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Ketosis Treatment in Lactating Dairy Cattle

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KEYWORDS

• Ketosis • Treatment • Systematic review • Propylene glycol

KEY POINTS

- Ketosis is a common disease in dairy cattle in early lactation.
- Multiple treatments have been used in dairy cattle, with varying levels of support of efficacy and varying results.
- There is a lack of well-designed ketosis treatment clinical trials.
- The best recommendation for treatment is 300 mL of 100% propylene glycol orally once daily for 5 days.
- Further research is required to determine the most effective ketosis treatment regimen for economically important outcomes.

INTRODUCTION

Subclinical ketosis is a common disease of the transition period in dairy cattle, affecting approximately 40% of lactations in North America.^{1,2} The incidence on individual farms varies widely and may be as high as 80%.² The costs associated with ketosis include treatment of the disease, increased risk and treatment of other diseases, decreased milk production, worse reproductive performance, and higher risk of culling in the first 30 days of lactation.^{3,4}

CLASSIFICATION

Historically, ketosis was classified as primary or secondary based on when signs commenced and what concurrent diseases were facing the animal.⁵ Recently, this nomenclature has fallen out of favor, because most ketosis is seen in the first

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10 days after calving in North America and may or may not be accompanied by other disease.¹ The terms subclinical and clinical are favored for ketosis definition. Clinical ketosis is characterized by an increase in blood, urine, or milk ketone bodies in conjunction with other visible signs, such as inappetence, obvious rapid weight loss, and dry manure. Subclinical ketosis is defined as an increase in blood, urine, or milk ketone bodies, above a threshold shown to be associated with undesirable outcomes, in the absence of obvious clinical signs.

Because of the housing system used in many North American dairies (large groups of loose-housed cattle), it has become difficult or impossible to determine if a specific animal is showing clinical signs of ketosis. Attempts have been made to classify ketosis as clinical or subclinical based on blood β -hydroxybutyrate (BHB) concentrations.³ However, our experience is that when examined, animals with high levels of ketonemia may show no clinical signs and animals with low levels may be obviously ill. The severity of clinical effect seems to depend on the individual animal's ability to process and tolerate ketone bodies.⁵ The disease may therefore be best described as hyperketonemia rather than trying to distinguish clinical from subclinical.

Classification of ketosis is most relevant for clarity and consistency in comparing incidence risk rates. Depending on the methods and frequency of screening, incidence rates of clinical ketosis are expected to be 2% to 15% in the first month of lactation, whereas 40% cumulative incidence of subclinical ketosis is typical if cows are screened weekly during the same period.² There is some evidence that greater ketonemia is associated with higher risk of negative outcomes, such as subsequent disease and culling.¹ However, the importance of the distinction between clinical and subclinical ketosis with regard to treatment is unclear. To our knowledge, there are no well-designed studies that have shown a difference in efficacy of treatments based on the initial level of ketonemia.

PHYSIOLOGY OF EARLY LACTATION AND KETOSIS

When considering effective treatment of ketosis, it is critical to consider the physiology of the animal during this period. At the beginning of lactation, animals are faced with a sudden and drastic increase in energy demand.⁵ This demand is coupled with a decrease in feed intake, which generally starts in the dry period. The rate of increase of feed intake post partum lags behind the demands of lactation, leading to a period of negative energy balance. Fat is mobilized from body stores in the form of nonesterified fatty acids (NEFA) to meet energy requirements. NEFA travel to the liver destined for 1 of 3 pathways, complete oxidation for energy, incomplete oxidation to ketone bodies, or re-esterification to fatty acids. All of these pathways are stimulated in the transition animal, but the magnitude of fat breakdown and tolerance of the individual determine the relative distribution of the paths.⁵

In early lactation, homeorhesis is the driving physiologic force.⁶ Homeorhesis was defined by Bauman and Currie as "the orchestrated or coordinated changes in metabolism of body tissues necessary to support a physiologic state."⁷ These processes facilitate breakdown of body stores of fat and protein in excess of what would be allowed based on homeostatic regulation. This situation leads to a period of insulin resistance, which is nearly universal in early lactation animals.⁶ Milk production requires large amounts of glucose. Because ruminants absorb only minimal amounts of glucose from their diet, gluconeogenesis is required to meet this need. This process is generally diminished in animals affected by ketosis, leading to hypoglycemia. Providing glucose, stimulating gluconeogenesis, and decreasing fat breakdown form the foundation for rational ketosis treatment.⁸

