

PAIN MANAGEMENT



BASICS

OVERVIEW

- Pain is defined by the International Association for the Study of Pain (IASP) as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage.”
- Types of pain: acute, chronic, visceral, and somatic.
- Untreated pain delays wound healing and prolonged and severe pain may impair immunity.
- Adhere to the guidelines of the Animal Medicinal Drug Use Clarification Act (AMDUCA) on extra-label drug use and the recommendations of Food Animal Residue Avoidance Databank (FARAD) on meat and milk withdrawal times to avoid human consumption of drug residue.

PHYSICAL EXAMINATION FINDINGS

- Behavioral indicators of pain in animals include grunting, vocalizing, tail swishing, limping, kicking or stomping of the feet, bruxism, touching the affected area, reluctance to move or lie down, depression, inappetence, abnormal recumbency.
- Physiologic signs of pain include tachycardia, increased respiratory rate, body temperature, and pupil size.

CAUSES AND RISK FACTORS

- Acute pain: soft tissue or musculoskeletal trauma, surgery, systemic diseases or abnormalities.
- Chronic pain: osteoarthritis, osteomyelitis, neoplasia, chronic hoof rot.



MEDICATIONS

- Choice of analgesics is based on type of pain, location of pain, species, breed, husbandry, meat and milk withdrawal times and other federal and state drug use restrictions.

DRUGS OF CHOICE

Local anesthetics (LA)

- LA produce local anesthesia via reversible blockade of sodium channels
- LA can be injected into the tissue at the wound or surgical site to produce local anesthesia, or can be administered in the peripheral area of major nerves to produce regional anesthesia.
- Types of LA: ester LA (procaine, tetracaine) and amide LA (lidocaine, mepivacaine, bupivacaine, ropivacaine).
- Lidocaine is the most popular LA with onset of anesthesia occurring within five minutes with a duration of 45 to 120 minutes. Epinephrine can be added to prolong lidocaine duration.
- Mepivacaine (5 mg/kg, 1.5 to 3 hours) and bupivacaine (2 mg/kg, 4 to 8 hours) can be used when longer duration of anesthesia is desired.
- Large doses of LA can result in toxicity. Seizuring and convulsions occur before cardiovascular collapse.

- Accidental IV administration of bupivacaine has greater cardiotoxicity in cattle.

α_2 agonists

- Xylazine, detomidine and medetomidine produce good visceral analgesia.
- Sedative dose of xylazine given IV or IM provides analgesia for 60 to 90 minutes.
- α_2 agonists can be given parenterally, epidurally, or intrathecally to produce analgesia.
- Premature parturition can occur when IV xylazine is given during the last trimester of pregnancy.
- Side effect of α_2 agonists include bradycardia, hypotension, decreased respiratory rate, cardiac arrhythmias, decrease gastrointestinal motility, hypoinsulinemia, hyperglycemia, and increased urine output. Severe hypoxemia and pulmonary edema can occur in sheep.
- The reversal agent α_2 agonist drugs, tolazoline, can be toxic, particularly to camelids, and alternative agents (yohimbine, atipamezole) should be considered for reversing these drugs if needed

Opioids

- Opioids produce analgesia via μ , κ , or δ receptors located centrally in the spinal cord and in the CNS and peripherally in the joints and cornea.
- Opioids can be administered systemically, epidurally, or can be deposited near the site of action to produce analgesia.
- Opioids are classified as pure μ agonist (morphine, meperidine, and fentanyl), partial μ agonist (buprenorphine), and κ agonist/ μ antagonist (butorphanol).
- Morphine is effective in relief of mild pain in ruminants. The drug is inactivated by ruminal microflora in ruminants and should not be given orally.
- Meperidine: 10 to 50% of the analgesic potency of morphine.
- Fentanyl: 75 to 100 times the analgesic potency of morphine. It can be administered parenterally and transdermally.
- Buprenorphine: 25 times the analgesic potency of morphine. Satisfactory analgesia was observed following bilateral orthopedic surgery in goats.
- Butorphanol: 3-5 times the analgesic potency of morphine. It is the most commonly used opioid in ruminants. It is effective in ameliorating established pain and provides excellent visceral analgesia in ruminants.
- Opioids can cause paradoxical excitement in some patients, particularly when given with no accompanying sedative agents.
- Side effects of μ agonists are respiratory depression, decreased gastrointestinal motility and increased gastrointestinal emptying time, increased appetite, sedation, and nausea. Tachycardia and hyperexcitability occur with high doses of opioids.
- Meperidine may cause histamine release.
- Slight CNS stimulation can occur with IV butorphanol.
- Propulsive walking, rapid and frequent head movements, chewing and hypersensitivity to auditory and visual stimuli occurred with buprenorphine administration to sheep.

Non-steroidal anti-inflammatory drugs (NSAIDs)

- NSAIDs produce analgesic, antipyretic, and anti-inflammatory effects via inhibition of cyclooxygenase (COX). These drugs provide pain relief by reducing inflammation.
- Aspirin and sodium salicylate have been used for their analgesic, antipyretic, and anti-inflammatory effects but have low oral bioavailability and slow absorption in ruminants.
- Flunixin meglumine is the only NSAID approved by the Food and Drug Administration (FDA) for use in beef and lactating dairy cattle for fever and inflammation associated with respiratory diseases,

endotoxemia, and acute bovine mastitis. Flunixin meglumine is an excellent visceral analgesic.

