# Prudent Use of Pain Relief in Food Animals

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**Abstract**

Relief of both acute and chronic pain in animals is an important part of the practice of veterinary medicine. Human pain medications are frequently used in small animal and equine practice. However, food animal practitioners must follow the Animal Medicinal Drug Use Clarification Act (AMDUCA), which puts restraints on the use of analgesics for pain management in food animals. This paper discusses the use of systemic pharmacologic agents for pain management in cattle, with an emphasis on nonsteroidal anti-inflammatory drugs (NSAIDs). Local anesthetic techniques for pain management are discussed in "Numbing-Nose to Tail".

**Résumé**

L'apaisement de la douleur aiguë ou chronique des animaux occupe une part importante de l'exercice quotidien de la médecine vétérinaire. Les analgésiques destinés aux humains sont fréquemment administrés aux petits animaux et aux chevaux. Toutefois, aux États-Unis, les vétérinaires spécialistes des animaux de consommation sont soumis à la loi intitulée *Animal Medicinal Drug Use Clarification Act* (AMDUCA), qui impose certaines contraintes à l'emploi des analgésiques comme antidouleur chez ces animaux. Cet article traite des agents pharmacologiques antidouleur systémiques employés chez les bovins et met l'accent sur les médicaments anti-inflammatoires non stéroïdiens (NSAID). Quant aux techniques d'anesthésie locale, elles sont décrites dans l'article intitulé : « *Numbing-Nose to Tail* » (*Les anesthésies, du museau à la queue*).

## Introduction

Pain research in animals can be very difficult to perform. Pain response in animals varies greatly between individuals, and the severity of clinical signs of pain doesn't always match the severity of a lesion. Common techniques used in humans, such as verbalization of pain scores, cannot be done in animals. Further hampering studies in cattle is the fact that they are a prey species, and may try to conceal pain as a survival instinct. As a result, developing a consistent pain model for research is very difficult. The clinical response to pain and the response to pain medications is highly variable between individuals.

The most widely studied pain medications in cattle are the nonsteroidial anti-inflammatory drugs (NSAIDs). Pharmacokinetic data, which tells us blood concentrations and half-life following a specific dose, are available for many NSAIDS. However, blood levels may not correspond to tissue levels. For many NSAIDs, the actual therapeutic concentration needed at the tissue level is not known. Pharmacodynamic data, which may help determine this, is scarce and is not always clinically relevant. Pharmacodynamic studies usually involve inducing a localized inflammatory reaction, then measuring the change in levels of inflammatory mediators following different drugs at different concentrations. The problem with this type of study is that different tissues may respond differently to the same stimulation, so extrapolation of data to other tissues or types of injuries is not always wise. The degree of inflammatory reaction does not always correspond to the degree of pain, therefore relief of the inflammatory response by an NSAID may not relieve the pain associated with it.

With this in mind it's not surprising that clinically relevant studies on pain in cattle are scarce. Many published studies measure levels of cortisol or other endogenous products of stress. Simple restraint of cattle can cause stress, and cortisol and catacholamines may also have analgesic effects, so increased levels of these products may not indicate increased pain levels.[3] In my opinion, one of the best studies in cattle related to pain management was performed by Williams *et al.*[5] This group evaluated bulls at a semen collection facility that had musculoskeletal pain. They titrated the dose of phenylbutazone until bulls were comfortable enough to be collected again, and then noted the daily dose and blood concentrations that corresponded to pain relief.

## Pain Management

Adaptive responses to pain make chronic pain more difficult to treat than acute pain. The longer the duration and/or the more intense the pain, the more difficult it is to treat, requiring higher and/or more frequent doses of analgesics.[1,3,4]

Preventative pain management is preferred, and can be performed for most elective and emergency sur-

gical procedures. Local and general anesthetics and some tranquilizers and sedatives can alleviate much of the immediate pain associated with surgical procedures, but effects are short-lived and they do not address the longer term post-operative pain associated with inflammation following surgery. Proper use of NSAIDs can greatly reduce longer term post-operative pain.[1]

Although preventive pain management in cattle is preferred, practitioners are faced more commonly with pain management after an injury or disease has already occurred. The drug classes used systemically for treating pain are the opioids, the α2 adrenergic agonists and the NSAIDs. Since the mechanism of analgesia is different for different classes of drugs, sometimes combinations of different systemic drugs, or combinations of systemic and local analgesia are best.[3]

## Opioids

The opioids commonly used in veterinary practice are buprenorphine, butorphenol, fentanyl, meperidine, methadone, morphine and oxymorphone. Opiods have a short duration of action and in ruminants have disappointing analgesic properties compared to other species, so they are not widely used in food animals. They are also controlled substances, and are not approved for food producing animals, so the tenets of AMDUCA have to be met before they area selected. Opioids can inhibit rumenoreticular contractions, and some cause abnormal behaviors such as propulsive walking and hypersensitivity/hyperexcitability, which can be dangerous for animals and personnel.[2]

Butorphenol is the most widely used opioid in food animal practice. The recommended dose is 0.05 mg/kg subcutaneously every four to six hours. Butorphenol may be indicated for short term analgesia for acute, severe post-operative pain. Suggested meat and milk withdrawals are four days and 72 hours, respectively. There are anecdotal reports of increased appetite following butorphenol administration.[1,2]

Transdermal fentanyl is used in other animal species, but absorption and analgesic efficacy in cattle is unknown. In goats, transdermal absorption of fentanyl was very good.[5] Rumenosalivary recyclying of this drug may prolong the effects, but may also pose problems with establishment of withdrawal times. Constant rate infusion techniques of analgesic cocktails have been used in food animals and may benefit animals with severe, acute pain.[1]

## α2 Adrenergic Agonists

The most common drug in this class used in food animals is xylazine. It has both analgesic and sedative effects. The analgesic effects are very short lived (<1 hour) but the sedative effects can last greater than 24 hours, which makes them poor choices for long-term pain management. Xylazine may be indicated alone or in combination with butorphenol for post-operative pain, especially if sedation is wanted.

