PEER-REVIEWED

Anticoagulant rodenticides: Deadly for pests, dangerous for pets

Valentina Merola, DVM

It's fall, and mice and rats are heading indoors to escape the cooler weather, making themselves unwanted visitors. Many people put out rodenticide baits to keep these pests from becoming permanent residents. Anticoagulant rodenticides are popular choices. But these rodenticides can harm other animals in the house as well. The prognosis for pets that have ingested anticoagulant rodenticides depends on the length of time between exposure and treatment, so you must diagnose and institute appropriate therapy immediately.

Origin

First-generation anticoagulant rodenticides were initially developed during the 1940s and 1950s by the Wisconsin Alumni Research Foundation (WARF). WARF was founded in 1925 as a nonprofit agency with the purpose of promoting, aiding, and encouraging scientific research and investigation at the University of Wisconsin-Madison. Dicumarol was the first anticoagulant that could be given orally to people, and warfarin (named after WARF) was the first compound marketed as an anticoagulant rodenticide. Rodents became resistant to the first-generation compounds over the next few decades, so second-generation anticoagulant rodenticides, such as brodifacoum, diphacinone, and bromadiolone, were produced. The second-generation compounds were developed to work more quickly and with greater efficacy than the first-generation products. They were also formulated to be highly palatable to rodents.[1] Because of this, second-generation anticoagulant rodenticides are both appealing and extremely toxic to nontarget species, especially domestic dogs (*Table 1*).

"Toxicology Brief" was contributed by Valentina Merola, DVM, Department of Veterinary Biosciences, College of Veterinary Medicine, University of Illinois, Urbana, IL 61802. The department editor is Petra A. Volmer, DVM, MS, DABVT, College of Veterinary Medicine, University of Illinois, Urbana, IL 61802. Dr. Volmer is also a diplomate of the American Board of Toxicology.

Available products

Anticoagulants are the most common type of rodenticide produced and used in the United States.[2] Anticoagulant rodenticides are available as grain-based pellets, wax blocks, dusts, and tracking powders and in a variety of other formulations and colors (*Table 1*). Some people assume that if they see a blue-green pellet it is an anticoagulant rodenticide. But be careful, because not every blue-green pellet is an anticoagulant rodenticide and not every anticoagulant rodenticide is a blue-green pellet. Other rodenticide baits that contain bromethalin, zinc phosphide, or cholecalciferol can be indistinguishable from an anticoagulant rodenticide. Second-generation anticoagulant rodenticides are most commonly found at a concentration of 0.005% (difethialone is found at 0.0025%), while warfarin is most commonly found at 0.025%.[3] When an animal is exposed to an anticoagulant rodenticide, always examine the package to determine the concentration of the active ingredient so that a dose can be calculated and appropriate treatment undertaken (*Table 2*).

Risk factors and susceptibility

Dogs allowed to roam may be more likely to encounter rodent baits. These baits may be improperly placed in areas pets have access to, or rodents may drag baits into these areas. Pets that live in rural or urban areas where rodent control is frequently used are also more likely to be exposed. An animal owner may be unaware that a pest control operator has placed these baits if the owner lives in a rental property or has recently

moved to a new home. In general, rodent baits are used most often in the fall when rodents are most likely to enter buildings. Finally, keep in mind that rodenticides are commonly used in malicious poisonings, and must be considered if the clinical signs are consistent, even in animals that are thought to be unlikely to have encountered the agent.

Relay toxicosis, the intoxication by ingestion of a previously poisoned animal, is unlikely to occur with these agents, because only a small amount of the rodenticide is in a rodent's gut (in general, the LD_{50} in rodents is lower). But relay toxicosis is possible in an animal that frequently preys upon rodents in an area where these baits are commonly used.[3]

Animals that are elderly or juvenile and those with liver disease, hypothyroidism, or other underlying illnesses are more susceptible to anticoagulant rodenticides.

