Acetonaemia (ketosis, slow fever)

Acetonaemia or ketosis is a metabolic disorder of high yielding lactating cows characterized by reduced milk yield, loss of body weight, inappetance and, occasionally, nervous signs. Ketone bodies, e.g. acetoacetate,bhydroxybutyrate or acetone, are present in all body fluids. Hypoglycaemia together with increased plasma free fatty acids and liver fat and decreased liver glycogen are also a feature of this disease. These changes are associated with an inadequate supply of the energy that is necessary to sustain high levels of milk production in early lactation. Pregnancy toxaemia, a common disease of pregnant sheep and characterized by hypoglycaemia

and hyperketonaemia, can also occasionally affect pregnant cows particularly when carrying twins . Friesian breed may have some effect on the disease incidence. Outbreaks are usually restricted to one or two cows but varying numbers of cows in the herd may be affected. If the incidence of the disease is high it can become a severe economic problem due to depressed milk production. The disease usually occurs three to six weeks after calving, when the cow is at her peak milk production but her appetite or DM intake has not yet reached its peak. During early lactation the dairy cow is in negative energy balance. The energy intake in feed is insufficient to meet the energy output in milk. This results in the mobilization of fat reserves to meet the energy deficit and a consequent loss in body weight. This should be considered a normal metabolic situation in high-yielding dairy cows. Such cows will have slightly raised blood ketone levels and may even excrete ketones in urine and possibly in milk. The cow in early lactation is therefore in a delicate metabolic balance and any stress that causes a reduction of feed intake can disturb this balance and result in the onset of clinical ketosis. Factors that can influence the occurrence of the disease include excessive feeding of silage that has a high content of butyric acid, a deterioration in forage quality, sudden changes in types of food on offer and excessive fatness at calving. Cows that are too fat at calving have lower DM intakes in early lactation and are therefore more likely to suffer acetonaemia. Acetonaemia is diagnosed in grazing cattle if the grass has a high moisture content and/or when the energy intake is insufficient. Cobalt is required for rumen microbial synthesis of vitamin B12 and is also essential for adequate utilization of propionic acid. In areas of cobalt deficiency acetonaemia will be commonly diagnosed in grazing cows . Secondary ketosis is common, if not more common, than primary ketosis and can result from any disease that causes a reduction in appetite in early lactation. Displaced abomasum and traumatic reticulitis are two common problems frequently associated with secondary ketosis.

Aetiology

To understand the aetiology of acetonaemia one must realize the precarious metabolic balance that exists in all cows in early lactation. To satisfy the requirements of milk production the cow can draw on two sources of nutrients, food intake and her body reserves. In the first two months

of lactation a cow producing up to 45 kg of milk daily will use up to 2 kg of body fat and up to 350 g of body protein per day. As far as the dietary supply of nutrients is concerned 80 per cent of the ingested carbohydrates are fermented by the rumen microflora into the volatile fatty acids, acetic, propionic and butyric acids, which are themselves absorbed. Acetate may be oxidized by various tissues or incorporated into milk fat by the mammary gland. Glucose is synthesized in the liver and renal cortex by the gluconeogenic pathway. Approximately half of the cow's glucose requirement is derived from dietary propionic acid, which is incorporated into the tricarboxylic acid (TCA) cycle and converted to glucose by gluconeogenesis. Glucogenic amino acids, lactic acid and glycerol can be converted into glucose by this process. Reduced production of propionic acid in the rumen will result in inadequate glucose production and a consequent hypoglycaemia. Hypoglycaemia leads to a mobilization of free fatty acids and glycerol from the fat stores. Hormones such as adrenaline, glucagon, adrenocorticotrophic hormone, glucocorticoids and thyroid hormones all influence this mobilization from the body fat stores. Skeletal muscle and heart can utilize fatty acids for energy production when glucose is short.

