

## **Ruminant Field Anesthesia and Analgesia**

*Penn Conference 2017*

*Sarah Depenbrock, DVM, MS, DACVIM (LAIM)*

*Davis, CA*

Provision of anesthesia and analgesia to production animals has long been a part of the veterinary profession. Increasing societal concern for farm animal welfare and research updates have led to developments in the way many veterinarians perform or prescribe anesthesia and analgesia for even routine processing in livestock. This presentation very briefly summarizes some of the common methods for provision of analgesia (with and without anesthesia) for cattle in a field setting.

In general, pain involves transmission of signals from a noxious stimuli in the periphery, via the spinal cord, to the brain and a subsequent negative experience. Pain can be difficult to quantify and many different research methods have been employed attempting to objectively measure pain, or compare pain between study groups. These methods include: measurement of serum biomarkers such as cortisol or substance P, specific measurement devices such as algometry and thermography, and a variety of movement or behavior scores. Most of these methods are not specifically practical for daily use by field veterinarians, so as a profession we rely on our physical exam skills and observation of specific behaviors that suggest our patients may be experiencing pain, or on the assumption that certain diseases or procedures are likely painful.

One of our most important roles is not only to identify pain in our patients, but to educate our clients and farm staff on how to identify and limit pain in their animals. One useful way to think about how to go about minimizing pain in livestock is to follow the French approach that uses the 3S's; Suppress, Substitute and Soothe (*Guatteo et al 2012*). Suppressing pain refers to suppressing procedures or events that might unnecessarily lead to pain. Substituting refers to reduce the chances for pain by selecting a less painful procedure over a more painful procedure to accomplish the same goal. Soothing pain refers to the provision of anesthesia and analgesia when pain must be induced or is already present in a diseased animal. As the attending veterinarians for livestock facilities, we have an excellent opportunity to become involved at all three levels of pain preventing and treatment. We provide the unique skillset necessary not only to evaluate management practices and look for opportunities to prevent painful conditions, but also to advise and create animal health Standard Operating Procedures (SOPs) to minimize or provide basic treatment for pain, and finally to provide on farm anesthesia and analgesia to the patients we are called out to treat. Having a specific "pain protocol" is an excellent opportunity to build on your existing farm SOPs and farm staff training events. Such a protocol may also help your producers assure those who may inquire that they are routinely addressing pain on their farm.

Recognizing pain in stoic ruminants can be challenging so it is important to educate farm staff on signs that may indicate an animal is painful or otherwise sick and should be further evaluated. Such signs include: abnormal gait or posture such as a limp or hunch, grunting, grinding teeth (bruxism) or vocalizing, nose pressing, other behavioral changes such as isolation

or differences in resting or eating behavior relative to the others, or production changes such as a sudden drop in milk production. In addition to recognizing the signs of pain in sick animals, certain procedures or disease processes should be assumed to be painful and SOPs can put in place empiric treatment for pain in these cases (ex: severe pneumonia, toxic mastitis or any on-farm surgical procedure such as castration can have SOPs for routine treatment with pain medication.)

Even when we have done all we can to prevent painful events or diseases, there will still be animals that require pharmacologic anesthesia and analgesia. This presentation discusses some drugs that are likely to be on your truck, and simple techniques for field anesthesia and analgesia. These drugs are all aimed to interfere somewhere along the pathway between the noxious stimulus, peripheral nerve transduction, transmission and spinal modulation and perception of pain in the brain.

Remember that despite their common use, very few of the drugs discussed below are labeled and FDA approved for use in cattle. As such, follow the guidelines set forth by the Animal Medical Drug Use Clarification Act (AMDUCA) to ensure appropriate Extra Label Drug Use (ELDU) and residue avoidance. It is of paramount importance that scientifically based Withdrawal Intervals (WDI) are communicated to the client and properly documented when ELDU has taken place in food animals. The AVMA algorithm for ELDU can be found at: <https://www.avma.org/KB/Resources/Reference/Pages/AMDUCA2.aspx>. More resources and advice on WDI recommendations can be found at: <http://www.farad.org>. Even with the guidance of these resources, it is ultimately the responsibility of the prescribing veterinarian to communicate appropriate ELDU and residue avoidance recommendations.

