Practical pain management in cows and calves – Keys to success

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Abstract

Negative public perception of pain associated with routine animal management practices such as dehorning and castration is increasing. Preemptive analgesia can be applied in advance of the painful stimulus, thereby reducing sensitization of the nervous system to subsequent stimuli that could amplify pain. Drugs that could be used to provide preemptive analgesia include local anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, α2-agonists, and *N*-methyl *D*-aspartate receptor antagonists. Pathological pain states in cattle occur as a result of tissue damage, nerve damage, and inflammation and are frequently associated with pain hypersensitivity. Chronic pain associated with lameness is considered one of the most significant welfare concerns in dairy cows. Inflammatory pain associated with lameness responds modestly to treatment with NSAIDs, but neuropathic pain (due to nerve damage or neuronal dysfunction) is considered refractory to the effects of NSAIDs, but may respond to gabapentin. In this session we will review the analgesic drug options available for practitioners to use in the United States (US). These proceedings contain excerpts that were previously published in a 2013 (Vol. 1: pp 11-28) issue of *Veterinary Clinics of North America: Food Animal Practice* and readers are urged to consult this text for more detailed information on this topic.

Key words: pain management, AMDUCA, gabapentin

Challenges Associated with Providing Analgesia in Food Animals

Several challenges are associated with providing effective analgesia in food animals in the US. Firstly, there are currently no analgesic drugs specifically approved for the alleviation of pain in livestock. Therefore, use of any drug for pain relief constitutes extra-label drug use (ELDU). Under the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA), ELDU is permitted for relief of suffering in cattle provided specific conditions are met. These conditions include that 1) ELDU is allowed only by or under the supervision of a veterinarian, 2) ELDU is allowed only for FDA approved animal and human drugs, 3) ELDU is only permitted when the health of the animal is threatened and not for production purposes, 4) ELDU in feed is prohibited, and 5) ELDU is not permitted if it results in a violative drug residue in food intended for human consumption. Therefore, use of an analgesic to alleviate pain associated with castration in calves in the US would be required by law to comply with these regulations.[4]

A second challenge to providing effective analgesia in cattle is that there is often a delay between the time of drug administration and the onset of analgesic activity. For example, local anesthetics require 2 to 5 minutes (min) before a maximal effect is achieved. This may slow animal processing, as producers must wait for local anesthesia to take effect. This delay may serve as a disincentive for them to provide routine preemptive analgesia. Furthermore, the requirement for large numbers of animals to be processed quickly may result in procedures being initiated before optimal analgesia is achieved. A third challenge is that the route or method of analgesic drug administration may require specialized training and expertise or may be hazardous to the operator. For example, the NSAID flunixin meglumine is only approved for IV administration to lactating dairy cows in the US. Therefore, administration requires the animal to be adequately restrained and the operator to be proficient in IV administration. Similar issues are encountered with epidural analgesic drug administration and administration of local anesthesia into the scrotum. The latter procedure is also considered especially hazardous by many livestock handlers. In addition, the majority of analgesic drugs that are available in the US have a short elimination half-life, necessitating frequent administration in order to be effective. This increases the stress on the individual animal and increases labor and drug costs.

In addition to the regulatory considerations discussed previously, certain drug classes such as the opioid and NMDA receptor antagonists are designated as Schedule 3 drugs and are subject to regulation by the US Drug Enforcement Administration (DEA). Therefore, administration of these compounds to provide preemptive analgesia is restricted to use by licensed veterinarians. Finally, the cost associated with providing preemptive analgesia contributes to the reluctance of producers to adopt these measures, especially since there is no perceived economic benefit for doing so. It may also be difficult for producers and veterinarians to determine if analgesic compounds are effective because cattle may not show overt signs of pain and distress, thus determining the need for analgesia and the dose, route, duration, and frequency of drug administration in cattle can be especially challenging.

