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Zinc toxicosis in a dog secondary to prolonged zinc oxide ingestion

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Abstract

Zinc toxicosis is commonly associated with ingestion of metallic zinc objects. This report documents an uncommon presentation of zinc toxicosis, secondary to prolonged ingestion of a zinc oxide cream. A 5.6 kg 6-year-old ovariohysterectomised female Poodle cross presented as a transfer to an emergency practice for severe anaemia, pigmenturia, weakness, and inappetence. She had a history of vomiting and nine days of diarrhoea. Amongst other supportive treatments, a zinc oxide cream had been applied to her hind end due to severe diarrhoea scalding, and in hindsight, the owners realised she had ingested large quantities of this cream. She developed a severe Heinz body haemolytic anaemia, along with spherocytosis, left-shift neutrophilia, prolonged activated partial thromboplastin time, and mildly elevated blood urea nitrogen. The serum zinc concentration was markedly elevated. She was treated supportively and made a full recovery. This case illustrates the importance of a thorough medical history. Zinc toxicosis can have a good prognosis when diagnosed and treated promptly.

Keywords: Canine, Haemolytic anaemia, Heinz bodies, Toxicosis, Zinc.

Introduction

Zinc toxicosis appears to be most commonly associated with ingestion of metallic zinc objects, including pennies minted in the United States after 1982, pennies minted in Canada between 1997 to 1999, Euro cents, toys, identification tags, galvanised products, nuts and bolts, garland, and even toilet paper holders (Torrance and Fulton, 1987; Latimer *et al.*, 1989; Lutgen *et al.*, 1990; Norman *et al.*, 1990; Robinette, 1990; Shaw *et al.*, 1991; Gandini *et al.*, 2002; Mikszewski *et al.*, 2003; Borst *et al.*, 2004; Volmer *et al.*, 2004; Bexfield *et al.*, 2007; Gurnee and Drobatz, 2007; Weingart and Kohn, 2009; Adam *et al.*, 2011; Clancey and Murphy, 2012; Blundell and Adam, 2013; Bischoff *et al.*, 2017).

This report documents a case of zinc toxicosis resulting from ingestion of a zinc oxide cream. Less commonly, toxicosis is associated with topical zinc oxide preparations when dogs chew whole tubes, or ingest excessive amounts applied to the skin over a period of time (Robinette, 1990; Inns, 1995; Welch, 2002). Preparations include nappy rash creams, sunscreen lotion, and shampoos (Robinette, 1990; Welch, 2002). Anecdotally, nappy rash creams are often used to treat diarrhoea scalding, as occurred in the current case. Zinc oxide is a strong gastric irritant, so most ingestions result only in self-limiting vomiting and/or diarrhoea that do not require any treatment (Robinette, 1990; Welch, 2002).

Case Details

History and clinical findings

A 5.6 kg 6-year-old ovariohysterectomised female Poodle cross presented as a referral to an emergency

practice for severe anaemia, pigmenturia, weakness, and inappetence. Nine days prior to presentation, the dog was taken to a local veterinarian for restlessness and scooting after a visit to the groomers - there, her tail base and perineum were markedly erythematous, and she was prescribed prednisolone and a mometasone cream. Subsequently, she vomited and developed diarrhoea, and was taken an emergency practice. There, buprenorphine and maropitant were administered, and she was prescribed cephalexin and Sudocrem® (Teva Pharmaceutical Industries). The prednisolone and mometasone cream were stopped. Two days later, she appeared painful again and the diarrhoea was continuing. She was taken to her regular veterinarian and received a buprenorphine injection, and was prescribed Neocort® (Troy Laboratories) and metronidazole in addition to the Sudocrem® and cephalexin. On the day prior to presentation, she became inappetent. On the morning of presentation, she was found at home collapsed and having passed red coloured urine. She was immediately taken to her referring veterinary practice. Blood was collected for haematology and biochemistry with an external laboratory. Her in-house haematocrit was 18% (reference range 41-58%). She was stabilised with intravenous fluid therapy, and received 1 g sucralfate orally and 3 mg dexamethasone intravenously for suspected immune-mediated haemolytic anaemia before transfer to the emergency practice on the same day.

She had no history of known access to toxins, including onion and garlic, and was not an indiscriminate eater.

