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Effects of a combination butaphosphan and cyanocobalamin product and insulin on ketosis resolution and milk production

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ABSTRACT

The objective of this study was to determine the effects of butaphosphan-cyanocobalamin (B+C), glargine insulin, and propylene glycol on resolution of ketosis and average daily milk yield after treatment. Cows from 16 herds in Ontario, Canada, and 1 herd in Michigan were tested at weekly intervals between 3 and 16 DIM. Ketosis was defined as blood β-hydroxybutyrate (BHB) ≥1.2 mmol/L. All ketotic cows were given a baseline treatment of 3 d of 300 g of propylene glycol orally. Animals were then randomly assigned to treatment with 3 doses of either 25 mL of B+C or 25 mL of saline placebo and 1 dose of either 2 mL (200 IU) of glargine insulin or 2 mL of saline placebo in a 2 × 2 factorial arrangement. Outcomes of interest on all farms were ketosis cure (blood BHB <1.2 mmol/L 1 wk postenrollment), maintenance of ketosis cure (blood BHB <1.2 mmol/L 1 and 2 wk postenrollment), and blood BHB concentrations at 1 and 2 wk postenrollment. Milk weights were collected daily in 1 large freestall herd. Repeated measures ANOVA was used to evaluate blood BHB concentrations 2 wk after treatment and milk production for 30 d after treatment. Poisson regression was used to examine the effect of treatment on cure and maintenance of cure. Due to a regulatory delay causing temporary unavailability of B+C in Canada, data were analyzed in 2 sets of models: one for insulin and the corresponding placebo (n = 620) and one for the full trial (n = 380). Animals with blood glucose concentrations ≤2.2 mmol/L at the time of ketosis diagnosis were 2.1 times more likely (95% CI = 1.2 to 3.7) to be cured if treated with B+C. Animals in lactation 3 or higher that had blood glucose concentrations <2.2 mmol/L at enrollment produced 4.2 kg/d (95% CI = 1.4 to 7.1) more milk if treated with insulin versus placebo and 2.8 kg/d (95% CI = 0.9 to 4.7) more milk if treated with B+C versus placebo. Animals in lactation 3 or higher with blood glucose ≥2.2 mmol/L that were treated with insulin produced 2.3 kg/d (95% CI = 0.3 to 4.4) less milk than untreated controls. No interaction was observed between treatments. This evidence suggests that B+C and insulin may be beneficial for ketosis treatment in animals with blood glucose <2.2 mmol/L at ketosis diagnosis. It also suggests that blood glucose concentration may be an important predictor of success of ketosis treatment.

Key words: ketosis, insulin, cyanocobalamin, propylene glycol

INTRODUCTION

The transition from the late dry period to early lactation requires a highly orchestrated series of physiological processes to occur to facilitate a smooth start to lactation (Bauman and Currie, 1980). In some animals, proper adaptation does not occur. These animals are prone to metabolic disease, especially hyperketonemia (Herdt, 2000).

Effective treatment of cows with ketosis is challenging. Recently, interest has been renewed in identifying efficacious ketosis treatments. One recent study examined the effects of propylene glycol (**PG**) treatment and found that treated cows were more likely to resolve ketosis, had increased milk production, and were less likely to have a displaced abomasum (**DA**) or be culled during the first 30 d of lactation (McArt et al., 2011, 2012a). This study provided a good base from which to investigate whether additional treatments would further alleviate the negative effects of ketosis.

A combination butaphosphan-cyanocobalamin (**B+C**, Catosal, Bayer, Shawnee, KS) product has been investigated for ketosis prevention and treatment (Lohr et al., 2006; Fürll et al., 2010; Rollin et al., 2010). Cyanocobalamin is a form of vitamin B_{12} that has been shown to be decreased in cows around the time of parturition (Kincaid and Socha, 2007). It has been hypothesized that administration of vitamin B_{12} may increase gluconeogenesis by increasing the activity of methylmalonyl-CoA mutase, a vitamin B_{12}-dependent

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enzyme in the tricarboxylic acid cycle (Kennedy et al., 1990). In combination with folate, vitamin B_{12} also plays an important role in AA synthesis through remethylation of homocysteine to methionine (Preynat et al., 2009a). Methionine is essential for protein synthesis and acts as a source of methyl groups, which are necessary for many pathways in milk protein production. Treatment of first lactation animals with injectable B_{12} was reported to increase milk production in one study (Girard and Matte, 2005), but not in another (Akins et al., 2013). Butaphosphan, an organic phosphorus source, may contribute to gluconeogenesis (Rollin et al., 2010) because intermediate compounds in gluconeogenesis must be phosphorylated to continue the cycle. However, it is unclear if this form of phosphorus is biologically available to the animal.