Pathophysiology of Pain in Food Animals

Pain perception involves the transduction of chemical signals at the site of injury into electrical energy (Figure 1).[4] This is followed by transmission of the electrical signal via nerve fibers up the spinothalamic tracts where modulation may occur in the dorsal horn.[8] Finally, the impulse is projected to the brain where pain perception occurs. The initial response to a noxious stimulus is typically brief, well-localized, and somewhat proportional to the intensity of the insult. The second phase of the response is prolonged, diffuse, and often associated with hypersensitivity around the point where the initial stimulus was applied. This effect may lead to persistent post-injury changes in the central nervous system resulting in pain hypersensitivity or central sensitization ("wind-up"). This leads to hyperalgesia (increased pain from previously painful stimuli) and allodynia (a previously non-painful stimulus now produces pain).

Surgery-induced pain and central sensitization consist of 2 phases: an immediate incisional phase and a prolonged inflammatory phase that arises primarily due to tissue damage. The goal of administering analgesic compounds prior to castration is to mitigate both the incisional and inflammatory phase of the pain response. Effective analgesia, therefore, requires a multimodal approach using compounds that act on different receptor targets along the nociceptive pathway (Figure 1). This can be achieved through a combination of local anesthesia, nonsteroidal anti-inflammatory drugs (NSAIDs), and sedative-analgesic combinations of opioids, α2-agonists, and *N*-methyl *D*-aspartate (NMDA) receptor antagonists.

Analgesic Compounds and their Effect in Food Animals

Local Anesthesia

Local anesthetics are the most commonly prescribed preemptive analgesic drugs used in food animal practice. These compounds produce reversible loss of sensation in a localized area without causing loss of consciousness. Local anesthetics enter and block open sodium channels of nerve cells and prevent generation and propagation of nerve impulses. Repeatedly stimulated nerve cells are therefore more susceptible to the effects of local anesthetics. Furthermore, unmyelinated nerve fibers that transmit pain signals are preferentially blocked by local anesthetics compared with myelinated fibers that are responsible for pressure sensation and motor activity. The quality of local anesthesia in an acidic environment, such as infected tissues, is often poor because these compounds are weak bases that must dissociate in an alkaline environment to exert their effect. Lidocaine has a fairly rapid onset of activity (2 to 5 min) and an intermediate duration of action (90 min). Local anesthetic administration into the epidural space has also been shown to provide regional analgesia of the perineal region commencing 5 min after administration of 0.2 mg/kg lidocaine and lasting 10 to 115 min.[4]