Provision of local anesthesia is an excellent way to provide a short term blockade to pain transduction. Lidocaine, 2%, is readily accessible, inexpensive, and relatively safe in large ruminants. Use caution in small ruminants; it is recommended not to exceed a total dose 5mg/kg in small ruminants, or 10mg/kg in cattle. See **Box 1** below for calculation of a toxic dose of lidocaine. This drug works by blocking sodium channels, and thus limiting nerve transduction. The duration of effect is variable and has been reported to average 90 minutes and the time to onset of full effect is approximately 2-5 minutes (*Coetzee 2013*). If performing routine procedures on groups of animals such as disbudding/ dehorning, several animals can be given the local anesthetic in a row (such as along hutches or head gates) and then the procedure can be carried out in the same order, allowing the drug to take effect. A tip to decrease pain associated with injection, which may help ease handling and restraint during injection, is to add sodium bicarbonate at a 1:10 ratio. This means for every 10 mL of 2% lidocaine used, add 1mL of 8.4% sodium bicarbonate immediately before use (*Coetzee 2013*). The most common sites that the author has used local anesthesia for field procedures include: cornual nerve and ring blocks for dehorning, four point and ring blocks for exenteration of the eye, Bier blocks for procedures of the distal extremity, distal and proximal paralumbar blocks for flank laparotomy (preferred over line block to avoid lidocaine deposition directly at surgical margins), and epidural anesthesia for obstetrical manipulations or surgical procedures on the hind end. Excellent references for a refresher on the anatomy and technique for local anesthesia in cattle include the 2016 Vet Clinics of North America, “Local, Regional and Spinal Anesthesia in Ruminants” by Edmondson and the text, “Handbook of Veterinary Anesthesia” by Muir and Hubbell.

**Box 1:** Calculation of a maximum dose of 2% lidocaine:

Case example: What is the maximum volume of 2% lidocaine that could be given to a 75kg goat for a local block?

Maximum dose:  $5 \text{ mg/kg} \times 75\text{kg} = 375\text{mg}$

Lidocaine concentration: % = g/100mL. 2% solution = 2g/ 100mL.

2g = 2000mg.  $2000\text{mg}/100\text{mL} = 20\text{mg/mL}$ .

Total volume:  $375 \text{ mg} / 20\text{mg/mL} = \mathbf{18.75\text{mL}}$

Non-steroidal Anti-inflammatory Drugs (NSAIDs) are also very commonly available, and flunixin meglumine is even, as you know, FDA approved for use in cattle! These drugs exert their effects via inhibition of cyclooxygenase (COX) enzymes peripherally *and* centrally to decrease prostaglandin production. Prostaglandin lowers the activation threshold for sensory neurons, and spinal prostaglandin increase the excitability of dorsal root ganglion. Inhibition of COX-1 inhibits constitutively produced prostaglandins and inhibition of COX-2 inhibits inducible production of prostaglandins. Despite the move for COX-2 selective NSAIDs, both COX-1 and COX-2 are likely important in pain pathways. Side effects of these drugs are generally due to inhibition of constitutively produced prostaglandin, and result in problems associated with GI ulceration and renal disease. Practitioners should be particularly concerned about side effects in animals that are hypo-perfused, anorectic, have pre-existing renal disease, or are over dosed with too much or too many repeated NSAID doses. Although flunixin is only approved for its anti-inflammatory effects, it is often used with apparent clinical success for the treatment of pain in cattle. When given according to the label dose, route and frequency the label withdrawal time can be used. However, investigations into flunixin residues associated with both diseased and healthy cattle were recently summarized in a 2017 FARAD Digest. The authors of that summary article recommend longer milk and meat withdrawal intervals of 84 hours and 7 days respectively (*Sidhu et al 2017*). It should also be noted that this drug is labeled for IV use only, and if the drug is given extra-vascular, meat withdrawal intervals have been recommended by the same group to be as long as 60 days. Although IV administration is an excellent way to achieve therapeutic plasma levels rapidly, this route and medication is not always feasible for farm staff, repeated daily treatments, or provision of long acting NSAID effects. Another NSAID that is gaining popularity in food animal practice is meloxicam. Generic meloxicam tablets provide an inexpensive, oral route of administration, and longer acting treatment for pain in cattle. Since this NSAID is not labeled for cattle in the US and flunixin is, it can be difficult to justify the use of meloxicam in food animals. However, such off-label use is not uncommon in cattle; the guidelines of AMDUCA should be followed and the clinician should be diligent to provide a withdrawal interval to avoid any tissue residue. There are multiple publications by Dr. Hans Coetzee relevant to the topic of meloxicam pharmacokinetics in cattle. Meloxicam is most commonly used in the field to treat pain in calves, particularly associated with procedures such as disbudding/ dehorning and castration where research has suggested efficacy (*Heinrich et al 2007 and 2009, Olson et al 2016*). One study found that meloxicam was useful in treating pain associated with diarrhea in calves (*Todd et al 2010*), and many veterinarians are treating a variety of painful conditions in calves with this drug. A range of doses is available in the literature; one

