

Constant-rate infusions: part two

Author : Andrew Bell

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Andrew Bell concludes his two-part article by examining two methods of administering constant-rate infusions, the drugs used and side effects

The first part of this article (VT39.18) discussed the rationale for the use of constant-rate infusions (CRI) of analgesic drugs and the pathophysiology of pain. This part discusses the practicalities of CRI administration and the drugs commonly used.

Practicalities

CRIs require the patient to have a patent IV cannula. This should be checked regularly for extravasation, inflammation and thrombophlebitis.

There are two ways of administering an accurate drug dose over a specific time; drugs may be delivered by syringe driver or included in the patient's fluid bag.

• Syringe drivers

These are becoming more affordable and represent the gold standard due to their accuracy. They are connected via an extension and multi-adaptor to the patient's IV cannula. Extension sets or adaptors should incorporate one-way valves to ensure drug delivery to the patient rather than into a connected fluid bag. Separate pumps can be used for different drugs – allowing the rate of each to be adjusted individually.

They are most suitable for perioperative and intensive care use, but their bulk and the multiple

extensions involved may make their use in wards difficult.

- **Fluid bag**

Analgesic drugs may alternatively be added to a bag of fluid and delivered along with the patient's fluid requirement. Most crystalloid fluids, such as normal saline, Hartmann's or glucose saline, are suitable. The volumes of drugs to be added should be calculated as shown in [Table 1](#), and are normally added to the maintenance fluid requirements.

Any additional fluids to account for hypovolaemia or ongoing losses can be piggybacked using IV-line multi-adaptors. It is also possible to reformulate fluids in an in-line burette for short periods where higher doses may be required. Although not absolutely essential, all fluids containing drugs should be administered by a volumetric infusion pump to avoid overdose. This is especially relevant in small patients.

Patients should be monitored frequently and staff should be familiar with the drugs used and their expected side effects. Monitoring should also include confirmation that the rate is appropriate plus a pain assessment.

Analgesic agents

Analgesic drugs used in CRIs include opioids, ketamine, lidocaine and alpha-2 agonists. The side effects, interactions and metabolism of each drug used should be appreciated. The drug choice and rate should take into account patient signalment, especially its age and any disease present.

CRIs can be contra-indicated in patients with reduced capacity to metabolise drugs, such as paediatric patients or those with liver disease, and dose rates may need to be dramatically reduced to avoid overdose.

No analgesic drugs hold a UK licence for administration by infusion and one must justify the use of other drugs via the cascade. In some cases, veterinary products are available, but not licensed for administration by infusion (for example, ketamine). In other cases, no suitable veterinary drug exists and a human preparation, such as morphine, may be used. Owners should be made aware that non-licensed drugs are being administered to their animals and consent sought. It is beneficial to use multiple drugs to provide multimodal analgesia and a popular combination is a CRI containing morphine, lidocaine and ketamine (MLK). Drugs may be omitted or added depending on the patient.

Opioids

Opioids should be the mainstay of any treatment protocol for moderate to severe pain. Opioids act by binding to opioid receptors. Traditionally, these were thought to exist exclusively in the central

nervous system (CNS), but they can be demonstrated at peripheral sites, such as joints, the cornea and also immunocytes. This underlies the rationale for intra-articular opioid administration.

In the CNS, opioids modulate pain by inhibiting the release of primary pain neurotransmitters in the spinal cord and stimulating descending inhibitory systems at supra-spinal levels. Three opioid receptor types are commonly recognised: mu (μ), kappa (κ), and delta (δ). The mu-opioid receptor is the most important with regard to analgesia, and all common opioid analgesics – with the exception of butorphanol – are agonists at this receptor. Unfortunately, agonism of the mu-opioid receptor is also associated with most of the commonly seen side effects.

No veterinary-licensed opioids are approved for administration by infusion. Butorphanol and buprenorphine are partial opioid agonists and have reduced efficacy in severe pain. A full-opioid agonist should be chosen to allow titration to effect. The only veterinary-licensed full-agonist opioid (pethidine) should not be administered intravenously, as it causes histamine release, which may be life threatening.

