CASE REPORT

Methaemoglobinaemia caused by hydroxycarbamide (hydroxyurea) ingestion in a dog

A three-year-old female neutered greyhound was presented after ingestion of its owner's hydroxycarbamide (hydroxyurea) tablets. The dog was found to be cyanosed, and methaemoglobinaemia was demonstrated by co-oximetry. Therapy included methylene blue, oxygen, packed red blood cell transfusion, N-acetylcysteine and crystalloid fluids. Methaemoglobinaemia resolved within 16 hours. Granulocyte colony-stimulating factor was administered for five days in an attempt to prevent severe neutropenia. Mild delayed transient myelotoxicity was suspected. The dog made a full recovery.

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INTRODUCTION

Methaemoglobinaemia describes a state where the iron moiety of haem groups within haemoglobin has been oxidised from the ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state and is no longer able to bind oxygen. Methaemoglobinaemia in cats and dogs may be congenital (because of absence of methaemoglobin reductase) but is more commonly acquired as a result of oxidant injury by drugs or chemicals (Harvey 2000).

Hydroxycarbamide (previously known as hydroxyurea) is an inhibitor of ribonucleoside diphosphate reductase. In small animal medicine, it has been used to treat polycythaemia vera (Peterson and Randolph 1982, Evans and Caylor 1995, Gray and others 2003), pathological thrombocytosis, hypereosinophilia and some leukaemias.

This case report describes intoxication of a dog by accidental ingestion of hydroxycarbamide in which methaemoglobinaemia was the principal presenting sign and its subsequent management.

CASE REPORT

A three-year-old neutered female greyhound weighing 25 kg was presented to the Centre for Small Animal Studies, Animal Health Trust with a history of ingestion of 5000 to 7500 mg (10 to 15 capsules) of hydroxycarbamide (Hydrea; Bristol-Myers Squibb) belonging to its owner three to six hours before referral. The owner had found the dog collapsed and dyspnoeic. The dog was presented to the referring veterinarian within 20 minutes, and initial physical examination findings demonstrated normothermia, tachypnoea, cyanosis and tachycardia of up to 240 beats per minute (bpm). Oxygen therapy and intravenous fluid therapy with Hartmann's solution was given and induced emesis attempted without success. Activated charcoal suspension (BCK granules; Fort Dodge) had been administered orally at an unrecorded dose.

At referral, the dog was collapsed, anxious, normothermic, tachypnoeic with a respiratory rate of 60 to 80 breaths/minute, had purple discoloured oral mucous membranes (Fig 1) and a tachycardia of 160 to 180 bpm with strong, synchronous peripheral pulses. Blood samples were taken for a complete blood count, biochemistry, plasma lactate and arterial blood gases, electrolytes and methaemoglobin percentage by co-oximetry (Table 1). The venous blood sample was dark brown on collection (Fig 2a,b) and did not redden in air. Urinalysis by cystocentesis demonstrated haemoglobinuria but was otherwise normal. Methaemoglobin percentages were only available retrospectively as co-oximetry was not available on-site. Nasal oxygen was given through intranasal prongs at a rate of 3 litres per minute. Lateral and dorsoventral thoracic radiographs demonstrated no abnormalities, and pulse oximetry displayed oxygen saturation of 87 to 88 per cent. An electrocardiogram demonstrated sinus tachycardia with a maximal rate of 220 bpm. Because of the history, cyanosis, absence of lung pathology or arterial hypoxaemia and brown-discoloured blood, a diagnosis of methaemoglobinaemia was made and confirmed retrospectively. Elevated creatine kinase (CK) and lactate were felt to be because of muscular hypoxia resulting from methaemoglobinaemia, or collapse

