

Managing pain with opioid analgesics in cats and dogs

Author : Karen Walsh

Categories : [Companion animal](#), [Vets](#)

Date : August 24, 2015

Opioid analgesics are often the mainstay of perioperative pain management, but have become increasingly popular for longer term use at home and for chronic pain management.

Table 1. Licensed opioids for use in animals in the UK						
Drug	Target species	Route of administration	Dose	Clinical use	Schedule	Agonist type
Methadone	Dog Cat	SC, IM, IV (not licensed for IV in cats)	0.1mg/kg to 0.5mg/kg 0.1mg/kg to 0.3mg/kg Every three to six hours	Management of moderate to severe pain. Pre, peri and postoperative period	Two	Full mu
Pethidine	Dog Cat Horse	IM or SC Do not administer IV - histamine release	2mg/kg to 5mg/kg Every 60 to 90 minutes	May be useful in preanaesthetic period because of sedation. Not very useful postoperatively because of duration of action	Two	Full mu
Fentanyl injection	Dog	IV	Perioperative 0.2mcg/kg/min to 0.4mcg/kg/min or bolus of 2mcg/kg to 5mcg/kg Postoperative 0.1mcg/kg/min to 0.16mcg/kg/min	Perioperative analgesia as a bolus or constant rate infusion (CRI) Postoperatively as a CRI. A syringe driver should be used for CRI	Two	Full mu
Transdermal fentanyl	Dog	Transdermal applied in dorsal scapula area	2.6mg/kg lasting up to four days Must not be repeated before seven days	Useful for perioperative and postoperative period. Licence is for preoperative administration	Two	Full mu
Buprenorphine	Dog Cat Horse	IV, IM, oral transmucosal	0.02mg/kg every six to 12 hours	Mild to moderate pain	Three	Partial mu
Butorphanol	Dog Cat Horse	SC, IV, IM (depending on species)	0.1mg/kg to 0.4mg/kg every 60 to 90 minutes	Mild pain	Not scheduled	Probably a Mu antagonist Kappa agonist

Table 1. Licensed opioids for use in animals in the UK.

Over the past few years a number of opioids have also been licensed for use in dogs and cats in the UK (**Table 1**).

This article aims to give the clinician the ability to choose the most appropriate opioid for a particular case and condition. While the choice of opioid medication only is discussed in this article, it is highly unlikely this will be the only analgesic in use – particularly for surgical procedures.

Many of the clinically used opioid analgesics are mu receptor agonists. These drugs work at the spinal and supraspinal levels, as well as in some peripheral sites, such as the gastrointestinal system and joints if there is inflammation. Pain perception and transmission is altered when the drug binds to the receptors.

The effects are usually dose-dependent, although this will depend on the type of opioid – for example, partial agonist or full agonist (**Panel 1**).

Receptor types

Panel 1. Agonist definitions

Agonist: a drug that binds to a receptor and produces an effect.

Full agonist: a drug that binds to the receptor and is capable of producing the maximal effect in a dose-dependent fashion – for example, methadone.

Partial agonist: a drug that binds to the receptor, but will never produce a maximal effect, even if the dose is increased – for example, buprenorphine.

Antagonist: a drug that binds to the receptor, but does not produce any effect – for example, naloxone.

Three receptor types are important for clinical pain management in veterinary patients.

- **Mu-opioid peptide receptors (MOPs)** – these are located throughout the CNS in areas involved in sensory and motor function. They are the receptors most important in clinical pain management and will alter the transmission of pain messages via C and A-delta fibres. Side effects include respiratory depression and gastrointestinal tract (GIT) stasis.
- **Delta-opioid peptide receptors (DOPs)** – these are less widely distributed and inhibit the release of neurotransmitters in spinal and supraspinal sites. Side effects also include respiratory depression and GIT stasis.
- **Kappa-opioid peptide receptors (KOPs)** – these receptors also mediate analgesia and tend not to produce respiratory depression. Side effects include diuresis, sedation and dysphoria.

Administering opioids

The following situations detail when to administer opioids.

Part of a sedative protocol

The administration of an opioid in combination with a sedative agent will enhance the sedative effects and enable a reduction in sedative dose. The choice of opioid will depend on the intended procedure and the pain the patient is experiencing.

