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The effect of different treatments for early-lactation hyperketonemia on blood β-hydroxybutyrate, plasma nonesterified fatty acids, glucose, insulin, and glucagon in dairy cattle

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ABSTRACT

Despite increased efforts in preventing the occurrence of metabolic disorders in transition cows, hyperketonemia remains a frequent early-lactation metabolic disease affecting an average of 40% of cows in herds in the United States. Despite the demonstrated economic effect of this disorder, controlled clinical trials comparing different treatment strategies in affected cows are lacking. The objective of our study was to investigate the effect of treatment with intravenous glucose, oral propylene glycol, or a combination of both on the reduction in blood β-hydroxybutyrate (BHB) concentrations of early-lactation hyperketonemic dairy cows. Multiparous Holstein cows between 3 to 9 d in milk were screened for hyperketonemia using a handheld meter 3 times per week, and enrolled at whole blood BHB concentration ≥1.2 mmol/L to 1 of 4 treatment groups: (1) 500 mL of a 50% dextrose solution i.v. once daily for 3 d (GLU, n = 9), (2) 300 mL of propylene glycol as a drench once daily for 3 d (PG, n = 9), (3) a combination treatment of a 500 mL of 50% dextrose solution i.v. and 300 mL of propylene glycol orally once daily for 3 d (GLU+PG, n = 8), or (4) an untreated control group (CTRL, n = 8). Blood samples were collected immediately before as well as at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 h after administration of the first treatment through a jugular catheter and 3 times per week thereafter from coccygeal vessels. Concentrations of BHB were measured in whole blood, and plasma samples were analyzed for glucose, fatty acid (NEFA), insulin, glucagon, and electrolyte concentrations. The EDTA-anticoagulated blood samples were assessed for red blood cell indices, and smears were made for evaluation of red blood cell morphology. Outcomes were analyzed using repeated measures analysis. Overall least squares means (95% CI) of whole blood BHB concentrations between 1 h and d 11 relative to first treatment were 1.11 (0.95 to 1.30), 1.26 (1.07 to 1.47), 0.96 (0.81 to 1.13), and 1.53 (1.30 to 1.80) mmol/L for the GLU, PG, GLU+PG, and CTRL groups, respectively. Treatment with both glucose and propylene glycol led to a greater magnitude and more prolonged decrease in BHB concentrations compared with individual treatments. The NEFA and glucagon concentrations were lower immediately after treatment in GLU and GLU+PG groups compared with CTRL, and treatment with both glucose and propylene glycol was associated with a greater increase in glucose and insulin concentrations immediately after treatment compared with CTRL and GLU treatment alone. Treatments did not lead to differences in plasma mineral concentrations. We conclude that treatments varied in the magnitude of decreasing blood BHB concentrations in hyperketonemic postpartum cows, with the greatest decline after treatment with a combination of intravenous glucose and oral propylene glycol.
Key words: ketosis, treatment, glucose, propylene glycol, insulin

INTRODUCTION

During the last decade, a considerable amount of work has been completed linking postpartum hyperketonemia to negative health outcomes, such as displacement of the abomasum, metritis, as well as an increased risk of herd removal and a loss in reproductive success and milk production (Duffield et al., 2009; Ospina et al., 2010; Roberts et al., 2012). Despite an increase in scientific knowledge about risk factors for early-lactation hyperketonemia (McArt et al., 2013; Tao and Dahl, 2013; Berge and Vertenten, 2014) and nutritional strategies aimed at preventing this metabolic disorder (Lean et al., 2013; Roche et al., 2013; Mann et al., 2015), an average of 40% of postpartum cows experience at least one hyperketonemic event during early lactation (McArt et al., 2012b), which we recently estimated to have an economic effect of $289 per case (McArt et al., 2015). A variety of treatment strategies for hyperke-

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tonemia are used and commonly include administration of intravenous dextrose, as well as oral medication with glucogenic precursor substances such as propylene glycol. We showed that oral drenching with propylene glycol not only helped resolve hyperketonemia but also reduced the risk for displacement of the abomasum, decreased early-lactation culling risk, and increased milk production (McArt et al., 2011, 2012a).

