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Toxicants that Interfere with the Function of Vitamin K (9-Aug-1999)

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1. Toxicants that Interfere with the Function of Vitamin K

Coagulation of Blood and the Function of Vitamin K

The circulatory system is a very dynamic tissue, which is in a continual state of repair and regeneration. The hemorrhage that occurs as a result of either normal activities or from various insults (trauma, infectious processes, shock, stress, malignancy, etc.) is arrested through an ordered interaction involving 3 major events.

The first phase is comprised of the platelet adhesion reaction in which activated platelets become sticky, attach to exposed endothelial connective tissue elements and build by aggregation to form a platelet plug. In the second phase, the so-called platelet release reaction, vasoactive and coagulation-triggering substances are released. The damaged vessel retracts, and the third phase, the coagulation mechanism by which soluble fibrinogen is converted to insoluble polymerized fibrin, is triggered.

This discussion addresses only those components of the coagulation mechanism (active in the second to third phases) whose concentration in plasma is influenced by vitamin K and only those compounds which act as vitamin K antagonists.

When the coagulation mechanism is set into motion, 2 separate "pathways" are simultaneously set into operation to effect hemostasis. The "intrinsic route" refers to a relatively slow process (lasting 5 - 15 minutes, in vitro), while the "extrinsic route" is a relatively rapid one (lasting 10 - 12 seconds), following contact between blood and damaged tissue. Following activation, both routes operate independently and eventually converge at the "common pathway." At this convergence, a single route (common coagulation pathway) is followed which eventually causes the soluble plasma protein, fibrinogen, to be converted into the insoluble fibrin (see Circulation diagram below).

Within each independent (intrinsic, extrinsic) pathway and in the common pathway, at least one coagulation (clotting) factor that depends on the action of vitamin K for its synthesis is involved. When vitamin K is deficient or inhibited, the flow of the cascade is interrupted, preventing eventual formation of the insoluble fibrin polymer.

The vitamin K-dependent clotting factors include factor VII (in the extrinsic pathway), factor IX (in the intrinsic pathway), and factors X and II (prothrombin) (in the common pathway). These clotting factors are synthesized in the liver and vitamin K is an essential cofactor allowing the carboxylation of the carboxy coagulation proteins to their functional form. Vitamin K metabolism is tightly conserved in the liver.

A very important enzyme, vitamin K epoxide reductase, is essential for the continued synthesis of new factors VII, IX, X and
prothrombin. The action of dicumarol and the anticoagulant warfarin (as well as all other anticoagulant rodenticides) is to tie up this enzyme, preventing recycling of the vitamin K and depleting the liver of the active, reduced form of vitamin K (see Hepatocyte diagram below). When this occurs, final carboxylation (activation of) factors VII, IX, X, or prothrombin ceases. However, factors VII, IX, X, or prothrombin already in the bloodstream (synthesized previous to the anticoagulant insult) are not affected and can participate in the normal clotting mechanism. It is when these still-viable, vitamin K-dependent clotting factors reach the end of their life span that unchecked hemorrhage begins to take place. This is the reason for the usual 5-day "lag" time between ingestion of a toxic dose of an anticoagulant and appearance of clinical signs. Factor VII has the shortest half-life (6.2 hours), and thus it and the extrinsic pathway are the first to shut down. When this occurs, hemostasis is impaired slightly, and a mild degree of hemorrhage may occur, but clinical signs are usually not apparent, because the other pathway (intrinsic) is still operational and serves as a sort of "back-up." During this period of time, laboratory evaluation of the blood will reveal an abnormality in the now defunct (extrinsic) pathway. This abnormality is in the form of an elevated prothrombin time (PT).

Once the lifespan of factor IX (in the back-up intrinsic path) is at an end (half-life 13.9 hours), that pathway will be shut down and be defunct. It is at this point that hemorrhage begins to go unchecked and the most common time that the first signs of observable clinical abnormalities are noted. It is also at this point that laboratory evaluation of the blood will reveal an elevated partial thromboplastin time (PTT or APTT) as representative of a defect within that particular (intrinsic) pathway. PT is still elevated. From this point, deterioration of the patient due to hemorrhage may be quite rapid (assuming that no more active vitamin K is added to the system).

**Figure 1. Circulation**

*APTT (intrinsic)*

XII

X

13.9

IX

6.2

VII

2.0

Thrombin

Fibrinogen

Fibrin (monomer)

XIII

Fibrin (cross-linked polymer)

Fibrinolysis

Plasminogen → Plasmin

FDPs = fibrin degradation products

- vitamin K-dependent coagulation proteins
- half-life, in hours
Damaged or Moldy Sweet Clover Hay

Melilotus alba - White sweet clover
Melilotus occidentalis - Yellow sweet clover
Melilotus indica - King Island Melilot

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Interfere with the Function of Vitamin K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cattle</td>
<td>Weeks to months</td>
<td>Days to weeks; often lethal</td>
<td></td>
</tr>
</tbody>
</table>

