

## **Veterinary Antidotes and Availability: An Update**

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### **Introduction**

Animal toxicoses are a frequent presenting complaint in veterinary emergency clinics and general practice. Acute poisonings represent a diagnostic and therapeutic challenge for veterinary practitioners, whether single or multiple animals are involved. The key to success in treating patients with toxicoses is early detection and treatment. Prognosis varies considerably, depending on the toxin involved, the amount of exposure, and the length of time that has elapsed between the exposure and presentation to the practitioner. The general approach to the poisoned animal includes stabilization of vital signs and institution of supportive care measures, obtaining a detailed clinical history and samples of the suspected toxic substance or source (eg., feed samples, plants) if possible, decontamination to prevent further absorption of the toxicant, enhancing elimination of absorbed toxicants, and administering a specific antidote if one exists and is available. The National Animal Poison Control Center (888-426-4435) can provide callers with species specific information regarding treatment of various poisonings and can be a valuable resource for veterinarians.

An antidote is a substance which can counteract the activity or effect of a poison. Antidotes may be classified according to their mechanism of action: chemical or pharmacologic. Chemical antidotes interact specifically with a toxicant, or neutralize the toxicant. For example, metal chelators combine with metals to form complexes that can then be eliminated by the kidneys. Pharmacologic antidotes may neutralize or antagonize the

effects of a toxicant. This type of antidote may act by preventing the formation of toxic metabolites (eg., 4-methylpyrazole for ethylene glycol toxicity), by competing with the toxicant's action at a receptor site (eg., naloxone for opioid toxicity), by facilitation of more rapid or complete elimination of a toxicant (eg., molybdenum for copper toxicity), by blocking receptors responsible for the toxic effect (eg., atropine for organophosphate toxicity), or by aiding in the restoration of normal function (eg., N-acetylcysteine for acetaminophen toxicity).<sup>1</sup> In addition, specific antidotes may act directly on the toxin (eg., antitoxins).

### **Availability of Antidotes**

The ready availability of antidotal agents has long been problematic for most veterinarians. Only a small number of antidotes have been approved by the Food and Drug Administration (FDA) for use in animals:

Antizol-Vet® (fomepizole): indicated as an antidote for ethylene glycol (antifreeze) poisoning in dogs that have ingested or are suspected of having ingested ethylene glycol.

Narcan (naloxone): indicated as a narcotic antagonist in dogs.

Yobine® (yohimbine): indicated to reverse the effects of xylazine in dogs.

Tolazine™ (tolazoline hydrochloride): indicated to reverse the effects of xylazine in horses.

Antisedan® (atipamezole hydrochloride): indicated to reverse the effects of medetomidine in dogs.

Also, atropine and epinephrine are approved for use in cattle, goats, sheep, pigs, cats and dogs, as outlined in the Code of Federal Regulations (CFR) Title 21, §500.55: **“Exemption**

**from certain drug-labeling requirements.”** Under this regulation, it is recognized that for certain drugs for which directions, hazards, warnings, and use information are commonly known to licensed veterinary practitioners, such information may be omitted from the dispensing package. Certain conditions of dosage form are prescribed in this regulation: Atropine sulfate as an injectable should not be in excess of 15 mg per dosage unit for cattle, goats, sheep, horses and pigs; and not in excess of 0.6 mg per dosage unit for dogs and cats. Epinephrine injection should be at the concentration of 1:1000 for cats, dogs, cattle, goats, horses, pigs and sheep. 21 CFR §500.65 provides further that epinephrine 1:1000 in 10-milliliter containers for emergency treatment of anaphylactoid shock in cattle, horses, sheep and swine can be made available for over-the-counter sale. The labeling must bear the following statements in a prominent manner: “For emergency use only in treating anaphylactoid shock. Usual dosage: Cattle, horses, sheep and swine – 1 cubic centimeter per 100 pounds of body weight. Inject subcutaneously.” The labeling must also bear a description of the symptoms of anaphylactoid shock as listed in 21 CFR §500.65(c).

