Introduction

Of the domestic farmed species, sheep are most susceptible to copper poisoning. There are few reports of copper poisoning in cattle. Calves, especially prior to weaning, are more susceptible to copper poisoning than adult cattle. The Veterinary Laboratories Agency (VLA) has diagnosed increasing numbers of cases of copper poisoning in adult dairy cattle in England and Wales since the mid 1990s and particularly since 1999 (Bidewell, David and Livesey, 2000). These cases have all been typical of chronic toxicity. No cases of copper poisoning have been reported in adult cattle in Scotland or in adult beef cattle in England and Wales.

Background to inclusion of copper in cattle rations

Copper is an essential part of a number of enzyme systems. It plays an important role in tissue respiration. Other important physiological roles of copper include erythropoiesis, development of connective tissue, bone and central nervous tissue, pigmentation and immune function. A deficiency of copper can therefore result in wide-ranging clinical signs but one of the first enzymes to be affected is tyrosinase which is critical in melanin synthesis (Underwood and Suttle, 1999). Grass is usually a barely adequate source of copper and when grazed from copper deficient soils can result in primary copper deficiency. Secondary copper deficiency occurs as a result of interactions between copper and other elements, especially sulphur, molybdenum, iron and zinc (Underwood and Suttle, 1999). Molybdenum and sulphur interact with copper to form copper-thiomolybdate complexes in the rumen. These complexes reduce the bioavailability of copper and secondary copper deficiency may occur even when dietary intakes of copper are apparently adequate (Suttle, 1991). Copper is commonly added to ruminant diets not only to overcome copper deficiency but also to avoid deficiency even when no signs of disease are present in livestock.

Pathogenesis of copper poisoning

The liver is the tissue reservoir for copper and liver copper concentration reflects the copper status of the animal. Acute copper poisoning is uncommon and usually only occurs when cattle are given excessive ‘therapeutic’ doses of copper or ingest very large doses of copper salts which may have accidentally contaminated feed or their environment. Chronic copper poisoning is more common and results from long term ingestion of copper in quantities which exceed the nutritional requirement and the capacity of the animal to excrete excess. Progressive copper accumulation can result in high copper concentrations in the liver prior to the onset of clinical signs and is referred to as the accumulation or pre-haemolytic phase. Copper is normally bound to a variety of proteins during transport and storage because copper ions released within metabolism cause oxidation of exposed cells. When the hepatic copper storage capacity is exceeded, hepatocyte necrosis occurs and copper is released from the liver into the blood. The release of copper ions into blood causes haemolysis and precipitates an acute haemolytic crisis (Underwood and Suttle, 1999).

Clinical signs of copper poisoning

These are variable in adult cattle. The clinical signs most commonly reported to the VLA are jaundice, malaise, brown mucous membranes and acute milk drop. Other clinical signs include recumbency, anorexia, ataxia and head pressing (as a result of hepatic encephalopathy), tachycardia, dyspnoea, photosensitisation, sub normal rectal temperature, red/brown urine,
cyanosis, ‘found dead’, pallor, pyrexia, abortion, nasal discharge, epiphora, polyuria, polydipsia and gut stasis.

Unexpected deaths are not unusual but, more typically, clinical signs are of 1 to 3 days duration. More protracted clinical disease is uncommon although occasional cows may survive into a post-haemolytic phase with signs of renal and or hepatic failure, which include malaise, ill thrift and poor production. Photosensitisation can occur secondary to liver damage due to faulty excretion of phylloerythrin. Clinical signs of photosensitisation include erythema and oedema, which may progress to tissue necrosis, affecting unpigmented skin exposed to sunlight. Only a small proportion of clinically affected cattle have survived. Herd mortality has ranged from 0.3% to 5%. Disease has occurred in all age groups, a range of herd sizes and at differing stages of production including the dry period. There is no particular seasonality with cases occurring both during housing and at pasture although the highest number of index cases has occurred in July (Livesey, Bidewell, Crawshaw and David, 2002).

**Differential diagnoses of copper poisoning**

During the haemolytic phase these include:
- Bacillary haemoglobinuria
- Nitrate/nitrite poisoning
- Plant poisoning especially brassicas
- Leptospirosis
- Post-parturient haemoglobinuria
- Babesiosis
- *C. renale* infection

**Pathology of copper poisoning**

Following haemolytic crisis the kidneys are swollen and dark brown to black in colour. The blood and tissues will usually show discoloration due to icterus or methaemoglobinemia and urine is commonly red to red/brown in colour. The gross appearance of the liver varies from a pale tan to bronze colour and in some cases sectioning the liver reveals a ‘nutmeg’ appearance due to severe zonal necrosis. The gall bladder is commonly distended with thick bile. Echymotic haemorrhages and petechiation, both subcutaneously and in various organs, are not uncommon.

Microscopic pathology is of acute to subacute necrotising hepatopathy with more variable nephropathy. Rubeniac acid staining of liver can be utilised to detect excess copper in the liver.