Images

- White sweet clover (*Melilotus alba*). Source: Cornell University, Poisonous Plants Informational Database (www.ansci.cornell.edu/plants/index.html). - To view this image in full size go to the IVIS website at www.ivis.org.
- Yellow sweet clover (*Melilotus officinalis*). Source: Cornell University, Poisonous Plants Informational Database (www.ansci.cornell.edu/plants/index.html). - To view this image in full size go to the IVIS website at www.ivis.org.
- Yellow sweet clover (*Melilotus officinalis* Lam.). - U.S. G.S. Northern Prairie Wildlife Research Center. - To view
Family -
Leguminosae (pulse or bean family)

Description

Melilotus spp.
- Plant: Annual or biennial, upright, branched herb, fragrant odor (similar to vanilla): 3 - 9 feet tall.
- Leaves: Alternate, pinnate, trifoliate, obvate, serrated along the entire margin: 1/2 - 1 inch long.
- Flowers: Small white/yellow, fragrant, appear in numerous slender clusters that arise from the axils of the leaves.
- Fruit: Ovoid, smooth pods contain 1 - 4 seeds.

Sources

Imported from Europe and Asia for hay or use as a cover crop and soil improver. Grows readily throughout the central and northern United States and southern Canada.

Toxic Principle

Dicumarol, also calledbishydroxycoumarin.

Toxicity

- Except for problems related to the formation of dicumarol, sweet clover hay compares favorably to alfalfa hay in quality, utility, and economics. Despite the potential for toxicosis, sweet clover hay has been in rather widespread use since the early 1900s.
- As a result, losses occur annually in Ohio, Indiana, Illinois, Wisconsin, the Dakotas, Nebraska, and other states.
- Formation of dicumarol results from the dimerization and oxidation of the nontoxic compound coumarin, a natural component of the plant which imparts the characteristic fragrance and bitter taste. The conversion process takes place when the clover plant is cut and baled during conditions of high moisture and mild conditions. Various fungi take advantage of the optimum environmental conditions of the hay and metabolize coumarin to dicumarol. Silage may also be affected.

Dimerization - induced by various causes of damage including bad weather, improper curing methods and especially fungi: Penicillium spp., Hemicolor spp., Mucor spp., Aspergillus spp.

\[
\text{Coumarin (nontoxic)} \quad \rightarrow \quad \text{Dicumarol (3,3' methylenebis 4hydroxy coumarin) (toxic)}
\]
The time period required to exhibit observable clinical signs in healthy cattle fed on contaminated hay or silage is dependent on the dicumarol concentrations in the hay. In toxicity trials conducted on 500 - 600 lb steers, no clinical signs were observed after 100 days of feeding hay containing 10 - 20 ppm dicumarol.

At 30 ppm clinical signs were noted at 132 - 139 days.
At 60 - 70 ppm clinical signs were noted at 17 - 23 days.

Susceptible Species

- Poisoning is restricted almost exclusively to cattle.
- Minor losses have been reported in pigs, horses and sheep, but these species are rarely affected.
- Cattle appear to be most likely to accept badly damaged sweet clover hay.
- Sheep much more resistant than cattle.

Mechanisms of Action

Proposed to interfere with normal blood clotting as a result of reduction of the concentrations of active forms of clotting factors II (prothrombin), VII, IX and X, due to competitive inhibition (competition between vitamin K epoxide and dicumarol) for the enzyme "vitamin K epoxide reductase" which converts inactive (used) vitamin K epoxide back to its active vitamin K form in the body (see previous discussion).

Signs

- The time from the onset of clinical signs to death is variable, from 24 hours to several weeks, and depends on the degree of exposure and condition of the animal prior to exposure.
- Observable clinical signs in subacute (lower dicumarol levels) cases may be confined to blanching or pallor of the mucous membranes and weakness of the animal apparently due to associated anemia.
- Prolonged or nonstop bleeding occurs in affected animals from minor surgical procedures (castration, dehorning), parturition, or wounds.
- Hematomas of variable size (up to several feet in circumference and protruding up to 12 inches) may be noted on any area of the trunk, neck or limbs.
- Swollen areas may "pit" on pressure (chronic cases) or may be fluctuant (acute cases).
- Gas is not present in these lesions.
- The heartbeat may be increased in strength or the pulse may be rapid and weak.
- Body temperature is normal to subnormal (which may aid in distinguishing the syndrome from infectious diseases), and there often is an absence of pain or inflammation in the areas of subcutaneous hematomas.
- Hemorrhage into the eye may cause blindness, and hemorrhage into the nervous tissue may cause various degrees of paresis, paralysis, or death.
- The animal may be lame from hemorrhage in joints or muscles, or it may be ataxic or motionless.
- Blood may be noted in the oral cavity, nostrils, and urogenital orifices as well as in the milk or excreta.
- Hemorrhage into the thoracic cavity, lungs, pericardium, or mediastinum may cause the animal to become dyspneic.
- Abortions have been noted in cattle. Also, newborn, nursing calves may be affected prior to any observance of illness in the dam.
- Migrating parasites have been suspected of precipitating fatal hemorrhages.

