TREATMENT OF POTASSIUM BALANCE DISORDERS

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Potassium is the third most abundant mineral element in ruminant tissues.[6] It is a monovalent cation that plays a critical role in determining resting cellular membrane potential, and thus, neuromuscular excitability. The terms *hypokalemia* and *hyperkalemia* refer to the concentration of potassium in the plasma (and extracellular fluid); however, only 2% of the potassium in the body resides in the extracellular fluid, so plasma concentration of potassium does not necessarily reflect the status of total body stores of that cation.[1] The vast majority of potassium in the body is located in the intracellular fluid of skeletal muscle, so shifts of potassium between intracellular and extracellular space can profoundly influence the concentration of potassium measured in the plasma. It is not practical to measure intracellular potassium content in clinical patients, although occasionally this is performed in a research setting.

POTASSIUM REGULATION

The concentration of potassium in plasma is determined by two functions: external potassium balance, or the net difference between intake and elimination of potassium, and internal potassium balance, or the shift of potassium ions between the intracellular and extracellular fluid spaces.[1]

External potassium balance is determined by the difference between dietary consumption of potassium and elimination, which includes renal, salivary, and gastrointestinal routes of elimination. The dietary po-

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tassium requirement for lactating cattle is approximately 0.8% of dry matter intake, but may be slightly higher in heat-stressed animals.[6] In normal cattle, dietary potassium is nearly completely absorbed (>85%). Potassium concentration of most forages is much higher than that typically required by cattle, and normal potassium balance is maintained through elimination of excessive potassium. In lactating cattle, 75% of potassium elimination is via the urine, 13% in feces (mostly unabsorbed dietary potassium), and 12% in the milk.[6, 14] The excretion of potassium in the milk accounts for the higher potassium requirement in lactating cows, compared with that of nonlactating cattle (0.5% dry matter). Because cattle-fed forages are adapted to eliminate excessive dietary potassium, a sudden decrease in appetite, and thus potassium intake, can result in hypokalemia, as the reduction of potassium elimination may not occur rapidly enough to offset the reduced intake.[2]

External potassium balance is achieved primarily through renal regulation of urinary excretion of potassium.[1, 4] Nearly all potassium that is filtered in the glomeruli is reabsorbed in the proximal renal tubules, and potassium elimination occurs primarily by excretion of that cation into the lumen of the distal tubules and collecting ducts. The excretion of potassium ions, which occurs in exchange for sodium ions, is an active process requiring ATP. The mineralocorticoid hormone, aldosterone, enhances the distal tubular secretion of potassium ions in exchange for the reabsorption of sodium ions. Excretion of potassium in the distal tubule is also dependent on volume of urine flow—diuresis will increase potassium elimination, and reduced urine flow (e.g., due to dehydration) may result in potassium retention.[1, 3, 4] Renal failure, or leakage of urine from the urinary tract into the abdomen, will also result in retention of potassium. Apparently, this reduced renal elimination of potassium can be compensated for by aldosterone-responsive excretion of potassium by salivary glands and possibly colonic enterocytes.[11] Metabolic alkalosis is also associated with increased elimination of potassium in the urine, although in ruminants with concurrent inappetence, the lower potassium intake results in marked reduction in potassium delivery to the renal tubules which may obscure the kaliuretic effect of alkalosis.[4]

Alterations in the equilibrium between intracellular and extracellular potassium can result in hyperkalemia or hypokalemia even though total body potassium content is not changed (Fig. 1). Disturbances of acid base balance most commonly influence internal potassium balance.[1, 3, 4] When metabolic acidosis occurs, the increased extracellular fluid concentration of hydrogen ions is buffered by movement of those ions into the cells.[10] Potassium ions leave the intracellular compartment to maintain electroneutrality, resulting in increased plasma potassium concentration. Similarly, in metabolic alkalosis, hypokalemia may result from redistribution of potassium from the extracellular to the intracellular compartment.[1, 4]

Insulin also enhances the movement of potassium into the intracellular compartment. Potassium accompanies the insulin-mediated uptake of glucose by liver and skeletal muscle.[1] Clinicians take advantage of