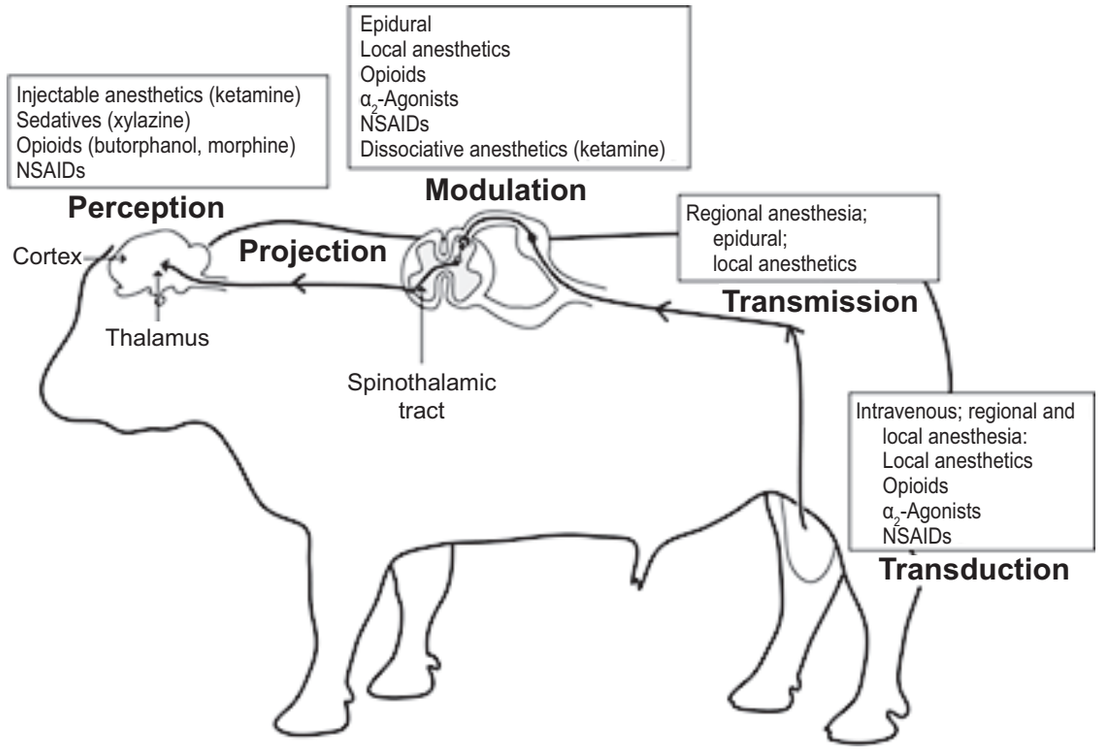

Figure 1. Anatomic location of sites of analgesic drug action.

Compounds that potentiate local anesthesia

Magnesium sulfate (MgSO4) – Magnesium sulfate has been combined with lidocaine to potentiate the local anesthetic effects. Magnesium competitively antagonizes NMDA receptors and their associated ion channels in the same manner as ketamine, thus reducing central sensitization caused by peripheral nociceptive stimulation. It was recently reported that the combination of lidocaine with magnesium sulfate produced epidural analgesia of longer duration than lidocaine with distilled water. In this experiment, local anesthesia with 2% lidocaine solution administered at 0.22 mg/kg was potentiated with 1 mL of 10% magnesium sulfate solution. Magnesium also reportedly has antinociceptive effects in animals and humans after systemic administration. These effects are considered to be associated with the inhibition of calcium influx into the cell and antagonism of NMDA receptors. Further studies with respect to the safety and efficacy of magnesium augmentation of local anesthesia are needed before this technique can be recommended.[4]

Sodium Bicarbonate – Commercial preparations of lidocaine are prepared as acidic solutions to promote solubility and stability. The addition of sodium bicarbonate before administration significantly reduces pain produced by infiltration of lidocaine in humans, probably due to the reduced acidity of the commercial formulation. The addition of sodium bicarbonate to lidocaine has also been found to reduce the time taken for the nerve block to take effect and enhance analgesia in humans. However, the addition of bicarbonate may decrease the duration of the block. A 10:1 ratio of 2% lidocaine with 8.4% sodium bicarbonate is recommended for optimal buffering of lidocaine. Thus 1 ml of commercially available 8.4% sodium bicarbonate solution can be added to 10 ml of 2% lidocaine immediately prior to administration in order to buffer the acidic effects of the formulation.[4]

Alternatives to local anesthesia

Ethanol injection demyelinates nerves fibers and may be a promising long-acting local anesthetic for use at the time of disbudding. When ethanol was administered as a corneal nerve block prior to disbudding, calves failed to display increased pain sensitivity in response to pressure algometry relative to their baseline values. Furthermore, ethanol-treated calves differed significantly from calves treated with the local anesthetic lidocaine at 1-hour (h) post-disbudding, when the lidocaine is assumed to be wearing off. Ethanol blocks appeared to desensitize the site of cautery dehorning for longer than 83 h, at which time the experiment concluded. In this experiment, 2 ml of 100% ethanol was injected at the site of the corneal nerve block. However, more than half the calves subjected to ethanol anesthesia required a second injection to achieve complete loss of sensation in 1 or both horns.[21] Further studies with respect to the safety and efficacy of ethanol blocks for local anesthesia are needed before this technique can be recommended.

