Practitioner report involving intravenous use of vitamin K₁ prompts label review and revision

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Vitamin K₁, or phytonadione, is used in veterinary medicine for the treatment of anticoagulant rodenticide toxicity, coagulopathies associated with hepatic disease, and hypoprothrombinemia caused by moldy clover poisoning. When vitamin K₁ is administered by injection, the IV route should be avoided because of the risk of life-threatening hypersensitivity-like reactions. Unfortunately, labels for vitamin K₁ products marketed for veterinary use have included dosing recommendations for IV administration, prompting some veterinarians to administer the product in a potentially unsafe manner. Vitamin K₁ is not approved for use in animals (ie, not an approved animal drug); therefore, the FDA's Center for Veterinary Medicine (CVM) has not had an opportunity to review data associated with the risks related to the various routes of administration. A report involving IV administration of vitamin K₁, which was submitted to the United States Pharmacopeia (USP) Veterinary Practitioners' Reporting (VPR) Program, stimulated the FDA/CVM to review vitamin K₁ product labeling. This review resulted in label and package insert revision for all injectable vitamin K₁ products marketed for veterinary use.

Vitamin K₁ in the Treatment of Anticoagulant Rodenticide Toxicosis

Animal ingestion of anticoagulant rodenticides such as warfarin, a first-generation rodenticide, and brodifacoum, a second-generation rodenticide, can inhibit the recycling of vitamin K₁, which can reduce the activity of circulating clotting factors II, VII, IX, and X. The resultant coagulopathy usually requires administration of vitamin K₁ to restore activity of these clotting factors. The greatest bioavailability for vitamin K₁ is achieved following oral administration, particularly when given with a fatty meal. Consequently, some sources, including the American Society for the Prevention of Cruelty in Animals (ASPCA) National Animal Poison Control Center, consider the oral route the preferred route for vitamin K₁ administration in all nonvomiting patients. Other sources in the veterinary literature recommend initial parenteral administration of vitamin K₁ immediately followed by oral administration of vitamin K₁. When vitamin K₁ is administered parenterally, the preferred route is subcutaneous, although the intramuscular route can also be used. Intramuscular injection is considered less desirable because of the potential for hematoma formation. Intravenous administration is not recommended because it offers no clinical advantage and introduces the risk of an anaphylactic reaction.

Vitamin K₁’s therapeutic effect on hemostasis is never immediate. A positive effect on the activation of clotting factors generally does not occur until 3 to 12 hours following parenteral administration of vitamin K₁, regardless of whether it is administered intramuscularly, subcutaneously, or IV. The delay in recognizable therapeutic effect relates to vitamin K₁’s mechanism of action, which involves promoting endogenous hepatic biosynthesis of vitamin K-dependent clotting factors. Consequently, immediate treatment of an acutely hemorrhaging animal generally requires the administration of whole blood, fresh plasma, or fresh frozen plasma in addition to vitamin K₁. In this way, active vitamin K-dependent clotting factors will be immediately made available to promote hemostasis while the liver resumes endogenous production.

Hypersensitivity-like Reactions

The human medical literature warns against IV administration of vitamin K₁ in people because of the risk of adverse events resembling hypersensitivity or anaphylactic reactions, which involve cardiac or respiratory arrest. Some patients develop these severe reactions when receiving the drug for the first time. It has been suggested that the polyoxylated fatty acid derivative used as an inactive carrier in vitamin K₁ products may be involved in these reactions. The labeling of FDA-approved human vitamin K₁ products contains a prominent warning that severe reactions, including fatalities, have occurred during and immediately following the IV administration of vitamin K₁.
even when precautions were taken to dilute the drug and avoid rapid infusion.\textsuperscript{11} Product labeling, therefore, warns that IV administration should be restricted to those situations where other routes are not feasible and the risk is considered justified.

**USP VPR Program Report**

In 1998, a veterinarian provided emergency care to 2 dogs suffering from warfarin toxicity. Because signs of acute hemorrhage were evident in both dogs, the veterinarian immediately administered definitive treatment with vitamin K\textsubscript{1}.\textsuperscript{12} Despite the fact that the only vitamin K\textsubscript{1} product available to the veterinarian had expired 5 years earlier. The product label listed an IV dose of 0.5 to 2.0 mg/kg (0.22 to 0.9 mg/lb) of body weight, to be administered slowly. Within minutes of slow IV administration of 2.0 mg/kg vitamin K\textsubscript{1}, both dogs collapsed in what clinically appeared to be anaphylactic shock. Despite resuscitation attempts, both dogs died. Subsequent analysis by the manufacturer of the expired vitamin K\textsubscript{1} revealed that the active ingredient phytonadione was at 50\% of the label concentration. Neither endotoxins nor bacteria were detected.