commonly used dose is 1mg/kg orally once prior to inducing pain during a procedure. There does not appear to be a consensus for repeated or long-term dosing regimens and there is little data on which to base withdrawal interval recommendations after long term/ repeated oral dosing in ruminants. A withdrawal interval for meloxicam has been recommended at 21 days for meat after a single oral dose of 1mg/kg to calves by FARAD based on work by Hans Coetzee, however it should be noted that a 35 day meat withdrawal is on the label for a Canadian product licensed and marketed for oral use at 1mg/kg in cattle.

Injectable opioids provide another way to treat pain and also aid sedation in drug combinations. Opioids work by inhibiting neurotransmission via opioid receptors present in primary afferent neurons, spinal cord, and brain. They are all G-protein coupled receptors that modulate down stream release of various signaling molecules to ultimately decrease neurotransmitter release. Opioid use in field medicine is most useful at the time of a painful procedure, likely in conjunction with sedation or for treatment of an acutely painful condition. Many large animal practitioners carry butorphanol, a  $\kappa$  agonist, partial  $\mu$  agonist or antagonist. The efficacy of butorphanol to treat pain in cattle is believed to be and this drug has a relatively short (hours) duration of action. Morphine, a pure  $\mu$  agonist, is typically less expensive than butorphanol and is another option for providing rapid pain control; this drug may be more effective for control of pain in ruminants. Side effects of  $\mu$  agonism include respiratory depression, decreased GI motility, sedation, euphoria, nausea and possibly increased appetite. Repeated doses of opioids, especially morphine, should be used with extreme caution to avoid side effects, especially ileus in ruminants. Butorphanol, and less commonly morphine, have been reported to cause excitement in ruminants. Since opioids are DEA controlled substances, they are not suitable for leaving on farm or having as part of animal health SOPs carried out by farm staff, but can be useful directly by the ambulatory clinician. Dosages vary depending on intended use and combination with other drugs.

Alpha-2 agonists are another category of sedative and anesthetic drugs commonly carried by the ambulatory practitioner. Xylazine is a very potent sedative in ruminants that also provides some analgesia by inhibiting the afferent pain pathway of the positive feedback mechanism for the release of norepinephrine. Sedation is thought to outlast analgesic effects. Systemic administration, IV or IM can be useful to sedate ruminants as well as provide some short duration of analgesia. Epidural administration at a dosage of 0.05mg/kg diluted with 5-12 mL of sterile saline can provide longer lasting analgesia to the hind end (perineum and tail with a smaller volume, and rear limbs with high volume) with mild sedation. The dosage range for systemic administration is highly variable depending on the level of sedation required, how excitable or fractious the animal is, and the ruminant species. Doses as low as 0.02 mg/mg IV may provide sedation during which the animal typically remains standing. Higher doses of 0.1 mg/kg IV typically induce recumbency, however some cattle will remain standing at this dose. Repeated dosing may be necessary to induce recumbency in systemically healthy adult cattle. Xylazine doses are typically doubled for IM administration. A casting rope can facilitate putting xylazine sedated cattle in recumbency. Detomidine is an alternative to xylazine, and is useful when standing sedation is desired in cattle; cattle sedated with 5 $\mu$ g/kg (0.005mg/kg) typically show signs of sedation and typically do not become recumbent at this dose. Side effects of alpha-2 agonist administration include bradycardia, decreased GI motility which may result in bloat or ileus, increased uterine tone which may lead to premature labor or fetal hypoxia in late

