The Veterinary Journal 198 (2013) 560–570

Contents lists available at ScienceDirect

The Veterinary Journal

journal homepage: www.elsevier.com/locate/tvjl

Review

Elevated non-esterified fatty acids and β-hydroxybutyrate and their association with transition dairy cow performance

Jessica A.A. McArt [a], Daryl V. Nydam [b,*], Garrett R. Oetzel [c], Thomas R. Overton [d], Paula A. Ospina [d]

[a] Department of Clinical Sciences, Colorado State University, Fort Collins, CO 80523, USA
[b] Department of Population Medicine and Diagnostic Sciences, Cornell University, Ithaca, NY 14853, USA
[c] School of Veterinary Medicine, University of Wisconsin, Madison 53706, USA
[d] Department of Animal Science, Cornell University, Ithaca, NY 14853, USA

ARTICLE INFO

Article history:
Accepted 8 August 2013

Keywords:
Negative energy balance
Subclinical ketosis
Non-esterified fatty acids
β-Hydroxybutyrate
Dairy cow

ABSTRACT

Dairy cows pass through a period of negative energy balance as they transition from late gestation to early lactation. Poor adaptation through this period, expressed as excessively elevated concentrations of non-esterified fatty acids (NEFAs) pre- or post-partum and elevated concentrations of β-hydroxybutyrate post-partum, increases an individual animal's risk of post-partum disease, removal from the herd, reproductive difficulty, and reduced milk production. Field studies have shown that subclinical ketosis often affects 40% of cows in a herd although the incidence can be as high as 80%. Peak incidence occurs at 5 days in milk, and cows that develop subclinical ketosis in the first week of lactation have a higher risk of negative effects and reduced milk production than cows that develop subclinical ketosis in the second week of lactation.

Herds with more than a 15–20% prevalence of excessively elevated concentrations of NEFAs and β-hydroxybutyrate in early lactation have higher rates of negative subsequent events, poorer reproduction, and lower milk yield than herds with a lower prevalence of negative energy balance. This paper reviews (1) strategies for testing of energy-related metabolites, (2) consequences of poor adaptation to negative energy balance (for individual animals and for herds), (3) treatment approaches for affected cows, and (4) economic considerations for testing and treating cows with poor adaptation to negative energy balance.

Introduction

Negative energy balance (NEB) is a normal occurrence in dairy cattle as they transition from late gestation to early lactation. This transition period is often considered to occur from 3 weeks pre-partum to 3 weeks post-partum (Grummer, 1995; Drackley, 1999), as during this timeframe homeorhetic regulation of metabolic functions is necessary in order to accommodate parturition and lactogenesis (Bauman and Currie, 1980). In addition, it has recently been shown that nutritional management in the early dry period, i.e. after cessation of milking, is important for maintaining the health and productivity of transition cows (Dann et al., 2006). Dry matter intake (DMI) decreases by over 30% in the last 3 weeks of gestation (Hayirli et al., 2002) and this limits the availability of energy sources during a time of increased demand; within 4 days post-partum, due to milk production, the demands for glucose, amino acids, and fatty acids are 2–5 times higher than pre-partum requirements (Bell, 1995).

For these reasons, the transition from late gestation to early lactation is a dynamic period for dairy cattle, during which most infectious and metabolic diseases are likely to occur (Goff and Horst, 1997; Mallard et al., 1998; Ingvartsen et al., 2003). Cows unable to adapt to this challenging time are more prone to negative subsequent events, and the associations between excessive NEB in dairy cows and these detrimental health effects have been presented by several authors (Andersson, 1988; Kehrli et al., 1989; Duffield, 2000; Hammon et al., 2006). The economic impacts of maladaptation are important and include increased risk of metabolic disease, reduced milk production, early removal from the herd, and poor reproductive performance.

