Avoiding violative flunixin meglumine residues in cattle and swine

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Flunixin meglumine is an NSAID that is approved by the FDA for the treatment of inflammatory conditions in cattle, horses, and swine and alleviation of pain associated with musculoskeletal disorders and colic in horses; it is not labeled for alleviation of pain in food-producing animals. Currently, there are no FDA-approved drugs for the treatment of pyrexia, inflammatory conditions, or pain in minor food-producing species such as sheep and goats. Owing to the lack of alternatives, veterinarians often administer food-producing animals products containing flunixin in an extralabel manner for the treatment of signs of pain. In the United States, NSAIDs are among the most frequently administered drugs for analgesia in cattle; however, such use is considered extralabel and must be in accordance with AMDUCA.[1] In a 1995 survey[2] of dairy veterinarians, NSAIDs (eg, flunixin, aspirin, phenylbutazone, and dipyrone) were the second most frequently prescribed class of drugs behind antimicrobials, and the majority of respondents listed flunixin as one of the top 20 most frequently prescribed drugs. Nonsteroidal anti-inflammatory drugs possess analgesic, antipyretic, and anti-inflammatory activities, which are produced through inhibition of prostaglandin synthesis secondary to inhibition of the cyclooxygenase enzyme.[3,4]

ABBREVIATIONS

5OHF	5-hydroxy flunixin
FARAD	Food Animal Residue Avoidance and Depletion Program
LPS	Lipopolysaccharide
M/D	Marker residue–to–parent drug ratio
MRL	Maximum residue limit
MRT	Mean residence time
ppb	Parts per billion
$t_{1/2}$	Elimination half-life
WDI	Withdrawal interval
WDT	Withdrawal time

Frequent extralabel use of flunixin for the treatment of unlabeled species or conditions or by routes or at doses other than those on the label has resulted in violative residues in tissues of treated animals.[5,6] In 2012, the USDA Food Safety and Inspection Service reported the identification of 1,166 drug residue violations in 928 cattle, sheep, and swine; 101 (9%) of those residues were caused by flunixin.[6] All 101 flunixin residues were detected in cattle, of which 64 were detected in dairy cattle, 22 were detected in veal calves, and 15 were detected in beef cattle **(Table 1)**.[6] In a study[7] that involved screening for 5OHF in milk samples obtained from large tanker trucks that transport milk to dairy processing plants, the marker residue (ie, the residue monitored in milk or tissues for regulatory purposes; can be the parent drug or a metabolite of that drug[8]) for flunixin, 1 of 500 (0.2%) samples contained 5OHF concentrations > 2 ppb, the tolerance for flunixin residues in milk in the United States. Although flunixin is approved for use in cattle, it is consistently one of the most frequently identified violative residues in meat and milk products obtained from cattle.[6]

As a reminder to readers, there is an important distinction between WDI and WDT. The WDI is a scientifically derived recommended withholding time for meat or milk products from animals following administration of a drug in an extralabel manner.[9] Accurate prediction of appropriate WDIs for flunixin following extralabel administration to food-producing animals is essential to help producers minimize the incidence of violative flunixin residues in products intended for human consumption and is in the best interest for consumer health and safety.[1] The WDT is defined as the time required after administration of a drug in accordance with its label for tissue concentrations of the drug or its metabolites to decrease below approved tolerances or MRLs established by a regulating body.[9] Mathemati-

cally, the WDT is the point following administration of the labeled dosage of a drug after which there is 95% confidence that 99% of treated animals in the reference population will have tissue or milk residues less than the tolerance or MRL for that drug.[10] The tolerance (established by the FDA in the United States) or MRL (established by the FDA equivalent in foreign countries) is the highest concentration of a chemical, drug, or drug metabolite that is legally acceptable in animal tissues or milk intended for human consumption (ie, the highest concentration that can be consumed without any adverse risk to health).[10] Tissue drug concentrations below established tolerances or MRLs are generally considered indicative of correct drug use and ensure compliance with legal requirements for low drug residues in unprocessed food. The tolerances and MRLs for flunixin are established for target tissues (liver and muscle) and milk on the basis of assessment of risk to human health and flunixin residue data.[11] In cattle and swine, the liver is used as the primary target tissue for establishing tolerances or MRLs for flunixin-free acid. Although the tolerance (United States) and MRL (other countries) are both defined as the highest legally acceptable concentration of a drug in tissues or milk intended for human consumption, the magnitude of those limits frequently varies among countries or jurisdictions **(Table 2)**,[12,13] and US veterinarians should be cognizant of those differences when treating food-producing animals that are destined for export to a foreign country. Tolerances established by the FDA for drugs approved for use in food-producing animals are published in the US Code of Federal Regulations Title 21 part 556.[12] The aims of this FARAD digest are to discuss the pharmacokinetics and tissue residue data for flunixin and to establish appropriate conservative recommendations for meat and milk WDIs following extralabel use of flunixin in cattle and swine.