SYSTEMATIC REVIEW OF KETOSIS TREATMENT

Background

Reviews have long been used to summarize the body of literature on a given topic. This material can be especially helpful for practitioners who have limited time to read primary scientific articles or require the information in a short period while working on a clinical case.⁹ Historically, these reviews were narrative reviews conducted by an expert on the subject.^{10,11} Even high-quality reviews are inherently biased, because selection of papers and interpretation of the information are consciously or unconsciously influenced by the author's opinions at the outset.

Systematic reviews help remove the bias of the reviewers by following a rigorous method in selection of materials to be included.^{9,11} Investigators provide a detailed framework for conducting the review that can be repeated and examined for accuracy. A specific question is formulated and an exhaustive search of the literature is performed. Methods for inclusion of materials are clearly defined and laid out before initiation of the review. The quality of all materials included is determined through specified criteria. Inclusion of all high-quality relevant material is the framework for a systematic review, so small studies that are well designed are not excluded because of lack of power.

Materials and Methods

A systematic review of ketosis treatment was performed in February 2011 to determine the most effective treatment(s) for ketosis in lactating dairy cattle. The search phrases "ketosis treatment cattle" and "acetonemia treatment cattle" were entered into 4 databases: CAB, PubMed, Agricola, and Google Scholar. These databases included references from 1900 to present in all languages. A complete list of references from the search was obtained from each database and abstracts were obtained for all references. Titles and abstracts were used to determine the relevance of each reference to the question. If abstracts were unavailable and the title was suggestive that the reference was relevant, the full reference was obtained and analyzed. Materials that seemed relevant based on the title or abstract were obtained in full and analyzed. In addition, a manual search of relevant conference proceedings (American Dairy Science Association, American Association of Bovine Practitioners) was conducted, and studies known to us that were not yet published in the peer-reviewed domain were solicited for evaluation.^{3,4,12}

The following criteria were used to determine the appropriateness of materials for the review:

1. Study animals were lactating dairy cattle
2. Animals experienced naturally occurring ketosis
3. Animals were diagnosed before initiation of treatment and method of diagnosis was clearly defined
4. A control group was included that was positive for ketosis
5. Control group was untreated or treated with a baseline treatment common to both groups (eg, dextrose vs dextrose and insulin)
6. Any intervention was considered: oral, injectable, or feed additive
7. Any outcome was considered, but must be clearly defined: ketosis cure, health data, milk production, reproductive performance

Results of the Review

A total of 1395 references were obtained from the search (**Fig. 1**). These references included journal articles, theses, conference proceedings, abstracts, and book

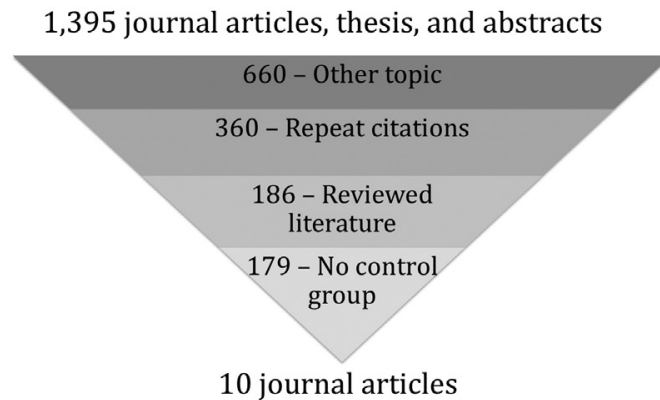


Fig. 1. Total number of articles and articles excluded by reason for exclusion.

articles. Of these references, 660 were excluded because they covered another topic, such as ketosis prevention, and 360 were excluded as duplicate citations. A further 186 were excluded because they reviewed the literature without presenting novel data. Of the 189 that remained, 179 did not include a control group, leaving just 10 articles considered appropriate for the review (**Table 1**).

