

Extralabel use of nonsteroidal anti-inflammatory drugs in cattle

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It has been over 10 years since the first FARAD Digest was published on the extralabel use of NSAIDs.¹ Several things have changed since that time, including increased attention for residue violations associated with the use of NSAIDs (especially phenylbutazone) in cattle. In 1992, a survey of food animal veterinarians found that 93% (1,325/1,424) reported using NSAIDs, and almost 60% (751/1,322) reported using these drugs more than once a week.² In 1995, a survey limited to dairy veterinarians reported anti-inflammatory drugs to be the second most prescribed class of drugs after antimicrobials.³ In this survey, veterinarians were asked to indicate how often they prescribed or administered a particular drug in dairy practice. From a list of 82 drugs, flunixin meglumine, phenylbutazone, and dipyrrone were all among the top 20 most frequently used or prescribed (ketoprofen was not included in the survey as it was not available in the United States at that time).

Results of the surveys also indicated that the WDI given to producers by veterinarians following NSAID administration varied substantially. Many veterinarians indicated that they recommended meat or milk WDIs on the basis of what was appropriate for the antimicrobial when one was used in combination with an NSAID.² It is important for food animal veterinarians to be familiar with regulations governing the use of approved and extralabel drugs in practice. One of the first rules of using drugs in dairy or beef practice is to decide whether there is a drug approved for cattle that is indicated and effective for the condition being treated. If such a drug exists, then extralabel drug use is not appropriate. However, when a drug is used in an extralabel manner, AMDUCA regulations require that there be a sufficiently extended WDI so that no residues are found in meat or milk products. It is also important to note that NSAIDs are considered drugs of high regulatory concern in food animals because of the potential for harm to humans consuming food and food by-products containing residues. Because of this, analytic methods have been developed

ABBREVIATIONS

FARAD	Food Animal Residue Avoidance Databank
NSAID	Nonsteroidal anti-inflammatory drug
WDI	Withdrawal interval
FDA-CVM	FDA Center for Veterinary Medicine
$t_{1/2el}$	Elimination half-life
MRL	Maximum residue levels
EU	European Union
WDT	Withdrawal time
LOQ	Limit of quantitation
$t_{1/2\beta}$	Terminal half-life

that simultaneously test for multiple NSAID residues in edible tissues. The only NSAID for which a tolerance has been developed in the United States is flunixin meglumine; therefore any other positive test results, despite the concentration, would be considered illegal. The primary objective of this report is to provide veterinarians with current information on NSAID use in cattle along with recommended meat and milk WDIs for drugs that have been reportedly used by bovine veterinarians.

Aspirin

Aspirin (acetylsalicylic acid) remains a commonly used NSAID in cattle to control pyrexia. It is available over-the-counter in 60, 240, or 480 grain tablets (1 grain = 65 mg). None of the products currently on the market in the United States are approved by the FDA for use in animals, and aspirin products do not have a new animal drug application number. A policy statement from the FDA-CVM indicated that aspirin was a new animal drug within the meaning of Section 201(w) of the Federal Food Drug and Cosmetic Act and does not meet the grandfather clause of the Animal Drug Amendments of 1968.⁴ The statement continues:

We are aware there are aspirin bolus products being marketed and labeled for use in treating cattle. They are available simply because the regulatory priorities of the agency have not enabled us to take a regulatory initiative against the products as a class. This does not mean that the FDA in any way sanctions the marketing and use of these products or that we will not institute enforcement actions against individual products or as a class action in the future.

In the past, FARAD has recommended a 24-hour meat and milk WDI following administration of aspirin

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in beef and dairy cattle (Table 1). However, given the questionable legality of this drug and the availability of approved alternatives (flunixin meglumine), FARAD strongly discourages the use of aspirin in food animals.

