The diagnosis of acetaminophen toxicosis in a cat

Andrew L. Allen

A 6- to 8-week-old kitten was submitted to the diagnostic laboratory of the Western College of Veterinary Medicine to determine the cause of its clinical signs. It had been presented to the submitting veterinarian in a state of collapse and coma. The veterinarian also noted very severe edema of the head. The kitten was euthanized.

At necropsy, the kitten's head was swollen due to marked edema within the subcutis, including the conjunctiva. The edema extended along the fascial planes of the neck into the thorax. About 3 mL of dark brown, translucent urine remained in the bladder (Figure 1). The differential diagnoses for the pigmenturia included myoglobinuria, hemoglobinuria, methemoglobinuria, and, possibly, hematuria. The color of the urine was most consistent with methemoglobinuria and suggested that the kitten had experienced methemoglobin formation and hemolysis. The most likely cause of methemoglobemia and hemolysis in cats is exposure to a strong oxidative agent.

Subcutaneous edema of the head and methemoglobinuria are suggestive of acetaminophen toxicity in cats. Therefore, the submitting veterinarian was queried about the possibility of the cat having come in contact with acetaminophen, and the urine was submitted to the medical laboratory of Royal University Hospital, Saskatoon, to determine the concentration of acetaminophen.

The submitting veterinarian was adamant that he had not administered acetaminophen to the kitten. The kitten's owners had not noticed monitory signs of illness and, therefore, had no motivation or opportunity to give the kitten any drugs. However, the urine was found to contain 3820 μmol/L of acetaminophen. When informed of this, the owners recalled giving the kitten an empty bottle that had contained acetaminophen tablets to play with on the day that the kitten had become moribund.

Acetaminophen, also known as paracetamol in many countries, has become a popular analgesic and antipyretic for human use since being advertised as a 'safer' alternative to aspirin many years ago. As acetaminophen became available in many over-the-counter and prescription products, reports of acetaminophen toxicity in dogs and cats became more common (1,2). The ingestion of acetaminophen by cats was reported several times to the Animal Poison Control Center, University of Illinois, during its first 36 mo of service, from September 1978 to August 1981, inclusive (3). During the 19 mo between January 1989 and July 1990, inclusive, the Georgia Animal Poison Information Center received 95 inquiries regarding acetaminophen toxicosis in dogs and cats (4), and over the 27 mo between January 1998 and March 2000, inclusive, veterinarians at the American Society for the Prevention of Cruelty to Animals National Animal Poison Control Center consulted on more than 1050 cases of accidental exposures to acetaminophen in dogs and cats (5). While dogs most often ingest toxic doses accidentally, cats are usually poisoned by well-intentioned but uninformed owners (4,6,7).

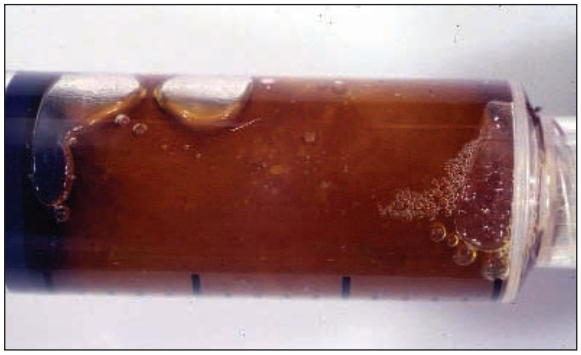

Figure 1. Syringe filled with dark brown urine (methemoglobinuria) from the bladder of a kitten poisoned with acetaminophen. The urine had been frozen for preservation.

In most mammals, acetaminophen is primarily biotransformed to nontoxic products in the liver via conjugation with glucuronic acid and, to a lesser degree, sulfate, and eliminated by the kidneys (4–8). Concurrently, a small proportion of acetaminophen is metabolized through the cytochrome P-450 enzyme pathway producing a highly reactive and toxic metabolite, N-acetyl-para-benzoquinoneimine (NAPQI) (5,7,8). The toxic effects of NAPQI are normally limited by its conjugation with glutathione. Glutathione, which is widely distributed in mammalian tissues, is essential for cellular protection against oxidative injury by electrophilic radicals (8). In most mammals, acetaminophen exposure becomes toxic when glucuronidation and sulfation pathways become saturated and cellular glutathione stores are depleted to less than 70% of normal values (5). In such cases, NAPQI binds to cellular proteins and membranes, causes disruption of protein function and damage to cell membranes, and leads to cell injury and death, typically of hepatocytes (5,8).