Cattle

Flunixin is the only NSAID approved by the FDA for use in beef and dairy cattle for the control of pyrexia associated with bovine respiratory tract disease and inflammation associated with endotoxemia and mastitis. The FDA has placed it on a list of drugs of high regulatory concern because of its extensive use in veterinary medicine and the potential risk consumption of food with flunixin residues poses to human health.[14] Flunixin is commercially available under the trade names of Banamine, Flunixamine, Prevail, Citation, Equileve, and Meflosyl Solution in the United States; Flunixin, Finadyne, and Cronyxin in the United Kingdom; Finadyne in South Africa and Australia; and Megludyne in India. In the United States, the FDA-approved preparations for cattle contain flunixin meglumine salt, which is to be administered by the IV route only. Intravenous administration can be stressful for treated animals and requires more time, skill, and training by the drug administrator. Unfortunately, on the basis of the number and nature of requests submitted to FARAD, it appears that

Table 1—Summary of US animals with violative drug residues detected at the time of slaughter in 2012 as reported by the USDA Food Safety and Inspection Service.[6]

Species	Production class	No. (%) of animals with violative residue for any drug	No. of animals with violative flunixin residues
Cattle	Dairy cows, heifers, and bulls	452 (49)	64
	Veal calves*	307 (33)	22
	Beef cows and steers	95 (10)	15
Sheep	Lambs†	2 (0.2)	0
Swine	Sows and market hogs‡	72 (7.8)	0
Total		**928 (100)**	**101**

*Veal calves were defined as immature cattle lacking a functional rumen intended for meat production and included both beef and dairy breeds. †Lambs were defined as sheep < 14 months old. ‡Market hogs were defined as pigs approximately 6 months old with a live body weight of approximately 91 to 136 kg (200 to 300 lb).

Table 2—Comparison of US tolerances[12] and European Union MRLs[13] for flunixin-free acid in various tissues of cattle and swine and 5OHF in milk of cattle.

Species	Tissue	US tolerance (ppb)	European Union MRL (ppb)
Bovine	Liver	125	300
	Muscle	25	20
	Kidney	—	100
	Fat	—	30
	Milk	2	40
Swine	Liver	30	200
	Muscle	25	50
	Kidney	—	30
	Fat	—	10

— = Not established.

flunixin is frequently administered by the IM or SC routes in field settings, and the number of beef and dairy cattle with violative tissue residues of flunixin at the time of slaughter associated with administration of the drug by an extralabel (IM or SC) route has been increasing.[15,16] In the United States, the labeled dosage for flunixin in cattle is 1.1 to 2.2 mg/kg (0.5 to 1.0 mg/lb), IV, every 24 hours or divided into 2 doses every 12 hours for 3 days with a WDT of 4 days for meat and 36 hours for milk.[17] However, there is a combination product containing florfenicol and flunixin[a] that is approved by the FDA for SC administration to beef and nonlactating (< 20 months old) dairy cattle for the treatment of bovine respiratory tract disease; this product has a longer meat WDT (38 days)[18] than flunixin-only products because of its florfenicol component.[19] In the European Union, a transdermal formulation of flunixin[b] has been approved for pour-on application to cattle for the treatment of pyrexia associated with bovine respiratory tract disease and acute mastitis at a dosage of 3.3 mg/kg (1.5 mg/lb), topically, once, with a WDT of 7 days for meat and 36 hours for milk.[20]

In the United States, extralabel drug use is allowed under AMDUCA. It is important to note that AMDUCA allows administration of a drug by an extralabel route for therapeutic purposes only; it expressly prohibits administration of a drug by an extralabel route for convenience purposes.[1] Therefore, administration of flunixin by any route other than IV because it is easier is illegal. Nevertheless, the fact is that flunixin is commonly administered to cattle by routes other than IV, and until recently, the FARAD-recommended WDIs were 30 days for meat and 72 hours for milk following a single IM injection and 8 days for meat and 48 hours for milk following a single PO administration of flunixin at the labeled dose (1.1 to 2.2 mg/kg).[15] However, review of the existing data[6,15,21–25] suggests that the WDI for meat may need to be extended to as long as 60 days following administration of multiple IM or SC doses of flunixin to ensure that violative residues are not detected in treated cattle. The WDI for milk following administration of multiple IM or SC doses of flunixin has not been established.