Carprofen

Carprofen is a newer NSAID commonly used in small animal veterinary medicine in the United States. This drug has a small volume of distribution (0.09 L/kg [0.04 L/lb]) and a much longer plasma $t_{1/2el}$ (30 to 40 hours) in cattle than flunixin meglumine and is poorly excreted in milk.^{5,6} Carprofen is currently approved in several European and Asian countries for control of inflammation associated with respiratory tract disease. The established MRLs for carprofen in the EU are 500 µg/kg (227 µg/lb) in muscle and 1,000 µg/kg (455 µg/lb) in liver and kidney.⁷ Based on these concentrations, the drug has been given a meat WDT of 21 days following single IV or SC doses of 1.4 mg/kg (0.64 mg/lb). In the EU, use of carprofen has recently been approved for control of fever associated with toxic mastitis in dairy cattle. Minimal concentrations of the drug appear in milk following administration at approved doses (1.4 mg/kg). In a study of milk residue depletion following either IV or SC administration in dairy cows, high-performance liquid chromatography revealed no drug concentrations > 25 µg/kg (11.4 µg/lb) in samples from any time point.⁷ Therefore this drug has been approved in the EU with no milk discard. However, it should be emphasized that because flunixin meglumine is approved in the United States for virtually the same indications in cattle, the use of carprofen would not be legal unless the veterinarian could provide justification as to why flunixin meglumine was not effective in that particular animal.

Dipyron

Dipyron continues to remain on the list of drugs specifically prohibited by the FDA-CVM for use in food animal species.⁸ Therefore, FARAD does not provide extralabel WDI recommendations. Dipyron can cause potentially serious toxicoses in humans including acute agranulocytosis, prolonged bleeding, and teratogenicity. The FDA removed approval for human products in 1977 and required that marketing of the drug for companion animals cease in 1995 to stop use in food animals. A few expired stockpiles of dipyron remain, and some veterinarians are able to obtain the drug from Canada, where it is still marketed for use in small animals and horses. However, in the United States, any use

of this drug in food animal species would be illegal and subject to regulatory action.

Flunixin Meglumine

In the United States, flunixin meglumine is the only NSAID labeled for use in beef and dairy cattle. It is indicated for the control of pyrexia associated with bovine respiratory tract disease and mastitis as well as for the control of inflammation associated with endotoxemia. Endotoxemia could potentially be associated with several diseases in cattle including toxic metritis, peritonitis, endocarditis, or acute salmonellosis. Following administration of the drug at the approved dose (1.1 to 2.2 mg/kg [0.5 to 1.0 mg/lb]) and by the approved route (IV) in cattle, the meat WDT is 4 days and the milk WDT is 36 hours. However, it must be emphasized that flunixin meglumine is approved in beef and dairy cattle for IV use only. Extravascular (IM or SC) injections are considered illegal on the basis of conditions set forth by AMDUCA. These conditions state that the extralabel use of a drug must be for therapeutic purposes only. Convenience of route of administration is not considered a valid reason for extralabel drug use. Some veterinarians are of the opinion that flunixin meglumine does not distribute into the milk and therefore it is not necessary to discard the milk. This opinion is based on older literature reporting that concentrations of the drug were not detected in milk following IV or IM administration.⁹ However, the current tolerance for flunixin meglumine concentrations in milk is set at 2 ppb (0.002 µg/mL), which is well below the LOQ of the analytic techniques used in these studies. Newer research conducted during the drug approval process revealed mean milk concentrations of 66, 20, and 14 ppb (0.066, 0.02, and 0.014 µg/mL), respectively, for the first, second, and third milkings in lactating dairy cows following IV administration of flunixin meglumine at a dosage of 2.2 mg/kg (1.0 mg/lb) per day for 3 days.¹⁰

A study in dairy cattle revealed the $t_{1/2\beta}$ after administration of a single dose of flunixin meglumine (1.1 mg/kg) was longer when given IM (5.2 hours), compared with IV (3.1 hour).⁹ The bioavailability was reported to be 76% (range, 44% to 119%). A more recent study of the pharmacokinetics of flunixin meglumine following repeated IM administration of 2.2 mg/kg revealed that the $t_{1/2\beta}$ increased from a mean of 4.1 hours IV to a mean of 26 hours after IM administration.¹¹ In that study, flunixin meglumine could be detected for up to 8 days in plasma following multiple IM doses.

