A Review of Analgesic Compounds Used in Food Animals in the United States

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KEYWORDS

• Local anesthetics • Nonsteroidal antiinflammatory drugs (NSAIDs) • Opioids
• α2-Agonists • *N*-Methyl D-aspartate receptor antagonists • Gabapentin

KEY POINTS

- Extralabel drug use for pain relief in the United States is regulated under the Animal Medicinal Drug Use Clarification Act.
- Agents that may provide analgesia in livestock include local anesthetics, nonsteroidal antiinflammatory drugs, opioids, α2-agonists, and *N*-methyl-D-aspartate receptor antagonists.
- The addition of sodium bicarbonate in a 1:10 ratio with lidocaine may decrease pain associated with drug administration and increase the speed of onset of local anesthesia.
- Oral meloxicam tablets provide an effective and convenient means of providing long-lasting analgesia to ruminant cattle.
- The pharmacokinetic profile of oral gabapentin supports clinical evaluation of this compound for management of neuropathic pain associated with lameness in cattle.

INTRODUCTION

Societal concern about the moral and ethical treatment of animals is increasing.[1] In particular, negative public perception of pain associated with routine animal management practices such as dehorning and castration is mounting, with increasing call for the development of practices to relieve pain and suffering in livestock.[2] 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. Agents that

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could be used to provide preemptive analgesia include local anesthetics, nonsteroidal antiinflammatory drugs (NSAIDs), opioids, α2-agonists, and *N*-methyl D-aspartate (NMDA) receptor antagonists.[3] However, less that 20% of US veterinarians currently report using analgesia routinely at the time of dehorning and castration.[4]

The capacity to experience pain is considered to have a protective role by eliciting behavioral responses that reduce further tissue damage and enhance wound healing.[5] However, persistent pain syndromes offer no biological advantage and are associated with suffering and distress.[5] Pathologic pain states in cattle occur as a result of tissue damage, nerve damage, and inflammation and are frequently associated with pain hypersensitivity.[6] Pain hypersensitivity manifests as hyperalgesia (exaggerated responses to painful stimuli) and allodynia (pain resulting from normally innocuous stimuli).

Hyperalgesia has been reported to persist in dairy cattle and lame sheep for at least 28 days after the causal lesion has resolved.[7,8] As a result, chronic pain associated with lameness is considered one of the most significant welfare concerns in dairy cows.[9] Inflammatory pain associated with lameness responds modestly to treatment with NSAIDs[10,11] but neuropathic pain (caused by nerve damage or neuronal dysfunction) is considered refractory to the effects of NSAIDs and many opioid analgesics.[5] Therefore, there is a need to identify novel drugs and drug targets for alleviating chronic pain of neuropathic origin in animals.[6]

This article reviews the challenges associated with providing analgesia in food animals in the United States and the salient pharmacokinetic and pharmacodynamic features of the analgesic compounds that are commonly used in livestock. The use of novel agents such as bicarbonate, magnesium, ethanol, gabapentin, and vitamin B complex to augment analgesia is also discussed.

CHALLENGES ASSOCIATED WITH PROVIDING ANALGESIA IN FOOD ANIMALS

There are several challenges associated with providing effective analgesia in food animals in the United States. First, there are currently no analgesic drugs specifically approved for the alleviation of pain in livestock.[12] Therefore, use of any drug for pain relief constitutes extralabel drug use (ELDU).[13] Under the Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994,[14] 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 US Food and Drug Administration (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 United States would be required by law to comply with these regulations.

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 before a maximal effect is achieved,[15,16] which may slow animal processing because 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 intravenous (IV) administration in the United States.[13] 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, most analgesic drugs that are available in the United States have a short elimination half-life necessitating frequent administration to be effective.[13] 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).[17] Therefore, administration of these compounds to provide preemptive analgesia is restricted to use by licensed veterinarians. In addition, the cost associated with providing preemptive analgesia contributes to the reluctance of producers to adopt these measures, especially because there is no perceived economic benefit for doing so. It may also be difficult for producers and veterinarians to determine whether 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.

