Phosphorus Homeostasis in Dairy Cattle: Some Answers, More Questions

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Abstract

Phosphorus homeostasis in dairy cattle has received increased attention in the last decades because of the possible association between hypophosphatemia and the downer cow syndrome, as well as because of increasing concerns about the environmental impact of excessive amounts of phosphorus **(P)** in manure. Assessing the P homeostasis in animals is difficult since the concentration of this predominantly intracellular ion in serum or plasma does not reliably represent the total body P pool. The plasma P concentration in dairy cows can drop considerably following a sudden loss of P as it occurs at the onset of lactation through the mammary gland, but hypophospahtemia can also be the result of a sudden shift of P from the extracellular space into the cells - where the total P pool remains unchanged - as it occurs following parenteral dextrose or insulin administration. Hypophosphatemia has been associated with a number of clinical signs and conditions in dairy cows, such as anorexia, pica, muscle weakness or recumbency, intravascular hemolysis, and more recently with disturbed liver function. Many of these signs and conditions have been empirically associated with P depletion or hypophosphateemia with unequivocal evidence often not being available. Also, it is not well understood if these signs would be caused by a decline of the plasma P concentration alone or if they require a depletion of the total body P pool. Treatment of hypophosphatemia requires the administration of phosphate salts, either orally or parenterally. Phosphite salts, frequently incorporated in solution for intravenous administration, are unsuitable to substitute phosphate as the organism does not convert biologically inactive phosphite into phosphate. With proper gastrointestinal motility, phosphate salts (sodium phosphate) when given orally result in a rapid and sustained increase of the plasma P concentration. Intravenous administration of phosphate salts results in an immediate but very short lived increase of the plasma P concentration and must therefore be accompanied by oral P supplementation. Phosphate salts given intravenously should neither be mixed nor given together with other salts (Ca, K, or Mg) because phosphate may precipitate with these salts.

Introduction

Phosphorus has a variety of important biological functions that make it essential for animal health and well-being. Oxidative phosphorylation, oxygen delivery, glycolysis, and maintenance of cellular structural integrity are among the processes that require P. It is a major component of bone as well as a buffer contributing to acid-base balance. Phosphorus is necessary for generation of adenosine triphosphate **(ATP)**, without which many physiologic processes could not occur.

Only a small proportion (< 1%) of total body P, mainly inorganic phosphate **(Pi)**, is found in extracellular fluid and is measured in serum or

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plasma. The simplest way to describe the distribution of dissolved Pi in the organism is a two-compartment model, with the intracellular space **(ICS)** representing one compartment and the extracellular space (**ECS**, of which plasma forms part) the other. Dissolved Pi is present as an anion (either HPO_4^{2-} or $H_2PO_4^-$) that depends on transport proteins to be absorbed from the gastrointestinal tract from the lumen of the renal tubuli, or to be transported from the extracellular into the intracellular space. The concentration of Pi ([Pi]) in ECS and thus in plasma is driven by the equilibrium between uptake from the GI tract; losses through the mammary gland, the salivary glands, and the kidneys; P uptake by cells, bones, or the fetus, and P release from bone.

Phosphorus concentration in serum or plasma is regulated through adjustments of the intestinal absorption rate; salivary and renal excretion rate; and through mobilization of P from bone (Mayer et al., 1966; Wright et al., 1984; Horst, 1986; Schröder et al., 1995). In ruminants, salivary glands excrete large amounts of P in saliva, providing the rumen with P needed for microbial metabolism as well as a buffer. A large portion of salivary P is reabsorbed in the small intestine, with the remainder contributing to fecal P losses. Renal P excretion under physiologic conditions is only of minor importance. With a renal threshold of approximately 7 mg/dL, the kidneys function as an "overflow valve" only excreting P when the plasma [Pi] exceeds the renal threshold (Symonds and Manston, 1974). Renal P excretion increases with decreasing urine pH due to decreased tubular P reabsorption, a mechanism known as titratable acidity (Lunn and McGuirk, 1990).

