Practical approaches to on-farm pain management in cattle

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Abstract

Cattle experience pain following routine husbandry procedures including castration and dehorning. Despite the lack of approved analgesics for cattle in the United States, veterinarians can still provide analgesic regimens to cattle undergoing painful procedures. Knowledge of available medications, data supporting use, and the ability to establish safe meat and milk withhold intervals are required.

Key words: dehorn, castration, analgesia, NSAID

Introduction

It is well established that cattle are capable of experiencing pain. The pain experienced by cattle may be the result of animal management procedures such as castration and dehorning, or medical conditions such as lameness and dystocia. The American Veterinary Medical Association and American Association of Bovine Practitioners have developed position statements recommending analgesic use in food animals following painful procedures. Furthermore, consumers are becoming more aware and concerned about the welfare and well-being of animals raised for food. This has increased pressure on suppliers to ensure animals entering their systems are treated humanely. Thus, programs such as the FARM® Program have included provisions for providing analgesia for painful conditions.

Drugs that may provide analgesia to cattle include local anesthetics like lidocaine, non-steroidal anti-inflammatory drugs (NSAIDs), N-methyl-D-aspartate receptor antagonist (ketamine), opioids and α-2 agonists such as xylazine. Although they provide analgesia, the use of the ketamine, opioids and α-2 agonists are not practical for routine use due to short duration of action, their sedative effects, and regulatory concerns including DEA scheduling. Thus, local anesthetics and NSAIDs are the cornerstones for practical on-farm pain management. Local anesthetics combined with an NSAID provide extended analgesia, are easy to administer, have low abuse potential, and do not have sedative effects.

Considerations for providing analgesia

In the United States, transdermal flunixin is the only drug with Food and Drug Administration (FDA) approval for the control of pain in food animals. The label indication for transdermal flunixin is limited to the control of pain associated with foot rot. Thus, using transdermal flunixin to control pain associated with disbudding, castration or other analgesic purpose would be considered an extra-label drug use (ELDU). The lack of additional U.S. FDA approved analgesics is a concern and hurdle for using analgesia at the time of disbudding and castration.[22] Even though lack of products with FDA approval for dehorning and castration pain is perceived as a concern and hurdle, the use of FDA-approved veterinary and human analgesics and anesthetics is legal under the Animal Drug Use Clarification Act (AMDUCA). Under AMDUCA, veterinarians can use/prescribe drugs in an extra-label manner to provide pain control. When doing so, the veterinarian must consider the following to remain compliant under AMDUCA:

- Used or prescribed under a valid veterinary-client-patient relationship (VCPR)
- Health and/or well-being of the animal is threatened (not for production purposes)
- In-feed use prohibited
- Use only FDA-approved animal or human drugs
- Use does not result in a violative food residue.

Local anesthesia

Local anesthetic blocks are a key component in a multimodal analgesia regimen. Benefits of local anesthesia include attenuation of acute pain response, decreased stress in animals, and synergistic action with NSAID use.[42] Local anesthetics have a short duration of action (< 4 hours) and are not recommended as the sole analgesic as a "rebound effect" is seen once the pharmacological effects diminishes.[52]

Lidocaine is the most common one used in food animals due to its relatively low cost and storage stability. To achieve shelf stability, lidocaine is prepared with hydrochloric acid to be soluble in solution. This results in lidocaine having a low pH and is painful on injection. Buffering with sodium bicarbonate can increase the pH of the lidocaine closer to physiological pH. To achieve this, a 10:1 ratio of lidocaine to bicarbonate is needed. Buffering lidocaine also extends the duration of action of lidocaine.

Bupivacaine is a second local anesthetic that may be potentially used. Bupivacaine has a higher pKa than lidocaine that results in a longer duration of action, but longer time to onset of anesthesia.[2] Bupivacaine is reported to prevent a cortisol response out to 8 hours, but two doses 20 minutes and 4 hours after dehorning were required. Recently, a liposomal bupivacaine formulation has been FDA-approved for post-operative pain in cats and dogs. When administered to calves 15 minutes prior to dehorning, calves administered liposomal bupivacaine had lower pain behavior scores and cortisol levels than control and lidocaine treated calves.[32]

For disbudding and castration, administering local anesthetic blocks is relatively easy and can be performed by trained individuals. For disbudding, the horn is anesthetized by blocking the cornual nerve as it travels under the frontal ridge of the skull at a spot half way between the horn and lateral canthus of the eye. Most calves will become anesthetized with 4-5 mL of lidocaine. A 5-15-minute interval from lidocaine injection to disbudding is recommended to allow the drug ample time to enter the nerve and block nerve transmission.

