CONSTANT RATE INFUSIONS: DON'T CRY – USE CRI

Tamara Grubb, DVM, PhD, DACVAA
President-Elect International Veterinary Academy of Pain Management

Constant rate infusions (CRI) of analgesic drugs are an excellent way to manage pain in both dogs and cats. A CRI of analgesic agents has several advantages over multiple repeated injections for pain relief, including:

1. A more stable plane of analgesia with less incidence of break-through pain (which can be difficult to treat);
2. A lower drug dosage delivered at any given time, resulting in a lower incidence of dose-related adverse effects;
3. Greater control of dosing (easy to make small adjustments, both up and down);
4. Decreased need for stimulation of resting patients to repeatedly administer drugs; and
5. Decreased cost (when compared to technician time, needles and syringes required for repeat injections).

Drugs that are useful for CRIs include fentanyl, hydromorphone, morphine, methadone, butorphanol, ketamine, lidocaine and a myriad of combinations of these drugs. Dosages are at the end of the notes.

Opioids: The opioid class of drugs includes some of the most potent analgesic drugs available and opioids should be considered for any patient experiencing moderate to severe pain. Although opioids are generally sedating in dogs, they can cause excitement in cats. Fortunately, the low dose of opioids delivered in a CRI rarely results in sedation or excitement. However, if excitement does occur, a light dose of a sedative (eg, acepromazine or dexmedetomidine) can be administered to the cat and the CRI rate maintained (if excitement is mild) or reduced (if excitement is moderate). If sedation occurs, the dose of the CRI can be decreased. Fentanyl, hydromorphone, morphine and methadone are potent full agonist opioids that provide profound dose-related analgesia. These full agonists are the most commonly used opioids but butorphanol, an agonist-antagonist, has an advantage in that this drug is more likely to provide sedation than excitement in cats. However, butorphanol provides only moderate analgesia and has a ceiling effect for pain relief (ie, a point is reached where higher dosages result in more sedation but not more analgesia). Thus, butorphanol is only appropriate for short-term mild to moderate pain and should be used as part of a multi-modal protocol rather than as a sole agent.

Lidocaine: Lidocaine can be administered systemically to provide analgesia. In addition to pain relief, lidocaine administered as an infusion has anti-inflammatory, antiarrhythmic and anti-endotoxic effects and improves postoperative GI function (proven in humans and horses – work still to be done in dogs and cats). The mechanism of action of systemic lidocaine is not entirely clear. Proposed mechanisms include blockade of sodium channels or potassium currents in the dorsal horn of the spinal cord and direct inhibition of abnormal electrical charges from injured or inflamed peripheral nerves. Lidocaine CRIs are extremely useful in dogs but are somewhat controversial in cats because: 1) cats appear to be more sensitive to the lidocaine-induced side effects than other species are, and 2) there is evidence that lidocaine may cause excessive cardiovascular depression in cats. Point 1 is potentially (although not unequivocally) true and a lower dosage of lidocaine is recommended for cats than is recommended for dogs. Point 2 has been reported in anesthetized cats and the cardiovascular depression could result from a physiologic interaction between lidocaine and anesthetic drugs. Also, some argue that lidocaine CRI has been used successfully for anti-arrhythmic therapy in cats without undue cardiovascular depression and should be appropriate for analgesia, especially since the dose for analgesic therapy is actually on the low end of the dose used for anti-arrhythmic therapy. Because of the uncertainty of lidocaine effects in cats, some veterinarians feel that lidocaine CRI is not warranted in cats at all while

others feel that it is an appropriate means to treat pain, especially in patients where other options may be limited. If lidocaine CRI is chosen, using low dosages in conscious cats (ie, not under anesthesia) is recommended. Lidocaine CRIs are commonly used in dogs, especially in dogs with gastro-intestinal pain (eg, pain from exploratory laparotomy, gastric dilatation-volvulus [GDV], pancreatitis, parvovirus, etc…).