Several possible explanations exist for the discrepancies between these 2 studies. The first explanation would be the sensitivity of the assays used. The assay used by Anderson et al⁹ had an LOQ of 0.05 µg/mL (50 ppb) in plasma, whereas the assay used by Odensvik et al¹¹ had an LOQ of 0.007 µg/mL (7 ppb). This increased sensitivity of the assay would allow for detection of more points along the terminal phase of the concentration versus time curve and a more accurate evaluation of the $t_{1/2\beta}$. Another possible reason for the differences in $t_{1/2\beta}$ in the 2 studies would be the volume of drug injected. Flunixin meglumine is highly irritating when injected IM.¹² Following a single IM administration of 2.2 mg/kg, serum creatinine kinase activities increased

Table 1—FARAD-recommended WDIs for several NSAIDs following extralabel use in cattle.

Drug	Route of administration	Meat WDI (d)	Milk WDI (d)
Aspirin	Oral	1	1
Carprofen	IV or SC	21	0
Flunixin meglumine	IM	30	3
Ketoprofen	IV or IM	7	1
Phenylbutazone	IM	55 (beef cattle only)	N/A
Phenylbutazone	Oral	50 (beef cattle only)	N/A
Tolfenamic acid	IV (single dose)	7	1

NA = Not applicable.

from baseline values of 86 to 136 U/L to a mean of 1,093 U/L (range, 769 to 1,340 U/L). In that study, flunixin meglumine was found to cause significantly more muscle damage than either ketoprofen or metamizole. This may be an effect of the vehicle used in the formulation, which contains propylene glycol, a substance known to be irritating to muscle tissue.¹³ Finally, the study by Anderson et al⁹ reported the $t_{1/2\beta}$ after only a single IM injection. Although they administered multiple doses IM during that study, they did not report the half-life after the multiple doses. The more recent study¹¹ examined the $t_{1/2\beta}$ after either 56 doses (2.2 mg/kg, IM, q 6 h) or 28 doses (2.2 mg/kg, IM, q 12 h).¹¹ Multiple injections would increase the amount of tissue damage induced. This damaged or necrotic tissue would create a depot of the drug, prolonging absorption into the circulation and possibly creating a flip-flop phenomenon with a highly prolonged absorption phase.

When determining an extralabel WDI for a drug, tissue concentrations are more important than plasma concentrations. The $t_{1/2el}$ values of flunixin meglumine in the tissues have been reported to be between 9 and 51 hours for liver and 22 and 37 hours in kidneys after 3 IV doses (2.2 mg/kg, q 24 h).^{14,15} This represents up to a 10-fold increase in the $t_{1/2el}$ in tissue, compared with plasma. Given the substantial increase in the plasma $t_{1/2\beta}$ after IM injections, it is logical to assume that an increase in tissue $t_{1/2el}$ would also be seen, although the magnitude of the increase cannot currently be determined on the basis of available data. Because of the problems associated with IM administration outlined, FARAD has previously recommended a conservative 30-day slaughter WDI for flunixin meglumine products given IM. If multiple doses are administered IM, the WDI may need to be extended out as far as 60 days. Although there are little data available, FARAD recommends a milk WDI of 72 hours following a single IM injection of flunixin meglumine in dairy cattle. Few pharmacokinetic data are available on SC administration of flunixin meglumine in cattle; therefore a WDI cannot be established.

Oral administration of flunixin meglumine has also been investigated in cattle. After receiving a single oral dose of 2.2 mg of granular flunixin meglumine/kg, the $t_{1/2\beta}$ was similar after oral administration (6.2 hours) and IV administration (5.2 hours).¹⁶ Reported bioavailability was 60%. Other pharmacokinetic parameters were similar between the 2 routes of administration, but the effects on prostaglandin synthesis were significantly prolonged after oral versus IV dosing. FARAD recommends a slaughter WDI of 8 days and a milk WDI of 48 hours following a single oral dose of flunixin meglumine. However, it is again important to stress that use of flunixin meglumine granules or paste is not covered under AMDUCA, and approved formulations should be used.