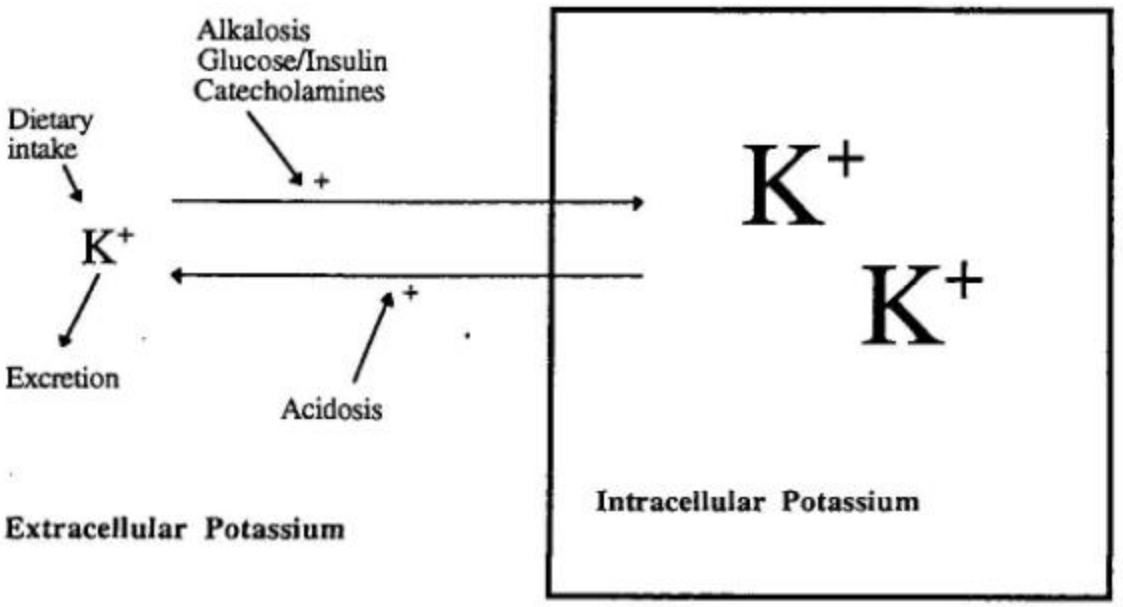

Figure 1. Factors affecting intracellular and extracellular potassium equilibrium.

this effect when treating hyperkalemia with intravenous infusions of insulin and dextrose.

HYPERKALEMIA

If renal function is normal and sufficient drinking water is available, cattle are well adapted to eliminate excessive potassium, whether administered orally or intravenously, and potassium "toxicity" alone without concurrent renal failure is rare. Gross miscalculation or overzealous administration of intravenous potassium chloride supplementation could result in hyperkalemia, although in the author's experience this is a rare occurrence. Experimentally, oral administration of more than 230 g potassium (approximately 450 g KCl) resulted in death, but smaller quantities did not.[14] Thus, most cases of hyperkalemia in cattle occur in animals with impaired renal elimination, shift of potassium out of the intracellular compartment, or a combination of both. Clinicians should also be wary of "pseudohyperkalemia," an artificial elevation of potassium concentration that results from leaching of potassium from red blood cells if the whole blood sample is held in the collection tube for an extended period before separation of the plasma for laboratory analysis, or if hemolysis occurs.[1]

The predominant clinical sign associated with hyperkalemia is bradycardia, whereas other cardiac arrhythmias, such as ventricular premature contractions or ventricular fibrillation, can occur with advanced hyperkalemia. An electrocardiogram reveals decreased amplitude of p waves, and increased-amplitude or spiked T waves. Skeletal muscle weakness may also be seen. Because of the potential for life-

threatening cardiac arrhythmia, hyperkalemia should be treated as an emergency.

