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Phosphorus and phosphate metabolism in veterinary patients

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Abstract

Objective: To review phosphorus and phosphate metabolism and the importance of phosphate abnormalities in veterinary patients.

Data sources: A review of recent human and veterinary medical literature.

Human data synthesis: There is a significant amount of original research on human patients with phosphate abnormalities. Hypophosphatemia has been studied in patients with diabetic ketoacidosis (DKA), head trauma, refeeding syndrome, hypothermia and in ventilator patients that fail to wean. Hyperphosphatemia has been studied in patients with renal failure and malignancy. Phosphate levels have also been evaluated for prognostic value in sepsis and acute liver failure.

Veterinary data synthesis: Although animal models were used in early experimental research, fewer studies have been published on the effects of phosphate abnormalities in veterinary patients. Hypophosphatemia has been studied in animals with DKA, with refeeding syndrome and with hyperparathyroidism. Hyperphosphatemia has been studied in animals with renal failure and with secondary hypoparathyroidism.

Conclusion: Phosphorus and phosphate are important in many biological functions. This paper is a review of their role in normal metabolism and the clinical importance of phosphate imbalances for our emergency and critical care patients.

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Introduction to Phosphorus and Phosphate

Elemental phosphorus, a non-metallic substance, is the 11th most abundant element in Earth's crust.[1] Phosphorus was discovered in 1669 by Hennig Brand during his attempts to make gold from silver.[1] The name phosphorus comes from Greek word 'phos' (light) and 'phoros' (bearer).[1] Many phosphorus compounds store and emit light.[1]

Phosphorus does not occur in a free state.[1] It is usually found as phosphate salts in phosphate rock, apatite, water and fertile soil, as well as an important component of all plants and animals.[1] Phosphorus is prepared by heating calcium phosphate rock with sand and coke in an electric furnace at very high heat.[1] Phosphorus has an atomic number 15, atomic mass of 30.97376 with 5 electrons in its outer energy level.[1] It is very unstable, spontaneously ignites in the presence of air at 34 °C and must be stored under water.[1] There are 3 forms of phosphorus (allotropes): white (ordinary) phosphorus, red phosphorus and black phosphorus.[1] White phosphorus is extremely poisonous. At temperatures between 230 and 300 °C, in absence of air, white phosphorus converts to red phosphorus, which is crystalline and non-toxic.[1] Black phosphorus is made by heating white phosphorus to 200 °C under high pressure and is not considered commercially or biologically important.[1] Among its many uses, white phosphorus is used in making rat poison and red phosphorus is used in making matches.[1]

The most important biological chemical compounds of phosphorus are phosphoric acid (H_3PO_4) and the salts of H_3PO_4, which are called phosphates.[1] White phosphorus may react with oxygen to form oxides such as phosphoric oxide, which in turn reacts with water to form H_3PO_4.[1] Phosphates are salts formed by replacement of some or all of hydrogens in H_3PO_4 with other substances.[2] In animals, phosphates are often compounds of calcium, sodium and potassium.[1]

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Phosphorus and Phosphate Physiology

A large percentage of total body phosphorus (approximately 85%) is in the form of organic phosphate stored as hydroxyapatite ($Ca_{10}(PO_4)_6OH_2$), the major component of bone and teeth.[3–6] A smaller amount of organic phosphate is part of the chemical structure of phospholipids, phosphoproteins, phosphoglycides, nucleic acids and nucleotides.[3,4,6–9] Phospholipids such as phosphatidylcholine, phosphatidylserine, phosphatidylethanolamine and sphingomyelin are major structural components of cellular membrane bilayers.[3,4] They also function in ion channels contributing both structure and ionic charge, and in cellular signaling pathways that require the phosphorylation of enzymes.[4] Phospholipids and phospholipases are also required for platelet aggregation and in activation of factors X and V of the clotting cascade.[4]

