.8	
5	67	1005	279	10.7	r=0.87 (P<0.05)
	22	1008	278	0.3	
	26	1012	272	8.3	
	38	1006	266	0.5	
	43	1005	279	0.2	
	48	1006	280	0.2	
6	60	1006	322	22.0	r=0.25 (P>0.05)
	14	1015	294	1.8	
	22	1015	—	1.2	
	27	1005	281	2.5	
	38	1008	295	3.3	
	51	1010	—	5.8	
	65	1010	280	0.7	
	74	1005	—	3.0	
	86	1008	295	4.6	
	92	1005	273	0.6	
7	96	—	300	6.3	
	102	1012	265	11.9	
	48	1009	267	7.7	
	57	1010	267	6.4	
8	144	—	291	0.6	
	145	—	307	0.2	
	146	1006	288	0.2	
9	27	1006	292	7.3	
	33	1005	297	7.6	
10	15	1022	327	1.4	
	76	1015	292	0.5	
11	72	1012	270	1.2	
	79	1006	—	0.8	
	84	1006	275	1.7	
	95	1008	273	0.4	
12	64	1016	261	0.5	

r=linear correlation coefficient between plasma AVP and plasma osmolality.

calculated. Blood gases and chest radiographs were performed at variable intervals depending on clinical indications. Plasma osmolality was measured on each sample using a vapour pressure microsmometer (Wescor Inc, USA). Plasma arginine vasopressin was measured by a cytochemical bioassay described previously.⁷ Ethical sanction for the project was obtained from St George's Hospital Ethical Committee.

Results

The plasma arginine vasopressin and osmolality and urine specific gravity measurements with the age of the baby are shown in Table 2. Correlation between the plasma arginine vasopressin concentration and plasma osmolality was determined only when at least four values for each were obtained for the infant. There is a significant correlation between plasma arginine vasopressin concentration and plasma osmolality in cases 1 and 5 (r=0.92, P=0.005; and r=0.87, P<0.05 respectively). Non-significant correlations (P>0.05) were obtained in cases 2, 3, 4, and 6 (r=0.82, 0.54, 0.67, and 0.25 respectively). The data from each of these babies is represented graphically in the Figure. No correlation could be found between any of the clinical parameters monitored and the plasma arginine vasopressin concentrations in any of the infants investigated. A full table of all data with the age of the baby is available from the authors by request.

Plasma arginine vasopressin concentrations ranged from 0.16 to 26.6 pg/ml with a median of 2.43 pg/ml. Plasma osmolality ranged from 227 to 327 mOsm/kg·H₂O with a median of 276 mOsm/kg·H₂O. In four infants (cases 2, 4, 5, and 6) there were intermittent peaks of plasma arginine vasopressin activity; on several occasions rising above 9 pg/ml. In one infant (case 3), who was breathing spontaneously throughout the study, there was a persistent, very high plasma arginine vasopressin concentration of 14.5 to 26.6 pg/ml.

All infants except case 10 survived. This baby developed necrotising enterocolitis and septicaemia at 3 weeks of age.

Discussion

Plasma arginine vasopressin concentrations have been shown to be highest in cord blood and fall rapidly in the first 24 hours of life, with a continuing fall over the first week, and then a rise to adult values (approximately 2 to 4 pg/ml) thereafter.^{2 4 5} The serial data presented in this study show no trends in the concentration during the first 24 hours, or in the first few days of life in any of the infants

investigated. The median plasma arginine vasopressin concentration in this study was well within the range seen in normal adults and was also similar to the other published data in the newborn using radioimmunoassay.^{2 5 8} Although most values were in the normal range, values as high as 26 pg/ml were observed. The cross sectional study by Rees *et al* in preterm infants with respiratory distress syndrome also showed large variations in plasma concentrations, with a maximum of approximately 30 pg/ml.⁵ In two infants, for whom enough serial data were available, we were able to show a strong correlation between plasma arginine vasopressin and the plasma osmolality (Figure). This is in contrast to the radioimmunoassay data of Rees *et al* who could find no such correlation.⁵ Although the four other serially sampled infants in our study did not show correlations reaching statistical significance, the regression suggested that this might be due to insufficient numbers of samples. In one infant in this study (case 10) very high plasma and urine osmolalities were seen, but circulating plasma arginine vasopressin concentrations were persistently low, this cannot be explained. No infants in our study were overtly hypotensive or hypovolaemic, thus we have no evidence to establish directly whether volume receptors are effective in the preterm infant. Rees *et al*, using urinary arginine vasopressin measurements, have shown that it is likely that the volume mechanism is functional.⁹

We know of only one previous study measuring serial plasma arginine vasopressin concentrations in the newborn. Speer *et al* showed raised plasma concentrations in term infants with birth asphyxia, and were able, with 12 hourly measurements, to show that these high concentrations fell to normal by the third day.¹⁰ We believe that the data presented in our study are the first serial plasma measurements reported in the preterm neonate.

Stresses such as asphyxia,¹¹ meningitis,¹² respiratory infections,¹³ pneumothorax,¹⁴ and intracranial and intraventricular haemorrhage,¹⁵ all of which are common in the preterm newborn, are recognised as leading to excessive secretion of arginine vasopressin in the absence of the normal physiological stimuli (syndrome of inappropriate antidiuretic hormone secretion). In five infants in our study, occasional bursts of arginine vasopressin secretion were observed which could not be correlated with any of the clinical parameters monitored. The infants all had respiratory distress, but by generally accepted management standards none were hypoxic or hypovolaemic and none developed pneumothoraces during the study. No infants in the study had a clinical intraventricular haemorrhage, but as serial intracranial ultrasound was not being performed, we have

not excluded the possibility of small intraventricular haemorrhages leading to release.¹⁵ It is possible that the release of arginine vasopressin was related to the stress of painful stimuli,¹⁶ as the babies were on ventilators. It is important to note that the surges of arginine vasopressin secretion shown were short lived and that even with the relative frequency of sampling of infants in this study, it is possible that some bursts of secretion may have been missed. Rees *et al*,¹⁷ measuring serial urinary concentrations, also showed bursts of arginine vasopressin excretion in the preterm infant. In some cases only could these be associated with the development of pneumothorax, mask ventilation, or intraventricular haemorrhage.

Although it has been reported that positive pressure ventilation may induce the inappropriate secretion of arginine vasopressin,^{18 19} it is noteworthy that the highest plasma concentrations seen in this study were in the spontaneously breathing infant (case 3, 14 to 26 pg/ml). This infant was not hypotensive or hypovolaemic. The dilute plasma osmolality and very high arginine vasopressin concentration suggested the diagnosis of syndrome of inappropriate antidiuretic hormone secretion, but urine specific gravities were persistently low. The formal criteria for the diagnosis of this syndrome could therefore only be invoked by presuming that the specific gravities were not maximally low. The condition would otherwise seem to be an end organ insensitivity to arginine vasopressin, possibly with an intact feedback.

Due to its cumbersome nature, the cytochemical bioassay for plasma arginine vasopressin can only be used for the retrospective evaluation of neonatal fluid balance, the results coming too late for direct action to be taken on the infant concerned. If any assay for plasma arginine vasopressin is going to be important in the management of the newborn, it will not only need to be as sensitive as the cytochemical assay, but also relatively rapid to perform.

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