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The effect of different treatments for early-lactation hyperketonemia on liver triglycerides, glycogen, and expression of key metabolic enzymes in dairy cattle

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ABSTRACT

Despite the widespread use of treatments for postpartum hyperketonemia in dairy cows, there is currently a lack of evidence comparing their effects on both the resolution of hyperketonemia and the potential effects on the liver of affected animals. The objective of our work was to investigate the effect of commonly used hyperketonemia treatments on hepatic triglyceride and glycogen content as well as on the mRNA and protein abundance of key enzymes involved in gluconeogenesis, ketogenesis, and lipid metabolism. Multiparous Holstein cows between 3 and 9 d in milk were screened 3 times per week and enrolled in the study when whole-blood β -hydroxybutyrate concentrations measured ≥ 1.2 mmol/L. Cows were randomly allocated to 1 of 4 groups: (1) 500 mL of a 50% D-glucose solution intravenously once a day for 3 d ($n = 8$), (2) 300 mL of propylene glycol orally once a day for 3 d ($n = 8$), (3) 500 mL of a 50% D-glucose solution intravenously and 300 mL of propylene glycol orally once a day for 3 d ($n = 8$), or (4) an untreated control group ($n = 8$). Liver biopsies were taken on the day of enrollment as well as on the day following completion of treatments. Liver triglyceride and glycogen content were determined by colorimetric and fluorometric methods, respectively. Gene and protein expression of pyruvate carboxylase, phosphoenolpyruvate carboxykinase 1, glucose-6-phosphatase, 3-hydroxy-3-methylglutaryl-CoA synthase 2, acetyl-CoA carboxylase, and carnitine palmitoyltransferase 1A were compared between groups and time points using quantitative reverse transcriptase PCR and Western blotting techniques, respectively. In addition, the ratio of light chain 3B II:I was determined

by Western blotting. Plasma samples from both time points for each enrolled cow were submitted for chemistry analysis. Data were analyzed using a repeated measures ANOVA taking into account the paired nature of the data, and differences between all groups and time points were controlled for multiple comparisons using the Tukey procedure. No difference was found in triglyceride or glycogen concentration between treatment groups. The gene expression of pyruvate carboxylase decreased in the group receiving both treatments, whereas protein expression of this enzyme increased in all groups over time. The autophagy marker light chain 3B II:I decreased in the group receiving both glucose and propylene glycol. No other changes in gene or protein expression of key hepatic enzymes were associated with treatments. We conclude that intravenous glucose and oral propylene glycol, commonly used treatments for ketosis in postpartum dairy cows, administered alone or in combination for a duration of 3 d did not have important beneficial or detrimental effects on selected indicators of liver composition and function in cows with hyperketonemia.

Key words: ketosis, liver, triglyceride, glycogen, enzyme

INTRODUCTION

Hyperketonemia is characterized by an excessive concentration of ketone bodies in blood and is a highly prevalent and costly metabolic disorder of postpartum dairy cows (McArt et al., 2015; Raboisson et al., 2015; Gohary et al., 2016). In an attempt to reduce the risk for negative health and production outcomes, cows that develop hyperketonemia (defined as a whole-blood BHB concentration of ≥ 1.2 mmol/L; McArt et al., 2013) are identified using herd screening programs and treated early in the course of the disorder (Ospina et al., 2013; Tatone et al., 2016; Gordon et al., 2017). Among the most commonly used treatments is daily administration

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of intravenous glucose and oral propylene glycol alone or in combination. Despite their widespread use, there is currently a lack of evidence comparing the effects of such treatments on the resolution of hyperketonemia and on the potential effects on the liver of affected animals. The liver plays an important role in the successful transition to lactation (Graber et al., 2010), and treatments for hyperketonemia aim to maintain or improve hepatic gluconeogenesis and glucose status as well as prevent or reduce the accumulation of triglycerides in the liver (Herd and Emery, 1992; Gordon et al., 2013).