### **Extralabel Uses of Antidotes**

The Animal Medicinal Drug Use Act (AMDUCA) of 1994 allows for veterinarians to legally administer or prescribe any human or veterinary approved drug in an extralabel manner. Extralabel use is defined in 21 CFR § 530.3: “actual use or intended use of a drug in an animal in a manner that is not in accordance with the approved labeling. This includes, but is not limited to, use in species not listed in the labeling, use for indications (disease or other conditions) not listed in the labeling, use at dosage levels, frequencies, or routes of administration other than those stated in the labeling, and deviation from the labeled withdrawal time based on these different uses.” For example, pralidoxime chloride (2-PAM)

and dimercaprol (BAL) are approved human drugs, and may be used extralabelly as antidotes for animals with organophosphate or lead intoxication, respectively. Any liability associated with the extralabel use of a drug is the responsibility of the veterinarian administering or dispensing the drug. This is an especially important issue if the drug is administered to animals intended for human consumption, as it must be assured that no drug or toxic residues remain in the animal's tissues. 21 CFR Part 530 sets forth in detail the provisions and regulations for extralabel drug use in animals. In general, extralabel use:

- May occur only within the scope of a valid veterinarian-client-patient relationship
- Is limited to treatment modalities when the health of an animal is threatened, or suffering or death may result from failure to treat
- Is allowed only if there is no approved animal drug that is labeled for such use that has the same active ingredient and the required dosage form and concentration, unless the veterinarian finds that the approved drug is clinically ineffective for its intended use

These regulations include special provisions for labeling and record-keeping requirements for drugs used in an extralabel manner. In addition, special conditions for extralabel use of a drug in food-producing animals are required, as noted below.

### **Compounding of Antidotes**

The AMDUCA also provides for the compounding of drugs for animal use in certain situations. The regulations regarding animal drug compounding are found in 21 CFR §530.13 (“**Extralabel use from compounding of approved new animal and approved human drugs**”), and guidance is provided in FDA Compliance Policy Guide (CPG) 7125.40, “**Compounding of Drugs for Use in Animals**” (July 2003). As used in the CPG,

the term “animal drug compounding” means a process by which a person combines, mixes, or alters ingredients to create a new animal drug that is not the subject of an application that has been approved under §512 of the FFDCA. Compounding may be appropriate under the following conditions:

- A legitimate medical need has been identified, and there is no marketed approved animal drug or combination of drugs available, which can be used as labeled or in an extralabel manner
- The drug is compounded for an individual patient
- The drug is compounded from an FDA-approved animal or human drug

According to 21 CFR §530.13, compounding of animal drugs must be performed by a licensed pharmacist or veterinarian within the scope of a professional practice; adequate procedures and processes must be followed to ensure the safety and effectiveness of the compounded product; and the scale of the compounding operation must be commensurate with the established need for a compounded product.

For companion animal veterinarians, extralabel use and compounding are viable options for legally obtaining and administering antidotes to their patients. The situation is quite different for food animal veterinarians.

### **Antidotes for Food-Producing Animals**

Currently, there are no antidotal drugs approved for use in food animals, with the special exceptions of atropine sulfate and epinephrine, as has been previously noted. The lack of safe and effective antidotes has been a long-standing problem for food animal veterinarians. Human food safety concerns are the major issue for food animal drugs. In addition, there is little economic incentive for veterinary pharmaceutical companies to pursue

approval of antidotes and other animal drug products which have a very small market. This leaves the food animal practitioner with few options for legally obtaining and administering antidotal therapies. Unfortunately, the economic impact of exposure of an entire herd to a toxicant can be devastating to food animal producers, since very large amounts of antidotes may be needed to treat an entire herd. Obviously, the need is great to provide food animal veterinarians more options for obtaining antidotes for use in their patients. Common food animal toxicoses involve exposures to copper, lead, organophosphates, arsenic, nitrates, and cyanide.

The extralabel use option does apply to food animals, but with specific restrictions. These restrictions are meant to ensure that no drug or toxic residues will be present in edible tissues from food animals treated with these drugs. 21 CFR §530.20 sets forth the regulations for extralabel use of approved human and animal drugs for food-producing animals. This regulation should be reviewed and well understood by veterinary practitioners contemplating the extralabel use of a drug as an antidote in food animals:

**§ 530.2 Conditions for permitted extralabel animal and human drug use in food-producing animals.** (a) The following conditions must be met for a permitted extralabel use in food-producing animals of approved new animal and human drugs:

- (1) There is no approved new animal drug that is labeled for such use and that contains the same active ingredient which is in the required dosage form and concentration, except where a veterinarian finds, within the context of a valid veterinarian-client-patient relationship, that the approved new animal drug is clinically ineffective for its intended use.
- (2) Prior to prescribing or dispensing an approved new animal or human drug for an extralabel use in food animals, the