Organic phosphates contribute energy from the metabolic cleavage of their high-energy phosphate bonds for maintaining membrane integrity and for powering metabolic pathways.[10] These compounds include adenosine triphosphate (ATP), guanosine triphosphate (GTP), cyclic adenosine monophosphate (cAMP) and phosphocreatinine. In addition to its role in red blood cell membrane structure and metabolic pathways, phosphate is a major component in the formation of 2,3 diphosphoglycerate (2,3-DPG), which is required for the normal release of oxygen from hemoglobin at the tissue level.[4]

Approximately 14–15% of the total body phosphate is intracellular.[5] The intracellular organic phosphates are the most abundant intracellular anions. Less than 1% of the total body phosphate is active extracellularly in plasma.[4,5,7]

Organic phosphates comprise two-thirds of total plasma phosphate, usually in the form of phospholipid.[11] One-third of total plasma phosphate exists as inorganic phosphate anion.[11] Measured inorganic phosphate includes all forms of H_3PO_4, i.e. H_3PO_4, $H_2PO_4^-$ and HPO_4^{2-}. These are measured and reported by laboratory analyzers as inorganic phosphorus (Pi).[5,9]

Normal total plasma concentration of Pi in adult humans is 3.9 mmol/L.[4] Normal plasma values in dogs and cats is 2.9–5.3 mg/dL depending upon chemistry analyzers and age of animal.[12] Young animals have the highest levels. Plasma Pi decreases into early adulthood and then gradually increases with age.[11,13]

Eighty-five percent of inorganic phosphate ion circulates unbound or 'free,' existing as HPO_4^{2-} or $H_2PO_4^-$, depending upon the acid-base status of the patient.[11] Phosphate is an effective buffer due to pKa within normal physiologic pH intracellularly, extracellularly and within the renal tubules. At pH of 7.40, the ratio of HPO_4^{2-} to $H_2PO_4^-$ is approximately 4:1 with a pKa of 6.8.[4,5,11] In the presence of increased acidity, $H_2PO_4^-$ will accept H^+ to become H_3PO_4 (pKa 2.0). Alternatively, in alkaline states, HPO_4^{2-} will dissociate to PO_4^{3-} (pKa 12.4).[5,9]

$$PO_4^{3-} + H^+ \overset{\text{pKa 12.4}}{\longleftrightarrow} HPO_4^{2-} + H^+ \overset{\text{pKa 6.8}}{\longleftrightarrow} H_2PO_4 + H^+ \overset{\text{pKa 2.0}}{\longleftrightarrow} H_3PO_4$$

Of the remaining 15% of inorganic phosphate, 10% is protein bound and 5% is complexed with either calcium or magnesium.[4,5,11] Serum phosphate is slightly higher than plasma concentrations due to release of phosphate from platelets and other cells during clotting.[11] Plasma concentrations are maintained within a narrow range. However, variations occur diurnally in people with peak levels early in the morning and the nadir approximately 7 hours later.[5,14]

Phosphate Absorption and Excretion

Daily dietary phosphate intake for humans is approximately 700–1600 mg.[4,8,14–16] Daily requirements for dogs vary with breed size and stage of growth. Pet foods generally contain from 0.8% to 1.6% phosphorus based upon a dry matter with a calcium to phosphorus ratio of approximately 1.2–2:1.[17,18] Absorption occurs in the duodenum and jejunum under the control of vitamin D_3.[4,15] Ten percent of phosphorus intake is excreted by the gastrointestinal tract.[8] Ninety percent is renally excreted.[4,8] Under normal conditions, net total body phosphate levels remain tightly controlled and vary little with daily variations in diet.[3,14]

Parathyroid hormone (PTH) and cholecalciferol (vitamin D_3) regulate movement of phosphate in and out of bone and the gastrointestinal tract.[10,18,19] PTH increases reabsorption of phosphate (and calcium) from bone and increases gastrointestinal phosphate absorption.