Rollin et al. (2010) gave B+C on the day of calving and the following day. Treatment with B+C significantly reduced the odds of development of subclinical ketosis development in cows in third lactation or greater, but it had no effect in younger animals. A German study examined the effects of B+C when it was administered to cows with a DA and reported that treated cows had an increase in rumination compared with untreated cows (Lohr et al., 2006). However, these data were collected subjectively and the clinical and economic importance of these outcomes is unclear. Butaphosphan-cyanocobalamin has never been used in a large-scale clinical trial for the treatment of subclinical ketosis.

Insulin might be useful in ketosis treatment by suppressing fat mobilization and slowing the production of ketone bodies (Hayirli, 2006). Secretion of insulin is decreased in dairy cattle postpartum (Weber et al., 2016). Tissue insulin responsiveness also decreases around the time of parturition to spare glucose for milk production (Hayirli, 2006). This decrease in responsiveness to insulin is exacerbated by the presence of ketone bodies in the blood (Sakai et al., 1993). Robertson (1966) found that the addition of insulin to steroid administration for treatment of ketosis increased milk production and improved appetite in treated animals over 5 d. Sakai et al. (1993) compared the effects of intravenous glucose in conjunction with subcutaneous insulin compared with glucose treatment alone and found that the addition of insulin decreased blood ketones and increased blood glucose. Seifi et al. (2007) reported that animals treated with insulin were more likely to develop ketosis and treated animals that were subclinically ketotic at time of enrollment were less likely to experience ketosis resolution than untreated animals. However, the animals treated in this study were not given a glucose source in conjunction with the administration of the insulin. Use of insulin in ketosis treatment is uncommon, likely due to the risk of severe hypoglycemia if administered without a glucose source (Hayirli, 2006).

The purpose of this study was to examine the effects of B+C and insulin administration, with concurrent PG treatment, on subclinical ketosis cure, blood BHB following treatment, and early lactation milk production.

MATERIALS AND METHODS

Study Population

Data were collected from 16 dairy herds in Ontario (farms A through P) and 1 dairy herd in Michigan (farm Z) from May 13 to September 14, 2011. Herds were purposively selected based on their proximity to study sites and willingness to comply with the proposed ketosis testing and treatment protocol. To be eligible for enrollment, herds were required to be enrolled in monthly milk testing through a DHI organization or collect daily milk weights on farm. Enrolled herds included tie-stall- ($n = 8$) and freestall-housed herds ($n = 8$) ranging in size from 50 to 3,200 lactating animals. In all herds, a TMR was fed to all lactating cattle.

Data Collection and Study Design

Herds were visited weekly on the same day of the week and at approximately the same time of day throughout the study period. All cows 3 to 16 DIM were tested for ketosis using the Precision Xtra meter (Abbott Laboratories, Abbott Park, IL). Ketosis was defined a priori as BHB $\geq$1.2 mmol/L. The Precision Xtra meter is a handheld device that measures BHB in whole blood. This meter has been previously validated for use in cattle and has a reported sensitivity of 88% and a specificity of 96% at this cut point (Iwersen et al., 2009). Cows were excluded from testing if they had been previously diagnosed with ketosis or a DA by farm personnel during the current lactation or had been enrolled in the study the previous week. Animals were not observed for clinical signs of ketosis by study personnel, so no determinations on clinical ketosis status could be made. This testing scheme provided 2 opportunities for enrollment for each animal, once at 3 to 9 DIM and once at 10 to 16 DIM.

Blood was drawn from the coccygeal vessels using a 20-gauge, 2.54-cm needle and 3-mL syringe. Ketone testing was performed immediately after blood collection according to the manufacturer's instructions. In animals that were classified as ketotic, blood glucose concentrations were also measured using a second Precision Xtra test. Blood was tested for glucose immediately after the ketone results were displayed. The