Lesions

- Carcass appears extremely "bruised".
- Subcutaneous swellings consist of fluid (serum) or blood in various stages of clotting.
- Hemorrhages, often subcutaneous and intermuscular, vary in size from petechiae to ecchymosis to hematomas. Gross hemorrhages may be found in almost all tissues. A "layer" of blood may be found beneath the scapulae.
- Histologic lesions may include fatty degenerative changes in the liver and nephritis.
- Notable changes in clinical pathology parameters:
  - Low hematocrit; decreased hemoglobin.
  - Prothrombin time (PT) is elevated (earliest onset).
  - Partial thromboplastin time (APTT) is elevated (intermediate onset).
Activated clotting time (ACT) is elevated (delayed onset).

**Diagnosis**
- History of exposure to sweet clover hay or silage.
- **Note:** Livestock are usually not affected by grazing sweet clover pasture.
- Clinical evidence of hemorrhages/hematomas.
- Confirmed by an elevated prothrombin time (PT). **Normal values** may vary between laboratories, but are generally in the range of approximately 20 seconds. Consult local hospitals for assistance in analysis if a veterinary diagnostic laboratory is not available. Special care is required for collection and handling: one part of 3.8% sodium citrate or sodium oxalate is added to a plastic or silicone tube, into which 9 parts of blood (1:9) are collected. Collected blood is kept on ice and centrifuged as soon as possible, preferably within 30 minutes of collection. Plasma is harvested and kept on ice or frozen during transport to the laboratory. To aid in interpretation, it is advisable to collect and submit blood (in the same manner) from a "normal" but unexposed animal (same species) for submission along with the blood of the clinically ill animal(s).
- Analysis of suspect hay or silage for dicumarol content. **Note:** Not all "moldy" sweet clover hay is toxic; conversely, highly toxic hay may have no obvious external manifestations of fungal growth. Stalks, when broken open, may reveal presence of mold growth.

**Treatment**
- Correction of hypovolemia and clotting factor deficit. If situation is very severe, and if the animal is of sufficient economic or esthetic value, transfusion of fresh whole blood from a donor animal (1 liter per 200 kg of body weight) is used to provide readily available clotting factors and erythrocytes.
- Circumventing the biochemical lesion. **Vitamin K**₁ (sold by several companies, e.g. Aquamephyton® injection, by Merck, Sharpe and Dohme; Veta K₁®, by Professional Veterinary Laboratories), at 1 - 3 mg/kg BW. Studies have shown that doses below 1 mg/kg are increasingly ineffective in reversing the toxicosis. A single dose of 1 mg/kg has been shown to be effective in lowering the prothrombin time to approximately normal levels within 24 hours. **Note:**
  - The smallest needle possible should be used, to prevent hemorrhage at the injection site.
  - The injection should generally be made IM or SQ. Intravenous injection has a greater risk of anaphylaxis.
  - Vitamin K₃ (menadione) has been shown to be ineffective as either a preventative or therapeutic measure.
- Remove suspect hay or silage and replace with alfalfa hay (a good dietary source of natural vitamin K). Mild cases of toxicosis tend to resolve without further treatment after withdrawal of the contaminated feed.
- Supportive care (quality feed and ample, fresh water; protection from environmental stresses) is very important. Avoid all unnecessary drugs. Note: All affected animals should be handled with care to prevent exacerbation of the anemic/hypoxic state and to avoid causing additional hemorrhage.
- Correction of organ dysfunction that results from accumulation of extravascular blood (e.g., thoracocentesis) should be attempted **only** if the situation is life-threatening (e.g., severe dyspnea).
Moldy *Lespedeza* Hay

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Interfere with the Function of Vitamin K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruminants</td>
<td>Weeks to months</td>
<td>Days to weeks; often lethal</td>
<td></td>
</tr>
</tbody>
</table>

**Images**

- Japanese Clover, *Lespedeza striata* - U.S. G.S. Northern Prairie Wildlife Research Center. - To view this image in full size go to the IVIS website at www.ivis.org . -
- Korean *Lespedeza, Lespedeza stipulacea* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -
- *Lespedeza cuneata* - Google Image Search. - To view this image in full size go to the IVIS website at www.ivis.org . -

**Sources**

- *Lespedeza stipulacea*, Korean *Lespedeza*.
- Sometimes grown in the midwestern USA.

**Toxicosis**

- Produces a hemorrhagic syndrome in ruminants, very similar to dicumarol toxicosis (moldy *Melilotus*).
- Rarely seen, but may be associated with particularly wet years when *Lespedeza* is put up in hay or silage.
- Deaths due to uncontrollable bleeding were seen in Missouri several years ago. Moldy hay was fed to rabbits and the bleeding syndrome was reproduced, indicating that the hay was involved. Toxic principle has not been isolated.
- Prothrombin time (PT) was elevated, suggesting a vitamin K-associated problem.

**Sericea Lespedeza** (*Lespedeza cuneata* (Dum.-Cours.) G. Don)
- **Family** - Pea (Leguminosae).
- **Growth Form** - Perennial herb.
Stems - Upright, arching, hairy, up to 4 feet long.
Leaves - Alternate, divided into 3 leaflets, the leaflets oblanceolate, cut straight across or slightly notched at the tip, tapering to the base, without teeth, usually silvery-silky on the lower surface, up to 3/4 inch long.

