Multimodal Pain Management in Small Animals – Parts One and Two

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With the recent availability of a newly approved fentanyl formulation called transdermal fentanyl solution (Recuvyra® by Elanco), we have one more option for the management of pain in dogs. What is unique about this fentanyl solution is that it is designed to be applied directly to the skin and has a 4-day duration of pain relief with the single application. Fentanyl is a potent opioid, and this product is labeled to treat moderate to severe pain in dogs.

With multimodal analgesic approaches for pain management, we can use more than one classification of analgesic agent to effectively treat pain. Current pharmacologic analgesic classifications include opioids (morphine, hydromorphone, fentanyl, butorphanol, buprenorphine and tramadol), local anesthetic agents (lidocaine, bupivacaine, mepivacaine, lidocaine patch), alpha-2 adrenergic agents (dexmedetomidine), dissociatives (ketamine, tiletamine) and non-steroidal or steroidal anti-inflammatory analgesic agents. We can effectively use all of these pharmacologic drug classifications to treat pain along the pain pathway.

Since multimodal application of analgesic agents has been practiced for a while, this presentation will focus mainly on how to effectively use and include the new fentanyl formulation in your pain management combination in dogs. I will use a question and answer format to share this information.

1. What is fentanyl?
   Fentanyl is a synthetic opioid. It is about 100 times more potent than morphine. Based on the opioid receptor classification, fentanyl is a full mu and kappa receptor agonist. This means that fentanyl is in the same class as morphine and hydromorphone. This also means that fentanyl can be partially reversed by butorphanol (which is a kappa receptor agonist but mu receptor antagonist).

2. What are the 3 common commercial formulations of fentanyl?
   There are 3 commercial fentanyl products on the market; two are approved for humans and one for use in dogs. The fentanyl patch (25, 50, 75 and 100 mcg/hr sizes) and injectable fentanyl (50 mcg/ml) are approved for use in humans and the transdermal fentanyl solution is approved for use in dogs (but not cats).

3. What is Recuvyra and what are the indications for use in dogs?
Recuvyra is a trade name of the new transdermal fentanyl solution. It is a 50 mg per ml transparent solution that is approved for use in dogs for acute pain with one topical application on the dorsal scapular area and it will provide analgesia up to 4 days. An easy way to think about Recuvyra use is that it is a fentanyl constant rate of infusion without the use of intravenous catheter and pump, or it is a fentanyl patch without the patch for dogs.

4. How is Recuvyra used for treatment of acute (surgical) pain?
Recuvyra is applied on the skin with a special applicator and a syringe at 2-4 hours prior to surgery. No hair shaving or clipping is needed when applying the solution on the skin. The solution will dry within 5 minutes. The fentanyl penetrates through the corneum stratum basal layer of the skin via a chemical penetrator, allowing the fentanyl to be absorbed into the bloodstream. In addition, the fentanyl contained in the skin layer serves as a depot for the drug.

5. What is the pharmacokinetic profile of Recuvyra and when can I anticipate the pain relief after treating a dog?
Once the Recuvyra is applied on the skin, it dries in 5 minutes. The fentanyl is detected in the bloodstream 30 minutes after application. This is usually accompanied with onset of signs of sedation. The therapeutic plasma concentration of fentanyl (0.5 ng/ml) is reached 1.5 hours after application, and reaches 1 ng/ml about 3 hours after application; peak plasma concentration occurs at 13.6 hours after application with a maximal concentration of 1.83 ng/ml. The minimal effective plasma concentration of fentanyl has been determined to be between 0.2-1.2 ng/ml. For comparison, if using injectable fentanyl in order to maintain 1 ng/ml of plasma concentration of fentanyl in dogs, a loading dose of 5 mcg/kg has to be given followed by 5 mcg/kg/hr of constant rate of infusion for maintenance.

6. Will the dog become sedate after Recuvyra treatment?
Signs of sedation (ranging from calming effect to sternal recumbency with moderate degree of sedation) of various degrees may appear roughly 30 minutes after Recuvyra is applied. The sedation induced by Recuvyra provides relaxation for the treated dogs. The sedation likely deepens over time as the plasma Recuvyra starts to occur. Some dogs may be having a mild sedation or no sedation, while other dogs may be having moderate degree of sedation. The degree of sedation depends on individual sensitivity to the drug. Clinical experience indicates that one can pick up the sense and degree of sedation of an individual dog within a couple of hours of Recuvyra application. The use of acepromazine, which has a long duration of action compared with other sedatives, should
be conservatively used as a premedication if one wants to avoid a prolonged or over sedation when used in conjunction with Recuvyra.

7. What precautions should be taken when using Recuvyra?
Recuvyra precautions can be divided into human and animal safety. For human safety, one has to be aware that Recuvyra is a schedule II controlled substance; the controlled substance law applies to Recuvyra just like any other opioid in the same category. Recuvyra is highly concentrated and can be absorbed if accidentally exposed. Precautions should be taken when using Recuvyra by wearing gloves, long sleeves and protective eyewear in order to protect the mucus membranes and skin in case of accidental exposure during an application. Once it is applied to the dog’s skin, the solution will dry in 5 minutes. During this 5 minutes, the application area (dorsal scapular area) should not be touched. The owner should be instructed not to touch the application area and children should be isolated from the dog for 72 hours after initial application of Recuvyra.

