Analgesic constant rate infusions in dogs and cats

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Analgesic constant rate infusions (CRIs) have become more popular in recent years and are a very effective way of providing analgesia. This article gives an overview of the most common analgesic CRIs, their indications and practical guidance on how to use them in daily practice. It also considers transdermal analgesia.

The drugs

The medications discussed in this article are not licensed for use in animals and their use must be justified according to the cascade system.

Morphine

Morphine is a pure μ (or OP3) opioid agonist. Using morphine in a CRI in dogs allows a steady-state of analgesia to be achieved and avoids some of the 'peak and trough' effects seen with intramuscular administration. Additionally, its use intraoperatively serves to reduce the amount of volatile anaesthetic gas required. It can be used safely in cats at the low end of the dosing spectrum, but it is advisable to avoid higher rates as this may induce significant dysphoria and excitation.

Morphine is contraindicated with head trauma patients unless CO_2 levels are monitored closely. Opioids marginally increase CO_2 levels in the blood, which has the effect of increasing the cerebral blood flow (CO_2 is one of the major factors in controlling intracerebral blood flow). This can lead to increased intracranial pressure (ICP). Morphine is also known to cause emesis, which would dramatically increase ICP. I and my immediate colleagues have taken to giving maropitant subcutaneously and omeprazole by slow intravenous injection before starting morphine-based CRIs, especially for long surgical cases to reduce the risks of emesis and regurgitation (Panti and others 2009). Anecdotally, this seems to have reduced any postoperative complications, such as oesophagitis or aspiration pneumonia related to sedative levels or nausea associated with morphine usage. Dose rates for morphine control and other drugs discussed in this article are summarised in Table 1.

Fentanyl

Fentanyl is a highly lipid-soluble, short-acting, potent μ opioid agonist with a duration of action of approximately 20 minutes. A benefit of fentanyl over morphine is its increased analgesic effect and the ability to alter dose rates almost instantaneously. For CRIs in hospitalised conscious patients, dosage regimes of 1 to 6 μg/kg/hour do not appear to cause respiratory depression in my experience. However, patients should be monitored closely for its sedative and cardiovascular depressant effects. Bradycardia can be significant and intermittent positive pressure ventilation (IPPV) may be needed under general anaesthesia if bolus doses are required. Dyson (2008) suggests that fentanyl may be preferential to morphine-based CRI in cats due to its short duration of action, thus reducing concerns with regard to overdosing and excitement.

Benefits and potential disadvantages of analgesic CRIs

Benefits

- Provide effective constant analgesia for patients, avoiding the peaks and troughs of traditional intramuscular techniques.
- Allow the veterinary surgeon to alter the dose of medication quickly and effectively to suit the patients' individual needs.
- Reduce the requirement for volatile anaesthetics and allow better maintenance of cardiovascular function during general anaesthesia.
- Distant control of dosing means minimal patient interference - useful in fractious patients as well as allowing vital rest and recuperation in recovering patients.

Potential disadvantages

- High dose rates of some drugs can cause profound bradycardia and respiratory depression.
- Potential increased cost implications to clients due to the requirement for larger drug volumes compared with intramuscular injection techniques.
- Increased set up time – do not underestimate the time taken to set up the infusion and sign out all the drugs properly.
- The need for infusion pumps or syringe drivers to ensure accurate dosing is essential but increases the costs to practices that do not already have this equipment.
- The need for skilled and trained personnel to monitor patients 24/7.

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Lidocaine

The addition of lidocaine to analgesia CRIs has several benefits. It is effective for both superficial and visceral pain (Flaherty 2010). Its mechanism of action is controversial but it is suggested that it activates descending inhibitory pain pathways by binding to M3 muscarinic receptors; it also inhibits glycine receptors and promotes the release of endogenous opioids.

Lidocaine is reported to have some cytoprotective effects and is a free radical scavenger making it potentially helpful with high risk disseminated intravascular coagulation (DIC) or systemic inflammatory response syndrome (SIRS) cases, that is, splenectomies and pancreatitis cases. It also has a significant anaesthetic-sparing effect under general anaesthesia.

Lidocaine has some activity in preventing ileus and I have found it particularly useful when used intra- and postoperatively for gastrointestinal surgeries. It is used routinely in my clinic for all gastric dilatation and volvulus (GDV) patients where it has three main benefits – effective analgesia, improvement of gastrointestinal motility and an anti-arrhythmic effect (Roux 2010).

