Ca, P balance in ELBW infants on aggressive AA infusion in TPN

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Question

A 585 g neonate is delivered at 24 weeks of gestation. On the first day following birth, parenteral nutrition includes an amino acid provision of 3.0 g/kg per day and a plan to advance by 0.5 g/kg per day to a goal of 4 g/kg per day. Enteral feeds of maternal milk are initiated at a volume of 10 mL/kg per day.
Of the following, parenteral amino acid supplementation places this neonate at risk for

A. hyperphosphaturia

B. hypocalcemia

C. hypocalciuria

D. hypophosphatemia

Correct Answer: D

Discussion

How does aggressive AA infusion in ELBW infant lead to Ca, P imbalance?

Provision of appropriate substrates and early initiation of parenteral nutrition can optimize growth and development of the extremely preterm infant. To avoid cellular catabolism and promote growth, a recommended administration regime for amino acids begins with 2 to 3 g/kg per day, and advances 0.5 to 1 g/kg per day for the preterm infant, with a goal of 3.5 to 4 g/kg per day. Early and aggressive provision of amino acids does not lead to azotemia, hyperammonemia, or metabolic acidosis.

However, amino acid intake in the growing infant is associated with increased demand for phosphorus. **For each gram of protein (nitrogen) retained, 0.3 mmol (10 mg) of phosphate is required for soft tissue accretion**.
When phosphate is taken up by the cells but inadequately supplied in parenteral (or enteral) nutrition, serum phosphate concentrations decrease, triggering phosphate release from bone and decreased urinary phosphate excretion. In this situation, calcium is simultaneously mobilized, leading to excess calcium in the extracellular space, hypercalcemia, and hypercalciuria.
In the term newborn, total body phosphorus comprises approximately 0.6% of body weight. Approximately 80% of phosphorus is accumulated in the fetus during the last trimester via active sodium-dependent transplacental transport. Fetal accretion occurs at a rate of 75 mg/kg per day, and 75% of transferred phosphorus is directed toward bone mineralization. In the body, 85% of phosphorus is found in bone, primarily as hydroxyapatite. The remaining 15% of total body phosphorus is located in the extracellular fluid, largely as inorganic phosphate ions.
Phosphate is the main anion in the intracellular space and facilitates cellular functions such as DNA and membrane lipid synthesis, energy metabolism, and intracellular signaling.
Normal serum phosphate concentration is higher in infants than adults:

- Preterm infant: 4 to 8 mg/dL (1.3-2.6 mmol/L)
- Term infant: 5.6 to 8.4 mg/dL (1.8-2.7 mmol/L)
- Adult: 3 to 4.5 mg/dL (1-1.5 mmol/L)

Circulating phosphate is a reflection of intestinal phosphorus absorption, storage in the skeleton, and renal phosphate reabsorption.
Parathyroid hormone (PTH) is the main regulator of phosphate homeostasis via receptors in bone and kidney. Parathyroid hormone increases renal phosphate clearance and stimulates $1,25(OH)_2D$ synthesis, which in turn stimulates intestinal phosphorus absorption. In the bone, PTH indirectly increases osteoclast activity via PTH receptors on osteoblasts, thereby releasing phosphate into the circulation. Parathyroid hormone is upregulated by increased serum phosphate concentrations, but primarily responds to decreased serum calcium concentrations.
Renal excretion is the major determinant of circulating phosphate. Phosphate is freely filtered at the glomerulus and most filtered phosphate is reabsorbed in the proximal tubule via an active and saturable reabsorption process that maintains serum phosphate at close to tubular phosphate threshold. Parathyroid hormone and fibroblast growth factor 23 (FGF23), which is produced by osteocytes, maintain tight hormonal control of renal reabsorption. During periods of growth, the kidneys contribute to a positive phosphate balance by reabsorption of a relatively high fraction of filtered phosphate (up to 99% in newborns). In the preterm neonate, phosphate is totally reabsorbed up to a plasma concentration of approximately 5 mg/dL (1.6 mmol/L), thereby representing the reference value for defining hypophosphatemia. In adults, whose phosphorus needs are lower, the reference value for hypophosphatemia is approximately 3 mg/dL (1 mmol/L).
Phosphorus needs are increased for the growing infant, owing to phosphate deposition in both lean body mass and bone. In the neonate in a state of positive nitrogen balance, phosphate preferentially goes to soft tissues with a nitrogen-to-phosphate (weight) ratio of 16:1 (approximately 0.33 mmol [10 mg] for each gram of protein retention), and then to bone with a calcium-to-phosphate (weight) ratio of 2.15:1. Therefore, phosphorus needs are closely related to both calcium intake and protein accretion.
Early and aggressive parenteral nutrition for the extremely low birth weight neonate intentionally places the infant in a state of tissue anabolism. However, enhanced provision of amino acids (nitrogen) necessarily increases phosphorus demand. During the first week after birth and with increasing protein intake, parenteral nutrition with calcium-to-phosphorus molar ratios between 1.2 and 2 can result in hypophosphatemia. The incidence of hypophosphatemia has been directly related to protein intake and inversely related to calcium-to-phosphorus ratio in parenteral nutrition. That is to say, serum phosphorus decreases as the ratio of calcium to phosphorus in the parenteral nutrition increases. During the first week after birth, with an optimal protein accretion rate of 2 to 2.5 g/kg per day and a calcium intake of 1 to 2 mmol/kg, the ideal calcium-to-phosphorus ratio may be estimated between 0.8 and 1. A similar phenomenon of phosphorus deprivation may occur in enterally fed preterm infants when protein supplementation is not accompanied by an appropriate modification of the calcium-to-phosphorus ratio.

PREP Pearls

- Early and aggressive parenteral provision of amino acids in the extremely low birth weight infant can lead to increased phosphorus demands and hypophosphatemia.

American Board of Pediatrics Content Specification(s)

- Know the changing requirements of calcium and phosphorous by the neonate at various gestational ages
- Know the nutritional composition of parenteral solutions
- Know the importance of protein and non-protein nutrients in achieving optimal utilization of energy and nitrogen
- Recognize the causes and clinical manifestations of metabolic complications of parenteral nutrition

Suggested Readings

- Bonsante F, Iacobelli S, Latorre G, et al. Initial amino acid intake influences phosphorus and calcium homeostasis in preterm infants – it is time to change the composition of the early parenteral nutrition. *PLoS One*. 2013;8(8):e72880. doi: http://dx.doi.org/10.1371/journal.pone.0072880
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- Senterre T, Zahirah IA, Pieltain C, de Halleux V, Rigo J. Electrolyte and mineral homeostasis after optimizing early macronutrient intakes in vlbw infants on parenteral nutrition. *J Pediatr Gastroenterol Nutr*. 2015;61(4):491-498. doi: http://dx.doi.org/10.1097/MPG.0000000000000854