ANALGESIC COMPOUNDS AND THEIR EFFECT IN CATTLE

Pain perception involves the transduction of chemical signals into electrical energy at the site of injury (**Fig. 1**). This transduction is followed by transmission of the electrical signal via nerve fibers up the spinothalamic tracts where modulation may occur in the dorsal horn.[18] The impulse is then projected to the brain where pain perception

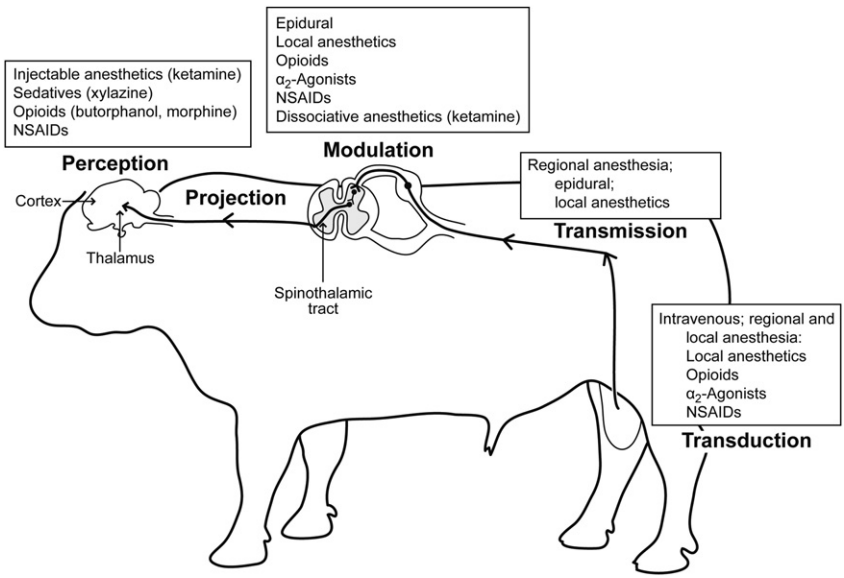

Fig. 1. The nociceptive pathway in cattle, indicating the anatomic location of target receptors for analgesic drug activity. (*Courtesy of* Mal Hoover, CMI, Kansas State University, Manhattan.)

occurs.[19] The initial response to a noxious stimulus is typically brief, well localized, and 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.[19] This effect may lead to persistent postinjury changes in the central nervous system (CNS) resulting in pain hypersensitivity or central sensitization (so called wind-up).[19,20] These effects lead to hyperalgesia (increased pain from previously painful stimuli) and allodynia (a previously nonpainful stimulus now produces pain).[21]

Surgery-induced pain and central sensitization consist of 2 phases: an immediate incisional phase and a prolonged inflammatory phase that arises primarily from tissue damage.[20] The goal of administering analgesic compounds before castration is to mitigate both the incisional and inflammatory phases of the pain response. Effective analgesia therefore requires a multimodal approach using compounds that act on different receptor targets along the nociceptive pathway (see **Fig. 1**).[18] This approach can be achieved through a combination of local anesthesia, NSAIDs, and sedative-analgesic combinations of opioids, α2-agonists, and NMDA-receptor antagonists.

LOCAL ANESTHESIA

Local anesthetics are the most commonly prescribed preemptive analgesic drugs used in food animal practice.[22] 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.[23] Nerve cells that are repeatedly stimulated 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 rapid onset of activity (2–5 minutes) and an intermediate duration of action (90 minutes). Local anesthetic administration into the epidural space has also been shown to provide regional analgesia of the perineal region commencing 5 minutes after administration of 0.2 mg/kg lidocaine and lasting 10 to 115 minutes.[22]

COMPOUNDS THAT POTENTIATE LOCAL ANESTHESIA

Magnesium Sulfate

Magnesium sulfate has been combined with lidocaine to potentiate the local anesthetic effects.[24] 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.[25,26] It was recently reported that the combination of lidocaine with magnesium sulfate produced epidural analgesia of longer duration than lidocaine with distilled water.[24] Local anesthesia with 2% lidocaine solution administered at 0.22 mg/kg was potentiated with 1 mL of 10% magnesium sulfate solution.[24] Magnesium also reportedly has antinociceptive effects in animals and humans after systemic administration.[27] 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.

