Anticoagulant Rodenticide Intoxication in Animals - A Review

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Abstract: The newest measures for the control of harmful rodent populations are from the anticoagulant rodenticide group, which are divided into 2 subgroups: first and second generations, and indandione derivatives. Non-target organisms are potentially at risk of direct consumption of baits (primary hazard) and of eating poisoned rodents (secondary hazard). Anticoagulant rodenticides inhibit the enzyme vitamin K-dependent carboxylase and thus impair the reactivation of vitamin K, indirectly affecting physiological blood coagulation. The diagnosis is made on the basis of clinical signs (massive hemorrhages), laboratory findings, and especially the changes in coagulation markers (APTT, PT, TT, PCT, ACT, FDPs, and PIVKA). The specific antidote is vitamin K. The general prophylaxis consists of placing baits out of reach of animals, daily control of baits and dead rodents, which are to be timely removed.

Key Words: Intoxication, anticoagulant rodenticides, animals

Introduction

Anticoagulant rodenticides are the largest group of pesticides used for control of harmful rodents (1-4). For the same purpose, derivatives of bromethalin, cholecalciferol, and sodium fluoroacetate are also used (5-7). However, their application is very limited while inorganic rodenticides (phosphorus- and arsenic-containing) are not used. Hydroxycoumarin compounds were discovered in the 1940s and have been in continuous use since then (4,8,9). At present, they are among the most commonly employed rodenticides and therefore responsible for numerous accidents involving humans and animals – both domestic and wild (10-33).

Classification of anticoagulant rodenticides.

Depending on their chemical structure, they are divided into 2 main groups: hydroxycoumarine and indandione (chloroprophacinone, diprophacinone, pindone, and valone) rodenticides (Figure 1). Hydroxycoumarin rodenticides are subdivided into first-generation (coumachlor, coumafuryl, coumatetralyl, and warfarin) and second-generation (brodifacoum, bromadiolone, difenacoum, difethialone and flocoumafen) compounds (Table 1) (1,2,4).

Routes of intoxication. Most commonly, domestic and wild animals are intoxicated by intake of baits containing anticoagulant rodenticides (primary opportunity). The lack of odor and its pleasant taste due to the saccharose content appear to be additional reasons for the extensive incidences of intoxication in humans and animals (10,11,14,34). Another main cause is the ingestion of dead or alive poisoned rodents (secondary opportunity) (14,32,33) by dogs, cats, swine, wild mammals, or birds (4,9,10,12,20,30,32,35). The number of incidents involving intoxitations following a direct skin contact (36) or through drinking water (hydroxycoumarin derivatives are water soluble) (10,11) are less frequent. The majority of reported cases in

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Figure 1. Chemical structure of anticoagulant rodenticides.
humans are due to the first-generation hydroxycoumarin preparation warfarin (37,38). It is used both as a rodenticide and for prevention and treatment of diseases related to enhanced blood hypercoagulability (thromboembolism) (39).

Spontaneous intoxications with anticoagulant rodenticides are reported in dogs (10,14,18,21,31,40-44), horses (16,23), cats (20,41), wild animals (deer, polecats, owls, eagles, falcons, ducks, martens, foxes, etc.) (10,12,13,19,25,30,32-35), and humans (39,45,46).

Experimental studies have been performed in laboratory animals (47), dogs (48), cats (49,50), chicks (51), and rabbits (52).

The biological half-life (T1/2) of warfarin, diphacinone, and brodifacoum is 14-15 h, 15-20 days, and 120 days, respectively (53).

The duration of the toxic effect after a single intake is approximately 14 days for warfarin, 21 days for bromadiolone, and 30 days for brodifacoum (53). These data determine the need for a more prolonged therapy – usually more than 1 month. A single intake of second-generation dioxycoumarin preparations is sufficient to cause hemorrhages unlike first-generation substances. In the latter group, the clinical effects are generally observed after a repeated treatment (41).

Anticoagulant rodenticides reach the highest blood plasma levels in animals in 12 h following oral intake, which is the highest in plasma protein up to 90%-95% (53). The preparations from this group are metabolized in the liver and excreted mainly with urine and partly with faeces. Hydroxycoumarin compounds of the second generation are more toxic compared to first generation representatives (52).

