# Pain Management in Small Animals Mini Series

## Session Two: Rational Approach to Drug Therapy for the Management of Acute Pain

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**Opioids**

Man has been using opioids for treating pain and for pleasure for almost 6 millennia. The poppy plant (Papaver Somniferum) from which opium can be extracted was first cultivated around 3400 B.C. and was termed the "joy plant". Morphine is the natural product derived from opium. Despite its early origins, opioids still form the back bone of peri-operative analgesia in man and are also a critical component of premedication, sedation and analgesic regimens in veterinary medicine.

**Why are opioids so widely used in veterinary medicine?**

- **Safety**: Compared to other licensed analgesic drugs such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) opioids have a greater margin of safety
- **Efficacy**: Opioids provide effective analgesia in cats and dogs
- **Can be given to effect**: Unlike NSAIDs, opioids can be redosed in order to achieve the required level of analgesia
- **Versatility**: Can be given by a variety of routes (e.g. intravenous, epidural, intra-articular) to provide systemic or regional analgesia. They can also be combined with a variety of sedative agents in order to provide analgesia and improve the quality of sedation.

With the exception of butorphanol, in the UK opioids are subject to the Misuse of Drugs Regulations 2001 and similar legislation applies to the keeping and registration of opioids in other European countries. Stringent regulation surrounding the keeping and administration of opioids has led to reluctance by some veterinary practices to keep a full Mu (μ) opioid agonists (such as methadone) in the practice. Full μ agonists are Schedule 2 Controlled Drugs and subject to the following requirements:

- Drugs are subject to safe custody requirements and should be stored in a suitable locked cabinet secured to the fabric of the building at all times.
- Access to Controlled Drugs should be restricted with keys kept by a responsible person (s) at all times. It is not acceptable to have a communal key kept in a drawer or other non-secure place.
- Receipt and supply of drugs must be recorded in a Controlled Drugs Register. When dispensing drugs for use in an individual animal the animal must be uniquely identified in the Register, the date of dispensing and the dose must be recorded, accompanied by the signature of the veterinary surgeon. A running total of the number of vials of the drug in the locked cabinet should be kept and the Register checked regularly for any disparity between drugs present in the cabinet and the record in the Register. The Register must be completed within 24 hours of dispensing the drug.

- Written requisitions must be made to wholesalers. This requisition must state the veterinary surgeon's name, address and professional qualifications.
- Drugs must not be destroyed, except in the presence of a person authorized under the Secretary of State.

Buprenorphine is a Schedule 3 Controlled Drug and the legal requirements surrounding its use are less stringent than for Schedule 2 drugs:

- Subject to safe custody requirements but do not have to be recorded in the Controlled Drugs Register.
- Written requisitions must be made to wholesalers (see Schedule 2 drugs above).
- Regulations regarding prescriptions are the same as for Schedule 2 drugs.
- Witnessed destruction requirements only apply to importers, exporters and manufacturers.

Due to the differences in legal requirements between keeping and prescribing Schedule 2 and Schedule 3 drugs, it is not unusual for some veterinary practices to only have buprenorphine and butorphanol available rather than a full μ agonist (Schedule 2). This imposes a significant limitation on the capability to provide adequate opioid analgesia in cases of moderate to severe pain.

**Recommendation: Keep at least one full μ agonist in the practice in order to ensure capability to manage moderate to severe pain in cats and dogs.**

**Clinical effects of opioids**

- **Analgesia**: Effective and versatile analgesics.
- **Sedation**: In healthy adult animals sedation from opioids alone is limited. May provide sedation in unhealthy or very young animals. Combined with sedative drugs such as acepromazine and alpha $_2$ adrenergic agonists will enhance sedation through synergism.
- **Euphoria**: May occur as a result of administration of inappropriately high doses of opioids to animals that do not require them.
- **Cough suppression:** Opioids are commonly used in antitussive medication.
- **Cardiovascular system:** Bradycardia is common following the administration of potent opioids such as fentanyl due to stimulation of vagal tone. Inappropriate bradycardias can be managed by the administration of anticholinergics such as atropine.
- **Respiratory system:** Respiratory depression mediated by the Mu receptor is a significant clinical problem following opioid administration in man. Respiratory depression in animals is unlikely following the administration of clinical doses of opioids to awake animals. Fentanyl, alfentanil and sufentanil may all cause

respiratory depression when administered during anaesthesia, respiration can be supported by instigation of Intermittent Positive Pressure Ventilation (IPPV).

