Building an Effective Analgesic Protocol for Patients in Acute Pain

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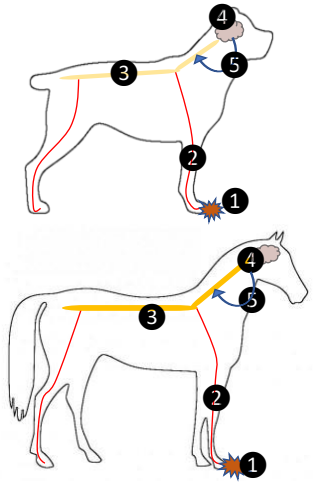
Pain has many sources and can impact the pain pathway in a myriad of different ways. Unfortunately, there is no 'one drug treats all' analgesic drug to address the complexity of pain. *Balanced or multimodal* analgesic protocols are essential for provision of adequate analgesia, which is essential for controlling FAS. The choice of analgesic drugs and techniques to balance the protocol should be made based on the location of action of that drug in the pain pathway.



5 **Descending inhibition:** Opioids, anxiolytics, CBD, acupuncture, etc.

4 **Perception:** Opioids, alpha-2 agonists, NMDA receptor antagonists, anxiolytics, etc.

3 **Modulation:** Opioids, alpha-2 agonists, NMDA receptor antagonists (ketamine), systemic lidocaine, etc.

2 **Transmission:** Local anesthetics, alpha-2 agonists (with local), some opioids (with local), ice, acupuncture, etc.

1 **Transduction:** Anti-inflammatory drugs, local anesthetics, opioids, acupuncture, ice, etc.

Diagram adapted from Grubb TL, et al. Anesthesia & Pain Management for Veterinary Nurses and Technicians. Teton New Media. 2020. Used with permission from the author.

Where do drugs work? Mammals have a pain pathway that is very well-preserved across species. Thus, we can scientifically say that animals do experience pain. The pain pathway includes:

- **Transduction** – activation of noxious (ie, painful) stimuli by peripheral receptors
- **Transmission** – transmission of that stimuli up peripheral nerves
- **Modulation** – modulation of that stimuli in the spinal cord (modulation often means amplification)
- **Perception** – recognition of pain by the brain
- **Descending inhibitory pathway** – reflex feedback from the brain to the spinal cord

When listing drugs for treating acute pain, the opioids are often listed as the first class we consider. However, based on their effect on the pain pathway, perhaps we should start with NSAIDs and local anesthetics.

Non-steroidal anti-inflammatory drugs (NSAIDS)
Inflammation is generally a major component of acute pain. Because inflammation is also the pathology producing pain, control of inflammation decreases further tissue damage and promotes healing. A traditional NSAID or EP4 receptor antagonist should be administered to all appropriate patients.

- Advantages: **Anti-inflammatory!!!** Most surgical and trauma pain is due to pain of inflammation.

- Disadvantages: Can cause or exacerbate hepatic/renal disease, GI ulceration and bleeding disorders.
- Contraindications: Most patients with renal or hepatic dysfunction, GI ulceration, clotting dysfunction, etc…
- Precautions: Dose carefully in cats, but do not with-hold NSAIDs from cats.

Local anesthetic drugs

The pain signal is transmitted from the periphery to the central nervous system almost solely by opening and closing of sodium channels. This provides a unique opportunity to control pain because propagation of the pain signal is almost totally dependent on this mechanism. Local anesthetic drugs block sodium channels and provide complete pain relief from the nerves that are blocked. This fact led to the recommendation '…because of their safety and significant benefit, local anesthetics should be utilized, insofar as possible, with every surgical procedure.' (AAHA/AAFP Pain Management Guidelines, Epstein et al. 2015). Often overlooked is the fact that local anesthetic blockade provides not only intra-operative but also post-operative pain relief. In humans, the inclusion of local blocks in analgesic protocols also decreases the likelihood that acute pain will lead to chronic pain. Because of the similarity of the pain pathway across mammalian species, this benefit is predicted in our patients.

- Advantages: **Total loss of pain sensation!** Cheap, easy to use, very effective.
- Disadvantages: None. Would be nice to have longer duration drugs.
- Contraindications: None
- Precautions: Dose carefully in cats and maybe in goats.
- This is one of the most effective, inexpensive and easy to use drug classes.
- Common blocks include: caudal maxillary, infraorbital, caudal mandibular, mental, auriculotemporal, brachial plexus, manus/pedus, thoracic, testicular, intraperitoneal, lumbosacral epidural, sacrococcygeal epidural, etc…
- **Infusions** (lidocaine only, controversial in cats) have been shown to provide analgesia in both acute (animals, humans) and chronic pain conditions (humans only so far – research needed in animals!)

Opioids

Opioids are potent, rapidly acting analgesic drugs, making them excellent for acute pain protocols. Full mu-opioid receptor agonists (morphine, etc) are the most potent but also the most impacted by regulatory control. Buprenorphine is less potent but with a long duration, especially the FDA-approved buprenorphine for cats (24-hour duration).

