

Options for pain manage

Because there are no FDA-approved pain medications for cattle, all pain medication administered to cattle is extra-label, but there are options.

By Geni Wren

The cattle industry is increasingly being asked to address issues of animal welfare, of which pain management in livestock is an important component. Though there are no FDA-approved drugs for pain management in cattle, there are veterinary drugs available that can be administered (in an extra-label manner) either pre-emptively before painful stimuli, or during a pain process in cattle.

There are two categories of pain in cattle, surgical and disease pain. "With minor and major surgical procedures, this is where pre-emptive analgesia is extremely important and effective," says Paul Walz, DVM, PhD, Auburn University. "Where it is difficult to control pain with the tools we have in a practical manner is the management-induced or naturally occurring pain such as obstetrics, lameness and abdominal pain."

Pre-treatment in anticipation of a painful event provides more analgesia than treatment with the same drug and dosage after robust pain sensations develop, Walz says. "Unfortunately,



Regional intravenous analgesia using the dorsal pedal vein.

pain associated with management and infectious diseases are much more difficult to treat and sometimes it is impossible to relieve pain associated with chronic disease processes such as lameness, peritonitis, pleuritis, chronic pneumonia, and chronic arthritis."

Pharmacologic agents used in cattle

Five general classes of drugs exist to treat pain, and mainly four of them are used in ruminants. These include the opioids, ketamine, the non-steroidal

anti-inflammatory drugs (NSAIDs), local anesthetics, and the alpha-2 adrenergics. The following are pharmacologic agents that can be used in cattle for the relief of pain. See the chart on page 17 for dosage and withdrawal information.

Opioids

Opioids may exist as pure agonists such as morphine, hydromorphone, and oxymorphone. Buprenorphine is considered a partial agonist. Butor-

ment



PAUL WALZ, DVM, PHD

phanol is used quite frequently and is considered an opioid agonist and antagonist because it has multiple opioid effects.

Morphine

Morphine is a drug Walz has used in a veterinary hospital situation. Morphine is a heavily restricted drug, but it's fairly inexpensive. Walz notes that in ruminants, morphine is not that great of a drug because it has poor analgesic properties and this is believed

Pharmacologic agents used in cattle for pain relief

All doses given below are in milligram per kilogram of body weight. To convert to milligram per pound, simply convert the dosage listed below by dividing by 2.2. For example, if you wished to use xylazine at a dose of 0.1 mg/kg IV, the equivalent dose would be 0.05 mg/lb. (Information provided by Paul Walz, DVM, PhD, Auburn University)

Drug	Dosage and route	Duration of effect	Appropriate withdrawals	
			Milk (hours)	Meat (days)
Morphine	0.05–0.1 mg/kg IV, SQ	4 hours	0	0
	0.1 mg/kg epidural Q12h	12 hours		
Butorphanol	0.02–0.25 mg/kg IV, SQ			
	20–30 mg/adult animal IV	4 hours	72	4
Xylazine	0.1–0.3 mg/kg IM	Analgesia is very short-lived ½ hour		
	0.05–0.15 mg/kg IV		72	7
	0.05–0.07 mg/kg epidural			
Detomidine	0.01 mg/kg IV	Short ½ hour	72	7
Flunixin meglumine	1.1 – 2.2 mg/kg IV	6–12 hours	72	4
Ketoprofen	3.3 mg/kg IV	24 hours	24	7
Aspirin	100 mg/kg PO	12 hours	24	1
			(FARAD)	(FARAD)

to be due to very few receptors in the central nervous system or ineffective disposition of morphine in the central nervous system. “An additional drawback of opioids is that they have a ceiling effect,” Walz explains. “There are a finite number of opioid receptors in the central nervous system, and once all receptors are occupied, very little benefit is achieved by giving more drug.” Use opioids to a dosage and do not use them in excess because negative effects may occur. Administer morphine parenterally; do not give it orally in ruminants. Treatment needs to be given every 4–6 hours to maintain therapeutic blood concentrations.

Side effects with morphine administration can include bradycardia, respiratory depression, hypotension, con-

stipation, and retention of urine. High doses may cause excitement. An additional side effect is hyperthermia.