Intestinal absorption is inhibited by glucocorticoids, dietary magnesium and by hypothyroidism. Decreased vitamin D synthesis or vitamin D resistance can result in decreased intestinal absorption of phosphorus.[15]

Although the plasma phosphate level fluctuates with various metabolic conditions, total body phosphate is regulated by the kidneys.[10] Phosphate is freely filtered by the glomerulus.[16] Eighty to ninety-five percent is reabsorbed by the proximal tubule and a small amount is reabsorbed by the distal tubule.[4,9,15] Phosphate transport occurs against an electrochemical gradient via the type II sodium-dependant phosphate co-transporter, NPT2a, located in the brush border of tubular cells.[9,19] This is the rate-limiting step in phosphate reabsorption.[20] Phosphate is then transported into the bloodstream by a carrier down its electrochemical gradient.[10,19] The amount of NPT2a co-transporter expressed on the apical membrane of the tubule cells is regulated by PTH,[16]

fibroblast growth factor 23 (FGF-23) and intestinal absorption of phosphate.[10] Decreased absorption of intestinal phosphorus, leading to decreased blood phosphate, will stimulate increased expression of NPT2a co-transporter protein and increased reabsorption of phosphate from the urine.[10] Increased levels of PTH cause endocytosis of NPT2a membrane protein into lysosomes for destruction resulting in decreased phosphate reabsorption and increased excretion.[10,19] The presence of NPT2a co-transporter is also inhibited by metabolic acidosis.[4]

Several genes have been identified that regulate phosphate such as PHEX (phosphate regulating gene with homologies to endopeptidases on the X chromosome) and FGF-23.[14,21] PHEX expression occurs in bone and teeth but not kidney. FGF-23 may be a substrate for the PHEX endopeptidase and affect renal phosphate excretion.[14,21,22] If FGF-23 is injected into mice it causes decreased levels of NPT2a co-transporter and 25-hydroxyvitamin D 1α-hydroxylase resulting in hypophosphatemia.[10,22,23] Mice lacking FGF-23 have hyperphosphatemia and high levels of 1,25 dihydroxyvitamin D3.[10,20,24] Patients with chronic hyperphosphatemia (hypoparathyroidism) have elevated serum FGF-23 levels.[25] It is postulated that 'FGF-23 is a potent regulator of phosphate and vitamin D homeostasis.'[24]

Two other classes of Na/Pi transporters have been identified. Type I, NPT1, may function in modulation of intracellular inorganic phosphate transport. Type III GLVR-1 and RAM-1 transporters are expressed in the basolateral membrane of the kidney. Their exact function is not well defined.[5]

Other isoforms of sodium-dependent phosphate co-transporters (NPT2) have also been recently identified. Type IIb NPT2b is located in the small intestine and is regulated by vitamin D3. Type IIc, NPT2c is located in the apical brush border but not regulated by PTH.[20,26]

Renal reabsorption of phosphate is stimulated by other factors including insulin-like factor growth-1 (ILFG-1), insulin, epidermal growth factor, growth hormone, thyroid hormone and calcitrol.[14] In addition to PTH, renal reabsorption is decreased by PTH-related peptide, atrial natriuretic factor, glucocorticoids, calcitonin, and transforming growth factors α and β.[14] In rats, blockade of renal serotonin receptors has been shown to decrease phosphate resorption.[27] Hyperparathyroidism-associated hypophosphatemia occurs due to renal phosphate wasting secondary to elevated levels of PTH.[15]

Phosphate Abnormalities

Phosphate imbalance can occur even though total body phosphate levels are normal.[4,15,19] Imbalances can occur as part of common medical disorders or may be secondary to standard medical treatment.[4,8,14] Animals at risk for developing significant clinical, and potentially life-threatening symptoms, include those with diabetic ketoacidosis (DKA), sepsis, head trauma, respiratory disease, metabolic or respiratory alkalosis, those receiving total parenteral nutrition, hyperparathyroidism and in refeeding syndrome. It has been suggested in the human literature that hypophosphatemia may be an early predictor of poor clinical outcome for acute liver failure and for septic patients.[28]