**Flower Arrangement** - Flowers 1 - 4, from the axils of the leaves.
**Flowers** - White, with purple veins, up to 1/3 inch long.
**Sepals** - 5, green, covered with white hairs.
**Petals** - 5, arranged to form a typical pea-shaped flower.
**Stamens** - 10.
**Pistils** - Ovary superior.
**Fruits** - Pod finely hairy, 1/4 inch long, 1-seeded.

**Habitat** - Open areas, particularly in fields and along roads where it is often planted for erosion control.
**Range** - Mostly in the southern half of the state.

**Time of Flowering** - September and October.

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### Anticoagulant Rodenticides

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Interfere with the Function of Vitamin K</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coumarin and indandione anticoagulant rodenticides and pharmaceuticals</strong></td>
<td>Most species</td>
<td>2 days to a week</td>
<td>Days to 6 weeks; often lethal</td>
<td></td>
</tr>
</tbody>
</table>

**Introduction**

- In North Dakota and Canada in the early 1920s, the hemorrhagic syndrome of cattle caused by dicumarol was first associated with consumption of improperly cured or moldy sweet clover (*Melilotus sp.*) hay. Later investigations found the coagulopathy to be a result of conversion of coumarin (a natural compound in *Melilotus*) to dicumarol (3,3 methylenebis-4-hydroxycoumarin) as a result of fungal spoilage during the curing process of the hay. (See Damaged or Moldy Sweet Clover handout).
- Subsequent research provided an analog, warfarin, which was shown in the early 1940s to be a more potent...
anticoagulant. Warfarin subsequently found therapeutic use for various thrombotic and coronary diseases as well as effective use in rodent control.

- Today's anticoagulants are structurally related to coumarin or a similar prototype compound, indanedione. Other commercial rodenticides, notably compound 1080® (sodium fluoroacetate), zinc phosphide, strychnine, cholecalciferol (vitamin D₃) and bromethalin operate by completely different mechanisms and present separate, specific problems for diagnosis and treatment.

Sources

Anticoagulant rodenticides are used extensively by the lay public and professional exterminators.

"First Generation" Anticoagulant Rodenticides

- Warfarin.
  - There are a multitude of commercial warfarin-based anticoagulant rodenticides available for rodent control. These vary widely in concentration and formulations from 0.025% baits (most baits) to 1.0% throw-packs are encountered. Baits are often tan in color and may be mixed with grain. Pharmaceutical preparations (2 - 10 mg tablets) for use in cardiac patients may be a source of accidental exposure to pets from the household medicine cabinet. The chemical name of warfarin is 3(alpha-phenyl-beta-acetylethyl)-4 hydroxycoumarin. All warfarin-containing products should have the "4-hydroxycoumarin" chemical suffix included under the "active ingredient:" on the package label. Some examples of synonyms and brand names: Warf 42®, Coumafene®, Rosex®, D-con® (some types), Warficide®, Prolin®, Ratox®, Raterex®, Banarat®, Coumadin® (pharmaceutical). Prolin® and Banarat® contain sulfaquinoxaline to inhibit synthesis of vitamin K by the bacterial flora of the small intestine.

- Indanediones.
  - Indanedione-containing anticoagulant rodenticides also vary in concentration between products and formulations. Products range from 0.025% bait to 5.0% powder. Pharmaceutical preparations include tablets containing up to 50 mg active ingredient. Indanedione-containing products should contain the chemical suffix "1,3'(2H)-dione" listed under "active ingredient:". Examples of generic names include: pindone, chlorphacinone, valone, anisindone (pharmaceutical), phenindione (pharmaceutical) and difethialone (pharmaceutical and rodenticide). Brand names include: Chemrat®, Drat®, Rozol®, Ramik®, Isoval®, Diadilan® (pharmaceutical) and D-Cease.

"Second Generation" Anticoagulant Rodenticides

- This group of anticoagulants was developed in the 1970s to answer the problems that existed with the use of the older, first generation anticoagulants. The basic coumarin or indanedione nucleus was retained to give the anticoagulant properties, but chemical structures were selected for increased potency (single lethal feeding potential), and efficacy against resistant rodents. These include the coumarin-based generics brodifacoum, difenacoum, and bromadiolone, and the indanedione diphacinone (sometimes called diphindione). These are among the most widely used and most toxic anticoagulants. The baits are often blue-green in color. The chemical suffix names of the coumarin types are not consistent, but some of the more common ones can be identified as "benzopyran-2-one" or "1-propanol-1". There are several pharmaceutical preparations available.
  - Brodifacoum-containing rodenticides (as of April, 1985) include:

- All of today's anticoagulant rodenticides have in common the basic coumarin or the structurally similar indanedione nuclei.
Toxicity and Susceptible Species

- The anticoagulant rodenticides are a potential hazard for all mammals, birds, and possibly other species. The susceptibility varies among animal species and the toxicity of the compounds also varies. Dogs and cats are most frequently involved, with occasional problems encountered in swine, ruminants, horses, pet birds, rodents and rabbits.
- Secondary toxicity.
  - Although consumption of warfarin-poisoned rodents or birds by carnivores does not appear to present a likely hazard for the predator, consumption of tissues from diphacinone-poisoned animals has caused secondary poisoning in eagles, rats, dogs, and mink. Secondary toxicity may rarely occur with other second-generation anticoagulants.

