Not so sweet as chocolate for Zak

Author: Roger Wilkinson

Categories: Vets

Date: June 1, 2009

Roger Wilkinson reports on a case study where poisoning by an oxidising agent and methaemoglobinemia were just the start of an American bulldog’s problems.

Case history

Zak, a two-year-old American bulldog, was presented to the surgery after he was found collapsed in his backyard 30 minutes previously alongside a piece of vomited meat that hadn’t been fed to him by his owners.

Although capable of standing, he was very weak, tachypnoeic and salivating excessively. Deep red-brown coloured urine was passed in the waiting room. On examination he turned out, somewhat unexpectedly, to have very strong pulses and normal capillary refill. The most striking finding, however, was that all of his mucous membranes were a muddy, chocolate-brown colour (Fig 1). A venous blood sample was the same deep brown and remained so, even when exposed to air (Fig 2).

His arterial oxygen concentration (PaO2) was entirely unremarkable. In fact, his blood gases suggested a moderate respiratory alkalosis. Meanwhile, pulse oximetry suggested an oxygenation of 85 per cent (Fig 3).

In other respects, Zak appeared physically well. He was afebrile, and there was no outward evidence of respiratory or cardiac disease. We were not keen to anaesthetise him for thoracic radiography, but thoracic ultrasound and echocardiography proved unremarkable, with there being no evidence of right-to-left shunting.
With strong circumstantial evidence of poisoning and few conditions characterised by chocolate-coloured blood that does not redden on exposure to air, the conclusion was rapidly reached that Zak had likely ingested an oxidising toxin (probably paracetamol) and incurred a significant degree of methaemoglobinaemia.

A 2.5mg/kg dose of activated charcoal was given orally at the outset of treatment, to try to reduce any further absorption of the intoxicating agent. Funds were relatively limited, but it didn’t seem to be pushing the boat out too much to pinch some methylene blue from the practice laboratory and a slow bolus was promptly administered intravenously. Almost to our surprise, he was still with us an hour later, so another dose was given.

By now, Zak had developed a rather alarming facial oedema – in fact, his periorcular tissues and conjunctivae were bulging like a frog and he was “crying” yellow-green tears. This is a well-documented feature of paracetamol intoxication in some dogs\textsuperscript{1,2}. Our initial success in keeping Zak alive encouraged his owners to splash out on some N-acetylcysteine, and this was infused into him over the next 24 hours, along with some 0.9 per cent saline.

The next day, Zak remained stubbornly alive and, with their money all spent and warnings about liver failure fresh in their ears, his owners took him home to take his chances. Although Zak’s liver parameters on day two defied our expectations and remained within normal limits, for the next four days he ate nothing. His owners weren’t easy to contact and didn’t return to the surgery – we feared the worst. On day five, they reappeared in evening surgery with the news that their dog had eaten his tea.

At first glance, Zak appeared his usual, solid self but, on lifting his lip, his mucous membranes revealed themselves to be a luminously banana-yellow (Figure 4) colour.

Liver parameters (postprandial bile acids, aspartate aminotransferase and alanine aminotransferase) were within normal limits, but Zak’s haematocrit had plummeted to 16 per cent – the jaundice being the sequel to haemolysis. Despite this, he was returning to his usual bullish demeanour and, after discussion, we elected to monitor the situation. The jaundice gradually resolved during the ensuing week, leaving Zak with extremely pale mucous membranes (Figure 5). A normal colour resumed by week three.

**Background**

Methaemoglobin is formed when the iron component of the haem group in haemoglobin is oxidised by drugs or chemicals from Fe\textsuperscript{2+} to Fe\textsuperscript{3+}. In this state, it is unable to bind oxygen.

Methaemoglobin usually comprises less than one per cent of circulating haemoglobin. Although there is an ongoing process of oxidation, this is usually matched by the body’s reductase enzyme systems. Clinical signs become apparent when levels exceed 20 per cent, and death may occur...
beyond 70 per cent.

Some of the most common agents incriminated are the drugs paracetamol (acetaminophen), hydroxyurea (used in the treatment of polycythaemia and some leukaemias) and topical benzocaine (used as a local anaesthetic), or naphthalene (moth balls).

Clinical signs

Methaemoglobinaemia is characterised by cyanosis, a muddybrown mucous membrane colour, and tachypnoea – usually with strong pulses and normal capillary refill time. In humans, altered mentation is an early sign. The fact this is not so in dogs has been attributed to the higher canine haematocrit\(^2\). The discovery of brown blood that does not redden on contact with the air after venepuncture is highly suspicious.

Paracetamol poisoning has specifically been associated with facial oedema, chemosis, salivation and tremors. The toxic dose of paracetamol in dogs is thought to be around 200mg/ kg (as opposed to 60mg/kg in cats). First signs are usually seen within four to 12 hours of ingestion. Evidence of hepatopathy frequently becomes apparent on biochemistry within 36 hours. However, early treatment may prevent this sequel, as there are other published cases in which signs were limited to the acute haematological consequences.