One of the most striking aspects of this venture was the lack of well-designed ketosis treatment literature. During the past 15 years, the extent of ketosis observed in North America has been clearly defined and the prevalence of ketosis initially surprised many veterinarians and producers. Because of the relative frequency of clinical and subclinical ketosis, it is surprising that there has been so little advancement in the body of evidence for treatment of a ketotic cow. Much treatment of ketosis is based on disease principles or past experience. Although both of these factors are critical

Table 1			
Studies remaining after exclusion criteria were applied			
Study	Treatment	Control Group	Random
McArt et al, ^{3,4} 2011, 2012	Propylene glycol	Untreated	Yes
Carrier et al, ¹² personal communication	Dextrose + dexamethasone + B ₁₂ + propylene glycol	Untreated	Yes
Sahoo et al, ⁴⁰ 2009	Dextrose + dexamethasone, Dextrose + dexamethasone + E/Se	Untreated	No
Seifi et al, ²³ 2007	Isoflupredone, isoflupredone + insulin (Ultralente, Eli Lilly)	Untreated	Yes
Lohr et al, ²⁹ 2006	Catosal	Untreated	Yes
Fetrow et al, ⁴¹ 1999	rBST	Untreated	Yes
Shpigel et al, ⁴² 1996	Dextrose + dexamethasone, dextrose + flumethasone	Dexamethasone or flumethasone	No
Sakai et al, ²⁵ 1993	Dextrose + insulin (lente)	Dextrose	No
Ruegsegger & Shultz, ³⁵ 1986	Propylene glycol, niacin	Untreated	Yes
Robertson, ²² 1966	Dexamethasone/flumethasone + insulin (protamine zinc), dexamethasone/flumethasone alone	Untreated	Yes

Abbreviations: E/Se, Vitamin E/Selenium; rBST, recombinant bovine somatotropin.

components for development of treatment strategies, stronger evidence is required to ensure rational and effective treatment.¹³ Because of the small number of studies that met the inclusion criteria and the large number of treatments represented by these studies, it is difficult to provide concrete information on many common treatments. However, some of the common treatments are discussed in relation to the findings of the review.

DEXTROSE

Background

The presence of hypoglycemia in ketosis was well established by the 1930s.¹⁴ Since that time, dextrose has been considered a staple in ketosis treatment. This treatment seems physiologically sound, because the requirement for glucose for milk production drives fat metabolism and hypoglycemia.⁸

There are concerns that the amount of glucose in a standard 500-mL bottle of 50% dextrose is excessive. A bolus of 500 mL 50% dextrose increases the blood glucose concentrations to about 8 times normal immediately after administration and returns to pretreatment concentrations by about 2 hours after administration.¹⁵ This increase is paired with an immediate 5-fold increase in circulating insulin concentration and a 12-fold increase after 15 minutes.¹⁵ Any glucose not used by the animal during this period is excreted via the kidneys, increasing the excretion of electrolytes and potentially increasing the risk of electrolyte imbalances.¹⁶ The decrease in blood BHB levels caused by dextrose treatment is short lived (<24 hours) and must be repeated or followed with another treatment for lasting effect.¹⁶

Some have expressed concern with the high level of glucose leading to abomasal dysfunction. There is evidence that high levels of glucose can lead to decreased abomasal motility, and displaced abomasum has been correlated with hyperglycemia.^{17–20} However, such effects of 1 treatment with dextrose have not been established.

Systematic Review

Dextrose was studied extensively early on (in the 1940s and 1950s) in case series or small studies without controls in which all affected animals were treated and the number that improved with treatment was determined. Since then, dextrose has been studied only in combination with other treatments or as the baseline for a positive control group. It has never been studied in a randomized clinical trial to determine efficacy as a standard treatment of all cases. None of the articles successfully passing the review process examined the efficacy of dextrose without the addition of other treatments.

