Ketosis: new approaches to monitoring and prevention

Author: Sara Pedersen

Categories: Farm animal, Vets

Date: September 7, 2015

The past few decades have seen a shift from the focus being treatment of clinical disease to one of prevention at a herd level. At the same time there has been a change in our understanding and definition of disease to not only include clinical, but also subclinical, disease (LeBlanc et al, 2006).

Figure 1. The percentage contribution of each direct and indirect cost for average case of ketosis (BHB >1.2mmol/L). Taken from McArt et al (2015). Note, this is North American data.

This is particularly applicable to the subject of metabolic disease in dairy cattle. Within the past few years there has been raised awareness of the effects on production and thus costs of subclinical hypocalcaemia and ketosis. It is the latter that has seen the greatest development of new monitoring tools and preventive treatments and, therefore, will be the focus of this article.

Defining ketosis
Ketosis (also known as slow fever, acetonemia or ketonaemia) has historically been classified as primary or secondary, dependent on the timing of the onset of clinical signs and whether the animal was suffering from any concurrent diseases (Herdt, 2000).

However, more recently, definition of ketosis has moved to clinical or subclinical. Cows suffering from clinical ketosis have raised ketone (beta-hydroxybutyrate; BHB) levels in their blood, urine or milk in conjunction with visible signs, such as anorexia and a noticeable rapid loss in body condition. Subclinical ketosis is defined as raised BHB levels in the absence of visible signs. The BHB level used as a threshold varies according to method of measurement and also stage of lactation, although thresholds of 1.0mmol/L to 1.4mmol/L in blood are typically reported (Walsh et al, 2007; Duffield et al, 2009).

However, it is important to remember this threshold is not clear-cut. Some cows with high BHB levels will show no clinical signs of ketosis, while other cows may have much lower BHB levels, but have overt clinical signs. Thus, it is the individual animal’s ability to process and tolerate ketone bodies that determines the severity of the clinical signs, rather than the absolute BHB value (Herdt, 2000).

**Early lactation physiology**

The onset of lactation sees the dairy cow undergo a sudden and extreme increase in energy requirements.

This occurs just at the time when its appetite decreases significantly due to the pressure of the growing calf on the rumen. Despite its feed intake increasing after calving, there is still an energy gap since the rate at which its intake increases lags behind that of the cow’s increasing energy demands. As a result, it will mobilise fat from its body reserves in the form of non-esterified fatty acids (NEFAs). These are transported in the blood to her liver where they either undergo complete oxidation producing energy, partial oxidation with the production of ketone bodies or re-esterification to fatty acids. While during transition all of these pathways will be occurring, their distribution is influenced by the individual cow and the degree of fat mobilisation (Gordon et al, 2013).

At the start of lactation all dairy cows will be insulin-resistant, due to down-regulation of homeostatic factors that would normally prevent the breakdown of body stores of fat and protein for gluconeogenesis to the degree required to meet the sudden rise in energy demands.

This is referred to as the “homeorhetic drive” with partitioning of available energy to milk production in early lactation, at the expense of reproduction. In ketotic animals this drive to produce more energy is diminished and thus the animal becomes hypoglycaemic.

When forming treatment strategies the focus has been on the provision of energy, stimulation of
gluconeogenesis and reduction in fat mobilisation.

**Productivity and profitability effects**

**Table 1. Effects of high BHB blood levels (>1.4mmol/L) in early lactation on disease risk and performance (Rabaisson et al, 2014)**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left displaced abomasum</td>
<td>3.33</td>
</tr>
<tr>
<td>Clinical ketosis</td>
<td>5.38</td>
</tr>
<tr>
<td>Early culling and death</td>
<td>1.92</td>
</tr>
<tr>
<td>Metritis</td>
<td>1.75</td>
</tr>
<tr>
<td>Retained fetal membranes</td>
<td>1.52</td>
</tr>
<tr>
<td>Clinical mastitis</td>
<td>1.61</td>
</tr>
<tr>
<td>Lameness</td>
<td>2.01</td>
</tr>
<tr>
<td>Doubling of somatic cell count</td>
<td>1.42</td>
</tr>
<tr>
<td>Mean (+SD) of 305 day milk yield loss</td>
<td>251 ± 73kg</td>
</tr>
<tr>
<td>Delay in calving to first service</td>
<td>8 days</td>
</tr>
<tr>
<td>Delay in calving to conception</td>
<td>16-22 days</td>
</tr>
</tbody>
</table>

The effects of ketosis on the productivity and survivability of affected cows has long been reported. When defining subclinical disease, fertility parameters and milk production are often used as the outcomes against which a threshold is calculated. A meta-analysis by Rabaisson et al (2014) of all the past research into outcomes of high BHB levels (as defined by a threshold of 1.4mmol/L) summarises the wide ranging effects of excessive negative energy balance in early lactation (Table 1).

Taking all these subsequent effects into account, it is clear excessive fat mobilisation in early lactation has a big impact on productivity and profitability in the dairy herd.