Ketamine: Painful impulses cause N-methyl-D-aspartate (NMDA) receptors (among others) in the dorsal horn of the spinal cord to depolarize and prolonged depolarization of these receptors can lead to an amplification of the pain stimulus, resulting in what we commonly refer to as 'wind-up' or 'hypersensitization', and technically called 'central sensitization'. When this occurs, the patient may feel more pain than expected (hyperalgesia) or even feel pain in response to a non-painful stimulus (allodynia). By administering drugs that antagonize these receptors (like ketamine), central sensitization can be alleviated, making pain easier to control. The analgesic effects of ketamine are achieved when administered as a low-dose CRI. A single high-dose bolus of ketamine (eg, like the anesthetic induction dose) can serve as a loading dose for a CRI but the analgesia effect from a single dose is unknown. Furthermore, the NMDA receptor antagonists strictly mediate central sensitization and do not provide true analgesia, thus, these drugs must be administered in conjunction with true analgesic drugs (eg, opioids or NSAIDs). This does not mean that ketamine must be administered with other drugs in the infusion, just that the patient must be receiving other analgesic drugs by some route.

Alpha-2 agonists: Alpha-2 agonists (generally medetomidine or dexmedetomidine in small animals) provide both sedation and analgesia and the effects are reversible. Because the infusion dose is very low, the patient is usually calmed but not sedated, but light sedation can be achieved if desired. The calming/light sedation makes this CRI very useful in patients that are excited or distressed. The alpha-2 agonists are generally added to an opioid CRI (or any other CRI) but can be used as a solo infusion.

Combinations of opioids, ketamine, and (possibly) lidocaine: CRIs that include multiple, rather than single drugs, are often more effective because the analgesic effects achieved by using different drug classes are generally synergistic. Combinations include opioids + ketamine or opioids + ketamine + lidocaine. However, infusions of a single drug are also effective, especially if the patient is receiving drugs administered by other routes (eg, oral or injectable NSAIDs and/or local anesthetic via tissue blockade) and the choice of multiple or single drug infusions is more personal preference than science.

Calculations of CRI dosages: Generally, dosing tables or individualized spread sheets should be used for constant rate infusions. These spreadsheets are technically 'calculators' which greatly improve the speed at which CRIs can be initiated and greatly decrease the chance of mathematical errors. There are very useful spreadsheets or 'calculators' available at multiple websites, including an excellent calculator at **IVAPM.org.** There is more information on calculations and calculators at the end of the notes. CRI dosages can also be easily calculated using the formula:

- A = desired dose in microg/kg/min OR mg/kg/hr
- B = body wt in kg
- C = Diluent volume in mls
- D = Desired fluid rate in mls/hr
- E = Drug concentration in mg/ml

For microg/kg/min: A x B x C x 60 / D x E x 1000 = mls of drug to add to diluent
For mg/kg/hr: A x B x C / D x E = mls of drug to add to diluent
NOTE: If the dose at A is in mg/kg/hr, the two conversion factors in the formula (60 in the numerator and 1000 in the denominator) should be removed from the formula.

Loading doses: Administering loading doses of the drugs to be infused is important since the loading dose provides a rapid increase in the serum concentration of the drug. The serum concentration of the drug will slowly increase with the infusion, but this may delay time to onset of analgesia. A separate loading dose for opioids or alpha-2 agonists may not be necessary if these drugs were used as premedicants and a separate loading dose for ketamine may not be necessary if ketamine was the induction drug. However, if a long delay (>30 mins) occurred between administration of these drugs and the start of the infusion, administer the loading dose. The loading dosages are very low and extremely unlikely to cause adverse effects so, if in doubt, administer the dose.

How to deliver: The easiest, most efficient and most accurate way to deliver infusions is to use an infusion pump. Infusions pumps will easily pay for themselves by allowing smaller volumes of drugs to be drawn up, thus decreasing waste. Syringe pumps can also be used in patients that require very small IV fluid volume (like cats/kittens/puppies) to ensure that volume overload does not occur. So multiple reasons to have a syringe pump! However, drugs can be easily administered by counting drops from fluid bags with the analgesic drug in the bag. When using a fluid bag, the bag is usually a separate bag from the regular IV fluids, at least intraoperatively. This is because anesthetized patients often need a bolus of IV fluids to support blood pressure and we don't want drugs in that bolus. Ketamine may be an exception since the dose is so very low. Postoperatively or in any other stable patient (trauma patient that has been volume stabilized, patients with medical pain like pancreatitis, etc…) the drugs can be placed directly in the IV fluids if desired. More information is at the end of this handout.