**Clinical pathology**

Laboratory findings most commonly associated with a diagnosis of copper poisoning are associated with the haemolytic phase of disease and include raised serum bilirubin, the presence of haemoglobin in urine and methaemoglobinemia.

Ante-mortem plasma copper concentration increases during the pre-haemolytic phase and plasma copper concentrations are highest when the haemolytic crisis is imminent. During the clinical phase of copper poisoning, plasma copper is usually greater than 50µmol/l (VLA...
reference range 9-19 µmol/l). Elevation of serum concentrations of liver enzymes is one of the earliest biochemical changes in the pre-haemolytic phase with increased GLDH, AST and GGT concentrations. The liver copper concentration typically exceeds the VLA reference range of 300-8000 µmol/kg DM. Kidney copper concentration is usually in excess of 1000 µmol/kg DM (VLA reference range 125 - 650 µmol/kg DM).

**Diagnostic criteria**

All factors should be considered in reaching a diagnosis including details of copper intake, clinical signs, biochemistry of blood and tissues, and gross and microscopic pathology. Table 1 shows a case definition formulated by the VLA. The case criteria in this table are strict and were applied to avoid false diagnoses of copper poisoning when it was felt inadequate sampling had been undertaken.

The minimum samples required to confirm copper poisoning in the laboratory are detailed in table 2.

**Food safety**

Livers with copper concentrations exceeding 500 mg/kg WM are considered to be a risk to public health and such cases should be treated as potential food safety incidents. The copper content of cow’s milk is low and increases in milk copper concentration resulting from supplementing the diet with additional copper are very small (Beck 1941). During the phase of clinical copper poisoning, it is likely, but not proven, that the copper content of the milk will rise because of the dramatic rise in blood copper concentration.

**Prevention and Treatment**

It should be presumed that chronic copper poisoning is a result of long-term ingestion of copper. Therefore, when poisoning occurs, the copper content of the ration (in mg/head/day) and mg/kg dry matter intake (DMI) should be assessed. In most cases the current ration will need replacing with one with reduced copper concentration. Supplementation of the diet with copper antagonists can decrease the absorption and accumulation of copper and increase excretion, but much of the information available on the use of in-feed antagonists gives details for sheep (Radostits, Gay, Blood and Hinchcliff 2000). Parenteral products such as ammonium tetrathiomolybdate are of use in the treatment of copper poisoning.

These parenteral products do not have a product licence and their use will therefore result in prolonged meat and milk withdrawal periods (The Medicines Regulations, 1994).

**Discussion**

During the 1990s copper poisoning has emerged as a disease of dairy cows in Great Britain. Copper poisoning should be considered as a differential diagnosis in a cow presenting with icterus, haemoglobinuria or methaemoglobinemia or blood parameters indicating severe liver pathology. The precise cause of this rising incidence of copper poisoning is not yet clear but it appears likely to be multifactorial. In other species, such as sheep and dogs, there is genetic predisposition to susceptibility to copper poisoning. No genetic predisposition has been proven in these investigations. The data collected by the VLA suggests that the Jersey breed may be more susceptible and this is consistent with a study reported in the USA (Du, Hemken and Harmon, 1996). In addition, one of the herds investigated showed a trend towards familial susceptibility, which deserves further investigation (Crawshaw 2002). The inclusion of

<table>
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<tr>
<th>Ante mortem</th>
<th>Post mortem</th>
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<tbody>
<tr>
<td>Clinical signs and Serum/plasma Cu &gt; 50 µmol/l</td>
<td>Pathology and supporting tissue chemistry</td>
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<tr>
<td>Kidney Cu &gt; 650 µmol/kgDM</td>
<td>Liver Cu &gt; 8000 µmol/kgDM</td>
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**Table 1. Case definition for copper poisoning in adult cattle**

<table>
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<tr>
<th>Ante mortem</th>
<th>Post mortem</th>
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<td>Heparinised blood: plasma copper (GGT, AST, GLDH and bilirubin useful)</td>
<td>Fixed and fresh liver and kidney for histopathology and copper assays</td>
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**Table 2. Samples required to diagnose copper poisoning**
chelated copper products in the ration has been suggested as a possible cause for the recent increased incidence of copper poisoning in dairy cows. There is however insufficient published data available on the bio-availability and safety of chelated copper supplements to assess if recently introduced supplements could be contributing to the problem. There is increasing evidence that the disease occurs because of long-term ingestion of excessive dietary copper (Aggett 1999). The Feeding Stuffs Regulations (2000) permit a maximum of 35mg/kg (plus “overage”) copper in dairy cow diets, equivalent to approximately 800mg copper/cow/day. The Regulations also specify a maximum proportion or amount of certain copper supplements. Larger amounts of copper can only be fed to ruminants on veterinary prescription, in situations where a higher copper requirement is demonstrated (Thomas 1999). It is recommended that care should be taken when formulating dairy cow rations and that veterinary advice is sought when copper is to be included at levels greater than 800mg/head/day or 35 mg/kg of dry diet (assuming 88% dry matter in the dry diet).

Acknowledgement

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References