Non-steroidal Anti-inflammatory Drugs (NSAIDS)

NSAIDs produce analgesia and anti-inflammatory effects by reducing prostaglandin (PG) synthesis through inhibition of the enzyme cyclo-oxygenase (COX) in the peripheral tissues and central nervous system. COX exists in 2 isoforms. COX-1 is constitutively expressed in both peripheral and central nervous systems, although expression is enhanced by pain and inflammatory mediators. COX-2 is ubiquitous in the CNS but only becomes the major enzyme for PG synthesis after induction by factors released during cell damage and death. It takes 2 to 8 h for maximal COX-2 mRNA expression to occur in the peripheral tissues; therefore, initial release of PG is primarily due to COX-1. PG in the peripheral tissues lowers the activation threshold of sensory neurons and may initiate nociceptive activity. PG also works in concert with substance P, histamine, calcitonin gene-related peptide (CGRP), and bradykinin to lower the firing threshold of sensory nerves and produce inflammation. Therefore, NSAIDs that inhibit COX-1 may have a more immediate impact on pain by inhibiting PG production in the periphery than COX-2 selective compounds. However, NSAIDs that inhibit COX-1 may be associated with increased risk for adverse gastrointestinal and renal effects.

Spinal PG, notably PGE_2, is responsible for increased excitability of the dorsal root ganglia leading to centrally mediated hyperalgesia. Given that COX-2 is constitutively expressed in the CNS, inhibition of spinal PGE_2 production by NSAIDs that inhibit COX-2 may be an important mechanism in preventing the establishment of hyperalgesia. The effect of NSAIDs on both central and peripheral PG synthesis suggests that these compounds have an important role in multimodal analgesic protocols.

The dose and pharmacokinetic parameters of the commonly used NSAIDs in the US are summarized in Table 1.[4]

Meloxicam

Meloxicam is a NSAID of the oxicam class that is approved in the European Union for adjunctive therapy of acute respiratory disease diarrhea, and acute mastitis when administered at 0.5 mg/kg IM or SC.[4] Heinrich and others demonstrated that 0.5 mg/ kg meloxicam IM combined with a cornual nerve block reduced serum cortisol response for longer compared with calves receiving only local anesthesia prior to cautery dehorning.[10] Furthermore, calves receiving meloxicam had lower heart rates and respiratory rates than placebo-treated control calves over 24 h post-dehorning. Stewart and others found that meloxicam administered IV at 0.5 mg/kg mitigated the onset of pain responses as measured by heart rate variability and eye temperature, compared with administration of a cornual nerve block alone.[20] Coetzee and others observed that meloxicam administered at 0.5 mg/kg IV prior to dehorning in 16-week-old calves reduced plasma substance P concentrations and improved weight gain over 10 days (d) compared with untreated controls.[3] These reports

Table 1. The dose and pharmacokinetic parameters of the commonly used NSAIDs in the US.

Drug	Approved species	Indications	Dose (cattle)	T ½ in cattle	Withhold period
Flunixin meglumine (Merck)	Cattle, horses and pigs	Antipyretic, Anti-inflammatory, BRD and mastitis Foot rot pain	2.2 mg/kg IV 3.3 mg/kg Topical	3-8 h Longer in topical	Meat-4 d (IV) Meat-8 d (topical) Milk-36 h
Phenylbutazone	Horses and dogs	Anti-inflammatory	4 mg/kg IV ONLY!	40-55 h	Not approved for cattle in the US
Ketoprofen (Merial)	Horses and dogs	Anti-inflammatory	1.5 mg/kg IV, IM	0.42 h	Not approved for cattle in the US
Aspirin	No FDA approval Horses and cattle	Reduction of fever, relief of minor aches and joint pain	50-100 mg/kg PO Oral F < 20%	0.5 h (IV salicylate)	No formal FDA approval. Not for use in lactating cattle
Carprofen (Zoetis)	EU approval in cattle Dogs	Adjunctive therapy of acute respiratory disease and mastitis	1.4 mg/kg bodyweight IV or SC Oral tablets	Age dependent < 10 weeks: 49.7 h	Not approved for cattle in the US EU-21 d (meat), 0 d (milk)
Meloxicam (Boehringer Ingelheim)	EU and Canadian approval in cattle Dogs and cats	Adjunctive for BRD; diarrhea and acute mastitis (EU). Analgesia after disbudding (Can)	0.5 IV, SC 0.5-1 mg/k PO Oral F=100%	27 h (range: 19.97-43.29 h)	Not approved for cattle in the U.S. 15 d EU and 20 d Canada. FARAD 21 d (meat)
Firocoxib (Merial)	Dogs and horses	Anti-inflammatory	0.5 mg/kg (PO) Oral F=98.4%	18.8 h (range: 14.2-25.5 h)	Not approved for cattle in the US or EU

demonstrate that administration of meloxicam prior to dehorning at 0.5 mg/kg IV or IM may be effective at alleviating pain and distress associated with painful procedures in cattle.