Sodium Bicarbonate

Commercial preparations of lidocaine are prepared as acidic solutions to promote solubility and stability.[28] The addition of sodium bicarbonate before administration significantly reduces pain produced by infiltration of lidocaine in humans probably because of the reduced acidity of the commercial formulation.[28] 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.[29,30] However, the addition of bicarbonate may decrease the duration of the block.[30] 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 before administration to buffer the acidic effects of the formulation.

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.[31] When ethanol was administered as a corneal nerve block before disbudding, calves failed to display increased pain sensitivity in response to pressure algometry relative to their baseline values.[31] Furthermore, ethanol-treated calves differed significantly from calves treated with the local anesthetic lidocaine at 1-hour after disbudding, when the lidocaine is assumed to be wearing off. Ethanol blocks seemed to desensitize the site of cautery dehorning for longer than 83 hours, at which time the experiment concluded.[31] In this experiment, 2 mL of 100% ethanol were 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.[31] Further studies with respect to the safety and efficacy of ethanol blocks for local anesthesia are needed before this technique can be recommended.

NSAIDS

NSAIDs produce analgesia and antiinflammatory effects by reducing prostaglandin (PG) synthesis through inhibition of the enzyme cyclooxygenase (COX) in the peripheral tissues and CNS.[21] COX exists in 2 isoforms. COX-1 is constitutively expressed in both the peripheral nervous system and CNS, 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.[32] It takes 2 to 8 hours for maximal COX-2 mRNA expression to occur in the peripheral tissues, therefore initial release of PG is primarily caused by COX-1.[33] 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.[21] 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.[21,33] 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 United States are summarized in **Table 1**.

FLUNIXIN MEGLUMINE

Flunixin is a highly substituted derivative of nicotinic acid. Flunixin meglumine is currently the only NSAID approved for use in cattle in the United States.[13] The plasma elimination half-life of flunixin is reported to be 3 to 8 hours.[34] Following a single IV dose of 2.2 mg/kg of body weight, plasma concentrations decreased from 16.16 $\pm$ 5.28 μg/mL to 1.22 $\pm$ 0.16 μg/mL in 2 hours, and reached 0.5 $\pm$ 0.02 μg/mL by 30 hours.[35] A peak concentration (C_{max}) of 0.9 $\pm$ 0.05 mcg/mL occurred at 3.5 $\pm$ 1.0 hours (T_{max}) after a single oral dose of 2.2 mg/kg with an estimated half-life of 6.2 hours and bioavailability of 60%.[35,36] Therefore, once-daily administration is likely required to maintain effective plasma drug concentrations. Although this drug class is recognized as having analgesic properties, flunixin is only indicated for control of fever associated with respiratory disease or mastitis and fever and inflammation associated with endotoxemia, rather than for control of pain. Studies showing the analgesic effects of flunixin administered alone at the approved dose of 2.2 mg/kg are deficient in the published literature. Use of flunixin meglumine is further complicated by the requirement for IV administration, which is more stressful on the animal and involves more skill and training on the part of the operator. Several reports have suggested that the intramuscular (IM) administration of flunixin may result in significant myonecrosis and tissue residues.[13]

PHENYLBUTAZONE

Phenylbutazone is not approved for use in cattle in the United States, although it has been used in veterinary medicine for more than 50 years.[37,38] The pharmacokinetics of phenylbutazone is characterized by a slow clearance and longer terminal half-life compared with other NSAIDs.[39] The oral bioavailability of phenylbutazone ranges from 54% to 69%, with peak plasma concentrations achieved in 8.9 to 10.5 hours.[39]

