Efficacy of oral potassium chloride administration in treating lactating dairy cows with experimentally induced hypokalemia, hypochloremia, and alkalemia

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ABSTRACT

Hypokalemia occurs commonly in lactating dairy cows. The objectives of this study were to determine (1) whether a 24-h oral KCl dose of 0.4 g/kg of body weight (BW) was effective and safe in hypokalemic cattle; (2) whether potassium was best administered as 2 large doses or multiple smaller doses over a 24-h period; and (3) the effect of oral KCl administration on plasma Mg concentration and urine Mg excretion in fasted lactating dairy cattle. Plasma K and Cl concentrations were decreased, and blood pH increased, in 15 lactating Holstein-Friesian cows by administering 2 intramuscular (i.m.) 10-mg injections of isoflupredone acetate 24 h apart followed by 2 i.m. injections of furosemide (1 mg/kg of BW) 8 h apart and by decreasing feed intake. Cows were randomly assigned to 1 of 3 treatment groups with 5 cows/group: untreated control (group C); oral administration of KCl at 0.05 g/kg of BW 8 times at 3-h intervals (group K3); and oral administration of KCl at 0.2 g/kg of BW twice at 12-h intervals (group K12). A 24-h KCl dose rate of 0.4 g/kg of BW increased plasma and milk K concentration and plasma Cl concentration, and corrected the metabolic alkalosis and alkalemia, with no clinically significant difference between 2 large doses (group K12) or multiple small doses (group K3) of KCl over 24 h. Oral KCl administration decreased peripheral fat mobilization in cattle with experimentally induced hypokalemia, as measured by changes in plasma nonesterified fatty acid concentration, and slightly augmented the fasting-induced decrease in plasma Mg concentration. Our findings support recommendations for a 24-h oral KCl dose of 0.4 g/kg of BW for treating moderately hypokalemic cattle. Additional Mg may need to be administered to inappetent lactating dairy cattle being treated with oral KCl to minimize K-induced decreases in magnesium absorption.

Key words: potassium, hypochloremia, hypomagnesemia, alkalemia

INTRODUCTION

Hypokalemia occurs commonly in lactating dairy cows with left displaced abomasum (LDA), right displaced abomasum, abomasal volvulus, abomasal impaction, clinical mastitis, retained placenta, and hepatic lipidosis (Smith et al., 2001; Wittek et al., 2005; Kalaitzakis et al., 2010; Constable et al., 2013). The high prevalence of hypokalemia in sick lactating dairy cows is most likely due to a combination of decreased DMI, alkalemia due to sequestration of chloride in the gastrointestinal tract in cattle with LDA, right displaced abomasum, abomasal volvulus, or decreased abomasal emptying rate, hyperinsulinemia secondary to hyperglycemia, the obligatory loss of potassium in milk (1.4 g of K/L of milk), sympathetic nervous system activation, aldosterone release in response to hypovolemia and the need for sodium retention, and decreased whole-body K stores due to the relatively low muscle mass in dairy cows (Grünberg et al., 2006; Constable et al., 2009, 2013). Whole-body depletion of K may be present in healthy dairy cattle immediately after calving, based on the results of K balance studies (Shalit et al., 1991), studies documenting decreased skeletal muscle K content at calving (Kowalczyk and Mayer, 1972), and decreased urine [K] immediately after calving (Hörügel and Fürll, 1998). Hypokalemia is most commonly defined as serum or plasma [K] <3.9 mEq/L in adult cattle (Radostits et al., 2007), although some studies have used a value <3.9 mEq/L for serum or plasma [K] to define hypokalemia (Constable et al., 1991, 2013).

Oral potassium administration is the method of choice for treating lactating dairy cattle with hypokalemia. Oral administration of KCl appears to provide the optimal salt formulation for treating cattle with hypokalemia in that K is needed in cattle with whole-body K depletion, and chloride is needed in cattle with alkalemia and pH-induced compartmental shift of K to

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the intracellular space (Constable et al., 2013). Current treatment recommendations are to administer 30 to 60 g of feed-grade KCl orally twice at a 12-h interval to inappetent dairy cattle with mild to moderate hypokalemia, thereby providing a total 24-h dose of 60 to 120 g of KCl (Constable, 2003). The KCl is administered by use of a balling gun and gelatin boluses or by ororumenal intubation. The treatment recommendation for dairy cattle with severe hypokalemia (<2.5 mEq/L) is 120 g of KCl orally, followed by two 60-g KCl oral treatments at 8-h intervals, for a total 24-h treatment of approximately 240 g of KCl (Sattler et al., 1998; Constable, 2003); this dose is equivalent to a daily KCl dose of 0.4 g/kg of BW for a 600-kg dairy cow. Total daily oral doses of KCl exceeding 0.4 g/kg of BW are not currently recommended except in cattle with profound hypokalemia because they have the potential to result in diarrhea, excessive salivation, muscular tremors of the legs, labored breathing, convulsions, and death (Dennis and Harbaugh, 1948; Peek et al., 2000; NRC, 2001; Constable, 2003).

We were interested in 3 questions related to the treatment of hypokalemia in lactating dairy cattle. The first was to verify whether a 24-h oral KCl dose of 0.4 g/kg of BW was effective and safe. The second was to determine whether KCl was best administered as 2 large doses or multiple smaller doses over a 24-h period. Two large doses over 24 h may be preferable because oral administration of KCl results in a dose-dependent increase in rumen [K] and, consequently, a dose-dependent increase in the number of moles of potassium absorbed per unit time (Scott, 1967). However, a large K dose may activate a gut or hepato-portal sensor that detects K intake and sends a signal to the kidney to increase K excretion in response to increased K ingestion (Greenlee et al., 2009), thereby resulting in less absorbed K being retained. The third issue was to determine the effect of KCl administration on plasma Mg concentration and urine Mg excretion. This was of interest because increasing dietary K intake decreases Mg absorption across the rumen epithelium (Leonhard-Marek et al., 2010) and apparent Mg digestibility (Weiss, 2004). Oral KCl administration therefore has the potential to decrease plasma Mg concentration. A randomized, controlled study in lactating dairy cows with experimentally induced hypokalemia and decreased feed intake was therefore undertaken to explore the 3 issues of interest related to oral KCl treatment. The experimental model was designed to provide a clinically relevant model of hypokalemia, hypochloremia, metabolic alkalosis, alkalemia, decreased feed intake, whole-body K depletion, and mild dehydration in sick lactating dairy cows.

MATERIALS AND METHODS

All methods were approved by the Purdue University Institutional Animal Care and Use Committee.

