Pour-ons, pills, and injectables: Analgesia and pain management in cattle

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Abstract

Pain mitigation strategies in cattle have been the subject of many research projects in recent years. The use of local anesthetic blockade and non-steroidal anti-inflammatory drugs (NSAID) at the time of painful procedures have been well documented. There are only a few local anesthetic agents available for the veterinary practitioner to use. However, there are a variety of NSAIDs that have been studied. In the United States there are no US Food and Drug Administration approved NSAIDs for the control of pain associated with dehorning or castration. Carprofen, firocoxib, flunixin, ketoprofen, and meloxicam have all been studied for their analgesic properties for castration and/or dehorning. Each of these drugs have distinct pharmacokinetic properties which need to be taken into account to formulate a dosing regimen. This review covers pharmacologic approaches to pain management in food animals following castration, dehorning, and lameness events with a special focus on NSAID therapy.

Key words: pain management, NSAID

Resume

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Introduction

The use of lidocaine and a non-steroidal anti-inflammatory drug (NSAID) are recommended as part of a pain mitigation strategy. Local anesthetic blocks stop the initial conduction of the nerve impulse to the central nervous system. Lidocaine's onset of action is relatively rapid (few minutes), but its duration of action is less than 2 hours. The use of lidocaine blocks also enhances the analgesic effects of NSAIDs. A recent meta-analysis of dehorning papers revealed that calves given a NSAID with a local anesthetic had lower cortisol concentrations, decreased sensitivity, and few behavior changes such as ear flicks.[23] The *Handbook of Veterinary Anesthesia* is a great reference for diagrams on how to perform these local anesthetic techniques. Additionally, there are numerous on-line videos from reputable sources available.

NSAIDs are an attractive option in pain management as they are relatively safe, have a longer duration of action, and do not cause sedation. At this time only transdermal flunixin has an approval by the Food and Drug Administration (FDA) for pain control, but its label indication is for foot rot only. Thus the use of transdermal flunixin for the control of pain associated with other indications such as castration, dehorning, or other pain not caused by foot rot is considered extra-label drug use (ELDU). So can other NSAIDs be used for pain mitigation at castration and dehorning? The short answer is yes as long as the specifications in AMDUCA are followed. When using these drugs in an extra-label manner, one must observe the tenants of AMDUCA.

- ELDU is permitted only by or under veterinary supervision with a valid VCPR
- FDA approved human or veterinary drugs
- For therapeutic purposes only
- Cannot result in a violative food residue

Unfortunately, there are still a limited number of NSAID options to choose when controlling pain. For each drug, the prescribing veterinarian must take into account the pharmacokinetics to formulate a logical dose, availability of efficacy data, medication costs, and if an appropriate withdrawal period can be determined. Additionally there are few 'head-to-head' clinical trials comparing NSAIDs and pain mitigation, thus one must proceed with caution in comparing NSAIDs. A brief description of selected NSAIDs and data regarding their analgesic properties is below.

Carprofen

Carprofen is a propionic acid NSAID. There is a cattle formulation available in the European Union with label indications for respiratory disease and mastitis. An oral generic formulation was studied by Stock et al in calves at the time of

dehorning.[16] In that study, they found carprofen treated calves had lower cortisol levels, tended to tolerate more pressure at the dehorn site, and had higher average daily gains. When carprofen is given to calves at the time of clamp (burdizzo) castration, it lowers the cortisol response only. Carprofen had no impact on ADG or acute phase proteins.[14]

Firocoxib

Firocoxib is a coxib class NSAID with increased COX-2 selectivity. In the United States, an oral formulations are approved for treatment of pain and inflammation associated with osteoarthritis in dogs and horses. An injectable formulation is available, but it has not been studied for pain control in cattle. The pharmacokinetics of oral firocoxib has been published. At a dose of 0.227 mg/lb (0.5 mg/kg) orally, firocoxib had a 98% bioavailability and reached maximum concentrations at 4 h with an observed half-life of 19 h.[18] Oral firocoxib was investigated for analgesic properties following dehorning in cattle. Firocoxib-treated calves had lower cortisol levels compared to controls, but no differences in pain sensitivity were observed.[19]

Flunixin meglumine

Flunixin meglumine is the only FDA approved NSAID for cattle in the United States. It is an anthranilic acid NSAID class derived from nicotinic acid. There are 2 formulations approved for cattle. The oldest is an injectable solution that is to be given by IV injection only; it is also approved for use in lactating dairy cattle. The second formulation is a pour-on formulation that is absorbed transdermally. Additionally, the pour-on formulation is the only drug with FDA approval for pain control in cattle. The FDA approval is for the control of pain associated with foot rot in beef cattle and dairy animals less than 20 months of age.