However, the liver has a limited ability to oxidize fatty acids because acetyl-CoA, which is the end product of fatty acid oxidation, cannot be adequately incorporated into the TCA cycle when levels of oxaloacetate, the result of active gluconeogenesis, are low. The excessacetyl-CoA is converted into the ketone bodies acetoacetate and b-hydroxybutyrate and, to a small extent, acetone. Tissues other than liver can utilize ketone bodies but, if their production exceeds the rate they are used by muscle and other tissues, they accumulate and ketosis is the result. Ketone bodies are excreted in milk and urine. The reduction of propionic acid production by the rumen is usually a feature of underfeeding or a reduced feed intake caused by inappetance. Cobalt deficiency, as mentioned above, will also have the effect of reducing propionic acid production. Butyrate is a precursor of acetyl-CoA and is therefore ketogenic. An increase in butyrate uptake from the rumen will therefore be ketogenic. This explains why silage high in butyric acid will induce ketosis in apparently normal cows.

Signs

Hypoglycaemia is the major factor involved in the onset and development of the clinical signs of acetonaemia. There will have been a gradual loss of body condition over several days or even weeks. There is also a moderate decline in milk yield over two to four days before the onset of the obvious clinical signs, which are refusal to eat grain and concentrate feeds and a more sudden

drop in milk output. At this stage a sweet smell (as in pear drops) of acetone is apparent on the breath and the discerning stockworker will even detect the same acetone smell in the milk. Once appetite is decreased weight loss is accelerated due to utilization of body stores. Rectal temperature, pulse rates and respiratory rates are normal in the early stages of the disease, as are

ruminal movements. Faeces will usually be firm with a dark 'waxy' appearance. A small number of cows with acute acetonaemia exhibit nervous signs, which include excessive salivation,

abnormal chewing movements and licking walls, gates or metal bars. Incoordination with apparent blindness will also be a feature. Some cows will even show a degree of aggression and will sometimes charge into walls, occasionally injuring themselves. The other signs observed above are also present. The nervous signs often only last for a few hours with the animals showing more normal behaviour in between.

Clinical pathology

Hypoglycaemia, hyperketonaemia and the presence of ketones in the urine and milk are the features of this disease. Cowside diagnosis is obtained by the detection of ketones in milk and urine using the Rothera's test reaction. A drop of milk or urine is added to a small quantity (which consists of sodium nitroprusside 3 g, sodium carbonate 3 g and ammonium sulphate 100 g) ofRothera's reagent on a white tile or piece of white card. A pink to purple coloration of the reagent confirms the presence of ketones. Urine normally contains low levels of ketones so a diagnosis is only positive when the milk is also positive. Blood glucose levels are reduced to below 1.4 mmol/l (25 mg/100 ml). Total blood ketone levels are raised to over 5 mmol/l (30 mg/100 ml). The plasma glycerol and free fatty acid levels (non-esterified fatty acid, NEFA) are also elevated. Subclinical ketosis has become more important in recent years with the introduction of the laboratory test for b-hydroxybutyrate (bHB). The level of bHB is frequently used on a herd basis as a measure of energy balance in both lactating and dry cows. Herds with subclinical ketosis have been identified using this test. Serum levels of bHB in excess of 1.75 mmol/l (10 mg/100 ml) will indicate a severe energy deficit in the diet . Although mortality is not normally a feature of acetonaemia, affected cows do possess fatty infiltration and degeneration of the liver.

Diagnosis

The diagnosis is made on the history of a cow in early lactation with a sudden fall in milk yield, some weight loss, refusing to eat concentrates, with normal temperature, pulse and respiratory rates and normal rumen movements. Many astute stockworkers will recognize the acetone odour on the breath or in the milk and report this to the attending veterinarian. The diagnosis is confirmed by a positive Rothera's reaction on milk and urine and, if this is not conclusive, a blood sample can be analysed for glucose and ketone levels. It is important to differentiate between primary and secondary ketosis so a complete clinical examination must be performed. Many cases presented by the farmer as acetonaemia are in fact suffering from displaced abomasum . Some cows with hypocalcaemia may also show acetonaemia. The differential diagnosis of the nervous form of acetonaemia can be sometimes confusing. The behavioural changes are similar to listeriosis, but usually with listeriosis pyrexia will be present. Hypomagnesaemia should be distinguishable by the presence of hyperaesthesia, particularly the tremors of the eye-lids and muscle tremors over the shoulders and the presence of tetanic convulsions. Bovine spongiform encephalopathy may also be confused with acetonaemia because of weight loss. However, the apprehension, kicking and progressive nature of BSE

should be distinguishing features, besides which blood glucose, magnesium and ketone levels will be normal in BSE. Rabies is characterized by mania, ascending paralysis and is always fatal.

