PEER-REVIEWED

5-Fluorouracil toxicosis in dogs

Jay Albretsen, DVM, PhD, DABT

5-Fluorouracil, a pyrimidine analogue, is considered an antimetabolite. It destroys rapidly dividing cells, so it is used to treat many neoplastic conditions.[1] In combination with other antineoplastic agents (*e.g.* doxorubicin hydrochloride, cisplatin), 5-fluorouracil is considered a first-line therapy for many cancers in people (*e.g.* stomach, breast, prostate). 5-Fluorouracil creams and solutions are used topically to treat solar keratitis and skin cancers in people.[1,2] In animals, 5-fluorouracil is also used to treat neoplastic conditions, but because of severe adverse reactions and death, its use has been limited.[1,3]

Pharmacists and other medical personnel may be unaware of the severe problems that arise when dogs ingest 5-fluorouracil.

Pharmacists and other medical personnel may be unaware of the severe problems that arise when dogs ingest 5-fluorouracil. Occasionally, owners are erroneously told that ingesting 5-fluorouracil is harmless or that dogs may develop only mild oral and gastrointestinal irritation. These potentially disastrous comments may stem from package insert information that states that no reports of overdosage have occurred with the product.[4] However, 5-fluorouracil frequently causes vomiting and seizures in dogs. The seizures soon become difficult to treat, and, despite aggressive therapy, the dogs often die.[3,5]

Formulations and toxic dosages

5-Fluorouracil is available by prescription in injectable and topical formulations. The injectable form is available as Adrucil (Pharmacia & Upjohn) or as a generic in 50-mg/ml vials.[1,2] Efudex (ICN Pharmaceuticals) is available as topical 2% and 5% solutions in 10-ml drop dispensers and as a 5% cream in 25-g tubes. 5-Fluorouracil is also available as Fluoroplex (Allergan), a 1% topical solution in a 30-ml plastic dropper bottle or a 1% cream in 30-g tubes.[1,2,4,6,7]

While any form of 5-fluorouracil can cause problems, dogs are usually poisoned when they chew the small containers of topical ointment or solution used to treat their owners' skin conditions. The ASPCA APCC determined that the lowest toxic dose at which dogs show adverse signs is 8.6 mg/kg. The lowest lethal dose of 5-fluorouracil in dogs is estimated to be 20 mg/kg.[6] This means if a dog weighing less than 160 lb (73 kg) ingests half the contents of a 25-g tube of 5% 5-fluorouracil, the dog will probably develop adverse signs. Even more alarming, any dog weighing less than 70 lb (32 kg) that ingests half the contents of a 25-g tube of 5% 5-fluorouracil has consumed a potentially lethal dose. The containers of 5-fluorouracil are quite small (about 11 cm long and 3 cm wide), so even small dogs could ingest the entire contents.

Another compound that can potentially result in 5-fluorouracil toxicosis is 5-flucytosine. This antifungal agent must be converted by cytosine deaminase to 5-fluorouracil to have cytotoxic effects. Mammalian cells lack cytosine deaminase. But if 5-flucytosine is taken orally, microbes in the digestive tract will convert it to 5-fluorouracil.[7]

Mechanism of action and manifestations of toxicosis

The mechanism of 5-fluorouracil toxicosis in dogs is not fully understood. As a pyrimidine analogue, 5-fluorouracil can inhibit RNA processing and function as well as DNA synthesis and repair processes. So 5-fluorouracil inhibits cell division, affecting actively dividing cell lines such as bone marrow stem cells and intestinal crypt epithelial cells.[1,3,5] It is not known why dogs develop such severe seizures with 5-fluorouracil toxicosis. It is thought that 5-fluorouracil's metabolism to fluorocitrate causes cerebellar ataxia and convulsions, because fluorocitrate interferes with the normal Krebs cycle mechanisms of cellular energy production.[3]

Clinical signs reported in dogs after 5-fluorouracil ingestion include vomiting, lethargy, tremors, seizures, cardiac arrhythmias, and respiratory depression.[2,6] As men-

Continued

tioned earlier, affected dogs often develop severe vomiting and uncontrollable seizures resulting in death or euthanasia despite aggressive decontamination procedures and intensive treatment. Out of 72 cases of 5-fluorouracil toxicosis reported to the ASPCA APCC between 1989 and 1998, 35 dogs died and 11 dogs were euthanatized.[6] The onset of clinical signs usually occurred within a half an hour to five hours after ingestion, and death occurred as quickly as seven hours after ingestion.