- **Vomiting:** Vomiting occurs due to stimulation of the chemoreceptor trigger zone and is most likely to occur following administration of morphine to animals before they are in pain. Avoid morphine administration to animals in which vomiting is contraindicated e.g. animals with raised intracranial or intraocular pressure.

- **Reduced gut motility and GI sphincter closure:** Opioids interfere with normal gastrointestinal motility by reducing gut transit time and stimulating non propulsive motility. Sphincters are stimulated, for example tone in the pyloric sphincter is increased. Constipation is a significant problem in man following opioid administration, although it appears to be less clinically relevant in animals.

- **Ocular effects:** In most species administration of opioids causes pupillary constriction due to an agonist effect at Mu or Kappa receptors located in the nucleus of the occulomotor nerve. Pethidine causes papillary dilation through its concurrent anticholinergic effects. Opioids cause pupil dilation in cats.

- **Pregnancy and neonates:** All opioids cross the placenta and may cause respiratory depression in neonates if given during a caesarian section. This can be managed by administration of a drop of naloxone under the tongue of the puppies or kittens after they are delivered.

**Classification of opioids (see table 1)**

Opioid are a wide and diverse group of drugs that can be classified according to certain aspects of their clinical pharmacology:

1. Which opioid receptor does the drug bind to?
2. Is the opioid an agonist, partial agonist or antagonist at the receptor?
3. Duration of action

**Which opioid receptor does the drug bind to?**

There are three opioid receptors that are universally recognized; Mu (μ), Kappa (κ), Delta (δ). Opioid receptors are located throughout the brain and spinal cord as well as throughout peripheral tissues. These receptors are normally stimulated by endogenous peptides such as endorphins, enkephalins and dynorphins, produced in response to noxious stimulation.

- Mu receptors: Mu analgesics are potent, effective analgesics, although the majority of side effects attributed to opioids (such as respiratory depression) also result from activity at the Mu receptor. Subtypes of the Mu receptor have been identified, particularly Mu1 and Mu2, with Mu1 related to analgesia, euphoria and serenity, while Mu2 is related to respiratory depression, pruritis and sedation. Opioids that bind to the Mu receptor are currently recognized to provide more efficacious analgesia in cats and dogs compared to opioids that bind to other opioid receptors (Kappa and Delta).

- Kappa receptors: Butorphanol is a Kappa receptor agonist with a veterinary license for use in dogs and cats. Currently available kappa receptor agonists provide reduced analgesia compared to Mu receptor agonists although in human medicine there is an interest in developing Kappa receptor agonists for the management of visceral pain. In man, centrally acting Kappa receptor agonists are associated with unacceptable dysphoria and sedation, although there is significant investment in developing peripherally restricted Kappa receptor agonists that may provide analgesia without these side effects.

- Delta receptors: No Delta receptor agonists are currently clinically used for provision of analgesia in man or animals. However they are analgesic and of significant interest in human medicine because of the absence of respiratory depression associated with their administration.


**Is the opioid an agonist, partial agonist or antagonist at the receptor?**

- **Full agonists:** Full opioid agonists bind to the opioid receptor and trigger a response by the cell, usually mimicking the action of the naturally occurring substance that would normally bind to the receptor. They display full efficacy at the receptor, e.g. analgesia. Examples of full Mu receptor agonists are methadone and morphine.