In the liver, propylene glycol metabolism increases the availability of oxaloacetate from pyruvate and thus provides a source for this important intermediary in the Krebs cycle often lacking in cows with ketosis (Nielsen and Ingvarsen, 2004). In addition, it is converted to glucose from propionate via the gluconeogenic pathway in the liver (Nielsen and Ingvarsen, 2004), and administration of propylene glycol may increase mRNA expression of gluconeogenic enzymes in the liver (Zhang et al., 2015). In contrast, intravenous glucose adds directly to the available glucose pool and circumvents a need for hepatic gluconeogenesis. As the expression of gluconeogenic enzymes is controlled by substrate availability and energy balance, one concern is that a surplus of glucose supply to the liver may have detrimental consequences if it leads to downregulation of gluconeogenic enzymes (Al-Trad et al., 2010b).

Successful physiologic adaptation to lactation also requires an upregulation of enzymes involved in lipid metabolism and β -oxidation (Bauman and Currie, 1980), which are often overwhelmed in cows with ketosis, leading to an accumulation of fat in the liver (Herd, 2000; Dann et al., 2005). Ideally, successful treatment or prevention of hyperketonemia controls or reduces the rate at which triglycerides are deposited in the liver by reducing lipolysis and increasing the oxidation of fatty acids in the liver.

To date, the effect of the commonly used hyperketonemia treatments (oral propylene glycol and intravenous glucose) on liver function and hepatic lipid content in the peripartum period have not been compared in a randomized controlled trial. The primary objective of our study was thus to determine the effect of these treatments on the expression of select key enzymes that regulate hepatic gluconeogenesis, ketogenesis, and lipid metabolism. In addition, we wanted to determine a possible association of treatments with liver triglyceride and glycogen content as well as with indicators of liver function determined by plasma chemistry analysis. We hypothesized that common treatments for hyperketonemia vary in their effects on liver metabolism based on the different metabolic pathways involved in their mode of action.

MATERIALS AND METHODS

All procedures were evaluated and approved by the Cornell University Institutional Animal Care and Use Committee (protocol no. 2015-0097). Housing, management, and enrollment of animals was as previously described (Mann et al., 2017). In brief, multiparous Holstein cows between 3 and 9 DIM at the Cornell University Ruminant Center in Harford, New York, were screened for blood BHB concentrations after the morning milking 3 times per week. Cows were enrolled in 1 of 4 treatment groups following a randomized block design when whole-blood BHB concentration was ≥ 1.2 mmol/L and were moved to individual sawdust-bedded tiestalls with feed bins until the end of the study period at 21 DIM. A TMR was offered ad libitum; cows were fed once daily at 0900 h, and amounts fed were adjusted to allow for a minimum of 5% refusals.

Treatments

Cows were allocated to 1 of 4 groups using a randomized block design: (1) 500 mL of a 50% D-glucose solution (dextrose 50% injection, VetOne, Boise, ID) intravenously once a day for 3 d (**GLU**; $n = 8$), (2) 300 mL of propylene glycol (100% propylene glycol, VetOne) orally once a day for 3 d (**PG**; $n = 8$), (3) 500 mL of a 50% D-glucose solution intravenously and 300 mL of propylene glycol orally once a day for 3 d (**GLU+PG**; $n = 8$), or (4) an untreated control group (**CTRL**; $n = 8$). Treatments were always administered immediately before the morning feeding at the same time every day. Propylene glycol was administered as a drench immediately before morning feeding using a manual drenching gun (Neogen, Lexington, KY). After warming to body temperature in a water bath, glucose was administered as a rapid infusion through the jugular catheter. Blood samples were taken into evacuated tubes with 158 units of sodium heparin (Beckton Dickinson, Franklin Lakes, NJ) at 0, 1, 2, 4, 8, 12, 24, 36, 48, and 72 h relative to treatment. Samples at 24 and 48 h were taken immediately before administration of the second and third treatments, respectively. All blood samples were placed on ice, and heparinized plasma was obtained within 60 min of sampling by centrifugation at $2,800 \times g$ for 20 min at 4°C. Whole-blood concentrations of BHB and plasma concentrations of fatty acids, glucose, glucagon, and insulin were determined as previously described (Mann et al., 2017). Heparinized plasma samples for 0- and 72-h time points were submitted to the Clinical Pathology Laboratory within the Animal Health Diagnostic Center at Cornell University (Ithaca, NY) for blood chemistry analysis (Roche P modular chemistry analyzer, Roche Diagnostics, Indianapolis, IN).

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