FARAD Digest

Extralabel use of nonsteroidal anti-inflammatory drugs

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In a recent survey of food animal veterinarians, it was found that 93% reported using nonsteroidal anti-inflammatory drugs (NSAID), and almost 60% reported using these drugs more than once a week.[1] Dairy practitioners use NSAID more frequently than beef practitioners, and flunixin meglumine is used more frequently than aspirin, phenylbutazone, or dipyrone. At this time, no commonly used NSAID has been approved for use in food animals in the United States. The purpose of this article is to provide practitioners with recommended milk and meat withdrawal intervals (WDI) for some uses of NSAID.

Aspirin

Aspirin (acetylsalicylic acid) is commonly used in food animals. Available over-the-counter, it is most commonly administered as 60- or 240-grain tablets (1 grain = 65 mg). Aspirin formulations have not been approved by the FDA-Center for Veterinary Medicine (FDA-CVM); however, the agency considers use of aspirin to be of low regulatory concern. Under this policy, the FDA-CVM assumes that veterinarians know how to use the drug properly and that the drug does not present a substantial food safety issue; therefore, formal drug approval is not necessary. However, it also means that uniform WDI recommendations have not been established for commercial aspirin products, although some product labels do contain warnings against use in lactating dairy animals. Despite the fact that aspirin is of low regulatory concern, some epidemiologic data suggest a link between salicylates and Reye's syndrome in children with chickenpox or influenza.[2] For this reason, FARAD recommends minimum meat and milk WDI of 24 hours for typical uses of aspirin in food animals.

Dipyrone

Extralabel use of dipyrone in food animals is specifically prohibited by the FDA-CVM; therefore, FARAD does not offer extralabel WDI recommendations for this drug. Reasons for this prohibition are described in the Dec 6, 1995 *CVM Update* and include a lack of data indicating that dipyrone is safe and effective as well as lack of pharmacokinetic and residue information that can be used to establish a WDI. In addition, dipyrone has been associated with toxic effects in human beings, including bone-marrow toxicosis, agranulocytic anemia, and teratogenicity.

Table 1—FARAD recommended withdrawal intervals

Drug	Species	Dosage*	Milk withdrawal interval (h)	Meat withdrawal interval (d)
Aspirin	All food animals	All usual dosages	24	1
Dipyrone		Not approved in food animals		
Ketoprofen	Cattle	3.3 mg/kg, IV or IM, q 24 h, for up to 3 days	24	7
	Goats	3.3 mg/kg, IV or IM, q 24 h, for up to 3 days	24	7
	Sheep	3.3 mg/kg, IV or IM, q 24 h, for up to 3 days	24	7
Flunixin meglumine	Cattle	1.1–2.2 mg/kg, IV or IM, q 24 h, for 3 to 5 days	72	10
	Swine	2 mg/kg, IM	NA	15
Phenylbutazone	Cattle	6 g/animal, IV or IM	96	12
		4–6 g/animal, IV or IM, followed by up to 2 g/animal daily	120	21

*To convert to mg/lb, divide by 2.2.
NA = not applicable.

Ketoprofen

There are few published residue or pharmacokinetic data for ketoprofen. Available data in cattle indicate a short terminal half-life of 30 minutes and a small volume of distribution (0.2 L/kg [0.09 L/lb]). Milk concentrations following IV administration at the rate of 3.3 mg/kg (1.5 mg/lb) of body weight to dairy cows were always less than the limit of quantitation (27 ng/ml). Results in lactating goats also indicated a short half-life (20 minutes) and a small volume of distribution (0.23 L/kg [0.10 L/lb]), suggesting limited distribution in tissue. Ketoprofen was not detected in milk from goats treated with a single IV bolus at 2.2 mg/kg (1 mg/lb). In France, ketoprofen is approved for use in cattle, and recommended meat and milk WDI for this

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References to studies mentioned in this report and references for FARAD determinations are available on written request.

Table 2—Flunixin veterinary products approved for use in food animals in foreign countries

Country approved	Species	Dosage*	Milk withdrawal interval (h)	Meat withdrawal interval (d)
England	Cattle	2.2 mg/kg, IV, q 24 h, for up to 5 days	36	7
France	Cattle	2 mg/kg, IV or IM	0	10
	Swine	2 mg/kg, IM	NA	15
Switzerland	Cattle	2.2 mg/kg, IV or IM, q 24 h	72	5

See Table 1 for key.

drug given IV or IM at 3.3 mg/kg, every 24 hours, for 3 days, are 4 and 0 days, respectively. On the basis of this information, FARAD recommends meat and milk WDI of 7 days and 24 hours, respectively, for use of ketoprofen in cattle, sheep, or goats at dosages of up to 3.3 mg/kg, every 24 hours, for up to 3 days (Table 1).

