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Bovine Pain Management

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Objectives of the article

- Understand pain physiology of ruminants
- Recognise clinical signs of pain in ruminants
- Understand drug selection criteria for ruminants
- Importance of pre-emptive analgesia and multimodal analgesia.

Pain management is a concern in ruminant practice because many husbandry procedures thought to improve productivity and safety, such as castration and dehorning, are commonly performed with minimal or no analgesia. An increased awareness of ruminant welfare issues has led to more extensive use of analgesic drugs and techniques to decrease pain and distress.

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" (International Association for the Study of Pain, 1994). Pain is a physiologic response to prevent further tissue damage following a traumatic event. However, pain can lead to distress. Distress, "is a state in which an animal cannot escape from or adapt to internal or external stressors or conditions it experiences, resulting in negative effects on its well-being". Pain can have serious consequences like decreased metabolism, productivity, and overall wellbeing affected. Persistent pain syndromes offer no biological advantage and pathologic pain states in cattle occur as a result of tissue damage, nerve damage, and inflammation and are frequently associated with pain hypersensitivity.

Pain hypersensitivity manifests as hyperalgesia (exaggerated responses to painful stimuli) and allodynia (pain resulting from normally innocuous stimuli). Hyperalgesia has been reported to occur in dairy cattle for at least 28 days after the causal lesion has resolved. Inflammatory pain associated with lameness responds modestly to treatment with non-steroidal anti-inflammatory drugs (NSAID's) but neuropathic pain (caused by nerve damage or neuronal dysfunction) is considered refractory to the effects of NSAID's and many opioid analgesics.

Most of our criteria for classifying an animal as being in pain are subjective. Recognisable signs of pain vary between species and individuals within a species. More importantly, cattle may be in pain without any visual evidence. Since cattle are a prey species, it is in their best interest revolutionary not to exhibit pain.

Pain control in livestock can be complex and controversial. Factors to consider when deciding when and how to control pain include: the animal and its needs, the production setting, and the availability and unfortunately, the economics of an intervention.

Clinical signs utilized to identify painful cattle.

Subjective Assessments	Objective Assessments
Reluctance to move	Identifiable decrease in production
Turning toward site of stimulus	Increased respiratory rate
Bruxism (grinding teeth)	Increase in plasma cortisol
Licking, biting at site of stimulus	Changes in blood pressure
Kicking, stamping	Increased heart rate
Inappetence	Weight loss
Limping	
Restlessness, pacing	
Vocalisation	
Change in facial expression	

July 2019

Classes of drugs:

- Nonsteroidal anti-inflammatory drugs,
- α_2 adrenergic drugs,
- Opioids,
- Local anaesthetics
- NMDA antagonists
- Anticonvulsants
- Magnesium and B vitamin complex

Unfortunately, most of the drugs that can be used for pain control do not have specific label claims for use in cattle. To legally use drugs in an extra-label manner, the practitioner must be able to establish a proper meat and/or milk withdrawal interval before administering the drug. If a withdrawal interval cannot be established, extra-label use of a drug is not permitted.

An understanding of the pathologic neurophysiological processes is paramount to the development and implementation of effective pain therapy but is outside the scope of this article.

THERAPEUTIC OPTIONS

The easiest type of pain to treat is that which we induce.

The magnitude of surgical pain is influenced by the procedure, the methods used, and the experience and skill of the practitioner. **Pre-emptive treatment in anticipation of a painful event provides more analgesia than treatment with the same drug and dosage after robust pain sensations are developed.**

NSAID's

NSAID's are used frequently by veterinarians because of their ease of parenteral administration, their duration of action, and their potent anti-inflammatory and analgesic actions. The most commonly used NSAID's in ruminants are the non-specific COX inhibitors flunixin meglumine (MSD), ketoprofen (Merial), aspirin, and the more selective COX-2 inhibitors meloxicam (Boehringer Ingelheim), and carprofen (Zoetis).