*Note that swine are particularly sensitive.

### Table 1. Values for Warfarin Toxicity

<table>
<thead>
<tr>
<th>Species</th>
<th>Toxic Level Single Dose</th>
<th>Toxic Level Repeated Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rats</td>
<td>50 - 100 mg/kg</td>
<td>1 mg/kg x 5 days</td>
</tr>
<tr>
<td>Dogs</td>
<td>5 - 50 mg/kg</td>
<td>5 mg/kg x 5 - 15 days</td>
</tr>
<tr>
<td>Cats</td>
<td>5 - 50 mg/kg</td>
<td>1 mg/kg x 5 days</td>
</tr>
<tr>
<td>Swine*</td>
<td>3 mg/kg</td>
<td>0.05 mg/kg x 7 days</td>
</tr>
<tr>
<td>Ruminants</td>
<td></td>
<td>200 mg/kg x 12 days</td>
</tr>
<tr>
<td>Poultry</td>
<td>50% of BW of feed containing 0.1 mg/kg</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Toxicity Values for Various Indanediones

<table>
<thead>
<tr>
<th>Generic</th>
<th>Rat</th>
<th>Mouse</th>
<th>Dog</th>
<th>Cat</th>
<th>Pig</th>
<th>Rabbit</th>
<th>Duck</th>
<th>Human</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphacinone</td>
<td>1.5</td>
<td>340</td>
<td>3</td>
<td>15</td>
<td>150</td>
<td>35</td>
<td></td>
<td>5 (LDLO)</td>
</tr>
<tr>
<td>Chlorphacinone</td>
<td>2.1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>50</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Pindone</td>
<td>280</td>
<td></td>
<td>5 (LDLO)</td>
<td></td>
<td>150</td>
<td></td>
<td>50 (LDLO)</td>
<td></td>
</tr>
</tbody>
</table>
Absorption, Distribution, Metabolism and Excretion (ADME)

- Absorption of warfarin is rather complete but occurs slowly, with peak plasma levels seen after 6 - 12 hours. Most of the warfarin is bound to plasma protein, but high concentrations are also found in the liver, spleen, and kidney.
- Metabolism of the coumarins occurs in the liver and involves mixed function oxidase enzymes. Inactive hydroxylated metabolites have been found in the urine. The acute toxicity of the coumarins is reduced when phenobarbital has been given to induce the hepatic enzymes. Vitamin K does not appear to enhance the rate of disappearance of the anticoagulant.
- The anticoagulant rodenticides are eliminated at various rates, depending on the compound and the amount ingested. The compound may accumulate with time, as in the case of an animal ingesting small amounts over several days. The half-life of warfarin in dog plasma is 14.5 hours. The half-life of diphacinone is 15 - 20 days in humans, which compares to a mean of 48 hours for warfarin in humans. The half-life of brodifacoum is yet to be reliably determined, but it is assumed to be at least as bioaccumulative and persistent as diphacinone. These differences in residual half-lives have very important implications when considering treatment of poisoned animals.

Predisposing Factors

- Animals may be of increased susceptibility due to various factors such as: 1) a high dietary fat intake [fatty acids displace the plasma protein bound anticoagulant increasing the free (active) fraction in the plasma so that more reaches the liver]; 2) prolonged oral antibiotic therapy (decreased synthesis of vitamin K by intestinal bacteria); 3) biliary obstruction and liver disease which presumably reduces metabolism and excretion of the anticoagulant and reduces clotting factor synthesizing ability.
- Plasma proteins (albumin) play a significant role in the patient's response to an anticoagulant. Warfarin is over 90% bound in canine plasma. The plasma proteins therefore constitute a great reservoir for warfarin. Warfarin cannot be excreted as long as it is in the tissues or bound to plasma proteins.
- Like fatty acids, certain drugs displace warfarin from the albumin and shunt it down a concentration gradient into the tissue (liver), unless the tissue is already equilibrated, then the warfarin will be free to be excreted in the urine. Drugs known to displace warfarin from albumin in the blood, include oxyphenbutazone, phenylbutazone (also decreases platelet integrity), diphenylhydantoin, sulfonamides, and adrenocorticosteroids.
- Uremia also causes decreased binding of the anticoagulant to serum proteins and may slow excretion of the unbound fraction.
- Aspirin interferes with platelet function. Other drugs generally contraindicated include promazine-type tranquilizers, local anesthetics, nitrofurans, antihistamines, anabolic steroids and epinephrine.
- Although evidence is very limited, there is some reason for concern regarding transmission of anticoagulants to young, perhaps via the milk. Because neonates tend to be hypoprothrombinemic, they may be particularly susceptible to anticoagulant exposure.

