Chocolate ingestion-induced non-cardiogenic pulmonary oedema in a puppy: a case report

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ABSTRACT: Chocolate intoxication in small animals may be life-threatening and associated with serious morbidity and mortality. The main clinical presentations are cardio-respiratory and neurological complications. One of the most common post-mortem findings is pulmonary oedema which can be a cause of immediate death. We report a case of non-cardiogenic pulmonary oedema thought to be triggered by chocolate intoxication in a three-month-old puppy Dachshund dog. To the authors' knowledge this is the first time such a complication has been reported after chocolate ingestion. The history, clinical signs, diagnostic approach (radiographs, methylxanthine concentrations, electrocardiography and echocardiography), and treatment are described. The effects of a combination of methylxanthines and other triggers of non-cardiogenic pulmonary oedema are discussed.

Keywords: chocolate intoxication; non-cardiogenic pulmonary oedema; methylxanthines; furosemide

Chocolate poisoning is one of the most common toxicological emergencies in dogs. The reason for the high prevalence of this intoxication is due to the fact that dogs often have access to a wide range of chocolate-containing foods with toxic ingredients including the methylxanthines theobromine and caffeine (ratio of approximately 3 : 10) (Albretsen 2004; Smit 2011). Poisoning is not dependent on the amount but rather on the type of ingested chocolate (Luiz and Heseltine 2008). Different concentrations of methylxanthines are present in different products and range from low levels as in white chocolate to cocoa beans which contain the highest levels (Gwaltney-Brant 2001; Jansson et al. 2001). The LD_{50} of caffeine and theobromine for dogs is 100–500 mg/kg (Albretsen 2004; Carson 2006). Interestingly, in the past, doses of 20 mg/kg theobromine were reported in the veterinary literature as a possible therapy for cardiac stimulation and diuresis (Carson 2006). Currently, these doses do not differ largely from described toxic doses (Carson 2006). At a low dose of 20–40 mg/kg mild signs may appear (restlessness, vomiting), from a dose of 40–50 mg/kg cardio-toxic effects can be observed such as rhythm disturbances, seizures might be evident from a dose of about 60 mg/kg, while higher doses than that may be lethal (Stidworthy et al. 1997). Though intoxication can also occur in cats and other species (Jansson et al. 2001; Smit 2011), dogs are mainly affected because of their appetite for sweet foods, and smaller dogs appear to be more susceptible to intoxication than larger dogs (Albretsen 2004; Kovalkovicova et al. 2009). If the ingested chocolate is highly fatty, gastrointestinal signs of intoxication include vomiting, diarrhoea, abdominal distention, and pancreatitis (Luiz and Heseltine 2008; Smit 2011). Increased diuresis and haematuria are reported and can progress to more detrimental cardio-respiratory and neurological signs such as tachycardia, rhythm disturbances, seizures, cyanosis and tachypnoea (Gwaltney-Brant 2001; Albretsen 2004; Carson 2006; Luiz and Heseltine 2008; Smit 2011). Death is caused mainly due to arrhythmias, hyperthermia, respiratory failure, congestion and oedema (Strachan and Bennett 1994; Stidworthy et al. 1997; Jansson et al. 2001). To our knowledge this complication has not yet been reported in cases of chocolate intoxication; the few cases of pulmonary oedema have been described only as a necropsy finding and not in a clinical patient.

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Case description

A three-month-old male Dachshund dog, weighing 2.2 kg was presented to the Clinic of Dog and Cat Diseases at the University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic for evaluation of a possible chocolate intoxication. Five hours before presentation the dog littered and ate a piece of home-made chocolate cake of approximately 200 g in weight. During the transportation the dog vomited and remains of digested food and cake were identified by the owner. Also, increased salivation and episodes of dyspnoea approximately 4 h after exposure were described. The dog had received the recommended vaccinations for his age prior to presentation; however, he was not yet dewormed.

On physical examination the dog appeared alert, mildly dyspnoeic, tachycardic (170 bpm), tachypnoeic (80 rpm), and his mucous membranes were pink and moist. The thoracic auscultation was normal and the abdomen was mildly dilated and painful. A complete blood count (CBC) and biochemical profile were performed in order to rule out infection and pancreatitis or other metabolic abnormalities. CBC and biochemistry revealed mildly increased liver activity (ALT: 1.91 μkat/l; reference range*: 0.1–1 μkat/l). Thoracic and abdominal radiographs were also taken to rule out other causes of vomiting such as ingestion of a foreign body. Abdominal radiographs were normal, but thoracic radiographs revealed a mild intersticial-to-alveolar pattern in the caudal lung lobes. There was no cardiomegaly and neither were there dilated pulmonary vessels. In addition, serum samples for determination of methylxanthine concentrations were also taken (Table 1). Based on the history, the clinical signs, and the radiological findings, a chocolate intoxication associated with a secondary non-cardiogenic pulmonary oedema (NCPO) was diagnosed.