A thorough analysis by McArt et al (2015) took into account all these potential outcomes to determine the cost associated with high BHB levels (greater than 1.2mmol/L) in early lactation at herd level.

While the exact figures cannot be directly translated to the UK due to differing costs, including feed and milk price, there are potentially some interesting points. The cost in first lactation animals was much higher than in second lactation animals onwards and, overall, the majority of the total costs were due to the subsequent effects on reproductive performance (Figure 1).
Treatment

Despite the prevalence of ketosis, relatively few robust clinical studies have assessed the effectiveness of different treatments, as evident by the review by Gordon et al (2013) of the available literature. While basing treatment on disease principles or past experience plays a vital role in the development of treatment strategies, it is also important to remember the need for an evidence base to ensure rational and effective treatment (Vandeweerd et al, 2012).

Gordon et al (2013) shows many of the treatments common in practice have little or no hard evidence supporting them. Hypoglycaemia has long been demonstrated to be present in ketotic cattle and thus, based on the physiological needs, dextrose has become part of many ketosis treatment regimes.

Concern over the effects of a large bolus of glucose could have prompted glucose tolerance tests to be conducted in ketotic and normal cattle (Sakai et al, 1996). Following a 500ml bolus of 50% dextrose, blood glucose concentrations were found to increase to around eight times normal levels, returning to pre-treatment levels by two hours after treatment.

Alongside the changes in glucose levels, there was also an immediate increase in circulating insulin level to approximately five times normal levels, with further increases after 15 minutes.

Wagner and Schimek (2010) demonstrated any excess glucose that goes unused will be excreted via the kidneys, thus increasing electrolyte excretion and, potentially, leading to electrolyte imbalances.

While BHB levels in the blood will decrease during treatment, there is a limited lag effect (less than 24 hours), therefore repeated treatments would be required for a longer effect. However, repeated doses leading to prolonged hyperglycaemia can potentially result in reduced abomasal motility (Holteinus et al, 2000). Therefore, dextrose is recommended in severe cases of ketosis with concurrent hypoglycaemia or in cases where nervous signs exist.

Figure 2. Cows with ketosis are 3.33 times more at risk of an LDA.
Glucocorticoids have long been used in cases of ketosis due to their effects on gluconeogenesis alongside their ability to inhibit the effect of insulin, allowing increased utilisation of fat and protein stores to produce energy.

Concentrations of both glucose and insulin have been shown to increase significantly approximately 48 hours after dexamethasone administration (Jorritsma et al, 2004). However, the evidence to support their use in ketosis treatment is unequivocal. In addition, the use of corticosteroids in non-ketotic animals shortly after calving may impair their metabolic state (Seifi et al, 2007).

In addition to glucocorticoids, vitamin B$_{12}$ is also sometimes used in a treatment plan due to its effects on gluconeogenesis through its indirect role in the Krebs cycle. There is evidence prophylactic use of vitamin B$_{12}$ can be beneficial at calving in reducing the risk of ketosis in older cattle (Rollin et al, 2010), but its role in the treatment of clinical cases is yet to be fully validated.

While insulin alone would never be given as the sole treatment for ketosis due to the risk of hypoglycaemia, it has been suggested its anabolic effects may be beneficial since it increases the use of ketones as energy sources.

The study by Gordon et al (2012) showed no benefit of using insulin alongside propylene glycol compared to propylene glycol in uncomplicated cases of ketosis. Although there is potentially some benefit in cases involving hepatic lipidosis (fatty liver; Hayirli, 2006) the lack of licensed product and cost of human formulations make this cost-prohibitive in the majority of cases.

Propylene glycol is perhaps the most commonly used treatment for ketosis, either alone or in combination with other treatments. Following ingestion it is either absorbed directly or converted to pronprionate in the rumen, both of which stimulate gluconeogenesis. Fifteen minutes following administration, blood insulin levels significantly increase and remain high for two hours, helping to decrease the breakdown of fat and thus the accumulation of ketone bodies (Studer et al, 1993).
**Figure 3.** Nutritional management during the transition period is crucial in reducing the risk of ketosis at herd level.

A large-scale study at Cornell University (McArt et al, 2011; 2012) demonstrated how in cows with BHB levels greater than 1.2mmol/L, those that received 300ml (310g) propylene glycol daily (median five days) were less likely to develop a displaced abomasum, leave the herd in the first 30 days of lactation and produced more milk than those that received a placebo (water).

Glycerol is sometimes used instead of, or in addition to, propylene glycol; however, a small-scale study by Piantoni and Allen (2015) suggests 300ml of propylene glycol is more effective at increasing plasma glucose concentration than glycerol and at least as effective as 600ml glycerol or a combination of glycerol and propylene glycol when given orally.

Based on this, daily oral doses of 300g of propylene glycol for five consecutive days is recommended in the treatment of ketosis (Gordon et al, 2013).