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Table 3. Values for Brodifacoum Toxicity*

<table>
<thead>
<tr>
<th>Species</th>
<th>LD₅₀ (mg/kg)</th>
<th>Species</th>
<th>LD₅₀ (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dog</td>
<td>0.25 - 3.6</td>
<td>Guinea pig</td>
<td>2.8</td>
</tr>
<tr>
<td>Cat</td>
<td>25</td>
<td>Rat, Mouse</td>
<td>0.27 - 0.50</td>
</tr>
<tr>
<td>Sheep</td>
<td>25 - 33</td>
<td>Mink</td>
<td>9.2</td>
</tr>
<tr>
<td>Pig</td>
<td>0.5 - 2.0</td>
<td>Mallard duck</td>
<td>2.7 - 4.6</td>
</tr>
<tr>
<td>Rabbit</td>
<td>0.2 - 0.29</td>
<td>Harrier hawk</td>
<td>10</td>
</tr>
</tbody>
</table>

*ICI Americas, 1983.
Mechanism of Action

- Interference with normal blood clotting as a result of reduced concentrations of clotting factors II (prothrombin), VII, IX, and X, due to competitive inhibition of the enzyme vitamin K epoxide-reductase. (See the section on Coagulation of Blood and the Function of Vitamin K.)
- There does not appear to be any direct hepatotoxic damage from warfarin. Hypoxia and anemia, however, can lead to hepatic necrosis.

Signs

- Although signs have been observed within 1 day of ingestion, there is usually a lag period of 3 - 5 days between exposure and appearance of clinical signs.
- Onset of death may be acute, without the presence of other clinical signs. This is most common when hemorrhage occurs in the cerebral vasculature, abdominal cavity, pericardial sac, mediastinum, or thorax. Outward signs of hemorrhage may not exist in these instances.
- More often, the animal may be initially only depressed, anorexic, and anemic. Pale mucous membranes, dyspnea (due to hypoxia or pulmonary hemorrhage), hematemesis, epistaxis, and bloody or "tarry" feces are common soon thereafter. The animal may be febrile and display nonlocalized abdominal pain. Scleral, intraocular, conjunctival, nasal, oral, urogenital, and subcutaneous hemorrhage may be noted.
- Staggering or ataxia can be observed with severe blood loss.
- The heart rate may be irregular, and the pulse weak.
- Extensive external hematomata may occur at pressure points or traumatized areas.
- Swollen, tender joints are common, especially in pigs.
- Abortions have been noted in cattle.
- Animals experiencing prolonged toxicosis may be icteric from breakdown of impounded blood.

Lesions

- Generalized hemorrhage, especially in the thoracic or abdominal cavities, mediastinal space, periarticular space, periarticular tissues, subcutaneous tissues, and subdural space. There may also be hemorrhage in the gut.
- The heart is often flaccid and hemorrhagic.
- Centrilobular hepatic necrosis may result from anemia and hypoxia.

Diagnosis

- History is very important. Question the owner.
- Clinical signs may vary, but there should be an indication of hemorrhage or swellings.
- Examine the patient carefully.
- Laboratory evaluation of clotting parameters:
  - An elevated prothrombin time (PT) shows up first (24 - 48 hours postingestion) due to the involvement of factor VII (which has the shortest half-life [6.2 hr] of the K-dependent clotting factors [II, VII, IX, and X]). This is followed soon thereafter by an elevated activated partial thromboplastin time (APTT). Platelet count will generally be in the normal to low-normal range.
  - Consult your local hospital if you need help. Send in a citrated blood sample (bright blue stopper) from a "normal" dog to help with the interpretation.
  - Clotting parameter times are suggestive if prolonged beyond 25% of the normal value.
- Chemical detection of specific anticoagulants in biological fluids, vomitus, or baits.
  - Antemortem or postmortem sample of choice is whole blood (refrigerate).
  - Another postmortem sample of choice is liver. Specimens should be wrapped in foil, well identified, sealed in plastic, and frozen during storage and shipment.

Treatment

- Patient is presented with clinical complications:
  - Correct low PCV and/or hypovolemia and provide clotting factors as needed using transfusion of fresh whole
blood.

- Handle affected animals with care; sedate (promazine contraindicated) if necessary.
  - 10 - 20 ml of fresh, whole blood/kg BW, IV; first 25% of the dose relatively fast, and the rest by slow drip.
  - Vitamin K₁ (phytonadione, phylloquinone) is the most effective form of the various forms of the vitamin. It is similar to the natural form of the vitamin and works rapidly (begins to reverse the situation in about 30 minutes provided the animal is not anemic and/or hypoxic). Oral vitamin K is faster acting and more effective than the parenteral form. It is absorbed from the GI tract and transported directly to the liver via the portal vein. It should be given with food to enhance its absorption. Use the oral form unless contraindicated (e.g., concurrent administration of activated charcoal, GI hemorrhage, severe depression, etc.). When the injectable form is required use the smallest possible needle and carefully wrap the leg to prevent hemorrhage.
    - Dogs: 3 - 5 mg/kg (lower dose in larger animals), SQ or IM. IV administration may cause anaphylaxis; if you use the IV route, be sure the product is approved for this route and administer over 20 minutes with continuous monitoring; dose may be divided into 2 daily doses if preferred.
    - Cats: 15 - 25 mg, total dose, SQ or IM.