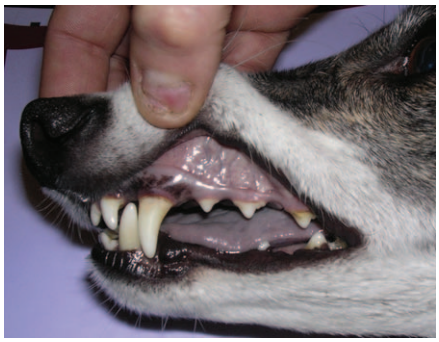

FIG 1. Mucous membrane colour at admission of the dog with methaemoglobinaemia caused by hydroxycarbamide ingestion

with CK also possibly elevated because of haemolysis or traumatic venepuncture. Blood gas findings were consistent with respiratory alkalosis. Reported acute toxicities of hydroxycarbamide in human beings are of methaemoglobinaemia and pneumonitis, with medium-term toxicities of myelosuppression (especially neutrophils and platelets) and hepatotoxicity (product data; Bristol-Myers Squibb). Approximately 20 minutes after presentation, 1 mg/kg methylene blue (Methylene Blue; Sigma) was given intravenously (iv) as a bolus, followed by a second dose of 1 mg/kg iv 30 minutes after the first dose. A dose of 150 mg/kg N-acetylcysteine (Parvolex; UCB) was administered iv once, followed by 70 mg/kg iv every four hours for forty-eight hours. Because of the clinical findings of severe hypoxaemic distress, unknown level of methaemoglobinaemia and cyanosis, it was decided to also administer packed red blood cells as a rapid means of increasing tissue oxygen delivery as, regardless of the elevated patient haematocrit, oxygen content of native red blood cells was suspected to be severely reduced. Alternatively, a haemoglobin-based oxygen-carrying solution could have been administered but with proportionally decreased ability to elevate oxygen content per unit volume than packed red blood cells. Iatrogenic volume overload was considered less likely with administration of packed red blood cells. One unit of packed red blood cells was prepared from a Dog Erythocyte Antigen (DEA) 1 negative donor and transfused over three hours starting approximately one hour after presentation and continued nasal oxygen was given. After completion of the transfusion, Hartmann's solution supplemented with 20 mmol/l potassium chloride was administered at a rate of 4 ml/kg/hr for a further 24 hours. The dog was able to stand unaided within five hours after initiating treatment and respiratory rate, heart rate and mucous membrane colour returned to normal within seven hours. Nasal oxygen supplementation was discontinued after six hours, with no change in mucous membrane colour or change in respiratory rate or character. Methaemoglobin percentage 16 hours after admission was 1 per cent and lactate was 1·25 mmol/l (0·5 to 2·5). Beginning the day after presentation, the granulocyte

Table 1. Laboratory findings at admission (before therapy) in the dog with methaemoglobinaemia caused by hydroxycarbamide ingestion

Analyte	Result	Reference range
Haematology*		
Haemoglobin (g/dl)	**23·5**	12·0-18·0
RBCs ($\times10^{12}$/l)	**8·7**	5·5-8·5
Haematocrit (l/l)	**0·656**	0·37-0·55
Mean cell haemoglobin (pg)	**27**	19·5-24·5
Mean cell volume (fl)	75·4	62-77
Mean cell haemoglobin concentration (g/dl)	35·8	32-36
White blood cells ($\times10^9$/l)	9·5	6-18
Neutrophils (band) ($\times10^9$/l)	0·00	0·0-0·5
Neutrophils (seg) ($\times10^9$/l)	8·08	4·0-12·0
Monocytes ($\times10^9$/l)	**0·67**	1·0-4·8
Lymphocytes ($\times10^9$/l)	0·76	0·1-1·8
Eosinophils ($\times10^9$/l)	**0·00**	0·2-1·2
Basophils ($\times10^9$/l)	0·00	0·0-0·01
Platelets ($\times10^9$/l)	**146**	200-500
	No evidence of Heinz bodies or other RBC abnormality seen on blood film	
Biochemistry†		
Alkaline phosphatase (iu/l)	Sample quite haemolysed; sample unsuitable	15-150
Alanine aminotransferase (iu/l)	40	0-100
Bile acids (µmol/l)	1·0	0-15
Cholesterol (mmol/l)	3·0	3·2-6·5
Amylase (U/l)	399	900-3000
Lipase (U/l)	51	0-500
Creatine kinase (iu/l)	**1299**	21-56
Urea (mmol/l)	7·8	2·8-8·3
Creatinine (µmol/l)	88	40-120
Glucose (mmol/l)	4·2	3·5-6·5
Sodium (mmol/l)	150	137-155
Potassium (mmol/l)	4·4	3·7-5·8
Chloride (mmol/l)	109	100-115
Calcium (mmol/l)	2·3	2·1-2·9
Phosphate (mmol/l)	Sample unsuitable	1·0-2·0
Total protein (g/l)	56	52-73
Albumin (g/l)	29	25-35
Globulin (g/l)	27	27-44
Lactate‡	**4·12**	0·5-2·5
Arterial blood gases§		
pH	**7·44**	7·407±0·0097
$PACO_2$ (mmHg)	**28·75**	36·8±3
PAO_2 (mmHg)	97·25	92·1±5·6
$HCO3^-$ (mmol/l)	21·9	22·2±1·7
Base deficit (mmol/l)	−4·1	
Co-oximetry ∞		
Methaemoglobin (per cent)	**72·9**	<1

