Anticoagulant rodenticides: Deadly for pests, dangerous for pets

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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. Because of this, second-generation anticoagulant rodenticides are both appealing and extremely toxic to nontarget species, especially domestic dogs (Table 1).

Available products
Anticoagulants are the most common type of rodenticide produced and used in the United States. 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%. 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 disposed of food scraps that could attract rodents.
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 LD₅₀ in rodents is lower). But relay toxicity 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 non-functional, precursor state. Anticoagulant rodenticides interfere with

### TABLE 1 Common Anticoagulant Products and Their Active Ingredient Concentrations, Formulations, and Acute LD₅₀*

<table>
<thead>
<tr>
<th>Trade Names</th>
<th>Active Ingredient</th>
<th>Generation</th>
<th>Common Concentrations</th>
<th>Common Formulations</th>
<th>Acute LD₅₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rodex, Blitz, Rid-a-Rat, Eagles, and many more**</td>
<td>Warfarin</td>
<td>First</td>
<td>0.025%–0.03%</td>
<td>Pellets, others</td>
<td>20–300 mg/kg (dogs); 5–30 mg/kg (cats)</td>
</tr>
<tr>
<td>D-Con, Havoc, Jaguar, Warrior Chunks, Enforcer, and many more</td>
<td>Brodifacoum</td>
<td>Second</td>
<td>0.005%</td>
<td>Chunks, blocks, pellets, others</td>
<td>0.2–4 mg/kg (dogs); unknown in cats</td>
</tr>
<tr>
<td>Hawk, Maki, Boot Hill, Just One Bite, Tomcat Ultra, and many more</td>
<td>Bromadiolone</td>
<td>Second</td>
<td>0.005%</td>
<td>Blocks, bars, pellets, others</td>
<td>11–15 mg/kg (dogs); unknown in cats</td>
</tr>
<tr>
<td>D-Cease, Generation, Hombre</td>
<td>Difethialone</td>
<td>Second</td>
<td>0.0025%</td>
<td>Pellets, others</td>
<td>4 mg/kg (dogs); &gt; 16 mg/kg (cats)</td>
</tr>
<tr>
<td>Assassin, Tomcat, Ditrac, Exterminator’s Choice, and many more</td>
<td>Diphacinone</td>
<td>Second</td>
<td>0.005%–0.2%</td>
<td>Blocks, bars, powder, liquid concentrates</td>
<td>0.9–8 mg/kg (dogs); 15 mg/kg (cats)</td>
</tr>
<tr>
<td>Enforcer Rat Bait, Duocide**</td>
<td>Pindone</td>
<td>Second</td>
<td>0.03%</td>
<td>Pellets, others</td>
<td>5–75 mg/kg (dogs); unknown in cats</td>
</tr>
</tbody>
</table>

*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.
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. 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. Any type of bleeding can occur, and hematuria, hematemesis, melena, hyphema, or epistaxis may be seen. 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. 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. 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. 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.

**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. 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 K1 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. 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.

In general, a threefold increase in PT or PIVKA is highly suggestive of anticoagulant rodenticide toxicity. Prior administration of vitamin K1 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 toxicity.
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 K1 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 K1 was administered, further treatment is
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 K₁) therapy (3 to 5 mg/kg orally divided b.i.d.). Treat pocket pets at the high end of this dosage range. Make sure to tell owners that the vitamin K₁ must be prescription strength and that vitamin supplements do not contain enough vitamin K₁ to be effective. Over-the-counter supplements contain micrograms of vitamin K₁, but milligrams are needed. Do not use vitamin K₁ (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. Vitamin K₁ can also be nephrotoxic and cause anemia. The length of time for treatment with vitamin K₁ depends on the type of anticoagulant rodenticide ingested. For first-generation anticoagulants, treatment with vitamin K₁ 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 K₁ therapy should be instituted for 30 days. Vitamin K₁ 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 K₁ will be delivered directly to the liver through the portal circulation.

<table>
<thead>
<tr>
<th>Condition</th>
<th>APTT</th>
<th>ACT</th>
<th>PT</th>
<th>PIVKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant ingestion</td>
<td>Marked</td>
<td>Marked</td>
<td>Marked</td>
<td>Marked</td>
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<tr>
<td>Immune-mediated thrombocytopenia</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>DIC</td>
<td>Marked</td>
<td>Marked</td>
<td>Marked</td>
<td>Marked</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>Normal</td>
<td>Marked</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>Marked</td>
<td>Marked</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>von Willebrand’s disease</td>
<td>Slight to moderate</td>
<td>Slight to moderate</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*Source: References 4, 8, and 10.
where the clotting factors are activated. In all patients, check the PT or PIVKA 48 hours after stopping vitamin K₁ therapy, and if the test result is prolonged, continue vitamin K₁ treatment for another week.⁵ Again, a patient must be tested for adequate clotting 48 hours after vitamin K₁ 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 K₁, 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 supply needed clotting factors. Nutritional support should be provided, if necessary.

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