For several reasons, cats are extremely sensitive to the toxic effects of acetaminophen. Cats form glucoronides

Department of Veterinary Pathology and Prairie Diagnostic Services, Western College of Veterinary Medicine, University of Saskatchewan, 52 Campus Drive, Saskatoon, Saskatchewan S7N 5B4.

Address all correspondence and reprint requests to Dr. Andrew Allen; e-mail: andrew.allen@usask.ca

with many compounds slowly, or not at all, because they possess fewer isoforms of the enzymes that mediate the conjugation, that is, glucuronyl transferases. More specifically, cats have a relative absence of a specific high-affinity acetaminophen glucuronoyl transferase that conjugates acetaminophen with glucuronic acid (4,6,8,9). This relative deficiency of the glucuronide conjugation pathway results in more drug being conjugated to sulfates; however, the sulfation pathway has a finite capacity, which is also lower in cats than other species (6). Once the sulfation pathway reaches its capacity, acetaminophen is allowed to persist in the blood and more is metabolized by cytochrome P-450 enzymes to NAPQI. Glutathione synthesis is suppressed by high levels of acetaminophen (8) and the presence of NAPQI rapidly depletes glutathione stores.

Erythrocytes are the cells most susceptible to the effects of NAPQI in cats, and there are 2 sites in erythrocytes that are most susceptible to oxidative injury: the iron in heme and the sulfhydryl groups of the globulin chains. Being electrophilic, NAPQI causes the oxidation of ferrous iron (Fe^{2+}) to ferric iron (Fe^{3+}), which converts hemoglobin to methemoglobin (5,8). Since cats also have a relative lack of methemoglobin reductase in erythrocytes (10), methemoglobinemia is a much earlier and more prominent feature of acetaminophen toxicity in this species, relative to most others. Further, feline hemoglobin contains 8 reactive sulfhydryl groups, compared with 2 or 4 in the hemoglobin of other species (6,8). Oxidation of hemoglobin leads to its denaturation and precipitation onto the surface of erythrocytes, where they appear as tiny granules known as Heinz bodies. Heinz body formation results in the increased fragility of erythrocytes and hemolytic anemia. Since methemoglobin is poor at transporting oxygen, it is the methemoglobemia and hemolytic anemia that accounts for the respiratory distress, depression, and weakness reported by owners, and the either dark brown or pale mucous membranes, icterus, and pigmenturia also noted by clinicians and researchers attending to cats poisoned with acetaminophen (1,5–7). The cause of the edema of the face and paws is not known.

Few, if any, veterinary laboratories offer an assay for acetaminophen in body fluids, but it is commonly available through human medical laboratories, because of the frequency of acetaminophen toxicity. In humans, intentional overdose is common and usually associated with attempts at suicide. Toxicity associated with chronic ingestion of supratherapeutic doses of acetaminophen is usually unintentional and involves adults seeking relief from syndromes of severe and prolonged pain. Adults who are malnourished or have underlying liver disease, as is often present in alcoholics, may be more susceptible to so-called chronic acetaminophen toxicity (2,11).

There is no safe dose of acetaminophen for cats (4,5). The toxic dose is reported as 50 to 100 mg/kg bodyweight (BW) (8), but a dose as small as 10 mg/kg BW has produced signs of toxicity and death (6). In humans, the ingestion of a toxic dose of acetaminophen will result in peak plasma levels of about 1200 μmol/L about 4 h later (2). Acetaminophen levels in the urine of the kitten described here were found to be more than 3-fold greater, which allowed for confirmation of the diagnosis, and provided a reminder of the acute and unique susceptibility of the species to the drug. Veterinarians and pet owners should also be aware that the conjugation of acetaminophen to form glucoronide in ferrets is as slow as in cats (9), which may also make them similarly susceptible to adverse effects.

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