

Extralabel use of ivermectin and moxidectin in food animals

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The Food Animal Residue Avoidance Databank (FARAD) access centers in the United States have been contacted in recent months about the extralabel use of several macrolide endectocides. The focus of this article is to provide an update on approved use of these drugs. Caution should be exercised with extralabel use of this class of drugs, particularly with moxidectin and ivermectin used in dairy animals. Macrolide endectocides are popular in livestock operations, because they are generally efficacious against most important internal and external parasites, and approved topical formulations can improve producer compliance.

Because many macrolide endectocides are lipophilic, substantial concentrations will be found in edible tissues. As much as 5% of the administered drug can be secreted in milk.¹ Only eprinomectin and moxidectin pour-on formulations are approved for use in dairy cattle. This is because of the intrinsic chemical behavior and unique formulation chemistry of these 2 drugs. Ivermectin and doramectin are not approved for dairy animals, and their meat withdrawal times are long, compared with other less lipophilic parasiticides. Parallel disposition data of milk and plasma ivermectin indicates a milk:plasma area under the curve (AUC) ratio of 1.08 for goats.² Compared with approved oral and subcutaneous routes of administration, approved topical application can result in less absorption but extended meat withdrawal times, because the dermal absorption process is rate limiting, and depletion of residues to established tolerances is prolonged. These pharmaceutical and pharmacokinetic differences are reflected in the approved withdrawal times (WDT; Table 1).

Extrapolated Withdrawal-interval Estimation Methods

This article will focus briefly on specific FARAD cases or requests for information regarding extralabel

use of ivermectin and moxidectin and the process involved in deriving recommended withdrawal intervals (WDI). The FARAD-derived WDI are based on pharmacokinetic data summarized in the FARAD database, which were published in peer-reviewed journals, FDA freedom of information summaries, and Food and Agriculture Organization monographs (Table 2). With complete data sets, the WDI are extrapolated from tissue kinetic information and the approved WDT. The latter are calculated by statistical analysis of tolerance limits containing the 99th percentile of the test animal population with 95% confidence. The FARAD has designated these extrapolated withholding times as WDI to differentiate them from WDT, which are approved by the US FDA. The WDI estimates are based on the effective residue half-life (ERH) derived from tissue kinetic information.^{3,4}

Extralabel Use of Ivermectin

Oral route in goats—Ivermectin is not approved for use in goats in the United States. However, the labeled drench dose for sheep (0.2 mg/kg of body weight [0.09mg/lb]) has an 11-day meat WDT. This is supported by an observed fat and liver depletion half-life of 1.1 days for the intraruminal route in sheep,⁵ recalling that it generally requires about 10 half-lives to eliminate 99% of the drug. Several studies further demonstrated that following intraruminal administration in goats,⁶ bioavailability was 2.5 times lower and the plasma half-life was 2.3 times shorter than in sheep.⁷ These pharmacokinetic differences were not observed with doses administered SC.² On the basis of these supporting data, FARAD estimates that if the oral drench approved for sheep is administered to goats at the labeled dose for sheep, then a meat WDI of 11 days should prevent meat residues in goats. If ivermectin is administered at up to 1.5 to 2.0 times the labeled dose for sheep, as is the common practice, then the WDI needs to be extended by at least 1 extra ERH. Based on the WDT for sheep, and in the absence of tissue depletion data for goats, FARAD assumes an ERH of 2.2 days obtained by dividing the WDT by a half-life multiplier (HLM) value of 5.^{3,4} The HLM represents the number of ERH needed for the concentration in tissue to reach the tolerance level. In summary, FARAD recommends a meat WDI of 14 days for up to 0.4 mg/kg (0.18 mg/lb)

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Table 1—List of approved macrolide endectocides for specific species and routes and approved withdrawal times (WDT)

Drug	Species	Route	Dose (mg/kg of body weight)	Meat WDT (days)	Milk WDT (days)
Ivermectin	Beef cattle	SC	0.2	35	NA
	Beef cattle	Oral	0.2	24	NA
	Beef cattle	Topical	0.5	48	NA
	Sheep	Oral	0.2	11	NA
	Swine	SC	0.3	18	NA
	Swine	Oral	0.1	5	NA
Doramectin	Beef cattle	SC or IM	0.2	35	NA
	Beef cattle	Topical	0.5	45	NA
	Swine	IM only	0.3	24	NA
Epinomectin	Beef and dairy cattle	Topical	0.5	0	0
Moxidectin	Beef and dairy cattle	Topical	0.5	0	0

NA = Not available.