Animals, Housing, and Feeding

Eighteen pluriparous Holstein-Friesian cows were monitored after parturition and acclimated to a tiestall at the Purdue Dairy Research and Education Center (West Lafayette, IN). All cows were healthy based on the results of routine physical examination and were enrolled into the study at 7 to 14 DIM. Cows were fed a balanced TMR that met the requirements of early lactating cows as recommended by the National Research Council (NRC, 2001). The ration was fed once daily between 0800 and 1000 h and was based on corn silage, alfalfa haylage, and high-moisture corn (typical analysis: CP, 17.3%; ADF, 20.1%; NDF, 30.2%; Ca, 0.97%; P, 0.37%; Mg, 0.34%; K, 1.42% in DM with an energy density of 1.72 Mcal of NE_L/kg of DM). Amounts of TMR fed and refused on a wet weight basis were recorded daily during the study period. Water was available ad libitum throughout the study. Cows were milked twice daily after calving between 0730 and 0900 h and between 1600 and 1930 h in a double-sided herringbone milking parlor. Milk weights were recorded for every milking.

Physical examination and sampling when done on a daily basis occurred between 0800 and 1200 h and before administration of any treatments. Urine samples were obtained daily by perineal stimulation and free catch of a midstream voided sample, except on d 4 when urine samples were collected via a Foley catheter in the bladder. Respiratory rate was determined by visual inspection of thoracic excursions for 30 s. Heart rate was determined by thoracic auscultation for 30 s. Cardiac rhythm was monitored daily, except on d 2, using a base-apex lead system connected to an electrocardiograph (PageWriter Xli, Hewlett-Packard, Boise, ID), which recorded a standard 10-s rhythm strip at 25 mm/s and 1 cm = 1 mV. Cattle were kept in a standing position during recording. Rectal temperature was determined by placing an electronic thermometer into the rectum for at least 30 s. Rumen contraction rate was determined by auscultation of the left dorsal paralumbar fossa for 3 min. Cows were weighed using a calibrated digital large-animal scale immediately after the morning milking on d 1, 4, and 7.

Experimental Method

Cows were administered 2 i.m. 10-mg injections of isoflupredone acetate (9-fluoro-prednisolone acetate;

Predef-2X, Pfizer Animal Health, Kalamazoo MI) 24 h apart on the morning of d 1 and d 2, immediately after physical examination and obtaining samples. The hypokalemic effect of isoflupredone acetate occurs because the mineralocorticoid activity of isoflupredone enhances renal and gastrointestinal (salivary and colonic) losses of potassium. Isoflupredone-induced hypokalemia reaches its nadir of approximately 60 to 70% of the normal value by 72 h after the first of two 10-mg injections (Neff et al., 1960; Coffey et al., 2006), equivalent to d 4 of the study reported here.

The amount of TMR fed on d 3 was decreased to 50% of that recorded on d 2. Feed reduction decreases the rumen potassium concentration and total potassium mass available in the forestomach for absorption and decreases plasma potassium concentration (Holtenius and Dahlborn, 1990).

An i.m. injection of furosemide (1 mg/kg of BW) was administered on the morning of d 3 immediately after physical examination and obtaining samples. A second furosemide injection (1 mg/kg of BW, i.m.) was administered on the afternoon of d 3 approximately 8 h after the first furosemide injection. Furosemide is a potent dose-dependent loop diuretic that inhibits the renal reabsorption of sodium, potassium, and chloride by binding to and inhibiting the activity of the $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ cotransporter, thereby inducing a hypochloremic, hypokalemic, metabolic alkalosis (Vestweber et al., 1989).

A jugular venous catheter was placed in the afternoon on d 3. The skin over the right jugular vein was clipped and aseptically prepared. One milliliter of lidocaine was injected under the skin over the jugular vein and the skin incised (1 cm incision) with a scalpel blade to assist in catheter placement. A 16-gauge, 8-cm-long catheter (Angiocath, Becton Dickinson, Franklin Lakes, NJ) was placed in the jugular vein, an extension set (T-Port extension set ET04TSR, Braun, Bethlehem, PA) attached to the catheter, and the catheter and extension set secured to the neck. After placement, the catheter was flushed every 8 to 16 h with heparinized 0.9% NaCl solution (40 U of heparin/mL). The jugular venous catheter was removed at approximately 72 h after placement or earlier if it became nonfunctional or clinical signs of thrombophlebitis were evident.

A Foley catheter (30 French, 16" $\times$ 30 mL balloon; Jorgensen Laboratories, Loveland, CO) was placed aseptically into the bladder on the morning of d 4 and fixed in position by inflating the balloon to approximately 60 to 65 mL with water. A high balloon inflation volume was used because the recommended inflation volume of 30 mL resulted in some catheters being extruded from the bladder. Silicon tubing was attached to the Foley catheter and routed to a 4-L collection jar for

timed volumetric collection of urine samples. Tubing was disconnected at milking time on d 4.

Treatment

Treatment was administered on the morning of d 4 at least 1 h after placement of the Foley catheter. This was approximately 16 h after the last furosemide injection and 24 h after TMR intake had been decreased by 50%. Fasting was then started for 24 h by removing all feed accessible to the cow; this provided a total duration of 48 h of reduced feed intake to facilitate detection of potassium changes due to treatment. The calculated dose of KCl (Sigma-Aldrich, St. Louis MO) was placed into gelatin capsules (Torpac Inc., Fairfield, NJ) and administered to the caudal aspect of the buccal cavity by a metal balling gun (Torpac Inc.).

Cows were randomly assigned to 1 of 3 treatment groups using a random number generator (Excel, Microsoft Corp., Redmond, WA). Randomization occurred in blocks of 3 to account for any seasonal effects during the study, which took place during September and October. The 3 groups, with 6 cows/group, were (1) control (**C**): insertion of the balling gun into the buccal cavity twice at 12-h intervals; (2) oral administration of KCl at 0.05 g/kg of BW 8 times at 3-h intervals (group **K3**; total 24 h dose of KCl = 0.4 g/kg of BW); and (3) oral administration of KCl at 0.2 g/kg of BW twice at 12-h intervals (group **K12**; total 24 h dose of KCl = 0.4 g/kg of BW). The 24-h dose rate for KCl was based on published recommendations (Constable, 2003; Constable et al., 2013), with K3 representing multiple smaller bolus doses and K12 representing 2 larger bolus doses. Treatment was administered at approximately 1000 and 2200 h (groups C and K12) and 1000, 1300, and 1600 h (immediately before the afternoon milking), 1900, 2200, 0100, 0400, and 0700 h (immediately before the morning milking; group K3). Cows were permitted ad libitum access to the TMR after the 24-h fast (d 5, 6, and 7). Cows were followed for 96 h after the start of treatment (d 4, 5, 6, and 7).