Flunixin meglumine is considered to be a drug of high regulatory concern. The FDA has recently investigated several cases of violative residues of flunixin meglumine in cattle, and most have been attributed to administration via extralabel routes. As a result of this investigation, the FDA-CVM recently released a reminder on the correct use of flunixin meglumine in cattle.¹⁷ It stresses the importance of following label directions for this drug. Because many drugs may be

administered to cattle by farm personnel, veterinarians need to emphasize the importance of following label instructions for this product. Extended WDI for meat and milk should be recommended when IM administration has already occurred.

Ketoprofen

Ketoprofen is another NSAID that has been used in ruminants for alleviating some of the clinical signs associated with endotoxemia. However, the use of this drug appears to have declined substantially in recent years because it does not offer an advantage over labeled drugs (ie, flunixin meglumine) and is much more expensive. Pharmacokinetic data in cattle following IV administration of ketoprofen indicate that the drug has a short plasma half-life (about 30 minutes) and a small volume of distribution (0.1 L/kg [0.05 L/lb]).¹⁸ In 6 healthy lactating dairy cattle, very low concentrations (< 90 ng/mL) of ketoprofen were detected in milk from 10 to 120 minutes following a single IV bolus of 3.3 mg/kg (1.5 mg/lb).¹⁸ Ketoprofen is rapidly eliminated by the kidneys following IV or IM administration¹⁹ and is substantially less irritating to tissues than either flunixin meglumine or phenylbutazone when injected IM.¹² After repeated IM administrations of radiolabeled ketoprofen at a dosage of 3 mg/kg (1.4 mg/lb) for 3 days, radioactivity could only be measured in the kidneys 24 hours after the third injection.¹⁹ In other tissues, concentrations were not detectable. On the basis of these data, FARAD recommends a meat WDI of 7 days and a milk WDI of 24 hours following dosages of up to 3.3 mg/kg every 24 hours for 3 days. However, with the approval of flunixin meglumine in the United States, the extralabel use of ketoprofen would not be allowed under the guidelines of AMDUCA and should not be considered appropriate for use in the supportive treatment of a cow with toxemia.

Meloxicam

Meloxicam is a newer NSAID in the oxicam group that has preferential (but not specific) binding to cyclooxygenase-2 receptors. It has been approved for use in cattle in several European countries including the United Kingdom as a single IV or SC dose of 0.5 mg/kg (0.23 mg/lb) with a WDT of 15 days for meat and 5 days for milk. A small animal formulation has been approved and is marketed in the United States. Pharmacodynamic studies^{20,21} have shown that when given according to label directions, there is no difference in the efficacy of meloxicam, compared with flunixin meglumine, for the treatment of respiratory tract disease in cattle; therefore, justifying the use of meloxicam in cattle in the United States would be difficult.^{20,21} There are no data available from which to make a recommended WDI for meat or milk after multiple doses of meloxicam.

Phenylbutazone

Phenylbutazone is another NSAID that has classically been used as an anti-inflammatory drug in ruminants. It has a much longer $t_{1/2\beta}$ than flunixin meglumine and was preferred by some veterinarians because once-daily or ev-

ery-other-day dosing could achieve and maintain plasma drug concentrations within the therapeutic range.²² However, in the past 5 years, the FDA-CVM has had substantial concerns about phenylbutazone residues in meat and milk. In 2000, the USDA and the FDA collaborated on a study looking at phenylbutazone residues in culled dairy cows. Over a 6-month period of sample collection from over 2,000 cows, residues were found in almost 0.1% of the animals. Because phenylbutazone is known to induce blood dyscrasias in humans, including aplastic anemia, leukopenia, agranulocytosis, and thrombocytopenia, there is a zero tolerance policy for residues. Therefore, in 2003 the FDA-CVM instituted a ban on the use of phenylbutazone in dairy cattle.²³ The policy stated the following:

We are issuing this order based on evidence that extralabel use of phenylbutazone in female dairy cattle 20 months of age or older will likely cause an adverse event in humans. We find that such extralabel use presents a risk to the public health for the purposes of the Animal Medicinal Drug Use Clarification Act of 1994.