**Prevention**
Table 2. Individual cow risk factors for ketosis

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parity 1 and 3+</td>
</tr>
<tr>
<td>BCS ≥3.5 in dry period</td>
</tr>
<tr>
<td>Dry period &gt;2 months</td>
</tr>
<tr>
<td>Loss of BCS during dry period</td>
</tr>
<tr>
<td>Twin pregnancy</td>
</tr>
<tr>
<td>Milk:fat protein ratio &gt;1.5 in previous lactation</td>
</tr>
<tr>
<td>First calving &gt;27 months of age</td>
</tr>
</tbody>
</table>

**Table 2. Individual cow risk factors for ketosis**

As with all conditions, due to the associated costs with clinical or subclinical cases, prevention is preferable. Therefore, identifying the risks, both at individual cow and herd level, are important when developing prevention programmes.

Herds at high risk of ketosis are those with an annual left displaced abomasum (LDA; **Figure 2**) incidence of greater than 5%, more than 10% of cows with a body condition score (BCS) equal to or greater than three weeks prior to calving and those with more than 40% of cows with a fat:protein greater than 1.5:1 at the first milk recording postcalving (Oetzel, 2004; Duffield, 2007).

Transition nutrition and management are crucial to reduce incidence at herd level (**Figure 3**). Overstocking, diet changes, insufficient access to feed (barrier design, availability and feed frequency) and group changes in the critical period prior to calving can all influence dry matter intake, and thus the degree of negative energy balance following calving.
Figure 4. Twins are a risk factor for the development of ketosis.

When a herd fits into the “high-risk” category a full appraisal of transition cow management should be undertaken to ensure solutions are found at herd level to alleviate ketosis in early lactation.

Individual cow risk factors are outlined in Table 2; Figure 4.

When herd risk factors have been identified and alleviated and individual cow risk factors still exist, these can be targeted for preventative therapy.

Kexxtone was launched in the UK two years ago by Elanco Animal Health and provides a novel solution for the at-risk cow to reduce risk of ketosis (Figure 5). An intraruminal bolus, providing a consistent daily dose of 335mg of monensin daily for approximately 95 days, is administered three to four weeks prior to calving.
Figure 5. Kexxtone boluses allow targeted treatment of individual at risk cows to reduce their risk of ketosis in early lactation.

The effects of monensin in dairy cattle have been researched since the late 1980s, leading to its use in many countries. It is a natural antibiotic and works by altering the microbial populations in the rumen. It selectively inhibits Gram-positive bacteria rather than Gram-negative bacteria due to the differences in their cell wall structure.

The result is a change in the ratio of volatile fatty acids in the rumen leading to an increase in propionic acid production and a decrease in butyric and acetic acid. This increased production of propionic acid increases hepatic gluconeogenesis and therefore glucose levels, reducing the risk of ketosis (Duffield et al, 2008). Administration three to four weeks prior to calving is crucial to allow the microbial populations to adapt in time for calving.

Many studies have been conducted looking at the effects of monensin on metabolic parameters, milk production and health outcomes; however, it is apparent delivery method has a big effect on the outcome. Many of the studies have been conducted in North America where, in addition to the bolus form, they also mix monensin into or top dress the ration. The threshold used to define disease also varies between studies, and therefore can affect the outcome.

The European clinical trial results for Kexxtone (reference AA9CEU0801) alleviate many of these issues. In the study, 1,312 dry cows were randomly allocated to two groups; treatment or placebo. Each group was comparable in terms of age, mean parity and previous milk production. Results showed significantly fewer cows in the treatment group had elevated BHB levels (using thresholds of 1.0mmol/L and 1.4mmol/L) in the second week of lactation in comparison to the placebo group (Table 3).

| Table 3. Prevalence of ketosis seven to 14 days following calving in cows treated with Kexxtone versus placebo (Elanco European Clinical Trial, AA9CEU0801) |
|-------------------------------------------------|----------------|----------|----------|----------|
| Ketosis prevalence seven to 14 days post-calving (based on measurement of blood BHB) | Test group (Kexxtone) | Placebo group | Reduction | P-value  |
| Proportion of cows >1.0 mmol/L (%)              | 8.2            | 32.1     | 74%      | <0.001   |
| Proportion of cows >1.4 mmol/L (%)              | 3.0            | 19.6     | 85%      | <0.001   |

In addition, the treatment group produced an additional 1.22kg milk/day over eight to 133 days postcalving. There are clearly benefits to using Kexxtone in at-risk cows, but it does not completely eliminate the risk of ketosis, although it significantly reduces it. However, as with all antimicrobial products, it must be used responsibly and not seen as a solution for poor management practices. It
must also be administered effectively and at the recommended time to maximise its benefit.

**Summary**

The high-producing dairy cow is at risk of ketosis and its subsequent detrimental effects on productivity and survival in the herd. Many treatments are commonly used in the treatment of ketosis, but very few have any robust evidence base to support their use.

Based on the studies available it is clear daily propylene glycol is a key component of any treatment regime, with animals displaying nervous signs also benefiting from intravenous dextrose. Monensin has a proven benefit when used in high-risk cows; however, as with all diseases, prevention is better than cure and the aim must always be to reduce the risk factors for ketosis both at herd and individual level.

**References**