Hyperkalemia in cattle is most commonly encountered in dehydrated calves with diarrhea.[10] Calves with diarrhea lose large quantities of potassium in feces, and depletion of body stores of potassium ensues; however, because of redistribution from the intracellular compartment, most likely associated with metabolic acidosis, calves dehydrated from diarrhea are often hyperkalemic. The hyperkalemia may also be enhanced because renal elimination of potassium is reduced secondary to reduced urinary flow associated with dehydration. In the field, when treating diarrheic calves empirically without the benefit of blood biochemistry analysis, the clinician should assume the presence of hyperkalemia when selecting replacement fluid therapy. Rapid infusion of solutions containing high concentrations of potassium is not recommended initially; however, some clinicians do include potassium, along with glucose and bicarbonate, in the initial fluids, and have not encountered problems associated with the hyperkalemia. The hyperkalemia is usually corrected readily when acidosis and renal perfusion are improved with administration of fluids, and addition of glucose (up to 5% concentration) to the fluids will enhance cellular uptake of potassium. It is generally not necessary to resort to insulin treatment. Once dehydration and acidosis have been corrected, it should be remembered that the whole-body stores of potassium are depleted, and continued fluid therapy without potassium supplementation will result in hypokalemia.

Reduced urinary elimination of potassium may result in hyperkalemia in animals with oliguric or anuric acute renal failure. Urethral obstruction from urolithiasis may lead to bladder rupture and uroperitoneum. Potassium diffuses across the peritoneal membrane into the extracellular fluid from the potassium-rich urine within the abdominal cavity; however, the plasma potassium concentration is quite variable in cattle with renal failure or uroperitoneum, and hyperkalemia cannot be assumed. Other factors—such as reduced potassium intake due to inappetence; hyponatremia, hypochloremia, and alkalosis; increased salivary excretion of potassium under the influence of aldosterone; and reduced gastrointestinal absorption of potassium—often result in normal or even low plasma potassium concentration in these patients.[11]

Specific treatment for hyperkalemia is rarely necessary in cattle with oliguric or anuric acute renal failure, and initial efforts are aimed at improving renal perfusion and establishing urine flow with intravenous fluids and possibly diuretics, such as furosemide. When cardiac arrhythmia is present, or if general anesthesia for surgical repair of ruptured bladder is considered, hyperkalemia can be corrected by administration of regular insulin IV or SQ (0.1 U/kg) accompanied by a continuous infusion of 5% glucose (2.2 to 4.4 mL/kg/hr) to induce redistribution of potassium into the intracellular space. This redistribution will be enhanced by supplementation with sodium bicarbonate if acidosis is present.

HYPOKALEMIA

Hypokalemia can result from changes in external or internal potassium balance. The clinical signs associated with hypokalemia relate primarily to the importance of potassium in maintaining the resting membrane potential and its role in neuromuscular transmission. Hypokalemia leads to skeletal muscle weakness, which in cattle is initially manifested as muscle fasciculation. As hypokalemia progresses, severe muscle weakness results in recumbency. Characteristically, the neck muscles are particularly affected and the patient will be unable to support the weight of its own head, laying with the head resting against its flank.[5, 9] If recumbency is prolonged, muscle ischemia and necrosis may ensue, leading to terminal recumbency. Also, a hypokalemic myopathy has been documented, characterized by myofiber vacuolation and necrosis particularly affecting type-2 muscle fibers. This may be due to an effect of lower potassium concentration on mitochondrial metabolism or due to focal ischemia caused by vasoconstriction associated with potassium depletion.[9, 12, 13]

External potassium balance can lead to hypokalemia if potassium intake is insufficient or if urinary excretion of potassium is enhanced. Because of the high potassium content of forages in use today, dietary potassium insufficiency is rarely reported, but could occur in lactating cattle fed rations consisting primarily of concentrates.[6, 14] Clinical signs reported in cattle experimentally depleted of potassium included decreased milk production, pica, poor hair coat, reduced appetite, and muscle weakness.[8] The condition was reversed by addition of potassium to the ration. More commonly, insufficient potassium intake results from reduced voluntary feed intake associated with illness. Particularly in cows adapted to potassium-rich feeds, abrupt cessation of potassium intake results in hypokalemia because urinary elimination of potassium cannot be sufficiently reduced to maintain external potassium balance. Thus, any illness that causes inappetence has the potential to cause hypokalemia; however, in most cases, the hypokalemia will be mild and usually not result in specific clinical signs unless other conditions that result in excessive urinary elimination or altered internal potassium balance, such as alkalosis, are superimposed.