Non-painful procedures

Butorphanol alone will sometimes result in adequate sedation to allow ultrasound and radiography. More commonly, it can be combined with an alpha-2 agonist to produce profound sedation that will allow positioning for radiography and CT imaging.

Moderately painful procedures

Moderately painful procedures will require an opioid that produces a greater degree of analgesia. Choices would include buprenorphine and methadone.

The sedation produced can be as profound as that with a butorphanol combination, but in some patients, higher doses of alpha-2 agonists may need to be administered. However, a low dose of ketamine (0.5mg/kg to 1mg/kg in dogs and 1mg/kg to 2mg/kg in cats) can be added to the protocol to improve the degree of sedation and muscle relaxation.

Painful procedures

If there is any question the patient may require surgical intervention then a full agonist opioid should be chosen to optimise analgesia.

Pre-anaesthetic medication



Figure 1. Personal protective equipment required when administering transdermal fentanyl.

The reason to administer opioids in the premedication is two-fold.

- To provide preventive analgesia for elective procedures or start analgesic therapy in patients already in pain.
- To enhance the sedative effects of drugs such as acepromazine and alpha-2 agonists in an attempt to decrease side effects with higher doses of sedatives and subsequently reduce the dose of maintenance agent to sustain anaesthesia.

Opioids may also be used as the sole agent for premedication where physical examination indicates the patient may be suffering some underlying disease. For example, in patients with cardiovascular disease, or conditions such as septic peritonitis, pethidine 3mg/kg to 5mg/kg intramuscularly or methadone 0.2mg/kg to 0.3mg/kg intravenously or intramuscularly, may be adequate as “sole” premedication prior to induction of anaesthesia.

Opioid drugs are commonly administered by injection in the pre-anaesthetic period. However, a licensed form of fentanyl in dogs exists that is administered transdermally, which will also help improve sedation when combined with acepromazine and alpha-2 agonists.

Transdermal fentanyl has an onset of action of two to four hours and analgesia should be provided until the drug becomes effective. Certain health and safety protocols should be followed when applying this drug and caring for the patient (**Figure 1**).

Intraoperative analgesia

The opioid administered in the premed will, of course, be effective into the perioperative period. However, there may be times when the drug is wearing off during the procedure or is not enough to minimise nociception and the patient may require additional analgesia.

It is important to be mindful of the opioid administered preoperatively – for example, pethidine will provide analgesia for 69 minutes to 90 minutes and will probably require “topping up” when used for most procedures. Transdermal fentanyl should reach adequate blood levels in two hours to four hours, but maintain the analgesia for four days.

If the dose of opioid has to be continually increased, the clinician should bear in mind another group of analgesic drugs may be more appropriate in the particular case. Using drugs from different groups of analgesics will help treat pain at different points in the pathway and lower the required doses of analgesics such as opioids.

Intermittent bolus

Additional doses of methadone or morphine can be administered during the procedure. This can be a cheap and effective way of maintaining analgesia; however, it allows there to be peaks and troughs of action. Shorter acting opioids, such as fentanyl, may be more appropriate in this situation to treat short periods of increased stimulation – for example, aligning a fracture. Care should be taken when using morphine for “top-ups” as the drug can produce histamine release when administered intravenously and it might be best to use methadone in this situation.

Continuous rate infusion

Short-acting drugs, such as fentanyl or remifentanyl, are best suited to continuous rate infusion (CRI). These drugs have a rapid onset of action and a short duration that allows the effect to be switched on and off when needed. It tends to smooth out the plane of anaesthesia and reduce the amount of inhalational agent required (Ueyama et al, 2009). A syringe driver should be used to allow accurate administration.

Fentanyl is licensed in dogs and so should be used in preference to other short-acting opioids. There should be the facility to perform intermittent positive-pressure ventilation as respiration may be compromised. The patient should also be monitored for bradycardia and the dose titrated to effect. The inhalational agent will often be able to be decreased and this will help maintain blood pressure within acceptable limits.

Longer acting drugs, such as methadone and morphine, can also be administered as a CRI, but, as they are longer acting than fentanyl, they are less easy to titrate to effect and are possibly more suited to postoperative analgesia.

Other methods of administering opioids

Other methods of administering opioids include epidural and spinal administration. Local administration of opioids allows lower doses to be used with potentially less side effects.

Epidural



Figure 2. Epidural catheter in place. Image: A Mathis.