- Recommended oral doses of vitamin K for dogs and cats range from 0.25 - 2.5 mg/kg/day for warfarin toxicosis and 2.5 - 5 mg/kg/day for long-acting rodenticide toxicosis.
  - Pigs: 2 - 5 mg/kg (lower dose in larger animals), SQ/IM.
    - Note: Vitamin K₃ (menadione sodium bisulfite), feed-grade, should be added to all swine rations at 20 g/ton of feed as a good preventative management tool because of the common idiopathic, vitamin K-responsive coagulopathy of swine.
  - Horses: Vitamin K₁ at not over 2 mg/kg, SQ/IM; use aseptic techniques for injection.
    - Note: Do not use vitamin K₃ (menadione) in Equidae. Deaths have occurred from use of injectable menadione at manufacturer's recommended dosages. Mechanism of toxicity is unknown, but acute renal failure is observed.
  - Ruminants: Vitamin K₁ at 0.5 - 1.5 mg/kg, SQ/IM, not more than 10 ml/injection site. Vitamin K₃ is reportedly of little or no value.

- Duration of therapy.
  - Warfarin.
    - Daily administration is recommended for 10 - 14 days, depending on the amount ingested and severity of the symptomatology.
  - Bromadiolone.
    - Daily administration for 21 days.
  - Diphacinone, brodifacoum (and others).
    - Suggested daily administration for 30 days.
    - Follow in 5 - 7 days after end of treatment period with a prothrombin time (in severe cases, very young, or debilitated patients, continued vitamin K therapy may sometimes be necessary).
  - Pasture and green forages provide some vitamin K and may lessen the need somewhat for prolonged treatment of anticoagulant-exposed herbivores.

Note: If patient is symptomatic at presentation, it is usually advisable to use a whole blood transfusion and vitamin K₁ injectable, the latter, for the first or 2 days of treatment, or until stable.

- If dyspnea continues, a thoracic radiograph may be indicated. Thoracentesis to remove extravasated blood may be indicated to save the patient's life, but extreme caution must be exercised to prevent further hemorrhage.
  - Oxygen may be beneficial in severely dyspneic animals.
  - Keep patient warm and still until stabilized. Minimal rates of balanced electrolyte solutions may be used if needed for extra fluids and only after sufficient clotting factors (generally whole blood) are on board.
    - Once stable, the patient can be sent home and dosed with oral form of vitamin K₁. Client education is very important to ensure that the medication is continued as directed.
  - Avoid elective surgery.
  - Avoid protein bound drugs as much as possible.
  - Contraindicated drugs during recovery period include corticosteroids, sulfā drugs, antihistamines, phenylbutazone, epinephrine, aspirin, others (see the section "Predisposing Factors").

- Owner take-home instructions:
• No large volumes of fatty foods (table scraps, etc.).
• Restrict exercise for duration of therapy.
• Strict attention to daily medication, even if patient looks and acts normal. Clinical relapses have occurred with premature withdrawal of medication.
• Patient is presented asymptomatic within several hours of a suspected or confirmed exposure:
  • Induce emesis if within 3 hours of ingestion with apomorphine (dog), syrup of ipecac, or xylazine (cat), or 3% H2O2 (either species). Do not induce emesis if patient is depressed or recumbent or if other contraindications are present.
  • Activated or superactivated charcoal.
  • Osmotic cathartic (sorbitol). Alternatively, a saline cathartic may be administered after being mixed with at least 5 times as much water. Administer via stomach tube or orally. Effective for as long as bait is in the gut.
  • Decision to begin vitamin K therapy will depend on the situation, i.e., amount ingested, effectiveness of emesis procedure, time since ingestion. In cases of suspected low dose exposures (i.e., < 1/8 of the LD50), may elect (after emetic and activated charcoal, etc.) to give an injection of vitamin K1, and send patient home with instructions to observe the animal closely for 10 - 30 days, depending upon the compound involved.
    • Vitamin K3 has the disadvantage of not being as effective as vitamin K1. Do not use vitamin K3 alone in symptomatic or highly exposed small animals; use vitamin K1.
  • Adverse effects related to vitamin K1 therapy generally stem from IV administration. Anaphylactoid reactions occur quite often, including cutaneous manifestations such as urticaria. Large doses (10 mg/kg) of vitamin K1 have been associated with Heinz body anemia and hemolysis.

\[
\text{Vitamin K}1
\]

**Prevention**

Client and pest control operator education.

