Methemoglobinemia and anemia in a dog with acetaminophen toxicity

Daniel P. Schlesinger

Acetaminophen is a popular over-the-counter analgesic included in many headache, influenza, cold, and pain relief medications. While an effective and relatively safe drug in humans, it has been associated with serious problems in companion animals. Acetaminophen toxicity in cats has been well described (1–6). One 325 mg tablet can cause cyanosis, methemoglobinemia, Heinz body anemia, facial swelling, icterus, and death (1–7). Dogs, on the other hand, exhibit greater tolerance for the drug. The toxic dose is estimated to be between 150 and 200 mg/kg body weight (BW) (4,5). Vomiting, anorexia, tachycardia, tachypnea, and acute liver necrosis are most commonly described (1–6). Further, dogs appear to be less susceptible than cats to erythrocyte damage (1,8). However, methemoglobinemia and oxidative injury have been reported clinically as a result of chronic exposure (8). This report describes a dog in which primary red blood cell pathology occurred following a single dose of acetaminophen. Despite appropriate and apparently successful initial therapy, severe anemia caused by oxidative damage followed several days later. Minimal evidence of liver pathology was detected by measurement of liver enzyme concentrations.

A 3-year-old, neutered male, miniature poodle was evaluated at the Veterinary Teaching Hospital (VTH), University of Saskatchewan, because of vomiting and lethargy for 12 h. The diet had not changed from commercial dry dog food and occasional table scraps. Vaccinations were current. Further questioning revealed that the dog had ingested 6 to 7 acetaminophen tablets (Extra-Strength Tylenol, MacNeil, Guelph, Ontario) of 500 mg each during the previous evening, from a bowl that the owner had inadvertently used to give the dog ice cream. The dog weighed 6.5 kg (ingested dose: 460 to 540 mg/kg BW).

Physical examination revealed hypothermia (rectal temperature 35.6°C), tachycardia (150 beats/min), and polypnea (30 breaths/min). The mucous membranes were ruddy brown in color with a prolonged capillary refill time (>2 s). The sclera and prepuce were slightly yellow and there was marked facial edema. The dog exhibited signs of abdominal discomfort during palpation.

The dog was hospitalized (day 1) and a source of external heat was provided. Blood (brown color) was collected for a complete blood count (CBC), serum biochemistry, and arterial blood gas analysis. Urine was collected by cystocentesis. Therapy was initiated with oxygen, intravenous fluids (0.9% sodium chloride, 40 mL/kg BW/h initially), acetylcysteine (Mucomyst, Bristol Pharmaceutical, Montreal, Quebec) 140 mg/kg BW, IV, and vitamin C (Centravite-C, Central Sales, Brampton, Ontario) 22 mg/kg BW, IV. The acetylcysteine was continued at 70 mg/kg BW, PO, q6h for 7 treatments. The vitamin C was continued at 22 mg/kg BW, PO, q6h for 4 d.

Significant abnormalities found in the CBC included a mature neutrophilia and a mild lymphocytosis, consistent with physiological corticosteroid and epinephrine release. There were occasional acanthocytes, slight anisocytosis, mild polychromasia, and slight hemolysis. Significant abnormalities identified in the serum biochemistry (Table 1, day 1) and urinalysis included a moderately high serum glucose, low carbon dioxide, low total protein, and brown-colored urine (consistent with methemoglobinuria). The serum bilirubin concentration was within the reference range. The elevated glucose was a stress response (based on the lack of concurrent glucosuria), while the low carbon dioxide was indicative of metabolic acidosis. The cause of the low protein was uncertain; it may have been a result of leakage into the edematous regions. Arterial blood gas analysis identified metabolic acidosis with respiratory compensation and severe hypoxemia. After 1 h in the oxygen cage, the dog appeared more comfortable. Arterial blood gas analysis showed improved oxygenation (Table 1, day 1, pm).