Table 2—Food Animal Residue Avoidance Databank recommended withdrawal intervals (WDI) for ivermectin and moxidectin in dairy species

Drug	Dairy species	Route	Dose (mg/kg of body weight)	Meat WDI (days)	Milk WDI (days)
Ivermectin	Goats	Oral	0.2	11	6
	Goats	Oral	0.2–0.4	14	9
	Cows	Oral	0.2	*24	28
	Goats	SC	0.2	35	40
	Cows	SC	0.2	*35	47
	Goats	Topical	0.5	NA	7
	Cows	Topical	0.5	*48	53
	Moxidectin	Goats	Oral	0.2	14
Goats		Oral	0.5	23	NA
Cows		Oral	0.2	NA	NA
Goats		SC	0.2	NA	NA
Cows		SC	0.2	49	NA
Goats		Topical	0.5	1	1
Cows		Topical	0.5	*0	*0

*FDA approved withdrawal times.
NA = Not available.

per os. These calculations assume that the kinetics of ivermectin are linear. The milk WDI would be 6 days based on a study by Scott et al,⁸ that demonstrated that at 6 days, goats' milk was clear of the drug after an oral dose of 0.2 mg/kg. Based on this information, oral administration up to 0.4 mg/kg will require a milk WDI of at least 8 days in dairy goats.

Oral route in cattle—Ivermectin has the same half-life in cattle as it does in sheep; however, because of a larger volume of distribution, plasma clearance is more rapid in sheep.⁹ For these reasons, WDT and WDI will be shorter in sheep and goats than in cattle. Surprisingly, there is limited depletion data for oral administration of ivermectin in cattle. Following intraruminal administration in cattle, depletion half-lives for ³H-ivermectin in fat and the liver were 4.2 and 5.9 days, respectively.³ This suggests a longer meat WDI (42 days) for the intraruminal route than the approved meat WDT (24 days) with the approved oral paste. Plasma data from that study demonstrated a plasma concentration of 1.0 ng/ml of total residues at 21 days and undetectable at 28 days after a 0.3 mg/kg dose. In the absence of milk residue data, it is possible to estimate a conservative milk WDI of 28 days if we assume parallel depletion for plasma and milk and use published data in which the milk:plasma AUC ratio is 0.766 in cattle.¹ This WDI will be con-

servative for oral administration, as the WDI was based on intraruminal administration of a ³H-labeled drug and a dose greater than the approved label.

Subcutaneous route in goats—Ivermectin was detected up to 25 days in milk from lactating goats given 0.2 mg/kg SC.² There were no differences between plasma and milk pharmacokinetic variables, and the milk:plasma AUC ratio was 1.08, as stated earlier. The elimination half-life was 4 days for plasma and milk, and it would take 40 days (10 half-lives) to eliminate 99% of the drug via milk when administered by this route. Limited tissue residue data from an NRSP-7 study¹⁰ provided an ERH of 4.34 days ($k_e = 0.1594 \text{ days}^{-1}$) in fat, which is the slowest depleting tissue. Application of our algorithm resulted in a WDI of 22 days. As this FARAD estimate is less than the cattle WDT, and there were limited available data, we recommend the cattle WDT of 35 days for an extra margin of safety.

Subcutaneous route in cattle—Ivermectin was detected in milk at 17.8 days and even beyond 29 days when lactating cows were given 0.2 mg/kg SC.¹ The mean milk depletion half-life was 4.72 days, which suggests that it would take at least 47 days to eliminate 99% of the drug via the milk. As seen with goats, a parallel disposition in milk and plasma was observed, and

the milk-plasma AUC ratio was 0.766. These data and WDI estimates are further supported by the observed plasma half-life of 4.32 days in another study of subcutaneous administration in cattle.¹¹

Topical route in goats—Topical application of ivermectin (0.5 mg/kg [0.23 mg/lb]) to dairy goats resulted in about 0.5 ng/ml of milk at 6 days.⁸ Because milk residues were not detected at 7 days, this time can be used as a milk WDI for goats given ivermectin topically. Tissues were not assayed, but plasma concentrations were less than 1.0 ng/ml at 6 days, supporting the milk-plasma relationship described.