Jugular Venous Blood Sampling and Analysis

Venous blood samples for plasma biochemical analysis were obtained on the morning of d 1, 4, 5, 6, and 7, and at 0.5, 1, 2, 4, 6, 12, and 18 h after the start of treatment on d 4. Blood samples were obtained by venipuncture of the left or right jugular vein using an 18-gauge needle (d 1 and 7) or via the catheter in the right jugular vein (d 4, 5, and 6). Jugular venous blood for plasma biochemical analysis was collected using a 4.5-mL syringe containing lithium heparin (Monovette; Sarstedt, Newton, NC) to minimize the effect of collec-

tion-induced hemolysis on increasing plasma potassium concentration (Schulze, 2009). Syringes containing blood were maintained vertically at room temperature because placing heparinized blood into ice water depresses cellular Na-K ATPase activity and results in the movement of intracellular potassium into plasma (Stankovic and Smith, 2004). Syringes were centrifuged within 30 min of collection at $1,000 \times g$ for 10 to 15 min at room temperature and the plasma harvested and stored at -75°C until analyzed (Stankovic and Smith, 2004). Biochemical analysis was performed on samples thawed at room temperature using an automated analyzer (Hitachi 911, Roche Diagnostics, Basel, Switzerland) to determine the plasma concentrations of Na (ion-selective potentiometry), K (ion-selective potentiometry), Cl (ion-selective potentiometry), total Ca (arsenazo dye binding), Mg (xylydyl blue), P (ammonium molybdate), creatinine (picric acid), and total protein (biuret). The change in plasma volume, relative to that on d 1, was calculated as a percentage change using measured plasma protein concentrations as described elsewhere (Constable et al., 2009). The metabolic status on d 1, 4, 5, 6, and 7 was evaluated by measuring the plasma concentrations of NEFA [acyl-CoA synthetase-acyl-CoA oxidase (ACS-ACOD) method], BHBA (3-hydroxybutyrate dehydrogenase), and glucose (hexokinase) using an automated analyzer (Hitachi 911, Roche Diagnostics) and the same plasma sample that had been analyzed for electrolyte and total protein concentrations.

Venous blood samples for blood pH and gas analysis were obtained in the morning on d 1, 4, 5, 6, and 7. Blood samples were obtained by anaerobic venipuncture of the jugular vein using an 18-gauge needle (d 1 and 7) or via the catheter in the jugular vein (d 4, 5, and 6) into a 3-mL polypropylene syringe containing lyophilized lithium heparin (3 mL Portex syringe, Smiths Medical ASD Inc., Keene, NH). Syringes were maintained at room temperature before being analyzed within 2 h using a blood gas analyzer (ABL5 pH and blood gas analyzer, Radiometer, Copenhagen, Denmark). Measured values from blood gas analysis (pH, partial pressure of CO_2 (pCO_2) and partial pressure of O_2 (pO_2)) were corrected for rectal temperature using standard equations (CLSI, 2009). The plasma concentration of bicarbonate (cHCO_3^- , mmol/L) was calculated using the Henderson-Hasselbalch equation, measured values for pH and pCO_2 , and documented values for the negative logarithm of the apparent dissociation constant ($\text{pK}_1' = 6.095$) for plasma H_2CO_3 and solubility of CO_2 ($S = 0.0307$ mmol/L per mm Hg) in plasma at 37°C (CLSI, 2009), whereby $\text{cHCO}_3^- = S \times \text{pCO}_2 \times 10^{(\text{pH} - \text{pK}_1')}$. Base excess of extracellular fluid [$\text{BE}_{(\text{ecf})}$, mmol/L] was calculated from the measured pH

and pCO_2 , and documented values for pK_1' and S , such that $\text{BE}_{(\text{ecf})} = \text{cHCO}_3^- - 24.8 + 16.2 \times (\text{pH} - 7.40)$ (CLSI, 2009). Alkalemia was defined as blood pH >7.45 (Constable et al., 1991).

Muscle Biopsy

Muscle biopsies of the external abdominal oblique muscle were obtained on d 1, 4, 5, and 7 from each cow using a Bergstrom 6 mm diameter muscle biopsy cannula (ZEPF Surgical Instruments Inc., Bayport, NY). A 10-cm² section of the right paralumbar fossa was clipped and aseptically prepared. An inverted L block with 2% lidocaine was performed using an 18-gauge, 3.8-cm needle attached to the syringe. The skin and subcutaneous fat was incised with a scalpel blade. A biopsy of the external abdominal oblique muscle of approximately 100 mg was obtained using the Bergstrom muscle biopsy cannula and the skin incision closed using tissue adhesive. All visible connective tissue and fat were quickly teased away from the biopsy sample using a 20-gauge needle and the resultant biopsy sample was placed into a preweighed 2-mL polypropylene vial (Fisherbrand cryogenic storage vial, ThermoFisher Scientific Inc., East Providence, RI) within 1 min of sampling. The vial was stored at 4°C for <8 h before being weighed to determine sample wet weight, frozen, and stored at -75°C . The biopsy site was examined for signs of inflammation (swelling) and infection (heat, pain, purulent discharge) daily while the cow was on the study and then for 5 to 10 d after completion of the study.

The total amount of potassium, sodium, magnesium, calcium, phosphorus, and chloride in skeletal muscle tissue was determined via inductively coupled plasma mass spectrometry after drying tissue samples at 95°C to constant weight (Braserton et al., 1997). Electrolyte contents measured in dry skeletal muscle tissue were expressed as micrograms per gram or milligrams per gram of dry weight. The electrolyte contents in dry tissue were converted to contents in wet weight based on the measured wet weight at the time of sampling.

Milk Sampling and Analysis

Representative composite milk samples (15 mL) were obtained on the morning of d 1, 4, 5, 6, and 7 by the milking crew at the dairy. The milk samples were stored at 4°C for up to 8 h and then stored at -75°C . Samples were thawed at room temperature immediately before being analyzed for concentrations of potassium (ion-selective potentiometry) by an automated analyzer (Hitachi 911, Roche Diagnostics). Potentiometry is a useful method to measure changes in milk [K] over time

because potassium in milk is >95% dissociated, with only 4.5% being complexed (Holt et al., 1981).

Urine Sampling and Analysis

Urine pH was measured immediately using a test strip that measures urine pH in 0.5-unit increments (Siemens Diagnostics 2181 Labstix Reagent Strips; Siemens Medical Solutions USA Inc., Malvern, PA). Samples of voided urine were collected in 15-mL vials and aliquots transferred to 3-mL polypropylene tubes if urine collection was successful. Urine samples were stored at -20°C until further analyzed for potassium and magnesium concentration using inductively coupled plasma-optical emission spectroscopy (Optima 4300DV, Perkin Elmer Instruments LLC, Norwalk CT) and creatinine concentration (Jaffe picrate method; Hitachi 911, Roche Diagnostics). This permitted calculation of potassium and magnesium excretion and endogenous creatinine clearance. Urine electrolyte concentrations (g/L) were indexed to urine creatinine concentration (mg/dL), thereby providing a unitless value that corrects urine electrolyte concentrations for changes in urine free water.