Toxicokinetics

Anticoagulant rodenticides are rapidly and well-absorbed orally. They are highly protein-bound in plasma. In an animal receiving another drug that is highly protein-bound, such as a nonsteroidal anti-inflammatory drug, the displacement interaction can cause more of either drug to be available.[3] The plasma half-life varies among products. The first-generation rodenticides have a half-life of about 14 hours in dogs; the second-generation rodenticides have a half-life of up to six days.[1] The rodenticides are metabolized in the liver and excreted in the urine.

Mechanism of action

Vitamin K is a necessary cofactor in activating clotting factors II, VII, IX, and X by carboxylation (*Figure 1*). Without vitamin K, these coagulation proteins will remain in a nonfunctional, precursor state. Anticoagulant rodenticides interfere with

TABLE 1 Common Anticoagulant Products and Their Active Ingredient Concentrations, Formulations, and Acute LD_{50}*

Trade Names	Active Ingredient	Generation	Common Concentrations	Common Formulations	Acute LD_{50}
Rodex, Blitz, Rid-a-Rat, Eagles, and many more**	Warfarin	First	0.025%–0.03%	Pellets, others	20–300 mg/kg (dogs); 5–30 mg/kg (cats)
D-Con, Havoc, Jaguar, Warrior Chunks, Enforcer, and many more	Brodifacoum	Second	0.005%	Chunks, blocks, pellets, others	0.2–4 mg/kg (dogs); unknown in cats
Hawk, Maki, Boot Hill, Just One Bite, Tomcat Ultra, and many more	Bromadiolone	Second	0.005%	Blocks, bars, pellets, others	11–15 mg/kg (dogs); unknown in cats
D-Cease, Generation, Hombre	Difethialone	Second	0.0025%	Pellets, others	4 mg/kg (dogs); > 16 mg/kg (cats)
Assassin, Tomcat, Ditrac, Exterminator's Choice, and many more	Diphacinone	Second	0.005%–0.2%	Blocks, bars, powder, liquid concentrates	0.9–8 mg/kg (dogs); 15 mg/kg (cats)
Enforcer Rat Bait, Duocide**	Pindone	Second	0.03%	Pellets, others	5–75 mg/kg (dogs); unknown in cats

*Source: References 1, 3, 4, and 12.
**Products containing warfarin and pindone are older, and most have been replaced. But these older products could still be in use.

Continued

TABLE 2 An Example of a Rodenticide Dose Calculation and Interpretation

A 75-lb dog is seen consuming 4 oz of a bait that contains 0.005% brodifacoum.

To calculate the dose of brodifacoum the dog ingested in mg/kg:

1. Convert the animal's weight to kilograms: 75 lb ÷ 2.2 lb/kg = 34 kg
2. Calculate how much bait the dog ingested: 1 oz = approximately 30 g; 4 oz × 30 g = 120 g
3. Calculate the amount brodifacoum in each gram of bait: 0.005% = 0.05 mg brodifacoum/g bait
4. Calculate how much brodifacoum the dog ingested: 0.05 mg/g × 120 g = 6 mg of brodifacoum ingested
5. Calculate the dosage in mg/kg: 6 mg ÷ 34 kg = 0.18 mg/kg

This dose is approaching the low end of the LD_{50} range (0.2–4 mg/kg; see *Table 1*). The LD_{50} is defined as the dose at which 50% of an experimentally exposed population will die. This means that nearly half of the exposed individuals die below the LD_{50}. Because some animals are sensitive to doses between the LD_{50} and 1/10 of the LD_{50}, it is recommended that any animal that received a dose in that range be decontaminated and monitored. In this case, the dose is high enough to warrant aggressive decontamination, monitoring, and treatment. Animals that received doses less than 1/2 of the LD_{50} (in this case, less than 0.1 mg/kg) should be decontaminated, and the PT should be monitored every day for 72 hours. Previous administration of vitamin K_1 may result in misleading PT results. In general, to be cautious and prevent clinical signs in the most sensitive individuals, it is recommended to decontaminate and monitor any animal that received a dose above 0.02 mg/kg.

