UPDATE ON THE ANIMAL MEDICINAL DRUG USE CLARIFICATION ACT OF 1994
REGULATIONS FOR WILDLIFE VETERINARIANS

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Abstract

With the passage and 1996 advent into law of the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA), several questions remain unanswered with regard to the implications for the practice of veterinary medicine involving free-ranging wildlife or zoological species. The practical application of the provisions of this act for wildlife species that are defined as food producing animals are largely left to the discretion of the veterinarian and include acquiring information relative to use of any drugs prescribed or dispensed for extra-label use, determining appropriate dosage, dose frequency, and meat withdrawal times. Therefore consideration must be given to the following questions and/or situations: 1) Does a valid veterinarian-client-patient relationship exist when drugs are used in an extra-label manner by lay personnel; 2) is there sufficient information to justify the extra-label use of a drug (reasonable basis, lack of approved drugs, withdrawal times can be followed, drug metabolism data); 3) is the veterinarian prepared to be responsible for consequences of extra-label use of a drug including adverse reactions and residue problems. Limited data are available for meat withdrawal periods for wildlife species that are considered to be food producing animals. Further information will be forthcoming as the provisions of AMDUCA are tested over time.

Introduction

The practice of veterinary medicine is filled with an ever changing world of animals and owners. When practicing on wildlife species, the excitement and challenges of veterinary medicine are magnified, sometimes to great magnitudes with the variety of wildlife species that could be faced.

The legal and logical use of drugs is one of the most prominent problems that face exotic animal veterinarians. The use of drugs in animals by veterinarians is regulated under the Code of Federal Regulations, specifically Regulation 21 or the Federal Food, Drug and Cosmetic Act (CFR 21 USC 360b(a)) which addresses the manufacturing, distribution, and usage of drugs in animals.

Currently, there are only five drugs that are approved for use in free-ranging wildlife species. Four of these drugs are limited to use in cervids and include xylazine hydrochloride (Cervizine, Wildlife Pharmaceuticals; Rompun, Bayer), yohimbine hydrochloride (Antagonil, Wildlife Pharmaceuticals) for the reversal of xylazine, carfentanil citrate (Wildnil, Wildlife Pharmaceuticals).
Pharmaceuticals), and naltrexone (Trexonil, Wildlife Pharmaceuticals) for the reversal of carfentanil. The fifth drug is fenbendazole (Safe-Guard/Panacur, Hoechst-Roussel) which is approved for use in bears, large cats, feral swine, several species of antelope, and bighorn sheep. The use of all other drugs in exotic animals is considered extra-label at best and illegal at worst.

Because the number of approved drugs is limited, veterinarians and non-veterinarians have often used many drugs in an extra-label manner in animals, especially for wildlife. Extra-label usage is defined as the use of a drug at a dosage, or frequency or in a species other than that which is approved. Extra-label use allowed veterinarians to use approved drugs in non-approved species and non-approved drugs and human label drugs in animals on an as needed basis.

**Provisions of AMDUCA**

In October 1994, the Animal Drug Use Clarification Act of 1994 (S 340) was passed, and as originally written, AMDUCA codified the extra-label use of drugs in animals by veterinarians. The final version of AMDUCA was approved in November 1996 and became effective on December 9, 1996. The basic provisions of ANMUCA are summarized below. Note that there is a major difference between the requirements for extra-label use of drugs between non-food and food producing animals.

Extra-label use of human or animal drugs is **NOT** allowed if:
1) the drug is to be used in or on animal feed
2) the Secretary of Health and Human Services prohibits certain uses of animal drugs
3) there is another animal drug with the same ingredients, dosage form and concentration that provides for the intended use
4) the Secretary of Health and Human Services finds that the use of the drug may present a risk to public health
5) the use of the drug results in residues exceeding safe levels as established by the Secretary of Health and Human Services

Extra-label use of animal drugs is allowed in non-food animals **if** the drugs use are:
1) approved by the Food and Drug Administration for use in animals
2) by or on the lawful written or oral order of a licensed veterinarian
3) within the context of a veterinarian/client/patient relationship
4) in compliance with rules under the Secretary of Health and Human Services