Clinical pathology

CO-oximetry, the definitive test, may be available through human laboratories. Cyanosis may be present in the absence of abnormal arterial oxygen concentration. PaO\(_2\) measures oxygen dissolved in blood, and not that bound to haemoglobin. Blood gases generally suggest respiratory alkalosis.

On pulse oximetry, readings tend to be about 85 per cent, with increasing methaemoglobinaemia. With compatible signs, this kind of level is suspicious, but otherwise not helpful in making a diagnosis of methaemoglobinaemia. It should also be noted that pulse oximetry tends to overestimate blood oxygenation in methaemoglobinaemia\(^3\).

Treatment

Supplemental oxygen should be provided. If packed red cells are available at short notice, then they may be life-saving.

The use of methylene blue (Table 1) is somewhat controversial. In human medicine, methaemoglobinaemia may be resolved within one hour of starting methylene blue treatment\(^4\) and, in the case described by Wray (2008)\(^2\), methaemoglobin levels were demonstrated to be just one
per cent of total haemoglobin after 16 hours of therapy with combined methylene blue and N-acetylcysteine. The usual dose is 1.0mg/kg methylene blue, initially followed by another 30 minutes later. However, there is some experimental evidence, at least in cats, that methylene blue plus N-acetylcysteine is no better than N-acetylcysteine alone. There is a risk of inducing haemolysis with methylene blue and although haemolysis is also reported as a feature of paracetamol poisoning itself (as evidenced by the haemoglobinuria), the haemolysis seen in the present case may well have been partially iatrogenic, since Heinz bodies were not prominent in a blood smear taken before treatment.

N-acetylcysteine is probably the most important single therapeutic tool in treating paracetamol intoxication and is a useful addition to the practice pharmacy. It acts as a glutathione precursor in the liver.

In dogs, most paracetamol is eliminated by the liver via glucuronidation pathways. However, a small proportion is converted by cytochrome p450-dependent mixed-function oxidases into metabolites that exhibit hepatotoxicity and include free radicals capable of inducing oxidative damage. It has been speculated that treatment with cimetidine – a competitor for cytochrome p450 – may reduce the potential for this conversion. Ascorbic acid, at 30mg/kg orally once, has been used as an agent that, at least theoretically, may promote the conversion of methaemoglobin to oxyhaemoglobin. Ursodeoxycholic acid may confer some hepatoprotection, as it promotes the production of the anti-oxidative glutathione by hepatocytes.

Supportive measures may include the use of intravenous fluids to correct dehydration and reduce the risk of haemoglobin-induced renal failure.

Références

Figure 1. Zak on first presentation. Chocolate-coloured mucous membranes are characteristic of methaemoglobinemia.
Figure 2 (left). Methaemoglobinemia patients have deep brown blood that fails to redden on exposure to air.
Figure 3 (right). Increasingly severe methaemoglobinaemia results in a trend towards 85 per cent oxygenation as determined by pulse oximetry.

<table>
<thead>
<tr>
<th>MAC</th>
<th>RR</th>
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<tr>
<td>2.2</td>
<td>PR</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>SP</td>
<td>85</td>
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<tr>
<td></td>
<td>O2</td>
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Figure 4 (left). Is this jaundice iatrogenic, caused by methylene blue, or due to the paracetamol poisoning?
Figure 5 (right). The jaundice was resolved to reveal the extent of the haemolytic anaemia.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Case for use</th>
<th>Dose</th>
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<tbody>
<tr>
<td>Activated charcoal</td>
<td>Probably useful, safe</td>
<td>2.5mg/kg PO once, as soon as possible after ingestion</td>
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<tr>
<td>Packed red cells</td>
<td>Can be life-saving, small risk</td>
<td></td>
</tr>
<tr>
<td>N-acetylcysteine</td>
<td>Mainstay of treatment, low risk</td>
<td>Given IV, diluted in 0.9 per cent NaCl or glucose and NaCl. 150mg/kg loading dose after more than 15 minutes. Then 50mg/kg after more than four hours. Then 100mg/kg after more than 16 hours.</td>
</tr>
<tr>
<td>Methylene blue</td>
<td>Possibly useful, some risk</td>
<td>Controversial, may or may not be beneficial. 1mg/kg by slow IV injection, followed by another similar bolus 30 minutes later</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Possibly useful, safe</td>
<td>5mg/kg tid IV</td>
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<tr>
<td>Ursodeoxycholic acid</td>
<td>Possibly useful, safe</td>
<td>10mg/kg sid PO</td>
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<tr>
<td>Ascorbic acid</td>
<td>Possibly useful, safe</td>
<td>30mg/kg orally once</td>
</tr>
<tr>
<td>S-adenosyl methionine (SAMe)</td>
<td>Possibly useful, safe</td>
<td>40mg/kg loading dose PO, then 20mg/kg PO sid for seven days</td>
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**Table 1.** Therapeutic agents used in the management of paracetamol poisoning in dogs