The dog was put in cage rest and received intravenous infusion (saline 0.9% 80 ml/kg/day with dextrose), and antiemetics (thiethylperazin 0.25 mg/kg *s.c.* bid Torecan, Novartis, Slovenia). On the second day the dog generally improved. He was alert, eupneic, and the heart rate decreased to 150 bpm. An abdominal ultrasound examination was normal. On the third day, the clinical status worsened; the dog seemed mildly lethargic, mildly dyspnoeic, tachypneic (66 rpm) and tachycardic (186 bpm). The CBC results were normal but biochemistry showed elevated liver activity (ALT: 3 μkat/l). An echocardiographic examination did not reveal any significant findings and an ECG examination revealed sinus tachycardia. Cage rest, oxygen therapy, bronchodilators (aminophyllin 5 mg/kg *i.v.* tid Syntophyllin, BB Pharma, Czech Republic) and diuretics (furosemide 2 mg/kg *i.v.* tid Furosemid forte, BB Pharma, Czech Republic) were administered for management of the pulmonary oedema. On the fourth day of hospitalisation the clinical status slightly improved, the dog seemed eupneic but tachycardia was still present (192 bpm). Samples were once again taken to determine the concentration of methylxanthines (Table 1). On the fifth day the dog was clinically normal and the vital signs returned to normal values (120 bpm; 30 rpm). The dog was discharged on the 6th day. The levels of intoxicants are shown in Table 1.

Table 1. Serial measurements of serum methylxanthines in a dog with chocolate intoxication

Methylxanthines (μg/ml)	Day 1	Day 4
Theobromine	1.3	0.3
Caffeine	0.5	0
Theophylline	0.3	1.7
Paraxanthine	0.1	0.3

DISCUSSION AND CONCLUSIONS

We report here the successful treatment of a case of chocolate intoxication in a dog. In general, no specific pathological lesions are associated with methylxanthine intoxication (Jansson et al. 2001; Carson 2006). Apart from gastrointestinal irritation, dilatation of coronary, systemic, and pulmonary vessels can develop that may lead to congestion or haemorrhage (Strachan and Bennett 1994; Stidworthy et al. 1997; Jansson et al. 2001), seen mainly in agonic stages. Signs of pulmonary congestion and oedema have been traditionally attributed to arrhythmias (Gwaltney-Brant 2001; Jansson et al. 2001; Albretsen 2004); however, based on the evidence of the effects of methylxanthines and the pathogenesis of NCPO these conditions might be related.

The systemic effects of methylxanthines include enhanced sympathetic stimulation due to increased circulating levels of catecholamines (Albretsen 2004; Kovalkovicova et al. 2009). It is interesting that the release of catecholamines has been associated with

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at least two of three causes of NCPO (decreased alveolar pressure and neurogenic NCPO) (Glaus et al. 2010). NCPO trigger factors can lead to a massive central neural sympathetic stimulation in the medulla oblongata that enhances the release of a large amount of catecholamines. Consequently, there is a marked pulmonary and peripheral vasoconstriction leading to pulmonary and systemic hypertension. This advances to an increase in left atrial pressure which produces increased hydrostatic pulmonary pressure and results in oedema (Glaus et al. 2010; Agudelo et al. 2011). Another alternative explanation is a catecholamine-mediated pulmonary venous and lymphatic vasoconstriction that redistributes blood from the systemic to the pulmonary circulation resulting in increased hydrostatic pulmonary pressure and decreased lymphatic drainage (Agudello et al. 2011).

The degree of toxicity highly depends on the oral dose and the metabolism (Kovalkovicova et al. 2009). The dog in this case ingested a homemade chocolate product, then part of it was vomited and therefore the total dose that was absorbed is uncertain; in such situations it is recommended to estimate the methylxanthine dose based on the "worst-case scenario" (Gwaltney-Brant 2001). The size of a dog is a recognized predisposing factor to the toxicosis (Albretsen 2004; Kovalkovicova et al. 2009), but also the age should be considered as very young animals do not yet have well developed metabolisms. There are several other factors that could have influenced the clinical symptomatology such as chocolate mucosal adhesion and lump formation (Carson 2006), increased pyloric sphincter tone, and potential entero-hepatic circulation, which is also described as a risk factor in chocolate toxicities (Gwaltney-Brant 2001; Albretsen 2004). Furthermore, the dog in this report did not receive repeated doses of activated charcoal since it was assumed that the majority of the contents were evacuated. This might be the explanation for the relapse of the clinical signs on the third day of hospitalisation.

