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Accidental colchicine poisoning in a dog

Zoë Wagenaar

Abstract

A 14-month-old toy poodle-cross was presented, after ingesting the owner's colchicine medication, with severe gastrointestinal disturbances and in shock. Despite aggressive medical management, the patient was euthanized approximately 24 hours after the ingestion. The clinical features, treatment, and necropsy findings of colchicine poisoning are discussed.

A 14-month-old, spayed female, 2.5 kg, toy poodle-cross was referred to the Western College of Veterinary Medicine (WCVM) teaching hospital with a history of vomiting, diarrhea, and lethargy after eating between 2 and 15 of the owner's 0.6-mg colchicine tablets, 6 to 9 h prior to presentation at the WCVM. The exact amount of colchicine ingested was unknown but in the range of 1.2 to 9.0 mg (0.5 to 3.6 mg/kg body-weight [BW]).

At the time of admission, the dog was severely depressed, hypothermic (34.6°C), bradycardic (60 beats/min), 8% to 10% dehydrated, and with pale mucous mem-

branes and a prolonged capillary refill time (CRT) of 5 s. The dog's packed cell volume (PCV) was 70 L/L; total protein, 50 g/L; and blood glucose, 3.6 mmol/L. Values obtained with a urine dipstick (Roche Chem-Strip 9; Roche Diagnostics Corporation, Indianopolis, Indiana, USA) after placement of a urinary catheter revealed specific gravity reflective of adequate concentrating ability (1.033), elevated protein (5 g/L), and the presence of red blood cells (250 erythrocytes/μL). A blood gas analysis indicated mild acidosis. An electrocardiogram showed mild bradycardia (60 beats/min) and an elevated electrocardiographic wave segment (ST) with a small positive deflection at the beginning of the ST.

An IV catheter was placed and warmed lactated Ringer solution was administered for shock treatment at 27 mL/h (for the first 6 h and then reduced to 13 mL/h). Gastric lavage was not considered due to the history of vomiting for the past several hours. Approximately 70 mL of activated charcoal was given PO. Metaclopramide (Sabex, Boucherville, Quebec), 0.2 mg/kg BW, IV, q8h, and ranitodine (Zantac; GlaxoSmithKline, Mississauga, Ontario), 2 mg/kg BW, IV, q8h, were administered. A closed circuit Foley catheter was placed in the bladder to monitor urine output. A heating pad and hot air blanket were used to warm the dog. Three hours after initial ket presentation, the body temperature had increased to 38.3°C and diarrhea contained a small amount of blood and charcoal. Hydromorphone (Sabex), 0.2 mg, IV, was administered to control severe abdominal pain.

During the night, the body temperature decreased to 36.5°C and remained in this range despite warming with a heating pad and hot air blanket. The dog was increasingly depressed, in lateral recumbency, and had started to pant (possibly an effect of the hydromorphone administration). Tachypnea, vomiting, and diarrhea continued. The CRT continued to be prolonged (3.5 s). Hematuria and hematochezia increased in severity with diarrhea consisting almost entirely of frank blood by morning. Urine production decreased to 1.2 mL/kg/h (normal, 2 mL/kgBW/h). Furosamide (Salix; Intervet Canada, Whitby, Ontario), 2 mg/kg BW, IV, was administered to increase urine production, which normalized briefly and then decreased to 0.6 mL/kg BW/h.

Fourteen hours after admission, the dog began to have seizures. Diazepam (Sabex), 5 mg, IV, was used repeatedly to control the seizures, which were occurring at approximately every 15 min. Venipuncture to collect a blood sample resulted in a large hematoma and disseminated intravascular coagulation (DIC) was suspected. seminated Heparin (Hepalean; Organon, Toronto, Ontario), 75 U/kg, BW, was injected SC to reduce the risk of pulmonary thromboembolism. An electrocardiogram revealed normal rhythm and wave forms and an increased heart

rate (200 beats/min), most likely due to seizure activity. Blood pressure was low (105/60 mm/Hg). Difficulties with blood collection limited analysis to obtaining an activated clotting time (ACT) and carrying out a biochemical panel. The ACT was 3.5 min, supporting a diagnosis of DIC. The dog was euthanized shortly after the biochemistry panel was done. A postmortem was conducted.

