



Peer Reviewed

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Pain Management: Constant-Rate Infusion

P PROFILE

Definitions

- Pain categories
 - *Adaptive* pain is physiologically important and essential for an animal's survival by preventing tissue damage or promoting healing once damage has occurred. This type of pain should be managed to the point of being tolerable while healing occurs.
 - *Maladaptive* pain reflects malfunction of the nervous system and serves no true purpose.
- Types of pain
 - *Nociceptive* pain is typically transient in response to noxious stimuli (ie, mechanical, chemical, thermal).
 - *Inflammatory* pain results from inflammatory mediators produced following tissue injury to activate or modify the stimulus response properties of nociceptor afferents,

setting up changes in the responsiveness of neurons in the CNS.

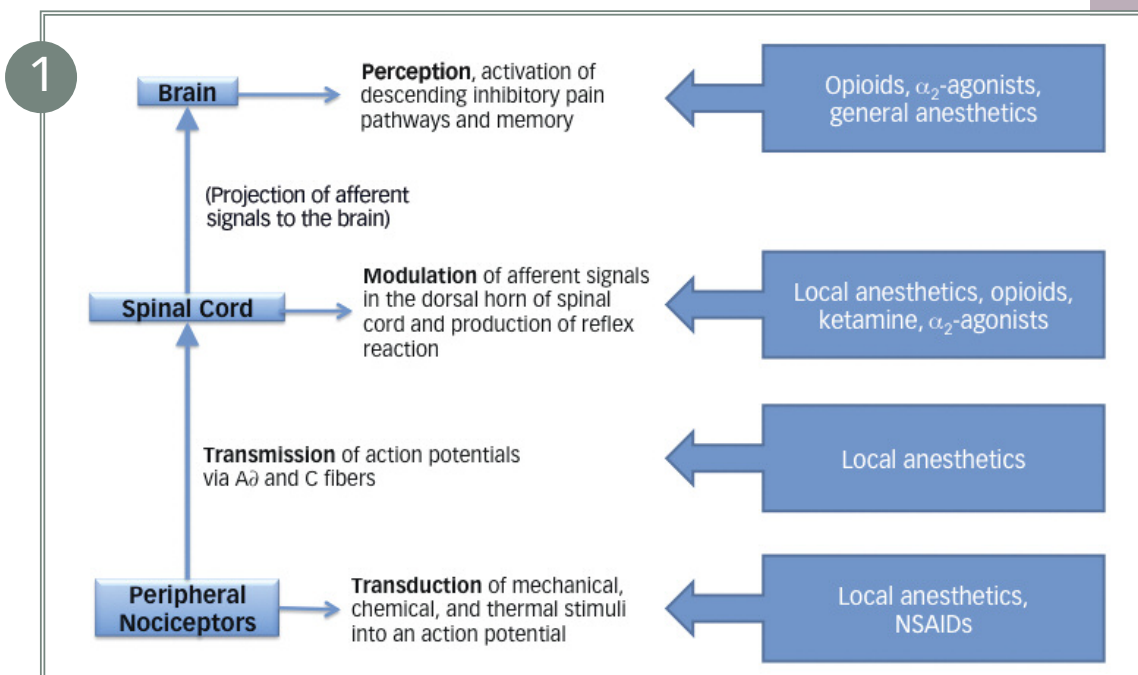
- *Neuropathic* pain is associated with damage to or dysfunction of central or peripheral neurons.
- *Functional* pain is not well understood. It is most likely associated with distorted pain generation/processing without evidence of tissue damage.

Pathophysiology

- Pain involves four physiologic processes amenable to pharmacologic intervention (**Figure 1**):
 - *Transduction* is the translation of a given noxious stimulus into an electric signal at the peripheral nociceptor.
 - *Transmission* is the propagation of action potentials in the axon of neurons.



CONTINUES



Any procedure considered painful in humans should be considered painful in animals and analgesics administered accordingly.