**Table 1. Classification and toxicological features of anticoagulant rodenticides.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Generic name preparations</th>
<th>Commercial formula</th>
<th>Chemical formula</th>
<th>Acute oral toxicity LD50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dogs</td>
</tr>
<tr>
<td>First generation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coumachlor</td>
<td>Tomorin</td>
<td>C₁₉H₁₅ClO₄</td>
<td>900</td>
<td></td>
</tr>
<tr>
<td>Coumafuryl</td>
<td>Kumatox, Ratafin</td>
<td>C₁₇H₁₄O₅</td>
<td>0.4</td>
<td>6-40</td>
</tr>
<tr>
<td>Coumatetralyl</td>
<td>Rodentin</td>
<td>C₁₉H₁₆O₃</td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>Warfarat, Zoocoumarin</td>
<td>C₁₉H₁₆O₄</td>
<td>58 (11-323)</td>
<td>20-50</td>
</tr>
<tr>
<td>Second generation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brodifacoum</td>
<td>Folgorat, Klerat, Talon, Rodend</td>
<td>C₃₁H₂₃BrO₃</td>
<td>0.26</td>
<td>0.25-3.56</td>
</tr>
<tr>
<td>Bromadiolone</td>
<td>Lanirat, Contrac, Bromorat, Musal</td>
<td>C₃₀H₂₃BrO₄</td>
<td>1.125</td>
<td>&gt;10 (11-15)</td>
</tr>
<tr>
<td>Difenacoum</td>
<td>Matrac, Rastop, Ratak, Silo</td>
<td>C₁₉H₁₆O₃</td>
<td>1.8</td>
<td>50</td>
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<tr>
<td>Difethialone</td>
<td>Frap, Quell</td>
<td>C₁₉H₂₀BrO₅S</td>
<td>0.56</td>
<td>5</td>
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<tr>
<td>Floccouafen</td>
<td>Storm</td>
<td>C₃₃H₂₅F₃O₄</td>
<td>0.46</td>
<td>0.075-0.25</td>
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<tr>
<td>Indandione</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloropacinone</td>
<td>Delta, Patrol</td>
<td>C₁₂H₁₅ClO₅</td>
<td>20.5</td>
<td></td>
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<tr>
<td>Diphacinone</td>
<td>Ratindan, Ratik</td>
<td>C₃₀H₂₀O₃</td>
<td>3</td>
<td>3-7.5</td>
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<tr>
<td>Pindone</td>
<td>Pival, Tri-ban</td>
<td>C₁₅H₁₄O₃</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Valone</td>
<td></td>
<td>C₁₅H₁₄O₃</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**Mechanism of the toxic activity (Figure 2).** The action mechanism of hydroxycoumarin and indandione anticoagulant rodenticides is identical, which yields similar clinical manifestations, hematological alterations or abnormalities, and treatment schedule, regardless of the preparation group (54,55). Anticoagulant rodenticides inhibit the recycling of vitamin K, a cofactor of primary importance for postribosomal carboxylation (activation) of blood clotting factors II (prothrombin), VII (proconvertin), IX (Christmas factor), and X (Stuart-Prower factor), by the enzyme vitamin K-dependent carboxylase, maintaining the active form of vitamin K (41,49,50,55). By the enzyme vitamin K-dependent carboxylase, the active vitamin K is transformed into an
inactive epoxide that is thereafter reconverted into vitamin K (vitamin K quinone), by the enzyme vitamin K epoxide reductase. In the next step, the vitamin K reductase converts vitamin K quinone into vitamin K1 hydroquinone that is integrated again in the carboxylation cycle of blood clotting factors II, VII, IX, and X. Then the enzyme vitamin K reductase converts vitamin K quinone into vitamin K1 hydroquinone that enters once again the carboxylation cycle of blood clotting factors II, VII, IX, and X (55).

Anticoagulant rodenticides inhibit vitamin K epoxide reductase, resulting in a lack of active vitamin K. This mechanism contributes to blood clotting factors II, VII, IX, and X (inactive factors II, VII, IX, X proteins S, C, Z) that are not carboxylated and remain nonfunctional (1, 4, 52-55). Because anticoagulant rodenticides do not block these factors, their concentrations in blood decrease about 12-24 h after the intoxication coinciding with the first massive bleeding episodes (20, 41, 44, 47, 49, 50).