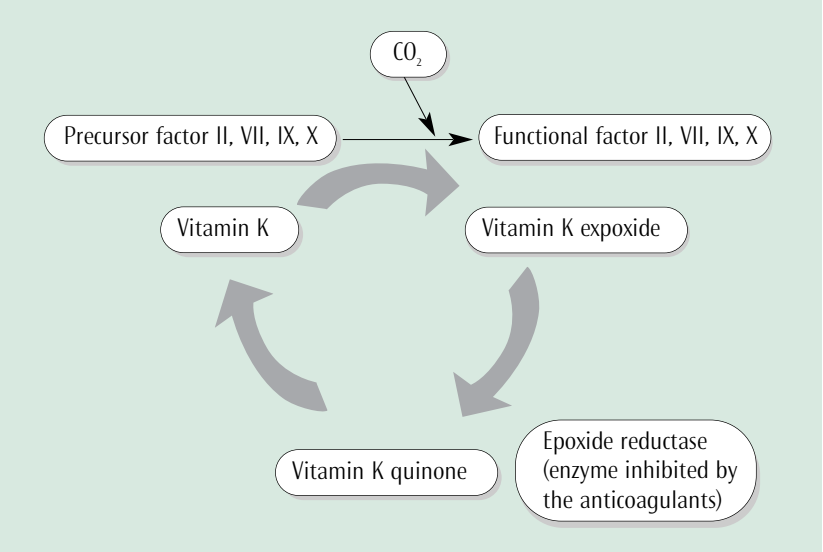
the activation process by inhibiting an animal's ability to conserve vitamin K. Vitamin K is consumed by carboxylation of the proteins and is present as vitamin K epoxide, which cannot activate clotting proteins.[4] Normally, the body converts vitamin K epoxide back to active vitamin K via the enzyme vitamin K epoxide reductase. Anticoagulant rodenticides inhibit this enzyme, resulting in a lack of active vitamin K.[4] As a result, concentrations of the clotting factors decrease, since no more precursor protein can be converted to an active form. The net result is a coagulopathy that begins as the natural breakdown of the clotting factors occurs. The half-lives of factors II, VII, IX, and X are 41, 6.2, 13.9, and 16.5 hours, respectively; thus factor VII will be depleted first.[4] If an external source of vitamin K is provided to an animal, normal activation of the proteins can occur, and no clinical signs will develop.

Clinical signs

Clinical signs in an exposed animal usually develop one to seven days after ingestion as the active

clotting factors are depleted, with three to five days being the most common time frame, depending on the agent consumed.[1] The clinical signs can vary, but they are always due to the coagulopathy. Animals may present with nonspecific signs such as lethargy, anorexia, or lameness due to intra-articular hemorrhage. In a recent retrospective study, dyspnea, coughing, lethargy, and hemoptysis were the most common clinical signs.[5] Any type of bleeding can occur, and hematuria, hematemesis, melena, hyphema, or epistaxis may be seen.[1] Petechia and ecchymosis of any mucosal surface or the skin are other possible findings. Acute bleeding into the thorax or abdomen can cause anemia, shock, and death.[4] If rapid bleeding into the brain or spinal cord takes place, it may be manifested as ataxia, seizures, or death. Sometimes an animal will present with no history of exposure, and the only sign is incessant bleeding from a wound. Another presentation can be of a dog with a vague history of nonspecific signs that bleeds and forms a large hematoma after venipuncture.[2] Clotting abnormalities can persist for 14 days in animals poisoned by a first-generation product and for 30 days or longer with second-generation rodenticides.[4] The extended duration of the clinical signs is related to the rodenticides' long half-lives, especially of the second-generation compounds, and depends on the amount of the agent consumed.

FIGURE 1



1. A diagram of the role that vitamin K plays in activating coagulation factors and the route through which it is recycled.