- ▶ *Modulation* is the modification of nociceptive transmission via the endogenous descending analgesic systems (ie, opioid, serotonergic, GABAergic, noradrenergic).
- ▶ *Perception* is the conscious subjective and emotional experience of pain that results from successful transduction, transmission, modulation, and integration of thalamocortical, reticular, and limbic functions.
- Uncontrolled or poorly controlled adaptive pain can become maladaptive. Pain perception is shifted and results in hyperalgesia—excessive pain in response to a noxious stimulus—and allodynia—pain in response to innocuous stimuli (Figure 2).
- Constant-rate infusion (CRI) of analgesics may prevent/revert such changes by maintaining more stable plasma concentrations of administered analgesics than with intermittent treatment. Homeostasis is better preserved, optimizing conditions for return to normal function (Figure 3).

Dx DIAGNOSIS

- Guidelines for pain recognition and treatment in dogs and cats have been published.¹
- Hyperalgesia or allodynia should be suspected

if a patient responds excessively to a mildly painful procedure or a procedure that is not considered painful.

- Any procedure considered painful in humans should be considered painful in animals. Analgesics should be administered and effectiveness assessed accordingly.

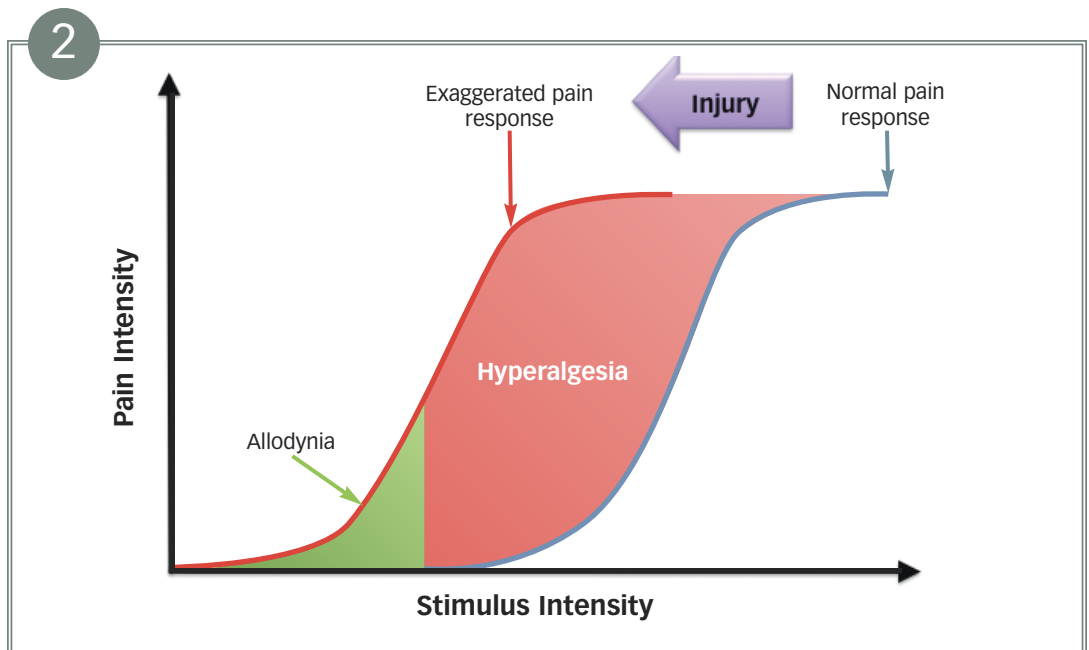
Tx TREATMENT

- Analgesic selection should be individualized and the underlying mechanisms of pain, side effects, and potential beneficial or deleterious effects on comorbidities considered.
- Preemptive and multimodal analgesics are generally more beneficial than analgesics that are provided after pain develops or are of single modality.