Results from the initial blood sample (taken on presentation) revealed erythrocytosis with a strong regenerative response and severe hypoproteinemia (50 g/L), considering the state of dehydration. Analysis of the blood sample showed that there was marked white blood cell disintegration, most likely due to the increased PCV, so a differential count and assessment of toxic change was not possible. Hepatic enzymes were elevated; alkaline phosphatase (ALP) was 584 U/L (normal, 0 to 128 U/L), alanine aminotransferase (ALT) was 463 U/L (normal, 22 to 56), and gamma-glutamyltransferase (GGT) was 24 U/L (normal, 0 to 7 U/L). A more complete biochemical panel could not be performed because of the low volume of serum. The urinalysis revealed 4+ proteinuria and 4+ blood. A urine protein:creatinine ratio analysis was not performed, so it is not known whether it was the presence of red blood cells, renal disease, or prerenal factors (high concentrations of hemoglobin or myoglobin in the blood) that were causing the proteinuria.

Blood chemical analysis of the sample collected immediately prior to euthanasia showed severe hypoglycemia (0.1 mmol/L) and a high gap metabolic acidosis with severe azotemia. The liver enzymes ALP, ALT, and GGT (2943, 763, 59 U/L, respectively) had increased substantially from the initial submission, reflecting the progression of hepatobiliary/cellular damage. Creatine kinase (CK) was elevated (1671 U/L, normal 0 to 330 U/L), indicating necrotizing muscle injury.

Gross necropsy findings included severe mucosal congestion and hemorrhage extending the entire length of the intestinal tract. Histopathologic examination of the small and large intestines showed severe multifocal crypt necrosis and stromal collapse, as well as severe multifocal mucosal, submucosal, and serosal hemorrhages. Ileal submucosal lymphoid follicles were moderately depleted.

Immunohistochemical testing was performed to rule out parvovirus; and the results were negative. Gross examination of the brain showed congested meninges and mild cerebellar coning. Histopathologic examination of the brain showed congestion of the parenchyma and prominent hemorrhage of the cerebellar meninges as well as numerous small hemorrhages scattered within the cerebellum, consistent with increased intracranial pressure. Hepatic sinusoids of the liver and the red pulp of the spleen were severely congested. Moderate to severe loss of periar-

teriolar lymphoid sheaths and splenic corpuscles was evident in the spleen. There was moderate diffuse congestion and hemorrhage in the adrenals and of the renal parenchyma. Epithelium of convoluted tubules had occasional cytoplasmic changes and the collecting tubules were frequently mildly dilated. Some collecting tubules had amorphous eosinophilic casts and small clumps of periodic acid-Schiff-positive material, which may be indicative of cellular damage.

Colchicine is an alkaloid of *Colchicum autumnale* (autumn crocus, meadow saffron) (3). Colchicine has been the drug of choice in humans for treatment of acute gouty arthritis and as a prophylactic agent against such attacks. It has also been used for the treatment of amyloidosis in familial Mediterranean fever (4) and condyloma acuminate (5). As it is a potent inhibitor of cellular mitosis, colchicine and its derivatives have been used recently in the treatment of some types of neoplasia (6). Colchicine binds selectively and reversibly to microtubules, causing metaphase arrest and preventing many bules, cell functions (7), such as degranulation, chemotaxis, and mitosis. Rapidly dividing cells are the most sensitive to colchicine. Mitosis blockade accounts for diarrhea, bone marrow depression, and alopecia. Inhibition of cellular function does not, however, account for all the organ failures seen in cases of severe overdose (3). Colchicine may have a direct toxic effect on muscle, the peripheral nervous system, and the liver. Colchicine decreases body temperature, depresses the respiratory center, constricts blood vessels, and causes hypertension via central vasomotor stimulation (1).

Colchicine is rapidly absorbed after oral administration, probably from the jejunum and ileum (1). Time to peak concentration is in humans 0.5 to 2.0 h, decreasing rapidly within 2 h (1). Volume of distribution is 2.2 L/kg BW (6). Colchicine accumulates in kidney, liver, spleen, the gastrointestinal wall, and leucocytes (3). Accumulation in these tissues may lead to toxicity. Elimination is primarily biliary with enterohepatic recirculation with 10% to 20% renal elimination (1). Because of the high degree of tissue uptake, only 10% of a single dose is eliminated within 24 h and elimination from the body may continue for 10 d or more (1). However, the severity and mortality rate of the poisoning is usually related to the dose ingested (8–10) as described in Table 1. The lowest lethal oral dose reported for dogs is 0.13 mg/kg (11). Fatalities in the first few days result from shock, respiratory or cardiac arrest, or rapidly progressive multiple organ failure (1).