Phenylbutazone has been associated with rare but fatal blood dyscrasias, including aplastic anemia, leukopenia, agranulocytosis, thrombocytopenia, and deaths in humans.[40] The risk for developing these lethal adverse effects in humans is not dose dependent. The human mortality following aplastic anemia induced by phenylbutazone and oxyphenbutazone is reported to be 94% and 71%, respectively. The risk of mortality from oxyphenbutazone is estimated to be 3.8/100,000 exposures and, from phenylbutazone, the rates varied from less than 1 death/100,000 for men aged 65 years to 6/100,000 for women aged 65 years and older.[41] No particular indication for treatment seemed to carry a higher risk. The primary concern was the use of these two drugs in elderly patients.[41] Hypersensitivity reactions of the serum-sickness type have also been reported. In addition, phenylbutazone is recognized as a carcinogen by the FDA.[40]

In light of these potential adverse effects associated with exposure to phenylbutazone, the FDA has issued an order prohibiting the extralabel use of phenylbutazone animal and human drugs in female dairy cattle 20 months of age or older.[40] There is also a zero tolerance for phenylbutazone residues in edible tissues from any class of animal.[40] Use of phenylbutazone as an analgesic in food animals is therefore strongly discouraged.[13]

Table 1
Nonsteroidal antiinflammatory compounds available for use in cattle

Drug	Approved Species	Indications	Dose (mg/kg)	Half-life	Withhold Period
Flunixin meglumine	Cattle, horses, and pigs	NSAID: antipyretic, antiinflammatory	2.2; IV only	3–8 h	Meat: 4 d Milk: 36 h
Phenylbutazone	Horses and dogs	NSAID: antiinflammatory	4; IV only 4.4 in horses 8 in dogs 10 loading dose in cattle followed by 5 mg/kg every 48 h	40–55 h	Not approved in cattle in the United States
Ketoprofen	Horses and dogs	NSAID: antiinflammatory	3 IV, IM	0.42 h	Not approved in cattle in the United States
Aspirin	No FDA approval Horses and cattle	NSAID: reduction of fever Relief of minor muscle aches and joint pain	50–100 by mouth Oral F < 20%	0.5 h (IV salicylate)	No formal FDA approval Not for use in lactating cattle
Carprofen	EU approval in cattle Dogs	NSAID: adjunctive therapy for acute respiratory disease and mastitis	1.4 IV or SC	Age dependent <10 wk: 49.7 $\pm$ 3.9 h (R$-$) and 37.4 $\pm$ 2.4 h (S+) Adult cows, 30.7 $\pm$ 2.3 h	Not approved in cattle in the United States
Meloxicam	EU and Canadian approval in cattle Dogs and cats	NSAID: adjunctive therapy for acute respiratory disease; diarrhea, and acute mastitis (Europe)	0.5 IV, SC 0.5–1 by mouth	27 h (range 19.97–43.29 h)	Not approved in cattle in the United States

Abbreviations: EU, European Union; IM, intramuscular; SC, subcutaneous.

KETOPROFEN

Ketoprofen is a member of the propionic acid class of NSAIDs.[42] Ketoprofen has a short plasma elimination half-life of 0.42 hours in adult cattle, making it less attractive for use as a preemptive analgesic.[43] Although it has been shown that concentrations of ketoprofen are higher in inflammatory exudates than plasma, 80% of a parenteral dose is reportedly eliminated in the urine within 24 hours of administration.[42] Therefore, multiple doses of ketoprofen are likely required to maintain adequate analgesic concentrations.

Ketoprofen exists in 2 enantiomeric forms: R(−) and S(+).[42] Commercial formulations contain a 50:50 mixture of the 2 enantiomers; however, it is estimated that 31% of the R(−) enantiomer is converted to the S(+) enantiomer in calves after IV administration. The extent of chiral inversion may vary depending on the age and production class of the animal. The S(+) enantiomer is thought to be 250 times more potent than the R(−) enantiomer in inhibiting PGE_2 production.[44] The duration of PgE_2 inhibition in a tissue cage model in sheep was 4 times longer with S(+)-ketoprofen compared with R(−)-ketoprofen.[45] The clinical significance of chirality in term of analgesic effects in cattle requires further investigation. The development and production of enantiomer-specific formulations could provide superior analgesia to current racemic mixtures in cattle in the future.