RBC Red blood cell
*Beckman Coulter ACT^{diff}
†Labmedics (Thermo Electron) Konelab 20i
‡Vettest 8008; Idexx
§Radiometer ABL 700 Series
∞Bayer 865 with Co-oximeter
Abnormal values in bold

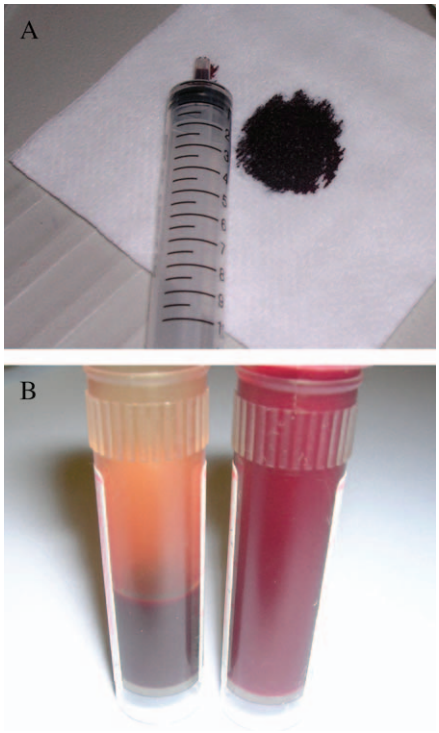

FIG 2. (a) Venous blood sample taken from the dog with methaemoglobinaemia caused by hydroxycarbamide ingestion. Note dark chocolate-brown discoloration, which did not improve on exposure to room air. (b) Comparison of venous blood samples taken before (left) and 16 hours after (right) treatment for intoxication with hydroxycarbamide in the dog

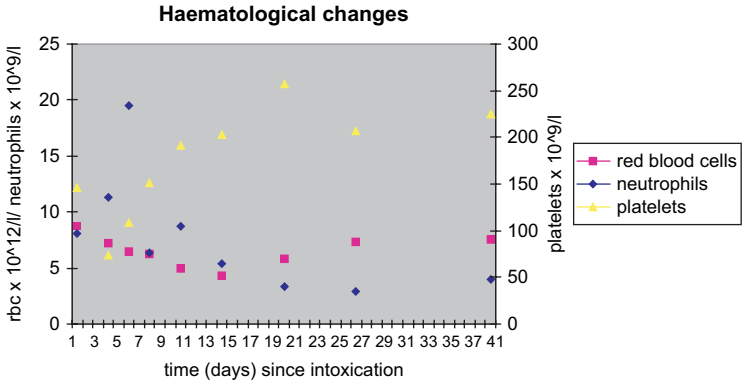

FIG 3. Changes in haematological parameters over days since intoxication in the dog with methaemoglobinaemia due to hydroxycarbamide ingestion