Morphine (0.1mg/kg) can be administered in saline at the lumbosacral junction to produce analgesia up to the thorax. This can be administered as a single injection or continuing into the postoperative period if an epidural catheter is placed (**Figure 2**). It should be diluted with sterile saline to increase the volume and aid distribution. The advantages are:

- increased duration (12 to 24 hours) of action compared to systemic administration
- low dose (0.1mg/kg) compared to systemic administration
- fewer side effects such as vomiting and respiratory depression (Valverde, 2008)

Disadvantages are:

- more technically difficult than an intramuscular or intravenous injection
- urinary retention and pruritus have been reported as side effects (Iff et al, 2012)

Spinal

Spinal or intrathecal administration can be achieved by injection or as a splash application during

surgery. The dose is usually reduced compared to epidural administration (0.05mg/kg compared to 0.1mg/kg morphine).

Intra-articular

Patients that have had ongoing inflammation will have an increase in opioid receptors. This can be exploited to achieve pain relief in the affected joint without systemic administration of the opioid. A dose of 0.1mg/kg morphine is often recommended.

Although improvements in pain scores have been recorded it did not significantly improve force plate pressures in one study (Gurney et al, 2012). For epidural, spinal and intra-articular administration, preservative-free morphine should be used as the preservatives may affect the tissues adversely.

Postoperative analgesia

As with preoperative choice of opioid drugs, the degree of pain and response of the patient is paramount in being able to choose the appropriate postoperative drug. It is important to remember each patient is an individual and during the course of the disease there will be variations in the opioid requirements and it should be reviewed regularly.

The drugs administered in the perioperative period will have some effect into the recovery and postoperative period depending on the one prescribed. However, pain and comfort should be monitored to ensure analgesia is adequate, even if a long-acting drug, such as transdermal fentanyl, has been administered and appropriate additional analgesia administered. Methadone and morphine can both be administered as an intermittent bolus, although this can tend to have a variation in analgesia level over the interdosing interval.

Continuous rate infusion

Longer acting drugs, such as methadone and morphine, may be more suited to the postoperative period when used as a CRI, although fentanyl can also be considered (at reduced doses compared to intraoperative).

A CRI will produce a more even blood level than intermittent injection and the total dose is likely to be less (Lucas et al, 2001). It also allows titration to the desired effect in an effort to optimise analgesia, but minimise side effects.

Longer term opioid analgesia and treatment at home

Some patients may require analgesia with opioids longer into the recovery period and for chronic pain on a long-term basis.

The type of drug and the side effects, as well as the potential risk of abuse, should be evaluated when deciding which, if any, opioid is to be used at home.

Transdermal fentanyl

Transdermal fentanyl may still be active when the patient is discharged from the practice, which may provide the analgesia required. Care must be taken to educate the client about the correct handling of the patient: children weighing less than 15kg should not handle the pet for 72 hours after the drug has been applied and all people in contact should wash their hands after handling their pet for 96 hours after application. Patients heavier than 20kg should also be hospitalised for 48 hours.

As there is a licensed form of transdermal fentanyl, it is not recommended to use fentanyl patches in the dog. Transdermal fentanyl is not licensed in cats, and should not be used due to different pharmacokinetics compared to dogs, so there may be some patients that may benefit from their use. Pain and comfort should be monitored when using both transdermal fentanyl and fentanyl patches.

Oral transmucosal buprenorphine

Oral transmucosal buprenorphine is used off-licence for postoperative pain and “flare ups” of pain in patients with chronically painful conditions. It appears to be efficacious in cats, with varying reports of effectiveness (Robertson et al, 2005; Giordano et al, 2010). The original pharmacokinetic paper indicated 0.02mg/kg buprenorphine administered oral transmucosally (OTM) produced similar, if not better, analgesia than when administered IV or SC, but a later paper suggested IV produced more profound analgesia. The difference may be due to the type of stimulus and the dose of the drug used. The formulation of the buprenorphine appears to affect how well the patient tolerates medication, with single use vials being tolerated well compared to buprenorphine from multi-use vials (Bortolami et al, 2012).

The use in dogs does not appear to be supported by pharmacokinetic studies as bioavailability appears to be less than 50% for both 0.02mg/kg and 0.12mg/kg OTM (Ko et al, 2011). However, this author has used it for mild to moderate pain in dogs at a dose of 0.02mg/kg OTM for conditions such as corneal ulceration.

