FARAD Digest

Antidotes in food animal practice

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Because of restrictions on compounding and a limited number of approved veterinary products, there are few antidotes available for treatment of food animals with toxicoses.[1] Because there is little economic incentive for pharmaceutical companies to pursue antidote approval for a limited market, it is unlikely that this situation will change in the near future. In most instances, practitioners seeking to treat food animals for toxicoses are compelled to either use products in an extralabel manner or to compound antidotes from bulk sources. There are relatively few data from which scientifically based **withdrawal intervals (WDIs)** may be developed for the protection of human health. This **Food Animal Residue Avoidance Databank (FARAD)** Digest provides a summary of regulatory and scientific information regarding the most commonly recommended antidotes used in food animals. None of the drugs covered in this digest have been approved by the **FDA Center for Veterinary Medicine (FDA/CVM)** as New Animal Drugs.

The information on residues presented in this digest is for the antidotes, not for the toxicants. When an antidote must be used to treat a food animal for a toxicosis, a WDI to ensure depletion of the toxicant is also required, and it may be longer than the WDI for the antidote. FARAD can provide WDI recommendations for a wide range of toxicants; however, these recommendations must be made on a case-by-case basis because of differences in exposure route, dose, and duration.

Unapproved Veterinary Antidotes Marketed with Veterinary Labels

The FDA/CVM has applied regulatory discretion and does not prohibit the commercial manufacture and marketing of several veterinary antidotes. These products do not have **New Animal Drug Approval (NADA)** numbers and have not been formally approved by the FDA/CVM. These products are manufactured under Good Manufacturing Practices, and their labels are reviewed and on file with the FDA/CVM. They may be used as antidotes in food animals, although higher dosages or more prolonged treatment than that indicated on the labels may be necessary. Animal Medicinal Drug Use Clarification Act requirements do not apply to these drugs because they are not approved drugs; however, veterinarians are strongly encouraged to follow AMDUCA requirements when using these drugs.[2] Veterinarians who must use these drugs as antidotes in any food animal species not covered herein should call FARAD for WDI recommendations.

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Atropine sulfate—Large animal atropine formulations containing 15 mg of atropine/mL are marketed for treatment for organophosphate toxicosis in cattle, sheep, and horses. Human atropine formulations are also approved and marketed. Published recommendations for treatment for cholinesterase inhibitor toxicosis range from 0.1 to 0.5 mg/kg (0.045 to 0.23 mg/lb) and are consistent with product label recommendations that indicate that approximately one fourth of the dose should be given IV with the remainder given IM or SC. Treatment may be adjusted and repeated as necessary every 4 to 6 hours. Practitioners are cautioned that these dosages far exceed those recommended for atropine as an adjunct to surgery. Exceeding the recommended dosage for treatment should be avoided because of the potential for atropine toxicosis. In the United Kingdom, atropine is approved for single-dose use in cattle, sheep, and pigs SC, IM, or IV, with a 3-day milk and 14-day meat **withdrawal time (WDT)**. When atropine is used as an antidote at multiple doses up to 0.2 mg/kg (0.09 mg/lb), a 6-day milk and 28-day meat WDI is recommended. Tissue residue depletion studies in food animals are not available, although results of kinetic studies in pigs and sheep indicate a short terminal elimination half-life of 1 to 3 hours. Results of radiolabeling studies in mice confirm that there is no appreciable long-term incorporation of atropine or its metabolites into body tissues, suggesting that the United Kingdom's 6-day milk and 28-day slaughter WDTs are appropriately conservative. Practitioners are reminded, however, that depletion of organophosphate residues must be considered when making withdrawal recommendations.

Epinephrine—In the body, epinephrine is a naturally occurring compound and when administered it is rapidly inactivated by metabolism after injection.

There are a variety of veterinary epinephrine products marketed for use in horses and food animals including cattle, sheep, and swine. Because of the rapid inactivation of epinephrine, FARAD recommends a zero-day meat and milk WDI. Epinephrine formulations are approved and marketed for use in humans.