Pathophysiology of Hypophosphatemia

Hypophosphatemia is generally considered to be a serum level less than 2.5 mg/dL. If hypophosphatemia is mild to moderate (1.0–2.0 mg/dL) symptoms are usually vague and may include generalized weakness, disorientation, anorexia and joint pain. When severe hypophosphatemia is present (<1.0 mg/dL), life-threatening symptoms may be present including acute respiratory failure, seizures, coma, cardiac arrhythmias and hemolysis.[8,15] At serum levels less that 0.5 mg/dL, there is interference with glycolysis.[15] Symptoms may be secondary to decreased production of ATP resulting in decreased energy production, decreased enzyme production, and loss of sodium-potassium ATPase pump function.[4,15] Disruption of cellular membranes occurs due to decreased phospholipid production and loss of ion gradients maintained by the Na/K-ATPase-dependent pumps.[4,15] This scenario can produce inappropriate membrane potentials leading to cardiac arrhythmias (often ventricular tachycardia) and neurologic dysfunction.[4,29–31] Hemolysis occurs due to alterations in red blood cell membrane deformability and decreased ATP availability.[4] Similar dysfunction related to hypophosphatemia has been found in brain cells, platelets and leukocytes.[4,15,30] Decreased leukocyte ATP levels in severely hypophosphatemic dogs was shown to result in decreased 'chemotactic, phagocytic and bacteriocidal' activity.[15,32] Hypophosphatemia may also result in decreased production of 2,3-DPG in red blood cells, a left shift of the hemoglobin-oxygen dissociation curve and decreased oxygen delivery to tissues.[4,29] Diaphragmatic weakness may occur secondary to decreased muscle contractility[4,6,15] leading to difficulty in weaning ventilator patients.[30,33] In severe cases of hypophosphatemia, rhabdomyolysis occurs presumably due to the decrease of energy stores in muscle cells.[30,34,35]

Conditions Associated with Hypophosphatemia

Diabetic ketoacidosis (DKA)

It is estimated that 20–40% of people presenting with DKA are hypophosphatemic.[8] Many more patients with DKA present initially with hyperphosphatemia but

serum levels may drop precipitously with therapy[4] within the first 6–12 hours of therapy with 15% of these having serum phosphate levels $<1.5\,mg/dL$.[8] Intravenous fluids, bicarbonate and insulin therapy cause intracellular movement of glucose and phosphate.[8] Once transcellular shifts have stopped, the serum phosphate level usually returns to normal[4]; however, phosphate supplementation may be required during the acute phase. Lysis of red blood cells can occur with severe hypophosphatemia leading to hemolysis[36] and anemia. Hemolytic anemia and seizures have been reported in diabetic cats and dogs related to hypophosphatemia.[36,37]

Sepsis

In human patients with sepsis, hypophosphatemia is a marker of poor prognosis.[4,38–40] Sixty to eighty percent of human intensive care unit patients with sepsis are hypophosphatemic.[4,8] Over 80% of neonates with sepsis are also hypophosphatemic.[41] Severely hypophosphatemic patients are known to have a 30% greater mortality compared with normal to mildly hypophosphatemic patients[4] and have higher Apache II scores.[42] These studies have suggested that hypophosphatemia is an indicator of early sepsis.[39,42,43] Phosphate levels less than 2.0 mg/dL are shown to be highly supportive of gram-negative sepsis.[39] Although the mechanism is still unknown, Barak et al. demonstrated significant correlation between hypophosphatemia and high levels of inflammatory cytokines such as IL-6 and tumor necrosis factor α (TNF-α) during the first 24 hours of infection and positive blood cutures.[39,44] Antachopoulos et al.[45] also found a significant relationship between rising C-reactive protein levels in septic children and the presence of hypophosphatemia. No published studies were found in small animals recognizing hypophosphatemia as a marker for sepsis, however a recent report by Toribio et al. describes significant hypophosphatemia among other electrolyte abnormalities in horses with induced endotoxemia.[46–48] Complications of hypophosphatemia commonly observed in sepsis include decreased cardiac contractility, decreased response to vasopressors and decreased tissue oxygen delivery.[38] Schwartz et al.[42] suggest that hypophosphatemic, septic patients are at higher risk for developing cardiac arrhythmias than normophosphatemic patients. Bollaert et al. showed that severe hypophosphatemia may be a 'superimposed cause of myocardial depression during sepsis' contributing to decreased cardiac output. Treatment for hypophosphatemia improved both myocardial performance and arterial blood pressure. Bollaert also suggests that hypophosphatemia seen in early sepsis may be caused by an increased uptake of glucose, insulin and endogenous catecholamines that create an intracellular shift of inorganic phosphate.[38,49]

