

FARAD Digest

Extralabel use of tranquilizers and general anesthetics

Arthur L. Craigmill, PhD; Martha Rangel-Lugo, PhD; Paul Damian, PhD, MPH;
Jim E. Riviere, DVM, PhD

Several injectable and inhalation anesthetics are approved for use in food animals; however, only 6 are currently marketed in the United States (Table 1). Numerous other veterinary drugs are commonly used in food animals to reduce stress associated with handling, for tranquilization, and to induce local and general anesthesia. The purpose of this FARAD Digest is to provide the information necessary for extralabel use of these drugs by veterinarians so that they can comply with AMDUCA and promote food safety. For many of the drugs covered in this article, foreign drug approvals and withdrawal times (WDT; Table 2) are the primary basis for FARAD withdrawal interval (WDI) recommendations. In addition, FARAD has gathered all available pharmacokinetic and tissue residue data on these drugs, and these data are included when this information is relevant to the FARAD WDI recommendation (Tables 3 and 4). In most cases, WDI recommendations for cattle are appropriate for use in sheep and goats.

Acepromazine Maleate

Acepromazine maleate is not approved for use in any food animal in the United States, but is approved in Canada and Australia. Plasma pharmacokinetic data for horses and metabolism of acepromazine in food animals has been reported, although few residue data are available in the published literature. The FARAD recommended WDI for acepromazine primarily is based on foreign approvals.

Detomidine Hydrochloride

In the United States, detomidine hydrochloride is approved for use in horses. In Switzerland, it is approved for use in cattle with a meat WDT of 1 day and milk WDT of 72 hours. Two published studies also provide tissue residue and milk data that FARAD has used to make a WDI recommendation for cattle of 3 days for meat and 72 hours for milk after extralabel use (Table 3).

From the Food Animal Residue Avoidance Databank (FARAD), Environmental Toxicology Extension, College of Agricultural and Environmental Sciences, University of California, Davis, CA 95616-8588 (Craigmill, Rangel-Lugo, Damian), and FARAD, Cutaneous Pharmacology and Toxicology Center, College of Veterinary Medicine, North Carolina State University, Raleigh, NC 27606 (Riviere).

References for determinations are available on written request.

Table 1—The FDA/CVM-approved tranquilizers and anesthetics for use in food animals

Drug	Species	Withdrawal time (d)	Market status
Azaperone	Swine	0	Marketed
Methoxyflurane	Beef cattle, dairy cattle, swine	0	Marketed
Proparacaine	Beef cattle, dairy cattle, swine, goats (ophthalmic use)	0	Marketed
Thiamylal sodium	Beef cattle, dairy cattle, swine	0	Marketed
Thiopental sodium	Cattle, sheep, swine	0	Marketed
Tricaine methane-sulfonate	Fish	21	Marketed
Lidocaine with epinephrine	Beef cattle, dairy cattle	0	Not currently marketed
Thialbarbitone sodium	Cattle, sheep	0	Not currently marketed
Chloral hydrate, magnesium sulfate, pentobarbital	Beef cattle, dairy cattle	0	Not currently marketed

Guaifenesin

In Switzerland, guaifenesin is approved for use in cattle with no listed WDT for meat or milk. Published data on guaifenesin residues and pharmacokinetics are limited to horses, and elimination is rapid; however, guaifenesin is transported across the placenta and can be detected in foal serum. The FARAD recommends that an extended WDI of 3 days for meat and 48 hours for milk be followed if guaifenesin is used in cattle.

Ketamine Hydrochloride

Ketamine hydrochloride is approved for use in non-food animals, and veterinary preparations are available and widely used in food animals. There are no published residue data available for edible tissues; however, there are extensive pharmacokinetic data for serum/plasma in calves, sheep, and swine. These data, along with WDT established for similar products in Switzerland and France, allow FARAD to set substantially extended WDI that will satisfy AMDUCA and protect public health.

Lidocaine

Lidocaine with epinephrine is approved for use in food animals, but is not currently marketed. Lidocaine is

Table 2—Foreign approvals for use of tranquilizers and anesthetics in cattle (1995 to 1997)

Drug	Country	Dose (mg/kg)*	Meat withdrawal interval (d)	Milk withdrawal interval (h)
Acepromazine maleate	Australia	0.13, IV; 0.27, IM	2	48
	Canada	0.055, IV; 0.11–0.44, IM; 0.13–0.26, PO	7	48
Detomidine	Switzerland	0.02–0.08, IM or IV	1	72
Guaifenesin	Switzerland	60–100, IV	None specified	None specified
Ketamine	Switzerland	Adult, 2, IV; calves, up to 10, IV or IM	1	72
Xylazine	France	5, IV; 10–20, IM	0	0
	United Kingdom	0.05–0.3, IM	14	48
	Canada	0.11–0.33, IM	3	48
	France	0.05–0.3, IM; 0.025–0.15, IV	2	0
	Germany	0.01–0.3, IM; 0.016–0.1, IV	3	72
	Germany	1.2–2.0, IM	7	120
	Switzerland	0.05–0.3, IM; 0.016–0.1, IV	3	72

*To convert dose to mg/lb, divide by 2.2.