Vitamin K_1—Phytonadione or vitamin K_1 is a naphthoquinone-derived compound also known as phylloquinone and phytomenadione. Its use in food animal practice includes treatment for sweet clover toxicosis, sulfaquinoxaline toxicosis, and anticoagulant rodenticide toxicosis. Exogenous vitamin K_1 enters milk freely and, as a lipid soluble vitamin, is stored in the liver. There are several vitamin K products marketed for use in cattle, swine, sheep, and goats that when administered at 0.5 to 2.5 mg/kg (0.23 to 1.14 mg/lb) IV, IM, or SC do not require a meat or milk WDI. Vitamin K_1 formulations are also approved and marketed for use in humans.

Antidotes Labeled for Humans Only

There are additional drugs for which approved human products exist and that could be used in an extralabel manner.

Pralidoxime chloride—Several oximes have been studied as adjuncts to atropine for treatment for organophosphate toxicosis in humans and other animals. Such compounds reactivate acetylcholinesterase by promoting dephosphorylation of the affected enzyme. The most frequently recommended agent is the water-soluble chloride salt of the quaternary ammonium drug **pralidoxime (2-PAM)**. After administration in pigs, sheep, and cattle, 2-PAM is rapidly absorbed and excreted with a terminal elimination half-life of only approximately 2 to 4 hours. Results of studies in calves suggest that IM administration of approximately 30 mg/kg (13.6 mg/lb) given every 8 hours is necessary to maintain therapeutic blood concentrations.[3,4] Tissue depletion data in animals are scarce, but results of radio-labeling studies in rats indicate that most of the drug is excreted within 24 hours. In treatment of organophosphate poisoning, 2-PAM will almost invariably be used as an adjunct to atropine administration. The 6-day milk and a 28-day slaughter WDIs recommended for atropine are appropriately conservative, as they are for 2-PAM, as well. 2-PAM is contraindicated for treatment of carbamate toxicosis. The only approved veterinary formulation of 2-PAM in the United States (NADA-039-204, Protopam) is no longer marketed by the manufacturer. Two formulations are approved and marketed for human use.

Dimercaprol—Dimercaprol (also known as British anti-lewisite or BAL) is a dithiol-chelating agent formulated in oil for deep IM injection only. It readily complexes with heavy metals and is indicated for use in arsenic, lead, and mercury toxicosis. Two water-soluble and orally active compounds derived from dimercaprol, meso-2,3-dimercaptosuccinic acid and **2,3-dimercaptopropane-1-sulfonic acid (DMPS)**, are more commonly used for treating humans with heavy metal intoxication.[5] Meso-2,3-dimercaptosuccinic acid and DMPS are not available in approved formulations and must be compounded from bulk drug. Meso-2,3-dimercaptosuccinic acid and DMPS have short half-lives in serum (< 4 hours)[5,6] and are 95% eliminated within 24 hours in rabbits, dogs, and humans. Dimercaprol requires frequent dosing (every 4 hours) in humans to maintain effective plasma concentrations. Dimercaprol may be concentrated in the liver and kidney at concentrations up to 5 times that in blood; however, no tissue residue depletion studies have been performed. No data on the elimination of these drugs in milk are available. For use in food animals, FARAD recommends a minimum preslaughter WDI and milk WDI of 5 days on the basis of the short half-lives in the 3 species studied.

Compounding Antidotes from Bulk Drug

There are a number of chemicals commonly recommended as food animal antidotes for which neither human nor veterinary products exist or for which FDA-approved human or companion animal formulations are impractical or infeasible (eg, EDTA, methylene blue, sodium nitrate, and molybdenum salts). Practitioners seeking to use these drugs must compound these antidotes from bulk product. Although AMDUCA permits compounding of animal medications from approved animal or human products under certain provisions, it does not allow for compounding of animal medications from a bulk drug substance. Compounding animal medications from bulk drugs is illegal under FDA law and regulations. However, the FDA does recognize the need for compounding in certain situations and will exercise regulatory discretion when appropriate. The FDA policy concerning the compounding of animal drugs is described in a recently updated section of the FDA **Compliance Policy Guide (CPG)** Manual.[7] Importantly, the CPG affirms that neither veterinarians nor pharmacists may legally compound finished animal drugs from bulk products. Compounding antidotes from bulk substances remains illegal; however, the FDA/CVM recognizes that circumstances arise in which emergency treatment necessitates compounding of antidotes that would not be available otherwise. The updated CPG outlines those factors the FDA will consider in determining whether regulatory action would be considered. Those factors include the following:

- The health of the animals was threatened, and suffering or death would have resulted from failure to treat.
- The compounding was performed under the confines of a valid veterinarian-client-patient relationship.
- Whether meat or milk residues were caused by the use of the compounded drug.
- There was no approved animal or human product that could have been effectively used in a label or extralabel manner to treat the condition.