- **Partial agonists:** Partial opioid receptor agonists such as buprenorphine (a partial Mu receptor agonist) bind and activate a given receptor but only have partial efficacy at the receptor relative to a full agonist. Buprenorphine has reduced analgesic efficacy compared to methadone.

- **Antagonists:** Naloxone is an example of a Mu receptor antagonist. It will bind to the Mu opioid receptor but does not provoke a biological response itself and will block or dampen agonist mediated responses. Naloxone is used to antagonize side effects that may occur following administration of high doses of Mu receptor agonists such as methadone or buprenorphine.


**Clinical relevance of receptor effects:**

Full Mu opioid receptor agonists currently provide the most efficacious analgesia compared to partial Mu receptor agonists such as buprenorphine or Kappa receptor agonists such as butorphanol. Therefore for the management of moderate to severe pain administration of a full Mu receptor agonist is indicated. It is important to understand the terms potency and efficacy.

- **Potency** refers to the concentration of the drug required to elicit half of the maximum biological response of the agonist. Buprenorphine is more potent than morphine and methadone.

- **Efficacy** refers to the maximum possible biological effect that the drug or receptor ligand can achieve following binding of the drug to the receptor. In terms of opioids this relates to the maximum possible analgesia that can be achieved by the drug.

Morphine and methadone are more efficacious analgesic agents than buprenorphine even though they are less potent.

**Opioid interactions**

There is the potential for an interaction between partial Mu receptor agonists (e.g. buprenorphine) and full Mu receptor agonists (e.g. morphine or methadone). Buprenorphine binds very tightly to the Mu receptor, therefore once administered may prevent binding of other drugs to the Mu receptor until the effects of buprenorphine have waned. This may limit the analgesia that can be provided by subsequently administered full Mu receptor agonists.

**Clinical significance:**

1. Don't use buprenorphine for premedication if administration of full Mu receptor agonists during anaesthesia (e.g. fentanyl) is anticipated.
2. Don't administer buprenorphine to animals with moderate to severe pain because it may impede the efficacy of full Mu receptor agonists that may be required subsequently if analgesia from buprenorphine proves inadequate.
3. If the animal remains painful after buprenorphine don't delay administration of a full Mu agonist. Give further analgesia but expect that higher doses or more frequent administration may be required to produce effective analgesia.

**Duration of action**

The duration of action of different opioids (given systemically) determines their suitability for different indications.

- Ultra-short acting e.g. remifentanil: Remifentanil is rapidly metabolized in the plasma by plasma esterases, therefore accumulation does not occur and the effects rapidly wear off once infusion of remifentanil is stopped. Only used intra-operatively for provision of antinociception (analgesia).
- Short-acting e.g. fentanyl, alfentanil, sufentanil: This group of opioids is short acting (a single bolus of fentanyl will have a duration of action of 10-15 minutes) therefore the drugs are given intravenously, usually by continuous rate infusion. They are primarily used intra-operatively for provision of antinociception or analgesia.
- Medium duration of action e.g. methadone, morphine, pethidine, butorphanol: Morphine and methadone have a duration of action of approximately 3-4 hours in cats and dogs, pethidine and butorphanol are much shorter acting, with a duration of action of about 90 minutes. All of these drugs can be used for premedication, provision of antinociception during anaesthesia and post-operative analgesia, however due to the relatively shorter duration of action of butorphanol and pethidine frequent redosing is required. Therefore methadone and morphine are more ideally suited to provision of post-operative analgesia as less frequent dosing is necessary.

- Long duration of action e.g. buprenorphine: The duration of action of buprenorphine is about 6 hours in cats and dogs. As long as adequate analgesia can be provided by administration of a partial agonist this has the advantage that less frequent dosing overnight is required.
- Very long duration of action: Transdermal fentanyl solution is licensed for administration to dogs and has a 96 hour (4 day) duration of action.