Recommendations

Use of dextrose should be considered a second-line treatment of cases of ketosis. Animals with severe ketonemia with concurrent hypoglycemia may benefit from treatment with dextrose. Animals with ketosis suffering from nervous signs (such as abnormal licking, chewing on pipes or concrete, gait abnormalities, and aggression) should also be treated promptly with dextrose to alleviate hypoglycemia and nervous signs. These animals should then be followed up with other treatments for longer-term effectiveness.^{8,16}

GLUCOCORTICIDS

Background

Glucocorticoids have been used in ketosis treatment because of their ability to produce hyperglycemia as a result of changes in glucose use.⁸ Steroids also block

the effects of insulin, allowing for increased catabolism of fat and protein stores. Plasma concentrations of both glucose and insulin increase significantly about 48 hours after injection with dexamethasone.²¹

Systematic Review

Two studies in the review used a glucocorticoid alone. One of these studies was the oldest study of the group and was well designed.²² In this study, enrolled animals were randomly assigned to receive dexamethasone or flumethasone, dexamethasone or flumethasone plus protamine zinc insulin, or no treatment. Animals were then followed for 5 days after treatment to determine milk production, presence of clinical signs of ketosis, and appetite. There was no difference between dexamethasone and flumethasone, so these treatments were grouped together as glucocorticoids. Treated animals were more than twice as likely to improve clinically compared with untreated controls based on appetite, behavior, and digestive examination coded subjectively (68% for glucocorticoid + insulin and 55% for glucocorticoid alone vs 23% for untreated animals). Treated animals also had increased milk yields in the first week after treatment (6.07 ± 0.79 kg/d for glucocorticoid + insulin and 3.73 ± 1.04 kg/d for glucocorticoid alone vs 1.11 ± 0.91 kg/d for untreated animals). This study was revolutionary in its time because of the use of an untreated control group, something not previously used in ketosis treatment studies. The major downfalls of this study are the short follow-up time and the lack of proper statistical methods available at the time to examine the influence of potential confounders such as parity.

The second study points to concerns for use of glucocorticoids.²³ Animals enrolled in this study were randomly assigned to treatment with 20 mg of isoflupredone (Predef 2x, Pfizer, Zoetis, Madison, NJ), 20 mg of isoflupredone plus 100 IU insulin, or a placebo, each treatment given once between calving and 8 days in milk [DIM]. This study was not designed as a ketosis treatment study, because all fresh animals were enrolled. However, blood was collected before enrollment and animals were later classified as subclinically ketotic or not based on serum BHB 1.4 mmol/L or greater. Animals that were ketotic at enrollment and were treated with isoflupredone and insulin were more likely than controls to remain ketotic in the 2 weeks after treatment. Animals that were not ketotic at the start and were treated with isoflupredone alone or isoflupredone and insulin were respectively 1.6 and 1.7 times more likely to become ketotic 1 week after treatment. There was no effect of treatment on reproduction or test-day milk production. This study suggests that there is no benefit of routine use of corticosteroids at the time of calving, and metabolic state may be impaired with their use. Furthermore, care should be exercised when using these products for ketosis treatment, because they may impair the animal's ability to overcome the disease.

Recommendations

Evidence for corticosteroids as therapy for ketosis is at best equivocal and indicates that steroids with insulin decreases cure. The lack of efficacy, combined with the risk of adverse side effects, does not support inclusion of corticosteroids in treatment of ketosis.

INSULIN

Background

Dairy cattle in early lactation are inherently insulin resistant.⁶ This characteristic is part of the complex mechanism of homeorhesis that allows dairy cattle to produce a large amount of milk during a period of negative energy balance. Animals with ketosis show

increased insulin resistance compared with their healthy herdmates.¹⁵ Insulin is used in the treatment of ketosis because of the anabolic effects of the hormone.²⁴ Insulin decreases fat breakdown, increases fat synthesis, and increases use of ketone bodies as energy sources, which should decrease the level and consequences of ketonemia.