Topical route in cattle—There are no available studies on topical application of ivermectin in dairy cattle. However, plasma concentrations were less than 0.1 ng/ml at 42 days, and terminal half-life in plasma was 5.3 days in steers treated topically at the label dose.¹² Assuming that milk-plasma ratios were 0.776, as described earlier, milk concentrations at 42 days should be 0.0776 ng/ml, and it would take at least 2 more half-lives (11 days) to arrive at a milk concentration of approximately 0.02 ng/ml. This milk concentration is equivalent to a safe concentration or a provisional acceptable residue for ivermectin in milk recently described in the literature.¹³ Based on these data and assumptions, a milk WDI of 53 days would be a conservative estimate for dairy cattle exposed to ivermectin pour-on.

Extralabel Use of Moxidectin

Oral route—Moxidectin is not approved for use in goats. Several goat farmers have been administering moxidectin to goats orally at the labeled pour-on dose (0.5 mg/kg) for cattle. It should be stressed that although the cattle label states that this drug has a zero meat and milk WDI by the topical route, it does not imply that the meat and milk WDI will be zero if given orally. Until FARAD obtains sufficient pharmacokinetic data for the topical formulation given orally at 0.5 mg/kg in goats, FARAD has based its WDI recommendation on European Union approvals in sheep and published studies on oral administration. It should be noted that oral bioavailability of moxidectin is 2.7 times lower in goats than in sheep,^{6,11} and the half-life in goats is 1.8 times shorter in sheep. This suggests that European Union WDI for moxidectin in sheep will be more than adequate for estimation of WDI for moxidectin drench in goats. In France and the United Kingdom, the oral formulation for sheep at a dose of 0.2 mg/kg [0.09 mg/lb] has a 14-day meat WDI.^{14,15} On the basis of these data, FARAD estimates an ERH of 3 days for this dose and, therefore, includes an additional 3 ERH (9 days; WDI, 23 days) for goats given of a moxidectin pour-on formulation (0.8 to 1.6 mg/kg [0.36 to 0.73 mg/lb]) orally. It must be recognized that there are pharmaceutical differences between the dermal formulations being used in goats and the European approved drench, and these differences may influence tissue depletion. It is also important to stress that, irrespective of the route of administration, moxidectin has a longer mean residence time than ivermectin in sheep and cattle when given orally or by the SC route.^{7,11,16}

This may be related to its greater persistence once absorbed systemically and, therefore, caution should be exercised when using this drug in an extralabel manner, especially when administering the pour-on formulation orally to goats.

Subcutaneous route—There are limited pharmacokinetic data available in the literature for subcutaneous administration in goats,⁶ which makes estimation of meat or milk WDI difficult. In cattle, the half-lives for total residue of moxidectin in fat, liver, kidney, and muscle ranged from 9.0 to 12.2 days after SC administration (0.2 mg/kg).¹⁷ At 49 days, injection sites and back fat concentrations were 1,178 and 141 µg/kg, respectively, and liver and kidney concentrations were less than 11 µg/kg. As European maximum residue concentrations for fat, kidney, and liver are 200, 20, and 20 µg/kg, respectively,¹⁸ then 49 days would be a conservative WDI for moxidectin given by the subcutaneous route to cattle. The FDA has also established tolerances of 50 µg/kg and 200 µg/kg for parent moxidectin in muscle and liver, respectively, in cattle.¹⁹ Unfortunately, FARAD has no milk residue information or milk-plasma AUC relationship from which to base milk WDI for this drug if given subcutaneously to dairy goats or dairy cattle.

Topical route—Moxidectin is approved as a pour-on only (0.5mg/kg) in cattle with zero meat and milk WDI, and it is possible that increasing the dose substantially by this route will most likely require estimation of meat and milk WDI (Table 1). In the absence of data for goats, FARAD assumes that plasma and tissue clearance would be greater in goats than in cattle, as described for ivermectin. However, FARAD would err on the side of caution and recommend a milk and meat WDI of 1 day if this drug was applied topically to goats.

The calculated WDI in this article were based on limited available pharmacokinetic data. Updated WDI can be obtained from our FARAD web site (www.farad.org) as more relevant data become available. It should also be noted that the recommended WDI are case specific and are not applicable for other doses or routes of administration, nor should they be extrapolated to other food animal species. If veterinarians are interested in obtaining such information, please contact us at 1-888-USFARAD, farad@ncus.edu, or farad@ucdavis.edu.

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