Providing local anesthesia at castration is more difficult due to the time required for lidocaine time to onset of action. Anesthesia of the scrotum can be achieved by infiltrating 4-5 mL of lidocaine into each spermatic cord and 2-3 mL into the median rafea of the scrotum. Timing of lidocaine injection to the time of castration should be a long as feasibly possible with 5-10 minutes being the goal.

Non-steroidal anti-inflammatory drugs (NSAIDs)

As discussed under regulatory considerations, the veterinarian has to ensure the tenants of AMDUCA are followed when prescribing NSAIDs for analgesia. Two key questions that must be answered before describing are: is this an approved human or veterinary formulation, and is there data to establish a withdrawal interval? If the prescribing veterinarian can answer "yes" to these questions, they should feel confident in prescribing a NSAID for pain control.

Flunixin meglumine

Regulatory approval for cattle? Yes. Both flunixin injectable solution and flunixin transdermal solution are approved by the U.S. FDA. Transdermal flunixin is approved for the control of pain associated with foot rot by the U.S. FDA. Approved for use in Canada and the European Union.

Ability to establish a withdrawal interval? Yes (meat and milk).

Scientific evidence: As mentioned above, there are two approved formulations of flunixin available. The pharmacokinetics of both formulations have been described as well as differences in age. Following IV administration the terminal half-life is 5.4 hours in 2-month-old calves and 3.5 hours in the same calves at 8 months of age.28 This difference in pharmacokinetics leads to a prostaglandin E2 suppression for 12 hours and 8 hours in calves at 2 months and 8 months of age, respectively. Thus, for effective analgesia, IV flunixin should be administered every 12 hours in younger calves and every 8 hours in older calves.

The pharmacokinetics of transdermal flunixin as well as the milk depletion profile have been described. The transdermal formulation has a half-life of 6 hours and reaches maximum concentrations at 2 hours post-administration.[27,24] Prostaglandin E2 production is suppressed for up to 48 hours.[48] Following two transdermal doses at 24 hours apart in lactating Holsteins, a milk withhold interval of 96 hours is suggested.[20]

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.[25] It has been reported that dehorning pain in calves alters the pharmacokinetics of transdermal flunixin. Following dehorning, calves had lower maximum concentrations compared to sham dehorn controls.[26]

Calves administered flunixin and lidocaine also had lower salivary cortisol and pain scores compared to placebo controls.[37] Calves treated with flunixin and given lidocaine as a local anesthetic at the time of castration had higher dry matter intakes compared to flunixin-only treated calves.[37,5] Following surgical castration, flunixin treated calves had longer stride lengths suggesting flunixin reduced pain associated with walking.[11] When used as the sole analgesic, transdermal flunixin reduced cortisol concentrations for 8 hours compared to placebo controls. However, there was negligible evidence of analgesia based on substance P concentrations and pressure mat kinetic gait analysis.[29]

Flunixin meglumine administered by intravenous injection has also been investigated in lameness models and clinical field trials.[41,4,50] Cattle administered intravenous flunixin following experimental lameness induction using amphotericin B had improved visual lameness scores and placed more pressure and surface area when walking across a pressure mat system.[41] Additionally, flunixin treated cattle has improved lameness scores and spent less time lying. In a clinical trial where cows were given flunixin before corrective hoof trimming and 24 hours later regardless of lameness status, no differences in weight distribution or lameness scores were observed.[4] In a follow-up study where lame cows were treated with flunixin following corrective trimming, flunixin-treated cows had decreased weight shifting, indicating pain alleviation compared to saline controls.[50]

As transdermal flunixin is FDA approved for the control of pain associated with foot rot pain, its use in lameness is highly recommended. According to the freedom of information summary supporting the FDA approval, transdermal flunixin-treated calves had improved lameness scores and increased contact force when walking across a pressure mat. When evaluated in an experimental arthritis/synovitis model in lactating dairy cows, flunixin-treated cows had lower joint temperatures as measured by infrared thermography and improved mechanical nociception threshold measures.[23] It should be noted that these improvements were not seen until after a second dose was administered. No differences in pressure mat gait outcomes such as contact force or stride length were noted in this study. These results indicate that multiple administrations of transdermal flunixin may be required to provide analgesia to cattle with lameness.

