Molybdenosis in calves

The pathophysiology of molybdenosis in both dairy and suckler calves is outlined by Conor G McAloon PhD MVB DipECBHM MRCVS, Catherine Carty MVB DipECBHM MRCVS, and Finbar Mulligan MAgrSc PhD Ass DipECVCN, University College Dublin

Over the past few years, the University College Dublin (UCD) herd health team has investigated a number of cases of molybdenosis in both dairy and suckler calves. The aim of this article is to revise the typical case presentation and current thinking regarding pathophysiology of this condition.

TYPICAL CASE PRESENTATION

The most notable presenting sign encountered on affected farms has been diarrhoea and ill-thrift in first grazing season calves. In many cases, these signs have been observed in consecutive grazing seasons, often occurring over many years. The condition may be associated with grazing particular paddocks and soil types. In a number of recent cases, grazing pastures from reclaimed bog has been associated with particularly severe clinical signs, especially if this ground has received lime application.

Diarrhoea presents shortly (<1 week) after turn-out to pasture. In many cases a presumptive diagnosis of coccidiosis or osteragiosis is made, however faecal parasitological examination is often negative and response to treatment unrewarding. In addition, the short timeframe between exposure to grass and the onset of clinical signs is less suggestive of ostertagiosis as a cause.

Over the course of three to four weeks, coat depigmentation may be observed and significant loss of condition occurs (see Figure 1). In some cases, secondary diseases such as dermatophytosis or respiratory disease may be observed. Signs persist until calves are brought inside and fed hay or silage, however farmers often report that the condition greatly improves by the beginning of August with clinical signs abating and coat colour returning to normal by the end of the grazing season. There is some anecdotal evidence of an increased susceptibility in the Limousin and Simmental breeds.

AETIOLOGY AND PATHOPHYSIOLOGY

Many of the clinical signs outlined, particularly coat depigmentation, have traditionally been associated with Cu deficiency, through primary deficiency, or secondary deficiency due to the presence of antagonistic minerals (Radostits, 2007). However, evidence of these 'typical' clinical signs and Cu status have been lacking. Mee (1991) found no association between blood Cu levels and coat depigmentation, whereas, Rowlands et al (1977) found no association between blood Cu and fertility. Such a lack of association could be explained by the accepted poor accuracy of blood samples for assessment of Cu status. However, several authors maintain that clinical signs classically associated with Cu deficiency are more related to molybdenum (Mo) toxicity than hypocupraemia per se (Bone, 2010; Telfer et al, 2004). For example, experimental studies have shown that, despite the induction of comparable hypocupraemia and reduced hepatic Cu levels, clinical signs of classic 'Cu deficiency' were only to be observed with Mo-induced Cu deficiency, as opposed to experimental iron (Fe)/sulpher (S)-induced Cu deficiency (Phillippo et al, 1987). It should be noted however, that other authors are not in agreement with this theory (Suttle, 2010).

Upon ingestion, Mo and S may combine in the rumen leading to the formation of a series of thiomolybdate compounds. Thiomolybdates have a high affinity for Cu, binding to available Cu in the rumen and producing an insoluble-Cu thiomolybdate complex leading to secondary Cu deficiency (Suttle, 1991). However, with low levels of rumen-available Cu, and in the presence of high-dietary Mo, thiomolybdates may be absorbed directly from the rumen and intestine and interfere with Cu-dependent enzymes which have wide roles in the body (Bone, 2010). In these cases, if sufficient amounts of Cu bypass the rumen, for example, if chelated Cu is fed, blood and liver copper status could be in the normal range, however, signs of traditional copper deficiency could persist (Telfer et al, 2004). Of the series of thiomolybdates produced (mono-, di-, tri- and tetra-thiomolybdate), tetra-thiomolybdate is the most potent in terms of copper affinity (Gould and Kendall, 2011). The relative proportion of tetra-thiomolybdate produced is influenced by rumen pH and S concentrations, with increasing proportions forming in lowered pH and increased S:Mo ratios (Gould and Kendall, 2011).

S and Fe exacerbate this toxicity by further reducing the availability of copper in the rumen, leading to increased availability of thiomolybdates for absorption. Mo reaching the small intestine in the form of thiomolybdate may cause significant and persistent diarrhoea, likely due to Cu being 'stripped' from the cytochrome-oxidase enzyme causing mitochondrial and cellular disruption within the cells of the intestinal mucosa (Suttle, 1991).