The pharmacokinetics of meloxicam after oral and IV administration have recently been described.[1] A mean peak plasma concentration (Cmax) of 3.10 ug/mL (range: 2.64 – 3.79 ug/mL) was recorded at 11.64 h (range: 10 – 12 h) with a half-life (T ½ λz) of 27.54 h (range: 19.97 – 43.29 h) after oral meloxicam administration. The bioavailability (F) of oral meloxicam corrected for dose was 1.00 (range: 0.64 – 1.66). These findings indicate that oral meloxicam administration could be an effective and convenient means of providing long-lasting analgesia to ruminant calves.

Meloxicam (20 mg/ml) is approved for use in cattle in several European countries with a 15-d meat withdrawal time and a 5-d milk withdrawal time following administration of 0.5 mg/kg IM or SC. An oral meloxicam suspension (1.5 mg/mL) and injectable formulation (5 mg/mL) are approved in the United States for the control of pain and inflammation associated with osteoarthritis in dogs. Furthermore, an injectable formulation (5 mg/ml) is approved for the control of post-operative pain and inflammation in cats. Several inexpensive generic tablet formulations containing meloxicam (7.5 and 15 mg) have recently been approved for relief of signs and symptoms of osteoarthritis in human medicine. In the absence of FDA-approved analgesic compounds in food animals, use of oral meloxicam tablets for alleviation of pain in cattle could be considered under AMDUCA. Research data support a 21 d meat withhold period and a 4 d milk withhold period in late-lactation dairy cattle.[5] A longer withhold period has been suggested in early lactation dairy cows.[8] Practitioners are advised to contact FARAD for the most up-to-date withhold period recommendations.

Transdermal Flunixin (Banamine Transdermal®, Merck Inc.)

On July 25, 2017, the US Food and Drug Administration announced the approval of Banamine Transdermal (flunixin transdermal solution), an animal drug approved for the control of pain associated with foot rot and the control of pyrexia (fever) associated with bovine respiratory disease. The pharmacokinetics of transdermal flunixin (FTD) in calves and dairy cows has been described by Kleinhenz and others.[9,13] In calves, transdermal flunixin could be detected at the first time point (10 min) indicating transdermal flunixin is rapidly absorbed. The time to maximum concentration was approximately 2 h with a half-life of 6.4 h. The authors report a bioavailability of 48% in calves.

When compared to other routes of administration, FTD is comparable in reported pharmacokinetics. Despite FTD having the lowest bioavailability (maximum concentration comparable to subcutaneous and oral dosing [TD 1.2 μg/mL; SQ 1.3 μg/mL; PO 0.9 μg/mL]), the half-life of FTD is slightly longer (6.4 h) than the extravascular routes (IM 4.5 h, SQ 5.4 h) of administration.[13]

Since dosing transdermal flunixin is very convenient with minimal restraint needed, a pharmacokinetic study investigating FTD took place. In Holstein cows (mature, lactating females), 3 doses of FTD was studied.[9,18] Cows

received 3 label doses of FTD (3.33 mg/kg; 1 mL/15 kg) at 24-h intervals. Following the 3 doses the half-life was 5.2 h, with maximum plasma concentrations being reached at 2.8 h. However, the range of the time to maximum concentrations was 1 to 8 h. When dosed at 24-h intervals, there was no plasma accumulation observed.

