Adjunctive and Advanced Therapies for Pain Management

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The vast majority of patients experiencing acute pain can be managed with conventional analgesics such as NSAIDs, opioids and local anaesthetics. Patients whose pain is unmanaged or who present in preexisting pain states may require additional therapy. In addition to the classic analgesic agents, medications with other indications can be used to help manage pain. These drugs are referred to as *adjunctive analgesics* and come from many separate classes of pharmacological compounds. *Adjuvant analgesics* are agents that can enhance analgesic drugs when co-administered, but have few or no analgesic properties when given alone. Some examples of adjunctive and adjuvant analgesics are:

- **Tranquilizers** (phenothiazines, benzodiazepines), which alter an animal’s response to pain and can relax muscles; used in combination with true analgesics. These drugs also reduce anxiety and fear, which can exacerbate pain.

- **N-methyl-D-aspartate (NMDA) receptor antagonists** such as constant rate infusion of ketamine or oral administration of Amantadine can enhance analgesia by blocking sensitization of neurons in the spinal cord and are especially useful for managing patients who have experienced wind-up phenomenon.

- **Anticonvulsants.** Gabapentin may play a role in reducing neuropathic pain and central sensitization in chronic pain patients.

- **Corticosteroids** (prednisolone) have powerful anti-inflammatory and immunosuppressive effects, “dampening the fires” of acute inflammation.

- **Tricyclic antidepressants** (amitryptiline, imipramine) are effective analgesics for chronic pain, especially neuropathic or cancer-related pain.

- **Alpha2-Agonists** Alpha2-agonists (α2-agonists) inhibit release of the excitatory neurotransmitter norepinephrine to produce analgesia and sedation. Alpha2-agonists are short-duration analgesics and can be rapidly reversed with α2-antagonists. This characteristic makes these drugs suitable for procedures requiring short-term restraint and analgesia. Alpha2-agonists may bind to the same receptors as opioids and act synergistically with them. The dosages of other analgesic and anaesthetic agents can be significantly reduced if given concurrently with α2-agonists. Alpha2-agonists can have profound effects on the cardiovascular and nervous systems, but these adverse events can be minimized by using low dosages. Bradycardia and vomiting are the most common side effects with α2-agonists. Medetomidine is a dose-dependent sedative analgesic commonly used as a preanesthetic agent in healthy animals. Onset of effect takes 5 to 15 minutes depending on route of administration (IV or IM) and sedation can last up to 90 minutes. Medetomidine administration results in physiologically normal peripheral vasoconstriction, temporary decreased heart rate, and a transient increase in blood pressure. All cardiovascular parameters smoothly return to pre-sedation levels upon reversal with atipamezole. Xylazine has a short duration of analgesia (30 minutes). Its central nervous system effects can be reversed with yohimbine or atipamezole. Both drugs can cause vomiting and cardiovascular suppression.
Analgesic Drugs for Constant Rate Infusion (CRI)

Constant rate infusion allows continuous low dose administration of various analgesics. Optimally CRIs are established prior to tissue damage (i.e. preoperatively) and run for 6 to 12 hours postoperatively. CRI analgesia is also quite effective in management of hospitalized patients with pre-existing or persistent medical pain.

**Ketamine.** NMDA (N-methyl-D-aspartate) receptors are present in the dorsal horn of the spinal cord and certain areas within the brain. Intense and/or chronic noxious input to the dorsal horn cells (mediated principally by C-fibers) results in the removal of magnesium from the NMDA receptors and their activation by glutamate. This causes prolonged depolarization of spinal neurons (an increase in the magnitude and duration of neuron firing), which leads to an “amplification” of the pain response. This is a significant part of the process of central sensitization (an increase in the excitability of spinal neurons) and may result in hyperalgesia (an excessive response to a painful stimulus) and allodynia (a painful response to a normally non-painful stimulus).

It is readily apparent that blocking (antagonizing) the NMDA receptors will help to minimize excessively painful responses. Additionally, studies suggest that antagonizing these receptors improves opioid receptor sensitivity, reduces opioid tolerance and minimizes the development of rebound hyperalgesia (the phenomenon of markedly increased pain when opioids are withdrawn).

Ketamine is the most commonly used antagonist of NMDA receptors in veterinary medicine. While its effects as a dissociative anaesthetic at standard doses are well known, a new realm of activity occurs when it is delivered at sub-aesthetic doses. At constant rate infusion doses, ketamine blocks receptor activity without causing any dissociative or other adverse effects.