The pharmacokinetics of both IV and transdermal flunixin have been described. Following IV injection, flunixin has a half-life of 3 hours and suppresses prostaglandin E_2 (PGE_2) production for up to 12 hours.[11] The transdermal formulation has a half-life of 5 hours and reaches maximum concentrations at 2 hours post-administration. PGE2 production is suppressed for up to 48 hours.[20] Significant age dependent effects have been observed, with younger calves having lower clearance than older cattle.[11]

There are published studies for both IV and transdermal flunixin administration for its analgesia effects at castration, dehorning, and lameness.[9,12,13] When given at castration, IV and transdermal flunixin lower cortisol concentrations. When administered with a lidocaine or xylazine epidural, IV flunixin increased stride lengths after castration.[4] However, there were no differences observed in stride lengths in cattle given transdermal flunixin at the time of castration.[13]

Both formulations of flunixin ameliorate the cortisol response in calves when administered at dehorning. Transdermal flunixin had no effects on MNT measures take at the dehorning site, but differences at a control site were seen. This indicates an improvement in central sensitization.[12] It should also be noted that the pain associated with dehorning altered the pharmacokinetics in calves. Following dehorning, calves had lower maximum concentrations compared to sham dehorn controls.[10]

Flunixin has been shown to provide analgesia to cattle diagnosed as lame. The transdermal formulation has a specific FDA approval for the control of pain associated with foot rot. In the materials submitted for the FDA approval, calves treated with transdermal flunixin applied more weight on the affected limb compared to controls. Cows treated with IV flunixin to treat lameness had decreased weight shifting on the rear limbs, suggesting pain relief in the lame foot.[21] Cattle treated with IV flunixin after lameness induction with intra-articular amphotericin B had improved visual lameness scores and placed more pressure and surface area when walking across a pressure mat system.[15]

Meloxicam

Meloxicam is a NSAID of the oxicam class. It is approved in Canada and the European Union as an adjunctive therapy in acute respiratory disease, diarrhea, acute mastitis, and as an analgesic to relieve pain following dehorning in calves. In the United States meloxicam is approved for control of pain associated with osteoarthritis in humans; control of pain associated with osteoarthritis in cats and dogs; and post-operative pain in cats. The pharmacokinetics of meloxicam after oral administration is described, and a prolonged half-life and a high bioavailability was reported.

When given as at the time of dehorning, meloxicam decreases sensitivity as measured by mechanical nociception threshold testing, at the dehorn site.[8] Additionally, meloxicam lowers the cortisol and substance P levels in calves.[7] In older calves undergoing amputation dehorning, meloxicam treated calves had higher ADG than controls.[7] When given at the time of castration, meloxicam lowers cortisol and substance P levels.[2] Meloxicam has been investigated in cattle with amphotericin B induced lameness. Meloxicam-treated calves placed more weight on the lateral (lame) claw, but these differences were not statistically different.[3]

Ketoprofen

Ketoprofen is a propionic acid NSAID. There are approved formulations for cattle in Canada. In the United States, ketoprofen is approved for controlling pain and inflammation associated with musculoskeletal disorders in horses. Ketoprofen has a short half-life of less than 1 hour, making sustained analgesia a concern. The analgesic potential for ketoprofen at a dose of 1.36 mg/lb (3 mg/kg) has been investigated. Following dehorning, ketoprofen reduced the cortisol response, but feed intake and ADG were not different.[5]

In castration studies, ketoprofen lowered the cortisol response for up to 5 hours when given with a local anesthetic, but failed to do so when given as the sole analgesic.[1] There was only a tendency for improved feed intake and weight

Table 1. Analgesic compounds available for use in cattle. Adapted from Stock et al in *Veterinary Clinics of North America – Food Animal Practice*.[23]

Drug	Dose (mg/kg)	Route	FDA Approval for Cattle	FDA Approval for Analgesia in Cattle	FDA Approval for Dairy Cattle	T ½ (h)	Meat withhold	Comments
Carprofen	1.4	IV, SC, PO	NO	NO	NO	40	FARAD†	Age effects the pharmacokinetics Veterinary generics available
Firocoxib	0.5	PO	NO	NO	NO	19	FARAD	No tissue residue data available in cattle
Flunixin	1.1 - 2.2	IV	YES	NO	YES	3-8	4 days	36 h milk hold
	3.3	TD	YES	YES*	NO	5	8 days	Multiple doses at 24 h intervals described
Ketoprofen	3.0	IV,IM	NO	NO	NO	0.4	FARAD	Multiple doses may be needed for sustained analgesia
Meloxicam	0.5 - 1.0	IV, SC	NO	NO	NO	22	FARAD	Injectable may be cost prohibitive
	1.0	PO	NO	NO	NO	27	FARAD	Inexpensive oral tablets
Sodium Salicylate	50	IV	NO	NO	NO	37	FARAD	No FDA approval

* For pain associated with foot rot only

† These medications are not approved for cattle in the USA. Contact FARAD for meat withhold times.

gains. A single dose of ketoprofen improved the weight distribution of cows with naturally occurring lameness.[6] A 3-day course given IM prevented the development of hyperalgesia.[22]

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