In a European study, FTD was found to suppress prostaglandin E_2 (PGE_2) production for 48 h. In this study, suppression of PGE_2 was determined using inflammatory exudate model with 80% reduction seen out to 48 h.[22] In data from the author's lab and using a whole blood ex vivo model, PGE2 production was decreased out to 30 h.[15] Thus, one can expect to see anti-inflammatory actions of FTD out to 30 h.

Recently our group described the milk depletion profile of flunixin and the 5-OH flunixin active metabolite in lactating dairy cows.[9] Ten lactating Holstein cows were enrolled into the study in mid-lactation. Following treatment, cows were milked 3 times a day (d) through 144 h. The geometric mean maximum concentration for flunixin in milk was 0.010 µg/mL and was 0.061 µg/mL for the active metabolite, 5-hydroxyflunixin. The geometric mean terminal half-life was 20.71 h for flunixin and 22.62 h for 5-hydroxyflunixin. Calculations to approximate a withdrawal time in milk following transdermal flunixin administration were accomplished using a statistical tolerance limit procedure. This analysis indicated that it would be prudent to observe a withdrawal period of 96 h following the last treatment. This is more than twice as long as the labeled withdrawal period of 36 h following use of the injectable formulation. The withdrawal period suggested by this work should be applied carefully, as this study was not conducted under the full quality control practices required by the US FDA for a full drug approval study.

Data advocating and supporting the use of analgesics at the time of painful procedures such as castration or dehorning has increased in the past 10 years. However, the implementation of such practices has been less than ideal. One of the major issues was the lack of labeled veterinary drugs in the US. With the approval of transdermal flunixin (FTD) for pain control in cattle, this has changed. Additionally, it has an easy-to-use dosing mechanism; reduces the need to restrain animals as compared to IV flunixin or oral meloxicam.

Dehorning

To date, only studies investigating FTD without a local anesthetic block at the time of dehorning have been published.[17] In that study, 8-week-old calves were hot-iron dehorned and followed for 72 h. Outcome measures collected include mechanical nociception threshold testing, plasma cortisol, ocular thermography, and substance P. Calves treated with FTD at the time of dehorning had lower cortisol levels than placebo controls. The MNT scores taken around the horn tissue were not different, but MNT taken at a central location were higher at 48 h post dehorning, thus FTD may have effects in decreasing central sensitization. There were no differences in substance P levels among treatment groups. Further work is needed to determine the role FTD could have in a multimodal analgesic plan. This plan should include timing of dose relative to dehorning as well as local anesthetic block.

Castration

The use of FTD at the time of surgical castration has been described.[16] Although the FTD did not inhibit a spike in cortisol associated with castration, it did lower the cortisol levels starting at 2 h post-castration. This lowering of cortisol may be beneficial when castration is done at arrival and vaccines are concurrently administered. A floor-based pressure mat system was used to analyze gait of calves following castration. No benefit of FTD was seen between castration groups (placebo vs FTD), but the castrated groups showed evidence of altering their gait following castration. Specifically, the castrated calves placed increased force on their font limbs following castration. This indicated they preferentially shifted their weight away from the castration site. Additionally, a significant difference in the impulse was observed. This difference was attributed to the sham-castrated steers moving at a faster speed across the mat. No differences in substance P were seen between groups.

Lameness

As previously mentioned, FTD is the only drug with a label for pain control in cattle. The label is specific for the pain associated with foot rot. Thus, pain associated with any other lameness modality (sole ulcer, arthritis/synovitis) would still constitute an extra-label drug use. Additionally, FTD is not approved for adult dairy cattle, which have a high prevalence of lameness. In an experiment conducted prior to FTD's label approval for pain control, adult dairy cows were subjected to lameness using an amphotericin B model and treated with FTD for 3 doses at 24-h intervals.[18] The model used induces a local arthritis/synovitis in the joint in which the amphotericin B is instilled. Cows in this study were compared to lame placebo controls and non-lame placebo controls. Outcomes measured included plasma cortisol, substance P, temperature of the coronary band via thermography, MNT testing, and gait analysis. Cows in the LAME groups were visually lame (2/5) following induction, with the FTD-treated cows being more lame. After 72 h there were no lame cows in the FTD group, but 4/10 lame cows in the placebo group. Furthermore, FTD-treated cows had MNT scores that approached pre-lameness levels by 48 h post-dosing, thus FTD does provide some analgesic benefit to lame cows. However, there were no observed changes in the gait analysis using the floor-based pressure mat. Another conclusion, drawn from comparing the MNT data and visual lameness scores is that cows may still be painful despite having a normal gait and lameness score.