Effect of administration route on WDI

Multiple studies[21–23,26–35,c] have been conducted in which the pharmacokinetics of flunixin following administration by various routes to cattle have been determined, and the apparent plasma $t_{1/2}$s for those studies were summarized **(Table 3)**. The $t_{1/2}$ of flunixin following IV administration varies substantially among studies,[21–23,26–29,32,33,35,c] which probably is a reflection of differences among those studies in production class, age, and health status of study animals; dosage administered; and methods used to determine the pharmacokinetics, particularly the terminal portion of the drug concentration versus time curve. The mean apparent plasma $t_{1/2}$ of flunixin following IV administration of 1 dose (1.1 to 2.2 mg/kg) of the drug to healthy mature cattle (lactating and nonlactating dairy cows and beef cattle) ranged from 3.14 to 5.70 hours in all studies[21–23,26,27,35,c] except one.[28] In the exception,[28] the mean ± SD apparent $t_{1/2}$ of flunixin (11.6 ± 8.0 hours) was 2 to 3 times as long as that in the other studies,[21–23,26,27,35,c] probably because the cows in that study[28] were administered 2.2 mg of flunixin/kg, IV, once daily for 3 days, whereas the cows in the other studies[21–23,26,27,35,c] were administered the drug only once and blood samples were collected for 96 hours after the last dose of flunixin was administered. Also, the $t_{1/2}$ in that study[28] was influenced by a fairly long concentration-time curve because the plasma flunixin concentrations were quantifiable for a longer duration owing to the increased sensitivity of

Table 3—Apparent plasma $t_{1/2}$ (hours) of flunixin meglumine in cattle following IV, IM, SC, or PO administration.

					Route of administration			
Reference	Production class	No. of animals	Dose (mg/kg)	Frequency	IV	IM	SC	PO
29	Calf	8	2.2	Once	6.87 ± 0.49	—	—	—
31	Calf	6	2.2	Once	—	6.25 ± 0.81	—	—
34	Beef cattle	32	2.2	Once	—	—	8.8	—
27	Beef cattle	8	2.2	Once	4.8 ± 1.0	—	6.3 ± 3.2	—
26	Lactating cattle	NA	1.1	Once	3.7 ± 0.7	—	—	—
c	Lactating cattle	3	2.2	Every 24 h for 3 d	4.0	4.4	—	7.1
21	Lactating cattle	6	1.1	Once	3.14	5.20	—	—
35	Lactating cattle	6	2.2	Once	5.70 ± 2.6	—	—	—
22	Lactating cattle	12	1.1	Every 12 h for 1 d	3.42 ± 0.98	4.48 ± 1.77	5.39 ± 2.47	—
28	Lactating cattle	5	2.2	Every 24 h for 3 d	11.6 ± 8	15.5 ± 8	—	—
30	Nonlactating cattle	10	2.2	Once	—	5.18 ± 0.98	7.46 ± 2.6	—
23	Nonlactating cattle	1	2.2	Once	3.80*	—	—	—
23	Nonlactating cattle	3	2.2	Every 12 h for 14 d	—	6.4–9.0†		
23	Nonlactating cattle	3	2.2	Every 6 h for 14 d	—	12.1–24.8†	—	—
33	Heifer	6	1.1	Once	8.12	—	—	—
23	Heifer	1	2.2	Once	4.30*	—	—	—
32	Heifer	6	2.2	Once	3.9–8.9†	—	—	5.3–6.7†

Values represent mean ± SD (when available) unless otherwise noted.
*Calculated value for 1 animal. †Range.
— = Not calculated. NA = Not available.

the detection method (limit of quantification, 0.5 ng/mL [0.5 ppb]) used, compared with that of the other studies.[21–23,26,27,35,c]

