Plasma ionised calcium in preterm infants: comparison with adults

PD MAYNE,* JA JAMES, IC BARNES,† IZ KOVAR

From the Department of Paediatrics, Queen Charlotte's Maternity Hospital, and the Departments of Child Health and Chemical Pathology, Westminster Hospital and Medical School, London

SUMMARY Plasma calcium (ionised and total) and albumin concentrations and pH were measured in preterm infants and in healthy adults and patients dependent on respirators. Plasma ionised calcium and total calcium values fell during the first week after birth and subsequently rose. Plasma ionised calcium concentrations in preterm infants were higher than those found in both healthy and sick adults. This difference was only partially explained by the lower blood pH in the infant population. There was no correlation between plasma ionised calcium or the ratio of ionised calcium to total calcium and total bilirubin concentrations. These results suggest that the metabolic control of plasma ionised calcium in preterm infants is different from that in adults.

Disorders of calcium metabolism are common in preterm infants;¹ hypocalcaemia with convulsions may present acutely within the first few days after birth, particularly if there have been complications of pregnancy or delivery.^{2,3} Late hypocalcaemia and defective bone mineralisation may occur insidiously due to inadequate dietary mineral substrate⁴ or impaired metabolism of vitamin D.⁵ The technological improvements in ion selective electrodes permits the rapid and precise bedside measurement of plasma ionised calcium, the biologically active fraction of plasma calcium.⁶ There is little information on the relation between plasma ionised calcium and total calcium in the preterm infant; better understanding of ionised calcium is necessary before this measurement can be introduced into standard clinical practice.

We have compared plasma ionised calcium concentrations in preterm infants and selected matched adults, with the aim of determining whether the accepted conventions on the relation of plasma ionised calcium to total calcium, albumin, and acid-base changes apply equally to the preterm infant.

Patients and methods

Three groups of preterm infants were studied and

compared with two adult groups. All infants were born at less than 34 weeks' gestation, weighed less than 1.4 kg, and were admitted to a single special care baby unit. Sick and well infants were included, but no infant had clinical, biochemical, or radiological evidence of rickets.

The infant groups were: group I (n = 12), less than one week of age; group II (n = 12), more than one week of age (range 1-6 weeks) but with no vitamin D prophylaxis; and group III (n = 12), infants receiving either 400 or 1000 IU of calciferol BP, age range 2-17 weeks.

Two groups of adults were studied: group IV (n = 12), healthy volunteers, and group V (n = 9), respirator dependent patients receiving intensive care who were hypoalbuminaemic but non-nephrotic. This latter group was included as a comparative group because many of the preterm infants are dependent on respirators with relative hypoalbuminaemia.

Arterialised plasma ionised calcium and pH were measured by ion selective electrodes (ICA-1 Radiometer A/S, Copenhagen, Denmark). The between day percentage coefficient of variation for ionised calcium was 1.35% and for pH less than 1%. Plasma total calcium was assayed by a manual cresolphthalene compleximetric method with a between batch coefficient of variation of 2%; plasma inorganic phosphate by a molybdate reduction method with a between batch coefficient of variation of 4%; and plasma albumin by an automated immunoprecipitation technique with a between batch

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*Present address: Department of Chemical Pathology, Royal Free Hospital, London.

†Present address: Department of Chemical Pathology, Bristol Royal Infirmary, Bristol.

Plasma ionised calcium concentrations in preterm infant and adult groups.

coefficient of variation of 1%. Plasma total bilirubin concentration was measured in group I by a bilirubinometer (American Optics) in order to determine whether there is any competitive interference between bilirubin and calcium for binding to plasma carrier proteins.

Biochemical variables in preterm infants and adult groups

	Infants			Adults	
	Group I	Group II	Group III	Group IV	Group V
No of patients	12	12	12	12	9
Postnatal age (wk)	0.55 ± 0.06	2.8 ± 0.47	8.2 ± 1.50		
Ionised calcium (mmol/l)	1.23 ± 0.06	1.40 ± 0.02	1.36 ± 0.02	1.27 ± 0.01	1.16 ± 0.03
	0.94 - 1.61	1.34 - 1.51	1.21 - 1.45	1.23 - 1.32	1.00 - 1.24
Total calcium (mmol/l)	1.90 ± 0.18	2.36 ± 0.04	2.34 ± 0.03	2.40 ± 0.02	2.20 ± 0.03
	1.57 - 2.75	2.03 - 2.50	2.08 - 2.50	2.31 - 2.55	2.04 - 2.29
Ionised calcium/total calcium (%)	60.5 ± 1.50	59.1 ± 1.04	58.2 ± 0.68	52.5 ± 0.29	52.8 ± 0.62
	49.8 - 71.9	54.8 - 68.5	53.3 - 61.4	51.0 - 54.5	48.3 - 55.8
Inorganic phosphate (mmol/l)	2.18 ± 0.06	2.18 ± 0.05	2.12 ± 0.05	1.24 ± 0.01	1.18 ± 0.02
pH	1.86 - 2.75	1.95 - 2.63	1.82 - 2.40	1.23 - 1.29	1.02 - 1.27
	7.33 ± 0.01	7.34 ± 0.01	7.33 ± 0.01	7.36 ± 0.01	7.42 ± 0.02
Albumin (g/l)	7.27 - 7.37	7.29 - 7.42	7.26 - 7.38	7.32 - 7.39	7.33 - 7.49
	29.3 ± 1.34	29.2 ± 1.28	30.2 ± 0.82	39.8 ± 0.62	26.2 ± 1.97
	18 - 36	22 - 35	26 - 37	36 - 42	18 - 36

Values given as mean ± SEM and range.

