Non-steroidal Anti-Inflammatory Drugs in Cattle- What's the Latest?

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Non-steroidal anti-inflammatory drugs (NSAIDs) play a part in the management of mild to moderate pain across species, and they are often used in combination with other drug classes, such as opioids, dissociative anesthetics, and local anesthetic drugs in the management of pain during and after surgical procedures.

NOTE: Most NSAIDs are not FDA approved for use in cattle. Applicable regulations, including the establishment of appropriate withholding times, must be followed for all extra-label drug treatments.

Part 1. The effects of NSAIDs as a class

It is a common conception that NSAIDs work to alleviate inflammatory pain by interfering with the production of pro-inflammatory prostaglandins via the arachidonic acid cascade, which is trigged by cellular damage due to mechanical trauma, infection, or other causes. Many studies in many species have demonstrated that prostaglandin levels are reduced in animals treated with NSAIDs. In addition, there is good evidence for the presence of some centrally mediated NSAID effects. In sheep, the NSAID drugs flunixin and ketoprofen have been found to provide analgesia, with the analgesic effects of the NSAIDs prevented by pre-treatment with the drug naloxone, which inhibits drug activity at opioid receptors (Chambers et al, 1995, Lizzaraga and Chambers, 2006). Although NSAIDs have been around a long time, they still are not entirely understood.

In addition to their therapeutic effects, the adverse effects of NSAIDs have also been described, with gastric ulceration and bleeding the most commonly observed adverse effects in dogs with chronic NSAID administration (Luna et al, 2007). The risk level for adverse effects of NSAIDs in cattle and other ruminants has not been established, but ruminants are considered to be at risk for the same NSAID-related adverse effects as other species. The following statement is part of the label for the Banamine brand of injectable preparation of flunixin meglumine: "Cattle: No flunixin-related changes (adverse reactions) were noted in cattle administered a 1X (2.2mg/kg; 1.0mg/lb) dose for nine days (three times the maximum clinical duration). Minimal toxicity manifested itself at moderately elevated doses (3X and 5X) when flunixin was administered daily for nine days, with occasional findings of blood in the feces and/or urine. Discontinue use if hematuria or fecal blood are observed."

Part 2. Aspirin

Aspirin is not FDA-approved for use in cattle in the US. Although aspirin is inexpensive and widely available, the drug is poorly absorbed after oral administration and there is not good evidence that is an effective analgesic drug in cattle at the usual oral dose of 50 mg/kg body weight (Wren, 2008).

Part 3. Flunixin and Meloxicam

Flunixin and meloxicam are commonly used NSAIDs in cattle in the United States. Meloxicam is not approved by the FDA for use in food animals, while certain flunixin products are approved for the treatment of specific conditions in cattle.

A recent review by Wagner et al (2021) examined the evidence for the efficacy of these two drugs for alleviating pain related to dehorning and castration, and their pharmacokinetic parameters. Combining the outcomes of 24 pharmacokinetic studies of intravenous flunixin administration in cattle (dose range 1.1 to 2.2 mg/kg body weight), the reported elimination half-life (T½) ranged from 3.14 to 12.9 hours. If the median T½ of the drug is about in the middle of that range (8 hours), once daily dosing is likely to be inadequate to provide sufficient pain control. Meloxicam, by contrast, has an estimated T½ between 20.4 and 21.9 hours after oral dosing at 0.5-1.0 mg/kg body weight, based on 2 studies. This makes the drug convenient for less-frequent dosing, but inconvenient for establishing a withholding time in lactating animals.

In terms of efficacy, the results from studies with these 2 drugs have been mixed, and the use of a local anesthetic drug in combination with an NSAID to manage acute procedural pain is recommended.

In 16 publications, only heart rate and CBC were affected more than half the time by treatment of calves with meloxicam around the time of castration, while more than a dozen other behavioral, productivity, and physiological outcomes were affected by drug treatment less than half the time they were evaluated. Among 15 publications evaluating meloxicam treatment for disbudding, maintenance behaviors, substance P, activity levels, and average daily gain were affected by drug treatment in more than half of the studies in which they were measured, while cortisol, pain sensitivity, and 4 other measures were affected by drug treatment less than half the time they were measured.