In general, the apparent plasma $t_{1/2}$ (range, 4.4 to 6.25 hours)[21,30,31,c] of flunixin following IM administration of the labeled dose (1.1 to 2.2 mg/kg) once was longer than that following a single IV injection of the same dose, and the apparent $t_{1/2}$ (range, 6.9 to 24.8 hours)[23,28] following IM administration of multiple doses of flunixin (2.2 mg/kg) was even longer (Table 3). The apparent positive association between the plasma $t_{1/2}$ and number of IM doses of flunixin administered is likely a function of drug retention in tissues damaged by injection of the drug. Drug absorption is frequently delayed by tissue damage, and persistent drug concentrations at an injection site may create a phenomenon known as flip-flop kinetics.[15] This issue warrants further investigation in regard to flunixin because, to our knowledge, a significant increase in serum creatine kinase activity, an indicator of skeletal muscle damage, following IM administration of flunixin has been reported by the investigators of only 2 studies.[36,37]

The fact that the mean apparent plasma $t_{1/2}$ of flunixin following SC or PO administration of a single dose of the drug was approximately 1.5 to 2 times as long as that following IV administration of a single dose in beef and lactating cattle (Table 3) suggests that administration of the drug by an extralabel route is a contributing factor associated with violative tissue residues in cattle at slaughter.[22,27,30,32,38] That observation was supported by results of another study,[28] in which the MRT (ie, the mean time that drug molecules stay in the body before elimination) of flunixin in lactating dairy cattle following IM administration (44.3 hours) was substantially longer than that following IV administration (36.7 hours). Collectively, the results of those studies[22,27,28,30,32,38] suggest that, in cattle, tissue elimination of flunixin varies with route of administration.

In the United States, the tolerance for 5OHF, the marker residue for flunixin, in milk is 2 ppb,[12] and the WDT for milk following administration of the labeled dosage of flunixin is 36 hours.[17] In a study[39] in which 8 lactating Holstein cows were administered ^{14}C-flunixin (2.2 mg/kg, IV, q 24 h for 3 days), the mean total radioactive flunixin residues in milk were 66, 20, and 14 ppb at 12, 24, and 36 hours, respectively, after the last flunixin injection. The mean milk 5OHF concentration was 6 ppb at 36 hours after the last injection; however, the investigators attributed that high mean concentration to exceptionally high 5OHF concentrations in the milk of 1 cow.[39] In a study[22] with a crossover design, 12 lactating Holstein cows were administered 2 doses of flunixin (1.1 mg/kg) with a 12-hour interval between doses by each of 3 routes (IV, IM, and SC). A milk 5OHF concentration > 2 ppb was detected at 36 hours after the last flunixin injection for 1 cow following IM administration and 1 cow following SC administration but was not detected in any of the cows following IV administration; however, the milk 5OHF concentration was < 2 ppb at 48 hours after the last flunixin injection for all cows following all 3 routes of administration.[22] Thus, the investigators concluded that administration of flunixin to lactating cows in accordance with the label consistently resulted in milk 5OHF concentrations less than the tolerance at the WDT, whereas milk 5OHF concentrations greater than the tolerance could persist at the WDT if flunixin was administered by an extralabel (IM or SC) route.[22] In yet another study,[28] 20 lactating dairy cattle underwent an IV infusion of either LPS (n = 10) or sterile saline (0.9% NaCl) solution (10) and then 5 cows in each group were administered flunixin (2.2 mg/kg) by either the IV or IM route once daily for 3 days. The milk 5OHF concentration was > 2 ppb for 6 and 2 cows at 36 and 48 hours, respectively, after the last flunixin injection.[28] Collectively, the results of those studies[22,28,39] indicate that administration of flunixin by an extralabel (IM or SC) route, particularly if multiple doses are administered by that route, can result in violative flunixin residues in the milk of dairy cattle.

The apparent $t_{1/2}$s of flunixin in milk, liver, and kidneys of cattle following IV administration of the drug as reported in the scientific literature[13,24,25,39–41] were summarized **(Table 4)**. Following IV administration of flunixin (2.2 mg/kg, q 24 h for 3 days) to adult cattle, the apparent $t_{1/2}$ in the liver (9 to 51 hours)[25] and kidneys (22 to 37 hours)[25] is substantially longer than the apparent $t_{1/2}$ in plasma (11.6 ± 8 hours).[28] Given that the apparent plasma $t_{1/2}$ of flunixin in adult cattle tends to be longer following IM or SC administration than that following IV administration (Table 3), it is likely that the apparent $t_{1/2}$s of flunixin in the liver and kidneys follow the same pattern. In the study[28] in which lactating dairy cows were administered flunixin for 3 days by the IV or IM route

Table 4—Apparent $t_{1/2}$ in the milk, liver, and kidneys of cattle following IV administration of flunixin.