The exact cause of these fatalities cannot be definitively identified. Two unrelated dogs' similar reaction to the same bottle of expired vitamin K\textsubscript{1} does raise the possibility that unidentified components may have contributed to or even been completely responsible for the negative outcome. Necropsy findings may have been helpful in determining the cause of the deaths. However, the report did alert the FDA to the inadequacy of information on vitamin K\textsubscript{1} animal drug labels. The need for regulatory review of label information became clear, and the FDA/CVM initiated action.

**FDA Review**

As stated, injectable vitamin K\textsubscript{1} is not approved by the FDA/CVM for use in animals. The marketing of these drugs is an illegal activity; however, in certain defined instances, the FDA/CVM may not object to product marketing based on a consideration of regulatory priorities within the CVM and of low level safety concerns. In consideration of limited resources, FDA/CVM regulatory actions may be directed more toward drugs that have a greater potential for adversely affecting animal and public health. Certain animal drugs, such as vitamin K\textsubscript{1} and large volume parenterals, have an established use as a component of overall veterinary therapeutics. Although pharmaceutical companies are required to inform the FDA/CVM of reported adverse events associated with FDA-approved drugs, this requirement does not include drugs approved for use in humans but not in animals, such as vitamin K\textsubscript{1}. Thus, CVM efforts to monitor the safety and efficacy of unapproved products are hindered. In fact, no reports involving vitamin K\textsubscript{1} were in the FDA/CVM Adverse Drug Event (ADE) Reporting System. The USP VPR Program report identified a concern with the adequacy of vitamin K\textsubscript{1} animal product labeling and presented an opportunity for the CVM to follow-up with a comprehensive review. As part of a cooperative effort with FDA/CVM, the USP promptly forwards to the agency all adverse event reports involving the use of drugs or devices in animals.

Nine injectable vitamin K\textsubscript{1} products are listed in the 1999 edition of *Compendium of Veterinary Products*; however, not all of these products are available at the present time.\textsuperscript{3} At the time of FDA/CVM review, the labels for all 9 products listed IV administration as an indicated route in the treatment of hypoprothrombinemia with hemorrhage. Package inserts for 6 of the products were available for review. Only 5 of the inserts warned that anaphylaxis is a possible consequence of IV use;\textsuperscript{4} and only 4 provided directions to dilute the product prior to IV administration.\textsuperscript{4-7} In short, there was considerable variation among products regarding information provided by product labeling.

All relevant information was analyzed, assessed, and summarized by the FDA/CVM pharmacovigilance group. This summary was in turn reviewed by the FDA/CVM Monitored Adverse Reaction Committee (MARC). The MARC consists of members from all areas of the CVM who are involved in drug approval and postmarketing efforts. The unique expertise of each MARC member contributes to the formation of final recommendations concerning the drug under review. Subsequent to MARC recommendations, revised vitamin K\textsubscript{1} labeling for animals was drafted, the content and format of which was based largely on the labeling for vitamin K\textsubscript{1} products approved by the FDA for use in humans. As recommended by the FDA Veterinary Medicine Advisory Committee (VMAC) in 1991 during its consideration of the issue of antidote availability, additional suggestions were requested from diplomates of the American Board of Veterinary Toxicology. In general, they supported the content and intent of the labeling.

**Label Changes**

The FDA/CVM label revisions are based primarily on the unnecessary risk associated with the IV injection of vitamin K\textsubscript{1}. The revised labeling (Appendices 1 and 2) reflects expert opinion that subcutaneous and intramuscular injections are the preferred route of parenteral vitamin K\textsubscript{1} administration, whereas IV administration is to be avoided whenever possible. In the event that the IV route is used, directions are provided regarding proper product dilution and slow administration. Proper warnings regarding the risk of hypersensitivity-like reactions following IV administration are provided. A statement regarding the potential for hematoma formation following intramuscular administration is also included. Finally, the revised labeling provides more in-depth product information in a standardized format for use by veterinary practitioners. Revised labeling instructions were mailed to all firms known to market vitamin K\textsubscript{1} injectable products for use in animals.

The FDA/CVM approval process for animal drugs provides the best means of establishing appropriate dosage recommendations. Because vitamin K\textsubscript{1} is not approved for use in animals, exact dosing recommendations based on efficacy studies cannot be made. Consequently, the updated label revisions retain the wide dosage ranges that were previously provided on the animal vitamin K\textsubscript{1} products. Only a review of spe-
specific vitamin K₁ study data would support an FDA approval and allow for more specific dosing information.

