Management of severe pain in small animals continues to be a challenge to veterinarians and veterinary technicians. The patients can be in severe pain when presented because of a primary disease or subsequent to a painful surgery. There are many modalities and drugs used to control pain in these patients. An analgesic drug is most frequently given in an intermittent and scheduled fashion. There are instances where the scheduled administration is not followed when the animal unexpectedly shows signs of severe pain. The focus of this presentation is on the use and techniques of constant rate infusion (CRI) for pain control in small animal patients.

The objective of CRI is to maintain a stable plasma or tissue concentration of the drug in the body. This can only be achieved by administering drug at a constant rate. Once a drug is administered, part of it is also eliminated. A steady state is considered to be achieved if the rate of infusion matches the rate of elimination. This relationship is illustrated using this formula:

\[
\text{Concentration at steady state (C}_{p}^{ss}) = \frac{\text{Infusion rate}}{\text{Body clearance of the drug (}\beta \cdot V_{d}^{'}})
\]

For simplicity, it is important to remember that a steady state can be achieved in an efficient manner by giving a bolus dose and then starting the infusion thereafter. There will be a delay between the start of an infusion and the establishment of a steady state. The longer the half-life of the drug, the longer it takes to reach a steady state or plateau. By 5 half-lives, it is noted that the amount of drug in the body provided by the infusion will reach 97 percent of the steady state value. During anesthesia, when a drug is given as a premedicant or part of anesthetic induction, a separate bolus dose is not necessary prior to starting the CRI of that drug.

Advantages and disadvantages

CRI of analgesic agents provides some advantages compared with other modes/routes of administration. CRI prevents the sudden peaks and valleys associated with intermittent IV boluses and IM injection. With IV boluses, there is a fast rise in plasma concentration which may result in adverse effects. It is also possible that drugs with rapid elimination given as IV boluses rapidly fall below the therapeutic levels. Even with IM and subcutaneous injections, the blood level can go below the therapeutic range. In painful patients, this will lead to breakthrough pain making the pain control more difficult. Because of the constant plasma drug concentration with CRI, pain control will be uniform and consistent. Based on our clinical experience, CRI appears to be a very effective technique in patients that are in severe pain. Depending upon the condition and response of the patient, the rate of infusion can also be changed to produce the desired effect. CRI of analgesic agent will also result in less total amount of drug used to provide pain control compared with intermittent administration. CRI has also been shown to result in faster recovery from the drug effect. This finding can be useful in patients that have worsening hemodynamic condition. Terminating the CRI will result in quicker lowering of the plasma drug concentration.

There are reasons why IV CRI is not as widely used as the other routes of administration (IV boluses, IM or SC). CRI should be administered using an in-dwelling IV catheter. This requires constant supervision by a staff member since the IV lines can be disconnected or kinked. To administer drugs accurately with CRI, the use of syringe pump is helpful. Unfortunately, syringe pumps are still relatively expensive (about $1,500 per unit). Some drugs used in CRIs are not extensively studied. The best infusion rates for different conditions need to be determined. In general, these drugs are administered to effect. These drugs can accumulate in
the body if given for a long time resulting in adverse effects. If the infusion takes longer than a day, the patient should be evaluated closely and the infusion rate should be adjusted accordingly. Further studies are needed to determine the best protocol for prolonged administration (greater than 24 hours). Different drugs may be used simultaneously in line with a multimodal approach to providing analgesia. This presents additional question as to the stability and compatibility of these drugs when mixed together. When toxicity develops, it is difficult to ascertain the specific drug that is responsible for the adverse effect. Despite these disadvantages, CRI has its definite place in pain control.

**Drugs**

Some drugs have to be given as CRI because of their short half-life and high potency. The drugs used in CRI for pain control do not necessarily have to possess a short half-life. These drugs are given as CRI to avoid the peaks and troughs associated with repeated IM or IV injections.