Morphine exerts the most benefit in the spinal cord, thus epidural administration puts morphine right in the area of the receptors. The duration of activity is 12 hours. Morphine is a very hydrophilic drug, so it takes a long time to diffuse into the spinal cord but once in, it stays there for longer durations. “I’ve used morphine epidurally in cows, and pain mitigation does not seem to occur in a small percentage of cases,” Walz says. Retention of urine and constipation are observed side effects even when administered epidurally.

Morphine has been shown to be beneficial in the relief of pain for the



Paul Walz, DVM, PhD, says it's difficult to control management-induced or naturally occurring pain in a practical manner with the tools we have.

perineum (obstetrical cases), the posterior abdomen, intestinal disease, and for rear-limb disease. Morphine may be given in the sacrococcygeal epidural space. The morphine can be followed by saline in order to move the morphine forward to the lumbar area. Alternatively, the morphine can be administered in the lumbosacral epidural space as well. Of paramount importance is to deliver the morphine epidurally rather than intrathecally. Dosages for epidural morphine are higher than for intrathecal administration, and signs of toxicity may be observed if the dura mater is punctured.

Butorphanol

Probably the most common opioid drug used is butorphanol. Walz has used it frequently for pain management; however, he says recently it has become quite expensive. Butorphanol has mixed properties so it's an agonist and antagonist; therefore, it will not be as potent of an analgesic as other opioids.

Butorphanol has a relatively short duration of activity. "It's a very effective drug at providing pain relief especially for those management cases where you have pain already existing and you want to provide some relief after the painful stimuli has already been there," Walz says. Butorphanol may increase appetite. There are re-

ports of it causing a kind of compulsive walking or trembling. Like morphine usage, this drug also is restricted.

Ketamine

Ketamine is an effective analgesic and blocks N-methyl-D-aspartate (NMDA), whose receptors in the dorsal horn of the spinal cord are important in the transmission of painful impulses from the peripheral to the central nervous system. Ketamine is not a practical pain management drug because it needs to be given constantly and doesn't have long-term pain relief effects. It needs to be given by a constant rate infusion, making it impractical for cattle.

"It would be nice if it had some residual and long-lasting activity because the actual compound is very important for central sensitization of pain and secondary hyperalgesia," Walz explains. "When animals hurt all over, it is because of NMDA receptor activity. Activation of NMDA receptors by neuromodulators induces 'wind-up' of the CNS and subsequent prolonged and exaggerated central responses to pain. Ketamine may prevent this 'windup' phenomena that is secondary hyperalgesia."

One advantage is that microdoses are used compared to the high doses used for anesthesia, but it must be given IV at a constant rate of infusion. This drug is also heavily restricted.

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) have the ability to work in a painful stimuli pre-emptively, and are antipyretic, analgesic, and anti-inflammatory. Most NSAIDs inhibit the enzyme cyclooxygenase (COX), and ketoprofen is an NSAID that has purported lipoxygenase activity in addition to cyclooxygenase inhibition. The cell membrane phospholipids are broken down during inflammation to arachidonic acid. Minimizing the prostaglandins and their effects is very important for pain management. Prostaglandin

E2 is important with respect to pain and tissue trauma.

Thromboxane is important because of the effects on platelets. With damaged tissue comes platelet aggregation, and this in turn results in thrombosis. Ultimately this causes tissue devitalization, Walz says. Minimizing these effects can be quite beneficial. But, you have to get to these fairly early because once all this material is present in the damaged tissue, it's difficult to modulate pain using non-steroidals.

Flunixin meglumine is the NSAID that is most frequently used since it is approved as an anti-inflammatory and antipyretic in the US. It may result in central analgesia or central inhibition of pain responses. Walz says research indicates there may be some effects similar to opioids, affecting some of the opioid receptors in the central nervous system. "Flunixin meglumine needs to be given IV," Walz explains.

Walz has not used aspirin as much for the control of pain. It purportedly has some analgesic properties like the other non-steroidals. "I don't have a lot of experience or real opinion whether it is really effective for managing pain in cattle," Walz says. Although aspirin is not approved for use in food animals by the FDA, aspirin may be used orally at a dose of 100 mg/kg of body weight.