Young calves appear to be particularly susceptible to the toxic effects of Mo, with the most affected cohort being weaned dairy calves following turn-out to pasture. Mo levels on pasture are influenced by soil moisture and temperature and tend to be highest in early spring and autumn with reduced levels in mid-summer (Suttle and Small, 1993). However, clinical signs in calves are most often noted in spring and may be explained by the combination of the younger age of the calves, elevated Mo and increased pasture S content. S content is highly correlated with protein and tends to be lower as pasture matures (Suttle, 2010).

Although the most dramatic clinical signs are seen in first grazing calves, wide-ranging effects of molybdenosis are expected in other age groups, due to the function of Cu

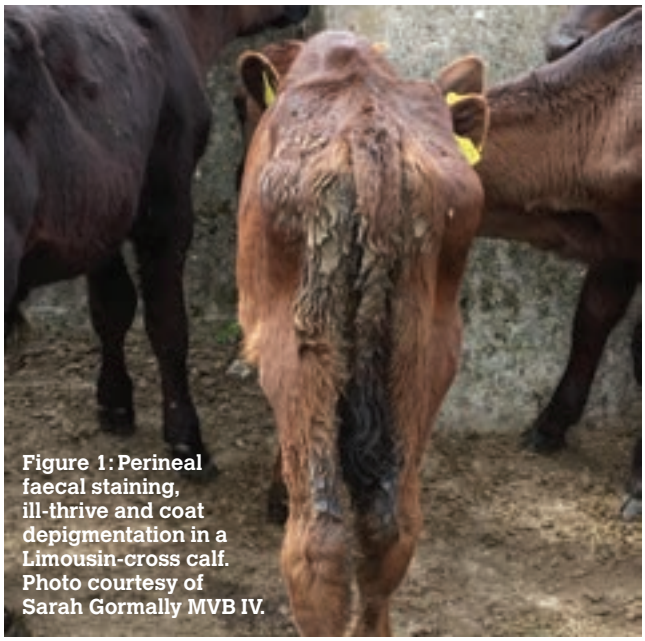

Figure 1: Perineal faecal staining, ill-thrive and coat depigmentation in a Limousin-cross calf. Photo courtesy of Sarah Gormally MVB IV.

as a cofactor in many important enzymatically-catalysed reactions (Reece et al, 2015). Immune function, in particular, is compromised through altered acute phase-protein response and lymphocyte proliferation (Athrington et al, 1996), reduced antibody production (Gengelbach and Spears, 1998), and decreased bacteriocidal competency in neutrophils (Torre et al, 1996). In growing-finishing animals decreased average dailt gain (ADG) has been observed (Dias et al, 2013) which was more closely related to dietary Mo and S intake than Cu *per se*. Effects of elevated Cu on fertility are also widely recognised, resulting in a prolonged interval to puberty in heifers (Phillippo et al, 1987) and decreased oestradiol production (Kendall et al, 2003). O'Gorman et al, (1987) also reported that high-Mo, low-Cu status can cause retarded embryo development. However, the hypothesis that Mo is always problematic needs careful consideration, particularly because a recent study reported an association between low-Mo status in the transition period with retained foetal membranes (RFMs) and endometritis (Bicalho et al, 2014).

Depression of cytochrome c oxidase enzyme activity, involved in cellular energy (ATP) production has been shown in cases of the 'moose-wasting disease' recently attributed to severe molybdenosis following widespread lime application in areas of Sweden, releasing large concentrations of molybdenum to grazing wild ruminants (Frank, 2004).

DIAGNOSIS

Diagnosis of molybdenosis is difficult and, in many cases, no definitive diagnosis is achieved. A history of diarrhoea shortly after turn-out and abatement of clinical signs within a week of housing and feeding hay or silage, should raise suspicion. A presumptive diagnosis may be made based on ruling out other causes of ill-thrift and diarrhoea, pasture-Mo content and response to appropriate treatment.