**Table 1: Pharmacological characteristics of opioids used clinically in dogs & cats**

| | Fentanyl, Alfentanil, Sufentanil | Morphine & Methadone | Pethidine | Buprenorphine | Butorphanol |
|---|---|---|---|---|---|
| Receptor effects | Full Mu receptor agonists | Full Mu receptor agonists | Full Mu receptor agonist | Partial Mu receptor agonist | Kappa receptor agonist |
| Relative analgesic efficacy | > morphine | Similar to morphine | Similar to morphine | < morphine | < morphine |
| Systemic routes of administration | IV (fentanyl is available as transdermal patches or as a transdermal solution (dogs only)) | IV, IM, SC Morphine must be given slowly IV due to the potential for histamine release | IM, SC Do not give IV due to histamine release | IV, IM, SC Recent evidence suggests that usual clinical doses are less effective SC | IV, IM, SC |
| Duration of action | 10-15 minutes | 3-4 hours | 90 minutes | 6 hours | 90 minutes |
| Indications | Intra-operative analgesia, fentanyl may be used for post-operative analgesia | Premedication Sedation Intra-operative analgesia Post-operative analgesia | Premedication Sedation Intra-operative analgesia Post-operative analgesia | Premedication Sedation Intra-operative analgesia Post-operative analgesia | Premedication Sedation Intra-operative analgesia Post-operative analgesia |

**Incorporation of opioids into premedication and sedative protocols:**

Opioids increase sedation produced by acepromazine (neuroleptanaesthesia), alpha $_2$ agonists and benzodiazepines. This allows lower doses of the primary sedative agent to be used, contributing to a balanced sedative or premedication technique with the potential to provide adequate sedation with reduced cardiovascular effects. Use of opioids for premedication and sedation also provides pre-emptive analgesia (in healthy animals) or ensures continued analgesia in animals that are already in pain. Pre-emptive analgesia is considered advantageous to obtund changes in nociceptive processing that occur as a result of noxious input to the central nervous system, and may facilitate adequate provision of post-operative analgesia. Morphine and methadone are ideally suited for premedication and sedation in animals with moderate to severe pain because of their analgesic efficacy and duration of action. Buprenorphine, with it's long duration of action, is also ideally suited for premedication in animals with mild pain, or animals in which a multi-modal approach to analgesia is adopted through the use of NSAIDs and local analgesia techniques such as epidural administration of drugs.

**Intra-operative opioid administration:**

For many types of surgery a single dose of an opioid is adequate to provide intra-operative analgesia. Morphine or methadone can also be given as a bolus during anaesthesia in order to provide additional analgesia. However opioids are commonly incorporated into anaesthesia protocols as a means of reducing the required concentration of inhalant agent and providing a balanced anaesthesia technique. This is commonly achieved by the administration of a potent opioid such as fentanyl, alfentanil or sufentanil intravenously by continuous rate infusion. Ventilation may need to be supported by IPPV and the infusion is usually discontinued 10-15 minutes before the end of surgery in order to facilitate a transition to spontaneous respiration. Fentanyl can also be given as intermittent boluses intravenously immediately prior to periods of intense surgical stimulation (e.g. ligation of an ovary), it is important to monitor heart rate and respiratory function following administration. The inhalant agent sparing effects of opioids are greater in dogs than in cats, this should be considered when determining the required inhalant agent concentration for surgery.

**Post-operative administration:**

The level of opioid analgesia required post-operatively depends on the individual animal, the administration of other analgesic drugs and the severity of the surgery that has been carried out. **It is imperative that post-operative opioid administration is always linked to pain assessment to ensure that the analgesic requirements of the individual animal are met.** Buprenorphine can be very effective in animals with mild to moderate pain, particularly when combined with other adjunctive agents such as NSAIDs or local analgesia techniques. It is also very effective in cats. Morphine and methadone given as intermittent boluses may provide effective analgesia in animals with moderate to severe pain, dosing interval is

approximately 3-4 hours although more frequent administration may be required in some animals. If intermittent morphine or methadone is inadequate, morphine given by continuous rate infusion (CRI) is a more intensive intervention to provide improved analgesia. Morphine is currently preferred over methadone due to the increased clinical data that are available regarding morphine CRI compared to methadone. Fentanyl, given at a low dose by CRI will provide greater analgesia than morphine and at a suitable dose will not cause respiratory depression. It is important to remember that multi-modal analgesia techniques, incorporating opioids as well as other classes of analgesic agents will provide superior analgesia compared to uni-modal analgesia protocols.