**Conclusion**

Although the FDA/CVM ADE reporting system works well in monitoring the continued safety and efficacy of FDA-approved animal drugs, the system is not adequate in monitoring the use of drugs not approved for use in animals or the permitted extralabel use of human drugs in animals. The USP VPR Program provides a valuable portal for reporting adverse events for these latter products. In this case, a USP VPR Program report alerted the FDA/CVM that potentially dangerous recommendations for IV administration were on the label of injectable vitamin K₁ products marketed for veterinary use. The reported observations of 1 veterinarian identified a potential concern with labeling, which following FDA/CVM review and action based on the VMAC’s recommendations concerning antidotes, resulted in improved product labeling for injectable vitamin K₁ products designed for use in animals. This article demonstrates the impact veterinarians can make by reporting clinical observations through appropriate avenues.

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References


Appendix 1

Revised product label

**FOR ANIMAL USE ONLY**

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian

Each ml contains: Phytonadione 10 mg; Polyoxyethylated fatty acid derivative 70 mg; Dextrose 37.5 mg; Water for injection q.s. with Benzyl Alcohol 0.9% added as a preservative.

Dosage and Administration:

- Cattle, Calves, Horses, Swine, Sheep, and Goats: Acute hypoprothrombinemia (with hemorrhage) and Non-acute hypoprothrombinemia - 0.5-2.5 mg/kg subcutaneously OR intramuscularly.
- Dogs and Cats: Acute hypoprothrombinemia (with hemorrhage) and Non-acute hypoprothrombinemia - 0.25-5 mg/kg subcutaneously OR intramuscularly. Use higher end of dose for second generation rodenticides.

In cases with hemorrhage, the use of whole blood or component therapy is indicated.

Multiple Dose Vial

For complete Warnings, Cautions, Adverse Reactions, Diluents, and additional information please read accompanying insert.

Protect from light-store in a dark place.

Store at controlled room temperature between 15 and 30 C (59–86 F)

Lot No Exp Date

Manufacturers and/or distributors name and address

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Appendix 2
Revised Package Insert

For Animal Use Only

Caution: Federal law restricts this drug to use by or on the order of a licensed veterinarian

DESCRIPTION:
Phytonadione is a vitamin, which is a clear, yellow to amber, viscous, odorless or nearly odorless liquid. It is insoluble in water, soluble in chloroform and slightly soluble in ethanol. It has a molecular weight of 450.70. Phytonadione is 2-methyl-3-phytyl-1,4-naphthoquinone. Its empirical formula is C3H14H6O2.

(Product name) is a yellow, sterile, aqueous colloidal solution of vitamin K1, with a pH of 5.0 to 7.0, available for injection by the intravenous, intramuscular, and subcutaneous routes. Each milliliter contains:

Phytonadione................ 10 mg
Inactive ingredients:
Polyoxyethylated fatty acid derivative.............. 70 mg
Dextrose......................... 375 mg
Water for Injection, q.s....... 1 mL
Added as preservative:
Benzy alcohol........... 0.9%

CLINICAL PHARMACOLOGY:
(Product name) aqueous colloidal solution of vitamin K1 for parenteral injection, possesses the same type and degree of activity as does naturally-occurring vitamin K, which is necessary for the production via the liver of active prothrombin (factor II), proconvertin (factor VII), plasma thromboplastin component (factor IX), and Stuart factor (factor X). The prothrombin test is sensitive to the levels of these three of these four factors—II, VII, and X. Vitamin K is an essential cofactor for a microsomal enzyme that catalyzes the post-translational carboxylation of multiple, specific, peptide-bound glutamic acid residues in inactive hepatic precursors of factors II, VII, IX, and X. The resulting gamma-carboxyglutamic acid residues convert the precursors into active coagulation factors that are subsequently secreted by liver cells into the blood. Phytonadione is readily absorbed following intramuscular administration. After absorption, phytonadione is initially concentrated in the liver, but the concentration declines rapidly. Very little vitamin K accumulates in tissues. Little is known about the metabolic fate of vitamin K. Almost no free unmetabolized vitamin K appears in bile or urine. In normal animals, phytonadione is virtually devoid of pharmacodynamic activity. However, in animals deficient in vitamin K, the pharmacological action of vitamin K is related to its normal physiological function, that is, to promote the hepatic biosynthesis of vitamin K dependent clotting factors. The action of the aqueous colloidal solution, when administered intravenously, is generally detectable within an hour or two and hemorrhage is usually controlled within 2 to 6 hours. A normal prothrombin level may often be obtained in 12 to 14 hours.