Despite widespread use, information from controlled clinical studies is lacking on the effect of intravenous glucose in the treatment of early-lactation hyperketonemia (Gordon et al., 2013). Wagner and Schimek (2010) showed that postpartum cows treated with 500 or 1,000 mL of 50% intravenous dextrose solution as a single bolus were at risk for hypophosphatemia, a condition that is associated with downer cow syndrome and postparturient hemoglobinuria (Grünberg, 2014). The usefulness of the few available controlled studies on possible detrimental effects of intravenous administration of a glucose bolus has partially been hampered by the fact that treatments were applied to nonlactating (Holtenius et al., 2000) or to fresh cows with or without hyperketonemia (Wagner and Schimek, 2010), which may differ drastically in hormonal milieu and energy balance, and thus response in reduction of BHB concentrations from the animals receiving these treatments on dairy farms.

Although the described treatments are among those most commonly recommended for treatment of hyperketonemia in postpartum dairy cattle, evidence for their use and a comparison of their respective metabolic consequences alone or in combination are largely unstudied, especially in randomized controlled studies. Important metabolic consequences include the effect of treatments on the concentrations of markers of negative energy balance, and hormonal control of metabolism through insulin and glucagon signaling because both pancreatic hormones play a role in early-lactation ketogenesis (Brockman, 1979). In addition, we wanted to describe possible effects on blood electrolyte balance and red blood cell toxicity because toxic side effects have been reported for propylene glycol and can occur at doses as low as 40 g (Nielsen and Ingvartsen, 2004). Although evidence from other species indicates this might be the case (Potter, 1958; Bauer et al., 1992), a possible effect of propylene glycol treatment on red blood cells has not been evaluated in hyperketonemic postpartum dairy cattle to the best or our knowledge.

Thus, our aim was to address the gap in knowledge regarding the effects of commonly used treatments alone or in combination in the appropriate study population, cows with naturally occurring hyperketonemia in the immediate postpartum period. Our hypothesis was that different treatment strategies commonly used for early postpartum hyperketonemia differ in their ability to reduce the concentrations of BHB and would differ in their effect on concentrations of plasma fatty acids (**NEFA**), glucagon, insulin, glucose, as well as plasma electrolytes. In addition we investigated possible effects of treatments on red blood cell morphology.

MATERIALS AND METHODS

All procedures were evaluated and approved by the Cornell University Institutional Animal Care and Use Committee (protocol no. 2015–0097). Multiparous Holstein cows between 3 and 9 DIM at the Cornell University Ruminant Center in Harford, New York, were screened for blood BHB concentrations between January and July 2016. After the morning milking at 0700 h, fresh cows were locked up 3 times per week and whole blood BHB concentration was measured by taking a 1-mL blood sample from the coccygeal vessels using a syringe and needle and immediately applying the sample to a handheld meter (TaiDoc, Pharmadoc, Lüdersdorf, Germany) recently validated for use with bovine blood samples (Bach et al., 2016). Cows were enrolled in 1 of 4 treatment groups following a randomized block design when whole blood BHB concentration was $\geq$1.2 mmol/L.

Samples and Treatments

At enrollment, cows were weighed and moved to a treatment area where an extended use 14 gauge $\times$ 13.3 cm jugular catheter (Milacath, Mila International, Florence, KY) was placed in 1 jugular vein after administration of 0.003 to 0.005 mg/kg of acepromazine maleate (VetOne, Boise, ID) i.v. as described previously (Mann et al., 2016). Blood samples were obtained through an intravenous extension set connected to the catheter immediately before the first treatment (0 h), as well as at 1, 2, 4, 8, 12, 24, 36, 48, 60, and 72 h relative to treatment, after which the jugular catheter was removed. From the day after removal of the catheter until the end of the study period at 21 DIM, blood samples (10 mL) were taken 3 times a week before feeding (between 0600 and 0700 h) from the coccygeal vessels.

Cows were allocated to 1 of 4 groups using a randomized block design: (1) 500 mL of a 50% dextrose solution (dextrose 50% injection, VetOne) i.v. once a day for 3 d (**GLU**, n = 9), (2) 300 mL of propylene glycol (100% propylene glycol, USP, VetOne) orally once a day for 3 d (**PG**, n = 9), (3) 500 mL of a 50% dextrose solution i.v. and 300 mL of propylene glycol orally once a day for 3 d (**GLU+PG**, n = 8), or (4) an untreated control group (**CTRL**, n = 8). Propylene glycol was administered as a drench immediately