This paper reviews testing of NEB-related metabolites and current research on the epidemiology of subclinical ketosis (SCK), individual animal and herd consequences, treatment, and economic considerations associated with poor adaptation to NEB in dairy cows.

Adaptation to negative energy balance

NEB occurs as the energy demands for milk production cannot be met by feed intake alone (Bauman and Currie, 1980; Baird,

* Corresponding author. Tel.: +1 607 253 3140.
E-mail address: dvn2@cornell.edu (D.V. Nydam).

1090-0233/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tvjl.2013.08.011

1982; Herdt, 2000). Glucose, a fundamental nutrient required for normal brain function in addition to use by other tissues, is under tight homeostatic control in order to allow for basic functioning of the animal. In ruminants, ingested carbohydrates are fermented to short-chain fatty acids by rumen microbes, and thus most glucose must be synthesized by the liver (Reynolds et al., 1988). As lactose is a major component in milk, gluconeogenesis is closely linked to lactogenesis as the amount of available glucose will determine the quantity of milk produced (Mepham, 1993).

After parturition, there is a decrease in insulin production by the pancreas (Drackley et al., 2001) which results in decreased glucose utilization by insulin sensitive organs (e.g. adipose tissue and muscle). Coupled with a transient state of insulin resistance, associated with an increase in adipose tissue sensitivity to catecholamines and an exuberant lipolytic response (Herdt, 2000; Holtenius et al., 2003), these mechanisms allow the mammary gland to have additional glucose for milk production (Komatsu et al., 2005). Thus alternative fuel sources are needed for certain tissues in the body to maintain normal function during this period of increased milk production.

In response to a decrease in available glucose, an increase in lipolysis releases non-esterified fatty acids (NEFAs) which circulate throughout the body in the blood (McNamara, 1991; Bertics et al., 1992; Herdt, 2000). NEFAs can be used directly as a fuel source by various tissues such as muscle, used for milk fat synthesis by the mammary gland, or taken up by the liver (Palmquist et al., 1969; Herdt, 2000). The liver removes ~15–20% of NEFAs from the blood (Drackley and Andersen, 2006), where they can be completely oxidized to provide energy (for the liver), partially oxidized to produce ketone bodies (acetone, acetoacetic acid, and beta-hydroxybutyric acid [BHBA]), converted into triacylglycerols (TAGs) and packaged into very low density lipoproteins for transport back to the adipose tissue, or stored as TAG.

Ketone bodies released by the liver act as an alternate fuel source for tissues such as the brain and heart (Herdt, 2000; Drackley and Andersen, 2006). Thus, a certain concentration of NEFAs and BHBA in the blood is part of a normal adaptation to NEB in early lactation. However, excessive concentrations of NEFAs or BHBA indicate an excess of NEB which is associated with detrimental health and production outcomes. Additionally, elevated concentrations of NEFAs and BHBA can be directly detrimental to immune function (Hammon et al., 2006; Contreras et al., 2010; Ster et al., 2012) and decrease appetite (Dale et al., 1979). The latter may be the result of food intake being controlled by signals from the liver to the brain (Allen et al., 2009).

When excessive NEFAs enter the liver, its capacity to fully oxidize them is overwhelmed and thus some NEFAs are re-esterified into liver TAGs. As the ability of ruminants to export TAGs from the liver as very low density lipoproteins is limited, this re-esterification results in fat accumulation in the liver (hepatic lipidosis). Excessive fat accumulation in the liver impairs normal liver function (Rukkwamsuk et al., 1999; Jorritsma et al., 2001; Murondoti et al., 2004), which may lead to hyperketonemia (Herdt, 2000). Hyperketonemia has been associated with clinical signs such as decreased in appetite, weight loss, and decreased milk production; unfortunately the practical evaluation of these clinical signs has been largely subjective.