Reference	Production class	No. of animals	Dose (mg/kg)	Frequency	$t_{1/2}$ (h)		
					Milk	Liver	Kidneys
25	Cattle	3	2.2	q 24 h for 3 d	—	34.2–36.3*	29.6–31.7*
13	Cattle	3	3.6	q 24 h for 3 d	—	115.6	52.7
24	Lactating cow	2	2.2	q 24 h for 2 d	—	27.9–30.3*	21.5–27.6*
40	Lactating cow	4	2.0	q 24 h for 3 d	6.68–22.7*	—	—
39	Lactating cow	8	2.2	q 24 h for 3 d	26.9	—	—
41	Lactating cow	8	2.2	q 24 h for 3 d	13.82	—	—

*Range. — = Not determined.

after IV infusion of LPS or saline solution, the mean concentrations of flunixin residues in liver, kidney, muscle, and other tissues following IV administration were similar or slightly lower than those following IM administration, and all liver and kidney residues were below the respective tolerances at 96 hours after the last IV dose. However, the flunixin residues at the IM injection sites were 100 to 300 times those at the IV injection sites.[28] Intramuscular or SC administration of flunixin-only formulations generally causes extensive tissue damage but SC administration of a florfenicol-flunixin combination does not because of differences in the vehicles used in the respective formulations. Flunixin accumulates in damaged tissue and is slowly released from that tissue into the systemic circulation, which results in extended retention of the drug in the body[15,36] and possible violative residues in tissues used for human consumption. It is also one of the reasons that, in cattle, flunixin is approved for IV administration only.

The apparent plasma $t_{1/2}$ of flunixin in calves and heifers is generally longer than that for adult cattle following IV administration of the same dose of the drug (Table 3). This suggests that the flunixin elimination rate may increase as the age of the animal increases.

Effect of disease on WDI

Sick cattle are frequently treated with flunixin and other drugs concurrently, and some of those drugs may alter the pharmacokinetic profile of flunixin and result in violative drug residues in milk or meat products from treated cattle.[42] For example, the apparent plasma $t_{1/2}$ of flunixin (4.35 ± 1.82 hours) in cows with naturally occurring mastitis that were treated with flunixin (2.2 mg/kg, IV, once), ceftiofur sodium (2.2 mg/kg, IM, q 24 h for 3 days), and ceftiofur hydrochloride (10 mL/mammary gland, intramammary, q 24 h for 5 days) or cephapirin sodium (10 mL/mammary gland, intramammary, q 12 h for 3 days) was longer than that (3.68 ± 1.97 hours) for healthy control cows that received the same treatments.[42]

In the study[28] in which lactating dairy cows were administered flunixin after IV infusion of LPS or saline solution, the MRT of flunixin for the LPS-treated cows (41.1 hours) was longer, although not significantly so, than that for the saline-treated cows (36.7 hours) following IV administration, whereas the MRT of flunixin for LPS-treated cows (62 hours) was significantly longer than that for saline-treated cows following IM administration (44 hours). Also, 1 LPS-treated cow had a liver flunixin concentration (177 ppb) that exceeded the tolerance (125 ppb) at 96 hours after IM administration of the drug, and the flunixin concentrations in other tissues of that cow were greater than those for the other cows of that study.[28] The investigators of that study[28] concluded that LPS inhibits the metabolism of flunixin in cattle, but that phenomenon does not appear to be unique to cattle. Following IV administration of 1 dose of flunixin (2.2 mg/kg), the plasma clearance rate was significantly slower and the apparent $t_{1/2}$ was significantly longer in rats with experimentally induced endotoxemia, compared with healthy control rats.[43]