Extra-label use of human drugs is allowed in non-food animals **if** the drugs used are:
1) approved by the Food and Drug Administration
2) by or on the lawful written or oral order of a licensed veterinarian
3) within the context of a veterinarian/client/patient relationship
4) in compliance with rules under the Secretary of Health and Human Services
Extra-label use of animal and human drugs is allowed in food animals if:
1) there is no approved animal drug labeled for such use (same active ingredient, dosage form and concentration)
2) the approved animal drug is clinically ineffective for its intended use
3) the veterinarian
   a) makes a careful diagnosis and treatment plan
   b) establishes a substantially extended withdrawal time
   c) ensures that treated animal(s) are identified
   d) ensures that withdrawal times are followed
4) such use is in accordance with appropriate medical rationale
5) no human food safety information is available, the animal must not enter the human food supply

Implications of AMDUCA

Now, what do all these regulations mean for veterinarians and wildlife health professionals? First, under AMDUCA, a veterinarian must select, prescribe and/or dispense drugs that are to be used in an extra-label manner within the context of a valid veterinary-patient-client relationship. Second, for extra-label use, AMDUCA requires that only Food and Drug Administration approved drugs be used. Third, AMDUCA requires that animal drugs approved for a particular use be used when they are available. Since there are approved formulations of xylazine, yohimbine, carfentanil, and naltrexone available for use in cervids, these are the forms of these drugs that should be used in deer. Using other products, although they may contain the same active ingredient in the same concentration, in species for which the drug is approved would appear to be contrary to the current requirements of AMDUCA. Fourth, AMDUCA requires that the veterinarian establish a scientifically appropriate withdrawal time for drugs used in an extra-label manner in food-producing animals. Since there are no residue studies available for drugs in wildlife species, the current recommendations are to use an extended withdrawal period for all drugs used in deer, although the extended period is undefined. Fifth, AMDUCA requires specific labeling requirements for drugs that are dispensed or prescribed for extra-label use. Finally, under AMDUCA, the extra-label use of drugs in or on food is illegal, except for treatments directed at individual animals. Drugs that are currently approved for use in this manner are still legal in the species for which they are approved, so, for instance, the use of Strongid-C, the equine pelleted dewormer, in horses is allowed; so is SafeGuard, the pelleted bovine dewormer, in cattle, bears, large cats, feral swine, ruminants in the families Antilopinae, Hippotraginae, and Caprinae, and bighorn sheep. But the use of these products is not legal in species for which they are not approved, even as an extra-label use. Therefore, in food-producing animals, including species of wildlife defined as food-producing animals, feed based drugs used in an extra-label manner should be considered prohibited.

So, given these regulations, what effect do they have on wildlife veterinarians and wildlife health personnel working in the field? Several questions regarding extra-label use of drugs in wildlife remain unanswered.
Under AMDUCA, extra-label usage of drugs should take place under supervision of a veterinarian. What is the definition of supervision within the context of the diversity of people involved in wildlife health? In essence, it becomes the responsibility of the veterinarian to decide if extra-label drug use is appropriate and whether people are capable of using the drugs appropriately and safely. Training of lay personnel is essential!

What sources of information are appropriate from which to obtain data for the establishment of withdrawal times in species in which drugs are used in an extra-label manner? Generally any reasonable source is fine, but again the veterinarian is responsible for the consequences of such use and decisions regarding appropriate withdrawal times.

Can data for appropriate drug dosages and withdrawal times be extrapolated between species? The answer is unclear. The veterinarian is responsible for decisions based on whatever data are available, but what if no data are available for the species in question? How then is a withdrawal time to be established? Table I lists some general information on meat withdrawal times for several drugs used in wildlife. The data for deer were based on theoretical use of the drug in a 70 kg deer. Notice that there is a major difference between suggested withdrawal times in cattle and deer, despite the fact that deer have a smaller body size and a higher metabolic rate per unit of body mass than cattle.

What allowances are made within AMDUCA for species in which there are established hunting seasons or for species in which subsistence hunting occurs? Again, the veterinarian is responsible for establishment of a withdrawal times in such situations and will be held responsible for any residue problems that may develop. However, some follow-up questions should immediately come to mind, like should wildlife that is captured, handled, or treated in any fashion prior to or during the hunting season be marked to allow private citizens to identify them prior to harvest? Because the veterinarian has no control over movements of animals, what should be done in the case of animals that move over the course of time? The answer was "to be careful."