Morphine is the preferred opioid for use in CRIs, although fentanyl's short duration of action makes it suitable for occasional intra-operative use and in critical intensive-care patients. Although morphine may cause histamine release when injected as an intravenous bolus, this does not appear to be a problem during infusions. Initial loading doses should be given slowly as a precaution. Veterinary surgeons should be aware that morphine and fentanyl are Schedule 2 controlled drugs and should be familiar with the rules governing their storage and use. Aside from analgesia, opioids have a number of other effects that are summarised below.

It should be noted that side effects tend to be dramatically reduced when opioids are used where pain is already present.

- **Sedation**

Sedation is often considered an advantage, but must not interfere with normal eating and drinking behaviour for long periods of time.

- **Bradycardia**

Opioids are vagomimetic and tend to slow heart rates. Their use sometimes results in vagally mediated arrhythmias, such as sinus arrhythmia and mild atrioventricular blocks. Heart rates as low as 50 to 60 beats per minute are well tolerated in dogs as long as no concurrent cardiovascular problems are present – for example, hypovolaemia. Severe bradycardia (less than 40 beats per minute) is uncommon, but may be treated with anticholinergics, such as atropine or glycopyrrolate.

- **Respiratory depression**

Opioids depress the responsiveness of the respiratory centre to CO₂, although this effect is much less pronounced in dogs and cats than humans. Assisted ventilation may be required when using potent opioids, such as fentanyl, under anaesthesia. Extreme care should be taken when administering opioids to animals with brain injury and raised intracranial pressure. Opioids may cause cerebral vasodilation via elevation of arterial CO₂ tensions, and this may further increase intracranial pressure – potentially impairing cerebral perfusion.

- **Nausea/vomiting**

Vomiting is uncommon in painful animals. Morphine is the only opioid to cause these effects.

- **Dysphoria/excitement**

Dysphoria is the opposite of euphoria and describes an uncomfortable and often restless mood. Dysphoria may be difficult to distinguish from pain or emergence delirium after anaesthesia. Appropriate treatments for dysphoria are the reduction of analgesic dose, sedation, and possible antagonism of the full opioid with a partial agonist, such as butorphanol or buprenorphine.

These three solutions are clearly not indicated if the animal's behaviour is due to pain, and a careful assessment should be performed. Some species, such as horses, are more prone to opioid excitement than others, and this is due to opioid receptor distribution in the CNS. Although often mentioned in older texts, opioids do not routinely cause excitement in cats at normal clinical doses.

- **Panting**

This is often seen after administration of bolus doses. Affected animals may actually hypoventilate, despite appearing to breathe excessively.

- **Reduced urine production**

This may be accompanied by urinary retention, so bladder size should be monitored.

- **Constipation**

Pain may also cause constipation, but this is not an argument for the avoidance of opioids.

- **Contraction of biliary smooth muscle**

Opioids cause contraction of the sphincter of Oddi and should be avoided in dogs and cats with biliary disease. A high percentage of cats have a common bile and pancreatic duct and full agonist opioids should probably be avoided in feline pancreatitis.

This is less of a concern in dogs. Buprenorphine appears to have little effect in this regard and is probably the opioid of choice in these patients.

- **Tolerance/hyperalgesia**

Over time, a shortened duration of action and decreased efficacy of the analgesic may become apparent – requiring greater doses to achieve analgesia. This is probably more of a concern in humans, where opioids are more commonly prescribed over long periods of time for chronic pain. The phenomenon can be readily induced in experimental animals, even after a few days, and clinicians should be aware of its presence. Additionally, opioids may increase rather than decrease sensitivity to noxious stimuli, and this is termed opioid-induced hyperalgesia.

Again, the phenomenon has been demonstrated in laboratory animals following alarmingly short periods of exposure (30 minutes). Both phenomena are likely due to activation of facilitating modulatory systems, and may be reduced by concurrent administration of N-methyl-D-aspartate (NMDA) receptor antagonists, such as ketamine, alpha-2 adrenoreceptor agonists, such as dexmedetomidine, and cyclo-oxygenase inhibitors, such as the NSAIDs.

It would appear that practising good multimodal analgesia may help in this regard, and it is difficult to say how significant tolerance and hyperalgesia are in acute pain management.