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On arrival to the emergency practice, she was dull and tetraparetic. She was tachycardic with a heart rate of 192 beats per minute (reference range 70-120 beats per minute), and tachypnoeic with a respiratory rate of 40 breaths per minute (reference range 18-34 breaths per minute). Her mucous membranes were pale pink and tacky.

A haematocrit and coagulation profile were performed whilst awaiting the external laboratory results. The haematocrit was 10% (reference range 41-58%) with a total protein of 64 g/L (reference range 59-78 g/L), and markedly haemolysed serum. The activated partial thromboplastin time was prolonged at 168.1 seconds (reference range 75-105 seconds), and prothrombin time normal at 18.4 seconds (reference range 14-19 seconds).

Haematology (Table 1) showed a marked regenerative anaemia with frequent spherocytes and Heinz bodies. Also of note was a moderate left-shift neutrophilia.

Table 1. Haematology results from an external laboratory on the day of presentation.

Parameter	Value	Reference Range
Haematocrit (L/L)	0.17	0.35-0.58
Haemoglobin (g/L)	51	100-206
Mean Corpuscular Haemoglobin (pg)	28	21-26
Mean Corpuscular Haemoglobin Concentration (g/L)	300	310-360
Mean Corpuscular Volume (fL)	94	64-76
Red Blood Cell (RBC) ($\times 10^{12}/L$)	1.8	4.9-8.2
Absolute Reticulocyte Count ($\times 10^9/L$)	144	10-110
% Reticulocyte (%)	8	0.0-1.5
Nucleated RBCs	6 per 100WBC	
Platelet Count ($\times 10^9/L$)	304	200-500
White Blood Cell (WBC) ($\times 10^9/L$)	37.1	4.5-17.0
Lymphocytes ($\times 10^9/L$)	0.7	0.9-3.5
Monocytes ($\times 10^9/L$)	1.9	0.0-1.1
Neutrophils ($\times 10^9/L$)	31.9	3.5-12.0
Band Neutrophils ($\times 10^9/L$)	2.2	0.0-0.2
Eosinophils ($\times 10^9/L$)	0.4	0.0-1.4
Basophils ($\times 10^9/L$)	0.0	0.0-0.1
Blood Smear	Moderate anisocytosis Moderate polychromasia Moderate spherocytosis Moderate numbers of Heinz bodies Mild toxic change	

Serum biochemistry (Table 2) demonstrated mild elevations in alanine aminotransferase, aspartate transaminase, creatine kinase and blood urea nitrogen.

Table 2. Serum biochemistry results from an external laboratory on the day of presentation.

Parameter	Value	Reference Range
Albumin/Globulin Ratio	1.0	0.6-1.4
Albumin (g/L)	30	23-40
Alanine aminotransferase (IU/L)	97	16-90
Amylase (IU/L)	1056	333-1500
Anion Gap (mmol/L)	20.4	14.0-32.0
Aspartate aminotransferase (IU/L)	459	18-80
Bicarbonate (mmol/L)	19	12-26
Calcium (mmol/L)	2.0	1.9-2.9
Calcium/Phosphate Ratio	1.1	
Chloride (mmol/L)	107	101-118
Cholesterol (mmol/L)	4.5	3.5-9.0
Creatine kinase (IU/L)	648	73-510
Creatinine (mmol/L)	0.08	0.05-0.13
Globulin (g/L)	31	25-45
Glucose (mmol/L)	4.7	3.3-6.8
Glucose fluoride oxalate (mmol/L)	5.8	3.3-6.8
Lipase (IU/L)	196	77-750
Sodium/Potassium Ratio	42.1	
Phosphate (mmol/L)	1.8	0.8-2.1
Total bilirubin ($\mu\text{mol/L}$)	Below assay linear range	0-7
Total protein (g/L)	61	52-80
Alkaline phosphatase (IU/L)	139	1-150
Blood urea nitrogen (mmol/L)	14.0	2.5-10.0
Gamma glutamyl transferase (IU/L)	0	0-9
Potassium (mmol/L)	3.4	3.9-5.9
Sodium (mmol/L)	143	139-153
Thyroxine (nmol/L)	10	13-52
Symmetric dimethylarginine ($\mu\text{g/dL}$)	3	0-14

There was a mild hypokalaemia and mildly increased sodium to potassium ratio. Total thyroxine was mildly decreased. Diagnostic imaging was not performed. The haematology results prompted encouragement of further anamnesis from the owners. They had been applying Sudocrem[®] to the dog's scalded skin five times daily for seven days, and had used an estimate of half of the 250 g container, or 125 g. They often saw her with cream on her nose, and in hindsight, suspected she must have been ingesting it. This led to a presumptive diagnosis of zinc toxicosis. A serum zinc concentration was requested with the external laboratory. The zinc concentration returned three days post-discharge, and was markedly elevated at 237.1 $\mu\text{mol/L}$ (reference range 7-25 $\mu\text{mol/L}$), confirming zinc toxicosis.