Flunixin persists in inflamed tissues and has anti-inflammatory activity that extends beyond the period associated with detectable plasma concentrations of the drug.[29] Following administration, most NSAIDs are highly bound to plasma proteins, and the percentage of flunixin bound to plasma protein can exceed 99% in some cases.[23] Although protein binding can limit the passage of a drug from plasma into interstitial fluid, it also facilitates the sequestration of NSAIDs in inflamed tissues because protein readily leaks into those tissues.[29,44] It is likely that inflammation alters the metabolism or disposition of flunixin, which results in a prolonged MRT of flunixin residues in milk and other tissues.[28,42] Detectable flunixin concentrations persisted in milk for up to 60 hours after administration in 3 of 10 cows with clinical mastitis that were treated with 1 (labeled) dose of flunixin in conjunction with parenteral and intramammary administration of antimicrobials (mean ± SD flunixin concentration, 13.02 ± 10.93 ppb), whereas flunixin was detectable in milk for only 24 hours after administration in all 10 like-treated healthy control cows.[42] In that study,[42] the ratios of 5OHF concentration (marker residue) to flunixin concentration (parent drug) in milk for healthy control cows (range, 1.25 to 2.5; ie, the concentration of the marker residue was greater than that of the parent drug) were several times greater than those for cows with mastitis (range, 0.023 to 0.167; ie, the concentration of the marker residue was less than that of the parent drug) within 24 hours after flunixin administration, which further suggests that flunixin is metabolized quicker in healthy cows than in diseased cows. Results of a study[8] in which a physiologically based pharmacokinetic computation model was developed to predict the M/D for flunixin and other drugs (ceftiofur, enrofloxacin, and sulfamethazine) in cattle and swine and evaluate how disease effects that ratio in various tissues (plasma, liver, kidneys, and muscle) similarly indicate the M/D for healthy animals is generally greater than that for diseased animals, regardless of the drug or tissue evaluated. Also, the M/D is not a fixed value; it changes over time.[8] Those findings challenge the wisdom of regulatory policies that use a fixed M/D determined from a limited number of studies involving healthy animals to establish tolerances or MRLs because, in practice, drugs are generally not administered to healthy animals.[8]

In a survey[45] of cull dairy cows performed at 21 US abattoirs between July 2003 and July 2004, the liver flunixin concentration was greater than the tolerance for 50 of 710 (7.04%) cows that appeared diseased, compared with only 2 of 251 (0.80%) cows that appeared healthy. In rats with experimentally induced acute liver or kidney disease that were treated with 1 dose of flunixin (2.2 mg/kg, IV), the apparent $t_{1/2}$ and total body clearance rate of flunixin were

significantly longer, compared with those of control rats without experimentally induced liver or kidney disease.[46] In diseased animals, inflammation and infection alter liver and kidney function, which can decrease the clearance rate of flunixin,[46–48] most likely because flunixin accumulates at inflammatory sites owing to its affinity for binding to inflammatory proteins.[49] The distribution of flunixin within the central and peripheral compartments may also be altered during certain disease conditions. In septic animals, the distribution of body fluid shifts such that the distribution of flunixin into the peripheral compartment increases while the distribution of flunixin into the central compartment decreases,[50] which can lead to violative residues. Thus, it is likely that the current flunixin WDT, which was determined on the basis of pharmacokinetic data obtained from a reference population of healthy animals, likely underestimates the time required for tissue clearance of the drug to below tolerances in diseased animals. Therefore, data obtained from both healthy and diseased animals should be used to more accurately estimate the WDT for drugs administered to food-producing species under normal practice conditions.

For cattle treated with the labeled dosage of flunixin, the WDT for meat is 4 days.[17] In a study[51] in which a population pharmacokinetic model was developed to predict tissue residues and the WDI for flunixin in cattle on the basis of data obtained from a diverse population (healthy and diseased animals of various ages) of cattle that were administered various dosages of the drug, the estimated WDI for meat was 7 days. In another study,[42] cows with mastitis had mean total flunixin concentrations in milk that exceeded the tolerance for > 60 hours after administration, whereas the mean 5OHF concentrations in milk exceeded the tolerance for only 36 hours after administration. The findings from that study[42] suggest that total flunixin concentration may be a better marker residue than 5OHF in milk in some cases. As previously mentioned, the M/D is not a fixed value,[8] and concentration data for the drug or drug metabolite that persists the longest in the target tissue of interest will provide the most conservative estimate of the WDI.

Recommendations

Following administration of a single labeled dose of flunixin (1.1 to 2.2 mg/kg) to adult cattle by an IV or extravascular (IM, SC, or PO) route, FARAD currently recommends a WDI of 84 and 96 hours, respectively, for milk[22,42] and 7 and 10 days, respectively, for meat.[28,51] Administration of multiple doses of flunixin by an extravascular route may require extending the WDI for meat to as long as 60 days to ensure that violative residues are not detected in treated cattle.[6,15,21–25] These recommendations were made on the basis of a review of the currently available pharmacokinetic data for flunixin in cattle and should be revisited as new data become available.