In addition, the antidotes should be compounded in conformance with applicable state law pharmacy regulations. The veterinarian and not the pharmacist should prescribe an extended WDI on the basis of suf-

ficient information that is adequate to prevent illegal residues. Last, the labeling of the compounded drugs should contain adequate information, such as WDIs for drugs for food-producing animals or other categories of information as is described in the AMDUCA regulations. In recognition of the urgent need for certain antidotes in emergency situations, Appendix A of the CPG lists 9 chemical antidotes against which FDA/CVM would presently not ordinarily object. The 9 antidotes include ammonium molybdate, ammonium tetrathiomolybdate, ferric ferrocyanide, methylene blue, picrotoxin, pilocarpine, sodium nitrite, sodium thiosulfate, and tannic acid. However, the list of drugs in Appendix A should not be construed as the only drugs for which the FDA would extend regulatory discretion for compounding. Inquiries by veterinarians and pharmacists about compounding from other bulk drugs should be directed to the FDA/CVM, Division of Compliance, 301-827-1168.[a]

Activated charcoal—Activated charcoal is administered orally as an adsorbent to prevent absorption and enhance the excretion of a wide variety of toxicants. It is not soluble, and the particles are not absorbed through the intestinal mucosa. It is used as an adjunct treatment and is often combined with kaolin, another adsorptive agent. It may be used for treatment of pesticide and metal intoxications and mycotoxicoses. There are no residue concerns with activated charcoal, and FARAD recommends zero-day meat and milk WDIs. There are numerous formulations of activated charcoal approved by the United States Pharmacopeia and marketed in the United States, and the bulk drug is also available from a number of chemical supply distributors.

Copper glycinate, copper sulfate, and copper disodium edetate—Copper glycinate, copper disodium edetate, and copper sulfate are used to treat animals with molybdenum toxicosis. Copper sulfate is usually added to the ration, whereas copper glycinate and copper disodium edetate are injected parenterally (excluding sheep because of this species' sensitivity to the toxic effects of copper). A copper disodium edetate formulation that had been approved for use in cattle was withdrawn by the FDA because of target animal safety concerns. Cupric gylcinate formulations are approved for use in nonlactating cattle with a meat WDI of 30 days; however, no approved formulations are presently marketed. Limited published data indicate that copper glycinate is slowly absorbed after SC injection.[8] FARAD recommends use of a 30-day slaughter WDI if cupric glycinate is administered SC in cattle.

EDTA—Edetate calcium disodium (also known as calcium disodium ethylenediaminetetra-acetate and as edetate) is a water-soluble, heavy-metal-chelating agent.[9] Ethylenediaminetetraacetic acid readily chelates divalent cations such as lead, zinc, cadmium, copper, iron, and manganese. Several research publications indicate that EDTA has a short half-life (< 1 hour) in humans and rats and is eliminated by glomerular filtration. It can be administered IV, IM, or SC but is not effective when administered orally because it is not absorbed. Ethylenediaminetetraacetic acid is approved for use in humans. No data are available on the elimination of EDTA in milk. Because of the very rapid elimination of EDTA[10] and its limited distribution within the body (it is confined to the extracellular fluid space),[11] FARAD recommends a 2-day meat and milk WDI after use in all food animals.

Methylene blue—Methylene blue is used in the treatment of methemoglobinemia attributable to chlorate and nitrate toxicosis and as an adjunctive treatment for cyanide toxicosis. Results of long-term feeding studies indicate it may be carcinogenic.[1] There are presently no human or veterinary formulations available for use in the United States. FARAD has reviewed a confidential report with data indicating the elimination of radioactive methylene blue in milk, pharmacokinetic blood data, and a single time-point tissue residue determination in 1 cow. Additionally, several studies[12–17] in food animals have provided serum pharmacokinetic data, and 1[18] provided milk data analyzed by use of a colorimetric method. On the basis of these data, FARAD recommends a minimum milk WDI of 4 days after the last treatment (the longest terminal half-lives in cow serum and milk are 21 and 23 hours, respectively, and radioactive residues in milk are at background concentrations by 72 hours). Because of concerns about carcinogenicity, an extremely conservative WDI for meat of 180 days has been recommended.[1] However, the nonlipophilic nature of the drug and the limited tissue residue data available suggest that a much shorter WDI of 14 days would be sufficient. By use of the longest measured serum half-life (23 hours) and 10 half-lives for virtually complete elimination from blood, and assuming no binding in edible tissues, a 14-day WDI would provide virtually complete elimination.