Meloxicam

Regulatory approval for cattle? No. U.S. FDA-approved human and veterinary formulations are available. Approved for use in Canada and the European Union for pain control.

Ability to establish a withdrawal interval? Yes. There is sufficient data in the published literature to establish meat and milk withholds.

Scientific evidence: The pharmacokinetics of meloxicam have been well-described. Following oral administration at 1 mg/kg, meloxicam has a longer terminal half-life (27 h) and complete oral bioavailability.[7] In the U.S., meloxicam is not approved and thus the tolerance of meloxicam residues in the edible tissues and milk is zero. The tissue and milk residue profile for meloxicam has been described in the literature.[10,31]

There are several studies supporting the use of meloxicam for dehorning pain control. Meloxicam has been shown to lower cortisol levels as well as the neuropeptide substance P.19 Meloxicam has been shown to improve mechanical nociception threshold tests 24 hours post-dehorning when used with a local anesthetic.[21] When used in larger calves, meloxicam treatment improved average daily gains over the course of the 10-day experiment.[1]

Meloxicam is approved for the control of pain following castration in Canada. Meloxicam-treated calves had a reduced inflammatory response compared to placebo controls following surgical castration based on lower salivary cortisol levels, white blood cell counts and reduced acute phase protein responses.[34] Interestingly, no additional benefit was observed when meloxicam was administered with lidocaine.[34] Meloxicam treatment resulted in increased average daily gains and reduced serum haptoglobin concentrations in calves following either surgical or band castration.[40] Furthermore, meloxicam lowered cortisol and substance P concentrations when given at the time of surgical castration.[8]

Meloxicam has been shown to improve lameness in cattle with clinical lameness.[36] Offinger et al reported that the use of meloxicam for 4 days following resection of the distal interphalangeal joint resulted in lower cortisol levels, improved lameness scores and increased time standing.[38] In cattle with experimentally induced lameness, meloxicam-treated cattle had increased step counts in lame limbs indicating a reduction in lameness. In that same study, plasma meloxicam concentrations were inversely associated with lameness scores and positively associated with contact pressure on gait analysis.[9]

Ketoprofen

Regulatory approval for cattle? Yes. Approved by the U.S. FDA for beef cattle and dairy cattle <20 months of age. Approved in Canada and the European Union.

Ability to establish a withdrawal interval? Yes (meat only).

Scientific evidence: Ketoprofen reaches peak concentrations of 6.3 µg/mL at 0.83 hours following subcutaneous injection at the label dose of 3 mg/kg. The reported terminal half-life is 2.7 hours.[12] Due to its short half-life and duration of action, it has been suggested ketoprofen is not a suitable choice for dehorning analgesia.[15] Ketoprofen has been shown to blunt the acute cortisol response when administered at label doses in conjunction with a local anesthetic.[47,13,33,35] Furthermore, when used with a topical anesthetic, ketoprofen improved mechanical nociception threshold measures.[16]

Ketoprofen has been shown to block cortisol following surgical castration. A tendency for increased weight gain and feed intake was observed as well.[14] Ketoprofen has been evaluated for controlling pain associated with lameness.[51,17,3] The use of ketoprofen would be legal if used for pain control not related to foot rot. Chapinal et al demonstrated a reduced variation in weight distribution in cattle administered ketoprofen.[3] This is consistent with the improved gait symmetry and weight distribution observed by Flower et al.[17] In a clinical study, ketoprofen was used with corrective trimming and block placement. A higher proportion of cows were non-lame 35 days later.[49]

Aspirin

Regulatory approval for cattle? Aspirin has not gained formal FDA approval.

Ability to establish a withdrawal interval? No.