**Opioids**: Opioids combine with opioid receptors in the CNS and periphery providing analgesia. This group of drugs is considered to be the most effective analgesic. The opioids that can be used for CRI are morphine, hydromorphone, fentanyl, methadone, and butorphanol. For severe pain, the full agonist opioids (morphine, hydromorphone, methadone, or fentanyl) are preferred because they are more efficacious. Efficacy is defined as the amount of drug that will produce the maximum effect. As the dosage of these drugs is increased, the effect produced also increases. This is in contrast to the agonist-antagonist (butorphanol) that has a ceiling effect on analgesia.

There are adverse effects associated with the use of full agonist opioids. The most common ones are sinus bradycardia, vomiting, defecation, dysphoria, respiratory depression and urinary retention. Critical patients with head trauma, seizures, depressed or debilitated should be monitored very closely when an opioid is administered as respiratory depression can become profound in these patients. The dose should be adjusted based on the mental state of the patient and oxygen be provided to minimize hypoxemia secondary to hypoventilation. Clinically, the degree of hypoventilation caused by opioids is related to the degree of CNS depression. The danger of hypoventilation remains very low in patients that are conscious and responsive.

Dysphoria is a known side effect of opioids. It has been reported in 30% of dogs that received CRI morphine. In this study, all dogs showing dysphoria were Greyhounds. In practice, other breeds have shown dysphoria and it can easily be managed using anxiolytic or sedatives like diazepam or acepromazine. If a sedative is given, the lowest dose possible should be tried first. Opioid overdose will lead to higher blood concentration and possible dysphoria. The best way to manage this is to give diluted naloxone very slowly until the undesired signs disappear.

Vomiting appears to be less common with fentanyl, hydromorphone, methadone, and butorphanol compared with morphine. In general, IM injection of opioid is associated with more vomiting when compared with IV. However, in a limited number of dogs comparing IM and CRI morphine, both groups had the same frequency of vomiting (2/10 dogs). In addition to vomiting, opioids also increase the duodenal, biliary, esophageal, and anal sphincter tone. It is best to avoid opioids in patients with obstructed biliary tract or biliary neoplasm.

For opioids, the bolus dose is necessary and then followed by CRI. All full agonist opioids mentioned above are suitable for patients in severe pain. Opioid should be part of a multimodal approach to pain management in dogs and cats. The factors affecting the decision of
clinicians include cost and familiarity with the certain drugs. The duration of the infusion will depend mostly on the course of the clinical disease and the presence of adverse effects.

**Lidocaine**: Lidocaine is a local anesthetic that has been used in CRI for providing analgesia. The analgesia produced by lidocaine has been attributed to sodium ion channel blockade in neuronal cells and membrane stabilization. Lidocaine has been shown to reduce the anesthetic requirement for inhalant anesthetic, decrease the amount of opioids needed for postoperative pain and minimize neuropathic pain. The postoperative effect of lidocaine still exists even when it has already been eliminated from the body partially because its metabolites have also analgesic properties. In addition to analgesia, lidocaine also has antiarrhythmic, anti-inflammatory, antishock, free radical scavenging and gastrointestinal promotility properties. It is a good choice for patients with nerve injury and gastrointestinal problems.

When administered at an infusion rate higher than the recommended dose, patients will exhibit signs characteristic of CNS stimulation. The signs will include nervousness, agitation, excitement, and seizure. Further signs of toxicity will be manifested as cardiovascular depression: hypotension, cardiac output reduction, and bradyarrhythmias. These effects may become worse in really sick patients because of their dependence on the sympathetic nervous system activity for survival. It is advisable not to use lidocaine in patients with high grade 2\textsuperscript{nd} or 3\textsuperscript{rd} degree atrioventricular block because it will suppress the ventricular escape beats. Any sign of agitation and excitement in a patient receiving CRI lidocaine should signal the possibility of toxicity and the infusion should be stopped. It is prudent to investigate the rate of infusion and ensure that the infusion rate is correct before the CRI lidocaine is started again.

Cats appear to be very sensitive to the cardiovascular depressant effects of lidocaine. It is recommended not to use lidocaine CRI in cats.