Tramadol

Tramadol has become popular in veterinary pain management over the past few years – perhaps because it was not as strictly regulated as other opioid analgesics. However, from June 2014 tramadol was changed to a Schedule 3 controlled drug, requiring certain alterations to dispensing. Although it is exempt from safe storage in the legislation, the RCVS recommends it is kept in a locked cupboard in a similar way to buprenorphine.

There is a large variation in the doses quoted and the frequency of administration in the literature. The variations may be explained by the degree of pain the patient is experiencing and, as with all analgesic protocols, regular re-evaluation is essential. Owners report some side effects such as sedation or abnormal behaviour and cats may find the tablets unpalatable. In dogs dosage is 2mg/kg to 5mg/kg every six to eight hours; and in cats 2mg/kg to 4mg/kg every eight hours.

Opioid practicalities

Figure 3. Example of a controlled drug register.

Opioids are subject to regulations regarding storage, dispensing and prescribing, which can sometimes be seen as obstacles to their use in practice. A standard operating procedure can help make sure their use falls within the law.

Schedule 2 drugs include methadone, morphine and fentanyl. The original written prescription must be received by the wholesaler before the drug is dispatched.

When the practice receives the drug, it must be recorded in the controlled drug register, which should be a bound book and kept for two years after the last entry. Each dose supplied should also be entered and signed in the register (**Figure 3**).

It is good practice to have a standard operating procedure in place for the use of controlled drugs within the practice. These drugs should be kept in a locked cupboard.

Schedule 3 drugs include buprenorphine and now tramadol. Buprenorphine must be kept in a locked cabinet and although this is not a requirement for tramadol, it is recommended as best practice. Invoices should be retained for two years.

Although there are some logistical difficulties when using scheduled opioids in practice, they are an invaluable part of any anaesthetic and analgesic protocol.

- Note some of the drugs mentioned within this article are used under the cascade.

References

- Bortolami E, Slingsby L and Love E J (2012). Comparison of two formulations of buprenorphine in cats administered by the oral transmucosal route, *Journal of Feline Medicine and Surgery* **14**(8): 534-539.
- Giordano T, Steagall P V, Ferreira T H, Minto B W, de Sá Lorena S E, Brondani J and Luna S P (2010). Postoperative analgesic effects of intravenous, intramuscular, subcutaneous or oral transmucosal buprenorphine administered to cats undergoing ovariohysterectomy, *Veterinary Anaesthesia and Analgesia* **37**(4): 357-366.
- Gurney M A, Rysnik M, Comerford E J, Cripps P J and Iff I (2012). Intra-articular morphine, bupivacaine or no treatment for postoperative analgesia following unilateral elbow joint arthroscopy, *Journal of Small Animal Practice* **53**(7): 387-392.
- Iff I, Valeskini K and Mosing M (2012). Severe pruritus and myoclonus following intrathecal morphine administration in a dog, *The Canadian Veterinary Journal* **53**(9): 983-986.
- Ko J C, Freeman L J, Barletta M, Weil A B, Payton M E, Johnson B M and Inoue T (2011). Efficacy of oral transmucosal and intravenous administration of buprenorphine before surgery for postoperative analgesia in dogs undergoing ovariohysterectomy, *Journal of the American Veterinary Medical Association* **238**(3): 318-328.
- Lucas A N, Firth A M, Anderson G A , Vine J H and Edwards G A (2001). Comparison of the effects of morphine administered by constant-rate intravenous infusion or intermittent intramuscular injection in dogs, *Journal of the American Veterinary Medical Association* **218**(6): 884-891.
- Robertson S A, Lascelles B D, Taylor P M and Sear J W (2005). PK-PD modeling of buprenorphine in cats: intravenous and oral transmucosal administration, *Journal of Veterinary Pharmacology and Therapeutics* **28**(5): 453-460.
- Ueyama Y, Lerche P, Eppler C M and Muir W W (2009). Effects of intravenous administration of perzinfotel, fentanyl, and a combination of both drugs on the minimum alveolar concentration of isoflurane in dogs, *American Journal of Veterinary Research* **70**(12): 1,459-1,464.
- Valverde A (2008). Epidural analgesia and anaesthesia in dogs and cats, *The Veterinary Clinics of North America: Small Animal Practice* **38**(6): 1,205-1,230.