Phenylbutazone has been used for musculoskeletal conditions, but probably isn't used as much because of concerns with withdrawals. Walz uses it occasionally, but provides lengthy withdrawals, usually six-months depending upon the amount and duration given. "For the initial single treatment, we usually have a withdrawal of 45 days followed by an additional 5 days for every subsequent dose given. Since phenylbutazone treatment is often repeated, withdrawal periods can become quite lengthy." The main problem with the withdrawal is that it's extensively protein-bound and has a very long half-life. Remember that phenylbutazone is illegal to use in dairy cattle 20-months of age and older.

The problem with unapproved pain drugs

Practicing veterinarians should keep in mind that none of the analgesic drugs they carry in their vet trucks have been formally approved by the FDA for alleviation of pain in cattle. The pioneer formulation of flunixin meglumine, for example is only approved “for the control of pyrexia associated with bovine respiratory disease, endotoxemia and acute bovine mastitis” and “the control of inflammation in endotoxemia”.

“Relying on the legal framework provided by AMDUCA that exempts certain compounds from extralabel use restrictions provided these are used to alleviate pain and suffering in animals is not an acceptable long-term solution to improving the welfare of livestock in our care,” says Hans Coetzee, BVSc, PhD, DACVCP, Kansas State University. “This is especially since we do not have sufficient information pertaining to the pharmacokinetics and pharmacodynamics of drug classes such as local anesthetics, narcotic analgesics, alpha-2 agonists and NMDA receptor antagonists in food animals to make science-based recommendations regarding their potential perioperative use during castration and dehorning.

“Furthermore, there is the issue of establishing adequate withdrawal times for these drugs off label which is complicated further since at this time FAR-AD is shut down due to a shortage of funding.”

A classic example of how this impacts practicing veterinarians is aspirin. Salicylic acid derivatives, which include sodium salicylate and acetylsalicylic acid (aspirin), were the first non-steroidal anti-inflammatory drugs (NSAID) to be used in modern medicine and are still widely used as analgesic, antipyretic and anti-inflammatory agents. Although veterinary forms of aspirin are marketed with label indications for pain relief, fever and inflammation, the drug has never been formally approved by the FDA-CVM for these purposes.

“A dose of 50–100 mg aspirin/kg bodyweight is commonly used to provide analgesia in cattle although the efficacy of this dose has not been conclusively demonstrated in peer-reviewed studies,” Coetzee explains. “Research at Kansas State found that when aspirin boluses are administered orally to cows at the recommended dose of 50mg/kg, we could not detect plasma salicylate concentrations above 10 µg/mL, suggesting that the bioavailability of oral aspirin in cattle is less than 30%. Furthermore, we found no attenuation of plasma cortisol response following administration of aspirin at this dose.”

As a clinical pharmacologist, one of Coetzee’s main interests is the relationship between plasma drug concentration and the amelioration of signs of pain. He recently published a report demonstrating attenuation of plasma cortisol response, even below levels of control animals (though not statistically significant) by administering intravenous sodium salicylate (same generic family of drugs as aspirin) within 60 seconds of castration. Plasma salicylate concentrations were only detectable for 4 hours after administration.

“Once salicylate concentrations dropped below our limit of detection, plasma cortisol concentrations in all castrated animals were significantly higher than the uncastrated controls,” Coetzee says. “This would suggest that drug plasma concentration was associated with mitigation of a stress response. I do not believe we know enough about the analgesic drugs we currently have available for use in food animals to make science-based recommendations about the appropriate dose to optimize efficacy and duration of activity. This is an area where a sustained and focused research effort is required.”

α₂ adrenergic drugs (agonists)

Xylazine is the most common of the α₂ adrenergic agonists and provides muscle relaxation and analgesia. It is a very potent sedative and causes profound central depression in cattle. However, the analgesia is much shorter-lived than the actual sedation, so animals can be heavily sedated but don’t have analgesia associated with xylazine.

Xylazine receptors are present in the dorsal horn of the spinal cord and this region is important in sensitization of pain. Xylazine is synergistic with opioids because it acts at a different area than the opioids do, so they can be used in combination.