- Advantages: **Potent** class of systemically administered analgesic drugs; **high safety margin**, **reversible**.
- Disadvantages: Short duration when compared to duration of pain if administered IV or IM; Potential for sedation in dogs (usually a good thing for anesthesia) and excitement in cats and horses; Potential for GI effects (nausea/vomiting, slowed motility) that are generally clinically insignificant but might impact certain patients; Some decrease in respiratory function but almost always clinically insignificant.
- Contraindications: No absolute contraindications.
- Precautions: Patients in which vomiting, slowed GI motility, excitement/sedation or slight decrease in respiratory function could be problematic.
- **Infusions** allow decreased opioid dosing. Butorphanol duration of action can be prolonged if the drug is administered as an infusion.

Alpha-2 agonists

Consider sedation as soon as possible in patients with FAS. Dexmedetomidine and medetomidine provide both sedation and analgesia and their analgesic effects are synergistic with those of the opioids, thus enhancing the effects of the lesser potent opioids.

- Advantages: **Sedation AND analgesia**, reversible
- Disadvantages: Increases cardiac work because of vasoconstriction
- Contraindications: Most cardiovascular diseases
- Precautions: Any precautions associated with deep sedation (ataxia in horses, cows; mild respiratory depression, etc…)
- **Infusions** provide calming (or sedation if administered at higher dosages) and analgesia. Excellent addition to multimodal CRI.

N-methyl-D-aspartate (NMDA) -receptor antagonist (ketamine)

Ketamine, administered as a sub-anesthetic dose infusion in a multi-modal protocol, prevents or decreases the development of central sensitization, a condition that significantly amplifies the pain signal. Ketamine can play a major role in the reduction of both pain and with opioid consumption. Consensus guidelines promoting the use of ketamine in both acute and chronic pain states in humans have been developed (Schwenk et al. 2018; Cohen et al. 2018).

- Advantages: **Role in controlling central sensitization**, which can be tough to treat.
- Disadvantages: Must administer as a constant rate infusion (CRI) to achieve this effect
- Contraindications: None (CRI dose is REALLY low!).
- Precautions: Patients that may not be able to clear the drug through hepatic or renal pathways; patients with seizures.

Potential adjunctive drugs

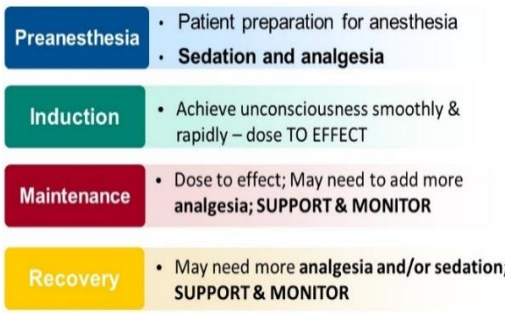
- Maropitant is a neurokinin-1 (NK-1) receptor antagonist. NK-1 receptors are found both in the emetic and pain pathways. Although minimal alveolar concentration (MAC) reduction studies do not prove analgesia (Reed and Doherty 2018), in a visceral pain model maropitant decreased MAC in cats (Niyom et al 2013) when administered at the label dose and in dogs when administered as an infusion (Boscan et al 2011). If not a true analgesic, the potential for increased patient comfort secondary to decreased vomiting makes maropitant a valid addition to a perioperative analgesic protocol.
- Gabapentin is used for treatment of chronic neuropathic pain and is unlikely to provide analgesia for acute inflammatory pain. However, gabapentin might be appropriate in patients with pre-existing neuropathic pain. NOTE: If administered for analgesia, the recommendation is continued dosing, rather than a single dose, at a minimum of 10 mg/kg PO BID. Gabapentin will also decrease FAS, which can decrease the intensity of pain.

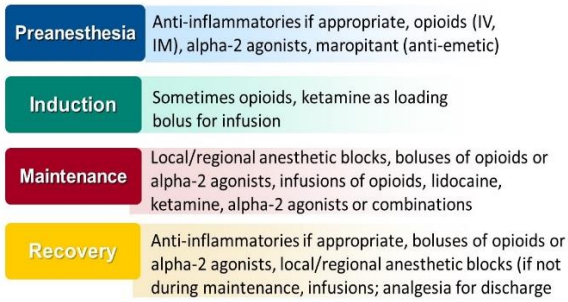
Designing analgesic protocols for perioperative pain: To use analgesic drugs most effectively, the principles of analgesia should be followed to provide <u>balanced analgesia</u>:

1. **Preemptive analgesia**
    - Drugs administered prior to the pain stimulus are more effective. In part because the block input to or decrease the response of the neurons in the dorsal horn of the spinal cord, which decreases the likelihood of central sensitization.
2. **Multimodal analgesia**
    - Using drugs from different classes or by different delivery routes (eg, IV vs epidural) 'interrupts' the pain pathway at different sites, allowing the effects of the drugs to be

synergistic or even additive. This is one of the most important components of an effective analgesic protocol.

3. **Postoperative and post-discharge analgesia**
    - Pain does not end at discharge from the hospital (in most cases) so analgesic drugs should not be discontinued on discharge from the hospital (in most cases). Pain should be controlled (remember – we don't usually eliminate pain – we just control it and improve quality of life!) until it dissipates to the level that it is not impacting patient welfare.





Summary: Balanced analgesic protocols are more effective than single-drug protocols at controlling pain and more efficacious pain management equates to lower FAS. Balance the protocol by choosing drugs from as many drug classes as appropriate, balancing both efficacy and safety. Include drugs to control FAS since FAS can amplify the sensation of pain.