Diagnosis

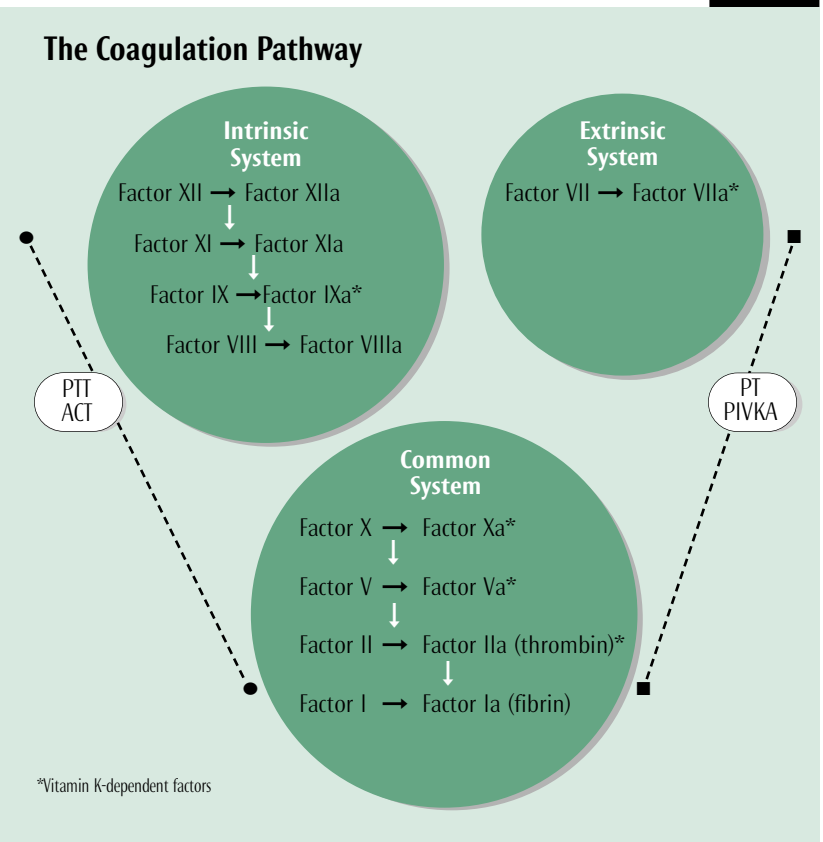
The one-stage prothrombin time (PT), activated partial thromboplastin time (APTT or PTT), and activated clotting time (ACT) will all be elevated before hemorrhage occurs, but the PT is the most sensitive test.[4] The PT is the first test to become elevated and the first test to return to normal after ingestion of an anticoagulant rodenticide, because of the shorter half-life of factor VII (*Figure 2*).

PIVKA (proteins induced by vitamin K_1 absence or antagonism), or Thrombotest (Axis-Shield), is another test that can be used to screen for the anticoagulant rodenticides. In a recent study, dogs with prolonged PTs had prolonged PIVKA times, regardless of the cause of the prolonged bleeding time.[6] The PIVKA times seem to be more sensitive than routine coagulation tests (PT and APTT) for detecting bleeding tendencies and are a valuable aid in rapidly diagnosing anticoagulant rodenticide intoxication.[7,8]

In general, a threefold increase in PT or PIVKA is highly suggestive of anticoagulant rodenticide toxicosis.[6] Prior administration of vitamin K_1 can cause the PT to be misleadingly normal, as new clotting factors can be synthesized six to 12 hours after treatment. In an animal that is hemorrhaging, a complete blood count may show regenerative anemia. A decrease in plasma proteins or in platelet number is also sometimes found. Urinalysis may also be helpful, but keep in mind that hematuria is not specific for anticoagulant rodenticide toxi-

Continued

FIGURE 2



cosis, and a negative result does not rule it out.

Radiography is another important ancillary test that can aid in diagnosis. Many dogs will have evidence of thoracic or abdominal effusions. Tracheal narrowing or soft tissue opacity in the mediastinum may be present if bleeding occurs in those locations.[9]

It is important to remember that an animal that has been acutely exposed (less than one to two days) may not have any of these findings. An animal may have been exposed to a potentially lethal dose and not have any changes in its laboratory parameters for the first few days. On necropsy, liver as well as blood or stomach contents can be tested for anticoagulant rodenticides at many veterinary diagnostic laboratories.[4]