Excessive urinary elimination of potassium has a negative effect on external potassium balance and leads to hypokalemia. Metabolic alkalosis leads to increased concentration of potassium in the distal renal tubular cells, and thus a greater diffusion gradient and increased elimination of potassium into the tubular lumen.[3–5] Hypovolemia may induce aldosterone release that will enhance exchange of sodium and potassium in the distal tubular cells, resulting in kaliuresis. Administration of glucocorticoids that have mineralocorticoid activity can induce negative potassium balance. Isoflupredone acetate, a corticosteroid commonly used to treat ketosis in lactating cows, has been shown to have mineralocorticoid activity in dogs and cause hypokalemia in humans.[9, 13] Its mineralocorticoid effect may be dose related, as hypokalemia in lactating

cows was most profound following multiple or higher than recommended doses.[7, 9] External potassium balance can also be disturbed by gastrointestinal losses of potassium. Excessive gastrointestinal losses can occur in cattle with diarrhea, resulting in potassium depletion; however, internal potassium balance may influence whether hyperkalemia or hypokalemia ensues following gastrointestinal loss of potassium. Empirically, hypokalemia, rather than hyperkalemia, is generally expected in adult cattle with diarrhea, in contrast with neonatal calves.

As noted previously, hypokalemia can result from altered internal potassium balance regardless of the status of the external potassium balance. The most commonly encountered disturbance to result in redistribution of potassium into the intracellular space is metabolic alkalosis, which accompanies abomasal displacement (particularly RDA or RDA with volvulus), pyloric obstruction (type III vagal indigestion), proximal intestinal obstruction, cecal volvulus, or functional ileus associated with traumatic reticuloperitonitis. Hypokalemia can be a cause or result of alkalosis, and it may not be possible to determine whether hypokalemia due to inappetence led to alkalosis or whether alkalosis caused hypokalemia.[4] Regardless of the pathophysiologic cause, hypokalemia should be suspected in cows with gastrointestinal disturbances frequently associated with metabolic alkalosis.

Internal potassium balance may also be influenced by treatment with glucose or glucose precursors, such as propylene glycol, or insulin. Administration of a bolus of intravenous glucose (e.g., in the treatment of ketosis) may stimulate endogenous insulin release. These treatments may contribute to hypokalemia through enhanced cellular uptake of potassium, but would unlikely result in clinically significant hypokalemia unless superimposed with other causes of hypokalemia.

The severity of hypokalemia is undoubtedly increased in syndromes involving a combination of external and internal potassium balance. For example, the hypokalemic metabolic alkalosis associated with abomasal displacement is due to a combination of reduced potassium intake from inappetence and intracellular redistribution of potassium, and is more severe than that observed due to fasting alone. The severe hypokalemia due to renal wasting of potassium following the treatment of ketosis with isoflupredone acetate may be exacerbated by alkalosis, or treatment with glucose and propylene glycol. In one study, administration of sodium proprionate enhanced the hypokalemic effect of isoflupredone acetate in normal cows.[7] Thus, while treatment for hypokalemia may be of benefit in the mild hypokalemia associated with inappetence, it is essential in those cases of hypokalemia with multiple causes, such as hypokalemic hypochloremic alkalosis or isoflupredone acetate treatment.

The most important aspect of treatment of hypokalemia is correction of the primary condition that led to the potassium balance disturbance. In fact, many cases will recover without specific attention to potassium balance if the primary problem is corrected, such as surgical correction of displaced abomasum; however, rate of recovery may be enhanced by providing potassium supplementation, and in those cases where

hypokalemia is sufficiently severe to cause clinically apparent muscle weakness or recumbency, potassium treatment is essential.