Other side effects are associated with Recuvyra application. For example, a small number of dogs will be inappetent up to two days following application of Recuvyra. Hypothermia may occur in some dogs. In addition, some dogs may exhibit significant sedation. While these adverse events may occur in only a small percentage of dogs, precautions should be taken to monitor each individual dog after application. Treatments for these side effects may be needed if severe or persistently occur.

8. What kinds of surgical cases can be treated with Recuvyra?
Recuvyra is for labeled use in both soft and orthopedic tissue surgeries associated with moderate to severe pain. At Purdue University, we have successfully used Recuvyra in the following types of cases: hit-by-car, major soft tissue trauma, orthopedic surgery, dorsal hemi-laminectomy, ventral slot, TPLO/TTA/Total hip replacement, long bone fractures, front or hind limb amputation, mandibulectomy, TECA, thoracotomy, median sternotomy for hernia/tumor repair, bladder tumor repair, and mammary gland removal surgeries.

9. Should I modify my preanesthetic protocols when using Recuvyra?
For sedatives (IV or IM):
   Dexmedetomidine (5-10 mcg/kg)
   Acepromazine: low doses (0.005-0.01 mg/kg); do not use doses of acepromazine higher than this suggestion at any time.
   Midazolam (0.2-0.4 mg/kg)
For opioids (IV or IM):
   Continue with pure opioid agonists (morphine, hydromorphone, fentanyl) if Recuvyra has been applied.
   Butorphanol may be used if Recuvyra is just applied or applied within a short time prior.
Avoid the use of buprenorphine as a premedication since it has a stronger affinity and will displace the Recuvyra off opioid receptors. Pending on the timing of Recuvyra application, opioid premedication dose may be reduced. Tramadol and other drugs used for chronic pain (gabapentin, amantadine, NSAIDs) may be used, being mindful of all specific precautions. Anticholinergics (atropine, glycopyrrolate) can be used normally.

10. How should I modify my anesthetic induction in dogs treated with Recuvyra?
   If Recuvyra premedication is used alone (without any other sedatives on board), it is anticipated to reduce the induction agent by ~ 1/3 of the calculated dose. For example, propofol (2 mg/kg) or midazolam-ketamine (1 ml of mixture per 30 lbs). Telazol induction dose is about 1 mg/kg.

11. How should I modify my inhalant anesthetic concentrations (maintenance) in dogs treated with Recuvyra?
   Do anticipate a 40-50% reduction in isoflurane concentration (1-1.5% and adjust to effect for surgery) or sevoflurane concentration (2-2.5% and adjust to effect for surgery) when used 4-24 hours after Recuvyra application. At these inhalant concentrations, blood pressure is well maintained.

12. How should I modify pain management techniques in dogs treated with Recuvyra?
   Remember that the multimodal analgesia techniques are vital to each patient’s therapy. Recuvyra by itself is not a panacea for all surgical pain. Epidural anesthesia remains a vital analgesic technique, even when Recuvyra is used. If an epidural is going to be used, it is suggested that it contain local anesthetic only (without morphine or other opioids frequently used concurrently in the epidural injection). The local anesthetic agent used in the epidural can be bupivacaine (0.5 mg/kg qs with saline to 1 ml/4.5 kg) or lidocaine (1 mg/kg, qs with saline to 1 ml/4.5 kg). Brachial plexus blocks and other types of local blocks containing local anesthetic infiltration can be used in conjunction with Recuvyra. NSAIDs may be used prior or after surgery with the same precautions taken as when used without Recuvyra. Additional opioids may be used for break through pain if Recuvyra is not adequately treating the patient’s level of pain. Opioid dosages such as hydromorphone (0.05-0.1 mg/kg, IV), morphine (0.25-0.5 mg/kg, IV), fentanyl (2-4 mcg/kg/hr, IV) may be administered if necessary.
   In addition to intermittent bolus use of opioids, constant rate of infusions include the use of lidocaine CRI (300 mg in 1-liter LRS, 1-4 ml/kg/hr), lidocaine-ketamine CRI (300 mg-60 mg in 1 Liter LRS, administer 1-4 ml/kg/hr), fentanyl CRI (2-4 mcg/kg/hr), or morphine CRI (60 mg in 1-liter LRS, 1-4 ml/kg/hr) may be used as supplementation for analgesia.
13. What should I do if the Recuvyra-treated animal has a rough recovery from isoflurane or sevoflurane?

Rough recovery awakening from general anesthesia can be due to delirium, lack of analgesia or having both delirium and pain. Various sedatives can be used to treat the dog experiencing delirium; for example, dexmedetomidine (1 mcg/kg, IV). This is especially useful and convenient to perform with a low concentration of Dexdomitor (0.1 mg/ml). Other sedatives that may be used include acepromazine (0.005 mg/kg, IV), or midazolam (0.2-0.4 mg/kg, IV). If the animal is lacking analgesia, then a small dose of morphine (0.25 mg/kg), or hydromorphone (0.005 mg/kg) can be given IV with continuous observation to ensure an appropriate pain relief response.

14. What is the cost comparison between Recuvyra, fentanyl patch and fentanyl CRI?

Analysis performed in both small size and large size dogs has shown that the most expensive form of fentanyl for treating pain is injectable fentanyl, followed by fentanyl patches; the most economical form of fentanyl is Recuvyra.

Details of how to include various anesthetic and analgesic techniques when using Recuvyra will be covered in the presentation.