It should be noted that a microdose ketamine CRI should not be used as a sole means of analgesia. It is intended to augment other pain relievers, and should always be used in conjunction with opioids or other analgesics.

**Dosing:** 2 to 20 ug/kg/minute (0.12 to 1.2 mg/kg/hr).

An initial 0.25 to 0.50 mg/kg IV bolus is given to rapidly achieve initial therapeutic blood levels of the drug (while the CRI is intended to maintain, or very slowly, increase blood levels). Failure to administer this "loading" dose will result in an excessive delay in the drug reaching therapeutic levels.

2 to 20 ug/kg/min = 0.002 to 0.020 mg/kg/min.

**Morphine.** When combined with ketamine in a constant rate infusion, significant analgesia is achieved. The steady-state levels of morphine help to avoid some of the “peak and valley” effects seen with PRN (Pro Re Nata) administration of opioids. Additionally, its use intraoperatively (as a “piggyback” onto anaesthetic maintenance fluids) serves to reduce the amount of anaesthetic gas required, which can be useful in decreasing the risk of hypotension.

It can be used in cats at the low end of the dosing spectrum (higher rates may induce significant dysphoria and excitation).
While other opioids can be substituted for morphine, we have elected to only include information for one other mu agonist, fentanyl, in the dosing information section. This reference is not intended to be an exhaustive review of all CRI options but to serve as a solid but basic reference for those adding CRI analgesia to their practice.

Dosing: 2 to 6 ug/kg/minute (0.12 to 0.36 mg/kg/hr).

If no previous mu agonist has been given, administer 0.5 mg/kg of Morphine IM (or very slowly IV) to rapidly achieve initial therapeutic blood levels.

Morphine is light sensitive. Make sure the syringe or IV bag is covered to protect the morphine from light when using long-term morphine CRIs.

2 to 6 ug/kg/min = 0.002 to 0.006 mg/kg/min.

**Lidocaine.** The addition of lidocaine has several benefits. For intractable/very severe pain, it adds to the analgesia and sedation. Lidocaine is reported to have some cytoprotective effects, such as weak calcium channel inhibition (which may be helpful in preventing reperfusion injury), and reduced neutrophil chemotaxis and platelet aggregation (which could help significantly in cases with the potential for DIC or SIRS, including GDV’s and splenectomies). Also, lidocaine has some activity in preventing ileus (potentially useful for enterotomies).

Various dosage rates of lidocaine have been advocated. In dogs, rates as low as 10 ug/kg/minute (0.6 mg/kg/hour) provide analgesia, though it may take up to 50 ug/kg/minute (3 mg/kg/hour) for the full cytoprotective and anti-ileus effects. Until further data is available, **lidocaine’s use in cats cannot be recommended**, due to the potential for toxicity, usually manifested as seizures and severe bradycardia.

Dosing: 10 to 50 ug/kg/minute (0.6 to 3.0 mg/kg/hr).

An initial 1 mg/kg IV bolus is given to rapidly achieve initial therapeutic blood levels.

Given the volume of 2% lidocaine this is, a similar volume of the diluent should be removed **BEFORE** any other drugs are added.

Lidocaine is light sensitive too. Make sure the syringe or IV bag is covered to protect the lidocaine from light when using long-term lidocaine CRIs.

10 to 50 ug/kg/min = 0.010 to 0.050 mg/kg/min.

**CRI Calculations**

The big question; how much drug do I need to put in the fluid bag?

What you need to know to begin:

- Dose of drug to be delivered (e.g. 3 µg/kg/min or 0.18mg/kg/hr)
- Patient’s body weight in kgs
- Fluid rate in mls per hour and fluid bag size
- Drug concentration
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For dosages given in mgs/kg/hr:

Step 1. Set up equation based on dosage
Step 2. Replace hash marks with time signs
Step 3. Enter known information
Step 4. Solve for hours.
Step 5. Solve equation
Step 6. Calculate drug volume and add to bag

For dosages given in µgs/kg/min:

Step 1. Set up equation based on dosage
Step 2. Replace hash marks with time signs
Step 3. Enter known information
Step 4. Solve for minutes.
Step 5. Solve equation
Step 6. Convert µgs to mgs
Step 7. Calculate drug volume and add to bag

*A controlled rate infusion pump is required since the rate of drug delivery must be precisely controlled. This can be a syringe pump, cassette pump or rotary pump.

References