Statistical Analysis

Results were expressed as mean $\pm$ standard deviation, or geometric mean or median and range for parameters not normally distributed. Values were log-transformed or ranked when necessary to obtain an approximately normal distribution (as assessed by kurtosis and skewness) and achieve homogeneity of variances before statistical analysis was performed. A statistical software package (9.2, SAS Institute Inc., Cary, NC) was used for statistical analysis, and a P -value <0.05 was considered significant. To determine the effect of treatment on feed intake and milk production, the mean daily intake of the TMR and mean daily milk production on d 5, 6, and 7 were expressed as a percentage of the value on d 1 for each cow, and group median values compared using the Kruskal-Wallis test.

Repeated-measures ANOVA was used to detect differences in measured parameters between treatment groups and over time using a mixed models procedure (PROC MIXED, SAS 9.2, SAS Institute Inc.). Bonferroni-adjusted P -values were used when indicated by significant F test; between-group comparisons at the same time were to group C, within-group comparisons were to the first value for the group on d 4 (i.e., immediately before the first treatment was administered). Primary variables of interest were plasma [K], milk [K], urine [K], skeletal muscle K content (wet muscle weight basis), and any significant interaction terms on

repeated-measures ANOVA. Presentation of the results of statistical analysis focused on those variables with a significant F test for the interaction between treatment and time or a significant F test for treatment.

RESULTS

Animals, Sample Collection, Feed Intake, and Milk Production

Sixteen cows (6 cows in K3 and 5 cows each in C and K12) completed the study. One cow in group K3 that completed the study developed an LDA on d 3 that recurred after rolling on d 5. The cow had marked ketonuria from d 4 onward and the LDA was surgically corrected immediately after completion of the study. Data from this cow were not included in the statistical analysis. One cow developed marked lameness and decreased appetite on d 3 of the study due to digital dermatitis. One cow developed marked ketonuria on d 3 of the study before the reduction in feed intake. Data from these 2 cows were not included in the statistical analysis. Accordingly, statistical analysis was confined to the 15 cows that remained healthy and that completed the study (5 cows in each group). Cows were 10.3 ± 2.2 d in milk when they started the study (d 1).

Blood samples and muscle biopsy samples were obtained at all sampling times. Spontaneously voided urine samples were obtained within 1 h of blood sampling from all cows at all sampling times, except 1 cow in group K3 on d 1. A Foley catheter was successfully placed on d 4 and retained for 24 h in 14 cows; in 1 cow (group C), the Foley catheter could not be easily placed into the bladder because of a narrowed urethral orifice. Urine samples were retained for biochemical analysis at the assigned sampling time from this cow if urine was voided after perineal stimulation; however, urine volume was not recorded.

Experimental Induction of Hypokalemia and Treatment Dose on d 4

The experimental model produced clinical and clinico-pathological changes frequently observed in sick lactating dairy cows; namely, decreased milk production (Figure 1), decreased plasma [K] and [Cl], metabolic alkalosis and alkalemia (Figures 2, 3, and 4), mild dehydration as determined by change in plasma volume (Figure 4), decreased plasma glucose concentration, and increased plasma [NEFA] and [BHBA] (Table 1). Whole-body potassium depletion was suspected to be present on the morning of d 4, as indicated by decreased [K] in plasma and milk in all 3 groups (Figure 2), and decreased skeletal muscle K content in 1 group (Figure

2). Rectal temperature, heart rate, and respiratory rate were not altered within each group on d 4, whereas rumen contraction rate and BW were markedly decreased (Table 1).

Atrial fibrillation was detected in 2 cows on the morning of d 4; both animals had marked hypokalemia ([K];

both 2.4 mEq/L) and alkalemia (pH 7.54 and 7.50) but normocalcemia ([Ca], 9.3 and 9.5 mg/dL). Both cows were randomized to receive KCl; one cow was in group K3 and the other was in group K12. The 2 cows converted to normal sinus rhythm within 24 h (by the morning of d 5) at which time their [K] had increased

Figure 1. Mean $\pm$ SD daily TMR intake (wet weight basis, top panel) and daily milk production (bottom panel) at different time points for cows in group C (black bar, $n = 5$), group K3 (light gray bar, $n = 5$), or group K12 (dark gray bar, $n = 5$) over time. Plasma K concentration was experimentally decreased in 15 multiparous Holstein-Friesian cows in early lactation by IM injection of isoflupredone acetate and furosemide, and by decreasing feed intake by 50% on d 3 and fasting on d 4. Cows were administered KCl orally 8 times on d 4 at 0.05 g/kg of BW every 3 h (group K3) or 2 times on d 4 at 0.20 g/kg of BW every 12 h (group K12), or received no treatment (group C). *Values differ significantly ($P < 0.05$, Bonferroni adjusted) from the value for the group on d 4.

Figure 2. Mean $\pm$ SD plasma K concentration (first panel), urine K concentration to urine creatinine concentration (second panel, semilog plot), milk K concentration (third panel), and skeletal muscle K content (fourth panel) at different time points for cows in group C ($\bullet$, $n = 5$), group K3 ($\circ$, $n = 5$), or group K12 (Δ , $n = 5$) over time. Plasma K concentration was experimentally decreased in 15 multiparous Holstein-Friesian cows in early lactation by IM injection of isoflupredone acetate and furosemide, and by decreasing feed intake by 50% on d 3 and fasting on d 4. Cows were administered KCl orally 8 times on d 4 at 0.05 g/kg of BW every 3 h (group K3) or 2 times on d 4 at 0.20 g/kg of BW every 12 h (group K12), or received no treatment (group C). The hatched bar indicates the time interval that treatment was administered. Data for group C and group K12 are slightly offset to improve readability. †Values differ significantly ($P < 0.05$, Bonferroni adjusted) from group C at the same time; *values differ significantly ($P < 0.05$, Bonferroni adjusted) from the first value for the group on d 4 (immediately before the first treatment was administered).

to 3.0 and 3.0 mEq/L, respectively, and their blood pH decreased to 7.47 and 7.47, respectively.

Cows were administered the following amounts of KCl on d 4; group C, 0 g; group K3, 230 ± 17 g; group K12, 219 ± 35 g. We observed no statistical difference in the 24-h KCl dose administered between groups K3 and K12. The administered oral KCl dose was equivalent to the following oral K doses; group C, 0 g; group K3, 121 ± 9 g; group K12, 115 ± 18 g, with no statistical difference in the dose between groups K3 and K12.

Significant treatment $\times$ time effects were detected and mean values differed from those immediately before treatment on d 4 for plasma [K] ($P < 0.0001$) and urinary [K] to creatinine ratio ($P = 0.0021$), plasma [Cl] ($P = 0.017$) and cHCO_3^- ($P = 0.041$), and blood

pH ($P = 0.048$). Significant treatment effects were detected for pCO_2 ($P = 0.019$), cHCO_3^- ($P = 0.047$) and [P] ($P = 0.034$).