**Routes of administration of opioids for post-operative analgesia**

- **Subcutaneous (SC):** Drugs can be given by this route easily and single-handed. However absorption is unreliable and slow compared to other routes of administration and it is generally recommended that this route is avoided. There is emerging evidence to suggest that routine clinical doses of buprenorphine given subcutaneously are less effective than buprenorphine given intramuscularly or intravenously.

- **Intramuscular (IM):** Repeated intramuscular injection of drugs can be painful, therefore avoid this route if possible. Pethidine, due to dose recommendations and the drug formulation, requires a large volume to given, which will be painful.

- **Intravenous (IV):** Route of administration of choice in animals in which intravenous access has been established through placement of an intravenous catheter. It can be useful to leave IV catheters placed for the purposes of anaesthesia in place until intensive analgesia is no longer required. Pethidine cannot be given IV due to histamine release, morphine should be diluted and given slowly IV, also because of the potential for histamine release.

- **Continuous rate infusion (CRI):** Giving analgesic drugs by CRI is designed to ensure a constant plasma concentration of the drug, avoiding peaks and troughs in plasma concentration and therefore analgesia, associated with bolus dosing. It is important to ensure that the CRI is checked frequently to safeguard that the animal is receiving the intended analgesia. Ideally all drugs should be given by CRI via controlled infusion apparatus such as a syringe pump to improve accuracy of administration. CRI syringes should be labelled adequately, with drug, concentration, dose and patient name and pain should be assessed frequently in the individual patient.

- **Transmucosal:** Preservative free buprenorphine is well absorbed by the oral transmucosal route in cats. This provides a non-invasive method to provide repeated analgesia to cats.

**Epidural administration of opioids:**

Preservative free morphine is the opioid that is most commonly administered into the epidural space in cats and dogs. As a result of the low lipophilicity of morphine compared to other opioids systemic absorption of epidural morphine is low, resulting in a long duration of action of approximately 12-18 hours. Morphine is commonly combined with a local anaesthetic such as bupivicaine when administered into the epidural space.

**Intra-articular administration of opioids:** Inflammation of peripheral tissues leads to increased synthesis and axonal transport of opioid receptors in dorsal root ganglion neurons, resulting in opioid upregulation and enhanced G protein coupling at peripheral sensory nerve terminals. This leads to increased efficacy of peripherally administered opioids, and hence the rationale for the administration of opioids intra-articularly in animals with joint disease. Although it is becoming more widespread practice to administer opioids such as morphine into the articular space at the end of joint surgery or arthroscopy, clinical evidence for efficacy is currently lacking in small animals. In man, the effectiveness of opioids administered by this route remains controversial with limited evidence of efficacy.

**Transdermal opioids:** Administration of opioids by the transdermal route using a patch that is placed on the skin is common in man for the management of severe pain in the home environment, for example pain resulting from metastatic disease. The continuous administration of opioids using a non-invasive route overcomes "breakthrough" pain associated with intermittent dosing. Fentanyl transdermal patches have been available for a number of years and a number of clinical and pharmacokinetic studies have evaluated their use in cats and dogs. Generally these studies have demonstrated that the bioavailability of transdermal fentanyl is low (approximately 60 % in cats and dogs), therefore it is not recommended to rely on transdermal fentanyl as a sole means of analgesia. There is a time lag of 12-18 hours before systemic fentanyl concentrations adequate to provide analgesia are present, therefore patch placement should precede the onset of pain, or appropriate adjunctive analgesia must be provided until 12-18 hours after patch placement. Transdermal buprenorphine patches are also available although they have undergone limited evaluation in cats and dogs, their use cannot be recommended until further data are available.