Treatment

There are three main components of successful treatment:

(1) To restore blood glucose levels as quickly as possible.

(2) To replenish oxaloacetate, an essential intermediate in the TCA cycle in the liver, so that fatty acids mobilized from the fat deposits are completely oxidized. This will reduce the rate of production of ketone bodies.

(3) To increase the availability of dietary glucogenic precursors, notably propionic acid. An intravenous infusion of 500 ml of 40 per cent glucose will cause a transient rise in blood glucose levels that lasts approximately two hours. This should be accompanied by oral administration of glucose precursors such as propylene glycol (150 ml, twice daily). Propylene glycol is preferred to propionate or glycerol because propionate is fermented in the rumen and may cause digestive disturbances and glycerol is converted to ketogenic acids as well as propionic acid in the rumen. Cobalt salts are frequently added to the propylene glycol and in cobalt-deficient areas at least 100 mg/day of cobalt should be administered. Glucocorticoid drugs are the most commonly used

therapy for acetonaemia, either used alone or in combination with glucose therapy or when followed by oral administration of glucose precursors. Glucocorticoid therapy results in a reduction of ketone body formation due to utilization of the acetyl-CoA derived from fatty acid oxidation and raises blood glucose levels due to a greater availability of glucose precursors in the liver. The commonly used glucocorticoids are dexamethasone, betamethasone and flumethasone and all are effective. Frequently, a single dose is administered but this does often result in relapses two to three days after the treatment, when the injection can be repeated. There is one disadvantage of repeated glucocorticoid therapy and that is that appetite and milk yield are reduced.

For successful treatment in most cases of acetonaemia the following regimen is to be recommended:

• 500 ml of 40 per cent glucose intravenously, followed by

• One dose of glucocorticoid, followed by

• Oral treatment twice daily with 150 g of propylene glycol containing cobalt for three to four days.

Anabolic steroids are also a useful treatment for acetonaemia and were used in Europe before their use was prohibited under the EC hormone ban. They are effective by increasing the levels

of the intermediates of the TCA cycle in the liver. They also stimulate appetite, which ensures an increased supply of the glucogenic precursors. They do not directly raise blood glucose levels. It is important that the cow's appetite returns to normal as soon as possible after treatment so access to good quality fodder is a prerequisite to successful treatment. If butyric silage is implicated in the cause of the problem this should be removed from the diet and only well-fermented silage or good quality hay offered. If acetonaemia is affecting a high proportion of the

herd it would be wise to obtain a supply of ground maize, as it has been shown that ground maize is readily digested in the small intestine and results in a rapid rise in blood glucose levels.

Prevention

The prevention of acetonaemia starts before calving. Cows should not be too fat at calving, a condition score of 2.5–3.0 would be optimum and anything higher would be considered too fat. Access to a plentiful supply of long coarse fibre to promote good rumen digestion is also important during the dry period. Concentrates used during lactation should be introduced in small quantities (1–2 kg/day) two weeks before calving to allow adjustments in the rumen microflora. Changes to diet in early lactation should be made gradually. Forage containing ketogenic substances such as butyric acid should be avoided in early lactation. Roughage should comprise at least 40 per cent of the diet. In cobalt-deficient areas measures should be taken to ensure adequate cobalt intake, e.g. by spreading cobalt sulphate on to pastures. The concentrates used need to be of good quality. This statement may seem obvious but unfortunately some concentrate manufacturers, under pressure from farmers, will produce substandard concentrates at a lower than normal price. By and large the quality of a concentrate food is reflected in its price. The use of metabolic profiles measuring blood glucose and BHB levels in groups of dry cows and cows in early lactation can be useful in the hands of the experienced veterinarian. This will often indicate an energy-deficient diet and one that could predispose to subclinical if not clinical acetonaemia. As already stated, acetonaemia is less common now than in previous years. This is due mainly to improvements in forage conservation techniques and the use of mixed forages, especially maize silage. Thus cows are fed better quality feeds and there is increased awareness that optimum output comes as a result of optimum input.