Differential diagnoses

Other causes of hemorrhage must be differentiated from anticoagulant rodenticide toxicosis. Immune-mediated thrombocytopenia, disseminated intravascular coagulation, thrombocytopathy, and inherited disorders such as hemophilia and von Willebrand's disease can usually be differentiated based on the results of the coagulation screenings (*Table 3*) and a patient's history and clinical signs. Coagulopathies due to liver disease can usually be determined based on elevated liver enzyme activities.[10] Canine ehrlichiosis can likewise usually be distinguished from other problems by the results of a complete blood count and serum chemistry profile (*e.g.* thrombocytopenia, anemia, leukopenia [or leukocytosis later in the disease], hyperglobulinemia, proteinuria, mildly elevated blood urea nitrogen, creatinine, and total bilirubin concentrations and liver enzyme activities) and serologic testing.

Treatment

In patients that present soon after exposure, perform decontamination measures. If the exposure occurred less than four hours prior, induce emesis followed by activated charcoal and a cathartic to limit gastrointestinal absorption.[1] Do not induce emesis in species that are unable to vomit, such as rabbits and rodents. At this point you must decide whether vitamin K_1 therapy should be started. If the ingested dose is small or decontamination was successful, it may be sufficient to monitor the PT or PIVKA at 24, 48, and 72 hours. If the PT or PIVKA remains normal at 72 hours, and no vitamin K_1 was administered, further treatment is

TABLE 3 Expected Results of Coagulation Tests in Various Coagulopathies*

	APTT	ACT	PT	PIVKA
Anticoagulant ingestion	Marked elevation	Marked elevation	Marked elevation	Marked elevation
Immune-mediated thrombocytopenia	Normal	Marked elevation	Normal	Normal
DIC	Marked elevation	Marked elevation	Marked elevation	Marked elevation
Thrombocytopathy	Normal	Marked elevation	Normal	Normal
Hemophilia	Marked elevation	Marked elevation	Normal	Normal
von Willebrand's disease	Slight to moderate elevation	Slight to moderate elevation	Normal	Normal

*Source: References 4, 8, and 10.

not necessary. If you are not sure how much rodenticide a patient has ingested, it is safest to assume it was a large dose.

In cases of large ingestions, begin phytonadione (vitamin K_1) therapy (3 to 5 mg/kg orally divided b.i.d.).[5] Treat pocket pets at the high end of this dosage range. Make sure to tell owners that the vitamin K_1 must be prescription strength and that vitamin supplements do not contain enough vitamin K_1 to be effective. Over-the-counter supplements contain micrograms of vitamin K_1, but milligrams are needed. Do not use vitamin K_3 (menadione) for treatment; it is poorly stored and requires metabolism for activity, so the onset of action is longer and the amount required is larger.[11] Vitamin K_3 can also be nephrotoxic and cause anemia.[11] The length of time for treatment with vitamin K_1 depends on the type of anticoagulant rodenticide ingested. For first-generation anticoagulants, treatment with vitamin K_1 for 14 days is usually sufficient. For second-generation anticoagulants, treatment should be instituted for at least 30 days. If the class of anticoagulant is unknown, vitamin K_1 therapy should be instituted for 30 days. Vitamin K_1 is well-absorbed orally, and absorption is enhanced when a fatty meal is fed at the same time the dose is given. Oral administration is ideal, because vitamin K_1 will be delivered directly to the liver through the portal circulation

Continued

where the clotting factors are activated. In all patients, check the PT or PIVKA 48 hours after stopping vitamin K_1 therapy, and if the test result is prolonged, continue vitamin K_1 treatment for another week.[1] Again, a patient must be tested for adequate clotting 48 hours after vitamin K_1 therapy has been discontinued. Exercise restriction during treatment is recommended.