Ketoprofen is approved in the European Union and Canada for the alleviation of inflammation and pain associated with arthritis and traumatic musculoskeletal injuries and as an adjunctive therapy for the alleviation of fever, pain, and inflammation associated with acute clinical mastitis.[42] The recommended dose is 3 mg/kg of body weight by IM or IV injection, every 24 hours for up to 3 days. Ketoprofen is commonly used in small animal and equine medicine in the United States; however; there are currently no approved formulations for use in livestock.[13]

SALICYLIC ACID DERIVATIVES

Salicylic acid derivatives, including aspirin (acetylsalicylic acid) and sodium salicylate, were the first NSAIDs to be used in modern medicine and are still widely used for their analgesic, antipyretic, and antiinflammatory properties.[46] Although the veterinary forms of aspirin are extensively marketed with label indications for the treatment of fever, inflammation, and pain relief, these have never been approved by the FDA Center for Veterinary Medicine for these indications.[47] Therefore, the legality of using salicylic acid derivatives in cattle is questionable because these are technically compounded products.

Aspirin is a weak acid with a pK_a of 3.5. In the alkaline environment of the rumen (pH 5.5–7.0), approximately 1000 times as much aspirin is in the ionized form compared with the more diffusible nonionized form,[47] which results in a slow absorption rate in cattle. It is estimated that the oral bioavailability of aspirin in cattle may only be 20%.[48] Aspirin is also highly protein bound (70%–90%), a characteristic shared by all NSAIDs discussed in this article. Administration of 2 NSAIDs at one time, or an NSAID in conjunction with another highly protein-bound drug, may result in higher concentrations of free drug in the plasma because of competition for binding sites.

Aspirin elimination half-lives after oral administration range from approximately 4 hours after oral administration in cattle to approximately 38 hours in cats.[47] The slow absorption rate after oral administration shown in adult dairy cows is evident in the difference between elimination half-times for IV sodium salicylate (0.54 ± 0.04 hours)[49] and oral acetylsalicylic acid (3.70 ± 0.44 hours).[50] The elimination half-life is longer after oral administration of aspirin because the rumen acts as a slow-release

reservoir for aspirin absorption. The low volume of distribution (0.24 ± 0.02 L/kg) indicates limited distribution to tissues. Salicylic acid derivatives are not associated with clotting deficits in cattle.[46]

In previous bovine castration studies, plasma concentrations of sodium salicylate of more than 25 μg/mL have coincided with decreased peak cortisol concentrations compared with castration with no analgesia.[48] In one study, an oral dose of 100 mg/kg (70 grains/100 lbs) maintained serum concentrations in excess of 30 μg/mL between approximately 1 hour and 5 hours after administration.[50] The mean peak serum concentration was close to 50 μg/mL. An oral dose of 50 mg/kg failed to reach serum concentrations of 30 μg/mL. Gingerich and colleagues[50] used 30 μg/mL as the minimum concentration for pain relief, based on the human serum concentrations required for relief of headaches, aches, and pains. Serum concentrations near 100 μg/mL are necessary in humans to relieve severe arthritis pain. The investigators noted clinical improvement in 2 cows with nonsuppurative tarsitis at 100 mg/kg orally, but noted no improvement at this dose in a bull with suppurative tarsitis.[50] They recommended 100 mg/kg every 12 hours to maintain serum concentrations at more than 30 μg/mL.

CARPROFEN

Carprofen is a member of the propionic acid class of NSAIDs.[51] The relative antiinflammatory, analgesic, and antipyretic activity of carprofen is reported to be greater than phenylbutazone or aspirin.[52] Carprofen exists in 2 enantiomeric forms: R(−) and S(+). In vitro studies in canine plasma suggest that the S(+) enantiomer is 100 times more active against COX-2 than the R(−) enantiomer.[53] Carprofen also shows age-dependent pharmacokinetics. The reported half-life of the R(−) and S(+) enantiomer in calves less than 10 weeks of age is 49.7 ± 3.9 hours and 37.4 ± 2.4 hours respectively.[51,52] In adult cows after subcutaneous (SC) administration, the half-life of the racemic mixture is 30.7 ± 2.3 hours.[51] Carprofen is approved in the European Union as an adjunct to antimicrobial therapy to reduce clinical signs in acute infectious respiratory disease and acute mastitis in cattle. The recommended dose for SC or IV administration is 1.4 mg/kg bodyweight. Carprofen is commonly used in small animal medicine in the United States; however; there are currently no approved formulations for use in livestock.[13]