Although 5-fluorouracil toxicosis in dogs rarely results in bone marrow suppression, 5-fluorouracil's mechanism of action makes myelosuppression possible.[1,2,6] In most instances, the severe vomiting, tremors, and seizures that develop after dogs ingest 5-fluorouracil result in death or euthanasia before evidence of bone marrow suppression occurs.[6] Myelosuppression is possible if dogs survive for more than four to seven days after 5-fluorouracil ingestion[6] and is manifested by leukopenia, depression, and hyperthermia. White blood cell counts as low as 750/µl have been reported (normal = 5,000 to 14,000/µl).[2,6,8]

Treatment

There is no antidote for 5-fluorouracil toxicosis. Early decontamination (*i.e.* emesis induction followed by oral activated charcoal administration) is the best option to prevent serious signs from developing.[2] However, once signs begin, do not induce emesis or administer activated charcoal until the vomiting and seizures are controlled and the animal's airway is protected so that aspiration does not occur. Inducing emesis is often not helpful more than two or three hours after ingestion, because the 5-fluorouracil will likely have passed through the stomach. Activated charcoal may be helpful up to 24 hours after ingestion; after 24 hours most of the 5-fluorouracil will likely be absorbed.

Once clinical signs are manifested, treatment includes gastrointestinal protection, tremor and seizure management, and other supportive care. For gastrointestinal protection, administer sucralfate (1 g in large dogs, 0.5 g in small dogs, orally t.i.d.), misoprostol (2 to 5 µg/kg orally [if the dog is not vomiting] t.i.d. to q.i.d.), or other gastric acid secretion inhibitors.[9] Administering metoclopramide hydrochloride (0.1 to 0.3 mg/kg intravenously or orally t.i.d.) in cases of protracted vomiting has been suggested, but use caution because it could cause additional neurologic signs.[2]

The seizures and tremors from 5-fluorouracil poisoning are rarely controlled with diazepam. Pentobarbital sodium (3 to 15 mg/kg intravenously slowly to effect), phenobarbital (3 to 30 mg/kg intravenously slowly to effect), isoflurane, and propofol (4 to 6 mg/kg intravenously or continuous-rate infusion 0.6 mg/kg/min) have controlled 5-fluorouracil-induced seizures successfully.[2,9] Other supportive treatments include intravenous fluid administration, thermoregulation, and pain control (*e.g.* butorphanol tartrate 0.2 to 0.4 mg/kg every two to five hours subcutaneously, intramuscularly, or intra-

Continued

venously).[9] Using broad-spectrum antibiotics to prevent secondary bacterial infections may also be warranted.[2]

If bone marrow suppression develops, filgrastim (Neupogen—Amgen) can be used to stimulate bone marrow stem cell proliferation in dogs.[6] Filgrastim is a granulocyte colony-stimulating factor of human origin. The dosage is 4.2 to 6 µg/kg given subcutaneously once a day for one to three days.[6] No adverse effects have been reported.

Conclusion

Based on the number of cases reported to the ASPCA APCC, 5-fluorouracil poisoning is uncommon in dogs. However, because severe signs or death can result from 5-fluorouracil toxicosis, you should consider the importance of early decontamination and proper treatment and be able to advise clients of the seriousness of an accidental ingestion.

REFERENCES

1. Calabresi, P.; Chabner, B.A.: Chemotherapy of neoplastic diseases. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 9th Ed. (J.G. Hardman *et al.*, eds.). McGraw-Hill, New York, N.Y., 1996; pp 1247-1251.
2. Dorman, D.C. *et al.*: 5-Fluorouracil toxicosis in the dog. *J. Vet. Intern. Med. 4* (5):254-257; 1990.
3. Weiss, H.D. *et al.*: Neurotoxicity of commonly used antineoplastic agents. *N. Engl. J. Med. 291* (2):75-81; 1974.
4. *Physicians' Desk Reference*, 55th Ed. Medical Economics Company, Montvale, N.J., 2001.
5. Harvey, H.J. *et al.*: Neurotoxicosis associated with use of 5-fluorouracil in five dogs and one cat. *JAVMA 171* (3):277-278; 1977.
6. Albretsen, J. *et al.*: Treatment of bone marrow suppression following toxic ingestion of 5-fluorouracil in dogs (abst.). *J. Vet. Intern. Med. 12*:240; 1998.
7. Heit, M.C.; Riviere, J.E.: Antifungal and antiviral drugs. *Veterinary Pharmacology and Therapeutics*, 7th Ed. (H.R. Adams, ed.). Iowa State University Press, Ames, 1995; p 858.
8. Duncan, J.R. *et al.*: *Veterinary Laboratory Medicine: Clinical Pathology*, 3rd Ed. Iowa State University Press, Ames, 1994; p 235.
9. Plumb, D.C.: *Veterinary Drug Handbook*, 3rd Ed. Iowa State University Press, Ames, 1999; pp 90, 91, 435, 497, 502, 547, 583. ■

"Toxicology Brief" was contributed by Jay Albretsen, DVM, PhD, DABT, ASPCA Animal Poison Control Center, 1717 S. Philo Road, Suite 36, Urbana, IL 61802; (888) 4ANI-HELP.