Acute liver failure

Baquerizo et al.,[28] in studies with acute hepatic failure patients, suggest that hypophosphatemia is a predictor of improved outcome over those with hyperphosphatemia. Giovannini et al. also recognized that the presence of hypophosphatemia might be a marker for increased perioperative monitoring and support.[40] It is hypothesized that during the first few days of rapid, effective tissue regeneration, an increased use of ATP will result in low plasma phosphate levels.[28] Hypophosphatemia is common, following hepatic surgical resection in both ill patients and healthy transplantation donors.[15,32,39] Alternatively, hyperphosphatemia is an indication of poor outcome since it implies that the liver does not have enough regenerative capacity and little ATP is being produced and consumed.[28]

Head trauma

Hypophosphatemia is a common sequelum of head trauma. Although the mechanism is unclear, increased diuresis occurs secondary to head trauma[33,50,51] and is believed to be one of the major causes of hypophosphatemia. Some theories include diuresis secondary to volume expansion or secondary to diabetes insipidus.[52] Central diabetes insipidus (CDI) is a common result of head trauma in dogs and cats.[53] Additionally, the use of diuretics such as mannitol which are standard in the treatment of head trauma cause increased diuresis.[52,53] Hyperglycemia is also a common finding in dogs and cats with head trauma.[54] Treatment for hyperglycemia will aggravate hypophosphatemia due to intracellular shift of glucose into cells.

Severe tissue trauma

Tissue trauma secondary to burns, wounds, or crushing injury is known to cause hypophosphatemia.[15,55] Hyperglycemia may develop secondary to insulin resistance and reduced ATP availability secondary to severe muscle trauma.[15,50,56] Decreased phosphate levels due to cell lysis[56] or development of sepsis will compound the hypophosphatemia. Increased plasma corticosteroid levels which occur in response to trauma also appear to induce hypophosphatemia in both rats and pigs.[51]

Hypothermia

Hypothermia is commonly used in human patients to decrease intracranial pressure secondary to head trauma and to decrease cellular metabolic requirements post-cardiac surgery or post-cardiopulmonary resuscitation. Hyperglycemia may occur secondary to brain

injury and is also common in hypothermic therapy secondary to sympathetic stimulation.[57] Endogenous release or therapeutic administration of insulin will cause redistribution of phosphate to the intracellular space. Hypothermia-induced diuresis occurs leading to decreases in many electrolytes including phosphate.[52]

Respiratory compromise

Ventilator patients and people with asthma or chronic obstructive pulmonary disease are susceptible to decreased phosphate levels.[8] Decreased diaphragmatic contractility is present due to hypophosphatemia and decreased levels of ATP.[6,15] Additionally, decreased production of 2,3-DPG leading to decreased tissue oxygen delivery may contribute to diaphragmatic muscle weakness.[8,6,15,34] Phosphate administration has been shown to improve ventilation and transdiaphragmatic pressure.[6] Lopez et al.[58] showed that acute respiratory and metabolic alkalosis in dogs caused severe decreases in PTH values. Respiratory alkalosis due to hyperventilation causes increased cellular uptake of phosphate and a decrease in available phosphate.[8,59] Conditions causing hyperventilation (respiratory alkalosis) such as hyperthermia and seizures have been demonstrated to cause a fall in plasma phosphate levels in dogs.[60] Drugs commonly used in respiratory disorders such as theophylline, corticosteroids and β-2 agonists may cause decreased phosphate reabsorption.[8,61] Although correction of the underlying pathology is preferable, administration of phosphate solutions may correct these problems.[8]