colony-stimulating factor (GCSF) filgrastim (Neupogen; Amgen) was administered at 5 µg/kg subcutaneously every 24 hours for five days. The rationale for pre-emptive GCSF therapy was in an attempt to ameliorate an expected delayed myelotoxic crisis as a result of the hydroxycarbamide ingestion. Possible reported adverse effects of GCSF in dogs include irritation at the injection site, and there are theoretical concerns that exogenous GCSF may risk induction of autoantibodies, myelofibrosis or medullary histiocytosis (Plumb 2005a). A complete clinical recovery was seen, and the dog was discharged on day 6. A complete blood count and smear examination was assessed every 48 hours for one week, then on two occasions per week for two weeks, then once weekly thereafter to monitor for nadirs in neutrophil and platelet counts (Fig 3). A repeat lateral thoracic radiograph taken five days after presentation was normal. A biochemistry panel including alanine aminotransferase, alkaline phosphate (ALKP) and fasting bile acids was performed six days after presentation and once every two weeks for two further occasions to monitor for hepatotoxicity. Normal results were obtained. Platelet numbers reduced to 74×10^9/l (200 to 500) at four days and returned to reference limits by 15 days after hydroxycarbamide ingestion. Red blood cell numbers decreased to $4{\cdot}3 \times 10^{12}$/l (5·5 to 8·5) with haematocrit 0·35 l/l (0·37 to 0·55) at 15 days and returned to reference limits by 21 days after ingestion. At no time was Heinz bodies or eccentrocytes found on examination of blood smears. Neutrophilia of $19{\cdot}5 \times 10^9$/l (4 to 12) was documented at six days with a subsequent nadir of $2{\cdot}9 \times 10^9$/l at 28 days after hydroxycarbamide ingestion. The neutrophil count was within reference limits 41 days after hydroxycarbamide ingestion.

DISCUSSION

Methaemoglobinaemia in dogs and cats has been most frequently reported because of intoxication with oxidative substances, such as acetaminophen (Finco and others 1975, Harvey and others 1986, Schlesinger 1995, Allen 2003, Webb and others 2003, Hill and others 2005), topical benzocaine (Harvey and others 1979, Wilkie and Kirby 1988), onion products (Harvey and Rackear 1985) and phenazopyridine (Harvey and Kornick 1976). Congenital deficiency in methaemoglobin reductase resulting in juvenile methaemoglobinaemia has been reported in both dogs and cats (Harvey and others 1974, 1994, Fine and others 1999, Harvey 2000). In human beings, the most common cause of acquired methaemoglobinaemia is ingestion or skin exposure to oxidising agents, such as aniline, benzocaine, dapsone, phenazopyridine, nitrites, nitrates and naphthalene (Wright and others 1999).

Hydroxycarbamide (hydroxyurea) is an enzyme-inhibiting cytotoxic agent whose action is mediated by inhibition of ribonucleoside diphosphate reductase. It is used in human medicine to treat neoplasia, polycythaemia vera, essential thrombocytosis, as adjunctive therapy for HIV/AIDS, psoriasis and sickle cell anaemia. In small animal medicine, it has mainly been used to treat polycythaemia vera or primary eythrocytosis (Peterson and Randolph 1982, Evans and Caylor 1995, Gray and others 2003) but also pathological thrombocytosis (Degen and others 1989, Bass and Schultze 1998, Favier and others 2004), hypereosinophilia (Muir and others 1993), basophilic and chronic myelogenous leukaemias (MacEwen and others 1975, Leifer and others 1983) and polycythaemia associated with right-to-left shunting patent ductus arteriosus (Moore and Stepien 2001). Advised dose range in dogs varies from 50 mg/kg three times per week to 50 mg/kg once daily (Plumb 2005b). It is of note that the minimum amount ingested in this case (200 mg/kg) is lower than the higher of these total weekly doses, suggesting there may be a low safety threshold in this species, although toxicity in this individual may have represented an idiosyncratic drug reaction or breed-related sensitivity.

It is rapidly absorbed after oral administration, and approximately 50 per cent of the dose is excreted unchanged in urine with 50 per cent hepatically metabolised and excreted in urine (Plumb 2005b). Reported LD50 toxicity after single oral dosing in mice and rats is 7330 and 5760 mg/kg, respectively (product data; Bristol-Myers Squibb), and methaemoglobinaemia has been mentioned as a potential consequence of dosage exceeding 500 mg in the cat (Plumb 2005b).