**Clinical signs.** The initial symptoms are general and non-specific – somnolence, weakness, pale mucosa, decreased (anorexia) or lacking appetite (arexia), frequent urination (polyuria), increased thirst (polydipsia), decreased locomotion and perception, and rapid and easy exhaustion (12, 19, 28, 29, 31, 33, 41, 51).

The data about rectal body temperature (BT) are contradictory. Petterino et al. (28) reported decreased BT, while Binev et al. (14) reported hyperthermia. These data result from the application of various doses and types of toxic compounds, but depend mostly on the stage of intoxication. In the early phase, hypothermia is rather encountered and at a later stage (after 2-3 days) BT increases (14). The findings about the changes in heart and respiratory rates are however uniform. All investigators report tachycardia and polypnea with dyspnea in spontaneous or experimental intoxications, regardless of the animal species, the amount or the type of the toxic substance, and the stage of intoxication (21, 23, 29, 45). Other clinical symptoms are bloody feces (hematochezia, melena) (14, 20, 22), hemorrhages (petechiae and ecchymoses) on the skin and mucosa (16, 20, 29), hyphema (hemorrhages in the anterior eye chamber between the cornea and the iris) and petechial hemorrhages in conjunctivae (20, 23, 45), vomiting and hematemesis (vomiting of blood) (20, 21), nasal bleeding, vaginal bleeding, and ear bleeding (16, 20-22), dysuria, and hematuria (21, 23, 45). The presence of pulmonary edema, intrapulmonary and pleural hemorrhages (20, 23, 26-28, 41), correlated with the observed 2-sided, air- and blood-containing nasal discharges (14, 21, 31).
Our clinical observations (14) showed that almost always, at a later stage of the intoxication (after 1 week) in dogs, a bilateral symmetrical enlargement of the abdomen was observed, frequently accompanied by prolapse of the ventral abdominal wall and lordosis of the vertebral column, resulting from hemorrhagic effusion (ascites). This is the cause of the decreased absolute cardiac dullness determined by percussion and the dullness in the ventral parts of the lung field with a horizontal upper limit, moving when the anterior part of the body is being lifted (pleural effusion). The patients frequently adopt the posture of a sitting dog. The formation of massive hematomas after venipuncture is also very characteristic.

**Blood laboratory analysis.** It is essential for the precise and confident diagnosis of anticoagulant rodenticide intoxication in animals (55).

a) Hematological abnormalities – anemia and hypochromasia (hypochromic anemia), decreased hematocrit values, leukocytosis with neutrophilia, thrombocytopenia, enhanced erythrocyte sedimentation rate, and decreased mean corpuscular volume (14,16,20,21,29).

b) Clinical biochemistry abnormalities. Hypoproteinemia, hypoalbuminemia, hyperglycemia, bilirubinemia, increased urea concentration, and enhanced activities of alanine aminotransferase, alkaline phosphatase, and gamma glutamyltransferase (14,16,19,20,43).

c) Coagulative profile abnormalities (Table 2). These are prolonged activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), partial thromboplastin time (PTT), activated clotting time (ACT), increased fibrin degradation products' concentration (FDPs), decreased amounts of factors II, VII, IX, and X, increased fibrinogen and increased values of the PIVKA (protein induced by vitamin K antagonism or absence) test, specific for this type of intoxication (14,20,21,29,31,36,48).

d) Changes in urine. Proteinuria, hematuria, and plenty of erythrocytes in the sediment (20,42,56).

**Gross pathology changes.** The most characteristic changes related to intoxication with anticoagulant rodenticides are extensive, generalized, and multiple hemorrhages. In the thorax, pleural, intrapulmonary, and pericardial bleedings are observed (26,27,57), pulmonary infiltrations, hemomediastinum (28,31), cardiac tamponade (20,23,26,27), extensive hematomas (causing obstruction of the trachea) (15,26,57), thymus gland hemorrhages, subdural and cerebral bleedings, vaginal and uterine hemorrhages and hematomas, gastrointestinal bleeding and hemoperitoneum (57), subcutaneous hemorrhages and abdominal hematomas (27,57), hemorrhages and hematomas in the renal parenchyma and bilateral hydronephrosis (42), bleedings, hematomas and dystrophic damage of liver parenchyma (18,42).