Treatment of hypokalemia can be accomplished with intravenous or oral supplementation with KCl. Because of its intracellular distribution, it is not possible to calculate an accurate potassium replacement dose based on measures of plasma potassium concentration. Therefore, potassium dosage recommendations are merely guidelines based on empirical observation, and if long-term treatment is necessary, dosages must frequently be adjusted in individual patients based on repeated monitoring of plasma potassium concentration. As noted above, although potassium toxicity is rare and the hypokalemic patient may be particularly resistant to potassium toxicity, care should be taken to avoid overly exuberant potassium supplementation. For intravenous supplementation, a maximum administration rate of 0.5 mEq/kg/hr is advised,[10] which at replacement fluid flow rates will usually amount to 20 to 40 mEq/L of fluid. Sterile aqueous solutions of KCl are commercially available for this purpose from numerous sources, usually at a concentration of 2 mEq K/mL. Alternatively, 1 g of KCl powder provides approximately 13 mEq of K^+ when added to fluids intended for IV administration.

For mild cases of hypokalemia in adult cattle in which the predisposing cause is readily corrected (e.g., displaced abomasum), administration of 40 mL/kg of 0.9% NaCl supplemented with 40 mEq/L of KCl, possibly accompanied by access to oral KCl, will be adequate; however, in cases of severe hypokalemia (plasma K^+ concentration <2.0 mEq/L) with muscle weakness or recumbency, intravenous supplementation at that concentration is unlikely to be effective. A solution of isotonic KCl can be prepared by adding 11.5 g KCl/L sterile water, administered at a rate of 4 mL/kg/hr. Great care must be taken to carefully monitor the flow rate to ensure that an overdose is not administered if the fluids "run away" or flow at an unexpectedly fast rate. Additionally, concentrated solutions of KCl can be prepared in small quantities (1 to 2 L) so that if the fluids do flow more rapidly than expected, the supply will run out before a lethal dose has been administered.

In the author's experience, oral potassium supplementation is preferred to intravenous because of lower cost, ease of administration, and ability to administer larger doses with less concern for adverse effects. Also, increased urine flow associated with intravenous replacement fluid administration may increase urinary excretion of potassium and negate some of the benefit of supplementation. Potassium chloride is not palatable, so providing access to KCl salt usually will not result in sufficient voluntary consumption. In mild cases of hypokalemia, provision of a free-choice oral electrolyte solution composed of 60 g NaCl and 30 g KCl dissolved in 15 L of water will be readily consumed and assist correction of the mild deficit. A 1-oz volume measure of KCl salt is approximately equivalent to 30 g. In more severe cases, administration of larger quantities intraruminally may be necessary. Typically, 120 g, but up to 240 g of KCl, is administered in gelatin capsule boluses or dissolved in water and administered by orogastric tube 2 to 3 times daily.

Administration of 500 g KCl dissolved in 8 L of water intraruminally in one case resulted in rapid correction of the hypokalemia (6 hours) but was followed by a brief episode of diarrhea.[9] If KCl powder is not available, commercially available low-sodium salt substitutes, such as Lite-Salt (Morton International, Chicago, IL), may be used. These contain roughly a 1:1 mixture of NaCl and KCl, and 30 g of Lite-Salt contains approximately 14 g KCl. Rumen liquor from a normal cow is also a good source of potassium and has the added benefit of aiding repopulation of the rumen flora following intraruminal administration. Correction of the plasma potassium concentration into the normal range will not necessarily be accompanied by immediate clinical improvement, as plasma concentration may not reflect the intracellular compartment potassium status. Also, hypokalemic myopathy may contribute to muscle weakness and delay clinical recovery.

SUMMARY

Potassium is the predominant intracellular cation and is critical for the maintenance of resting cellular membrane potential. Abnormalities of potassium balance can manifest as skeletal and cardiac muscle dysfunction. Abnormalities of potassium concentration in plasma can result from changes in external potassium balance (intake vs. excretion) or internal balance (intracellular to extracellular). Hyperkalemia can result from renal failure, uroperitoneum, or severe dehydration and acidosis in calves with diarrhea. Hypokalemia occurs due to reduced forage intake, when increased gastrointestinal losses occur as with diarrhea, due to increased renal losses as with metabolic alkalosis or exogenous corticosteroid administration which promote kaliuresis, or with redistribution of potassium into the intracellular compartment with alkalosis or in association with insulin-mediated glucose uptake. Aggressive intravenous and oral therapy are often necessary to correct potassium balance disorders, in addition to therapy aimed at correcting any underlying disorder contributing to the potassium imbalance.

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