It is also possible to antagonise opioids in the case of overdose, where side effects are detrimental to the patient. Naloxone is a pure opioid antagonist and reliably reverses the effects of mu-agonist opioids, as well as the actions of endogenous opioids. It can be administered intravenously or intramuscularly. In a potentially painful animal, administration may result in intense acute pain, so naloxone should be carefully titrated to effect and only used with very good reason. Naloxone is also very short acting (about 20 to 40 minutes) and animals should be carefully monitored for re-narcotisation.

Full mu-agonist opioids may be antagonised with partial agonists, such as buprenorphine, and this is termed sequential analgesia. The advantage of this technique is that some analgesia is retained and buprenorphine is long-acting enough to outlast most full-opioid agonists.

Ketamine

Although unsuitable for analgesia on its own, ketamine is a good adjunctive analgesic when given at sub-anaesthetic doses. It acts by antagonising central NMDA receptors and helps to prevent, and even reverse, central sensitisation. It may also activate opioid receptors and potentiate descending inhibitory pathways.

In a study of dogs undergoing forelimb amputations, ketamine administered as an adjunct to opioids resulted in lower pain scores postoperatively and increased mobility three days post-

surgery. At the doses given in [Table 2](#), it is devoid of significant cardiovascular effects. Occasional dysphoria is seen and if bolus-loading doses are given, dogs may develop strange gazing behaviour. For this reason the loading dose is often omitted in conscious animals.

Lidocaine

Lidocaine (lignocaine) may be given intravenously to provide analgesia and reduce required doses of injectable and inhalant anaesthetics. It is often useful when dealing with pain that appears refractory to other therapies, and is popular as an analgesic for patients with severe pancreatitis. Intravenous lidocaine is also an anti-arrhythmic agent and may be used to treat ventricular arrhythmias. It may also have positive effects on gastrointestinal motility, in the prevention of reperfusion injury, and in reducing the magnitude of the pressor response and cough reflex induced by endotracheal intubation, although these indications are controversial.

At clinical doses, lidocaine is devoid of adverse cardiovascular effects. It should not be used in animals that are unable to metabolise the drug, as toxic effects become more likely. It should be used cautiously in animals that have received concurrent local anaesthetic blocks (such as epidurals) as toxicity is cumulative, irrespective of the local anaesthetic used. Toxicity is manifested by excitatory CNS effects, such as disorientation, twitching and seizures. The dose required to cause seizures is reported to be 11mg/kg in dogs as an IV bolus dose, and this is significantly higher than clinical doses. The infusion should be discontinued if these effects are seen.

Adverse cardiovascular effects are seen at plasma concentrations roughly four times higher. Although the addition of lidocaine is relatively safe in dogs as long as they are healthy and well monitored, it should not be used in cats, as it causes cardiovascular depression at clinical doses. Preparations of lidocaine without adrenaline should be used for CRIs.

Alpha-2 agonists

Occasionally, alpha-2 agonists may be added to these infusions to augment analgesia and provide some sedation. Alpha-2 agonists have potent antinociceptive actions via a number of CNS pathways. Alpha-2 receptors are found in close association with opioid receptors in regions of the brain that are associated with pain, and this may explain the synergistic effects when the drugs are administered together. Due to their profound cardiovascular effects, this should only be considered in relatively healthy, well-monitored patients.

Alpha-2 agonists cause an increase in peripheral vascular resistance and a marked bradycardia. These effects are still seen at very low doses when sedation may not be evident. Dexmedetomidine may be more suitable for administration by infusion than medetomidine, as the inactive enantiomer, levomedetomidine is not present. High doses of levomedetomidine have been shown to enhance the bradycardia and reduce analgesic effects associated with dexmedetomidine. This is not of clinical significance following a single bolus, but may become important after a

prolonged infusion.

Atipamezole is an alpha-2 adrenergic antagonist, which may be used to reverse the effects of medetomidine or dexmedetomidine if problems occur, although antagonism of cardiovascular effects is not complete. There is also a theoretical possibility that administration of atipamezole may reverse opioid effects too, although clinical studies yield conflicting results.

NSAIDs are unsuitable for use by infusion, but are often given concurrently to painful animals, where they may be very effective. There is more potential for renal impairment and gastrointestinal ulceration in critically ill patients, and their use in this group of patients should be subject to a careful risk and benefit evaluation.