Systematic Review

Insulin is never given as the sole treatment of ketosis, because of the risk of hypoglycemia. There were 3 studies from the review of the literature that used insulin as an adjunct therapy in which the added benefits of insulin could be examined. Two of these studies are discussed in the glucocorticoid section.^{22,23} Results from the Robertson study²² indicated that the addition of insulin increased cure rate and milk production compared with treatment with glucocorticoids alone. Beyond the concerns that were mentioned earlier regarding this study, the insulin used was an animal-source protamine zinc formulation that is no longer available. It is difficult to say if recombinant human forms of insulin would yield the same results. In a study from 2007 by Seifi and colleagues,²³ treatment with a recombinant insulin (Humulin Ultralente, Eli Lilly, Indianapolis, IN) increased the risk of animals developing and remaining ketotic compared with animals treated with isoflupredone alone.

The third study was performed by Sakai and colleagues²⁵ to examine the effects of insulin when added to dextrose therapy. Animals were diagnosed with ketosis using a combination of urine ketone body concentrations and clinical signs. All animals received 500 mL 50% dextrose intravenously (IV) once a day for 5 days after diagnosis. Half of the cows were assigned to receive 200 IU of lente insulin subcutaneously for 3 days from day 2 to 4 after enrollment. On day 6 after enrollment, urine ketone body concentrations were measured to determine the effectiveness of treatment. Blood was collected on enrollment and at day 6 and later analyzed for BHB concentrations. In this study, animals treated with insulin had significantly lower blood BHB concentrations and significantly higher glucose and insulin concentrations at day 6 after enrollment than cows treated with dextrose alone. However, this study had a short follow-up period and did not look at any economically important outcomes, such as milk production and culling.

We conducted a ketosis treatment study in the summer of 2011, in which we used insulin glargine (Lantus, Sanofi Aventis, Lavla, Quebec, Canada) or a placebo in addition to propylene glycol in animals diagnosed with ketosis using 1.2 mmol/L or greater blood BHB with a validated hand-held meter (Precision Xtra, Abbott, Abbott Park, IL). Based on preliminary results, insulin had no effect on blood ketone body concentrations 1 or 2 weeks after treatment or on the likelihood of cure of ketosis based on blood BHB concentrations.²⁶

Recommendations

There is limited evidence in support of insulin therapy as part of a ketosis treatment regimen. This finding, coupled with the high cost of most insulin preparations, precludes wide-scale use of insulin in ketosis treatment. It is possible that there may be some benefit in refractory cases, especially those involving hepatic lipidosi,²⁴ but more research is needed in this area.

VITAMIN B₁₂/PHOSPHORUS COMBINATION PRODUCT

Background

Cyanocobalamin (a form of vitamin B₁₂) has been used as an adjunct therapy in ketosis treatment because of its role in gluconeogenesis. It has been hypothesized

that administration of vitamin B₁₂ may increase gluconeogenesis by increasing the activity of methylmalonyl-coenzyme A (CoA) mutase, a vitamin B₁₂-dependent enzyme and important component of the Krebs or tricarboxylic acid (TCA) cycle.²⁷ With an increase in the activity of this enzyme, energy may be produced more efficiently and TCA cycle activity and gluconeogenesis may be increased.

Butaphosphan, an organic phosphorus source, has been also been used because of its presumed role in gluconeogenesis.²⁸ Phosphorus is required at many stages in the gluconeogenic pathway, because all intermediate compounds must be phosphorylated to continue the cycle. However, it is unclear if this form of phosphorus is available to the animal.

Systematic Review

One study from the review used a vitamin B₁₂ product.²⁹ One hundred and twenty lactating cows were enrolled in the study when they were presented to veterinary clinics in Germany for left displaced abomasum (LDA) and were determined to have ketosis based on a urine test. After correction of the LDA, animals were randomly assigned to receive 3 days of a commercial combination butaphosphan and cyanocobalamin (Catosal, Bayer, Shawnee Mission, KS) product or a placebo. Blood samples were collected during treatment and animals were monitored for feed intake, milk production, and rumination. Animals were considered to have healthy rumination if there were at least 3 ruminations/min. Individuals evaluating the animals were blind to treatment. Treatment with this product resulted in a significant increase in proportion of animals with healthy rumination at days 2 (65 vs 48%) and 3 (82 vs 63%) after treatment. Treated animals also tended to have a larger decrease in plasma BHB concentrations compared with values on the day of enrollment.