Table 3—The FARAD recommended withdrawal intervals for cattle, sheep, and goats for single and multiple treatments

Drug	Dose (mg/kg)*	Meat withdrawal interval (d)	Milk withdrawal interval (h)
Acepromazine	Up to 0.13, IV; up to 0.44, IM	7	48
Detomidine	Up to 0.08, IM or IV	3	72
Guaifenesin	Up to 100, IV	3	48
Ketamine	Up to 2, IV; 10, IM	3	48
Lidocaine with epinephrine	Infiltration, epidural	1	24
Ultra-short-acting barbiturates	Thiamylal (up to 5.5)† Thialbarbitone (up to 9.4)†	1	24
Xylazine	0.016–0.1, IV; 0.05–0.3, IM	5	72
Yohimbine	0.3–2.0, IM Up to 0.3, IV	10 7	120 72

*To convert dose to mg/lb, divide by 2.2. †Approved doses for preparations that are not currently marketed.

rapidly metabolized and eliminated after absorption, with half-lives of 0.6 to 1 hour in most species. To satisfy the AMDUCA requirement that an extended WDI be used after extralabel use of drugs, FARAD recommends that a 24-hour milk and meat WDI be followed when lidocaine (with or without epinephrine) is used for local anesthesia in food animals.

Ultra-short-acting Barbiturates

When ultra-short-acting barbiturate formulations similar to those approved for use in food animals are used (even though they are not currently marketed), FARAD recommends a 24-hour WDI be followed for milk and meat. Considerable pharmacokinetic and residue data are available for these drugs.

Table 4—The FARAD extralabel withdrawal interval recommendations for tranquilizers and anesthetics used in swine for single and multiple treatments

Drug	Dose (mg/kg)*	Meat withdrawal interval (d)
Acepromazine	Up to 0.055, IV; up to 0.44, IM	7
Ketamine	Up to 10, IV or IM	2

*To convert dose to mg/lb, divide by 2.2.

Tiletamine Hydrochloride and Zolazepam

Telazol is a combination product of tiletamine hydrochloride (an anesthetic in the ketamine/phencyclidine hydrochloride class) and zolazepam (benzodiazepine tranquilizer). The FARAD has received numerous requests for WDI recommendations for use of Telazol in food animals. An extensive literature search failed to find any relevant published articles on which a recommendation could be based, and a search of veterinary drug compendia from 5 foreign countries failed to discover any foreign food animal approval. At this time, FARAD cannot provide a WDI recommendation for Telazol.

Xylazine

Although it is not approved for use in food animals, xylazine is one of the most widely used sedatives, particularly in ruminants. It is approved for use in food animals in at least 5 foreign countries (Table 2). Extension of cattle recommendations to goats and sheep is supported by pharmacokinetic data that indicate similar half-lives and volumes of distribution in all species studied.

Several xylazine preparations are approved for use in cervidae (elk, fallow deer, mule deer, sika deer) with no specified WDT, because these species are not considered to be food animals. If these species were to be used for food after use of xylazine, a minimum 14-day WDI is recommended.

Yohimbine

Yohimbine is marketed in the United States as a reversal agent for xylazine, but is not approved for use in any food animal. The FARAD could not locate any foreign approval for yohimbine in food animals. A comparative pharmacokinetic study provided data in steers, which FARAD has used to establish a safe WDI after its use in cattle, sheep, and goats.

Capture Drugs

Several anesthetic/capture/restraint agents are approved for use in wildlife (eg, deer, elk, moose) that also have established new animal drug applications. These include etorphine, carfentanil citrate, yohimbine, and xylazine. The drugs are for species that are not considered food animals; however, there is a "preharvest" interval of 30 to 45 days before hunting season for most of these drug formulations.

Atropine

Atropine often is used as a preanesthetic and also is an antidote for organophosphate intoxication. There are

no FDA-approved formulations of atropine for any species, but there are injectable prescription products marketed under 21 CFR 500.55, which is an exemption from certain drug labeling requirements. In the United Kingdom, atropine is approved for single dose use in cattle (0.03 to 0.06 mg/kg [0.01 to 0.03 mg/lb] of body weight), sheep (0.08 to 0.16 mg/kg [0.04 to 0.07 mg/lb]), and pigs (0.02 to 0.04 mg/kg [0.009 to 0.02 mg/lb]), SC, IM, or IV, with a 3-day milk and 14-day meat WDT. When 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 WDT is recommended if

the veterinarian is satisfied that there are no toxic residues from the poison.

Information from published studies indicate that WDT established by the United Kingdom are particularly adequate to protect human health after use of atropine in food animals. In fact, based on available data, FARAD finds a meat WDI of 7 days adequate after use of atropine as an adjunct to anesthesia. Atropine is a highly water soluble tertiary amine, and it is unlikely that it would pass into the milk; thus, a 24-hour milk WDI should be adequate.

Correction: FARAD Digest

In the FARAD Digest titled "Residue avoidance after topical application of veterinary drugs and parasiticides" (*JAVMA*, May 1, 1997, pp 1288-1289), the withdrawal time for Co-Ral was stated to be 10 days. The correct withdrawal time is 0 days. Suggested milk withholding intervals are not affected by this change. The authors regret the need for this correction. We also remind readers that if any recommendation appears to be incorrect, please contact the authors so that this public record may be updated.

The authors wish to stress that extralabel use of pesticides (such as Co-Ral) is *not* covered by AMDUCA, which applies only to approved animal drugs. There is no extralabel use policy that applies to EPA-registered pesticides, and such use would be illegal under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The FARAD milk withholding intervals for such pesticide preparations were developed to apply to accidental uses in lactating animals.