MELOXICAM

Meloxicam is an NSAID of the oxicam class that is approved in the European Union for adjunctive therapy for acute respiratory disease, diarrhea, and acute mastitis when administered at 0.5 mg/kg IM or SC.[54] Heinrich and colleagues[55] showed 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 before cautery dehorning. Furthermore, calves receiving meloxicam had lower heart rates and respiratory rates than placebo-treated control calves in the 24 hours after dehorning. Stewart and colleagues[56] found that meloxicam at 0.5 mg/kg IV mitigated the onset of pain responses as measured by heart rate variability and eye temperature, compared with administration of a cornual nerve block alone. Coetzee and colleagues[57] observed that meloxicam administered at 0.5 mg/kg IV before dehorning in 16-week-old calves reduced plasma substance P concentrations and improved weight gain over 10 days compared with untreated controls. These reports show that administration of meloxicam before dehorning at 0.5 mg/kg IV or IM may be effective at alleviating pain and distress associated with painful procedures in cattle.

The pharmacokinetic-pharmacodynamic relationship and dose response to meloxicam in horses with induced carpal arthritis has been reported.[58] Based on this work, the reported median effective concentration (EC_{50}) for meloxicam in the plasma of lame horses is approximately 0.2 μg/mL. The pharmacokinetics of meloxicam after oral and IV administration have recently been described.[59] A mean plasma C_{max} of 3.10 μg/mL (range 2.64–3.79 μg/mL) was recorded at 11.64 hours (range 10–12 hours) with an elimination half-life (T 1/2 λz) of 27.54 hours (range 19.97–43.29 hours) after oral meloxicam administration. The bioavailability (F) of oral meloxicam corrected for dose was 1.00 (range 0.64–1.66).[59] 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-day meat withdrawal time and a 5-day milk withdrawal time following administration of 0.5 mg/kg IM or SC.[54] 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 postoperative 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.[14]

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 coadministered. A recent survey of Canadian veterinarians found that respondents who did use an analgesic at the time of castration used xylazine (>50% of respondents) more frequently than lidocaine (<30% of respondents).[60] 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.[60] Sedative-analgesic compounds may replace the need for intratesticular anesthetic injection and thus enhance animal well-being and operator safety. A subanesthetic 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 (so-called ketamine stun) is reported to provide mild sedation without recumbency in cattle.[61,62] Butorphanol (0.01 mg/kg) or morphine (0.05 mg/kg) may be included for enhanced analgesic effects.[61]

OPIOID ANALGESICS

The analgesic effect of opioids are associated with binding to spinal and supraspinal μ, κ and δ receptors.[63] Drug binding decreases propagation of the nociceptive signal by activating receptor-linked potassium channels and inhibiting voltage-gated calcium channels. In addition to producing analgesia, μ-receptor activation is associated with respiratory depression, decreased gastrointestinal motility, increased appetite, sedation, euphoria, and nausea. Therefore, partial and mixed receptor opioids have been developed with fewer adverse effects and, in some cases, a lower abuse potential than pure μ agonists. There are currently no narcotic analgesics approved for use in cattle in the United States. Opioids are designated as schedule 3 drugs in the United States and are subject to regulation by the DEA.[17]

Butorphanol is a κ-opioid–receptor agonist and either a partial μ agonist or antagonist. The potency of butorphanol is reported to be 5 to 7 times that of morphine, although some investigators dispute this.[63] The efficacy of butorphanol is limited to mild and moderate pain but it is one of the most common narcotic analgesics used in veterinary medicine. The half-life of butorphanol in dairy cows administered 0.25 mg/kg IV was 82 minutes.[64] Baldridge and colleagues[65] reported a peak plasma concentration for butorphanol of 7.07 ± 0.55 ng/mL at 9.5 ± 0.50 minutes after coadministration of 0.025 mg/kg butorphanol, 0.05 mg/kg xylazine, and 0.1 mg/kg ketamine IM immediately before dehorning and castration with a plasma elimination half-life of 71.28 ± 7.64 minutes. In dogs, a plasma concentration of 45 ng/mL is considered an effective analgesic concentration, but this has not been confirmed in cattle.[63]