It is challenging to determine the usefulness of a butaphosphan cyanocobalamin combination product for ketosis treatment based on this study. The outcomes found to be different between treatments are subjective (ruminations) and have questionable economic significance. It is also difficult to determine if animals with ketosis, but without an LDA, would respond in the same manner. A large study using this product at calving showed a decreased risk of ketosis in treated cows that were in their third or higher lactation,²⁸ but this does not prove efficacy in ketosis treatment.

In a recent study,²⁶ we treated animals with 3 days of butaphosphan and cyanocobalamin or a placebo; all cows received propylene glycol. Based on preliminary results, this product tends to increase the likelihood of cure of ketosis (blood BHB <1.2 mmol/L in the week after treatment), decrease blood BHB concentrations 1 week after treatment, and increase milk production in the first 30 days.²⁶

Recommendations

This butaphosphan-cyanocobalamin combination product may prove useful in ketosis treatment in the future, if effects on milk production, culling, and disease risk can be confirmed. There is insufficient evidence to suggest routine use of this product for ketosis treatment.

PROPYLENE GLYCOL

Background

Propylene glycol was first described as a treatment of ketosis in 1954.^{30,31} It is generally given as an oral drench once a day. When propylene glycol enters the rumen, it is either absorbed directly or converted to propionate.³² Propylene glycol that is absorbed directly enters the TCA cycle to increase oxidation of acetyl CoA and

stimulate gluconeogenesis. Propionate from propylene glycol can also be used for gluconeogenesis and helps stimulate insulin release.³³ There is a significant increase in insulin by 15 minutes after administration, and insulin remains increased for 2 hours or more after drenching.³³ This spike in insulin helps decrease fat breakdown and hepatic ketone body production.

Because of the physical labor required to administer propylene glycol, many producers and veterinarians have expressed interest in propylene glycol feed additives.³² The concern with this method of delivery is that there is no resultant insulin spike caused by the small, relatively steady amount of propylene glycol that is supplied to the rumen throughout the day.³² This chronic delivery of propylene glycol also alters the environment in the rumen to favor more propionate production.³² According to the hepatic oxidation theory, this situation would likely decrease feed intake, increasing fat mobilization and perpetuating the problem of ketosis, although the clinical relevance of this has not been determined.³⁴

Systematic Review

Previously, much of the work carried out with propylene glycol and ketosis involved prevention of ketosis.³² Two of the studies that remained at the end of the systematic review selection process used propylene glycol without other treatments.^{3,4,35} In the study conducted in 1986 by Ruegsegger and Shultz,³⁵ cows from study herds were tested once a week for milk ketone bodies and enrolled if they had ketosis without other complicating diseases. Enrolled animals were randomly assigned to receive no treatment, 125 mL propylene glycol, or 125 mL propylene glycol with 12 g of niacin daily for 7 days. There were no differences in blood BHB, milk production, or milk composition between any of the groups. The small sample size may have resulted in a lack of power to detect these differences, and the low amount of propylene glycol used in this trial is insufficient for lactating cattle.³²

One of the best-designed and highest-impact trials on ketosis treatment was conducted in 2010 by researchers at Cornell University.^{3,4} For this trial, all animals 3 to 16 DIM were tested for ketosis on Mondays, Wednesdays, and Fridays using a hand-held meter (Precision Xtra). All animals with 1.2 to 2.9 mmol/L blood BHB that had not been previously treated for ketosis by farm personnel were enrolled. Cows were randomly assigned to receive 300 mL (310 g) propylene glycol or 300 mL water daily until their blood BHB levels were less than 1.2 mmol/L or greater than 3.0 mmol/L or they reached 16 DIM. Blood BHB was measured 3 times a week until 16 DIM and daily milk weights, culling, and reproductive records were collected.

Animals that were treated with propylene glycol were 1.5 times more likely to be cured of subclinical ketosis (blood BHB <1.2 mmol/L) and half as likely to progress to blood BHB greater than 3.0 than control cows. Treated animals were also 40% less likely to develop a displaced abomasum and half as likely to die or be sold in the first 30 days of lactation. Milk production was increased by 1.3 and 1.6 kg/d in treated cows in the first 30 days of lactation in 2 of the herds, whereas the third herd showed no difference in milk production between groups.