The use of phenylbutazone in dairy cattle is now considered illegal, and a milk WDI cannot be provided by FARAD. The meat WDI discussion that follows pertains to beef cattle only because phenylbutazone cannot be used in dairy cattle. FARAD is not able to provide a meat WDI for dairy cattle.

FARAD strongly discourages the use of phenylbutazone in beef cattle, and a veterinarian would need to provide justification for why flunixin meglumine was not effective in the animal being treated to legally use the drug. The half-life of phenylbutazone in the plasma of cattle has been reported to be greatly prolonged, compared with the value of horses (5 hours) and dogs (4 to 6 hours).²⁴ Numerous studies^{22,24-31} have reported the $t_{1/2el}$ of phenylbutazone in cattle via various routes of administration. These have ranged from a mean of 36 to 65 hours. Unlike flunixin meglumine, concentrations of phenylbutazone in tissues tend to parallel those in the plasma.³²

Williams et al³⁰ reported an upper limit of the 95% confidence interval of 95 hours for the $t_{1/2el}$ of phenylbutazone following multiple oral doses in bulls. Assuming that it takes 10 $t_{1/2el}$ for 99.9% of a drug to be eliminated from the body, and taking into account the zero tolerance policy for phenylbutazone residues in the United States, FARAD recommends a 40- to 50-day WDI after oral or IV administration of phenylbutazone in beef cattle.

Intramuscular administration is expected to cause tissue damage and possible prolonged absorption from the injection site, similar to that induced by flunixin meglumine.¹² This may vary with the volume per injection site, as higher doses have been shown to cause an incremental increase in the amount of tissue damage.³³ Therefore, FARAD recommends a minimum 55-day WDI for phenylbutazone following IM administration in beef cattle.

Another factor to consider is the age of the animal being treated. Plasma half-lives of phenylbutazone in neonatal (24 to 36 hours) calves were typically 207

hours and 168 hours in healthy and endotoxemic animals, respectively.²⁸ Elimination half-lives have also been reported to be twice as long, with plasma clearances 40% to 50% lower in 1-month-old calves, compared with 3- to 6-month-old calves.²⁹ Phenylbutazone has also been shown to cross the blood-placental barrier, and concentrations were detectable in calves born to cows treated with drug. Continued exposure through the milk can lead to detectable plasma concentrations in newborn calves with $t_{1/2el}$ as long as 4 days.³⁴ The use of phenylbutazone in young animals is highly discouraged, as the WDI would need to be considerably prolonged.

Tolfenamic Acid

Tolfenamic acid is an NSAID in the anthracilic acid (fenamate) class that is approved in the EU and Canada for use in cattle with acute mastitis or respiratory tract disease. Although there are no data to indicate tolfenamic acid is more effective than flunixin meglumine (a drug approved for the same indication in the United States), it has occasionally been used in an extralabel manner by veterinarians or producers. Tolfenamic acid has a large volume of distribution (about 1 L/kg [0.45 L/lb]) and a long $t_{1/2\beta}$ (8 to 10 hours) in cattle, compared with other NSAIDs.^{35,36} The longer $t_{1/2\beta}$ is likely a result of extensive enterohepatic recirculation in cattle, and a single injection can maintain therapeutic blood concentrations for at least 48 hours. The EU has set MRL for tolfenamic acid as 50 $\mu\text{g}/\text{kg}$ (22.7 $\mu\text{g}/\text{lb}$) in muscle and milk, 100 $\mu\text{g}/\text{kg}$ (45.5 $\mu\text{g}/\text{lb}$) in the kidneys, and 400 $\mu\text{g}/\text{kg}$ (181.8 $\mu\text{g}/\text{lb}$) in the liver.³⁷ Based on these MRLs, the approved meat WDT following SC injection of 2 mg of tolfenamic acid/kg (0.9 mg/lb) in beef cattle is 7 days. Extravascular administration is not permitted in dairy cattle, and the drug may be given only by the IV route. In Canada and the EU, a dose of 4 mg/kg (1.8 mg/lb) is approved as a single IV injection, which is associated with a milk WDT of 24 hours. However, this drug is not approved in the United States and would not be legal unless a veterinarian could provide justification for its use.

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