The following morning, analysis of an arterial blood gas sample taken without oxygen supplementation demonstrated marked improvement (Table 1, day 2). Mucous membranes were pink, rectal temperature and femoral pulses were normal, and the facial edema had decreased markedly. The abdomen was no longer painful and the dog began eating. The dog was observed for the next 24 h and sent home at the owner's request, because of financial constraints. The owner was advised of the potential for acetaminophen-induced hepatic damage. Reassessment was advised in 1 to 2 d.

The dog was reexamined the next night (day 4), because it had stopped eating, vomited once, and become listless. Physical examination found slightly icteric mucous membranes. Capillary refill time was less than 1 s and blood glucose concentration was normal. The owner described the dog's urine as appearing a brown color.

The dog was admitted to hospital for observation. The following morning the dog was extremely lethargic and had pale, icteric mucous membranes. Its temperature was 38.6°C, heart rate was 200 beats/min, and respiratory rate was 36 breaths/min. Differential diagnoses considered for the pale, icteric mucous membranes included anemia caused by red blood cell destruction and hypovolemic shock secondary to liver damage. Blood was collected for CBC and serum biochemistry (Table 1, day 5). The significant abnormalities found in the CBC

Can Vet J 1995; 36: 515–517

Department of Veterinary Internal Medicine, Western College of Veterinary Medicine, University of Saskatchewan, Saskatoon, Saskatchewan S7N 0W0.

Present address of Dr. Schlesinger: Ranchlands Veterinary Hospital, Bay 17, 7750 Ranchview Drive NW, Calgary, Alberta T3G 1Y9.

Reprints not available.

Table 1. Selected hematological and biochemical data from a dog suffering from acetaminophen toxicity

	Reference values	Day 1[a]	2	5[c]	6	7	8	11	32
PCV L/L	0.37–0.55	0.48		0.097 am 0.35 pm[d]	0.38 am 0.41 pm	0.41	0.40	0.396	0.44
RBC × 10^{12}	5.5–8.5	6.9		1.28				5.6	6.29
Reticulocyte × 10^9/L	20–80	200		156				557	0
Urea mmol/L	3.0–10.5	6.0		9.5				2.3	3.0
Creatinine µmol/L	60–140	86		82				88	74
ALP U/L	23–87	39		143				145	96
ALT U/L	5–69	60		339				84	40
CALP U/L	0–12	0		0				16	3
Total bilirubin µmol/L	0–17	1		27				7	6
Amylase U/L	300–1700	436		2739				671	1005
Lipase U/L	0–560	140		296				50	125
GGT U/L	0–8	3		0				7	2
Anion gap mmol/L	14–26	23		34				18	15
Total protein g/L	51–72	44		60				64	61
Albumin g/L	22–38	23		29				31	33
Total CO_2 mmol/L	17–29	8		11				22	23
Glucose mmol/L	3.3–5.6	11.9		5.7				5.9	5.7
Arterial blood gas									
pH	7.31–7.42	7.238 am 7.329 pm[b]	7.329						
pO_2 mm Hg	80–110	49.1 am	94.7						
(kPa)	(10.7–14.7)	(6.5)	(12.6)						
mm Hg		74.8 pm							
(kPa)		(10.0)							
pCO_2 mm Hg	35–42	23.4 am	27.4						
(kPa)	(4.7–5.6)	(3.1)	(3.6)						
mm Hg		28.5 pm							
(kPa)		(3.8)							
HCO_3 mmol/L	20–28	9.8 am 14.4 pm	13.6						

[a]pretreatment
[b]post-oxygen cage
[c]pretransfusion
[d]posttransfusion
ALP = alkaline phosphatase, ALT = alanine aminotransferase, CALP = steroid induced ALP, GGT = gamma glutamyl transferase, pO_2 = partial pressure oxygen, pCO_2 = partial pressure carbon dioxide, HCO_3 = bicarbonate

included a severe anemia (PCV 0.097 L/L) with poor regeneration and slightly icteric serum. There were fragmented red blood cells, anisocytosis, many eccentrocytes, mild agglutination, and some spherocytes. Differential diagnoses included toxic oxidative damage by acetaminophen metabolites and immune-mediated hemolytic anemia. There was a neutrophilia with a mild shift to the left and monocytosis. This may have been a response to damaged red cells. Alternatively, it could have reflected increased bone marrow activity. A negative direct Coombs' test made immune-mediated disease less likely.