This study clearly showed the potential benefits of oral propylene glycol in treatment of subclinical ketosis. The identification of significant differences in economically important outcomes was a first for the ketosis treatment literature and is a trait that future studies should strive to emulate. A limitation of this study was the failure to treat animals with blood BHB levels 3.0 mmol/L or greater. It can be expected that propylene glycol would be efficacious in animals with higher blood BHB levels, but higher initial BHB levels might decrease the cure rate and milk response. The variable amount of time that animals were treated in this study can also prove challenging for

interpretation. Although the median time for treatment was 5 days, it varied from 2 to 13 days. Many producers would like a specific protocol for treatment and few would likely be willing to drench animals for 13 days.

Recommendations

Treatment of ketotic animals with 300 g of propylene glycol daily should be considered the base of ketosis treatment. The length of time that animals should be treated still needs to be determined, but based on results of the McArt study³ and other studies in propylene glycol use,³² 5 days of treatment seems to be sufficient without being overly taxing on farm labor. When choosing a product, it is critical to examine the concentration of propylene glycol in the product and ensure that animals are being treated with sufficient volume to provide 300 g of propylene glycol. Propylene glycol should be considered for treatment of all ketotic animals, although more research is needed to determine the efficacy for animals with BHB higher than 3.0 mmol/L.

COMBINATION THERAPIES

Background

Many studies of ketosis treatment have used combinations of therapies. Many of these studies have shown that animals treated with more than 1 product have better outcomes than animals treated with only 1 treatment. However, many of these studies have used short follow-up periods and outcomes that were not economically important.

Systematic Review

An excellent example of a trial involving multiple treatment modalities was conducted at the University of Minnesota.¹² Urine was collected daily from all animals in the first 15 days of lactation for ketone body testing using Ketostix (Bayer, Pittsburgh, PA). Animals that were classified with a small level of ketosis or higher were enrolled in the study and randomly assigned to the treatment or control groups. Treated cows ($n = 279$) were given 20 mg dexamethasone, 500 mL 50% dextrose, 5 mg vitamin B₁₂ (all IV), and 500 mL propylene glycol orally on the day of enrollment and for 2 days after enrollment. Control animals ($n = 282$) were left untreated. In this study, treatment tended ($P = .1$) to lower milk production (1 kg/d over the lactation) and significantly increased the risk of culling (by 40%) in the first 60 days. Although outcomes were not different or poorer for treated animals, treatment did decrease BHB and NEFA values in treated animals in the first week after treatment compared with controls. This study is a critical addition to the ketosis treatment literature for 2 reasons: it shows the importance of long-term follow-up and use of economically important outcomes, and it requires us to reconsider common ketosis treatment regimens.

Recommendations

No combination therapy can be recommended. It is essential that future work tests individual treatments alone or in factorial study designs, so the efficacy of each product can be determined. Any combination that is studied should be based on treatments previously proved efficacious (ie, propylene glycol) and with the addition of 1 other treatment. By taking this stepwise approach, the efficacy of treatment combinations can be established.

Summary of Treatment Recommendations

The only treatment of ketosis that has been shown to improve resolution of ketosis, cow health, and productivity is oral propylene glycol.^{3,4} The concentration of

propylene glycol in the product should ensure that animals are receiving 300 g once a day for 5 days. Dosing once a day is sufficient and decreases the labor requirement for treatment. Use of a drenching gun increases the ease with which animals can be treated, increasing producer compliance. Subclinically ketotic animals should not receive other treatments, because the risk of detriment likely outweighs the benefit. Animals experiencing nervous signs of clinical ketosis may also benefit from a single treatment with 500 mL 50% dextrose IV.

SUMMARY

There is a scarcity of well-designed ketosis treatment trials and information on effective ketosis treatment. In the past, the focus was on treating ketonemia, rather than improving productivity. Research has shown that blood BHB concentrations 1.2 mmol/L or greater in the first 2 weeks post partum increase the risk of disease and culling and decrease milk production.^{36–39} Increased emphasis on economically important outcomes (disease risk, milk production, culling, and reproductive performance) is required in subsequent research to increase understanding of effective ketosis treatment.

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