Molybdate salts—Ammonium molybdate and ammonium tetrathiomolybdate are useful in the treatment for copper toxicosis via oral and parenteral administration, respectively. Neither chemical is approved for use in any species. No published data are available on molybdenum excretion in milk after use of either chemical; however, 1 study[19] evaluated the kinetics of molybdenum in sheep after IV dosing with tetrathiomolybdate. A serum half-life of 24 hours was found after an IV dose of 1.7 mg/kg (0.77 mg/lb). A human study of the transfer of molybdenum in food into human milk found a transfer factor (the food concentration divided by the milk concentration of molybdenum) of 77, indicating that substantial transfer of molybdenum into milk can occur.[20] On the basis of these data, if either of these chemicals were to be used in a food animal, FARAD recommends a minimum 10-day preslaughter WDI and a minimum 5-day milk-withholding interval.

Penicillamine—d-Penicillamine (3-mercaptovaline) may be useful in treatment for heavy metal toxicoses caused by lead and mercury. It is rapidly absorbed orally and is water soluble. Excretion occurs primarily in the urine and feces. Although penicillamine is a breakdown product of penicillin and peni-

cillin-sensitive individuals may react positively to ID challenge with penicillamine, the risk of severe reaction to orally administered penicillamine in penicillin-sensitive individuals is likely quite low.[21] Published studies on the pharmacokinetics or tissue residues of penicillamine are not available for any food animal species; however, extensive human, rat, and dog data are available. These data indicate limited distribution of penicillamine into edible tissues (tissue blood ratio < 1.0 at all time points measured) and terminal elimination half-lives of 4 to 8 hours for the parent compound. For one of the metabolites that is a disulfide albumin conjugate, a half-life of > 120 hours was found in 1 study in rats. On the basis of these data, FARAD recommends a minimum 21-day preslaughter WDI if penicillamine is used in food animals. No data are available on the elimination of penicillamine in milk; however, in human medicine, breast-feeding is not recommended for women taking penicillamine daily for treatment of rheumatoid arthritis. On the basis of the rapid serum half-life, FARAD recommends a minimum 3-day milk WDI if penicillamine is used in lactating animals.

Sodium nitrite, sodium thiosulfate, and sodium sulfate (inorganic salts)—Sodium nitrite and sodium thiosulfate may be used IV in treatment for cyanide toxicosis, and sodium sulfate may be used orally as a saline cathartic to hasten fecal excretion of toxicants. These salts are rapidly excreted and are not considered residue concerns in animal tissues; therefore, a 24-hour preslaughter WDI would be sufficient. Nitrite (and nitrate metabolite) excretion in milk could represent a food safety concern, particularly for human neonates. Results of numerous studies of dietary and water-related intake of nitrate and nitrate excretion in milk have been published; however, results of studies of nitrite or nitrate excretion in milk after IV administration of nitrite have not been published. On the basis of sheep data indicating half-lives of 0.5 and 4.2 hours for nitrite and nitrate ions, respectively, after IV administration of sodium nitrite,[22] a 48-hour milk WDI is recommended after IV administration of nitrite in lactating ruminants.

Conclusion

For many of the antidotes listed in this digest, limited information is available concerning tissue residues; however, WDI recommendations can be made for most antidotes on the basis of pharmacokinetic principles. For some of the chelating agents, it is well known that they affect the disposition of the toxicant itself (eg, metals such as lead and cadmium), which also makes determination of a WDI difficult regarding the toxicant. For metal intoxications, the WDI for the metal toxicant will almost always be longer than the WDI for the antidote. Because of the complexity of these interactions, practitioners are advised to contact FARAD for case-specific advice because general withdrawal recommendations for most toxicants cannot be made. A complete list of references for this FARAD Digest is available at the FARAD Web site: www.farad.org.

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