Impact of disease on NSAID pharmacokinetics

Pharmacokinetic data is often generated in healthy groups of animals without evidence of disease. However, most

drug usage occurs in animals with disease or experiencing conditions that alter normal physiology. There is a growing body of literature that shows age, disease state, altered physiology due to pain, and stage of lactation have influence on pharmacokinetics.

NSAIDs are used in all ages of cattle. Kissell et al suggested that extended withdrawal times are needed for calves intended for veal production.[11] Flunixin was detectable in the hepatic, renal, and muscle tissue at 120 h post-dosing. Since flunixin in veal calves is considered ELDU, any detectable flunixin would be considered a violation. Kleinhenz et al were able to show that age influences the pharmacokinetics of flunixin when given by IV and transdermal routes. Unlike other studies investigating the influence of age on NSAID pharmacokinetics, the study used the same groups of cattle. Other studies looking at ketoprofen, carprofen, and phenylbutazone use separate animal groups, and thus individual animal variations are not accounted for. Following IV administration, calves at a younger age had lower clearance and a longer half-life. In the same group of calves following transdermal administration, maximum concentrations, mean absorption time and mean residence time were different. Calves had a higher maximum concentration, shorter mean absorption times, and shorter mean residence times.[15]

It has been well documented that pain causes changes in physiology, but there are no studies that investigate pain's influence on pharmacokinetics. Pain causes blood to be redirected from the skin to more vital organs such as the heart and skeletal muscles. These changes, when induced by dehorning, have an impact on the absorption of transdermal flunixin.[17] Pain from dehorning is associated with longer half-life, lower maximum concentration, and lower bioavailability. A local anesthetic block was not used at dehorning, and further research is needed to guide the use of transdermal flunixin at dehorning.

Mastitis has been shown to influence the pharmacokinetics of flunixin and ceftiofur.[6] Kissell et al observed elevated flunixin concentrations in cows with severe mastitis.[11] Specifically, cows with mastitis had flunixin levels above the tolerance at 36 h (label withdrawal time), thus a prolonged milk withholding period is recommended for cows being treated with flunixin by IV route for mastitis. In the study, 3 of 10 cows had detectable flunixin levels at 60 h post-administration. Additionally, ceftiofur pharmacokinetics were different in cows with severe mastitis and clinically normal cows. Cows with severe mastitis (confirmed coliform) had longer half-life, higher clearance, and lower peak plasma ceftiofur levels following 3 IM doses of ceftiofur.[6] Similarly, cows with induced coliform mastitis and treated with ceftiofur crystalline free acid had a longer half-life, but higher maximum ceftiofur concentrations.[7]

Changes in the pharmacokinetics of meloxicam at the time of calving have also been described.[8] Specifically, the clearance of meloxicam in the plasma and milk are seen, thus the half-life of meloxicam in the immediate postpartum period is significantly longer. Due to this prolonged half-life, the estimated withdrawal period of meloxicam in fresh cows is 8 d, not 4 d (96 h) as in mid-lactation cows. Reasons for the differences are not fully understood, but it is likely due to the bioavailability and distribution in postpartum cows.

Sedative-analgesic Drugs

Opioids, α2-agonists, and NMDA receptor antagonists are the most commonly used sedative analgesic compounds in veterinary medicine. These compounds may act synergistically and are therefore increasingly co-administered. A recent survey of Canadian veterinarians found that respondents that did use an analgesic at the time of castration used xylazine (>50% of respondents) more frequently than lidocaine (< 30% of respondents). Administration of local anesthetics into the testicles is considered by some to be dangerous and time-consuming with unpredictable efficacy, especially when circumstances do not allow sufficient time for maximal anesthesia to take effect.