- Phenylbutazone is effective in relieving musculoskeletal injuries and chronic osteoarthritis pain. Phenylbutazone has high level of regulatory concern due to a long elimination half-life and lack of predictable withdrawal time.

- Ketoprofen has been used to alleviate inflammation and pain associated with arthritis and traumatic musculoskeletal injuries.

- Carprofen has greater potency and lower ulcerogenicity than phenylbutazone and aspirin.

- Meloxicam is useful for sustained pain relief of longer than three days.

- Diclofenac is effective for acute aseptic arthritis and myositis in cattle and buffalos and for castration-induced pain in lambs.

- NSAIDs are contraindicated in animals with preexisting gastrointestinal ulceration, bleeding or renal dysfunction.

- IM administration of flunixin meglumine is not recommended due to significant myonecrosis and tissue residues.

- Use of phenylbutazone in female dairy cattle older than 20 months is strictly prohibited, and its use in other milk- and meat-producing animals is strongly discouraged.

- Fatal anaphylactoid reaction was reported once in an Ayrshire cow following IV meloxicam administration.

N-Methyl-D-Aspartate (NMDA) antagonist

- At subanesthetic dose, ketamine blocks NMDA receptors and is effective in minimizing pain of neuropathic origin and windup syndromes. One tenth to one fifth of the anesthetic plasma concentration is correlated to its analgesic effect.

- Ketamine can be given intermittently, in combination with other analgesics, or as CRI for long duration of analgesia.

Drug Combinations Used for Constant Rate Infusion (CRI)

- Advantages of CRI is the ability to use low doses of analgesic(s) to maintain steady-state plasma concentrations, avoid peak and trough fluctuation of the drug effect, and provide continuous pain relief.

- In cattle, lidocaine CRI has been given to provide long term pain relief following laparotomy.

- Lidocaine CRI with IV detomidine can be used to alleviate abdominal and peritoneal pain.

- Morphine, lidocaine, and ketamine CRI was given to a Holstein heifer with severe burns with improved signs of comfort and appetite.

Table 1 summarizes recommended doses for anesthetic and analgesic agents in ruminants.

Table 1. *Drugs Used for Systemic Pain Management in Cattle, Sheep, Goats, and Camelids.*

Drugs	Dosages (mg/kg)			Duration (hours)
	Cattle	Sheep & Goats	Alpacas & Llamas	
Local Anesthetics				
Lidocaine	---	1-2, SC; 2.5, IV	---	1
Lidocaine	200 mg in 40 ml saline, 2 ml/hr	LD: 2-5, IV CRI: 3-6 mg/kg/hr	LD: 1.3, IV CRI: 3 mg/kg/hr	---
Lidocaine	LD: 1.3-2, IV over 5 min CRI: 1.2-3 mg/kg/hr	LD: 2.5, IV CRI: 6 mg/kg/hr (during isoflurane anesthesia)	LD: 1-2, IV CRI: 1.2-3 mg/kg/hr	---
Trifusion				
Butorphanol	LD: 0.05-0.1, IV CRI: 0.02 mg/kg/hr	In sheep during isoflurane anesthesia: ---	LD: 0.05-0.1, IV CRI: 0.02 mg/kg/hr	---
Lidocaine	LD: 1, IV CRI: 3 mg/kg/hr	CRI: 1.2 mg/kg/hr	LD: 1, IV CRI: 3 mg/kg/hr	
Ketamine	CRI: 0.6 mg/kg/hr	CRI: 0.6 mg/kg/hr	CRI: 0.6 mg/kg/hr	
Or				
Morphine	CRI: 0.025 mg/kg/hr	---	CRI: 0.025 mg/kg/hr	---
Lidocaine	LD: 1, IV CRI: 3 mg/kg/hr	In goats: CRI: 3 mg/kg/hr	LD: 1, IV CRI: 3 mg/kg/hr	
Ketamine	CRI: 0.6 mg/kg/hr	---	CRI: 0.6 mg/kg/hr	
Opioids				
Buprenorphine	---	0.0015-0.006, IV, IM	---	0.75-3.5
Buprenorphine	---	0.005-0.01, SC	---	6
Buprenorphine	---	0.005-0.1, IV, IM	---	4; 8-12
Butorphanol	0.05, SC	0.05-0.5, IV, IM; 0.05, SC	---	2-4; 6
Butorphanol	---	0.05-0.5, IM; 0.4, IV; sedation	0.05-0.1, IV, IM	4-6
Butorphanol	---	0.5, IV, IM	0.1-0.5, IV, IM	2-3
Butorphanol	---	0.05-0.2, IV, IM	---	1-3
Butorphanol	0.005, IM	---	LD: 0.05-0.1, IV CRI: 0.022 mg/kg/hr	---
Acepromazine	0.022-0.03, IV	---	---	---
Butorphanol	0.01-0.044, IV			
Diazepam	---	0.1-0.5, IV, IM	---	---
Butorphanol		0.01, IM		
Midazolam	---	0.025-0.05, IV, IM	---	---
Butorphanol		0.01, IM		
Fentanyl patch	---	0.2, TD	50 µg/hr/30-50 kg, TD 4 of 75 µg/hr/150 kg, TD	48-72
Fentanyl Injectable	---	5 mg or 10 mg/70 kg, TD	---	72-96