When to start/stop: Start as soon as possible! As soon as a painful patient has an IV catheter in place, consider a CRI. For patients with pain from trauma (eg, hit-by-car or attacks from other animals) or medical conditions (eg, pancreatitis), pain relief is a component of stabilization and infusions can be started immediately after triage. For patients undergoing surgery, start the infusion prior to anesthesia if possible since pre-emptive analgesia is more effective than analgesia that is administered after pain has started. Often surgical patients do not have an IV catheter prior to induction so for these patients, start right after induction or when the patient has been moved into the operating room. Infusions can be started postoperatively if the need for an infusion was not recognized until the postoperative period. It is never too late to start! However, infusions should be started pre- or intra-operatively whenever possible so that the patient can benefit from infusion-delivered intraoperative analgesia and infusion-mediated decreases in the dosage of inhalant drugs necessary to keep the patient anesthetized. The infusion can be stopped at the end of surgery if appropriate on-going analgesia (eg, NSAIDs, local blocks, etc….) has been administered, or the infusion can be continued for several hours, overnight, or even several days. The infusion duration should be based on the continued analgesic need of the patient. Patients with severe medical (eg, from pancreatitis) or trauma pain often remain on infusions for several days. If the analgesic level of the patient is questionable, the infusion can be slowly weaned off by cutting the dose in half every 1-2 hours and carefully assessing the patient's pain.

SUMMARY: Constant rate infusions are extremely easy to use and extremely beneficial to the patient. A variety of drugs can be used in the CRI and drug choice should be based not only on what is best for the patient (eg, analgesic potency and safety) but also on what is best for the hospital (eg, comfort level with and availability of drugs). Because calculating CRI dosages can be cumbersome, math is often the only limitation to using these valuable tools. Thus, rather than calculating drug dosages for each CRI, a CRI calculator (IVAPM.org, etc…) and/or dosing sheets (as in this document) are recommended.

TABLE 1: Dosages for constant rate infusions (CRIs) used in CATS. Administer all infusions in this table at 1 ml/kg/hr.

Drug	Loading Dose **mg/kg IV unless indicated**	CRI dose **mg/kg/hr unless indicated**	Quick Calculation* for **mg/kg/hr** unless indicated	Comments **This spread sheet is designed for drugs added to 500 ml fluid and fluid rate of 1 ml/kg/hr.**
Morphine (M)	0.10 IM	0.05-0.1	Add 30 mg for 0.06 mg/kg/hr	Cat may need light sedation; can be combined with K &/or L
Hydro-morphone (H)	0.025	0.01-0.02	Add 5 mg	May cause hyperthermia; can be combined with K &/or potentially L
Fentanyl (F)	0.001-0.003	Intraop: 0.003-0.04 (0.05-0.7 mic/ kg/min; Postop: 0.002-0.010 (0.03-0.2 mic/kg/min)	Add 2.5 mg for 0.005	2.5 mg=50 ml F, remove 50 ml LRS before adding F; can be combined with K &/or L.
Methadone	0.1-0.2	0.12	Add 60 mg	MAY cause sedation; can be combined with K &/or potentially L
Butorphanol	0.1-0.2	0.1-0.2	Add 50 mg for 0.1	Only moderately potent & has ceiling effect - use as part of multimodal protocol
Ketamine (K)	0.5	0.12-0.6 (2 -10 mic/kg/ min) Intraop dose=10 mics	Add 60 mg for 0.12	Generally combined with opioids; might cause dysphoria (but unlikely)
Lidocaine (L) ***Controver-sial in cats**	0.25 Some recommend skipping loading dose in cats	1.5 (25 mic/kg/min) Some sources recommend ≤10 mic/kg/min in cats. Some recommend no lidocaine in cats.	Add 750 for 25 mic/kg/min and 300 for 10 mic/kg/min	750 mg=37.5 ml, remove 37.5 ml LRS before adding L; can be combined with opioid &/or K; **Controversial in cats due to cardiovascular effects.**
Medetomi-dine (Med) or Dexmedeto-midine(D)	0.001-.005 Med 0.0005-0.002 D IV or IM	0.001-0.004 mg/kg/hr Med 0.0005-0.002 mg/kg/hr D	Add 500 mic Med or 250 mic D (0.5 ml of either) for low end dose	Provides analgesia and light sedation. Excellent addition to opioid CRI or can be administered as solo drug CRI.
Morphine / Ketamine	M: 0.10 IM K: 0.5 IV	0.05 M 0.12 K	Add 25 mg M & 60mg K	Can be administered up to 3 ml/kg/hr but might case dysphoria. Can substitute, F, or methadone for M.
Morphine / Lidocaine/ Ketamine (MLK)	M: 0.10 IM L: 0.25 or NONE K: 0.5	0.05 M 1.5 or 0.75 L 0.12 K	Add 25 mg of M, 750 mg (or 300 mg) L 60 mg K	Can substitute H, F or methadone for M.