Treatment and outcome

The dog received a 207 mL stored whole blood transfusion, and her haematocrit subsequently increased to 26%. She was then treated with intravenous fluid therapy using Hartmann's solution with 20 mmol potassium chloride, s-adenosyl methionine (SAME) at 40 mg/kg initially followed by 20 mg/kg once daily, 150 mg cephalexin twice daily, and 5 mg prednisolone twice daily in case of an immune-mediated component to the anaemia. She responded rapidly to therapy and was discharged three days later.

Repeat haematology performed at the dog's family veterinarian a week later showed resolution of red cell abnormalities. Within a month of admission, the dog was clinically normal based on physical examination, and her owners considered her to have her normal demeanour and activity levels.

Discussion

The oral median lethal dose for zinc "salts" is reported as 100 mg/kg (Talcott, 2013). An estimated toxic dose of zinc oxide in dogs has been reported to be 108 g (Talcott, 2013). In the current case, the dog ingested an estimated maximum of 125 g of Sudocrem[®] over seven days. Sudocrem[®] contains 15.25% w/w zinc oxide. Thus, the dog could have ingested 386.4 mg/kg elemental zinc per day.

Zinc salts such as zinc oxide are relatively stable in the stomach (Talcott, 2013), whereas metallic zinc dissolves more rapidly in more acidic environments (Van Der Merwe and Tawde, 2009). This may be why zinc toxicosis is seen more commonly with ingestion of metallic objects. With acute zinc salt ingestion, there would be comparatively limited absorption of zinc in the gastrointestinal tract. Additionally, its gastric irritant effects often cause vomiting which prevents further absorption of zinc (Robinette, 1990; Welch, 2002). Presumably with chronic exposure, as occurred in the current case due to daily ingestion over approximately a week, there would be more time for zinc absorption to reach toxic concentrations.

In health, zinc has many important roles within the body and is required in more than 200 metalloenzymes (Cummings and Kovacic, 2009). It protects cellular membranes and thiol-dependent macromolecules against oxidative damage (Cummings and Kovacic, 2009). Zinc toxicosis, however, can cause severe disease, and commonly results in haemolytic anaemia. Its mechanism is still unknown. One hypothesis is that erythrocyte antioxidant pathways are inhibited leading to erythrocyte membrane oxidative damage (Cummings and Kovacic, 2009). Oxidative damage is associated with the formation of Heinz bodies. However, a case series of 19 dogs reported only 33% had Heinz bodies, suggesting other mechanisms may be involved (Gurnee and Drobatz, 2007). These include

direct damage of red blood cells and hapten-induced immune destruction (Blundell and Adam, 2013).

In the current case, it was fortunate that Heinz bodies were present, as this prompted further anamnesis. The owners had been unaware of the potential adverse effects associated with the use of the zinc oxide cream, and only in hindsight realised the dog had potentially been ingesting large quantities.

The dog in the present case also displayed a moderate left-shift neutrophilia and moderate spherocytosis. Neutrophilia may result from non-specific bone marrow stimulation, or the release of cytokines by phagocytic cells (Bexfield *et al.*, 2007). Spherocytosis occurs infrequently, with one study reporting it in 20% of 19 cases (Gurnee and Drobatz, 2007). Spherocytes are typically associated with immune-mediated haemolytic anaemia and this should still be suspected in animals with severe spherocytosis (Gurnee and Drobatz, 2007). A case of suspected zinc-induced secondary immune-mediated haemolytic anaemia has previously been reported (Cummings and Kovacic, 2009).