veterinarian must: (i) Make a careful diagnosis and evaluation of the conditions for which the drug is to be used; (ii) Establish a substantially extended withdrawal period prior to marketing of meat, milk, eggs, or other edible products supported by appropriate scientific information, if applicable; (iii) Institute procedures to assure that the identity of the treated animal or animals is carefully maintained; and (iv) Take appropriate measures to assure that assigned timeframes for withdrawal are met and no illegal drug residues occur in any food-producing animal subjected to extralabel treatment. (b) The following additional conditions must be met for a permitted extralabel use of in food-producing animals an approved human drug, or of an animal drug approved only for use in animals not intended for human consumption: (1) Such use must be accomplished in accordance with an appropriate medical rationale; and (2) If scientific information on the human food safety aspect of the use of the drug in food-producing animals is not available, the veterinarian must take appropriate measures to assure that the animal and its food products will not enter the human food supply. (c) Extralabel use of an approved human drug in a food-producing animal is not permitted under this part if an animal drug approved for use in food-producing animals can be used in an extralabel manner for the particular use.

In addition, there are certain drugs that are prohibited for any extralabel use in food-producing animals which are listed in 21 CFR §530.41.<sup>2</sup> Extralabel use of an approved new animal drug in or on an animal feed is prohibited as well.

Compounding is also an option for food animal antidotes under certain circumstances. The current compounding CPG allows compounding from approved human or animal drugs,

if a legitimate medical need is identified, and the drug is compounded for an individual patient or herd. However, there are several chemicals commonly recommended as antidotes for food animal toxicoses, for which there are no approved human or veterinary products. In these cases, veterinary practitioners are faced with the need to compound an antidotal drug from a bulk drug substance. Compounding animal medications from bulk drug substances is currently not permitted under AMDUCA, or under the current compounding CPG. Although the FDA regulations do not permit the use of bulk drugs in compounding, it is recognized that this is sometimes unavoidable and is necessary to prevent the suffering and death of a poisoned animal or animals. In fact, the current compounding CPG "Appendix A" includes a list of substances for compounding and subsequent use in animals to which the FDA would not normally object:

- Ammonium molybdate
- Ammonium tetrathiomolybdate
- Ferric ferrocyanide
- Methylene blue
- Picrotoxin
- Pilocarpine
- Sodium nitrite
- Sodium thiosulfate
- Tannic acid

Compounded antidotes should not be stockpiled by compounding pharmacies, and should not be promoted, advertised or marketed as unapproved new animal drugs. In addition, the compounded drug must be formulated under good compounding practices, and records

should be maintained for treated patients by the attending veterinarian. As noted in the extralabel use regulations, the use of compounded drugs cannot result in violative residues, and measures must be taken to ensure that substantially extended withdrawal periods are established for the treated animal prior to marketing of milk, meat, eggs, and other edible products. These extended withdrawal times must be supported by scientific information; if not, then the veterinarian administering the compounded drug must take appropriate measures to prevent the animal and its food products from entering the human food supply. Veterinarians may be able to obtain information regarding withdrawal times by consulting the Food Animal Residue Avoidance Database (FARAD). Of note, the current compounding CPG is undergoing modifications which may not include the list in Appendix A.

When faced with the need to obtain an antidote, practitioners should first employ approved drugs if available, followed by extralabel use and/or compounding options as permitted by regulation. However; in view of the current limitations in legally obtaining life-saving antidotal therapies for food animals, other options should be explored. The following four additional options are offered for consideration purposes only:

- 1.) Utilize the Minor Use and Minor Species Act of 2004 (MUMS). This legislation helps make more medications legally available to veterinarians and animal owners to treat minor animal species and uncommon diseases in major animal species. It is found in Sections 571, 572 and 573 of the Federal Food, Drug, and Cosmetic Act. Minor use drugs are drugs for use in major species (cattle, horses, swine, chickens, turkeys, dogs and cats) that are needed for diseases that occur infrequently or in limited geographic areas. Minor species are defined by exclusion, as any species other than the major species listed above. Because of the small market shares, low-profit margins involved, and capital investment required, it is

generally not economically feasible for pharmaceutical firms to pursue approvals for minor species, and/or uncommon diseases and conditions of major animal species. Three mechanisms are possible for improving the availability of new animal drugs under the MUMS legislation:

a.) Conditional Approval – A sponsor of a veterinary drug can request conditional approval for the drug, which allows the sponsor to make the drug available before collecting all necessary effectiveness data, but after proving the drug is safe for its intended use. The drug sponsor can keep the product on the market for up to five years while collecting the required effectiveness data.

b.) Indexing – This mechanism provides for the index listing of a new animal drug for use in a minor species. The “Index” is intended to be a means by which pharmaceutical companies can legally market veterinary drugs for minor species with no human food safety concerns without having to go through the process of new animal drug approval. Inclusion in the Index will largely be based on the evaluation of the target animal safety and effectiveness of each specific product, by a panel of qualified experts who will report their findings to the FDA. Of note, the “Index” is limited to nonfood-producing minor species, with a limited exception for some early life stages of food animals, such as fish eggs. Also, indexing is not an option until the Final Rule for Indexing is published (as of this writing, the Final Rule is still under review by FDA).

c.) Designation – This section of the MUMS Act is similar to the “Orphan Drug Act” for humans, which provides incentives to pharmaceutical firms that develop drugs for rare diseases or conditions. Companies who gain approval for designated new animal drugs will be granted seven years of marketing exclusivity. In addition, grants and tax credits will be

provided for companies to develop certain new animal drugs. At the time of this writing, grants have been authorized under this program, but have not been appropriated.