Epidural xylazine is an effective mechanism for providing analgesia locally and in less concentration. There seems to be variability with the effect of xylazine epidurals. “Some animals will have good analgesia within 5–10 minutes, some will take longer,” Walz says. “The other thing that happens is the sedation effects are quite variable, as some animals may become sedate and recumbent while others do not, so you have to be extremely aware of that when you are using xylazine epidurals in cattle while restrained in a chute.” Other negative effects that have been described include paralysis following epidural usage due to demyelination of the spinal cord.

Local anesthetics

Walz uses local anesthetics frequently because they are easily administered, not restricted for use, inexpensive, and have limited toxicity in cattle. Walz says signs of toxicity are not usually observed in cattle unless the dose exceeds 10 mg/kg of body weight, so for a 1,000-lb. animal, up to 250 ml of lidocaine may be used without demonstrating toxicity.

Lidocaine is relatively short-lived with one- to two-hour duration of activity.

Epinephrine may be incorporated in the lidocaine block to prolong the duration of analgesia. Lidocaine



If you are doing a standing surgery, xylazine epidurally or parenterally can induce sedation, so be aware for your safety and the safety of others.

blocks action potentials along the nerve roots, and it has no preference for sensory or motor neurons. The motor neurons that control fine movement of the muscles are blocked preferentially to the sensory nerves.

Local anesthetics available for use are lidocaine, mepivacaine and bupivacaine. Most are acidic and even more acidic if epinephrine is added.

Xylocaine is available as a lidocaine/epinephrine combination. It is extremely acidic, and causes pain upon injection. Walz says lidocaine may be buffered 10:1 with 8.4% bicarbonate which will elevate the pH of the lidocaine so there is less "burning" underneath the skin. It doesn't appear to alter the effect on analgesia even if buffered to a pH level of 7.4. "Once lidocaine is buffered, it needs to be used quickly, within several hours,"

Walz cautions. Lidocaine remains stable in an acidic solution. Once lidocaine is injected in the tissues, the alkaline environment of the tissues makes it effective.

Local anesthetic blocks or intravenous regional blocks are extremely easy to perform on distal extremities, Walz notes and can be performed by using several different veins. "I like to use the dorsal pedal vein which is also referred to as the dorsal metatarsal or dorsal metacarpal veins," Walz says. Place a tourniquet on the limb, and the vein can be found distal to the tourniquet. At the level of the fetlock at a 30-degree angle, a 19-gauge butterfly needle is used to catheterize the vein. "Once you get flashback, inject the lidocaine and 3–4 minutes later there is analgesia to the foot. With this form of analgesia, digits may be amputated."

Walz also uses this for diagnostic purposes in examinations. If you anticipate considerable debridement and hoof wall resection with a severe toe abscess, perform the block right away, he suggests. It probably doesn't provide long-term analgesia, but it provides enough short-term analgesia to perform procedures easily and effectively.

There are also abaxial vessels called palmar or plantar abaxial veins located approximately a finger-width from the edge of the dewclaw. "Usually you have to go deeper in that area but this is another vein that works very well for providing analgesia," Walz says.

Local anesthetics can also be given parenterally. "Lidocaine given intravenously has analgesic properties especially when we're dealing with the central sensitization of pain." Central sensitization is where an animal essentially hurts all over. Providing them intravenous lidocaine or local anesthetics can be pretty beneficial, however, the problem is they are not practical because you have to give them by a constant-rate infusion.

Multimodal therapy

Effective pain relief may be achieved by using combinations of agents. "In our individual patients, we often use butorphanol combined with an NSAID, or opioids combined with local anesthetics," Walz explains. "Using different drugs that act upon different receptors and different mechanisms of action allows one to use smaller doses, safer doses, with less sedation."

There is a term called neurolept analgesia. The classic example is Demerol, which makes people indifferent to pain or problems, combined with an opioid. For cattle use, Walz uses xylazine and/or opioids combined with local anesthetics, which work very well for relief of pain. "Using multiple different modes of analgesia combined together, you can do a lot of different surgical procedures for controlling pain," Walz says. ■

Procedures and pain management

Paul Walz, DVM, PhD, discusses the different types of pain management for these surgical procedures of cattle.