Milk production has a strong impact on P homeostasis in dairy cows as milk contains considerable amounts of P (~ 0.5 g/lb), and the [Pi] in milk is maintained constant, independent of the plasma [Pi] (Neville and Peaker, 1979; Morse et al., 1992). Effective reduction of P losses through the mammary gland can only be achieved through a decrease in milk production. Increasing milk production, in contrast, results in increased P demand.

Compartmental shifts of P are strongly influenced by the cellular carbohydrate metabolism, insulin secretion, insulin sensitivity, and by acid-base homeostasis. Inducing an insulin release, for example, by parenteral dextrose administration will result in enhanced cellular uptake of glucose together with P and thereby result in a decrease of plasma [Pi]. Intravenous administration of hypertonic dextrose solutions, as commonly done in the field, will transiently reduce plasma [Pi] by over 30%, without causing obvious clinical signs (Grünberg et al., 2006). Alkalemia stimulates the intracellular carbohydrate metabolism thereby enhancing cellular uptake of glucose and P (decrease of plasma [Pi]); whereas, the opposite is the case in acidotic states (elevated plasma [Pi]).

Current literature suggests a reference range of 4 to 8 mg/dL (1.3 to 2.6 mmol/L) for plasma [Pi] in dairy cows (Goff, 1999; Satter, 2002), with plasma [Pi] tending to decrease with age (Roussel et al., 1982). Stage of lactation also influences plasma [Pi], with a substantial decrease in [Pi] possible in the early postparturient period due to increased activity of parathyroid hormone **(PTH)** and a sudden loss of P into colostrum and milk (Goff, 2000).

Phosphorus nutrition in dairy cows has received increased attention over the past decade. Excessive dietary P intake leads to high fecal P loss and surface runoff. This has raised environmental concerns and resulted in incentives to lower dietary P intake (Satter, 2002). In an effort to reduce fecal P output, the National Research Council recently reduced dietary P recommendations for dairy cows, with justification that a lower P intake does not interfere with fertility, milk yield, or health (NRC, 2001).

Deregulation of Phosphorus Homeostasis

Plasma or serum [Pi] is commonly used to assess P homeostasis in animals and humans, but as with any predominantly intracellular ion, the serum or plasma concentration does not reliably represent the total body stores of the ion. Gradual changes in total body P can be accommodated without noticeable changes in plasma or serum [Pi], as mechanisms regulating homeostasis will attempt to maintain plasma [Pi] within the physiologic range (Knochel, 1977). On the other hand, P can considerably and rapidly shift from the ECS to the ICS without a change in the total body P pool (Lentz et al., 1978; Grünberg et al., 2006). Therefore, hypophosphatemia does not necessarily imply total body P depletion, and the degree of P depletion does not necessarily reflect in plasma [Pi].

An acute decline of the plasma [Pi] is commonly the result of a sudden disruption of the equilibrium between P uptake, P loss, and compartmental shifts in association with the lag time of the homeostatic mechanisms regulating P homeostasis (Littledike, 1976). For example, such a disequilibrium could be caused by the sudden increase in milk production at the onset of lactation, a decrease in feed intake of a sick cow, or compartmental shifts of P into the cells following parenteral administration of carbohydrates.

Metabolic profiling has demonstrated that plasma [Pi] in dairy cows is at its lowest around parturition. Periparturient dairy cows are at risk of hypophosphatemia because of the sudden and substantial loss of P into milk at the onset of lactation and reduced feed intake, which often occurs around calving time. A deregulation of the calcium homeostasis frequently seen in periparturient high yielding and older cows may also be detrimental to maintenance of normal serum or plasma [Pi] because of an increase in PTH secretion. This increase of PTH results in a rise of salivary and renal Pi excretion in the affected animal (Horst, 1986). Common periparturient diseases, such as ketosis, abomasal displacement, hepatic lipidosis, metritis, and mastitis, also reduce feed intake, resulting in a decrease in serum [Pi]; in a recent retrospective study, 35% of cows with left displaced abomasum were hypophosphatemic (plasma [Pi] < 4.3 mg/dl; Grünberg et al; 2005).

Effects of Hypophosphatemia: Myths or Facts?

A number of clinical signs, such unthriftiness, pica, muscle weakness, and anorexia, have been associated with hypophosphatemia (Gerloff and Swenson, 1996; Haque and Verma 1992). Nonetheless, it is not well understood whether these signs are the result of a drop in plasma [Pi], are caused by subnormal intracellular [P], or a decline in the total body P pool that may accompany hypophosphatemia.