Sedative-analgesic compounds may replace the need for intra-testicular anesthetic injection and thus enhance animal wellbeing and operator safety. A sub-anesthetic combination of xylazine, administered at 0.02 to 0.05 mg/kg and ketamine at 0.04 to 0.1 mg/kg given IV or IM ("Ketamine Stun") is reported to provide mild sedation without recumbency in cattle. Butorphanol (0.01 mg/kg) or morphine (0.05 mg/kg) may be included for enhanced analgesic effects. Currently FARAD recommends a 4-d meat withhold period and a 24-h milk withhold period for xylazine. The recommended withhold period for ketamine for both meat and milk is 72 h. A reasonable withdrawal time for opiates in cattle of at least 48 h has been suggested in the literature.

Several alternatives to xylazine monotherapy have been recommended to provide sedation in cattle. Romifidine (Sedivet®) administered at 0.05 mg/ kg (0.5 mL/ 100 kg) is needed for recumbency in sheep. Personal experience suggests that for standing procedures in cattle a dose of 0.2 to 0.3 mL (2 to 3 mg) of romifidine IV in adult cows provides excellent chemical restraint with minimal occurrences of recumbency. Detomidine (Dormosedan®) administered at 2.5 to 10 mcg/kg IV (0.025 to 0.1 ml/ 100kg) has been suggested for sedation. A dose of 40 mcg/kg IV (0.4 ml/100kg) produces profound sedation and recumbency in cattle lasting 30 to 60 min. Similarly, medetomidine (Domitor®) administered at 30 mcg/kg IM reportedly produces recumbency in calves and 10 mcg/kg IV produces recumbency in sheep. Sedation lasts about 1 h.

Alternatives to reverse the sedative effects of xylazine in cattle

Xylazine has an alpha-2: alpha-1 selectivity of 160:1. Detomidine is 260:1, romifidine is 360:1, and medetomidine is 1620:1. In regards to xylazine antagonists, atipamezole is more selective than yohimbine which is more selective than tolazoline for alpha-2 adrenergic receptors. Based on

the receptor selectivity of these reversal agents for alpha-adrenergic receptors, the following ratios of xylazine to reversal agent dosages are recommended:

- Reversal - xylazine:tolazoline is 1:10
- Reversal - xylazine:yohimbine/atipamezole is 10:1
- Medetomidine:atipamezole ratio (calves) is 1:4 (0.03 mg/kg agonist:±0.1 mg/kg antagonist)
- Studies in horses have used the same dose tolazoline to reverse detomidine and xylazine

Future Prospects for Treating Chronic Pain and Central Sensitization in Cattle

Gabapentin

Gabapentin (1-(aminomethyl) cyclohexane acetic acid) is a γ-aminobutyric acid (GABA) analogue originally developed for the treatment of spastic disorders and epilepsy. Studies have reported that gabapentin is also effective for the management of chronic pain of inflammatory or neuropathic origin. Although the mechanism of action of gabapentin is poorly understood, it is thought to bind to the α2-δ subunit of voltage-gated calcium channels acting pre-synaptically to decrease the release of excitatory neurotransmitters. Efficacy of gabapentin in humans is associated with 2 μg/mL plasma drug concentrations. It has also been reported that gabapentin can interact synergistically with NSAIDs to produce anti-hyperalgesic effects. In a recent study we report a mean peak plasma gabapentin concentration (Cmax) of 3.40 μg/mL (range: 1.70 to 4.60 μg/mL) at 7.20 h (range: 6 to 10 h) after oral gabapentin administration at 15 mg/ kg. An elimination half-life (T ½ λz) of 7.9 h (range: 6.9 to 12.4 h) was recorded.[2,19] Oral administration of gabapentin at 15 mg/ kg may be associated with plasma concentrations of >2 μg/ mL for up to 15 h. The pharmacokinetics of gabapentin suggests that this compound may be useful in mitigating chronic neuropathic and inflammatory pain in ruminant cattle.

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