Castration

In some European countries, it is illegal to castrate calves beyond a certain age without local anesthetics. In other areas it's strongly recommended to use the Burdizzo method. An epidural of 0.05 mg/kg xylazine combined with the 0.4 mg/kg lidocaine (1mL per 100 kg of body weight) is a good combination. Epidural morphine does not work well. Intrascrotal or intratesticular administration of lidocaine can also be used.

An Irish study compared four different methods: a Burdizzo method, a Burdizzo method with ketoprofen, a Burdizzo method with a local anesthetic prior to castration, and a Burdizzo method with an epidural. Cortisol responses, haptoglobin and average daily gain for 35 days were measured. The study indicated that many of the groups were not different except for the ketoprofen group. Calves provided with a non-steroidal anti-inflammatory prior to the procedure had less elevations in haptoglobin and cortisol and increased average daily gain over 35 days compared to the other groups. "There were only 10 animals per group," Walz explains. "However, it does provide some information that non-steroidals may be beneficial."

Another study showed greater feed intake, less cortisol and less scrotal swelling during the first 72 hours following castration using an NSAID. Calves that are dehorned or castrated without analgesia may have initial negative effects, but they may have a compensatory gain later, Walz says.

Transpalpebral enucleation/ablation

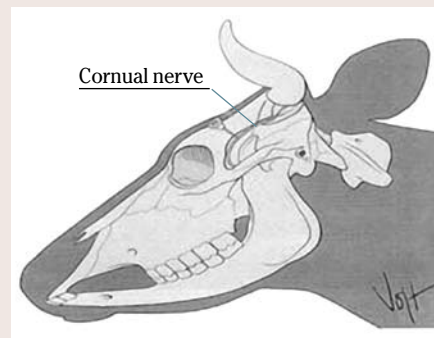
For enucleation surgery, Walz likes to use butorphanol and lidocaine. "The success of analgesia for enucleation is positively correlated to the quantity of lidocaine used behind the eye," he says. Walz gives butorphanol 0.05 mg/kg IV prior to the procedure. Local anesthetic is administered circumferentially approximately 2 inches from the eyelid margins and administered in the retrobulbar cone using a 3.5 inch, 18-gauge needle. Approximately 30-40 ml of lidocaine is deposited in the retrobulbar area. Alternatively, the Petersen nerve block may be performed, which deposits local anesthetic at the foramen orbitorotundum.

Dehorning

In some European countries it is illegal to sell horned livestock and it's illegal to disbud or dehorn calves greater than 14 days of age without an anesthetic.

Providing analgesia to the cornual nerve is very effective at providing analgesia to the bottom part of the horn, Walz says. If you can also perform a line block over the base of the poll, you can actually get more analgesia.

Pain relief after dissipation of the local anesthetic is an important issue. Providing a local anesthetic probably doesn't provide long-term pain relief. "Sometimes I think if we dehorn with a local anesthetic, it probably makes us feel better, but as soon as the local is worn off in two to three hours, they are just as painful as those that did not get a local anesthetic," Walz notes. "This may be an area where non-steroidals may be beneficial."



Obstetrical procedures

Walz doesn't use epidural xylazine as it does have some effects on uterine myometrial contractility. "The problem with using epidural lidocaine is that it is difficult to eliminate pain in the anterior portions of the reproductive tract. In obstetrical cases where the animal is painful as evidenced by excessive vocalization, butorphanol can be effective."

Lameness

Lameness is a big hurdle when it comes to pain management. "It's probably one of our bigger welfare issues," Walz says. "Managing the pain of lameness is a real challenge because we lack drugs that provide long-term control of pain. Short-term pain relief may be provided through intravenous analgesia techniques with local anesthetics. Morphine has also been used in these intravenous blocks or epidurally, but it's very difficult to control pain."

Abdominal pain

Bloat cases, intestinal obstructions or twists of the intestine are painful abdominal conditions. Epidural xylazine is very effective at mitigating abdominal pain. "I've observed cases of volvulus of the root of the mesentery where the epidural xylazine has shown some benefit," Walz says. However, the problem with using xylazine epidurally or parenterally is that sedation may occur, so be aware if you are trying to do a standing surgery.