The National Research Support Project-7 (NRSP-7) is a program that provides funds for research to generate data in support of drug approvals for minor uses. NRSP-7 submits data from research projects to the FDA-CVM for inclusion in a Public Master File (PMF). Once accepted, the data is available for sponsors to refer to, in support of an NADA for minor use. Further information is available at <http://www.nrsp-7.org>.

As noted above, antidotes for use in food animals would not qualify for Indexing under the MUMS Act. In addition, to qualify for Conditional Approval or Designation, the status of a drug as a “minor use” must be determined by expert opinion. Veterinary pharmaceutical firms may be unlikely to pursue the route of Conditional Approval or Designation, because the costs of conducting the required tissue residue studies, and also manufacturing costs under cGMPs would most likely outweigh the profits that could be obtained from marketing the product in such a small demand market.

- 2.) Amend 21 CFR § 500 Subpart D- Requirements for Specific Animal Drugs- to include specific antidotal therapies, as has been allowed for the emergency use of epinephrine to treat anaphylactoid reactions. For food animal antidotes, the proposed regulation would not include antidotes with known potential carcinogenic activity, such as methylene blue. Developing a regulation of this sort would seem attractive in the effort to provide a legal means to increase the rapid availability of potentially life-saving antidotes; although the time and resources involved in such an effort may not be readily obtainable.
- 3.) Establishment of a “Low Regulatory Priority (LRP) List for Food Animal Antidotes” (similar to the “LRP” list that has been established for certain aquaculture drugs, reference

[www.fda.gov/cvm/Policy\\_Procedures/4200.pdf](http://www.fda.gov/cvm/Policy_Procedures/4200.pdf) - Part C). This “LRP” list would include known food animal antidotes and identify them as “new animal drugs of low regulatory priority” which have undergone a limited review by the FDA. This review would include a Human Food Safety review conducted by CVM’s Division of Human Food Safety (HFV-150), Residue Chemistry and Toxicology teams. The Food Animal Residue Avoidance Database (FARAD) may also be consulted, and milk discard and slaughter withdrawal times would be based on the Human Food Safety review and FARAD information. Manufacturers of the antidotes would be encouraged to follow current Good Manufacturing Practices (cGMPs) and veterinary practitioners administering or prescribing the antidotes must follow specific conditions of use, i.e., indications, prescribed levels, and ensure that withdrawal times are followed.

Model labeling could be drafted as standard labels for these antidotes, to provide adequate directions for use including indications, species, contraindications, warnings, adverse reactions, user safety, dosage and administration, and discard or withdrawal times. In addition, the product manufacturer would be required to register with the FDA, and the product must be drug-listed with CVM.

The veterinarians and staff of FARAD are available to assist veterinarians in determining appropriate withdrawal times for drugs used as antidotes in food animals. FARAD has published withdrawal times for some commonly known drugs that are used extralabelly as antidotes for food animals; some of these drugs could be considered for inclusion in an “LRP” listing. For example, FARAD has published withdrawal times for the following antidotal drugs used in food animals:<sup>3</sup>

<b>ANTIDOTE</b>	<b>TOXICITY</b>	<b>WITHDRAWAL TIMES</b>
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Atropine sulfate	Organophosphate toxicosis	Single dose (0.03-0.06 mg/kg) IM, SQ, IV in cattle sheep and swine: 3 day milk and 14 day meat WDT. Multiple doses up to 0.2 mg/kg: 6 day milk and 28 day meat WDT.
Epinephrine	Anaphylaxis	Zero day WDT for cattle, sheep and swine.
Vitamin K <sub>1</sub>	Anticoagulant rodenticides, sweet-clover toxicosis	Zero day WDT at 0.5-2.5 mg/kg IV, IM, SQ for cattle, sheep, goats and swine.
Pralidoxime hydrochloride (2-PAM)	Organophosphate toxicosis	6 day milk and 28 day meat WDT in cattle, sheep and swine
Dimercaprol	Arsenic, lead and mercury toxicoses	Minimum 5 day milk and 5 day meat WDT (based on data from other animal species)
Copper glycinate	Molybdenum toxicosis	30 day meat WDT for cattle; not for use in dairy cattle