Their analgesic action is through inhibition of various inflammatory mediators (e.g. inhibition of release of various prostaglandins). NSAID's are effective for mild to moderate pain only. Their pharmacokinetics and length of activity differ significantly between products. Nephrotoxicity can be of concern in severely dehydrated and hypovolemic cattle.

Systemic use of NSAID's:

The pre-emptive use of NSAID's in combination with local anaesthetic techniques and sedative/analgesic drugs is common during general anaesthesia and procedures under sedation, and positive effects have been demonstrated in several studies.

FLUNIXIN MEGLUMINE

Clinical observations suggest that flunixin meglumine provides excellent visceral analgesia but has less potent effects for many musculoskeletal injuries.

Studies showing the analgesic effects of flunixin meglumine 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.

Several reports have suggested that the intramuscular (IM) administration of flunixin meglumine may result in significant myonecrosis and tissue residues.

Following administration of the drug at the approved dose (2.2 mg/kg) and by the approved route (intravenous) in cattle, the meat withdrawal time is 4 days and the milk withdrawal time 36 hours.

Despite being an approved drug, residue violations in beef and dairy cattle as well as veal calves are common.

Multiple studies have demonstrated a longer plasma elimination half-life following intramuscular or subcutaneous administration of flunixin meglumine that could prolong the elimination of drug from tissue, possibly resulting in residue violations.

When determining an extra-label withdrawal interval for a drug, tissue concentrations are more important than plasma concentrations. Up to a 10-fold increase is shown in the elimination half-life in tissue compared with plasma.

Food Animal Residue Avoidance Databank (FARAD) has previously recommended a conservative 30-day slaughter withdrawal interval for flunixin meglumine products given intramuscularly. If multiple doses are administered intramuscularly, the withdrawal interval may need to be extended to as long as 60 days.

Oral administration of flunixin meglumine has also been investigated in cattle. After receiving a single oral dose of 2.2 mg of granular flunixin meglumine per kilogram, the effects on prostaglandin synthesis were significantly prolonged after oral versus intravenous dosing. FARAD recommends a slaughter withdrawal interval of 8 days and a milk withdrawal interval of 48 hours following a single oral dose of flunixin meglumine.

Some veterinarians are of the opinion that flunixin meglumine does not distribute into the milk, therefore obviating the necessity to discard the milk. This opinion is based on older literature wherein concentrations of the drug were not detected in milk following intravenous or intramuscular administration.

However, the current tolerance for flunixin meglumine concentrations in milk is set at 2 ppb (2 ng/ml), which is well below the limit of detection of the analytical technique used previously. Following administration by extra-label routes (intramuscular or subcutaneous), milk elimination of flunixin meglumine can be prolonged for up to 72 hours.

CORTICOSTEROIDS

The role of these agents in treating pain is less understood. They result in suppression of inflammation and therefore, in theory, should have some pain relief action.

To date there is no evidence of their direct analgesic effect. Because many painful conditions are mediated by inflammation, glucocorticoids could be useful as an adjunct.

Therefore, administration of corticosteroids should not be assumed to provide pain relief in clinical settings. The presumed benefit must be weighed against the potential adverse effects.

KETOPROFEN

Ketoprofen has a short plasma elimination half-life of 0.42 hours in adult cattle, making it less attractive for use as a pre-emptive analgesic. 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.

Ketoprofen is approved 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.

Ketoprofen is rapidly eliminated by the kidneys following intravenous or intramuscular administration, and when injected intramuscularly is substantially less irritating to tissues than either flunixin meglumine or phenylbutazone.

After repeated intramuscular administrations of 14C-ketoprofen at a dosage of 3 mg/kg for 3 days, radioactivity could only be measured in the kidneys 24 hours after the third injection. In other tissues, concentrations were not detectable.

CARPROFEN

The relative anti-inflammatory, analgesic, and antipyretic activity of carprofen is reported to be greater than phenylbutazone or aspirin. Carprofen is approved 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. This drug has a small volume of distribution (0.09 l/kg) and a much longer plasma elimination half-life (30–40 hours) in cattle in comparison with flunixin meglumine and is poorly excreted in milk.

