Acid-base state of the preterm infant and the formulation of intravenous feeding solutions

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Abstract

An acidic intravenous source of phosphorus (Addiphos) was compared with dipotassium hydrogen phosphate in 25 preterm infants to study acid-base state. Eight infants were given either Addiphos or dipotassium hydrogen phosphate alternately for 48 hour periods and similar amounts of calcium and phosphorus were delivered. There were no significant differences in calcium and phosphorus intake, calcium and phosphate plasma concentrations, or acid-base state between study periods on the two solutions. Seventeen infants were given the two solutions alternately for 72 hour periods; Addiphos was used to increase the amounts of calcium and phosphorus being delivered. Calcium and phosphorus intake was decreased on dipotassium hydrogen phosphate, but Addiphos significantly increased calcium and phosphorus intake and plasma calcium and phosphate concentrations. It also lowered the pH of the urine and raised the titratable acidity. Acid-base state, however, was not significantly different.

It is therefore possible to increase intake of calcium and phosphorus in preterm infants without causing a significant metabolic acidosis.

Metabolic bone disease is common in the sick preterm infant on intravenous alimentation.¹ An increased intravenous mineral intake decreases the incidence of this disorder.² In the third trimester the in utero accretion of calcium and phosphorus approximates 2.5-3.0 and 2.0-2.5 mmol/kg/day respectively.³ Some authors have claimed that it is not possible to deliver comparable amounts of mineral in an intravenous solution at a physiological pH (7.4) because of dibasic calcium-phosphate precipitation.⁴ Few parenteral solutions have a pH near 7.4; the pH of 5% dextrose, for example, varies between 3.5 and 5.5,⁵ and intravenous feeding solutions themselves are invariably mildly acidic.⁶

The calcium and phosphorus content of an intravenous feeding solution can be increased by using a mildly acidic source of phosphorus during formulation in vitro, but at the expense of increasing the titratable acid load.⁷ We wished to test the hypothesis that an increase in hydrogen ion load would enable calcium and phosphorus to be infused at in utero accretion levels, and yet not have any deleterious effect on the acid-base state of the preterm infant.

Patients and methods

Twenty five preterm infants who were admitted to a single neonatal intensive care unit and who required both ventilatory support and parenteral nutrition were studied. The prescription and formulation of parenteral nutritional solutions were assisted by modification of a pre-existing computer protocol.⁸ Calcium was supplied as 10% calcium gluconate in the trace element preparation (Ped-El, KabiVitrum) and in the amino acid solution (Vamin 9 glucose, Kabi-Vitrum). Phosphorus was supplied in the trace element preparation (Ped-El) and as either 8.7% dipotassium hydrogen phosphate (pH 8.8), or as Addiphos (KabiVitrum, pH 7.02).

The infants were randomly allocated to receive initially either 8.7% dipotassium hydrogen phosphate or Addiphos at 8 days of life. This was then alternated every 48 hours (part I) or 72 hours (part II). The interval during which the phosphorus source was kept constant was termed a 'study period'. At the end of each study period the overall acid-base state of the infant was assessed by calculating the mean blood pH, carbon dioxide pressure, standard bicarbonate, and base excess measurements during the last 24 hour period. The urinary pH and titratable acidity/mmol creatinine were determined in a random urine sample at the end of each study period.

Plasma calcium phosphate concentrations were assayed every 48 hours using approved methods on a Parallel Analyser (American Monitor Corporation). Blood gas estimations were assayed at least every four hours while the infant received assisted ventilation, using an IL-1302 blood gas analyser (Instrumentation Laboratories). The pH of each urine specimen voided was measured to one decimal place using pH indicator strips (British Drug Houses). The urine titratable acidity was determined by titrating a known volume of urine to pH of 7.4 using 0.025M sodium hydroxide.

PART I

This part of the study was designed to compare the affect of using either 8.7% dipotassium hydrogen phosphate or Addiphos on the acid-base state while delivering similar amounts of calcium and phosphorus. The eight infants studied had a median birth weight of 1080 g (range 870-1640 g) and a median gestational age of 29.0 weeks (range 27.0-29.5). There were 30, 48 hour study periods using 8.7% dipotassium hydrogen phosphate (group 1) and 29 using

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Table 1 Part I: comparison of intravenous intake, plasma values, and acid-base state in the 48 hour study periods in which the infants received either 8.7% dipotassium hydrogen phosphate or Addiphos to deliver equal amounts of calcium and phosphorus. Results are mean (SD)

	Group 1 (n=30)	Group 2 (n=29)	p Values
Phosphorus source	Dipotassium hydrogen phosphate	Addiphos	
Intake:			
Calcium (mmol/kg/day)	1.27 (0.35)	1.28 (0.30)	NS
Phosphorus (mmol/kg/day)	1.22 (0.31)	1.26 (0.27)	NS
Dextrose (MJ/kg/day)	0.21 (0.03)	0.21 (0.04)	NS
Vamin 9 glucose (ml/kg/day)	44.30 (7.04)	46.90 (7.01)	NS
Lipid (g/kg/day)	1.99 (1.01)	2.12 (1.20)	NS
Plasma:			
Calcium (mmol/l)	2.35 (0.18)	2.40 (0.15)	NS
Phosphate (mmol/l)	1.54 (0.40)	1.48 (0.13)	NS
Blood:			
pH	7.32 (0.04)	7.33 (0.05)	NS
Carbon dioxide pressure (kPa)	6.07 (0.80)	6.00 (0.80)	NS
Standard bicarbonate (mmol/l)	22.60 (1.08)	22.60 (1.07)	NS
Base excess (mmol/l)	-2.70 (4.06)	-2.50 (4.04)	NS
Urine:			
pH	5.25 (0.39)	5.20 (0.81)	NS
Titratable acidity (mmol/mmol creatinine)	6.12 (2.55)	5.54 (2.02)	NS