Calcium disodium EDTA	Lead toxicosis	2 day milk and 2 day meat WDT for food animals
Activated charcoal	Adsorbent	Zero day milk and meat WDT for food animals
D-Penicillamine	Lead and mercury toxicoses	Minimum 3 day milk and minimum 21 day meat WDT for cattle, sheep and swine
Sodium nitrite, sodium thiosulfate, sodium sulfate	Cyanide toxicosis	48 hour milk and 24 hour meat WDT for food animals

For most of these antidotes, limited information is actually available concerning tissue residues, but WDT recommendations can be made for many antidotes based on pharmacokinetic principles. Complex interactions may occur between the toxicant and antidotal agent, which may also affect WDT recommendations. For this reason, practitioners are advised to contact FARAD for specific advice on a case-by-case basis, as general withdrawal recommendations for most toxicants cannot be made. Withdrawal times change as further data is collected and generated through controlled studies. To obtain the most current information regarding appropriate withdrawal times, FARAD may be contacted at 888-873-2723 or at the FARAD Web site: [www.farad.org](http://www.farad.org).

There are increased toxicological and food safety concerns regarding molybdic acid salts (ammonium molybdate, ammonium tetrathiomolybdate) and methylene blue.<sup>4</sup> For this

reason, in contrast to previously published FARAD recommendations<sup>3</sup>, CVM has assigned extended withdrawal periods for these compounds when administered to ruminants:

- Molybdcic acid salts (for copper toxicosis): 30-day meat WDT
- Methylene blue (for nitrate, nitrite and chlorate toxicosis): 180-day meat WDT.

Molybdcic acid salts and methylene blue are not recommended for use in lactating animals.

Recently, methylene blue has been recognized to have carcinogenic activity and has been listed by the National Toxicology Program (NTP), Annual Report on Carcinogens (June 2006), as reasonably anticipated to be a human carcinogen. One month, three month, and two year studies in mice and rats were conducted; under the conditions of the two year studies, there was some evidence of carcinogenic activity of methylene blue trihydrate in male F344/N and male B6C3F<sub>1</sub> mice.<sup>5</sup> The withdrawal times for molybdcic acid and methylene blue are subject to change as additional residue data is collected.

4.) Establish “Antidote Depots” - with cooperation of veterinary schools, state diagnostic laboratories or agriculture departments, and/or state veterinary associations. Local antidote distribution sites could be established that are managed by such institutions. The advantage of veterinary antidote depots would be the increased availability of antidotes on a regional basis, prevention of stockpiling at compounding pharmacies, and the assurance that antidotes would only be used for treating animal toxicoses.<sup>4</sup> This type of program could allow for 24-hour availability and a means of acquisition of sufficient quantities of antidotes to reduce the economic impact of large animal poisonings. Antidotes should be available only for emergency treatment and with a veterinary prescription. An example of an antidote supply program that has been presented in the scientific literature in the past is one that involved a local city Poison Control Center in cooperation with the state’s veterinary medical

association. The Poison Control Center served as an antidote depot and provided service 24 hours daily, every day of the year, and thus offered emergency access to the antidotes. The state association created awareness of this service to its membership through publications and was responsible for the cost associated with acquiring the antidotal substances. Veterinarians who elected to obtain the antidotes under this program were responsible for reimbursing the state association for the cost of replenishing the depleted antidote stock.<sup>6</sup> In the absence of an FDA-approved product, this antidote depot approach may be the most desirable in terms of product availability, timeliness of treatment, and food safety.

### **Conclusion**

At present, obtaining antidotes for companion animal toxicoses may be accomplished through judicious extralabel use and compounding as needed. In contrast, there is no single solution for increasing the availability of antidotes for food animals. The situation is different for food animals due to tissue residue concerns and the lack of approved human or animal drugs that may be legally compounded or used in an extralabel manner for certain toxicoses. However, for producers, the economic impact is great when there is loss of multiple animals in a herd due to poisoning. Every effort should thus be made to increase the availability of life-saving antidotal therapies for these animals. A combination of exercising enforcement discretion (such as through an “LRP” list), utilization of MUMS legislation when possible, legislative action to amend existing regulations, and establishment of programs for the development of antidote depots should be considered. Stakeholders from both within and outside government are encouraged to participate in efforts to develop an acceptable way to resolve this important issue.