Flunixin Meglumine

In the United States, flunixin meglumine is labeled for use in horses only. Only limited pharmacokinetic and residue data are available in food animals. In 1 study, 1 cow was given 2.2 mg of flunixin meglumine/kg (1 mg/lb), IV, twice, 12 hours apart. Concentrations of flunixin meglumine in milk 24 hours after treatment were similar to concentrations in milk from untreated control animals. In a radiolabel study in which cows received 2.2 mg/kg, IV, background concentrations were reached in milk by 72 hours. In a multiple dosing study, lactating cows received 1.1 mg/kg (0.5 mg/lb), every 8 hours. Residues were not detected in milk at any sampling time at a detection limit of 50 ng/ml. The terminal elimination half-life in sheep and cattle has been reported as ranging from 3 to 9 hours. In the only tissue residue study available, liver and kidney samples from cattle given 2.2 mg/kg, IV, had residues of about 0.05 µg/ml 5 days after treatment.

Flunixin meglumine is approved for use in food animals in several other countries, including England, France, Switzerland, and Germany (Table 2). For the same dose in cattle, foreign WDI recommendations vary widely. For cattle given the typical dosage of 1.1 to 2.2 mg/kg (0.5 to 1.0 mg/lb), IV or IM, every 24 hours, for 3 to 5 days, FARAD recommends use of the milk WDI specified by the Swiss product (72 hours) and the meat WDI specified by the French product (10 days). For swine given up to 2 mg/kg (0.9 mg/lb), IM, FARAD recommends use of the French meat WDI of 15 days (Table 1).

Phenylbutazone

Although not approved for use in food animals in the United States, phenylbutazone (PBZ) is widely used in cattle. Two types of treatment are common: a single dose of 4 to 6 g/animal, IM or IV, or a multiple dose regimen consisting of a loading dose of 10 to 25 mg/kg (4.5 to 11.0 mg/lb), IM or IV, followed by a maintenance dosage of 2.5 to 14.0 mg/kg (1.1 to 6.4 mg/lb), every 24 or 48 hours. The potential for residues in treated animals is high because of its long elimination half-life in cattle. Plasma elimination half-lives ranging from 30 to 80 hours have been reported, with about 40 hours being most common. Phenylbutazone is also excreted in milk. In cows given a loading dose of 24 mg/kg (11 mg/lb) followed by 12 mg/kg (5.5 mg/lb), every 24 hours, milk residues were detected until 82 hours after the last dose. In another study, milk residues declined to the detection limit (0.05 µg/ml) 5 days after cows received 2.5 g, PO, every 12 hours, daily, for 5 days. Only 1 tissue residue study for PBZ in food animals could be located. In cows given a single IV injection of 7.5 mg/kg (3.4 mg/lb; 3.75 g/animal), about 14 days were required for muscle and liver residues to decline to < 0.1 µg/g. The half-life of PBZ was 56 days in liver and muscle.

Table 3—Phenylbutazone veterinary products approved for use in food animals in foreign countries

Country approved	Species	Dosage*	Milk withdrawal interval (h)	Meat withdrawal interval (d)
Switzerland	Cattle	4–6 g/animal, slow IV or IM	120	12
	Calves	1–2 g/animal, IM		12
	Swine	1–4 g/animal, IM		12
France	Cattle	4 g/animal, IV or IM, on the first day, 2 g/animal on subsequent days	96	21
	Calves	2 g/animal, IV or IM, on the first day, 1 g/animal on subsequent days	NA	21
	Swine	2–3 g/animal, IV or IM, q 24 h	NA	21
Germany	Cattle	4–6 g/animal, slow IV or IM	96	12
	Calves	1.2–2 g/animal, IM	NA	12
	Swine	1.4–3 g/animal, IM	NA	12

See Table 1 for key.

Several PBZ products have been approved for use in cattle and swine in Germany, Switzerland, and France (Table 3). Meat WDI range from 3 to 21 days, whereas milk WDI range from 48 to 120 hours. On the basis of residue and pharmacokinetic data mentioned, as well as foreign withdrawal time recommendations, FARAD recommends cattle meat and milk WDI of 12 days and 96 hours, respectively, for a single dose of up to 6 g of PBZ/animal. For a multiple dose regimen in which a loading dose of 4 to 6 g/animal is given IV or IM followed by up to 2 g daily, FARAD recommends meat and milk WDI of 21 days and 120 hours, respectively (Table 1).

References

1. Kopcha M, Kaneene JB, Shea ME, et al. Use of nonsteroidal anti-inflammatory drugs in food animal practice. *J Am Vet Med Assoc* 1992;201:1868–1872.
2. In: Gilman AG, Goodman LS, Rall TW, et al, eds. *The pharmacological basis of therapeutics*. 7th ed. New York: MacMillan Publishing Co, 1985.