*Any of the drug amounts in the bag of fluids can be decreased and the fluids administered at a higher rate if necessary. For example, for morphine, ketamine and morphine/ketamine infusions, 7.5 mg of morphine & 30 mg of ketamine can be used and the CRI administered at 2 ml/kg/hr if more fluids are needed.

TABLE 2: Dosages for constant rate infusions (CRIs) used in DOGS. Administer all infusions in this table at 1 ml/kg/hr.

Drug	Loading Dose **mg/kg IV unless indicated**	CRI dose **mg/kg/hr unless indicated**	Quick Calculation* for **mg/kg/hr** unless indicated	Comments This spread sheet is designed for **drugs added to 500 ml fluid and fluid rate of 1 ml/kg/hr.**
Morphine (M)	0.25 SLOWLY IV or 0.5 IM	0.12-0.3 mg/kg/hr (2.0 mic/kg/min- 5.0 mic/kg/min)	Add 60 mg for 0.12 mg/kg/hr	MAY cause sedation; can be combined with K &/or L.
Hydromor-phone (H)	0.05-0.1	0.01-0.05 mg/kg/hr	Add 10 mg for 0.02	MAY cause sedation; can be combined with K &/or L.
Fentanyl (F)	0.002-0.005	Intraop: 0.003-0.04 mg/kg/h (0.05-0.7 mic/kg/min); Postop: 0.002-0.010 mg/kg/h (0.03-0.2 mic/kg/min)	Add 2.5 mg for 0.005	2.5 mg=50 ml F, remove 50 ml LRS before adding F; can be combined with K &/or L; Intra-op up to 0.02-0.04 mg/kg/hr
Methadone	0.1-0.2	0.12-0.3	Add 60 mg for 0.12	MAY cause sedation; can be combined with K &/or L.
Butorphanol	0.1-0.2	0.1-0.2	Add 50 mg for 0.1	Only moderately potent & has ceiling effect - use in multimodal protocol
Ketamine (K)	0.5	0.12-0.6 (2 -10 mic/kg/ min)	Add 60 for 0.12 and 120 mg for 0.24	Generally combined with opioids; may cause dysphoria; intra-op dose is high end of range
Lidocaine (L)	0.5 – 1.0	1.5-3.0 (25-50 mic/kg/min)	Add 750 mg for 25 mic/kg/min	750 mg=37.5 ml, remove 37.5 ml LRS before adding L; can be combined with opioid &/or K.
Medetomi-dine (Med) or Dexmedeto-midine(D)	0.001-.005 Med 0.001-0.002 D IV or IM	0.001-0.004 Med 0.0005-0.002 D	Add 500 mic Med or 250 mic D (0.5 ml of either) for low end dose	Provides analgesia and light sedation. Excellent addition to opioid CRI, or can be administered as solo drug CRI.
Morphine / Ketamine	M: 0.25 slow IV or 0.5 IM K: 0.25-0.5 IV	0.12 M & 0.12 K	Add 60mg M & 60mg K	Can be administered up to 3 ml/kg/hr but sedation or dysphoria MAY occur. Can substitute H, F or methadone for M
Morphine / Lidocaine/Ket amine (MLK)	M: 0.25 slow IV or 0.5 IM L: 0.5 K: 0.25-0.5	0.12 M 1.5 L 0.12 K	Add 60 mg of M, 60 mg K & 750 mg L	Can substitute H, F or methadone for M.