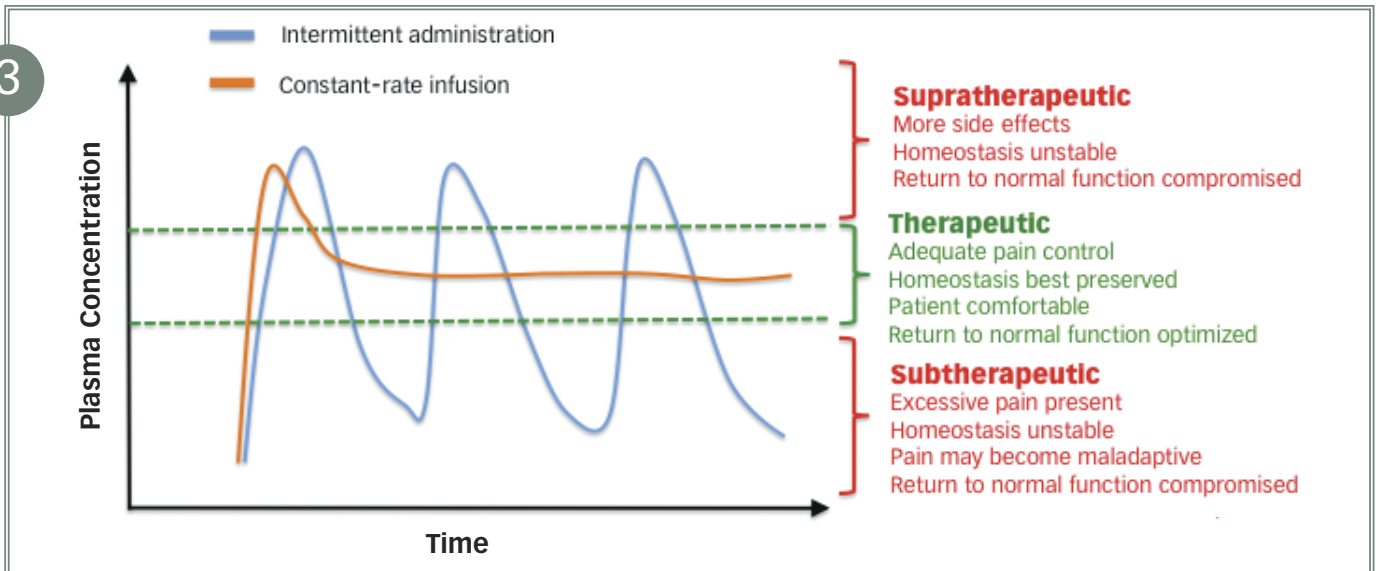
Analgesic Drugs

Morphine

- Pharmacology
 - ▶ Prototype opioid agonist that acts at mu- and kappa-opioid receptors.
 - ▶ Inhibits ascending nociceptive neurotransmission via inhibition of presynaptic neurotransmitter release and by hyperpolarizing projecting neurons in the spinal cord dorsal horn.



GABA = γ -aminobutyric acid



- ▶ Activates descending inhibitory pathways by activating the monoaminergic system.
 - Dose
 - ▶ Dogs: 0.12–0.3 mg/kg/hr is clinically useful. Lower doses may be helpful for analgesia in conscious dogs and higher doses for use in anesthetized dogs as part of balanced anesthesia.^{2,3}
 - To avoid histamine release with loading dose, it can be omitted or administered IM, as this route does not induce histamine release.
 - ▶ Cats: No studies have evaluated morphine via CRI in cats.
 - Precautions
 - ▶ May cause dose-dependent vasodilation, bradycardia, respiratory depression, and histamine release²⁻⁵ associated with the loading dose or CRI.
 - ▶ During anesthesia, control ventilation to avoid hypercapnia.
 - ▶ Syringe or fluid pumps are preferred when administering morphine CRI, as inadvertent increases in the rate may result in overdose and induce significant histamine release.
 - ▶ Avoid or use with caution in patients predisposed to cardiac arrhythmias or at increased risk for bleeding.
 - Histamine can predispose to cardiac arrhythmias directly and indirectly via stimulation of epinephrine secretion.
 - Release of heparin, stored in mast cell granules, may impair coagulation.
 - ▶ Hypotension resulting from histamine release can be treated with H₁- and H₂-receptor antagonists (ie, diphenhydramine, cimetidine), fluid administration, vasopressors, bronchodilators, and respiratory support.
 - ▶ Inhalant anesthetics should be given to effect to maintain adequate surgical anesthesia without anesthetic overdose.
- Hydromorphone**
- Pharmacology
 - ▶ Morphine derivative with similar pharmacokinetics.
 - ▶ 5–10 times more potent than morphine.⁶
 - ▶ Minimal to no risk for histamine release.⁷
 - Dose
 - ▶ Pharmacokinetic data in dogs available⁶ but no CRI studies have been published.
 - ▶ Loading dose of 0.05–0.1 mg/kg followed by CRI of 0.03–0.06 mg/kg/hr may produce clinically useful analgesia.
 - Precautions
 - ▶ Similar to morphine; in compromised patients, administer loading dose slowly to minimize risk for small but clinically significant (ie, sufficient to cause hypotension) histamine release.⁷