**Table of Antidotes for Selected Animal Toxicoses**

<b><u>ANTIDOTE</u></b>	<b><u>INDICATION</u></b>	<b><u>MECHANISM OF ACTION</u></b>	<b><u>DOSAGE</u></b>
N-Acetylcysteine	Acetaminophen poisoning	Donates sulfhydryl groups during biotransformation of acetaminophen; maintains cellular glutathione concentrations and prevents organ damage caused by reactive metabolites	Dog, Cat: 140-150 mg/kg PO or IV loading dose; followed by 50-70 mg/kg q 4-6 hrs for 3-5 treatments (Plumb)
Ammonium molybdate and tetrathiomolybdate	Copper poisoning	Promotes excretion of copper	Cattle, Sheep: Ammonium molybdate: 200 mg per head PO once daily for 3 weeks (Plumb) Ammonium tetrathiomolybdate: 1.7-3.4 mg per head IV or SQ every other day for 3 treatments (Plumb)
Antivenin <i>Crotalidae</i>	Rattlesnake, copperhead, water moccasin snake bites	Neutralizes snake venom	Dog, Cat, Horse, Cattle, Sheep, Goats: 1-5 reconstituted vials (10-50 ml) diluted in 100-250 ml saline; give slowly IV and repeat q 2 hrs prn (Hare)
Antivenin <i>Micrucus</i>	Coral snake bites	Neutralizes snake venom	Same as above
Atipamezole HCl	Reversal agent for medetomidine, xylazine, and potentially amitraz	$\alpha_2$ -adrenergic antagonist	Dog: Give IM an equal volume of medetomidine that was given (Antisedan® package insert) For amitraz toxicity: 50 mcg/kg IM (Plumb) Rabbits: 1 mcg/kg IV, IP or SQ (Plumb) Pocket pets: 0.1-1 mg/kg IM, IV, IP or SQ (Plumb) Birds: 0.5 mg/kg IM (Plumb)
Atropine sulfate	Organophosphate/carbamate insecticide poisoning	Anticholinergic	Dog, Cat: 0.2-0.5 mg/kg, ¼ dose IV and remainder IM or SQ (Plumb) Cattle, Sheep, Goats: 0.2-0.5 mg/kg, ¼ dose IV and remainder IM or SQ, may repeat q 3-4 hrs for 1-2 days (Plumb) Horse, Swine: 0.22 mg/kg, ¼ dose IV, remainder IM or SQ (Plumb) Rabbits, Pocket pets: 10 mg/kg SQ q 20 min (Plumb) Birds, Reptiles: 0.1-0.2mg/kg SQ or IM prn, until cessation of signs (Plumb)
Calcium-EDTA	Lead, zinc poisoning	Heavy metal chelator – calcium ions replaced by lead and zinc to form water-soluble complex eliminated in urine	Dogs, Cats: For lead – Give as 1% solution in D5W - 25 mg/kg SQ q 6 hrs for 5 days; rest for 5 days and repeat prn. (Plumb) For zinc – Dilute in D5W, 100 mg/kg divided into 4 SQ doses per day (Plumb) Cattle, Sheep, Goats, Horse: 73 g/kg divided q 8-12 hrs given slowly IV for 3-5 days; rest for 2 days and repeat 5 day treatment prn. (Plumlee) Birds: 35-40 mg/kg IM q 12 hrs for 5 days; with 5-7 day rest if further treatment needed (Plumlee)