gestation, and activation of pulmonary intravascular macrophages which can result in hypoxia particularly in small ruminants. It should also be noted that these drugs also act as diuretics, and thus should be used with caution in animals with urethral obstruction. There is no labeled withdrawal information for these drugs in cattle, sheep or goats so a WDI must be provided. Updated recommendations listed on FARAD are 5 days meat and 72 hours milk after IV administration up to 0.1mg/kg, and 10 days meat and 120 hours milk after IM administration from 0.3 to 2mg/kg.

Another drug with analgesic effects commonly carried by the ambulatory practitioner is Ketamine, an NMDA receptor antagonist. This drug is most useful in combination with other drugs for field sedation and analgesia. The NMDA inhibition decreases glutamate release, thus depressing the thalamocortical and limbic systems and is thus responsible for dissociative anesthetic effects. Additionally, ketamine is reported to have opioid receptor binding effects that provide some analgesia. The use of ketamine alone is not recommended due to muscle rigidity. Ketamine is commonly combined with alpha-2 agonists and opioids to provide standing or recumbent sedation referred to as, “ketamine stun”. The dosages of each of these three components varies depending on the desired level of sedation and positioning of standing vs recumbent. Ketamine is also commonly used in combination with guaifenesin (with or without xylazine) for drip administered field anesthesia (referred to as double drip, or triple drip if xylazine is included). Alternatively, ketamine can be given with just xylazine for recumbent sedation or anesthesia. There are a variety of dosages for all of these combinations and the author recommends consulting the Vet Clinics of North America article by Seddighi et al listed in the references for more detailed dosage information.

Benzodiazepines such as diazepam and midazolam, and phenothiazines such as acepromazine can also be quite useful for field sedation or anesthetic combinations. These drugs do not provide analgesia, and thus should be used in combination with other drugs when analgesia is desired.

## References:

Guatteo R1, Levionnois O, Fournier D, Guémené D, Latouche K, Leterrier C, Mormède P, Prunier A, Servièrè J, Terlouw C, Le Neindre P. Minimizing pain in farm animals: the 3S approach - 'Suppress, Substitute, Soothe'. *Animal*. 2012 Aug;6(8):1261-74.

Coetzee, J. A review of analgesic compounds used in food animals in the united states. *Vet Clin North Am Food Anim Pract*. 2012 Dec; 29 (1):11-28.

Sidhu et al. FARAD Digest: Avoiding violative flunixin meglumine residues in cattle and swine. *JAVMA* 2017 Jan; 250(2).

Heinrich A1, Duffield TF, Lissemore KD, Millman ST. The effect of meloxicam on behavior and pain sensitivity of dairy calves following cauterly dehorning with a local anesthetic. *J Dairy Sci*. 2010 Jun;93(6):2450-7.

Heinrich A1, Duffield TF, Lissemore KD, Squires EJ, Millman ST. The impact of meloxicam on postsurgical stress associated with cauterly dehorning. *J Dairy Sci*. 2009 Feb;92(2):540-7.

Olson ME, Ralston B, Burwash L, Matheson-Bird H, Allan ND. Efficacy of oral meloxicam suspension for prevention of pain and inflammation following band and surgical castration in calves *BMC Vet Res*. 2016 Jun 13;12(1):102.

Todd CG, Millman ST, McKnight DR, Duffield TF, Leslie KE. Nonsteroidal anti-inflammatory drug therapy for neonatal calf diarrhea complex: Effects on calf performance. *J Anim Sci*. 2010 Jun;88(6):2019-28.

Seddighi R, Doherty TJ. Field Sedation and Anesthesia of Ruminants. *Vet Clin North Am Food Anim Pract*. 2016 Nov;32(3):553-570.