**Ketamine**: Ketamine produces analgesia by its antagonistic effect on the N-methyl-D-aspartate (NMDA) receptors. Stimulation of NMDA receptors is associated with CNS sensitization. To antagonize the NMDA receptors, microdose of ketamine is used. It is important to remember that ketamine by itself will not provide adequate analgesia and should be used with an opioid. During anesthesia, infusion rate of 0.6 mg/kg/hour (10 μg/kg/min) is used. The lower dose rates of 0.18-0.3 mg/kg/hour (3.0-5.0 μg/kg/min) are used postoperatively and in other painful non-surgical patients. The use of ketamine has been shown to reduce the tolerance of patients to opioids.

**Dexmedetomidine**: Dexmedetomidine produces analgesia by stimulating the α\textsubscript{2}-adrenergic receptors in the brain and spinal cord. These receptors are located at various sites in the pain pathway. The activation of α\textsubscript{2}-adrenergic receptors in the dorsal horn of the spinal results in the release of substance P. CRI of dexmedetomidine can be used intraoperatively and postoperatively. Dexmedetomidine reduces the requirement for inhalant anesthetic. Postoperatively, dexmedetomidine is given in patients that continue to vocalize and show signs of restlessness and agitation despite repeated administration of opioid and acepromazine. When given for this condition, it is difficult to determine if the dexmedetomidine has significant analgesic property.

**Methods of providing CRI**

Better analgesia can be provided to patients using a combination of an opioid, ketamine, and lidocaine. With more than one drug involved, administering the correct dosages becomes a challenge. There are two main methods of administering the infusions: (1) use of syringe pump

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and 2) “bag” technique which involves adding the drug(s) to the bag of crystalloid and administering it as maintenance fluid in most cases.

Syringe pumps are big-ticket items for veterinary clinics. However, their main advantages are accurate drug dosing, no dilution required, and less drug waste. If different drugs are to be given simultaneously, one syringe pump per drug is an option. If only one syringe pump is used, the three drugs will be mixed in one syringe and the syringe pump will be set to deliver at milliliters per hour. This is the preferred technique during anesthesia.

The “bag” technique can be utilized and the rate of administration will be the maintenance fluid rate. This rate can be more accurately administered using a volumetric infusion pump. The question then is how much of the drugs are to be added to the fluid bag. Using the following equation, the amount of the drug in milligrams will be known:

\[
\text{Drug (mg)} = \left(\frac{\text{Infusion rate of the drug (mg/kg/hour)}}{\text{Fluid infusion rate (ml/kg/hour)}}\right) \times \text{diluent volume (ml)}
\]

To apply this formula, a 20-kg dog that needs maintenance fluid and a CRI of morphine, lidocaine, and ketamine will be used as an example.

These are the rates that will be used in this example:
- Maintenance fluid rate - 2.0 ml/kg/hour
- Morphine CRI dose - 0.1 mg/kg/hour
- Lidocaine CRI dose - 3.0 mg/kg/hour (50 \( \mu \)g/kg/min)
- Ketamine CRI dose - 0.18 mg/kg/hour

Drugs to be added to the maintenance fluid (e.g. 1000 ml of Normosol)
- Morphine to be added in mg = \( \frac{0.1 \text{ mg/kg/hour}}{2.0 \text{ ml/kg/hour}} \times 1000 \text{ ml} = 50 \text{ mg} \)
- Lidocaine to be added in mg = \( \frac{3.0 \text{ mg/kg/hour}}{2.0 \text{ ml/kg/hour}} \times 1000 \text{ ml} = 1500 \text{ mg} \)
- Ketamine to be added in mg = \( \frac{0.18 \text{ mg/kg/hour}}{2.0 \text{ ml/kg/hour}} \times 1000 \text{ ml} = 90 \text{ mg} \)

The total amount of each drug to be added to the maintenance fluid was determined by the concentration of the drugs (morphine-10 mg/ml, lidocaine-20 mg/ml, and ketamine-100 mg/ml) will be: morphine - 5 ml, lidocaine - 75 ml, and ketamine - 0.9 ml.

The total volume of the drugs to be added to the bag of fluid will be 80.9 ml. Before adding the drugs, 80.9 ml of fluid has to be discarded for more accurate dosing.