Statistical analysis was carried out using Student's *t* test, and correlation coefficients were determined by the method of least squares.

The study was approved by the hospital ethical committee, and informed consent was obtained from the parents of all infants and from the adult patients.

Results

The mean plasma ionised calcium, total calcium, inorganic phosphate, and albumin concentrations for all groups are given in the Table.

Plasma total calcium and ionised calcium values were lower in group I compared with either of the older infant groups ($p < 0.01$). There was no correlation between plasma ionised calcium or the percentage ratio of ionised calcium to total calcium and total bilirubin. The mean ($\pm$ standard deviation) for plasma total bilirubin in this group was $252 \pm 26 \mu\text{mol/l}$ (range 51–370 $\mu\text{mol/l}$).

There was no difference in any of the biochemical variables between group II and III. The range of plasma ionised calcium concentrations in the combined groups II and III was 1.21–1.51 mmol/l compared with 1.23–1.32 mmol/l in the healthy adults (group IV). The percent ratio of ionised calcium to total calcium was higher in the infant groups ($p < 0.01$), but the plasma pH was lower ($p < 0.01$). When the plasma ionised calcium concentrations in infants in groups II and III were matched with those in adults who had the same blood pH the plasma ionised calcium and the percent ratio of ionised calcium to total calcium remained significantly higher in the preterm infants ($p < 0.01$).

There was no difference in plasma inorganic phosphate values between any of the infant groups, although the concentration was increased ($p < 0.01$).

compared with the two adult groups. There was no correlation between inorganic phosphate and ionised calcium or inorganic phosphate and the percent ratio of ionised calcium to total calcium in any of the groups.

In infants older than one week there was a positive correlation between ionised calcium and total calcium concentrations ($r = 0.47$, $p < 0.005$), but the correlation between ionised calcium and hydrogen ion concentrations and between total calcium and albumin concentrations did not reach statistical significance. In the combined adult groups (IV and V) there was a positive correlation between ionised calcium and total calcium concentrations ($r = 0.86$, $p < 0.001$), between total calcium and albumin concentrations ($r = 0.72$, $p < 0.001$), and between ionised calcium and hydrogen ion concentrations ($r = 0.61$, $p < 0.005$).

Discussion

Plasma biochemical variables may alter significantly with increasing postnatal and postconceptional age in newborn infants. Biochemical values found in adults and in older children are often applied to preterm infants, but they may not be appropriate for this age group. In our study sick and well preterm infants were considered together to form a representative population of a special care baby unit.

The lowest plasma calcium concentrations (ionised calcium and total calcium) in this study were seen in the first week after birth (group I); a plasma ionised calcium concentration of 0.94 mmol/l (total calcium 1.57 mmol/l , pH 7.37) was recorded in one asymptomatic preterm infant. Early neonatal hypocalcaemia is probably due to transient functional hypoparathyroidism of the normal neonate.^{1*} Increased placental transfer of calcium during the last trimester of pregnancy exceeds the fetal threshold of parathyroid hormone release, resulting in transient parathyroid gland suppression.

The plasma total calcium concentration was within the childhood reference range by the second postnatal week; the ionised calcium value at this time was higher than that seen in adults. The explanation for this absolute increase in ionised calcium and the increased ratio of ionised calcium to total calcium noted in preterm infants is not clear, but it is only partially explained by the lower blood pH often found in this age group. The relation persists when an allowance is made for blood pH. Possible explanations include altered calcium binding affinity for carrier proteins in the preterm infant or alteration in the negative feedback control of ionised calcium on parathyroid hormone release. The absence of any correlation between plasma total bilirubin and ion-

ised calcium concentrations or the ratio of ionised calcium to total calcium supports the concept that bilirubin does not interfere with or displace calcium binding to carrier proteins.

It is unlikely that inorganic phosphate concentrations affect ionised calcium in the preterm infant. There was no evidence of phosphate depletion in the infant groups.

There was no difference in plasma ionised calcium or total calcium concentrations between the two older infant groups. This does not necessarily imply that calciferol prophylaxis (400 IU or 1000 IU calciferol BP per day) does not positively affect plasma calcium concentrations and bone metabolism, as the two groups are not comparable for age. It has been recently reported, however, that high dose ergocalciferol (2000 IU/day) does not prevent rickets developing in very low birthweight infants.⁹

Our study shows that plasma ionised calcium concentrations fall in the first week after birth but subsequently increase and are higher than those seen in healthy and sick adults; the difference is only partially explained by the lower blood pH. The control of calcium metabolism and in particular plasma ionised calcium concentrations differ in preterm infants and adults.

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Requests for reprints to: Dr IZ Kovar, Department of Paediatrics, Charing Cross Hospital Medical School, Fulham Palace Road, London W6, England.