MELOXICAM

The 20mg/ml formulation of meloxicam is registered in South Africa with a 5-day milk and 15-day meat withdrawal in cattle. The registered dose for cattle is 0.5mg/kg by subcutaneous or intravenous injection. Approved for adjunctive therapy for acute respiratory disease, diarrhoea, and acute mastitis.

Oral meloxicam administration could be an effective and convenient means of providing long-lasting analgesia to ruminant calves. An oral meloxicam suspension (1.5 mg/ml) and injectable formulation (5 mg/ml) are available for the control of pain and inflammation associated with osteoarthritis in dogs.

Research has shown that meloxicam is very effective in relieving pain associated with castration and disbudding or dehorning. Meloxicam has also been shown to help mitigate the pain associated with calf diarrhoea.

One study compared ruminant and pre-ruminant dairy calves that received oral meloxicam at a dose of 0.5 mg/kg (delivered mixed in water via stomach tube), or a dose 0.5 mg/kg either by gavage or suspended in one feeding of milk replacer.

The Cmax was significantly lower in pre-ruminant calves that received meloxicam suspended in milk (1.27 _ 0.43 mg/ml) when compared with gavaged pre-ruminant calves (2.20 _0.46 mg/ml) or ruminant calves (1.95 _ 0.96 mg/ml).

The apparent volume of distribution per fraction of the dose absorbed was also considerably higher in pre-ruminant calves that received meloxicam suspended in milk (365 _ 57 ml/kg) than in gavaged pre-ruminant calves (177 _ 63 ml/kg) or ruminant calves (232 _ 83 ml/kg), likely indicating significant differences in drug bioavailability when meloxicam is fed directly with milk.

Based on these data, when using oral meloxicam in pre-ruminant calves (i.e., before disbudding), it would be preferable to administer directly into the rumen (i.e., stomach tube) or by waiting at least 1 to 2 hours after milk feeding.

Without tissue elimination data, one alternative for calculation of withdrawal intervals in food animal species is to multiply the terminal plasma half-life by 10.

A conservative meat withdrawal interval of 21 days is recommended.

SALICYLIC ACID DERIVATIVES ASPIRIN

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 anti-inflammatory properties. 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.

Therefore, the legality of using salicylic acid derivatives in cattle is questionable. Aspirin is a weak acid with a pKa of 3.5. In the alkaline environment of the rumen (pH 5.5–7.0), approximately 1000 times as much aspirin is in the ionised form compared with the more diffusible non-ionised form, which results in a slow absorption rate in cattle. It is estimated that the oral bioavailability of aspirin in cattle may only be 20%.

Aspirin (acetylsalicylic acid) remains a commonly used nonsteroidal anti-inflammatory drug (NSAID) in cattle for the control of pyrexia. It is available over the counter in 60-, 240-, or 480-grain tablets (1 grain = 65 mg).
Not registered.

SEDATIVE-ANALGESIC DRUGS

Opioids, alpha-2-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 in an attempt to provide multimodal analgesia.

OPIOID's

There are currently no narcotic analgesics approved for use in cattle. Factors that constrain the use of opioids in ruminants under farming conditions include their schedule classification for controlled substances, and the preference among practitioners for drugs such as NSAID's, alpha-2-agonists, and local anaesthetics. Compared with other species, there is little information about the use of opioids for analgesia in ruminants, and their clinical use is usually as a component of anaesthetic combinations rather than individual use for analgesic purposes. Opioids are, however, effective for many types of pain, not just perioperative pain. Butorphanol, fentanyl, buprenorphine, and meperidine in sheep and morphine in cattle have proven to be effective analgesics for thermal noxious stimulation when administered intravenously.

Opioids have strong analgesic effects in most animal species. Unfortunately, in ruminants, their potency as analgesic is likely less than in other species. Opioids may also result in suppression of the function of fore-stomachs and changes in behaviour (e.g. propulsive walking, hyper-excitability, hypersensitivity, maniacal behaviour) that may be dangerous for other cattle and humans. No opioid is registered for cattle in South Africa.