Commercial chocolate cakes are found in the range of 700–1000 g and are very similar to the common homemade chocolate cakes. Most of the home recipes include cocoa powder (737 mg theobromine per oz; and 70 mg caffeine per oz), baking chocolate (393 mg theobromine per oz; and 47 mg caffeine per oz) and dark-sweet chocolate (138 mg theobromine per oz; and 20 mg caffeine per oz). A 200 g piece of cake in a "worst case scenario" has a toxic dose ranging from 100–200 mg/kg which is in any case enough to induce a mild to severe toxicosis. Cooking books describe that the common homemade chocolate cake is made of 1/3 cup of cocoa powder (60 mg ~ 2 oz) and approximately 200 mg of dark-sweet chocolate (~ 7 oz). These ingredients are equivalent to about 2440 mg of theobromine and about 280 mg caffeine. According to this recipe one 200 g piece of cake (seven pieces per cake) contains approximately 388 mg of methylxanthines which corresponds to an ingested dose of 176 mg/kg.

Elevated levels of methylxanthines and their metabolites can be detected in the stomach contents, plasma, serum, urine, and liver of poisoned animals three to four days after the initial exposure (Jansson et al. 2001; Carson 2006). A wide range of variability between the serum concentration and the presence of clinical signs has been observed (Gwaltney-Brant 2001; Smit 2011). A serum concentration of 133 μg/ml theobromine was associated with death in a dog (Stidworthy et al. 1997). In contrast, a different canine patient with a serum concentration of 250 μg/ml theobromine survived (Reising et al. 1999). In humans life-threatening cardiac arrhythmias and generalized seizures may occur at serum theophylline concentrations >30 μg/ml with chronic dosing (Thomson and Montvale 2005). This is relevant since seizures also have been reported to be a trigger factor for NCPO (Glaus et al. 2010; Agudelo et al. 2011). Also of importance is that caffeine recently has been described to be more related to the genesis of vascular congestion and pulmonary oedema than theobromine (Carson 2006). This might help us to explain and understand the pulmonary oedema in our patient. Serum concentrations of theobromine, caffeine and other methylxanthines in this patient were lower than in other affected animals described in the literature despite the fact that sampling was carried out at an early stage of the intoxication. The increase in theophyllin levels can be explained by the use of aminophyllin during the pulmonary oedema episode. Though decontamination and supportive therapy were performed, the patient in this report developed classical clinical signs including serious NCPO.

To the authors' knowledge, this is the first report of a NCPO after chocolate intoxication in the veterinary literature. Diagnosis of NCPO should be performed based on the radiographic signs of pulmonary oedema, ruling out of primary cardiac disease (normal ECG and echocardiography) and if possible identification of the trigger factors. In parallel to the approach for treatment of chocolate intoxication, there must be a rational approach for NCPO that takes into account the patent airway, oxygen administration and decreasing of stress. In

human medicine the approach to NCPO includes resting, oxygen administration and mechanical positive ventilation (Agudelo et al. 2011). Therapies such as corticosteroids, diuretics and bronchodilators have not been shown to be beneficial (Stidworthy et al. 1997). Ventilation in intoxicated animals should be considered, although it is labour intensive, expensive and not available in all practice settings. According to our experience it is possible to administer bronchodilators to relieve signs of bronchospasm and to administer low to medium doses of furosemide (1–4 mg/kg) to treat NCPO as long as the patient has sufficient infusion support which enhances urinary excretion of toxic metabolites (Kovalkovicova et al., 2009). Furosemide is still a mainstay of therapy of both cardiogenic and non-cardiogenic pulmonary oedema in veterinary medicine (Reising et al. 1999; Adin et al. 2003; Agudelo et al. 2011). We have experienced good outcomes using furosemide in bolus administration (2–6 mg/kg to effect) as reported in the literature (Erling and Mazzaferro 2008); however, there is growing evidence that constant rate infusion (0.2–1 mg/kg/h) might have better effects and decrease the risk of complications (Reising et al. 1999; Adin et al. 2003). It has been shown in humans and dogs that administering furosemide by CRI causes more diuresis, natriuresis, and calciuresis, with less kaliuresis as compared to intermittent bolus delivery (Adin et al. 2003).

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