The dog weighs 20 kg in this example. This means that the fluid should be delivered at the rate of 40 ml/hour (2.0 ml/kg/hour x 20 kg). This preparation can also be used in dogs of different body weights. If you have another dog in the clinic that needs CRI analgesia and maintenance fluid that weighs 30 kg, you simply change the infusion rate to 60 ml/hour. CRI dose rate for the analgesic drugs will be the same.

It is important to remember that this formula will work if the CRI dose of the drug is in mg/kg/hour! (See table below.)

For the syringe pump technique, the total volume of the solution (saline and the drugs) is determined by the approximate duration of surgery and body weight of the animal. The size of the largest syringe in the clinic will be the maximum volume that can be prepared. This is usually 60 ml. The rate of fluid infusion should be \( \leq 1.0 \text{ ml/kg/hour} \). The bigger the patient, the lower the fluid rate should be to reduce the number of times a syringe is refilled with drugs and diluent. For example, if 1.0 ml/kg/hour is used as fluid rate for a 40-kg dog, 40 ml/hour is needed. If the procedure lasts for 3 hours, total volume needed will be 120 ml; this means that a 60-ml syringe has to be refilled once. The solution for this is to reduce the fluid rate until the total volume for 3 hours will be equal or less than 60 ml or simply use this formula to determine the fluid rate:

\[
\text{Fluid rate} = \left[\frac{\text{Maximum volume in the syringe} + \text{body weight (kg)}}{\text{hours of procedure}}\right]
\]
Calculation of the fluid rate for a 40-kg dog that will have approximately 3 hours of surgery is shown below:

Fluid rate = \[\frac{60 \text{ ml} \div 40 \text{ kg}}{3 \text{ hours}} = 0.5 \text{ ml/kg/hour}\]

Drugs needed for this preparation will be calculated given the formula above.

Morphine to be added in mg = \(0.2 \text{ mg/kg/hour} \div 0.5 \text{ ml/kg/hour}\) x 60 ml = 24 mg (2.4 ml)
Lidocaine to be added in mg = \(3.0 \text{ mg/kg/hour} \div 0.5 \text{ ml/kg/hour}\) x 60 ml = 360 mg (18 ml)
Ketamine to be added in mg = \(0.6 \text{ mg/kg/hour} \div 0.5 \text{ ml/kg/hour}\) x 60 ml = 72 mg (0.72 ml)

These drugs will be put in a 60-ml syringe and then saline is added to make a total volume of 60 ml. The syringe pump is set at 20 ml/hour (40 kg x 0.5 ml/kg/hour).

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Loading dose (IV)</th>
<th>Infusion rate (IV)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>0.3 mg/kg slow</td>
<td>0.1-0.3 mg/kg/hour</td>
<td>Use higher dose for severe pain.</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.025-0.05 mg/kg</td>
<td>0.01-0.04 mg/kg/hour</td>
<td>Use the lower range of dose in cats.</td>
</tr>
<tr>
<td>Methadone</td>
<td>0.1-0.2 mg/kg</td>
<td>0.12-0.2 mg/kg/hour</td>
<td>Less likely to cause vomiting</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>5.0 mcg/kg</td>
<td>0.002-0.005 mg/kg/hour (2.0-5.0 μg/kg/hour)</td>
<td>Relatively expensive</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>0.1-0.2 mg/kg</td>
<td>0.1-0.2 mg/kg/hour</td>
<td>Excellent in cats with mild to moderate pain; more expensive than morphine</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>1-2 mg/kg</td>
<td>1.2-3.0 mg/kg/hour (20-50 mcg/kg/min)</td>
<td>Not recommended for cats</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0.5 mg/kg</td>
<td>0.12-0.6 mg/kg/hour (2-10 μg/kg/min)</td>
<td>Use highest infusion rate during painful surgery; use lower dose postop and other painful patients</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>1-2 μg/kg</td>
<td>0.0005-0.0025 mg/kg/hour (0.5-2.5 μg/kg/hour)</td>
<td>Useful in managing aggressive dog postoperatively and dogs that continue to vocalize despite the use of opioids and acepromazine</td>
</tr>
</tbody>
</table>

Reference