For wildlife, none of these questions have clear answers, but we must be aware of the current situation and the decisions that must be considered prior to the use of drugs in an extra-label manner in wildlife species. Interpretation of AMDUCA is underway and only time and experience will provide better definition to these and other questions.

LITERATURE CITED

1. Food Animal Residue Avoidance Database, United States Department of Agriculture.
Table 1. Drug dose and withdrawal times for deer and cattle.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>FARAD Deer</th>
<th>USA Cattle</th>
<th>NZ Deer</th>
<th>NZ Cattle</th>
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</thead>
<tbody>
<tr>
<td><strong>Fenbendazole</strong></td>
<td>Dose</td>
<td>10 mg/kg p.o. q 24 hr x 3 days</td>
<td>5 mg/kg p.o. q 24 hr x 3 days</td>
<td>7.5 mg/kg p.o. q 24 hr x 3 days</td>
</tr>
<tr>
<td></td>
<td>Withdrawal</td>
<td>21 days(^a)</td>
<td>8 days</td>
<td>14 days</td>
</tr>
<tr>
<td><strong>Ivermectin</strong></td>
<td>Dose</td>
<td>0.2 mg/kg s.c. once</td>
<td>0.2 mg/kg s.c. once</td>
<td>0.2 mg/kg s.c. once</td>
</tr>
<tr>
<td></td>
<td>Withdrawal</td>
<td>49 days</td>
<td>35 days</td>
<td>49 days</td>
</tr>
<tr>
<td><strong>Oxytetracycline</strong></td>
<td>Dose</td>
<td>11 mg/kg i.m. q 48 hr x 5 days</td>
<td>11 mg/kg i.m. q 48 hr x 5 days</td>
<td>20 mg/kg i.m. q 48 hr</td>
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<tr>
<td>(LA 200)</td>
<td>Withdrawal</td>
<td>45 days</td>
<td>28 days</td>
<td>29 days</td>
</tr>
<tr>
<td><strong>Penicillin</strong></td>
<td>Dose</td>
<td>30,000 U/kg i.m. q 24 hr x 7 days</td>
<td>22,000 U/kg i.m. q 24 hr x 7 days</td>
<td>no approval</td>
</tr>
<tr>
<td>Procaine G</td>
<td>Withdrawal</td>
<td>21 days</td>
<td>10 days</td>
<td>no approval</td>
</tr>
<tr>
<td><strong>Carfentanil</strong></td>
<td>Dose</td>
<td>0.026-0.086 mg/kg i.m.</td>
<td>no approval</td>
<td>no approval</td>
</tr>
<tr>
<td></td>
<td>Withdrawal</td>
<td>30 days(^b)</td>
<td>no approval</td>
<td>no approval</td>
</tr>
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<td><strong>Ketamine</strong></td>
<td>Dose</td>
<td>5 mg/kg i.m.</td>
<td>2 mg/kg i.m.</td>
<td>no approval</td>
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<td></td>
<td>Withdrawal</td>
<td>3 days</td>
<td>no approval</td>
<td>no approval</td>
</tr>
<tr>
<td><strong>Xylazine</strong></td>
<td>Dose</td>
<td>2 mg/kg i.m. once</td>
<td>0.05-0.3 mg/kg i.m.</td>
<td>0.05-4 mg/kg i.m.</td>
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<tr>
<td></td>
<td>Withdrawal</td>
<td>10-30 days(^b)</td>
<td>no approval</td>
<td>3 days</td>
</tr>
<tr>
<td><strong>Tolazoline</strong></td>
<td>Dose</td>
<td>3 mg/kg i.v.</td>
<td>no approval</td>
<td>no approval</td>
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<td></td>
<td>Withdrawal</td>
<td>Unknown</td>
<td>no approval</td>
<td>no approval</td>
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<td><strong>Yohimbine</strong></td>
<td>Dose</td>
<td>0.2-0.3 mg/kg i.v.</td>
<td>no approval</td>
<td>0.25 mg/kg i.v.</td>
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<tr>
<td></td>
<td>Withdrawal</td>
<td>30 days(^b)</td>
<td>no approval</td>
<td>5 hr</td>
</tr>
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</table>

\(^a\) withdrawal time for bears, large cats, feral swine, antelope, and bighorn sheep is 14 days for the oral formulation.

\(^b\) These drugs should not be used in free-ranging cervids within 30 days of the hunting season.