Plasma Biochemical Concentrations

Plasma [K] and [Cl] were decreased in cows administered isoflupredone acetate and furosemide and fasted (Figures 2 and 3). As anticipated, oral administration of KCl rapidly increased plasma K and Cl concentrations, with the maximal increase in plasma [K] and [Cl] occurring approximately 18 h after the start of administration in groups K3 and K12. Plasma and milk [K] and skeletal muscle K content on d 7 were not increased above pretreatment values (d 4) in any group.

Figure 3. Mean $\pm$ SD plasma Cl concentration (top panel) and plasma bicarbonate concentration (bottom panel) at different time points for cows in group C (●, n = 5), group K3 (○, n = 5), or group K12 (△, n = 5) over time. Plasma K concentration was experimentally decreased in 15 multiparous Holstein-Friesian cows in early lactation by IM injection of isoflupredone acetate and furosemide, and by decreasing feed intake by 50% on d 3 and fasting on d 4. Cows were administered KCl orally 8 times on d 4 at 0.05 g/kg of BW every 3 h (group K3) or 2 times on d 4 at 0.20 g/kg of BW every 12 h (group K12), or received no treatment (group C). The hatched bar indicates the time interval that treatment was administered. Data for group C and group K12 are slightly offset to improve readability. †Values differ significantly ($P < 0.05$, Bonferroni adjusted) from group C at the same time; *values differ significantly ($P < 0.05$, Bonferroni adjusted) from the first value for the group on d 4 (immediately before the first treatment was administered).

Plasma [Mg] did not change in cows up to d 4 (Figure 5); however, oral administration of KCl decreased plasma [Mg], with a significant decrease being evident in group K12 at 18 h and 24 h (d 5) after the start of treatment, and in group K3 at 2 d after the start of treatment (d 6).

Small changes in plasma [Na], [Ca], [P], and [total protein] were detected over time with no clear pattern, whereas plasma [creatinine] remained constant.

Figure 4. Mean $\pm$ SD blood pH (top panel) and percentage change in plasma volume (bottom panel) at different time points for cows in group C (●, n = 5), group K3 (○, n = 5), or group K12 (△, n = 5) over time. Plasma K concentration was experimentally decreased in 15 multiparous Holstein-Friesian cows in early lactation by IM injection of isoflupredone acetate and furosemide, and by decreasing feed intake by 50% on d 3 and fasting on d 4. Cows were administered KCl orally 8 times on d 4 at 0.05 g/kg of BW every 3 h (group K3) or 2 times on d 4 at 0.20 g/kg of BW every 12 h (group K12), or received no treatment (group C). The hatched bar indicates the time interval that treatment was administered. Data for group C and group K12 are slightly offset to improve readability. †Values differ significantly ($P < 0.05$, Bonferroni adjusted) from group C at the same time; *values differ significantly ($P < 0.05$, Bonferroni adjusted) from the first value for the group on d 4 (immediately before the first treatment was administered).

Feed Intake, Milk Production, and Energy Metabolism

Mean daily intake of the TMR on d 5, 6, and 7 (Figure 1), when expressed as a percentage of the intake on d 1, did not differ between groups [$P = 0.70$; group C, 71% (42, 105%); group K3, 91% (64, 98%); group K12, 92% (29, 113%); median values and range in parentheses]. Mean daily milk production on d 5, 6, and 7 (Figure 1), when expressed as a percentage of the milk production on d 1, did not differ between groups [P

Table 1. Mean $\pm$ SD values (or geometric mean and range in parentheses) for physical examination findings and plasma biochemical concentrations at different time points for 15 Holstein-Friesian cows in early lactation with plasma K concentration that was experimentally decreased by IM injection of isoflupredone acetate and furosemide, and by decreasing feed intake by 50% on d 3 and fasting on d 4