Scientific evidence: Aspirin is rapidly metabolized to salicylic acid after administration. Following oral administration at 50-100 mg/kg, aspirin has a short half-life of 0.5 hours, requiring at least twice-a-day dosing.18 Salicylic acid failed to provide analgesia following castration and induced lameness.6,30 The use of aspirin is strongly discouraged due to the lack of FDA approval and no evidence of benefit in the literature.

Phenylbutazone

Regulatory approval for cattle? No. Furthermore, the ELDU of phenylbutazone in dairy cattle over 20 months of age is explicitly prohibited by the U.S. FDA.

Ability to establish a withdrawal interval? No.

Scientific evidence: Phenylbutazone did not impact the pain response in calves at dehorning. Due to lack of supporting data in the literature, no established tolerances, and ELDU prohibitions, the use if phenylbutazone is strongly discouraged.

Carprofen

Regulatory approval for cattle? No. U.S. FDA-approved veterinary formulations are available. Approved in the European Union.

Ability to establish a withdrawal interval? No. There is no established tolerance for carprofen in the U.S.

Scientific evidence: Generic carprofen tablets have been evaluated for pharmacokinetics and analgesic properties following dehorning in calves. Oral carprofen reaches maximum concentrations around 24 hours, but has a terminal half-life of approximately 60 hours. Oral carprofen has been evaluated at 1.4 mg/kg at the time of dehorning. Carprofen-treated calves had lower cortisol levels, tended to tolerate more pressure at the dehorn site, and had higher average daily gains. Additionally, oral carprofen decreased prostaglandin E2 production to 96 hours post-dehorning.[43] A second study found that carprofen failed to attenuate the acute stress response in the first 24 hours following dehorning.[45] Carprofen lowers cortisol response following Burdizzo castration, but failed to improved average daily gain or acute phase protein responses.[39]

Firocoxib

Regulatory approval for cattle? No. U.S. FDA-approved veterinary are formulations available.

Ability to establish a withdrawal interval? No. Data regarding tissue concentrations over time are deficient in the literature.

Scientific evidence: The pharmacokinetics of firocoxib via the oral route have been described. Oral administration at 0.5 mg/kg reached maximum concentrations at 4 hours with a mean terminal half-life of 19 hours. Oral bioavailability was determined to be 98%. The 0.5 mg/kg dose was investigated for analgesic properties at dehorning.[44] Firocoxib decreases prostaglandin E2 production for 48 hours following a single dose. Decreased cortisol concentrations were observed, but no differences in pain sensitivity.[46] When compared to other oral NSAIDs at 2.0 mg/kg at the time of dehorning, firocoxib had similar decreases in the acute stress response as meloxicam.[45]

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Table 1:

Drug	Approved species	Indications	Dose (cattle)	Withhold periods	Comments:
Flunixin meglumine	Cattle, horses, and pigs	Antipyretic, anti-inflammatory in BRD & mastitis Foot rot pain	2.2 mg/kg IV 3.3 mg/kg topical	4 d meat (IV) 36 h milk 8 d meat (topical)	
Meloxicam	Cats and dogs EU: cattle	Pain and inflammation with osteoarthritis	0.5 mg/kg IV, SQ 0.5-1 mg/kg PO	FARAD 28 d meat, 96 h milk	Label indications for pain control in Canada and EU
Ketoprofen	Cattle and horses	Antipyretic in BRD, anti-inflammatory and pain in horses	3 mg/kg SQ	48 h meat Not approved for lactating dairy cows	Label indications for pain control in Canada and EU
Aspirin	No formal FDA approval; Horses and Cattle	Reduction of fever, relief of minor aches and joint pains	50-100 mg/kg	No formal FDA approval.	
Phenylbutazone	Horses	Anti-inflammatory	4 mg/kg IV	Not approved for cattle.	ELDU in dairy cattle >20 months of age prohibited
Carprofen	Dogs EU: cattle	Pain and inflammation with osteoarthritis	1.4 mg/kg IV, SQ	Not approved for cattle US EU: 21 d meat; 0 milk	Label indication as antipyretic with BRD in EU
Firocoxib	Horses and dogs	Pain and inflammation with osteoarthritis	0.5 mg/kg PO	Not approved for cattle	

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