Table 1

Clinical symptoms and mortality rate as related to ingested dose of colchicine (11)

Dose absorbed mg/kg	Symptoms	Mortality rate
< 0.5	Gastro-intestinal symptoms	
	Decrease of coagulation factors	0%
0.5–0.8	+ Bone marrow aplasia	
> 0.8	+ Alopecia	10–50 %
	+ Circulatory failure	100%

Therapy for colchicine toxicity is supportive, as there is no approved antidote available. Treatment for a severe overdose includes gastric and/or administration of activated charcoal to decrease absorption. Because of colchicine's extensive biliary elimination and enterohepatic recirculation, repeated doses of activated charcoal are theoretically of value but have not been proven (7). Due to colchicine's high volume of distribution and tissue binding, forced diuresis, peritoneal dialysis, hemodialysis, charcoal hemoperfusion, or exchange transfusion will not remove significant quantities of the medication (1). Supportive care includes correcting dehydration via fluid replacement and instituting other measures to prevent or treat shock. This may include administration of a vasopressor, if necessary, and correcting electrolyte imbalances and metabolic acidosis (1). Antibiotics can be used to treat fever, leukopenia, and/or sepsis (1). Atropine can be used to correct bradycardia. Benzodiazepines are used to treat seizures (1). For respiratory distress, endotracheal intubation, administration of oxygen, and assisted or controlled respiration may be required. Treatment for bone marrow suppression and resultant coagulation defects include Vitamin K_1, fresh frozen plasma, platelets, and/or red blood cells (1). Prolonged observation is recommended because the most severe toxic effects generally do not appear until 24 h or more after ingestion of an acute overdose (1).

In this case, the course of acute colchicine toxicity was consistent with that reported in the human literature describing severe colchicine poisonings. On presentation, gastrointestinal toxicity, shock, dehydration, severe hypoproteinemia, and myocardial and hepatocellular injury were present. The type of shock was likely a combination of hypovolemic, (dehydration and vascular damage) septic

(damage to intestinal mucosa) and cardiogenic (bradycardia, EGG findings). The elevated ST segment with a small positive deflection at the beginning of the ST segment, noted in the first ECG, indicated myocardial hypoxia and/or microscopic intramural myocardial infarctions. Decreased cardiac contractility and myocardial hypoxia and/or infarctions are consistent with known cardiotoxic effects of colchicine (muscle necrosis and vascular injury) (1). However, on necropsy, no abnormalities were found in the heart. Considering the severe damage to the intestinal mucosa, the most significant cause of the severe hypoproteinemia was loss through the intestine. Proteinuria was thought to be caused by traumatic hemorrhage of the urinary tract from placement of the urinary catheter. However, myoglobinuria and renal damage could not be ruled out as causes of the proteinuria. Liver enzymes were moderately elevated on presentation and increased substantially over the following 24 h, reflecting the progression of hepatobiliary/cellular damage.

Approximately 24 h after ingestion, severe azotemia, muscle damage, hypoglycemia, hypotension, DIC, and convulsions were present. Azotemia was likely prerenal and renal (failure due to hypoxia, hypotension, and myoglobinuria). Hypoglycemia was likely due to sepsis and/or in vitro glycolysis. Blood pressure was low (105/60), a consequence of vascular damage and consequential fluid extravasation, fluid losses caused by severe diarrhea and vomiting, and shock. On necropsy, congestion of the brain, liver, spleen, adrenal glands, kidney, and intestine, along with an increased ACT prior to euthanasia, supported a diagnosis of DIC. Convulsions may have been ported caused by the direct toxic action of the drug on brain cells rich in microtubules, insufficient cerebral perfusion, or increased intracranial pressure.

Necropsy findings indicated increased intracranial pressure as the most likely cause. Antibiotics were not included in the treatment protocol as the severity of the damage to the intestinal mucosa and sepsis had not been anticipated.

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