Factor and group ¹	Day				
	1	4	5	6	7
Physical examination values					
Rectal temperature (°C)					
C	38.3 $\pm$ 0.5	38.3 $\pm$ 0.4	38.0 $\pm$ 0.4	38.2 $\pm$ 0.2	38.7 $\pm$ 0.8
K3	38.3 $\pm$ 0.3	38.4 $\pm$ 0.4	38.0 $\pm$ 0.2	38.3 $\pm$ 0.1	38.7 $\pm$ 0.2
K12	38.4 $\pm$ 0.3	38.5 $\pm$ 0.4	37.9 $\pm$ 0.6	38.5 $\pm$ 0.3	38.5 $\pm$ 0.3
Heart rate (beats/min)					
C	76 $\pm$ 8	77 $\pm$ 12	71 $\pm$ 10	84 $\pm$ 15	83 $\pm$ 6
K3	76 $\pm$ 6	73 $\pm$ 7	69 $\pm$ 5	78 $\pm$ 7	76 $\pm$ 11
K12	80 $\pm$ 4	84 $\pm$ 18	72 $\pm$ 12	82 $\pm$ 9	80 $\pm$ 8
Respiratory rate (breaths/min)					
C	34 $\pm$ 7	37 $\pm$ 7	30 $\pm$ 9	46 $\pm$ 15	39 $\pm$ 8
K3	46 $\pm$ 8	33 $\pm$ 8	31 $\pm$ 7	40 $\pm$ 8	39 $\pm$ 4
K12	41 $\pm$ 16	50 $\pm$ 23	33 $\pm$ 12	43 $\pm$ 12	36 $\pm$ 10
Rumen contraction rate (contractions/3 min)					
C	6.4 $\pm$ 1.3*	3.2 $\pm$ 1.3	4.2 $\pm$ 0.8	6.0 $\pm$ 1.2*	5.6 $\pm$ 1.3*
K3	7.4 $\pm$ 1.1*	4.2 $\pm$ 0.8	3.8 $\pm$ 1.5	5.2 $\pm$ 1.1	7.0 $\pm$ 2.0
K12	7.2 $\pm$ 1.3*	3.8 $\pm$ 1.3	4.2 $\pm$ 2.0	5.6 $\pm$ 1.3	4.8 $\pm$ 1.1
BW (kg)					
C	569 $\pm$ 51*	533 $\pm$ 43	ND ²	ND	518 $\pm$ 27
K3	627 $\pm$ 41*	575 $\pm$ 43	ND	ND	589 $\pm$ 41
K12	598 $\pm$ 92*	548 $\pm$ 69	ND	ND	548 $\pm$ 69
Plasma [Na] (mEq/L)					
C	141 $\pm$ 2	140 $\pm$ 4	140 $\pm$ 2	138 $\pm$ 5	140 $\pm$ 5
K3	137 $\pm$ 4	135 $\pm$ 2	142 $\pm$ 6*	138 $\pm$ 3	137 $\pm$ 4
K12	138 $\pm$ 1	137 $\pm$ 2	141 $\pm$ 4	138 $\pm$ 3	139 $\pm$ 2
Plasma [Ca] (mg/dL)					
C	9.7 $\pm$ 0.3	9.6 $\pm$ 1.0	9.4 $\pm$ 0.8	8.4 $\pm$ 0.5	9.3 $\pm$ 0.5
K3	9.1 $\pm$ 0.3	9.2 $\pm$ 0.8	9.4 $\pm$ 0.8	8.8 $\pm$ 0.2	8.9 $\pm$ 0.6
K12	9.7 $\pm$ 0.7	9.2 $\pm$ 0.7	9.4 $\pm$ 0.5	9.1 $\pm$ 0.5	8.9 $\pm$ 0.8
Plasma [P] (mg/dL)					
C	5.0 $\pm$ 0.7	5.9 $\pm$ 0.9	6.7 $\pm$ 0.9	6.3 $\pm$ 1.5	4.2 $\pm$ 0.8
K3	4.2 $\pm$ 0.7*	5.9 $\pm$ 1.1	6.5 $\pm$ 1.0	5.1 $\pm$ 0.7	3.9 $\pm$ 0.7*
K12	4.1 $\pm$ 0.6*	5.1 $\pm$ 0.5	6.8 $\pm$ 0.6*	4.8 $\pm$ 0.4	4.0 $\pm$ 0.7
Plasma [total protein] (g/dL)					
C	7.3 $\pm$ 0.9	7.9 $\pm$ 1.0	8.7 $\pm$ 0.9	7.7 $\pm$ 0.3	8.0 $\pm$ 0.6
K3	7.3 $\pm$ 0.7*	8.0 $\pm$ 0.9	8.9 $\pm$ 0.8	7.6 $\pm$ 0.2	7.4 $\pm$ 0.4
K12	7.6 $\pm$ 0.8	7.8 $\pm$ 0.9	8.4 $\pm$ 0.5	7.4 $\pm$ 1.0	7.5 $\pm$ 1.0
Plasma [creatinine] (mg/dL)					
C	0.9 $\pm$ 0.1	0.9 $\pm$ 0.1	0.9 $\pm$ 0.1	0.9 $\pm$ 0.1	0.9 $\pm$ 0.1
K3	0.9 $\pm$ 0.2	0.9 $\pm$ 0.2	0.9 $\pm$ 0.2	0.9 $\pm$ 0.2	0.8 $\pm$ 0.2
K12	0.8 $\pm$ 0.1	0.9 $\pm$ 0.2	0.8 $\pm$ 0.1	0.8 $\pm$ 0.1	0.8 $\pm$ 0.1
Plasma [glucose] (mg/dL)					
C	56 $\pm$ 6	59 $\pm$ 8	49 $\pm$ 8	58 $\pm$ 8	57 $\pm$ 12
K3	57 $\pm$ 11	58 $\pm$ 11	50 $\pm$ 8	56 $\pm$ 12	52 $\pm$ 11
K12	58 $\pm$ 5	59 $\pm$ 11	43 $\pm$ 9	58 $\pm$ 21	54 $\pm$ 17
Plasma [BHBA] (mmol/L)					
C	0.56 (0.37 to 0.88)	0.77 (0.58 to 1.12)	1.63 (1.19 to 1.95)	2.33 (1.18 to 5.04)*	2.08 (0.91 to 4.36)*
K3	0.69 (0.46 to 1.85)	0.79 (0.43 to 2.39)	1.70 (0.59 to 5.22)	1.72 (0.73 to 6.39)	1.63 (0.71 to 5.34)
K12	0.79 (0.55 to 1.85)	1.00 (0.65 to 2.67)	2.25 (1.14 to 8.12)	1.42 (0.33 to 8.76)	1.85 (0.79 to 10.20)
Plasma [NEFA] (mmol/L)					
C	0.55 (0.37 to 0.75)*	1.76 (1.11 to 2.50)	1.79 (0.77 to 2.52)	1.17 (0.47 to 2.24)	1.41 (0.83 to 2.37)
K3	0.46 (0.19 to 0.69)*	1.67 (1.24 to 2.49)	1.70 (0.59 to 5.22)	0.58 (0.73 to 6.39)*	0.70 (0.71 to 5.34)*
K12	0.69 (0.33 to 1.41)*	1.80 (1.15 to 2.70)	1.66 (1.00 to 2.43)	0.64 (0.25 to 2.41)*	0.79 (0.42 to 1.98)*
Blood gas analysis ³					
pCO ₂ (mm Hg)					
C	48.6 $\pm$ 7.0*	58.2 $\pm$ 1.9	50.6 $\pm$ 2.9*	51.0 $\pm$ 3.5*	48.2 $\pm$ 4.3*
K3	46.2 $\pm$ 4.1*	56.8 $\pm$ 2.3	51.8 $\pm$ 4.0	48.8 $\pm$ 2.9*	50.4 $\pm$ 3.0
K12	46.0 $\pm$ 5.1*	53.6 $\pm$ 4.4	48.0 $\pm$ 4.6	44.2 $\pm$ 3.1*	45.0 $\pm$ 4.5
pO ₂ (mm Hg)					
C	34 $\pm$ 3	37 $\pm$ 4	37 $\pm$ 3	40 $\pm$ 7	38 $\pm$ 7
K3	31 $\pm$ 6	35 $\pm$ 3	39 $\pm$ 11	41 $\pm$ 7	35 $\pm$ 5
K12	36 $\pm$ 2	39 $\pm$ 3	36 $\pm$ 6	35 $\pm$ 10	37 $\pm$ 5

Continued

Table 1 (Continued). Mean $\pm$ SD values (or geometric mean and range in parentheses) for physical examination findings and plasma biochemical concentrations at different time points for 15 Holstein-Friesian cows in early lactation with plasma K concentration that was experimentally decreased by IM injection of isoflupredone acetate and furosemide, and by decreasing feed intake by 50% on d 3 and fasting on d 4

Factor and group ¹	Day				
	1	4	5	6	7
Urine biochemical analysis					
Urine pH					
C	8.5 $\pm$ 0.0	8.4 $\pm$ 0.2	7.1 $\pm$ 0.8	8.5 $\pm$ 0.0	8.3 $\pm$ 0.4
K3	8.4 $\pm$ 0.2	8.4 $\pm$ 0.2	8.0 $\pm$ 1.1	8.5 $\pm$ 0.0	8.5 $\pm$ 0.0
K12	8.5 $\pm$ 0.0	8.1 $\pm$ 0.9	7.2 $\pm$ 1.1	7.9 $\pm$ 1.3	8.0 $\pm$ 1.1
Urine [creatinine] (mg/dL)					
C	114 $\pm$ 9	107 $\pm$ 22	129 $\pm$ 20	107 $\pm$ 29	108 $\pm$ 32
K3	100 $\pm$ 27	78 $\pm$ 26	108 $\pm$ 48	118 $\pm$ 51	76 $\pm$ 34
K12	97 $\pm$ 16	85 $\pm$ 56	90 $\pm$ 50	94 $\pm$ 28	86 $\pm$ 39

¹Cows were administered KCl orally 8 times on d 4 at 0.05 g/kg of BW every 3 h (group K3) or 2 times on d 4 at 0.20 g/kg of BW every 12 h (group K12), or received no treatment (group C).