Calcitonin	Cholecalciferol rodenticide poisoning; vitamin D toxicosis	Prevents calcium mobilization from bone, increases urinary excretion of calcium	Dog: 4-6 IU/kg SQ q 2-3 hrs; monitor serum calcium levels (Roder)
Deferoxamine mesylate	Iron, aluminum poisoning	Chelator of iron and aluminum; the chelated complex is excreted in urine	Dog, Cat: 10 mg/kg IM or IV q 8 hr for 24 hrs (Plumb)
Digoxin specific antibody fragment	Digitalis, Digoxin poisoning; also Bufo toads, plants- eg., foxglove ( <i>Digitalis purpurea</i> ), oleander ( <i>Nerium oleander</i> )	Neutralizes and binds with molecules of digitoxin and digoxin	Dog, Cat, Cattle, Horse: 6-12 mg/kg slowly IV (Hare) (Digibind® contains 38 mg/vial)
Dimercaprol (BAL)	Arsenic, mercury poisoning	Chelator of metal ions which form sulfhydryl group-ion complexes excreted in urine	Dog, Cat: 2.5-5 mg/kg IM q 4 hrs for 2 days then q 8 hrs on 3 <sup>rd</sup> day, then q 12 hrs for 10 days (Plumb) Horse: 5 mg/kg IM initially then 3 mg/kg IM q 6 hrs for 1 <sup>st</sup> day, then 1 mg/kg q 6 hrs for 2 additional days (Plumb) Cattle: 6 mg/kg IM q 8 hrs for 3-5 days (Plumb) For mercury: Cattle, Swine: 3 mg/kg IM q 6 hrs for 4 days then q 12 hrs for 10 days (Plumb)
Fomepizole (4-MP; Antizol-Vet®)	Ethylene glycol poisoning	Alcohol dehydrogenase inhibitor; prevents metabolism of ethylene glycol to glycolic and glyoxylic acids	Dog: 20 mg/kg IV loading dose; then 15 mg/kg IV at 12 and 24 hrs; then 5 mg/kg IV at 36 hrs (Antizol-Vet® package insert) Cat: Within 3 hrs of ingestion, 125 mg/kg slow IV initially then 31.25 mg/kg at 12, 24 and 36 hrs (Plumb)
Methylene blue	Methemoglobinemia-Nitrate, chlorate poisoning; Phenol poisoning (dog and cat)	Oxidation-reduction agent which reduces ferric ion in oxidized hemoglobin to the ferrous form, allowing for regeneration of hemoglobin	Dog: 4 mg/kg single slow IV infusion (Plumb) Cat: 1-1.5 mg/kg single slow IV infusion (Plumb) Cattle, Sheep: 8.8 mg/kg slowly IV as 1% solution in normal saline; repeat in 6-8 hrs prn (Plumb) Horse: 1-10 mg/kg slowly IV as 1% solution, prn (Hare) Swine: 1-2 mg/kg IV slowly as 1% solution (Radostits)
Naloxone	Narcotic overdose/ poisoning	Pure opiate antagonist	Dog: 0.04 mg/kg IV, IM or SQ (Plumb) Cat: 0.05-0.1 mg/kg IV (Plumb) Pocket pets: 0.01-0.1 mg/kg SQ (Plumb) Rabbits: 0.005-0.1 mg/kg IM or IV (Plumb) Horse: 0.01-0.022 mg/kg IV (Plumb)
Penicillamine	Arsenic, copper, mercury, lead poisoning	Heavy metal chelator – complexes eliminated in urine	Dog (for lead): 110 mg/kg/day PO divided q 6-8 hrs for 1-2 weeks (Plumb) Cat (for lead): 125 mg PO q 12 hrs for 5 days (Plumb) Sheep, Goats (for copper): 52 mg/kg daily for 6 days (Plumb) Swine: 30-125 mg/kg PO in divided doses daily, prn (Hare)

			Birds (for lead, zinc, copper): 55 mg/kg PO q 12 hrs for 1-2 weeks; rest for 3-5 days; retreat prn (Gfeller)
Phytonadione (vitamin K <sub>1</sub> )	Anticoagulant rodenticide poisoning; sweet clover (dicumarol) poisoning	Provides synthetic source of vitamin K <sub>1</sub> to promote regeneration of clotting factors II, VII, IX, X	Dog, Cat: 2.5-5 mg/kg SQ followed by 2.5-5 mg/kg PO divided daily for 1-4 weeks (Plumb) Pocket pets: 1-10 mg/kg IM (Plumb) Birds: 0.2-2.5 mg/g IM prn (Plumb) Cattle, Sheep, Goats, Horses, Swine: 0.5-2.5 mg/kg IM or diluted with normal saline and given slowly IV; subsequent doses IM or SQ prn (Plumb) Cattle (for sweet clover poisoning): 1 mg/kg IV or IM, repeat 2-3 times daily for 2 days (Plumb)
Pralidoxime (2-PAM)	Organophosphate insecticide poisoning	Reactivates acetylcholinesterase	Dog, Cat: 50 mg/kg (Cat: 20 mg/kg) slowly IV over 30 minutes; repeat in 1 hr if signs persist, then q 8 hrs for 24-48 hrs (Plumb) Cattle: 25-50 mg/kg slowly IV in 5% dextrose q 12 hrs, prn (Hare) Horse: 20-35 mg/kg slowly IV in 5% dextrose q 6 hrs, prn (Hare) Birds: 10-100 mg/kg IV as slow infusion over 24-48 hrs, or IM q 8-12 hrs (Gfeller)
Sodium thiosulfate	Cyanide, arsenic poisoning	Provides exogenous source of sulfur, allowing detoxification of cyanide using the enzyme rhodanese. Rhodanese converts cyanide to thiocyanate ion which is excreted in urine. The sulfate moiety may also act as a chelator of arsenic.	Dog: 50-200 mg/kg as 25% solution (Hare) Swine: 10-20 mg/kg as 25% solution (Hare) Horse: For cyanide: First give sodium nitrite in 20% solution at 10-20 mg/kg IV, followed by 20% solution of sodium thiosulfate at 30-40 mg/kg IV (Plumb) For arsenic: 20-30 g in 300 ml water PO with BAL at 3 mg/kg IM q 4 hrs (Plumb) Ruminants: For cyanide: 660 mg/kg IV in 30% solution given rapidly (Plumb) For arsenic: 30-60 g PO q 6 hrs for 3-4 days (Plumb) Sheep, Goats: 20-60 mg/kg IV or IP as 25% solution; or 10-30 mg/kg IV or IP as 25% solution when administered with sodium nitrite (Hare)
Succimer	Lead, mercury, arsenic poisoning	Heavy metal chelator- soluble complexes excreted in urine	Dog, Cat (for lead): 10 mg/kg PO q 8 hrs for 5 days then 10 mg/kg PO q 12 hrs for 2 weeks (Plumb) Birds: 15-35 mg/kg PO q 12 hrs for 5 days (Plumb)
Tolazoline	Reversal of xylaxine	$\alpha_1$ and $\alpha_2$ -adrenergic antagonist	Horse: 4mg/kg slowly IV at administration rate of ~ 1 ml/second (Tolazine® package insert) Dog, Cat: 4 mg/kg slowly IV (Plumb) Birds: 15 mg/kg IV (Plumb) Cattle, Sheep, Goat, Deer: 2-4 mg/kg