Significant abnormalities found in the serum biochemistry (Table 1, day 5) included elevated anion gap and increased concentrations of total bilirubin, amylase, alkaline phosphatase (ALP), and alanine aminotransferase (ALT). The elevated liver enzymes were probably the result of hepatic damage. It was uncertain whether these elevations were caused directly by the acetaminophen metabolites or by hypoxia from anemia. The increased bilirubin was likely a result of accelerated red blood cell destruction. An elevated anion gap suggested metabolic acidosis. The cause of the amylase increase was uncertain. The possibility of pancreatitis could not be ruled out; however, there were few clinical signs and the lipase concentration was within the reference range.

Intravenous fluid therapy (0.9% sodium chloride at 50 mL/kg BW, q24h) and a blood transfusion were administered (350 mL over 6 h). Within 3 h the patient was brighter, sitting up, and had pink mucous membranes. No vomiting was observed. By the end of the transfusion, the PCV had reached the target level (35). The following morning (day 6), the PCV had risen further and continued to rise through the day. The next day it stabilized and there was no longer any evidence of icterus. The dog was bright, active, and hungry. Because of the liver enzyme elevations, the dog was sent home on K/D diet (Hills Pet Products, Topeka, Kansas, USA).

The owner was advised to return the dog the next day for reassessment. On day 8, the dog was doing well and its PCV was 0.40 L/L. On day 11, the CBC showed

evidence of marked regeneration (reticulocytes, anisocytosis, nucleated erythrocytes, polychromasia) and normal plasma protein. The ALP concentration remained the same, the concentration of steroid isoenzyme of ALP (CALP) had increased slightly, and the ALT concentration had decreased. This suggested that there was probably no ongoing hepatic damage. The slightly low urea was likely the result of K/D diet rather than evidence of liver failure. A liver function test would have been required to rule out functional liver disease (9). The owner was advised to resume feedings with regular dog food over the next 3 to 4 d. Reexamination on day 32 found no significant abnormalities in the CBC or the serum biochemistry. Telephone follow-up 2 mo later reported no further problems.

Acetaminophen is rapidly absorbed from the intestinal tract. It is conjugated with glucuronate and sulfate and a portion is oxidized via a cytochrome P-450 dependent process to form a reactive intermediate (5,8). The intermediate is then conjugated with glutathione and excreted as a biologically inactive compound. Toxicity results if the active metabolite depletes glutathione stores (5). Once the glutathione is lost, the metabolite begins to bind iron and cellular material causing methemoglobin formation, red cell pathology (oxidative damage, Heinz body formation), and hepatocellular damage. Cats are more susceptible to toxicity than dogs, probably because they have a limited ability to form glucuronides (5,7).

N-acetylcysteine is a mucolytic compound that contains a high number of sulfhydral groups (5). It counters acetaminophen toxicity by increasing serum sulfate and supplies of glutathione (2,5,6). Vitamin C is used as an antioxidant. Activated charcoal can inactivate acetylcysteine administered PO and should not be used concurrently (2). Some authors also advocate the use of cimetidine for decreasing the activity of the P-450 enzymes (1).