## NSAIDs

NSAIDs are used for their analgesic, antipyretic and anti-inflammatory properties. They produce most of their therapeutic effects through inhibition of prostaglandin synthesis. There is also some evidence that they produce analgesic effects by central mechanisms other than inhibition of prostaglandin synthesis. In most instances, they have good oral bioavailability, making the oral route of administration a feasible alternative. There are significant differences in clearance between animal species and age groups. They also have therapeutic indexes that are relatively close to there toxic indexes. For these reasons, extrapolation of drug dosage regimes between species can be dangerous. The inhibition of prostaglandin synthesis and clinical response may continue long after NSAIDS are cleared from the body. Therefore, formulating dosage regimes from pharmacokinetics alone, without taking into account pharmacodynamics, can potentially lead to toxicity.

Of the NSAIDS commonly used in large animal practice, only aspirin and flunixin meglumine are approved for use in food-producing animals, and only aspirin is approved for pain. Flunixin meglumine is approved for pain in horses, but not cattle. Other veterinary products used in an extra-label manner in food animals are phenylbutazone and ketoprofen. Dipyrone use in food animals is *prohibited.*

Aspirin is approved for fever and for minor joint/muscle pain. Higher doses are required on a per lb or kg basis in ruminants compared to other species due to a high clearance (Cl) and low volume of distribution (VD). Some product labels have no withdrawal times (WD) listed, but FARAD recommends a 24 hour slaughter and milk WD.

Flunixin meglumine under the tradename Banamine® is approved for use in beef and lactating dairy cattle for fever and inflammation associated with respiratory disease and endotoxemia. The approved dose is 0.5 mg/lb (1.1 mg/kg) BID to 1.0 mg/lb (2.2 mg/kg) SID IV for up to three days. The label slaughter and milk withdrawal times are four days and 36 hours respectively. This drug is only approved for IV administration. The generic products are for lactating cattle and one is only labelled for horses.

Phenylbutazone is not approved for use in food producing animals, and is *prohibited for use in dairy cattle greater than 20 months.* Since flunixin meglumine and aspirin are both approved for use in food animals,

even though not necessarily for pain, they should be considered first. However, many practitioners consider phenylbutazone a superior analgesic for chronic osteoarthritis. Because of human health concerns, this drug should be reserved for valuable beef breeding stock with chronic osteoarthritis where slaughter is not an option, such as temporary relief of pain for embryo or semen collection followed by euthanasia. Phenylbutazone has a very long half-life in cattle (~30-80 hours) compared to other large animal species, including goats and sheep (half-life ~15-20 hours). Due to the long half-life, a loading dose is required to reach therapeutic levels more quickly. The recommended dose in cattle based on pharmacokinetic and clinical trials in lame bulls is 7.7-11.4 mg/lb (17-25 mg/kg) loading dose, followed by 1.8-2.7 mg/lb (4-6 mg/kg) SID, or 4.5-6.4 mg/lb (10-14 mg/kg) EOD. My clinical experience is that the SID dosage regime is more effective for pain control than EOD. The long half-life also dictates the use of extended withdrawal times. Currently, FARAD discourages use of phenylbutazone in food producing animals. Previous recommendations were of a minimum 45 day slaughter WD for the first dose, with another five days added for each day of therapy beyond the first.

Ketoprofen is not approved for use in food animals and offers no benefits over flunixin meglumine, therefore it should be avoided in food animals.

GI ulceration is the most commonly described side-effect from NSAID therapy, but is rare as long as animals are eating. The first sign of GI side effects are anorexia, followed by mild diarrhea, which should subside when the NSAID is discontinued. Renal toxicity has also been described following NSAID administration. This usually only occurs if the animals are severely hypovolemic, or are also receiving other potentially nephrotoxic drugs concurrently. As long as animals are rehydrated before or immediately after administration, nephrotoxicity should not be a concern.

## Other Pain Management Considerations

Analgesics therapy is a very important part of pain management, especially if the animal is in enough pain to prevent it from eating. However, some minor short term pain may be beneficial to prevent animals from moving excessively, especially for severe musculoskeletal injuries. But, every effort should be made to control movement by controlling the housing space, not from withholding analgesics.

There is much that can be done to alleviate pain that does not involve pharmacologic agents. Treatment of whatever is causing the pain is essential, and early recognition of pain, so that the cause can be addressed as soon as possible, is important.

"Cow comfort" is very important in managing and minimizing the effects of pain. Easy access to clean water and palatable feed to encourage intake is important. Level surfaces with good footing and soft bedding should also be provided.

## References


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