In a symptomatic animal, decontamination by using emetics and activated charcoal is generally not necessary or beneficial because of the length of time between exposure and the development of clinical signs. Aim treatment at preventing further hemorrhage by providing clotting factors and vitamin K_1, as well as appropriate supportive care. Handle all patients gently to avoid inducing further bleeding. Monitor patients closely, and if anemia becomes severe, a blood transfusion may be required. Polymerized bovine hemoglobin glutamer-200 (Oxyglobin—Biopure) could also be used in a severely anemic animal to help provide oxygen to tissues, but it will not supply needed clotting factors. Animals that are bleeding should be given plasma to provide clotting factors until enough time has passed for the animal to begin producing clotting factors, based on clinical signs (bleeding), changes in the hematocrit, and PT results.[5]

In symptomatic patients, vitamin K_1 should be given at a loading dose of 2.5 to 5 mg/kg orally and continued at a dosage of 3 to 5 mg/kg orally divided twice a day for an appropriate period of time. Vomiting or anorectic patients or pocket pets that may be difficult to treat orally may require subcutaneous injection of vitamin K_1, but bleeding could occur at the injection site.[5] If possible, vitamin K_1 should be given orally, and intramuscular or intravenous routes should be avoided because of the risk of hematoma formation or anaphylaxis if given intravenously. A patient that is bleeding into the thoracic cavity may require thoracocentesis or pericardiocentesis and oxygen therapy in addition to plasma and vitamin K_1. Intravenous fluids may be needed to support the blood pressure, and broad-spectrum antibiotics should be used when indicated. Nutritional support should be provided, if necessary.

Check the PT or PIVKA 48 hours after stopping vitamin K_1 therapy.

Prognosis

The prognosis for animals with anticoagulant rodenticide toxicosis is variable depending on the stage of illness at the time of presentation. If treatment is instituted before clinical signs develop, the prognosis is good to excellent. Otherwise, the prognosis is guarded to good, depending on the type and severity of bleeding.

REFERENCES

1. Murphy, M.J.; Talcott, P.A.: Anticoagulant rodenticides. *Small Animal Toxicology* (M.E. Peterson; P.A. Talcott, eds.). W.B. Saunders, Philadelphia, Pa., 2001; pp 406-419.

2. Woody, B.J. *et al.*: Coagulopathic effects and therapy of brodifacoum toxicosis in dogs. *J. Vet. Intern. Med. 6* (1):23-28; 1992.

3. Dorman, D.C.: Toxicology of selected pesticides, drugs, and chemicals. Anticoagulant, cholecalciferol, and bromethalin-based rodenticides. *Vet. Clin. North Am. (Small Anim. Pract.) 20* (2):339-352; 1990.

4. Mount, M.E.: Diagnosis and therapy of anticoagulant rodenticide intoxications. *Vet. Clin. North Am. (Small Anim. Pract.) 18* (1):115-130; 1988.

5. Sheafor, S.E.; Couto, C.G.: Anticoagulant rodenticide toxicity in 21 dogs. *JAAHA 35* (1):38-46; 1999.

6. Rozanski, E.A. *et al.*: Thrombotest (PIVKA) test results from 25 dogs with acquired and hereditary coagulopathies. *J. Vet. Emerg. Crit. Care 9*:73-78; 1999.

7. Center, S.A. *et al.*: PIVKA clotting times in dogs with suspected coagulopathies (abst.). *Proc. ACVIM*, ACVIM, San Diego, Calif., 1998.

8. Mount, M.E.: Proteins induced by vitamin K_1 absence or antagonism ("PIVKA"). *Current Veterinary Therapy IX Small Animal Practice* (R.W. Kirk, ed.). W.B. Saunders, Philadelphia, Pa., 1986; pp 513-515.

9. Berry, C.R. *et al.*: Thoracic radiographic features of anticoagulant rodenticide toxicity in fourteen dogs. *Vet. Radiol. Ultrasound 34*:391-396; 1993.

10. Staus, J.H.: Bleeding disorders and epistaxis. *Quick Reference to Veterinary Medicine* (W.R. Fenner, ed.). Lippincott Williams & Wilkins, Baltimore, Md., 2000; pp 70-90.

11. Puls, R.: Vitamin K. *Vitamin Levels in Animal Health*. Sherpa International, Clearbrook, B.C., 1994; pp 116-117.

12. Liphatech Worldwide: The veterinarian's guide to managing poisoning by anticoagulant rodenticides. http://www.liphatech.com/vetguide.html; July 2002. ■