Methemoglobinemia has been reported in both cats and dogs after acetaminophen ingestion (5,8). It is a reversible injury to hemoglobin, caused by exposure to oxidants, and results in a decreased oxygen carrying ability and the characteristic chocolate brown discoloration of blood and mucous membranes. Membrane oxidative injury (eccentrocytes) and Heinz body formation are permanent injuries leading to shortened erythrocyte survival. Heinz bodies (oxidative damage to hemoglobin) are difficult to visualize in dogs but may be found concurrently with eccentrocytes (8,10). New methylene blue preparations can aid in detection (10).

The dog reported herein received approximately 3 to 4 times the toxic dose of acetaminophen. Clinical features observed in this dog, such as facial swelling, methemoglobinemia, hypoxia, oxidative injury, and anemia, are usually described in cats. Experimentally, doses of 500 mg/kg BW produced some of the clinical signs observed in this dog; however, severe anemia was not described (11). The reported species difference in clinical signs may reflect susceptibility to toxicity and the usual ingested doses. Dogs are more efficient at metabolizing the acetaminophen and, therefore, a much higher dose is required to produce some of the signs. Many of the previously reported cases of canine toxicity may have involved either chronic exposure or lower ingested doses.

Evidence of only mild hepatocellular injury in this dog, however, is puzzling. This is the most commonly described abnormality associated with acetaminophen toxicity in dogs and is usually much more severe. It rarely occurs in cats, and some authors speculate that cats may die from hypoxia with doses of acetaminophen that are too low to cause hepatocellular damage (5). Despite ingesting a very large dose of acetaminophen, this dog experienced primarily red blood cell pathology with minimal hepatocellular damage. Perhaps prompt treatment prevented hepatotoxicity, while the extensive oxidative damage to the erythrocytes had already occurred. The therapy did not reverse these blood cell changes and the damaged cells were destroyed. This case serves to illustrate the importance of both hematological and biochemical follow-up of patients with acetaminophen toxicity, regardless of the response to initial therapy. In contrast to what is commonly reported in veterinary texts (2–4), erythrocyte pathology should be considered a potential consequence of acetaminophen toxicity in the dog. CVJ

References

1. Murphy MJ. Toxin exposure in dogs and cats: Drugs and household products. J Am Vet Med Assoc 1994; 205: 557–560.
2. Grauer GF, Osweiler GD. Household drugs. In: Morgan RE, ed. Handbook of Small Animal Practice, 2nd ed. New York: Churchill Livingstone, 1992: 1335–1340.
3. Mount ME. Toxicology. In: Ettinger S, ed. Textbook of Veterinary Internal Medicine, 3rd ed. Toronto: WB Saunders, 1989: 456–483.
4. Oehme FW. Aspirin and acetaminophen. In: Kirk RW, ed. Current Veterinary Therapy IX. Toronto: WB Saunders, 1986: 188–190.
5. Hjelle JJ, Grauer GF. Acetaminophen-induced toxicosis in dogs and cats. J Am Vet Med Assoc 1986; 188: 742–746.
6. Cullison RF. Acetaminophen toxicosis in small animals: Clinical signs, mode of action, and treatment. Compend Contin Educ Pract Vet 1984; 6: 315–321.
7. Davis LE. Clinical management of adverse drug reactions. In: Kirk RW ed. Current Veterinary Therapy IX. Toronto: WB Saunders, 1986: 176–183.
8. Harvey JW, French TW, Senior DF. Hematological abnormalities associated with chronic acetaminophen administration in a dog. J Am Vet Med Assoc 1986; 189: 1334–1335.
9. Schlesinger DP, Rubin SI. Serum bile acids and the assessment of hepatic function in dogs and cats. Can Vet J 1993; 34: 215–220.
10. Weiser MG. Erythrocytes and associated disorders. In: Ettinger S, ed. Textbook of Veterinary Internal Medicine, 3rd ed. Toronto: WB Saunders, 1989: 2145–2180.
11. Savides MC, Oehme FW, Nash SL, Leipold HW. The toxicity and biotransformation of single doses of acetaminophen in dogs and cats. Toxicol Appl Pharmacol 1984; 74: 26–34.