Zinc is absorbed from the intestines and transported to the liver, which regulates the body's metabolically active zinc pool (Cummings and Kovacic, 2009). From there, it is distributed, and accumulates in high concentrations in the pancreas, kidneys and spleen (Cummings and Kovacic, 2009; Talcott, 2013). Given this distribution, it is unsurprising that zinc toxicosis can lead to gastrointestinal dysfunction, hepatic dysfunction, renal failure, and pancreatitis or pancreatic fibrosis (Torrance and Fulton, 1987; Shaw *et al.*, 1991; Gandini *et al.*, 2002; Mikszewski *et al.*, 2003; Hammond *et al.*, 2004; Volmer *et al.*, 2004; Gurnee and Drobatz, 2007; Weingart and Kohn, 2009; Blundell and Adam, 2013). Gastrointestinal disease appears most commonly caused by zinc's irritant and corrosive effects. (Blundell and Adam, 2013) Zinc may also have a direct toxic effect on renal and hepatic tissue (Gandini *et al.*, 2002). Haemolysis also releases free haemoglobin, which is toxic to tissues (Gandini *et al.*, 2002). Pancreatitis can occur secondary to excessive zinc accumulation, which damages pancreatic acinar cells causing release of digestive enzymes. Ischaemia and hypoxia secondary to haemolysis also contribute (Mikszewski *et al.*, 2003).

In the present case, the dog had a mild elevation in aspartate aminotransferase with near-normal alanine aminotransferase. This suggests that the elevated aspartate aminotransferase was more likely from haemolysis or muscle hypoxia rather than hepatic disease (Gurnee and Drobatz, 2007). The dog also had an elevated activated partial thromboplastin time with normal prothrombin time.

Zinc is speculated to cause inhibition of coagulation factors VIII, IX, XI, and XII, which are part of the

intrinsic coagulation cascade (Gurnee and Drobatz, 2007). Other common biochemical changes are elevations in urea, most likely from gastrointestinal haemorrhage, and hyperbilirubinaemia, most consistent with haemolysis (Gurnee and Drobatz, 2007).

Treatment of zinc toxicosis involves removal of the zinc source and supportive therapies, including blood transfusion, intravenous fluid therapy, gastroprotectants, anti-nausea medications, antioxidants, antibiotics, and sometimes chelation (Torrance and Fulton, 1987; Hammond *et al.*, 2004; Gurnee and Drobatz, 2007; van der Merwe and Tawde, 2009; Talcott, 2013; Bischoff *et al.*, 2017).

When a metallic zinc object is ingested, increasing gastric pH with antacids and gastroprotectants helps to reduce the rate of zinc dissolution until the object can be removed (van der Merwe and Tawde, 2009). Chelation with d-penicillamine or calcium sodium EDTA may be considered if zinc concentrations do not improve after removal of the zinc source (Lee *et al.*, 2016).

Given the evidence of oxidative injury in the present case, SAME was used for its antioxidant role. It is a precursor of glutathione, a major cellular antioxidant (Lu, 2000; Oz *et al.*, 2005). SAME has shown protection against oxidative stress in models of colitis, intestinal ischaemia, liver disorders, and even neurological disorders in humans (Lu, 2000; Oz *et al.*, 2005; Camara-Lemarroy *et al.*, 2011; Michael Brown *et al.*, 2012; Au *et al.*, 2013). In dogs, SAME is hepatoprotective, and has been used as an alternative to N-acetylcysteine in acetaminophen toxicity (Wallace *et al.*, 2002; Au *et al.*, 2013). To the author's knowledge, no studies have specifically examined the use of antioxidants in zinc toxicosis. It would be interesting to investigate their use in a clinical setting, particularly to determine their impact on recovery times and hospitalisation duration.

The prognosis for zinc toxicosis can be good depending on the severity of disease at the time of diagnosis. In a case series of 19 dogs, 89% survived to discharge and the median duration of hospitalisation was 2 days (Gurnee and Drobatz, 2007).

Conclusions

Zinc toxicosis is commonly associated with the ingestion of metallic objects, but can occur with ingestion of commonly available topical preparations. When prescribing treatments for animals, including over-the-counter medications, potential adverse effects should be discussed even if uncommon or unexpected. In cases of haemolytic anaemia, the medical history should rule out all potential toxicities. Zinc toxicosis can have a good prognosis with prompt recognition and treatment.

Conflict of interest

The authors declare that there is no conflict of interest.

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