To maintain adequate surgical anesthesia without anesthetic overdose, inhalant anesthetics should be given to effect.

CONTINUES

Multimodal analgesic techniques can provide beneficial pain control while optimizing homeostasis and return to function.

Fentanyl

- Pharmacology
 - Synthetic mu-opioid receptor agonist.
 - 50–100 times more potent than morphine, with similar adverse effects but no risk for histamine release.
 - Preferred opioid for patients with hemodynamic instability or that react unfavorably to morphine.
- Dose
 - Dogs: Loading dose of 2–10 µg/kg and CRI of 1–40 µg/kg/hr are clinically useful. Lower doses may be helpful for analgesia in conscious dogs and higher doses as part of balanced anesthesia.
 - Cats: Loading dose of 1–5 µg/kg and CRI of 1–20 µg/kg/hr may be used.⁸ Infusion can be discontinued 30 minutes before end of anesthetic event to minimize potential for dysphoric recovery.
 - Dogs and cats: For dysphoria, consider reducing dose, administering tranquilizer/sedative (ie, acepromazine, dexmedetomidine), or discontinuing fentanyl.
- Precautions
 - Similar to morphine, except for histamine release; high doses are more likely to result in bradycardia (responsive to anticholinergic) and respiratory depression (managed with controlled ventilation).
 - May have significant anesthetic-sparing effect. Titrate inhalant anesthetic to effect to avoid excessive anesthetic depth.

Ketamine

- Pharmacology
 - Injectable anesthetic with analgesic properties (NMDA-receptor antagonist).

- Prevents or reverses CNS hypersensitization and hyperalgesia.
- For neuropathic and chronic pain, may provide analgesia and/or improve response to opioids.^{9,10}
- Minimal to no respiratory and hemodynamic effects at subanesthetic doses.
- In dogs, undergoes mainly hepatic metabolism. In cats, excreted by kidneys, mostly unchanged.
- Dose
 - Dogs: CRI of 10 µg/kg/min reduces isoflurane minimum alveolar concentration (MAC) by 29%.³
 - Cats: CRI of 23 µg/kg/min reduces isoflurane MAC by 45% but can prolong recovery from anesthesia.¹¹
 - Dogs and cats: Loading dose of 0.25–0.5 mg/kg may be used.
- Precautions
 - Indirect cardiovascular stimulating effects increase central sympathetic output.
 - Myocardial-depressant effects may predominate in critically ill patients with protracted catecholamine stores.
 - Avoid or use cautiously in cats with impaired renal function.

Lidocaine

- Pharmacology
 - Local anesthetic that can be administered IV as adjunct to decrease inhalant anesthetic requirement in dogs.³
 - Antioxidant and inflammatory modulator; potentially valuable against ischemia-reperfusion injury.¹²

Drug Combinations

- Ketamine significantly potentiates opioid analgesia,¹⁴ allowing a decrease in the opioid dose and dose-related adverse effects.
- A combination of ketamine, lidocaine, and morphine can significantly decrease isoflurane requirement in dogs.³ Morphine may be substituted for fentanyl in compromised patients.
- Ketamine and fentanyl administered postoperatively can produce better analgesia and comfort compared with fentanyl alone in dogs undergoing forelimb amputation. The beneficial effects are still apparent 3 days following surgery.⁹
- Studies evaluating these combinations have not been conducted in cats.