It may be useful to measure Cu levels in suspect calves, however, the poor accuracy of blood samples in estimating Cu status in cattle is well-accepted (Vermunt and West, 1994) and liver biopsy is not routinely conducted in young calves. Importantly, diarrhoea occurs in these calves before blood and liver levels begin to reduce (Suttle et al, 1991). In addition, both serum- and liver-Cu levels may be normal or elevated in cases of molybdenosis (Bone, 2010). Alternatively, diagnosis may also be made based on activity of Cu-containing enzymes; ceruloplasmin and serum oxide dismutase. However, disease may impact on the accuracy of these results as both plasma Cu and caeruloplasmin may increase with infectious disease or vaccination, even in initially hypocupraemic animals (Suttle et al, 1994). The use of caeruloplasmin and serum Cu for the diagnosis of molybdenosis is a contentious issue with some authors advocating its use (Telfer et al, 2004) and others sceptical of its use (Suttle, 2010).

Forage mineral analysis is particularly useful in providing support for a clinical suspicion of molybdenosis. However, it is important that forage samples are taken at representative times of the year. Pasture levels are lowest in mid-summer, samples should therefore be taken when the problem is observed, ie. spring or autumn. Conservation of Mo-rich forage will reduce availability, presenting a potential mitigation option for dealing with high-Mo paddocks.

Given the complex interaction of minerals, an overly deterministic interpretation of thresholds is not advised. However, pasture levels <3mg/kg dry matter (DM) are considered low risk; 3-10mg/kg DM are considered high risk, especially in the case of reduced Cu content; and >10mg/kg DM considered very high risk. Herd cases referred to UCD herd health group over the last few years have often been in the range of 8-15mg/kg DM with Cu levels in the range of 6-10mg/kg DM. Rogers and Murphy (2000), reported the mean-Mo concentration in Irish forages increased from 2.0mg/kg DM to 3.5mg/kg DM from 1990 to 1993. In addition, 42.1% of samples had Mo levels greater than 2mg/kg DM, with 10.1% of pastures greater than 5mg/kg DM and 2.3% greater than 10mg/kg DM. Elevations in sulphur and iron are also known to exacerbate the problem of high molybdenum. Rogers and Murphy (2000) reported that 80% of Irish forages were considered high (>0.3%), similar reports are not available for Fe, however Fe:Cu ratios, in excess of 100, should be considered high risk (Suttle, 2010). Water sources may also be additional sources of Fe. It is also important to remember that certain soil conditions can precipitate the accumulation of Mo in grass, such as increasing soil moisture and pH. Particular paddocks may, therefore, be more affected at certain times of the year depending on specific soil conditions.

CONTROL

The success of control options varies between farms. An underlying principle of control is to reduce the intake of Mo. In the short-term, pasture profiling of paddock-Mo concentrations will identify high-risk paddocks, which could be used for silage as conservation, reduces the bioavailability. In the medium, long-term, soil-management options should be explored to reduce the uptake of Mo.

In particular, aeration and drainage of the soil, as well as monitoring soil pH, may result in a dramatic improvement in forage-Mo content. Soil-mineral management, however, is a specialised area which is beyond the scope of this article. We therefore recommend seeking specialist advice to manage this aspect of control. Appropriate Cu supplementation will likely improve clinical signs in many cases. However, in the case where pasture-Mo content exceeds 10mg/kg DM, it may be difficult to manage livestock, regardless of the supplementation adopted. There is risk of Cu toxicity as well as poor response to clinical signs if excessive copper is supplied in an inappropriate chemical form (Bone, 2010). The theory of Cu supplementation in cases of molybdenosis centres around the idea of 'sacrificial Cu', which will bind thiomolybdates within the rumen forming an insoluble complex (Telfer et al, 2004). In this way excess thiomolybdates are less likely to be absorbed through the intestinal tract and, therefore, may not act in a systemic manner. Cu, therefore, should be available within the rumen, ie. Cu salts such as sulphate or carbonate. The duration of effect however may vary depending on the farm, the rumen conditions and the level of Mo. It should be remembered that several sources of Cu may not be maximally available within the rumen. For example, Cu oxide may be largely released in response to low abomasal pH and chelated Cu, by design, may bypass the rumen entirely.

Molybdenosis is by no means a novel condition, however, increasing stocking densities and pasture management practices have potentially increased the risk in Ireland over the past 10 years. The most obvious clinical signs may be observed in calves, and practitioners should suspect this condition in non-responsive cases of diarrhoea shortly after turnout, especially when parasitological examinations are negative, and calves respond rapidly to housing and provision of alternative feed. However, other less obvious but significant production-limiting effects may add to the hidden costs of this condition.

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