Malnutrition, refeeding syndrome and TPN

Low dietary intake of phosphorus is rare except in prolonged starvation or forced feeding of vegetarian diets.[16,62] Starvation decreases whole-body phosphorus although serum levels may remain normal due to transcellular shifts.[15] During refeeding without sufficient phosphate supplementation or if a high carbohydrate diet is supplied, life-threatening hypophosphatemia may occur.[15] Dogs fed a phosphorus-deficient diet developed subclinical muscle damage. With acute refeeding of a high calorie, high carbohydrate, low phosphorus diet, the dogs developed severe neurologic disorders, seizures, rhabdomyolysis and death.[30] Increased glycolysis leads to increased phosphorylation of glucose and intracellular shifts of phosphate due to increased glucose uptake.[15] It is presumed that decreased intracellular, inorganic phosphate levels also led to decreased levels of ATP leading to loss of energy supply within the cell.[30] Severe hypophosphatemia and hemolytic anemia have been seen in cats 12–72 hours after refeeding.[63] A 2004 study by Pyle, Marks et al. involving complications associated with total parenteral nutrition in cats, showed that 20 hypophosphatemic cats had increased mortality at 96 hours after inititation of TPN.[64]

Hyperparathyroidism

Primary hyperparathyroidism in dogs is an uncommon condition that may lead to renal wasting of phosphate. PTH elevations lead to inhibition of tubular phosphate reabsorption. In humans, respiratory failure frequently occurs in hyperparathyroid crisis possibly due to decreased phosphate levels and subsequent diaphragmatic weakness.[15,18,65,66]

Treatment with phosphate antacids

Antacids which bind phosphate (especially those containing aluminum) can cause severe hypophosphatemia.[14,15] These agents are commonly used to lower phosphate levels in patients being treated for chronic renal failure.[13,65,67,68]

Conditions Associated with Hyperphosphatemia

Hyperphosphatemia is defined as a plasma level greater than 3.0 mg/dL. Clinical symptoms include weakness, tetany, seizures, tachycardia, and torsades de pointes. Hypomagnesemia, hypernatremia and metabolic acidosis may accompany hyperphosphatemia.[4] Hyperphosphatemia is associated with chronic renal failure, hypervitaminosis D, acute tumor lysis syndrome, hypoparathyroidism, and with the administration of phosphate containing enemas.

Chronic renal failure

Decreased renal function alters calcium/phosphate homeostasis. In the early stages, there is decreased serum calcitriol and decreased calcium levels leading to increased synthesis of PTH. Later, decreased vitamin D and calcium receptors contribute to further increase of PTH. Increased PTH leads to decreased phosphate excretion, increased dietary phosphate retention and increased serum phosphate levels. Increased serum phosphate will lead to further PTH synthesis.[69] This condition is known as secondary hyperparathyroidism.[9,70] Increased calcium-phosphorus product ($Ca \cdot P = 58–70$) leads to increased calcium deposition (in the form of $Ca_{10}(PO_4)_6OH_2$) in tissues including cardiac muscle and vasculature.[26,71] Dialysis patients are at increased risk of high $Ca \cdot P$ products.[71] $Ca \cdot P > 72\,mg^2/dL^2$ had 34% higher risk of death than those with normal $Ca \cdot P$ products.[72] A 27% higher mortality occurs in patients with serum phosphorus greater that 6.5 mg/dL than in those with phosphorus levels between 2.4 and 6.5 mg/dL.[67,68] In humans a high calcium phosphate product is a poor prognosis

with high risk of vascular calcification,[26,72] myocardial infarction and coronary calcification.[26,73,74] Although metastatic calcification does occur in animals, a recent study by Gear et al. suggested that the calcium phosphate product was not a useful predictor of renal failure in dogs.[75]