Cows can also have an excess of circulating ketone bodies without obvious clinical signs (SCK) (Andersson, 1988). The term hyperketonemia (i.e. blood BHBA $\geqslant$ 1.2 mmol/L) will be used throughout this review to encompass animals with either SCK or clinical ketosis; it is important to note that SCK and clinical ketosis are not different diseases, just variations in severity of a single disorder. The distinction between SCK and clinical ketosis can either be based subjectively on clinical assessment or more objectively through measurement of BHBA. Clinical ketosis is generally associated with higher BHBA concentrations than SCK. Oetzel (2004) stated that cows with clinical disease generally had blood BHBA concentrations $\geqslant$3.0 mmol/L which is much higher than the BHBA threshold generally used to determine SCK.

Most hyperketonemic cows do not show clinical signs; Duffield et al. (2009) reported that of 264 cows with blood BHBA $\geqslant$ 1.2 mmol/L in the first week post-partum, only 13 were diagnosed with clinical ketosis, while Ospina et al. (2010c) and McArt et al. (2012a) both showed that <20% of cows with hyperketonemia (blood BHBA $\geqslant$ 1.2 mmol/L) had blood BHBA concentrations $\geqslant$3.0 mmol/L. This review will focus on the associations of elevated blood NEFAs and BHBA on subsequent outcomes but the impacts of clinical ketosis and its treatment will not be discussed.

Testing methods

Blood NEFA concentrations have been found to be a more accurate measure of NEB than ketone bodies. Studies by Ospina et al. (2010b, 2010c) found that, in general, the area under the curve for receiver operating characteristic curves is greater for NEFAs than BHBA, which means that NEFAs have a higher combined sensitivity and specificity for evaluating health and production outcomes than BHBA. Research by Chapinal et al. (2011) provided additional data for this theory and showed that NEFA concentrations, both pre-partum and post-partum, offer more information on odds of negative health outcomes than BHBA.

Blood NEFA concentrations are also a stronger indicator, based on risk and odds ratios, of disease, reproductive performance, and milk production than blood BHBA concentration (Ospina et al., 2010b, 2010c; Chapinal et al., 2011; Huzzey et al., 2011). However, with current technology, collection and processing of blood samples to get accurate NEFA concentrations can be comparatively difficult in the field (Stokol and Nydam, 2006) and relatively expensive. In addition, the stress of sample collection on cows can increase NEFA concentration (Holmes and Lambourne, 1970; Leroy et al., 2011).

Samples for NEFA analysis should be collected in EDTA or non-anticoagulant tubes, placed on ice immediately after collection, kept at 4 °C until processing, and the serum separated within 24 h (Stokol and Nydam, 2005); samples with a hemolytic index $\geqslant$300 should be interpreted with caution. Additionally, pre-partum NEFA values are commonly measured between 14 and 3 days prior to calving because NEFA concentrations naturally rise a few days before parturition (LeBlanc et al., 2005). This is a very narrow time window and difficult to predict because of the normal variability of gestation length.

The current cost of NEFA testing at the New York State Animal Health Diagnostic Center is US$11[1] per sample.[2] Time of collection is also important as NEFA concentrations are generally highest before feeding (Quiroz-Rocha et al., 2010); however, NEFAs seem to be less sensitive to time of sample collection than BHBA concentrations (Eicher et al., 1999) which fluctuate throughout the day and are usually highest 4–5 h after feeding (Oetzel, 2004).

Testing for ketone bodies is less expensive and more practical when compared to NEFAs; urine, milk, or blood can be used as test substrates. The gold standard is analysis of blood BHBA in a laboratory by kinetic enzymatic assay, as BHBA are the most stable ketone bodies in the blood (Tyopponen and Kauppinen, 1980). However, there are many relatively accurate cow-side tests available which make on-farm testing very practical. It is important to note that the sensitivity and specificity of the different tests can have a large impact on individual test results and, as a consequence, herd diagnosis and treatment.

[1] US$1 = approx. £0.64, €0.75 at 7 August 2013.
[2] See: http://ahdc.vet.cornell.edu.