Nalbuphine is a synthetic opioid that is a κ-receptor agonist and a μ-receptor antagonist with similar pharmacologic effects to butorphanol. Nalbuphine has analgesic potency similar to morphine on a milligram basis.[63] The onset of activity of nalbuphine reportedly occurs within 2 to 3 minutes after IV administration in humans with a plasma elimination half-life of 5 hours. Duration of activity of 3 to 6 hours has been reported after nalbuphine administration in human clinical studies.[63]

Nalbuphine injection may be associated with fewer adverse effects than morphine because κ agonists cause less respiratory depression compared with μ-receptor agonists. Furthermore, κ agonists carry a significantly lower risk of dependency because opioid addiction is mediated primarily through activation of the μ receptor. As a result, nalbuphine is presently not scheduled as a controlled substance in most parts of the United States in accordance with the Controlled Substances Act (21 U.S.C. § 812) based on the exclusion detailed in 21 C.F.R. § 1308.12.[17] Therefore, special storage and record keeping is not necessary. The potential for fewer adverse effects and reduced regulatory restrictions may make nalbuphine an attractive narcotic analgesic option for use in cattle if clinical efficacy were shown.

α2-ADRENERGIC AGONISTS

α2-Adrenergic agonists produce profound sedation, chemical restraint, and analgesia in cattle. Activation of α2-adrenergic receptors inhibits the positive feedback mechanism for the release of norepinephrine from the presynaptic nerve endings by reducing calcium conductance.[66] Attenuation of norepinephrine release causes dose-dependent sedation and inhibits the afferent pain pathway.[66] In addition, α2-adrenergic agonists decrease cardiac output, cause a centrally mediated reduction in respiratory rate, produce muscle relaxation, and depress gastrointestinal motility. Epidural administration of α2-agonists can produce analgesia with minimal sedative and cardiovascular effects compared with IV administration.

Xylazine is the most commonly used α2-adrenergic agonist used in cattle and is approved in the European Union for IM administration at 0.05 to 0.3 mg/kg. Administration of the lower dose is characterized by a slight decrease in muscle tone but the ability to stand is maintained. Higher doses cause recumbency, very deep sedation, and a degree of analgesia. It is recommended that cattle are starved before systemic administration of higher doses of xylazine to reduce the risk of rumen tympany and aspiration of rumen contents.

Xylazine epidural has been shown to produce greater perineal analgesia than xylazine given intramuscularly.[67] Xylazine epidural has been proposed as a method of providing sedation and analgesia to facilitate castration in mature bulls.[68] Grubb and colleagues[69] compared the time of onset and duration of analgesia produced

by lidocaine and xylazine alone and in combination. The onset of analgesia following administration of xylazine alone was significantly longer (11.7 ± 1 minute) than the combination of xylazine and lidocaine (5.1 ± 0.9 minutes) and lidocaine alone (4.8 ± 1.0 minutes). The combination of lidocaine and xylazine produced analgesia of significantly longer duration (302.8 ± 11.0 minutes) than xylazine alone (252.9 ± 18.9 minutes) or lidocaine alone (81.8 ± 11.8 minutes). Xylazine induced mild to moderate sedation and ataxia. Ataxia was also noted in cattle receiving lidocaine alone.

Grant and Upton[70] (2004) reported that 0.05 mg/kg xylazine IV in sheep produced analgesia lasting 25 minutes with only 3 out of 7 animals showing signs of mild sedation. Garcia-Villar and colleagues[71] (1981) reported that an IV dose of 0.2 mg/kg xylazine in cattle was associated with a peak plasma concentration of 1.050 μg/mL, a plasma elimination half-life of 36 minutes, and a total body clearance of 42 mL/min/kg. Baldridge and colleagues[65] (2010) reported a peak plasma concentration for xylazine of 20.95 ± 1.68 ng/mL at 9.5 ± 0.50 minutes after coadministration of 0.025 mg/kg butorphanol, 0.05 mg/kg xylazine, 0.1 mg/kg ketamine IM immediately before dehorning and castration in calves. The plasma elimination half-life of xylazine was 96.40 ± 20.33 minutes.