Fentanyl Injectable	---	0.001-0.006 µg/kg, IV; 0.001-0.005 µg/kg/hr, IV	---	1-2
Fentanyl Injectable	---	0.01, IV in sheep	---	---
Meperidine	2, IM; 3.3-4.4, IM, SC	2, IV, IM; 3.3-4.4, IM, SC	1-5, IM	2-4
Meperidine	5, IM	5-10, IM in goats	---	0.25-0.5
Morphine	0.05-0.1, IV, IM; 0.05-0.5, IV, IM	0.05-0.1, IV, SC	0.1, IV, IM	4-6
Morphine	0.4, IM	0.1-0.5, IV, IM	0.05-0.1, IV, IM; 0.25, IV	4
Morphine	---	---	0.5-1, IM	3-6
Morphine	---	0.5-1, IV	---	12
Acepromazine	0.02-0.04, IV	---	---	---
Morphine	0.1-0.5, IV	---	---	---
Oxymorphone	0.005, IM	0.005, IM	---	---
Tramadol	---	---	2, IV, IM; 4, IM	2-3
Tramadol	---	---	11, PO	8
α-2 Agonists				
Xylazine	0.05-0.2, IV, IM; 0.1, IM	0.05-0.2, IM, IV	---	2-4
Xylazine	---	---	0.1-0.3, IV, IM, SC	1-2.5
Xylazine	0.01-0.02, IV; 0.05-0.1, IV	0.1-0.2, IV; 0.02, IM	---	---
Butorphanol	0.01-0.02, IV	0.01-0.02, IV; 0.05-0.07, IM	---	---
Detomidine	0.003-0.01, IV, IM	0.003-0.01, IV, IM	---	2-4
Medetomidine	0.005-0.01, IV, IM	0.005-0.01, IV, IM	---	2-4
Romifidine	0.003-0.02, IV, IM	0.003-0.02, IV, IM	---	2-4
Nonsteroidal Anti-inflammatory Drugs (NSAIDs)				
Aspirin	100, PO	50-100, PO; 100, PO	---	6-12; 12-24
Carprofen	---	1-2, IV, PO, SC; 2-4, IV, SC; 4, SC	---	24; 24-48
Carprofen	---	0.7, IV, in sheep	---	---
Diclofenac	---	1, IV, IM	---	---
Flunixin Meglumine	1-2, PO, IV, IM	1-2.2, IV, IM, PO, SC	1.1, IV	12-24
Ketoprofen	2-3, IV, PO	2, IV; 3, IV, IM, PO	1-2, IV	12-24
Meloxicam	---	0.5, IV, SC, 1 st day; PO, once daily for 5 days	0.5, IV	12
Meloxicam	---	0.5, IV; 0.5, IM, PO	---	8; 24
Meloxicam	---	2, PO, 1 st day; 1 mg/kg, PO, once daily	---	24
Meloxicam	---	---	1, PO	72
Phenylbutazone	2-6, PO, IV; 5, PO	5, PO	5, IV, PO	24

Phenylbutazone	10, PO Prohibited in dairy cattle > 20 mo	10, PO	---	8
Phenylbutazone	Lame bull: 17-25, IV	---	---	24
Others				
Ketamine	CRI: 0.4-1.2 mg/kg/hr	CRI: 2.4 mg/kg/hr	CRI: 0.4-1.2 mg/kg/hr	---
Ketamine	CRI: 2.4 mg/kg/hr	CRI: 3 mg/kg/hr	2.4 mg/kg/hr	---
Gabapentin	---	3-5, PO	---	8
Gabapentin	10, PO	---	---	12
Gabapentin Meloxicam	15, PO 0.5, PO	---	---	6-12
Gabapentin Meloxicam	10-20, PO 1, PO	---	---	---

LD: Loading dose; CRI: Constant rate infusion; TD: Transdermal



MISCELLANEOUS

ABBREVIATIONS

- CNS: Central nervous system
- COX: Cyclooxygenase
- CRI: Constant rate infusion
- FDA: Food and Drug Administration
- LA: Local anesthetics
- NMDA: N-Methyl-D-Aspartate
- NSAIDs: Nonsteroidal anti-inflammatory drugs

Suggested Reading

Smith E, Modric S. Regulatory Considerations for the Approval of Analgesic Drugs for Cattle in the United States. *Vet Clin N Am: Food Animal Pract.* 2013;29:1-10. Lin HC. Pain Management for Farm Animals. In: "Farm Animal Anesthesia: Cattle, Small Ruminants, Camelids, and Pigs", ed. by Lin HC and Walz P, Wiley/Blackwell, Ames, Iowa. 2014, p 174-214.

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