²ND = not determined.

³pCO₂ and pO₂ = partial pressure of CO₂ and O₂, respectively.

**P* < 0.05 (Bonferroni adjusted): differ significantly from the first value for the group on d 4 (immediately before the first treatment was administered). There were no significant differences in studied variables between the control group and groups K12 and K3 on any day.

= 0.20; group C, 70% (65, 88%); group K3, 79% (74, 122%); group K12, 84% (66, 95%); median values and range in parentheses].

A significant treatment or interaction effect for plasma [glucose], [NEFA], and [BHBA] was not present; however, plasma [NEFA] decreased in groups K3 and K12 after d 4 but not in group C, and plasma [BHBA] increased in group C after d 4 but not in groups K3 and K12 (Table 1).

Acid-Base Balance

As expected in lactating dairy cows administered isoflupredone acetate and furosemide and feed restricted, all acid-base indices changed over time (Figure 3, Figure 4, Table 1). Alkalemia due to metabolic alkalosis (as demonstrated by the marked increased in the plasma bicarbonate concentration) on d 4 was partially compensated by an increased venous pCO₂ with no detectable change in respiratory rate. Oral administration of KCl in groups K3 and K12 decreased plasma bicarbonate concentration within 24 h, with group K12 having a lower plasma bicarbonate concentration than the control group on d 5 and 6 (Figure 3).

Muscle Biopsy

Skeletal muscle K content (wet weight basis) varied markedly from cow to cow; such variability may have been due, in part, to the relatively small sample size of tissue analyzed (mean, 92 mg; Figure 2). Skeletal muscle K content was decreased on d 4 in group K12, indicating whole-body K depletion, and was not significantly decreased in group K3 or group C. Changes

in skeletal muscle content for the 3 d after d 4 did not reveal a consistent pattern.

Milk Biochemical Analysis

Milk K concentration was decreased on d 4 in all 3 groups due to the administration of isoflupredone acetate, furosemide, and fasting (Figure 2). The amount of K lost in the milk over 24 h starting on d 4 was similar in all 3 groups: group C, 42 $\pm$ 10 g; group K3, 44 $\pm$ 12 g; group K12, 42 $\pm$ 10 g. In other words, cows administered KCl every 12 h did not have an increased loss of K into their milk relative to cows administered KCl every 3 h.

Urine Biochemical Analysis

Endogenous creatinine clearance was constant over 24 h on d 4 for all 3 groups (overall mean, 1.75 mL/min per kg). The 24-h urine volume on d 4 was higher in group K3 (12.7 $\pm$ 2.5 L, *P* = 0.015) than in group C (8.0 $\pm$ 2.0 L); the 24-h urine volume in group K12 (11.9 $\pm$ 2.6 L) tended (*P* = 0.035, Bonferroni-adjusted *P*-value for significance <0.025) to be higher than that in group C. Because mean daily urine volume differed between groups (when measured on d 4), but urinary [creatinine] remained constant on d 1, 4, 5, 6, and 7 (Table 1), urine electrolyte concentrations (expressed in g/L) were indexed to urine creatinine concentration (in mg/dL). This provided a unitless value for the ratio of urine electrolyte concentration to the urine creatinine concentration.

Cows in group K12, but not group K3, had a higher urinary [K]:[creatinine] than cows in group C for much

Figure 5. Mean $\pm$ SD plasma magnesium concentration (top panel) and urine magnesium concentration (bottom panel) at different time points for cows in group C ($\bullet$, $n = 5$), group K3 ($\circ$, $n = 5$), or group K12 (Δ , $n = 5$) over time. Plasma K concentration was experimentally decreased in 15 multiparous Holstein-Friesian cows in early lactation by IM injection of isoflupredone acetate and furosemide, and by decreasing feed intake by 50% on d 3 and fasting on d 4. Cows were administered KCl orally 8 times on d 4 at 0.05 g/kg of BW every 3 h (group K3) or 2 times on d 4 at 0.20 g/kg of BW every 12 h (group K12), or received no treatment (group C). The hatched bar indicates the time interval that treatment was administered. Data for group C and group K12 are slightly offset to improve readability. *Values differ significantly ($P < 0.05$, Bonferroni adjusted) from the first value for the group on d 4 (immediately before the first treatment was administered).

of the 24-h period immediately after treatment (Figure 2). More importantly, the amount of K excreted in the urine on d 4 (24 h) in group K12 (52 ± 9 g) and group K3 (49 ± 14 g) was greater than the amount excreted in group C (23 ± 7 g; $P = 0.0019$; vs. group K12, $P = 0.0037$; vs. group K3). We observed no difference in the 24-h mean urinary excretion of K between groups K12 and K3 ($P = 0.70$). In other words, cows administered KCl every 12 h did not have an increased loss of K in their urine relative to cows administered KCl every 3 h.

Urinary [Mg]:[creatinine] was numerically decreased during fasting for cows in all 3 groups, with some recovery after the end of fasting (Figure 5). The decrease

in urinary [Mg]:[creatinine] was statistically significant at many time points for group K12 and for several time points for group K3. More importantly, the amount of Mg (overall mean, 2.2 g) lost in the urine over 24 h on d 4 was similar for all 3 groups.

DISCUSSION

The major finding of the study reported here was that a 24-h dose rate of KCl of 0.4 g/kg of BW appeared suitable for the initial treatment of lactating dairy cattle with moderate hypokalemia, with no clear difference between 2 large doses (group K12) or multiple small doses (group K3). Our finding that plasma and milk K concentrations and skeletal muscle K content on d 7 were not increased above pretreatment values (d 4) in the 2 treatment groups suggests that the duration of treatment was too short or that feed intake was not adequate for the level of milk production.