NMDA-RECEPTOR ANTAGONISTS

Ketamine is an NMDA-receptor antagonist that produces analgesia and dissociative anesthetic effects when administered to calves at a dose of 2 to 4 mg/kg IV.[66] Ketamine and its active metabolite, norketamine, also bind μ-opioid and κ-opioid receptors producing analgesia.[72] Data from rats suggest that norketamine contributes to the analgesic effect of ketamine, with a potency that is one-third that of the parent drug.[73]

Subanesthetic ketamine administered at 0.1 to 1 mg/kg as an IV bolus is effective in managing acute postoperative pain in human medicine.[74] In humans, plasma ketamine concentrations more than 4 to 5 μmol/L (1000 ng/mL) are required to produce anesthetic effects, whereas analgesic effects are associated with plasma concentrations less than 1 μmol/L (275 ng/mL) or one-tenth to one-fifth of the anesthetic dose.[75] Grant and colleagues[76] reported that plasma ketamine concentrations ranging from 40 to 150 ng/mL were associated with analgesia in humans. Our group previously showed that mean plasma ketamine and norketamine concentrations in cattle decreased to less than 40 ng/mL and 10 ng/mL after 30 and 60 minutes respectively after administration of a subanesthetic combination of xylazine (0.05 mg/kg) and ketamine (0.1 mg/kg).[77] NMDA-receptor antagonists are designated as schedule 3 drugs and are subject to regulation by the DEA.[17]

FUTURE PROSPECTS FOR TREATING CHRONIC PAIN AND CENTRAL SENSITIZATION IN CATTLE

Gabapentin

Gabapentin, or 1-(aminomethyl) cyclohexane acetic acid, is a γ-aminobutyric acid (GABA) analogue originally developed for the treatment of spastic disorders and epilepsy.[78] Studies have reported that gabapentin is also effective for the management of chronic pain of inflammatory of neuropathic origin.[79] 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 presynaptically to decrease the release of excitatory neurotransmitters.[80] Efficacy of gabapentin in humans is associated with 2 μg/mL plasma drug concentrations.[81] It has also been reported that gabapentin

can interact synergistically with NSAIDs to produce antihyperalgesic effects.[79,82] In a recent study, we reported a mean plasma gabapentin C_{max} of 3.40 μg/mL (range 1.70–4.60 μg/mL) at 7.20 hours (range 6–10 hours) after oral gabapentin administration at 15 mg/kg. A T 1/2 λz of 7.9 hours (range 6.9–12.4 hours) was recorded.[83] Oral administration of gabapentin at 15 mg/kg may be associated with plasma concentrations of greater than 2 μg/mL for up to 15 hours. The pharmacokinetics of gabapentin suggest that this compound may be useful in mitigating chronic neuropathic and inflammatory pain in ruminant cattle.

Vitamin B Complex Injections

B vitamins have been found to produce antinociceptive and antiinflammatory effects in the rat tail pressure test,[84] and are able to significantly decrease the responses evoked in spinal dorsal horn nociceptive neurons in the cat.[85] An SC injection of a combination of vitamin B_1:B_6:B_{12} at 20:20:0.2 mg/kg has been proposed. Several studies have documented that lower NSAID doses are needed for pain relief when combined with B vitamins.[85,86] Cocktails of B vitamins have also been shown to ameliorate allodynia and formalin-evoked hyperalgesia in diabetic rats, suggesting that the use of such a cocktail may prove to be a potentially inexpensive and safe long-term approach for treating neuropathies such as lameness.[87] However, in the absence of controlled studies, further research is needed to determine whether this would be effective in cattle. Further studies with respect to the safety and efficacy of vitamin B augmentation of NSAID analgesia are needed before this technique can be recommended.

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