*Any of the drug amounts in the bag of fluids can be decreased and the fluids administered at a higher rate if necessary. For example, for morphine, ketamine and morphine/ketamine infusions, 30 mg of morphine & 30 mg of ketamine can be used and the CRI administered at 2 ml/kg/hr if more fluids are needed.

Table 3: SAMPLE Chart for adding analgesic drugs to IV fluids for dogs (appropriate if the IV fluid rate is unlikely to change – if the patient might need a fluid bolus it is better to have the CRI in a separate fluid bag or syringe)

Amount of **lidocaine**[+] (20 mg/ml) to add to a 1-L fluid bag:

Fluid Rate:	Maintenance* (50 ml/kg/ 24hr)	1/2 Maintenance	2x Maintenance	Surgical (5-10 ml/kg/hr)
Lidocaine Dose:	Amount of **lidocaine** (20 mg/ml) to add to a 1-L fluid bag:			
25 microg/kg/min	36 mls	72 mls	18 mls	15 mls (5 ml/kg/hr) 7.5 mls (10 ml/kg/hr)
50 microg/kg/min	72 mls	144 mls	36 mls	30 mls (5 ml/kg/hr) 15 mls (10 ml/kg/hr)
75 microg/kg/min	108 mls	216 mls	54 mls	45 mls (5 ml/kg/hr) 22.5 mls (10 ml/kg/hr)

***** Maintenance is generally considered as 40-60 mls/kg/24 hrs, with the lower end of that rate used in cats. If the infusion rate is halved, the amount of lidocaine in the bag should be doubled to keep the dose constant. [+]Volumes are rounded to nearest whole milliliter or to one decimal point if <1 ml. Before adding the lidocaine, remove the same volume of LRS as you will be adding of lidocaine. Lower dosages (25-50 microg/kg/min) are used for analgesia while all 3 dosages are used for antiarrhythmic therapy.

QUICK CALCULATION: You can split the difference on the two analgesic dosages and administer 36 microg/kg/min: add 50 mls of 2% lidocaine to 1-L of LRS and administer at 0.5 ml/kg/hr.

Amount of **morphine**[+] (15 mg/ml) to add to a 1-L fluid bag:

Fluid Rate:	Maintenance* (50 ml/kg/24hr)	1/2 Maintenance	2x Maintenance	Surgical (5-10 ml/kg/hr)
Morphine Dose:				
0.5 microg/kg/min (cat dose)	1 ml	2 mls	0.5 mls	0.40 mls (5 ml/kg/hr) 0.20 mls (10 ml/kg/hr)
1 microg/kg/min	2 mls	4 mls	1 ml	0.80 mls (5 ml/kg/hr) 0.40 mls (10 ml/kg/hr)
2 microg/kg/min	4 mls	8 mls	2 mls	1.60 mls (5 ml/kg/hr) 0.80 mls (10 ml/kg/hr

***** Maintenance is generally considered as 40-60 mls/kg/24 hrs, with the lower end of that rate used in cats. If the infusion rate is halved, the amount of lidocaine in the bag should be doubled to keep the dose constant. [+]Volumes are rounded to nearest whole milliliter or to one decimal point if <1 ml.

QUICK CALCULATION Ketamine CRI: Add 60 mg (0.6 mls of 100 mg/ml) ketamine to a 1-L bag and run at 2 mls/kg/hr to provide 2 microg/kg/min or at surgical fluid rate (10 ml/kg/hr) to provide 10 microg/kg/min (intra-op dose).