INDICATIONS:
(Product name) is indicated in coagulation disorders which are due to faulty formation of factors II, VII, IX and X when caused by vitamin K deficiency or interference with vitamin K activity.
(Product name) is indicated in cattle, calves, horses, swine, sheep, goats, dogs, and cats to counter hypoprothrombinaemia induced by ingestion of anticoagulant rodenticides.
(Product name) is also indicated to counter hypoprothrombinaemia caused by consumption ofbishydroxycoumarin found in spoiled and moldy sweet clover.

DOSAGE AND ADMINISTRATION:

Cattle, Calves, Horses, Swine, Sheep, and Goats: Acute hypoprothrombinemia (with hemorrhage) and Non-acute hypoprothrombinemia - 0.25-5 mg/kg subcutaneously or intramuscularly.

Dogs and Cats: Acute hypoprothrombinemia (with hemorrhage) and Non-acute hypoprothrombinemia - 0.25-5 mg/kg subcutaneously or intramuscularly. Use higher end of dose for second generation rodenticides.

Whenever possible, [Product name] should be given by the subcutaneous or intramuscular route. When intravenous administration is considered unavoidable, the drug should be diluted and injected very slowly, not exceeding 1 mg per minute.

Directions For Dilution:
(Product name) may be diluted with 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or 5% Dextrose and Sodium Chloride Injection. Other Diluents Should Not Be Used. When dilutions are indicated, administration should be started immediately after mixture with the diluent, and unused portions of the dilution should be discarded.

Whole blood or component therapy may be indicated if bleeding is excessive. This therapy, however, does not correct the underlying disorder and [Product name] should be given concurrently. In the event of shock or excessive blood loss, the use of whole blood or component therapy is indicated.

CONTRAINDICATIONS:
Hypersensitivity to any component of this medication.

PRECAUTIONS:

Drug Interactions:
Temporary resistance to prothrombin-depressing anticoagulants may result, especially when larger doses of phytonadione are used. If relatively large doses have been employed, it may be necessary when reinstituting anticoagulant therapy to use somewhat larger doses of the prothrombin-depressing anticoagulant, or to use one which acts on a different principle, such as heparin sodium.

Laboratory Tests:
Prothrombin time should be checked regularly as clinical conditions indicate.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

CAUTIONS:
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

WARNINGS:
WARNING—INTRAVENOUS USE: Severe reactions, including fatalities, have occurred during and immediately after INTRAVENOUS injection of phytonadione, even when precautions have been taken to dilute the phytonadione and to avoid rapid infusion. Typically these severe reactions have resembled hypersensitivity or anaphylaxis, including shock and cardiac and/or respiratory arrest. Some patients have exhibited these severe reactions on receiving phytonadione for the first time. Therefore the INTRAVENOUS route should be restricted to those situations where other routes are not feasible and the serious risk involved is considered justified.

An immediate coagulant effect should not be expected after administration of phytonadione. It takes a minimum of 1 to 2 hours for measurable improvement in the prothrombin time. While blood or component therapy may also be necessary if bleeding is severe. Phytonadione will not counteract the anticoagulant action of heparin.

When vitamin K1 is used to correct excessive anticoagulant-induced hypoprothrombinemia, anticoagulant therapy still being indicated, the patient is again faced with the clotting hazards existing prior to starting the anticoagulant therapy. Phytonadione is not a clotting agent, but may also be necessary if bleeding is severe. Phytonadione will not counteract the anticoagulant action of heparin.

Whole blood or component therapy may be indicated if bleeding is excessive. This therapy, however, does not correct the underlying disorder and [Product name] should be given concurrently. In the event of shock or excessive blood loss, the use of whole blood or component therapy is indicated.

Repeated large doses of vitamin K are not warranted in liver disease if the response to initial use of the vitamin is unsatisfactory. Failure to respond to vitamin K may indicate that the condition being treated is inherently unresponsive to vitamin K.

ADVERSE REACTIONS:
Deaths have occurred after intravenous administration (SEE BOX WARNING ABOVE).

Pain, swelling, and tenderness at the injection site may occur. Intramuscular injection may result in hematomas. The possibility of allergic sensitivity, including an anaphylactoid reaction, should be kept in mind.

STORAGE:
Protect from light at all times. Store in a dark place.
Store at controlled room temperature 15/30°C (59/86°F).