Approximately 3 per cent of haemoglobin in dogs may be oxidised to methaemoglobin each day from spontaneous autoxidation but most is reduced by the action of NADH-methaemoglobin reductase resulting in methaemoglobin levels normally being less than 1 per cent of total haemoglobin (Harvey 2000). However, the rate of this spontaneous reduction may be slow, and in human beings, it occurs at 15 per cent per hour. Additionally, the enzyme NADPH-methaemoglobin reductase (NADPH dehydrogenase, NADPH diaphorase, NADPH flavin reductase) is capable of methaemoglobin reduction in the presence of a suitable electron carrier. It has strong affinity for redox dyes, such as methylene blue, which it reduces to leucomethylene blue. Leucomethylene blue in turn acts as a reducing agent for methaemoglobin (Harvey 2000).

Clinical signs of methaemoglobinaemia in human beings are usually seen at levels above 20 per cent, and levels above 70 per cent may cause coma and death (Rehman 2001). It is interesting that in this case the patient did not have identifiable signs of depressed mentation seen in human beings with similar methaemoglobin levels. The author speculates that this may be in part because of the higher haematocrit and athletic nature of this breed compared with human beings, as tissue oxygen delivery is dependent on both cardiac output and oxygen content of blood of which the major component is degree of saturation and quantity of haemoglobin. Methylene blue treatment in human beings is effective in reducing methaemoglobin concentrations within an hour (Wright and others 1999). Although in this case, access to co-oximetry, limited methaemoglobin measurement to before and 16 hours after institution of therapy, the measured value after 16 hours was 1 per cent, which is below the 4 per cent level expected at this time point if the human being value of 15 per cent per hour of endogenous methaemoglobin reduction is used. However, this may be an underestimation of the expected time for endogenous reduction in this case, as dogs have been shown to demonstrate much lower concentrations of methaemoglobin reductase than human beings (Rockwood and others 2003). The combination of methylene blue, N-acetylcysteine and packed red blood cell transfusion therefore seemed effective in correcting the methaemoglobinaemia in this case faster than predicted for endogenous processes. Although methylene blue is itself an oxidising agent, the delay in decline of red blood cell numbers in the absence of Heinz bodies in this case was assumed to be because of hydroxycarbamide toxicity rather than methylene blue toxicity. However, the red blood cell nadir was rather soon after the intoxication to be adequately explained by myelosuppression, as insufficient time had relapsed to reflect both marrow transit time and circulating half-life of native mature red blood cells. An immune-mediated haemolytic anaemia may be an alternate explanation, but cytological evidence of a regenerative response (such as polychromasia or spherocytosis) was not noted on serial blood smear examinations.

N-acetylcysteine has been proposed as an additional agent in treating methaemoglobinaemia or an alternative to methylene blue in human patients with glucose-6-phosphate dehydrogenase deficiency (Wright and others 1999). It contains cysteine, which is a component of glutathione, and in turn contains a reduced sulphydryl group and acts both as a precursor to glutathione synthesis and as a direct electron donor. In vitro studies have shown that N-acetylcysteine significantly increases the rate of methaemoglobin reduction compared with controls (Wright and others 1996).

PAO_2 measures dissolved oxygen in blood and not oxygen bound to haemoglobin, therefore in cases of methaemoglobinaemia, PAO_2 levels are expected to be normal as was the case in this dog. Similarly, pulse oximetry is neither useful in documenting methaemoglobinaemia nor does it accurately reflect the haemoglobin oxygen saturation when methaemoglobin is present. Methaemoglobin absorbs light almost equally at both 660 and 940 nm, and in the presence of 100 per cent methaemoglobin, pulse oximetry displays a trend towards 85 per cent oxygen saturation (Wright and others 1999) as was seen in this case.

Observed toxicity in this case was limited to methaemoglobinaemia and probable myelotoxicity. It is not possible to describe whether the GCSF was effective in ameliorating neutropenia. However, the demonstration of acute moderate thrombocytopenia and more delayed albeit mild neutropenia suggested that myelosuppression was occurring, and it is possible that more marked neutropenia may have occurred had GCSF not been administered.

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