BUTORPHANOL

Butorphanol is a k-opioid–receptor agonist and either a partial mu-agonist or antagonist. 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. A conservative slaughter withdrawal interval for butorphanol would be 5 days; however, in the absence of tissue elimination data, longer withdrawal intervals might be warranted.

Epidural Administration of Opioids:

Epidurally administered morphine (0.1 mg/kg) has been used clinically in cattle. Morphine is administered at the sacro-coccygeal or first inter-coccygeal. Analgesia of 6–12 hours' duration has been achieved after abdominal surgery, hind limb amputation, and other painful musculoskeletal conditions. Epidural administration of non-lipid soluble opioids, such as morphine or hydromorphone, provides a longer duration of analgesia than systemic administration. Epidural administration of lipid soluble opioids, such as fentanyl or butorphanol, does not result in a longer duration of analgesia than systemic administration; therefore, they provide no advantage by this route, unless administered as a CRI.

Intra-articular Administration of Morphine:

Intra-articular administration of morphine is effective in other species (rats, dogs, horses, humans) for the relief of pain resulting from inflammatory processes of the joint. The recommended dose (0.05–0.1 mg/kg) is diluted with sterile saline (5–15 ml) according to the joint size. Either a preservative-free or preservative-containing morphine preparation can be used.

ALPHA-2-AGONISTS

Alpha-2-Adrenergic agonists produce profound sedation, chemical restraint, and analgesia in cattle.

Unfortunately, analgesia is accompanied by adverse effects, including sedation, bradycardia, vasoconstriction, hypertension and/or hypotension, decreased cardiac output, and these drugs should not be used in animals that are hypovolaemic or have cardiorespiratory compromise.

Epidural administration of alpha 2-agonists can produce analgesia with minimal sedative and cardiovascular effects compared with IV administration.

XYLAZINE

Xylazine hydrochloride is still the most commonly used sedative in cattle. Withdrawal times ranging from 2 days (France) to 14 days (United Kingdom). Canada has a meat

withdrawal time of 3 days and a milk withdrawal time of 48 hours. FARAD recommends a meat withdrawal interval of 4 days and a milk withdrawal interval of 24 hours following xylazine administration in cattle. However, when xylazine sedation is reversed using tolazoline, both the meat and milk withdrawal intervals need to be increased.

DETOMIDINE

Detomidine hydrochloride is approved for use in horses. Through its selective agonist action on alpha-2-receptors, it produces both analgesia and sedation in very low doses. Although xylazine is much more commonly used in ruminants, detomidine administration has been described as both an epidural and intramuscular sedative in cattle.

Epidural Administration of alpha-2-agonists:

Epidural administration of alpha-2-agonists at the sacro-coccygeal or first inter-coccygeal space in cattle and sheep or at the lumbosacral space in sheep and goats, results in analgesia.

Ultimately, absorption into the circulation results in clinically important depression of the cardiorespiratory and central nervous systems, similar to systemic administration of these drugs. After epidural administration of alpha-2-agonists, analgesia is more profound in the hind limbs, perineum, and abdomen. Systemic absorption may also result in generalised analgesia and sedation

YOHIMBINE

Yohimbine is occasionally used to reverse xylazine sedation in cattle. Minimal data are available on yohimbine in cattle.

FARAD has recommended a meat withdrawal interval of 7 days. Despite the lack of any milk elimination data in dairy cattle, the recommended milk withdrawal interval is 72 hours.

TOLAZOLINE

Tolazoline is an alpha-adrenergic receptor antagonist that is commonly used to reverse the pharmacologic effects of xylazine (or detomidine) and to decrease the recovery time associated with xylazine-induced sedation.

KETAMINE

Ketamine has analgesic properties at sub-anaesthetic doses through antagonism of the NMDA receptor, decreasing postsynaptic excitability and long-term potentiation. In calves undergoing castration, those receiving IV xylazine (0.05 mg/kg) and ketamine (0.1 mg/kg) had lower cortisol concentrations and fewer behavioural changes than placebo-treated calves.