			slowly IV; titrate to effect (Plumb)
Yohimbine	Reversal of xylazine; and potentially amitraz	$\alpha_2$ -adrenergic antagonist	Dog: 0.11 mg/kg slowly IV (Yobine® package insert) Cat: 0.5 mg/kg IV (Hare) Rabbit: 0.2 mg/kg IV prn (Plumb) Mice, Rats: 0.2 mg/kg IP prn (Plumb) Birds: 0.1 mg/kg IV (Plumb) Cattle, Sheep, Goats: 0.125 mg/kg IV (Plumb, Hare) Horse: 0.075 mg/kg IV (Plumb) Deer: 0.2-0.3 mg/kg IV (Antagonil® package insert) Llama: 0.25 mg/kg IV (Hare)

Table References:

Gfeller RW, Messonnier SP: Handbook of Small Animal Toxicology and Poisonings, 2<sup>nd</sup> ed. Mosby, St. Louis, MO, 2004.

Hare W, et al:

Plumb DC: Plumb's Veterinary Drug Handbook, 5<sup>th</sup> ed. PharmaVet, Stockholm, WI, 2005.

Plumlee KH: Clinical Veterinary Toxicology. Mosby, St. Louis, MO, 2004.

Radostits OM, et al: Veterinary Medicine – A Textbook of the Diseases of Cattle, Sheep, Pigs, Goats and Horses, 9<sup>th</sup> ed. W.B. Saunders, London, 2000.

Roder JD: Veterinary Toxicology. Butterworth-Heinemann, Woburn, MA, 2001.

## References

<sup>1</sup>Osweler GD (1996). Antidotes. In *Toxicology*. Williams & Wilkins, Philadelphia, PA, pp. 57-58.

<sup>2</sup>21 CFR §530.41: Drugs prohibited for extralabel use in food-producing animals:  
chloramphenicol, clenbuterol, diethylstilbestrol (DES), dimetridazole, ipronidazole, other nitroimidazoles, furazolidone, nitrofurazone, sulfonamide drugs in lactating dairy cattle (except approved use of sulfadimethoxine, sulfabromomethazine,

sulfaethoxypyridazine), fluoroquinolones, glycopeptides, and phenylbutazone in female dairy cattle 20 months of age or older.

<sup>3</sup>Haskell SR, et al. FARAD Digest: Antidotes in food animal practice. *JAVMA* 2005; 226(6): 884-887.

<sup>4</sup>Post LO, et al. Current status of food animal antidotes. *Vet Clinics of N Amer: Food Anim Pract* 2000; 16(3): 445-453.

<sup>5</sup>Draft Abstract (NTP)- Toxicology and carcinogenesis studies of methylene blue trihydrate (CAS No. 7720-79-3) in F344/N rats and B6C3F<sub>1</sub> mice (Gavage Study).

<sup>6</sup>Krenzelok EP, et al. The poison center as a reservoir for antidotes for veterinary poisoning emergencies. *Vet Hum Toxicol* 1992; 34(2): 168-169.