Toxicities

Hyperphosphatemia is observed in small animals given phosphate-containing enemas. Severe dehydration and electrolyte abnormalities often result in death even with aggressive therapy. Ingestion of vitamin D3 skin preparations such as calcipotriene, used to treat psoriasis, may cause acute severe hypercalcemia, hyperphosphatemia and wide-spread soft tissue mineralization.[76–78] Cholecalciferol-containing rodenticides have similar effects within 12 to 36 hours post-ingestion and are often fatal.[79,80] Overdose of phosphorus supplementation or urinary acidifiers may also cause hyperphosphatemia. Zinc phosphide, used in pesticides such as gopher bait, forms fatal phosphine gas on contact with gastric acid.[79]

Acute tumor-lysis syndrome

Acute tumor lysis syndrome (ATLS) may occur in patients within 48 hours after their first chemotherapy treatment.[81] It often occurs in animals being treated for highly responsive lymphoma and is due to cell destruction resulting in massive release of postassium and phosphate.[81] Animals at risk are those with a large tumor burden, which undergoes rapid cell destruction.[81] Those patients that are being treated for stage IV or V lymphoma and that are volume-depleted and azotemic may be at higher risk for ATLS.[81]

Hypoparathyroidism

A rare cause of hyperphosphatemia is hypoparathyroidism, which is usually diagnosed secondary to symptoms of hypocalcemia-associated neuromuscular symptoms.[82,83] The underlying cause of hypoparathyroid disease is due to parathyroid hormone deficiency. Patients may present on emergency with acute seizures or tetany. Presumptive diagnosis is made based upon clinical symptoms, hypocalcemia, hyperphosphatemia with normal renal values. Confirmation of a low serum PTH is recommended. Acute treatment involves calcium supplementation and with vitamin D therapy for long-term management.[82,83]

Treatment for phosphate abnormalities

The goal in treatment of hypophosphatemia is to maintain serum levels above 2.0 g/dL.[4,8] For mild to moderate hypophosphatemia, oral supplementation in the form of sodium phosphate or potassium phosphate can be administered. Treatment with intravenous supplementation should begin when levels are less than 1.0–1.5 mg/dL or if clinical symptoms are present.[4,8,34] Intravenous administration of potassium phosphate is recommended at 0.01–0.06 mmol/kg/hr IV.[4,8,27] and should be administered in saline or dextrose. Calcium-containing solutions such as LRS may form precipitates and should be avoided.[4] Potassium phosphate is readily available and contains 3 mmol/mL (93 mg/mL) of phosphate and 4.3 mEq/mL potassium.[4,34] Serum phosphate levels should be monitored every 4–6 hours.[84] Once levels exceed 2.0–2.5 mg/dL, the patient may be maintained on oral phosphorus supplementation.

Therapy for rapid correction of hyperphosphatemia includes crystalloids containing dextrose that will correct acidosis, increase intracellular uptake of phosphate, resolve azotemia, and correct calcium imbalances. The preferred treatment for hyperphosphatemia is to treat the underlying disorder. Phosphate binders are often used in chronic renal failure because improved renal function may not be attainable.

Conclusion

There are few studies in the literature that evaluate phosphorus and phosphate metabolism in veterinary patients. Most information is extrapolated from numerous human studies. Assays for plasma phosphate are inexpensive and readily available on most chemistry analyzers, so correlating clinical problems in veterinary patients with changes in serum phosphate should be relatively easy to achieve. The association of decreased phosphate levels with sepsis and its potential use as an early marker for sepsis is intriguing.

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