Perioperative use

CRIs are suitable for use in animals under anaesthesia – where good analgesia will contribute to good cardiovascular stability as sympathetic stimulation will be reduced. Analgesic agents will dramatically reduce the amount of inhalational and injectable anaesthetics required. Morphine alone may reduce the minimum alveolar concentration (MAC) of isoflurane by up to 60 per cent. MLK infusions appear to reduce MAC by about 45 per cent, although substitution of morphine with fentanyl may reduce MAC by more than 90 per cent. Addition of alpha-2 agonists may cause similarly significant changes in the amount of anaesthetic required. Reducing the concentration of volatile anaesthetic administered reduces associated cardiopulmonary depression and should improve the outcome, especially in higher-risk cases.

Cats

CRIs are also suitable for use in cats, but should always be delivered by a volumetric infusion pump or syringe driver to reduce the risk of overdosage or volume overload. Lidocaine should be avoided and morphine dosages should be reduced to compensate for cats' reduced ability to glucuronidate drugs. A reasonable range for morphine dose rates is 0.05-0.1 mg/kg/ hr (with 0.08 mg/kg/hr recommended as a starting dose). Opioids may cause hyperthermia in some cats, so rectal temperature should be monitored. Ketamine may be used at similar doses to those used in the dog. Anecdotally, opioid infusions appear to improve the temperament of some fractious cats.

Further reading

- Gaynor J S and Muir W (2009). *Handbook of Veterinary Pain Management*, second edition, Mosby, Elsevier.
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- Seymour C and Duke-Novakovski T (2007). *BSAVA Manual of Canine and Feline Anaesthesia and Analgesia*. BSAVA Publications.
- Wagner A E, Walton J A, Hellyer P W, Gaynor J S and Mama K R (2002). Uses of low doses of ketamine administered by constant rate infusion as an adjunct for postoperative analgesia in dogs. *Journal of the American Veterinary Medical Association*, **221**(1): 72-75.



Constant-rate infusions delivered by syringe driver are most suitable for intraoperative and intensive care use.



Analgesic drugs are easily administered when mixed into a bag of intravenous fluid. Bags should always be clearly labelled.

1. Decide on fluid rate: $2\text{ml/kg/hr maintenance requirement} \times 20\text{kg} = 40\text{ml/hr}$.
2. Calculate how many hours of treatment will be contained in one bag: $500\text{ml bag} = 500\text{ml} \div 40\text{ml} = 12.5 \text{ hours}$.
3. Calculate the volumes of analgesic drugs required: Morphine infusion rate = 0.1mg/kg/hr . Morphine required in mg = $0.1\text{mg/kg/hr} \times 20\text{kg} \times 12.5\text{hrs} = 25\text{mg}$. Morphine required in ml = $\text{mg} \div \text{concentration (mg/ml)} = 25\text{mg} \div 10\text{mg/ml} = 2.5\text{ml}$. Lidocaine $50\mu\text{g/kg/min} \times 20\text{kg} \times 60 \text{ minutes} \times 12.5 \text{ hours} = 750,000\mu\text{g} = 750\text{mg}$, which is 37.5ml of a 20mg/ml solution. Ketamine $5\mu\text{g/kg/min} \times 20\text{kg} \times 60 \text{ minutes} \times 12.5\text{hours} = 75,000\mu\text{g} = 75\text{mg}$, which is 0.75ml of a 100mg/ml solution.
4. Remove the volume of liquid from the bag equivalent to the drugs to be added, and then add the drugs. Administer at the predetermined rate.

Table 1. Calculation of analgesic fluid additives for postoperative MLK infusion in a 20kg dog

Drug	Loading dose	Maintenance rate
Morphine	0.1mg/kg	0.1-0.3mg/kg/hr
Fentanyl (intraoperative)	1-4µg/kg	0.1-0.5 (0.2)µg/kg/min
Fentanyl (postoperative)	1-2µg/kg	2-5µg/kg/hr
Ketamine	0.5mg/kg	2-5-10µg/kg/min
Lidocaine	1-2mg/kg	25-50µg/kg/min
Dexmedetomidine	1-2µg/kg	0.25-2 (0.5)µg/kg/hr
The author's initial recommended doses are highlighted in blue.		

Table 2. CRI drug dosages in dogs