Clinical Pharmacology of Analgesic Drugs in Cattle

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KEYWORDS

• Local anesthetics • Nonsteroidal anti-inflammatory drugs • Opioids • α2-Agonists • *N*-methyl-D-aspartate receptor antagonists • Gabapentin

KEY POINTS

- The Animal Medicinal Drug Use Clarification Act regulates the extralabel drug use of analgesics in cattle within the United States.
- Compounds including local anesthetics, nonsteroidal anti-inflammatory drugs, opioids, α2-agonists, *N*-methyl-D-aspartate receptor antagonists, and gabapentin are reviewed, with an emphasis on evidence of analgesia in cattle during pain states.
- Given the variety of pharmacokinetic and pharmacodynamic properties of pain-relieving drugs, evidence needs to drive the development of analgesic protocols for cattle during pain-related events.
- A multimodal approach using both local anesthesia and an anti-inflammatory drug optimizes pain relief in livestock procedures known to cause distress and pain.
- The use of meloxicam, ketoprofen, and flunixin in the development of analgesic protocols is potentially supported by randomized controlled trials.

INTRODUCTION

Pain states in cattle are common. Both iatrogenic pain attributable to livestock management procedures such as dehorning or castration and disease-associated pain including lameness, abdominal disorders, or sepsis are frequently encountered. Regardless of the origin, a noxious insult is typically translated into a chemical and electric signal, which is modulated in the dorsal horn of the spinal cord and perceived in the brain.[1,2] This initial phase is often associated with acute pain; however, a second prolonged and diffuse phase often results in local hypersensitivity.[2] Persistence of this

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delayed response may cause systemic hypersensitivity known as central sensitization ("wind-up"),[2,3] clinically manifesting as hyperalgesia (ie, increased pain from a painful stimulus) and allodynia (ie, pain from a nonpainful stimulus).[4] Analgesics are provided, if possible, to mitigate both the acute and prolonged phases of pain associated with the noxious stimuli.

Pain associated with castration and dehorning results in both the described acute and delayed responses. Following the initial noxious insult either from a surgical incision (eg, scrotal incision, Barnes dehorners) or cautery dehorning, stress as determined by cortisol concentrations peaks approximately 30 minutes after the procedure.[5,6] Subsequently a delayed response occurs, as evidenced by increased sensitivity and behavioral, physiologic, and immunologic changes that may persist for up to 44 hours.[7–9] Recent studies suggest that dehorning results in a more acute stress response in comparison with castration as evidenced by cortisol concentrations obtained under the same experimental conditions.[10,11] Furthermore, dehorning 2 to 3 weeks postcastration resulted in an increased stress response and decreased average daily gain (ADG) in comparison with animals that were dehorned first and castrated later.[12] Conversely, castration in cattle resulted in an amplified immune response when compared with dehorning in the same study, suggesting more of an inflammatory effect.[10] When dehorning and castration were combined, the acute cortisol changes were additive, whereas the immune changes were not.[10,11]

Lameness is a disease that may be recognized during an acute or chronic phase. Progression of acute pain to chronic disease may result in neurologic changes, making individuals refractory to analgesic treatment.[13] As such, naturally occurring lameness may represent issues concerning chronic pain whereby treatment failures are common because of the complexity of neuropathic pain development.[13] Drugs targeting neuropathic pain such as gabapentin may be useful for analgesic treatment in these cases of chronic pain.

Providing analgesia to cattle is not without its challenges. Primarily, from a regulatory perspective no analgesic drugs are specifically approved for the alleviation of pain in livestock.[14] The Animal Medicinal Drug Use Clarification Act (AMDUCA) of 1994 permits extralabel drug use (ELDU) to relieve suffering in cattle.[15] As such, analgesics would be permitted under AMDUCA given that the criteria for ELDU are followed. In addition to these regulations, pain medications can be costly, difficult to administer, and short-acting, requiring frequent administration, and may be controlled substances necessitating a veterinary license.[7] Moreover, cattle do not overtly demonstrate signs of pain, making it difficult for some producers to observe the value in providing pain relief, especially given a lack of support for economic gain.[7]

Despite these challenges, analgesics have demonstrated numerous benefits to cattle during pain states. Following castration, analgesics have reduced the physiologic, behavioral, and neuroendocrine changes that occur following the noxious stimuli (**Figs. 1** and **2**).[16] These changes are also observed in cattle after dehorning or disbudding using analgesics (**Figs. 3** and **4**).[8,17] Lameness models have demonstrated improvements following administration of NSAIDs as detected by pressure mats; however the use of NSAIDs have provided minimal analgesic effects in naturally occurring lameness as determined by locomotion scoring (**Fig. 5**).[18–21] This may be a result of the differences associated with acute and chronic pain states or potentially due to an increase sensitivity of pressure mats to detect differences between lame cattle. Perhaps a more compelling motivation for the use of analgesia in cattle may concern the relationship between the autonomic nervous system and the immune response. Activation of the sympathetic nervous system has demonstrated immunosuppressive effects that may incite and progress systemic infections.[22] Although this