Low doses of xylazine and ketamine prior to castration may offer an efficacious and cost-effective way to improve analgesia for castration and can be combined with local anaesthetic techniques.

CONCLUSION:

Based on the available literature, it is apparent that the single most important tool available in modern veterinary medicine is the provision of pre-emptive and multimodal analgesia.

Veterinarians must capture “opportunities” to prevent the onset of pain, prevent noxious stimuli or their perception, a limit the pain-stress-distress cascade that results in altered behaviour and deviation from physiological norms.

Rational treatment of pain requires an appreciation of its consequences, a fundamental understanding of the mechanisms which are responsible for its production and a practical appreciation of the analgesic drugs that are available. The goal of treatment of pain should be to restore normal (physiologic) pain responses and to eliminate pathologic pain processes. In this context pain therapy should be directed at the multiple mechanisms (multimodal therapy) responsible for its production and analgesic therapies should be instituted before (pre-emptive therapy) pain is initiated (e.g., surgery) whenever possible.

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QUESTION 1

"Allodynia" is:

a. Pain caused by stimuli that are usually not painful
b. Not associated with nerve damage
c. Complete lack of pain sensation
d. Relaying a noxious stimulus to the spinal cord
e. None of the above

QUESTION 2

The advantages of using multi-modal analgesia are:

a. Act on different receptors actioning different mechanisms of action
b. Allow the use of lower doses of individual groups of drugs
c. Decrease the side effects if higher dose of a single drug is used
d. None of the above
e. All of the above

QUESTION 3

Ketamine is an effective analgesic. Which of the following statements is not true?

a. Must be given constantly preferably via constant rate infusion.
b. Does have long-term pain relief effects
c. When used alone, it does not have any analgesic effect.
d. It blocks NMDA receptors in the spinal cord preventing wind-up.
e. Form part of multimodal analgesia

QUESTION 4

Which of the following agents is LEAST effective in inducing pre-emptive analgesia?

a. mu opioid agonists
b. NSAID's
c. Benzodiazepines
d. alpha adrenergic agonist's
e. local anaesthetics

QUESTION 5

Which of the following compounds is an NMDA receptor antagonist?

a. fentanyl
b. xylazine
c. methadone
d. zolazepam
e. ketamine

QUESTION 6

Non-steroidal anti-inflammatory drugs (NSAID's) are

a. antipyretic
b. analgesic
c. anti-inflammatory
d. synergistic with opioids
e. all of the above

QUESTION 7

Which of the following drugs are not used to reverse the clinical effects of alpha 2 agonists?

a. Atipamezole
b. Tolazoline
c. Yohimbine
d. Flumazenil
e. Idazoxan

QUESTION 8

Which of the following statements best describes physiologic pain?

a. it protects the animal from a cause of potential tissue damage
b. it is caused by dysfunction of internal organs
c. it occurs with systemic diseases
d. it is an autonomic reaction to severe pain
e. all of the above

QUESTION 9

Regarding flunixin meglumine, which statement is not true?

a. Provides excellent visceral analgesia but have less potent effects for many musculoskeletal injuries.
b. Intramuscular administration of flunixin meglumine may result in significant myonecrosis and tissue residues
c. Intramuscular administration of flunixin meglumine prolong the elimination half-life
d. Flunixin meglumine does not redistribute to the milk requiring a milk withdrawal period to be imposed.
e. Oral administration of flunixin meglumine is off-lable.

QUESTION 10

Regarding the use of meloxicam, which statement is true?

a. Registered for cattle subcutaneous or intravenous injection.
b. Approved for adjunctive therapy for acute respiratory disease, diarrhoea, and acute mastitis.
c. Effective in relieving pain associated with castration and disbudding
d. Direct administration in the rumen prior to milk feeding is preferential in pre-ruminant calves.
e. All of the above

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