Skeletal muscle K content is considered the most sensitive and specific method for assessing whole-body K status (Johnson et al., 1991) and therefore is considered the reference method. Skeletal muscle is considered the best tissue to sample because it contains approximately 75% of the whole-body stores of K. A standardized muscle should be evaluated in cattle because differences in K content of greater than 15% are present in individual animals and this muscle-to-muscle variation is greater than that produced by breed (Sim and Wellington, 1976). Skeletal muscle K content in the external abdominal oblique muscle was measured to determine the clinical utility of measuring the K content of this muscle during surgical correction of LDA by right flank omentopexy with the cow in a standing position. Our failure to identify marked and consistent changes in skeletal K content following injections of isoflupredone acetate and furosemide, as well as following treatment, may reflect the absence of whole-body K depletion; possibly a longer duration of decreased feed intake or higher level of milk production is required to mimic naturally occurring cases of severe hypokalemia in lactating dairy cows.

The purpose of measuring milk [K] was to calculate milk K losses and to determine whether measuring milk [K] would be clinically useful for monitoring the response to treatment in hypokalemic dairy cows. Milk K concentration is theoretically more sensitive than serum or plasma [K] in detecting whole-body K depletion in individual cows because milk [K] is constant for an individual cow over a short period. Moreover, milk [K] is closer to intracellular fluid constituents than serum or plasma [K] and, on this basis, may provide useful insight into K homeostasis over time in an individual cow. Potassium depletion in lactating dairy cows

caused milk K concentration to decrease from 37.1 to 32.7 mmol/L (Pradhan and Hemken, 1968); this was a greater percentage decrease than that in plasma or whole blood of cattle with whole-body K depletion. However, milk [K] changes during lactation, being 42 mmol/L in early lactation, 40 mmol/L in mid lactation, and 27 mmol/L in late lactation, with a mean bulk milk [K] of 37 mmol/L (Gaucheron, 2005). The large change in milk [K] during lactation means that there is marked individual variation in milk [K] in healthy cattle, with variations of up to 50% occurring between cows (Sasser et al., 1966; Pradhan and Hemken, 1968; Sattler et al., 2001). This variability appears to be due to changes in milk fat, protein, and lactose percentage, with milk [K] being most strongly associated ($r = -0.74$) with milk lactose concentration (Oshima and Fuse, 1977). The relationship between K and lactose concentration in milk is due to the fact that these are important contributors to milk osmolality, which is constant and isotonic (Oshima and Fuse, 1977). The large cow-to-cow variability in milk [K] makes it difficult to identify a suitable cut-point for milk [K] that accurately predicts whole-body K depletion in sick lactating dairy cows. However, monitoring milk [K] in individual cows may have clinical utility as a monitoring tool to gauge the response to therapy with KCl.

The purpose of measuring the ratio of urine [K] to [creatinine] was to determine whether this measurement would be clinically useful in monitoring the response to treatment. Urine K concentrations are normally high in lactating dairy cattle but variable, with a mean fractional clearance of 82% and a coefficient of variation of 61% (Neiger and Hagemoser, 1985). The large variability in urine K concentration would make it difficult to produce a suitable cut-point for identifying whole-body K depletion. However, determination of urine K concentration has clinical utility in an individual cow ingesting a constant diet over time because it reflects K homeostasis.

Hypokalemia commonly occurs due to a compartmental shift of K from the extracellular to intracellular space in cattle with hyperinsulinemia due to hyperglycemia or alkalemia due to metabolic alkalosis (Svendsen, 1969; Grünberg et al., 2006; Constable et al., 2013). The study design did not allow us to determine the relative contribution of alkalemia and metabolic alkalosis to the experimentally induced hypokalemia. Alkalemia and metabolic alkalosis are frequently present in dairy cattle with clinical signs of severe hypokalemia (Sielman et al., 1997; Sattler et al., 1998; Peek et al., 2000). It is widely accepted that serum [K] accurately reflects intracellular K stores in euglycemic or hypoglycemic animals with blood pH within the reference range; however, it is generally believed that in severe

alkalemia, serum [K] must be <2.5 mEq/L to reflect the presence of significant intracellular K depletion (Burnell and Scribner, 1957). Experimental induction of metabolic alkalosis by oral administration of sodium bicarbonate in 3 Jersey cows caused marked metabolic (strong ion) alkalosis, hypokalemia, and an increase in muscle K concentration of 6 to 10%, indicating an intracellular shift of K from the extracellular space to the intracellular space (Svendsen, 1969). The association between hypokalemia and alkalemia raises the interesting question as to the change in skeletal muscle K concentration in dairy cattle with LDA; affected animals are inappetent, which will lead to whole-body K depletion and decreased skeletal muscle K concentration. However, cattle with LDA also have alkalemia and metabolic (strong ion) alkalosis, which will lead to increased skeletal muscle K concentration, and sequestration of K-rich abomasal fluid associated with abomasal displacement, which will lead to decreased K absorption.

Marked abnormalities in serum [K], both hypokalemia and hyperkalemia, are frequently associated with cardiac arrhythmias (Fosha-Dolezal and Fedde, 1988). Although no large-scale studies have examined the association between hypokalemia and cardiac arrhythmias in adult cattle, we have frequently observed hypokalemia, hypocalcemia, and alkalemia in lactating dairy cattle with LDA and atrial fibrillation. In the study reported here, 2 of 15 lactating dairy cows with experimentally induced hypokalemia and alkalemia developed atrial fibrillation that resolved within 24 h of administration of KCl, accompanied by an increase in plasma [K] and a decrease in blood pH. Atrial fibrillation was diagnosed in 4 of 10, 2 of 14, and 5 of 17 cows with naturally acquired hypokalemia (Sielman et al., 1997; Sattler et al., 1998; Peek et al., 2000), and in 1 of 7 lactating dairy cows with experimentally induced hypokalemia following i.m. administration of two 20-mg doses of isoflupredone acetate at a 48-h interval (Coffer et al., 2006). Taken together, these findings suggest that hypokalemia plays a role in the development of atrial fibrillation in adult cattle.

We did not observe a significant treatment or interaction effect between treatment and time for feed intake, milk production, or plasma [glucose], [NEFA], or [BHBA], despite moderate numerical differences in some of these variables between groups. This result is similar to the findings of many other short-term studies in early lactation dairy cows and most likely reflects a type II error (inadequate statistical power). Relatively large between-cow variability in early lactation means that group sizes greater than 5, such as 15 cows/group (Fürl et al., 2010), are usually needed to detect an effect on energy metabolism, feed intake, or milk pro-

duction. Nevertheless, our findings that plasma [NEFA] decreased in groups K3 and K12, but not in group C, after d 4, and that plasma [BHBA] increased in group C, but not in groups K3 and K12, after d 4, suggest that oral KCl administration decreased peripheral fat mobilization in cattle with experimentally induced hypokalemia.

Our findings suggest that a prospective clinical study in sick dairy cows in early lactation is indicated to determine the clinical efficacy and safety of oral KCl (daily dose of 0.4 g/kg of BW in 2 divided doses) in treating cattle with naturally acquired hypokalemia. Our results indicate that oral KCl may need to be administered for more than 1 d in hypokalemic cattle.

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