Chronic P deficiency is characterized by pica; unthriftiness; poor growth or weight loss; decreased milk production; low fertility; and in late stages, osteodystrophy with decreased bone weight and osteopenia. Although reproductive abnormalities have frequently been attributed to hypophosphatemia, it remains to be elucidated whether this effect is directly due to a deficiency of P or rather to a concurrent energy deficiency frequently seen in affected animals (Call et al., 1987). Recent trials presented evidence that there is no beneficial effect on fertility or milk production of feeding P in excess of recommended requirements (Wu and Satter, 2000).

Conditions such as the "downer cow syndrome" and postparturient hemoglobinuria (PPH) have been associated with hypophosphatemia. Postparturient hemoglobinuria occurs sporadically in multiparous, high-producing dairy cows and has a high mortality rate (Jubb et al., 1990). High P requirements for late gestation fetal growth and onset of copious milk production are believed to

exacerbate dietary P deficiency in cows with PPH. Severe hypophosphatemia has been proposed to result in decreased erythrocyte ATP concentration, which can lead to hemolytic anemia and hemoglobinuria. However, after inducing severe hypophosphatemia in cows, self-limiting hemoglobinemia, but no hemoglobinuria, was observed (Ogawa et al., 1989). Also, unresponsiveness to parenteral treatment with phosphate salts has been reported in several cases of PPH (Jubb et al., 1990).

Of particular importance to the dairy industry is the role of hypophosphatemia in postparturient recumbency. Hypocalcemic parturient paresis (milk fever) is a well-documented cause of recumbency in postparturient dairy cows. Hypophosphatemia routinely accompanies hypocalcemia in cows with milk fever, with plasma [Pi] often < 2 mg/dL. In most cases, hypophosphatemia resolves spontaneously after treatment with an IV of Ca, and the cow recovers uneventfully; however, in some cases, [Pi] fails to increase and the animals may become "downer cows". Empirical observations suggest that persistent hypophosphatemia is a major contributor to the "downer cow syndrome", but unequivocal documentation is not available. Experimentally decreasing plasma [Pi] to values as low as 0.9 to 1 mg/dL over an extended period of time by limiting the dietary P uptake neither resulted in recumbency (Rodehutscord et al., 1994) nor do recumbent cows with hypophosphatemia routinely respond to P administration. Nonetheless, it must be emphasized that models inducing hypophosphatemia by reducing dietary Pi uptake are ill suited to mimic the decline of plasma [Pi] at the onset of lactation where the mammary gland suddenly withdraws substantial amounts of Pi from the ECS, which is more likely to overwhelm the regulatory mechanism and thus possibly result in clinical signs.

In the recent literature, a possible link between hypophosphatemia and disturbed liver function in dairy cows has been discussed based on negative associations found between serum [Pi] and indices for disturbed liver function or liver injury (Staufenbiel and Gelfert, 2002; Grünberg et al., 2005). Decreased serum [Pi] also is frequently associated with liver failure in humans (Knochel, 1977). However, it remains unclear whether patients with liver failure are inclined to develop hypophosphatemia or if hypophosphatemia is a predisposing factor for liver failure (Dawson et al., 1987). Similarly, in ruminants, it is not known whether the liver is directly involved in the regulation of P homeostasis or if plasma [Pi] decreases solely as a result of reduced feed intake in animals with hepatic dysfunction.

Hypophosphatemia: To Treat or Not to Treat?