Similarly, in 8 publications investigating calves undergoing castration, treatment with flunixin affected only respiratory rate and serum cortisol levels more than half the time they were measured, while more than a dozen other behavioral, productivity, and physiological outcomes were unaffected by drug treatment more than half the time they were evaluated. In 4 studies evaluating flunixin for the treatment of calves at disbudding, one study found that the drug affected glucose and glutathione levels, oxidative capacity, prostaglandin E levels, white blood cell count, maintenance behaviors, and average daily gain. This study is evidence of the need to validate measures of pain in cattle- the relationship between glutathione levels and

pain in calves is not known. Heart rate, respiration rate and 4 other measures were unaffected by flunixin across studies of calves being disbudded.

Taken together, these studies suggest some inadequacies in either how pain is measured experimentally in calves, limitations to the efficacy of these drugs, or both. Nevertheless, there is some evidence that each of these drugs provides some analgesia to calves at disbudding or castration. Meloxicam, with its low cost and relatively long proposed duration of action, appears to be relatively frequent choice for use in calves at dehorning.

Both oral meloxicam and injectable flunixin have also shown evidence of alleviating pain in lame cattle. A single oral dose of meloxicam was found to improve locomotion in beef cattle with naturally occurring lameness (Nagel et al, 2016). In that study, the dose was 1.0 mg/kg body weight (at the higher end of the typically investigated dosing range), and the product used was an oral suspension, not the human-approved tablets typically used in an extra-label fashion in cattle in the United States. Injectable flunixin has been observed to alleviate weight shifting between the limbs, a sign of lameness, in dairy cows with naturally-occurring lameness (Wagner et al, 2017). Transdermal flunixin is approved by the FDA for the alleviation of pain in cattle with foot rot, based on its efficacy in alleviating gait abnormalities in cattle with foot rot induced 6 hours prior to treatment by subcutaneous injection of the causative pathogen. Transdermal flunixin did not improve locomotion in cows with induced arthritis of the distal interphalangeal joint (Kleinhenz et al., 2019). Meloxicam administered by injection has been found to benefit calves with naturally-occurring diarrhea (Todd et al, 2010), but the possibility of orally administered meloxicam having the same benefit has not been established.

The wide availability of flunixin and meloxicam and their relative affordability have made them popular as extra-label analgesic drugs in cattle in the United States, and there is some evidence to support their use.

Part 4. Ketoprofen

Ketoprofen is FDA approved for use for the alleviation of musculoskeletal pain in horses in the United States. It approved for use as an analgesic drug for cattle in Canada, and there is evidence that is efficacious for this use. It is injectable and administered once daily according to the Canadian label. Ketoprofen has been found to decrease behavioral signs of pain in calves after disbudding (Duffield et al, 2010), and to decrease locomotion abnormalities and weight-shifting in dairy cows with naturally-occurring lameness (Flower et al, 2008, Chapinal et al, 2010). Until recently, Ketoprofen has been substantially more expensive than flunixin or meloxicam and this has limited its use. However, in 2021, the FDA approved the first generic injectable ketoprofen product for horses, which may reduce the cost of injectable ketoprofen and lead to increased extra-label use of the drug in other species.

Part 5. Firocoxib

Like ketoprofen, firocoxib has been more expensive than meloxicam and flunixin in the United States. Firocoxib is approved by the FDA for use in cattle and dogs. Recent work with firocoxib in re-weaned calves determined that after oral administration in tablet form it has an elimination half-life of over 15 hours (Wagner et al., 2021), so it may also have a prolonged duration of action. In addition, firocoxib is COX-2 selective in other species, which reduces the risk of gastric adverse effects; but, COX-2 selectivity has not been confirmed in cattle. Should firocoxib become more affordable, it may become a useful, moderately long duration analgesic drug in cattle.

Part 6. Summary

NSAIDs are often used to provide anti-inflammatory and analgesic effects in cattle, despite the availability of only one drug, flunixin, that is FDA approved for use in cattle for limited indications. There is evidence that some of these drugs do alleviate pain in some conditions, but more work remains to be done to establish validated measures of pain and consistently effective therapeutic regimens for NSAIDs in cattle. In the meantime, extra-label use of NSAIDs can provide a tool for the management of mild to moderate pain in food animals.

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