Various dosage rates of lidocaine have been advocated. In dogs, rates as low as 0.6 mg/kg/hour will provide analgesia, though it may take up to 3 mg/kg/hour for the full cytoprotective and anti-ileus effects. An initial 1 mg/kg intravenous bolus is given to rapidly achieve initial therapeutic blood levels. Plasma levels decrease rapidly when an infusion is stopped. Higher doses cause sedation and, when combined with other analgesics, these effects can be marked. It is important that all patients on CRIs are monitored closely as a potential complication of this sedation is possible aspiration.

Cats are more sensitive to the toxic side effects of lidocaine and hence it is not recommended for analgesia in this species. Signs of toxicity include severe bradycardia and muscle twitching progressing in some cases to generalised convulsions. Some dogs will show nausea and inappetence with lidocaine CRI, but, anecdotally, this seems to be uncommon.

Ketamine

Ketamine is a non-competitive NMDA (N-methyl-D-aspartate) receptor antagonist. NMDA receptors are present in the dorsal horn (DH) of the spinal cord (SC) and certain areas within the brain (Lamont 2008). Blockage of these receptors causes analgesic, amnesic, psychomimetic and neuroprotective effects. By blocking the NMDA receptors, ketamine helps to minimise excessively painful responses. Low doses of ketamine can prevent wind-up and sensitisation of DH cells.

Ketamine potentiates the antinociceptive effects of opioids and α2-agonists by improving receptor sensitivity. It reduces opioid tolerance and minimises the development of rebound hyperalgesia (the phenomenon of markedly increased pain when opioids are withdrawn). This means that giving smaller doses of an opioid in combination with ketamine will produce more effective analgesia with reduced side effects.

The direct effects of ketamine have a duration of action of about 20 to 30 minutes, but recent evidence

Fig 1: Infusion pump with the line tagged with blue Vetwrap to indicate CRI

suggests that it has an effect of reducing longer term hyperalgesia (Flaherty 2010). At CRI 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 should always be used in conjunction with opioids or other analgesics.

Ketamine is also known to be effective at treating neuropathic pain (nerve-based pain). Its use as part of a balanced analgesic regime in amputation cases as an infusion is advised during surgery and for 24 hours beyond where possible (Flaherty 2010).

The side effects of ketamine CRIs include central nervous and cardiovascular system stimulation and respiratory depression (generally at high doses). Low doses tend not to result in these unwanted effects. Dysphoria can be seen, especially in cats, so it is advisable to start with conservative rates. Ketamine has the potential to increase intracranial pressure so should be avoided in head trauma patients. It is important to slowly taper off ketamine-containing CRIs to avoid the potential development of hypersensitivity.

α2-adrenergic agonists

Another agent type that has been useful as an analgesic CRI infusion is low dose medetomidine and dexmedetomidine, both α2-adrenergic agonists. These drugs have shown analgesic properties with few cardiovascular side effects at the doses suggested and tend to result in the reduced dysphoric effects than are seen with opioids (Roux 2010). They can, however, be combined with opioids to maximise their analgesic effects as they appear to have a synergistic action (Lamont 2008).

These drugs exert their effects by interacting with α2-adrenergic receptors in the central nervous system (mainly at the site of the DH of the SC and the locus ceruleus in the brainstem). Side effects include bradycardia, increased left atrial pressure and

Fig 2: Dog on CRI infusion with red Vetwrap indicating cannula placement and blue Vetwrap indicating CRI infusion

reduced oxygen delivery to tissues, which means that they are not suitable agents for haemodynamically unstable patients or those with heart disease (Roux 2010). The drugs are suitable for young active patients in postelective surgery where a small degree of sedation is optimal (Hansen 2008). Sedation tends to be more marked if the patient is hypothermic so postoperative patients should be monitored closely.

Morphine/lidocaine/ketamine (MLK) infusions

MLK is probably the most commonly used combination analgesic CRI. There are various recipes and formulas in the literature which are readily available (an example formula is given in Box 1). An invaluable tool is the online resource www.vasg.org. This site has an excellent range of easily downloadable spreadsheets – to which you can input values, allowing you to make up individual CRIs for your canine patients.

All three drugs are used routinely in dogs and in any combination. However, in cats, the routine use of morphine CRIs is not as common. CRIs can be an effective option if the feline patient is monitored closely for dysphoric trends. Always start at the low end of the opioid CRI dose range in both dogs and cats and titrate up. I have found using fentanyl or fentanyl/ketamine infusions in cats very successful and well tolerated at the low end of the dose range. Watch closely for mydriasis and hyperthermia (Robertson 2008) and remember to always avoid using lidocaine-containing infusions in cats because of their marked side effects.