MAC = minimum alveolar concentration, NMDA = N-methyl-D-aspartate

- ▶ May be beneficial for neuropathic pain.¹⁰
- Dose
 - ▶ Loading dose of 0.5–1.0 mg/kg may be given, followed by CRI of 1.5–3.0 mg/kg/hr (dogs only)
- Precautions
 - ▶ Excessive doses may cause adverse CNS effects (eg, depression, ataxia, muscle tremors, seizures, nausea, vomiting) and cardiac effects (eg, prolonged PR and QRS interval, shortened QT interval).
 - ▶ Patients with atrial fibrillation may experience increases in ventricular rate. Hypotension may occur if IV bolus given rapidly.¹²
 - ▶ In cats, not recommended for reducing isoflurane requirements.¹³ Systemic doses adequate to produce analgesia are unknown.

- intermittent administration; in addition, patients are more closely monitored.
- Depending on length of hospitalization and equipment used: \$–\$\$\$
 - Hourly drug cost for 20-kg patient:

Drug	Low-End Dose	High-End Dose
Morphine	\$0.50	\$1.50
Hydromorphone	\$1.72	\$5.16
Fentanyl	\$0.11	\$4.48
Ketamine	\$0.084	\$0.42
Lidocaine	\$0.15	\$0.30

Cost Key

\$ = up to \$100	\$\$\$\$ = \$501–\$1000
\$\$ = \$101–\$250	\$\$\$\$\$ = more than \$1000
\$\$\$ = \$251–\$500	



IN GENERAL

Relative Cost

- The overall cost of using CRI analgesics to manage pain (eg, drugs, placement and maintenance of IV catheter, patient monitoring, equipment) is typically higher than that for intermittent analgesics.
- When considering drugs alone, CRI of analgesics is less costly and more efficacious than

Future Considerations

- The benefits of pain management are increasingly recognized. Multimodal analgesic techniques, including CRI analgesics, can produce the best possible pain control while optimizing homeostasis and return to function.

See **Aids & Resources**, back page, for references & suggested reading.



AT A GLANCE

General Guidelines: Analgesic Constant-Rate Infusions

Drug	Loading Dose	CRI	Indication*	Species
Morphine ^a	None or 0.1–0.3 mg/kg	0.12–0.3 mg/kg/hr	Nociceptive >> inflammatory > neuropathic	Dog
Hydromorphone ^a	0.05–0.1 mg/kg	0.03–0.06 mg/kg/hr	Nociceptive >> inflammatory > neuropathic	Dog
Fentanyl ^b	1–10 µg/kg	1–40 µg/kg/hr	Nociceptive >> inflammatory > neuropathic	Dog, cat
Ketamine	0.25–0.5 mg/kg	2–10 µg/kg/min	Neuropathic >> nociceptive > inflammatory	Dog, cat
Lidocaine	0.5–1.0 mg/kg	1.5–3 mg/kg/hr	Nociceptive = inflammatory = neuropathic	Dog
Morphine, ^a lidocaine, ketamine	Same as above or none	M: 0.2 mg/kg/hr L: 3.0 mg/kg/hr K: 0.6 mg/kg/hr	Nociceptive = inflammatory = neuropathic	Dog
Fentanyl, ^b ketamine	Same as above or none	F: 20 µg/kg/hr K: 0.6 mg/kg/hr	Nociceptive = inflammatory = neuropathic	Dog, cat

*Anticipated analgesic effectiveness based on drug pharmacology and biology of each pain type.

^a May cause histamine release. Administer loading dose slowly (3–5 min). Morphine does not cause detectable histamine release when administered IM, and this may be used as an alternative route for loading dose. Hydromorphone is considerably less likely to cause histamine release than morphine.

^b Choose lower doses for cats and terminate infusion 20–30 min before end of anesthesia to reduce risk for dysphoric recovery.