Table 2 Part II: comparison of intravenous intake, plasma values, and acid-base state in the 72 hour study periods in which the infants received either 8.7% dipotassium hydrogen phosphate or Addiphos to deliver significantly increased amounts of calcium and phosphorus. Results are mean (SD)

	Group 3 (n=35)	Group 4 (n=32)	p Values
Phosphorus source	Dipotassium hydrogen phosphate	Addiphos	
Utate:			
Calcium (mmol/kg/day)	0.67 (0.25)	1.63 (0.48)	<0.001
Phosphorus (mmol/kg/day)	0.60 (0.13)	1.38 (0.40)	<0.001
Dextrose (MJ/kg/day)	0.23 (0.07)	0.22 (0.07)	NS
Vamin 9 glucose (ml/kg/day)	35.00 (7.03)	37.00 (5.90)	NS
Lipid (g/kg/day)	2.20 (1.38)	2.24 (1.23)	NS
Plasma:			
Calcium (mmol/l)	2.33 (0.20)	2.47 (0.23)	<0.05
Phosphate (mmol/l)	1.30 (0.33)	1.60 (0.32)	<0.005
Blood:			
pH	7.32 (0.05)	7.30 (0.05)	NS
Carbon dioxide pressure (kPa)	6.27 (0.87)	6.13 (0.76)	NS
Standard bicarbonate (mmol/l)	23.29 (2.3)	22.07 (1.80)	<0.05
Base excess (mmol/l)	-1.50 (4.55)	-2.15 (6.45)	NS
Urine:			
pH	5.56 (0.71)	5.22 (0.47)	<0.02
Titratable acidity (mmol/mmol creatinine)	5.49 (1.89)	8.06 (2.25)	<0.001

Addiphos (group 2). Amino acid solution was infused to a maximum rate of 50 ml/kg/day.

PART II

This part was designed to test the affect on the acid-base state using Addiphos in order to deliver increased calcium and phosphorus. Seventeen infants were studied with a median birth weight of 1120 g (range 750–1500 g) and a median gestational age of 28.5 weeks (range 24.0–30.0). The amino acid infusion rate was reduced to a maximum of 40 ml/kg/day because of concern about hyperphenylalaninaemia, which had been reported coincidentally during the conduct of this study. This change altered the solubility limits of calcium and phosphorus thereby limiting the amount of calcium and phosphorus that could be delivered if 8.7% dipotassium hydrogen phosphate was used.⁶ There were 35, 72 hour study periods using 8.7% dipotassium hydrogen phosphate (group 3) and 32 using Addiphos (group 4).

The last 24 hours of each study period in both parts were analysed and each period was treated as an independent event. The results were expressed as mean (SD). Tests of significance were performed using the Student's *t* test.

The study was approved by the hospital ethics committee.

Results

In part I, there was no significant difference between groups 1 and 2 for overall calcium and phosphorus infusion, plasma calcium and phosphate concentrations, or the indices of acid-base state in either blood or urine (table 1).

In part II, the calcium and phosphorus intake was decreased in group 3 when 8.7% dipotassium hydrogen phosphate was used as the source of phosphorus. When using Addiphos, however, the amounts of calcium and phosphorus infused were significantly increased as were both the plasma calcium and phosphate concentrations (table 2). There was no significant difference in blood acid-base state between groups 3 and 4, with the exception of a small difference in the calculated standard bicarbonate, which remained within the reference range of 21–30 mmol/l. During the study period in which Addiphos was used, the pH of the urine was significantly lower ($p<0.02$) and titratable acidity higher ($p<0.001$) than when 8.7% dipotassium hydrogen phosphate was used.

Discussion

We are not aware of a comparable study in which the ability of a preterm infant to tolerate an increased hydrogen ion infusion load was tested. Although metabolic acidosis is a recog-

nised complication of parenteral nutrition, the incidence has been reduced by using crystalline amino acid preparations when compared with the earlier protein hydrolysate solutions.⁹

An increased hydrogen ion load is buffered in blood and excreted in urine. Urinary pH reflects the acidity, but not the buffering capacity of the urine. Urinary titratable acidity is a more appropriate assessment of the total hydrogen ion excretion. Measuring the pH from a random urine sample introduces further inaccuracies. Obtaining accurate 24 hour urine collections repeatedly can be difficult, particularly in infant girls. We felt it appropriate to measure urinary titratable acidity in relation to creatinine excretion, in order to obtain comparative results.

There was no change in acid-base state in the infants given Addiphos rather than 8.7% dipotassium hydrogen phosphate despite the increased hydrogen ion infusion load. The amount of calcium and phosphorus that could be delivered is increased if the rate of amino acid infusion is increased as the extra hydrogen ion load alters their solubility. High infusion rates of amino acids may, however, be associated with hyperphenylalaninaemia.¹⁰ The amount of calcium and phosphorus that could be infused in part II using 8.7% dipotassium hydrogen phosphate as the phosphorus source was less compared with Addiphos, which is the more acidic agent. The increased hydrogen ion load associated with the use of Addiphos did not produce a metabolic acidosis, and the extra load was successfully excreted in the urine. Whether

or not the more prolonged use of relatively acidic, high calcium, high phosphorus parenteral nutrition protocol could be associated with nephrocalcinosis will have to be borne in mind in future studies.

These studies demonstrate that it is possible to increase significantly the intravenous intake of calcium and phosphorus in the preterm infant by using an acidic source of phosphorus without causing a significant metabolic acidosis.

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