QUICK CALCULATION: Morphine/Lidocaine/Ketamine (MLK; from Dr. Muir – my doses are a little lower):

To a 500 ml bag of LRS add:

–10 mg morphine (0.66 cc)
–120 mg lidocaine (6.0 cc 2%)
–100 mg ketamine (1.0 cc)

Administration at10 ml/kg/hr will deliver:

morphine 0.2 mg/kg/hr
lidocaine 2.5 mg/kg/hr
ketamine 2.0 mg/kg/hr

Calculating Constant Rate Infusions (for people that really like math☺).

For drugs that don't need dilution (ie, many drugs – if not too concentrated - delivered by infusion pump):

How many total mgs or microgs do you need?

Dose of infusion in mg/kg/hr or mic/kg/min or whatever (lets use mg/kg/hr for now) x body weight in kg = total mg/hr needed

Now divide the calculated mg/hr by the concentration of the drug in mg/ml and now you have the mls/hour

If you divide this by 60, you get the mls/min; divide by 60 again and you get the mls/second and most drip sets are either 10 drops/ml or 60 drops/ml and you can figure out how many drops/second the patient needs by multiplying the number of drops/ml by the number of mls/second. Of course if you have a syringe pump, you can stop at mls/min and just program the pump!

SO, a dog weighs 40 kg and needs a CRI of 5 mg/kg/hr and the drug is 0.2%.

5 mg/kg/hr x 40 kg = 200 mg/hr divided by 2 mg/ml = 100 ml/hr (program the pump now or move on to drops)

100 ml/hr divided by 60 = 1.666, divide by 60 again = 0.027 x 10 drops/ml = 0.2 drops/second or (to make counting easier) 1 drops per every 5 seconds

For drugs that need dilution (ie, very concentrated drugs administered by syringe pump or drugs administered in bags of fluids):

Again calculate out the number of mg/hr that you need.

Decide the fluid rate you want to deliver in ml/kg/hr. Multiply this by the body weight to get the mls/hour.

We need to deliver 'x' mg/hr of a drug in 'x' mls/hr of a drug so all we need to do is figure out how many mgs that we need in each ml. Do this by dividing mg/hr by mls/hr and that gives us mg/ml.

Now just multiply the total number of mls you plan to deliver (eg, 500 mls, 1-liter, etc…) and that gives you the number of mgs that you need to put in the fluids.

Finally divide these mgs by the concentration of the drug and you have the number of mls to add to the fluid.

SO, a dog weighs 20 kg and needs a CRI of 5 mg/kg/hr and a fluid rate of 2 ml/kg/hr and we have 1 liter of fluids and a drug that is 0.5%.

5 mg/kg/hr x 20 kg = 100 mg/hour. 2 ml/kg/hour x 20 kg = 40 ml/hour. 100 mg/hour / 40 ml/hour = 2.5 mg/ml. 2.5 mg/ml x 1000 mls = 2500 mg. 2500 mg / 5 mg/ml = 500 mls of the drug to add to the 1-L of fluids.

(For all you math whizzes, you probably see that the kgs could be deleted from this formula and it would still work! Regardless of the wt, you would add 250 mls of the drug to 1000 mls of the fluid and deliver at 2 ml/kg/hr to get 5 mg/kg/hr.)

To make math REALLY easy, use a CRI calculator or an excel spreadsheet. An excellent calculator is available through the International Academy of Pain Management (IVAPM.org). It is open access to all – just click on the Professionals tab and open up the calculator! There are also numerous spreadsheets in the members sections of VIN (of course there are many sources – these are just some ideas). FAQ for the IVAPM calculator: 'Three-drug and one-drug calculations are available. What do I do if I want to use a two-drug combination?' Answer: Use the 3-drug choice and put a zero in the dose for the drug you don't want. For instance, if you want a combination of morphine and ketamine, but not lidocaine, choose the morphine/ketamine/lidocaine infusion and choose zero for the lidocaine dose.