Some texts suggest protecting the solutions from light – this seems to be a US-based trend and is not routinely advised or performed in the UK (Hansen 2008).

Box 1: Example MLK recipe

10 mg morphine + 150 mg lidocaine + 30 mg ketamine added to a 500 ml intravenous fluid bag of NaCl or Hartmann's.

Give the patient a loading dose of 10 ml/kg of the mixture as a bolus, then infuse at 10 ml/kg/hr.

The benefit of using spreadsheets (such as those available at www.vasg.com) is that you can titrate each CRI analgesic infusion to suit each patient. It is important to remove the volume of drugs from the fluid bag before adding the MLK so that the calculations are still correct, ie:
10 mg morphine (10 mg/ml) = 1 ml
150 mg lidocaine (20 mg/ml) = 7.5 ml
30 mg ketamine (100 mg/ml) = 0.3 ml
Total drug volume = 8.8 ml
Therefore remove 8.8 ml from saline bag before adding the MLK drugs.

Practicalities of CRIs in practice

Patients on CRI are likely to require two or more intravenous lines or at least a dividing giving set to allow you to provide normal fluid support and analgesia separately. This is especially important under general anaesthesia where it is preferable to have the flexibility to alter the fluid rate significantly in response to the patient's status. CRIs need to be accurately controlled and this is only possible when using syringe drivers or infusion pumps. Severe side effects could occur if these potent solutions are left to 'drip in' via more traditional means.

To avoid confusion, I would suggest clearly labelling all lines and infusion pumps as soon as they are set up. My practice uses red Vetwrap to indicate the presence of an indwelling catheter and then uses light blue Vetwrap to indicate if a patient is on a CRI (Figs 1 and 2). To add to your analgesic flexibility and control, you may consider having separate fluid bags of fentanyl and ketamine/lidocaine – this allows the clinician far greater control but does requires further infusion pumps (Fig 3).

Pain scoring is beyond the scope of this article, but it is important to be able to differentiate between patients which are dysphoric because of drug doses being too high and those vocalising due to severe pain (Hellyer and others 2007). This can sometimes be very difficult, but I have found that there is a tendency for dysphoric patients to vocalise in a continuous monotone. A trial dose change is often useful to assess the response to less or more analgesia. The benefit with CRI techniques is that you can quickly alter the analgesia level to assess for this problem, that is, drop the rate if you feel the patient is dysphoric and get the nursing team to monitor it closely for a change in behaviour.

CRIs are a practical and useful in-practice tool, but they need to be used appropriately and with due caution. Without proper monitoring and dose adjustment, conscious patients with CRIs can often become very sedated. Due to the risks of aspiration in these sedated patients, my own view is that 24 hour nursing care is vital when using these techniques. Care should also always be advised when using opiate-based infusions in patients with pre-existing depressed ventilation. Under general anaesthesia, patients on opioid-based CRIs will often need less volatile agents but may need extra ventilatory support due to reduced spontaneous ventilation.

All controlled drugs must be appropriately recorded and stored in a locked secure cupboard. By having spreadsheets dated and specific to each individual, the use of these drugs is much easier to track and monitor.

Fig 3: Multiple infusion pumps allow greater flexibility and control

Fig 4: Fentanyl patch with date of placement and dosage

Transdermal analgesia

Transdermal analgesia is a completely different technique requiring minimal equipment and resources and can be very effective in the correct circumstances. It relies on the drug having a low molecular weight, high lipid solubility and high potency so that it can penetrate the system effectively. At present, the two main drugs used in this manner are fentanyl and buprenorphine.

Transdermal fentanyl

Fentanyl patches (Durogesic DTrans; Janssen-Cilag) can provide very good and effective analgesia in the appropriate patient. Studies seem to show conflicting data regarding the efficacy of these patches (Lee and others 2000); however, my own view is that they do have a role to play in analgesic management in veterinary medicine providing that all animals are continually assessed on an individual patient basis. Some patients may need to be supplemented with additional oral intramuscular full opioid μ agonists or other non-opioid analgesics (Hellyer and others 2007).

The patch selected should be based on a dose of about 2 to 4 μg/kg/hour. For small patients requiring less than a 12 μg patch, just uncover half the patch. Cutting of the patches is not recommended. Before application, the hair should be clipped and the area cleaned gently. Ensure the site is dry before attaching the patch and ensure the person applying the patch wears gloves to avoid inadvertent drug absorption. Warm the patch to body temperature before the application and hold firmly against the skin for at least two minutes to ensure good adherence.