**Differential Diagnosis**

• Poor response to vitamin K1 therapy is helpful in ruling out anticoagulant toxicosis, provided that the animal is not anemic or in liver failure in addition to being poisoned by an anticoagulant.
• Autoimmune thrombocytopenia (AITP):
  • Initial presentation: petechial to ecchymotic hemorrhages on mucous membranes, sclera, skin are characteristic; due to lack of platelets.
  • Platelet numbers will be low (generally below 20,000) unless there is a functional platelet disorder, then numbers may be normal.
  • Otterhound, Foxhound, Basset Hound are predisposed.
• DIC (disseminated intravascular coagulation).
  • Important to identify a primary disease such as neoplasia, pancreatitis, heat stroke, sepsis, chronic active hepatitis, etc. Involves a careful history and physical workup or necropsy.
  • Hematology to confirm: AT III, fibrinogen, plasminogen are decreased.
  • Fibrin degradation products (fibrin split products) are present in blood; kits are available to test in clinics.
• Hereditary diseases (not as common).
  • Von Willebrand's disease.
- Hemorrhage is often less severe than with anticoagulant toxicosis.
- Deficiency of a key component (von Willebrand factor) of the coagulation factor VIII, which is itself functional. The defect affects platelet function.
- Analysis for factor VIII-C and factor VIII-RAg.
- Scottish Terriers and Doberman Pinschers are predisposed.
- Hemophilia A.
  - Factor VIII deficiency.
  - Irish Setter, French Bulldog, Cairn Terrier, Greyhound, Poodles, others.
  - Intrinsic pathway is defective in coagulation . elevated APTT.
- Liver disease.
  - All coagulation factors except factor VII are synthesized in the liver.
  - Severe liver disease usually occurs before coagulation is significantly disrupted. Liver enzymes may indicate damage or, if chronic, may be normal.
  - Portal hypertension may cause a backup and redistribution of platelets to the spleen, resulting in a deficiency in the circulation.
  - Lack of bile secretion into the gut. Required for absorption of fat-soluble vitamin K. Biliary function tests indicate obstruction.

### Idiopathic Coagulopathy in Swine

<table>
<thead>
<tr>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
<th>Full Table for Toxicants that Interfere with the Function of Vitamin K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swine</td>
<td>No etiologic agent known</td>
<td>Days to weeks; often lethal</td>
<td></td>
</tr>
</tbody>
</table>

- A sporadic but notable problem in swine throughout the U.S.
- Affects young, healthy, fast growing pigs under good management conditions.
- Etiology is not known, but appears to involve a variety of factors (nutritional, mycotic, stress, gut flora changes, others?).
- Condition is a primary coagulopathy; liver is not damaged to any great extent.
- Swine coagulation system appears more susceptible to insult than other species of livestock.
- The coagulopathy is vitamin-K responsive (characterized by decreases in factors II, VII, IX, and X).
- Clinical signs: bleeding from mouth, into body cavities, joint areas, and muscles, and deaths.
- Vitamin K₃ in the feed (menadione sodium bisulfate, feed grade) at a dose of 20 grams/ton of feed is effective in preventing and at alleviating the problem. Initially, higher doses suggested such as 100 grams/ton are provided for the first several days.
2. Other Toxicants that Affect Hemostasis

Other Toxicants that Affect Hemostasis

<table>
<thead>
<tr>
<th>Specific Agents</th>
<th>Major Species</th>
<th>Usual Time of Onset</th>
<th>Usual Duration (if survives)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicants that Affect the Liver and Secondarily Cause a Coagulopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aflatoxin and many other hepatotoxic agents</td>
<td>See Mycotoxins that Affect the Liver</td>
<td></td>
<td></td>
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<tr>
<td>Many others</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Toxicants that Harm the Bone Marrow</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bracken fern Pteridium</td>
<td>See Thiaminase-Containing Plants and Other Substances</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trichloroethylene-extracted soybean oil meal</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzene</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lead</td>
<td>See Toxicants with Mixed Effects on the CNS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cadmium</td>
<td>See Toxicants that Affect the Kidneys</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicants that may Cause Severe Shock and Either Disseminated Intravascular Coagulation or Other Coagulopathy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthetic and natural estrogens</td>
<td>-</td>
<td></td>
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</tr>
<tr>
<td>Lindane in human beings</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garbage Toxicoses</td>
<td>See Toxicants that Cause Shock</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pit Vipers</td>
<td>See Toxicants that Cause Shock</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Toxicants that Affect the Liver and Secondarily Cause a Coagulopathy
- Aflatoxin (See Mycotoxins that Affect the Liver)
- Many others

Toxicants that Harm the Bone Marrow
- Brackenfern (*Pteridium*) (See Thiaminase-Containing Plants and Other Substances)
- Trichloroethylene-Extracted Soybean Oil Meal
- Benzene (bone marrow effect)
- Lead (See Toxicants with Mixed Effects on the CNS)
- Lindane (in human beings)
- Chloramphenicol (especially in human beings)

Toxicants that may Cause Severe Shock and Either Disseminated Intravascular Coagulation or Other Coagulopathy
- Garbage Toxicoses (See Toxicants that Cause Shock)
- Pit Vipers (See Toxicants that Cause Shock)

References

Damaged or Moldy Sweet Clover Hay

Anticoagulant Rodenticides

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