Clearly, chronic hypophosphatemia caused by long-standing dietary P deficiency must be treated and is best done by oral P supplementation (Goff, 1998). Treatment of acute hypophosphatemia is more controversial. For decades, it has been common to treat cows with milk fever by parenteral administration of solutions containing both Ca and P. Phosphorus is incorporated into many Ca solutions because it is recognized that cows with milk fever frequently have low plasma [Pi] in addition to low plasma Ca concentration. However, the P in these solutions is usually phosphite or hypophosphite, salts that have been shown to be unsuitable for correction of hypophosphatemia in cattle (Cheng et al., 1998). In many cases, the hypophosphatemia in cows with milk fever resolves spontaneously after treatment with Ca alone, suggesting that P administration is not necessary. The increase in plasma [Pi] after Ca administration may be due to a decrease in PTH secretion, which reduces urinary and salivary P loss, and to resumption of gastrointestinal motility, which allows absorption of dietary and salivary P (Goff, 1998). Acute hypophosphatemia can also accompany diseases that result in anorexia in cows, such as a

displaced abomasum. In these cases, it is essential to correct the underlying disease, with hypophosphatemia often resolving spontaneously thereafter (Grünberg et al., 2005).

Should the above observations lead us to conclude that therapeutic P administration to cows with acute hypophosphatemia is unnecessary? It has been reported that hypophosphatemia induced in people through parenteral administration of dextrose and insulin (for treatment of acute diabetic ketoacidosis) results in anorexia, bone and muscle pain, changes in mentation, and decreased cardiac output, symptoms that are relieved rapidly when plasma [Pi] is restored (Knochel, 1977; Rajesh and Romesh, 2000). Although the hypophosphatemic effect of parenteral carbohydrate administration is very similar in dairy cows to what has been reported in humans, it is not known whether a hypophosphatemic state causes similar clinical signs in cattle (Grünberg et al., 2006). Many of these symptoms, even if present, would remain unnoticed in cattle but would impact the animal's well-being and possibly its recovery. Moreover, P depletion and hypophosphatemia in ruminants are believed to cause or exacerbate feed intake depression (Milton and Ternuth, 1985). Therefore, P administration may be appropriate for asymptomatic cows deemed at risk for hypophosphatemia (eg., those with anorexia), as well as cows with symptomatic hypophosphatemia (eg., allotriophagia, abnormal licking, weakness, or recumbency).

How to Treat Hypophosphatemia

Prevention of hypophosphatemia is preferable to treatment. Astute clinicians will anticipate potential hypophosphatemia and either administer supplemental P orally or carefully monitor the patient for hypophosphatemia.

As mentioned above, solutions containing phosphite or hypophosphite salts are unsuitable for correction of hypophosphatemia because the organism is unable to convert biologically inactive phosphite into phosphate. Instead, the monobasic monophosphate (NaH_2PO_4) or the dibasic monophosphate (Na_2HPO_4) form of sodium phosphate can be used (Cheng et al., 1998; Staufenbiel, 1999; Constable, 2003). These salts can either be administered orally (available as gel or pills) or intravenously. Sodium phosphate salts (either monobasic or dibasic) are typically used for intravenous administration, whereas oral gels or pills frequently contain mixtures of different sodium and calcium phosphate salts. Intravenous treatment with sodium phosphate results in an immediate but very short lived increase in plasma [Pi] (Cheng et al., 1998). Sodium phosphate salts administered orally increase plasma [Pi] within one hour, provided there is adequate rumen motility, and has a sustained effect over at least 12 hours (Cheng et al., 1998). Therefore, if intravenous treatment is chosen and the underlying cause of the hypophosphatemia cannot be rapidly corrected, it must be accompanied by oral phosphate administration to obtain both an immediate and sustained increase in plasma [Pi]. Phosphate salts should not be mixed with or administered in association with an IV of Ca, K, or Mg because of the possibility that calcium, potassium, or magnesium phosphate precipitates may form (Constable, 2003). The dose necessary to replete a patient is difficult to predict. Recommendations for treatment of an adult lactating cow with severe hypophosphatemia range from 10 to 20 mg P/kg administered intravenously, which is equivalent to 6 to 12 g of P for a 600 kg (1320 lb) cow. The intravenous treatment with 30 g of NaH_2PO_4 dissolved in 300 ml of distilled water, which is equivalent to 7 g of P, has been reported to be effective to rapidly correct hypophosphatemia (Cheng et al., 1998), as has been a treatment with 90 g of Na_2HPO_4 (approximately 9 g of P) dissolved in 500 ml of distilled water (Staufenbiel, 1999). Orally, hypophosphatemia can effectively be treated with a dose of 200 to 300 g of Na_2HPO_4 or NaH_2PO_4 providing about 50 to 60 g of P.

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