Common sites of placement are on the lateral thorax or back of the neck. Side effects may include inappetence, agitation/dysphoria, sedation and hyperthermia (in cats), but in my own experience, these are rarely seen.

It is important to provide initial additional analgesia while the patch is building up to full therapeutic levels. My clinic uses full opioid agonists (morphine/methadone) at this time to avoid any potential problems with full and partial agonist combinations.

Patients should be fitted with a buster collar to prevent patient self removal and potential ingestion of the patches. The patches are also best covered with a small dressing to help identify and secure the patch – it is advisable to write the drug, dose and date and time on the dressing to avoid any confusion as to when the patch is due for replacement (Fig 4).

Avoid using heat pads on patients with patches in situ as this will significantly increase the fentanyl absorption rate which could cause marked respiratory and cardiovascular depression. Patients need to be well hydrated in order to ensure adequate perfusion of the subcutaneous tissues. There is some debate as to whether to allow patients home with these patches in place due to the potential risks of abuse or accidental ingestion by the patient, or accidental removal of the patch requiring appropriate safe disposal. The author assesses the risk benefit on a case-by-case basis and, if patients are sent home, they are always discharged with written instructions regarding the patches (a useful information sheet can be downloaded from the BSAVA website, www.bsava.com, for this use).

I find the patches very cost-effective and appropriate for cases such as feline road traffic accidents (RTAs), which are likely to require at least two to four days of analgesia, and canine and feline pancreatitis patients requiring ongoing background analgesia. It is important that all patients are regularly re-evaluated regarding their comfort levels when patches are in situ – some patients will require top up analgesia with pure opioids or other analgesics.

Buprenorphine patches

I have no personal experience of using these patches in practice. Robertson (2008) reported that, in cats, plasma concentration levels were very variable and that, over a four-day period, no effective analgesia was achieved.

Table 1 : Dose rates for the drugs discussed in this article

Drug	CRI dose rate	Other notes	Reference
Ketamine	0.12 to 1.2 mg/kg/hr Often used between 0.1 to 0.3 mg/kg/hr	Loading dose of 0.25 to 0.50 mg/kg IV bolus is given to rapidly achieve initial therapeutic blood levels of the drug	White 2008
Fentanyl	2 to 30 µg/kg/hr Start at 1 to 2 µg/kg/hr in both cats and dogs and increase to provide effective analgesia (normally 4 to 6 µg/kg/hr is more than sufficient)	Intraoperatively can give fentanyl at 0.3 to 0.7 µg/kg/min Loading doses – 2 to 3 µg/kg IM or IV Fentanyl – Sublimaze 50 µg/ml (Janssen-Cilag)	White 2008 Hansen 2008
α2 adrenergic agonists	Medetomidine 1 to 2 mg/kg/hr Dexmedetomidine 0.5 to 1 ug/kg/hr		Roux 2010
Fentanyl patch	2 to 4 µg/kg/hr	In dogs, the patches provide 72 hours of constant analgesia, but it takes up to 24 hours till peak effect In cats, the patch provides up to 120 hours analgesia and takes approximately 8 hours to peak effect	Flaherty 2010
Lidocaine (dogs only)	0.6 to 3 mg/kg/hr	Commonly use 1.5 mg/kg/hour initially and assess response An initial 0.5 to 1 mg/kg IV bolus is given to rapidly achieve initial therapeutic blood levels	Stein and Thompson 2004
Morphine	0.12 to 0.36 mg/kg/hr	If no previous µ agonist has been given, administer 0.25 to 0.5 mg/kg of morphine IM (or very slowly IV) to rapidly achieve initial therapeutic blood levels	Dyson 2008

IV Intravenously, IM Intramuscularly

Summary

Analgesia in small animal practice is an exciting and rapidly changing area. Even throughout the course of writing this article, attitudes and thoughts have changed. It is vital that we keep ourselves abreast of the current thinking in this field of expertise, and make progress from the values that, not long ago, suggested that pain was good as it helped keep patients more rested after surgery! I hope that this article goes some-way to encouraging other practitioners to try newer analgesic techniques with more confidence. I would suggest always starting with low doses and slowly titrating up to provide optimal analgesia. This approach should be safe for both you and your patients and avoid confidence issues with newer drugs and techniques.

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