First-generation dioxycoumarin anticoagulant rodenticides provoke the calcification of blood vessels (of aorta, liver, mesenterial, femoral, renal, and other arteries) and heart valves and tracheobronchial calcification (45).

| Table 2. Changes in blood clotting factors in dogs with spontaneous intoxication by anticoagulant rodenticides. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Factor | Normal values | Bromadiolone | Bromadifacoum | Bromadifacoum |
| (s) | (Schmid and von Forstner) | (Binev et al.) | (Petrus and Henik) | (Petrus and Henik) |
| ACT | <110 | 182 | <67 | 225 |
| APTT | 12-16 | 86 | 36 | - |
| PT | 10-14 | 122 | - | >150 |
| PIVKA | <25 | 148 | - | - |
| TT | 7-12 | 82 | 327 | - |

Legend: ACT – activated clotting time, APTT – activated partial thromboplastin time, PT – prothrombin time, PIVKA – protein induced by vitamin K antagonism or absence, TT – thrombin time.

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Treatment. The administration of emetics and active charcoal suspension are recommended in the first 4 h of the intoxication (4,40,43,58,59). At the time of the appearance of clinical signs, it is necessary to begin the specific antidote therapy. It consists in the application of high doses of vitamin K₁ (39,58-60). In dogs, the preparation is applied perorally at average doses of 1.5-2.5 mg/kg twice daily (4). In small canine breeds, cats, exotic animals, and birds, the doses could be increased to 4-5 mg/kg. In large dog breeds, the therapy begins with low doses of 1.5-2 mg/kg (4,19,40,43). In cats, the dose could reach 7 mg/kg (20). When administered orally, in order to increase its absorption, it is given together with food (40,43). The parenteral administration of vitamin K₁ is not recommended because of the potential risk of anaphylactic reactions (58). Vitamin K₃ is not effective in such intoxications and therefore is not used (4,40). In emergency cases, especially following intoxications with second-generation hydroxycoumarin anticoagulant rodenticides, vitamin K₁ should be applied subcutaneously at a dose of 5 mg/kg at several sites after the stabilization of the patient via transfusion of whole blood or blood plasma (39,58). As its effect occurs very rapidly, to restore the activity of vitamin K-dependent blood clotting factors, the next application of vitamin K₁ is after 12 h and applied only orally at 2.5-5 mg/kg once per 24 h for 3-6 weeks (4,19,40,43). If prothrombin time remains considerably prolonged after that period, the treatment is continued for another 2 weeks (4,40,43,58).

In large animals (horses, cattle, etc.), the parenteral (intramuscularly or subcutaneously) use of vitamin K₁ is more appropriate. In ruminants, it is used subcutaneously at 1-2 mg/kg. In these species, the application of vitamin K₃ is less effective. In horses, vitamin K₁ is applied intramuscularly at 0.5-2.5 mg/kg. The administration of K₃ in this species results in a significant renal damage (4,16). The duration of the treatment with vitamin K₁ is different, but almost all investigators state that it should be pursued for at least a month (47,58). This period depends on many factors: type and amount of ingested rodenticide, animal species, route of intake, but mostly on the rapid and precise diagnosis and the timely, appropriate treatment. The recovery of the ACT factor is a sign that the animal has overcome the intoxication by anticoagulant rodenticides (4,40,43).

Prognosis. It is poor. It is supposed that if the animals overcome the acute coagulopathy, the prognosis after day 2 is more favorable (4). Our clinical observations (14) support the idea that even when the symptoms of intoxication in dogs have disappeared, in most instances, there is a prerequisite for a periodically recurring ascites as a result of dystrophic damage to the liver parenchyma.

Prevention. The prevention of intoxication in animals requires the placement of baits in inaccessible places. A daily control is needed on both baits and on dead rodents, the latter being regularly removed and buried.

Conclusion

The intoxications with anticoagulant rodenticides in animals are relatively frequent. To date, these preparations have been the only means for effective control of rodent populations, and therefore they have caused intoxications mainly in pets (dogs and cats) and wild animals by ingestion of baits. Therefore, the principles of diagnostics, treatment, and prevention should be observed with regard to the protection of animals against these types of intoxication.

References

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