Swine

In swine, flunixin is approved for control of pyrexia associated with respiratory tract disease at a dosage of 2.2 mg/kg, IM, once, and the WDT for meat is 12 days.[52] Lameness is a frequent complication associated with low growth rate and poor reproductive performance in breeding-age swine, which represents a welfare concern and has a large negative economic impact for producers.[53] In the United States, lameness is the third most common reason cited for culling sows, and lame sows comprise 15% of the cull market.[54] Appropriate pain management, regardless of the etiology, is critical for veterinarians and producers.[53–55] Currently, there are no analgesics approved for use in swine in the United States. Review of the FARAD inquiry database suggests that flunixin is frequently used in swine, and it is frequently administered by extralabel (PO or SC) routes. In a study[56] with a crossover design in which the pharmacokinetics of flunixin was determined following administration of a target dose of 2.2 mg/kg to adult swine by IV, IM, and PO routes, the mean apparent plasma $t_{1/2}$ did not differ significantly following IV (6.29 hours; range, 4.84 to 8.34 hours), IM (7.49 hours; range, 5.55 to 12.98 hours), and PO (7.08 hours; range, 5.29 to 9.15 hours) administration. In that study,[56] the mean ± SD plasma flunixin concentration at 48 hours after IM administration (10.2 ± 8.8 ng/mL) was 3.8 and 4.6 times that following IV (2.68 ± 1.80 ng/mL) and PO (2.2 ± 1.1 ng/mL) administration, respectively. The bioavailability of flunixin following PO administration was 22% (range, 11% to 44%), whereas that following IM administration was 76% (range, 54% to 92%).[56] In growing swine, the apparent $t_{1/2}$ of flunixin was 7.7 to 7.8 hours after IV administration of the drug at doses ranging from 2.0 to 3.0 mg/kg.[57,58] The mean apparent $t_{1/2}$ of flunixin following IV administration (6.29 to 7.8 hours)[56–58] is almost twice that following IM administration (3 to 4 hours).[52] The difference in the $t_{1/2}$ of flunixin following IV and IM administration is likely attributable, at least partially, to differences in assay sensitivity and breed, age, and health status of the study pigs.

In swine, protein binding of flunixin is > 98% at physiologically relevant plasma flunixin concentrations (0.30 to 10 µg/mL).[57] The volume of distribution of flunixin at the steady state is fairly large (1.83 to 2.35 L/kg) in growing pigs,[57,58] which is likely a reflection of the drug's high lipophilicity and protein binding characteristics. Unfortunately, aside from the data generated by the flunixin manufacturer during the FDA approval process,[52] no studies have been conducted to determine tissue residues in swine following IV or extravascular routes of administration. Therefore, following extralabel use of flunixin, WDIs calculated solely on the basis of plasma drug concentrations may result in violative tissue residues, and further tissue residue studies need to be conducted.

Recommendations

Following administration of a flunixin formulation that does not have a swine label, even at the labeled dosage (2.2 mg/kg, IM, once), FARAD recommends a meat WDI of 13 to 15 days. That WDI was calculated by adding a safety factor of 10% to the label WDT (12 days) to be in compliance with AMDUCA stipulations.[59] Following IV or PO administration of 1 or more doses of flunixin (2.2 mg/kg), FARAD recommends a meat WDI of 21 days. That WDI was calculated by use of the half-life multiplier technique as described.[59] For swine, veterinarians are advised to prescribe flunixin formulations specifically labeled for swine at the labeled dosage to avoid greatly extended WDIs and violative tissue residues of the drug.

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Footnotes

a. Resflor Gold, Merck Animal Health, Summit, NJ.
b. Finadyne transdermal, MSD Animal Health, Kenilworth, NJ.
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Appendix

List of useful websites that provide more detailed information regarding the use of flunixin meglumine in cattle and swine in the United States.

- FARAD (www.farad.org).
- Food and Drug Administration Center for Veterinary Medicine (www.fda.gov/AnimalVeterinary/default.htm).
- United States Department of Agriculture Food Safety and Inspection Service, Residue Testing, National Residue Program (www.fsis.usda.gov/wps/portal/fsis/topics/data-Collection-and-reports/chemistry/residue-chemistry.
- AVMA AMDUCA extralabel drug use algorithm (www.avma.org/KB/Resources/Reference/Pages/AMDUCA2.aspx).