**Transdermal ('spot on') fentanyl solution**

In contrast to fentanyl patches, transdermal fentanyl solution (TFS) has recently been licensed in dogs for the control of pain associated with orthopaedic and soft tissue surgery (Recuvyra®, Elanco Animal Health). The solution comprises very concentrated fentanyl (50 mg/ml) combined with the volatile solvent isopropyl alcohol and the penetration enhancer octyl salicylate, which is in many human skin products such as sunscreens. Solvent evaporation and drying following application of TFS ensures absorption of fentanyl and octyl salicylate into the stratum corneum within 2-5 minutes of application. Fentanyl is then

available for prolonged systemic absorption providing a sustained level of analgesia for 96 hours after application, with data from both experimental and clinical studies demonstrating reliable and consistent absorption with minimal inter-dog variability. The solution is **not suitable** for use in cats due to different absorption characteristics through feline skin. Potential advantages of TFS are described in Fig. 1.

- Fentanyl is a μ opioid analgesic with proven efficacy in dogs
- Non-invasive and pain free to administer
- Provides a long duration of analgesia (96 hours) avoiding peaks and troughs in plasma fentanyl concentration that can occur with bolus dosing of opioids, reducing the likelihood of breakthrough pain and continued sensitisation of pain pathways
- A single dose with long duration of action may reduce likelihood of missed analgesic doses and therefore sensitisation of pain pathways
- Avoids first pass metabolism that is problematic following administration of opioids orally
- Single 'sign out' of fentanyl from the Controlled Drugs register for 96 hours of analgesia, reduces the likelihood of dosing errors and discrepancies in the register
- Licensed in dogs, with data to support dose, duration of action and safety. These data are available in the public domain in open access manuscripts
- The opioid is administered by the veterinary surgeon in the veterinary clinic, removing the possibility of opioid misuse by the public

Figure 1. Advantages of transdermal fentanyl solution for analgesia in dogs

**What do you need to know about TFS in dogs?**

There are robust scientific data to support drug dose and efficacy; however, there are also significant human health considerations that accompany use of the product, particularly with respect to the dog owner and other cats and dogs that may come into contact with the treated patient following discharge. Important considerations regarding the pharmacokinetics of TFS are described in Fig. 2.

- TFS must be applied to the dorsal neck of the dog (refer to the Summary of Product Characteristics), as pharmacokinetics vary depending on the site of application
- No clipping of the hair is required prior to application, unless the hair coat is so thick it prevents the applicator from contacting the skin
- Application of external heat to the site of TFS application does not significantly influence absorption characteristics of fentanyl from the stratum corneum and subsequent plasma fentanyl concentrations.

- Although there are no formal data, the peripheral vasoconstriction promoted by medetomidine and dexmedetomidine does not appear to alter the predictability of TFS analgesia.

Figure 2. Pharmacokinetics of TFS: key facts

**Clinical use of TFS**

Optimal use of TFS requires appropriate understanding of its role in an analgesic regimen, as well as some safety considerations:

**1. Case selection**

TFS is licensed as a peri-operative analgesic for dogs expected to experience moderate to severe pain. In the first instance it is pragmatic to use TFS in dogs that you would otherwise expect to treat with methadone for at least 24 hours after surgery, with a transition to buprenorphine thereafter. Opioid related side effects (sedation / dysphoria, low body temperature) are much more likely to occur if TFS is applied to dogs that do not require significant post-operative opioid analgesia based on their previous pain history and tissue trauma caused by surgery. Other considerations that determine case selection are primarily practical (Fig.5).

**2. Incorporation of TFS into a multi-modal analgesia regimen.**

TFS is a flexible analgesia treatment that can be incorporated into commonly used anaesthetic and analgesic regimens. As with any analgesic drug, there will be some dogs that require supplementary analgesia following TFS and, in these circumstances, supplemental opioid analgesia can be administered. In order to reduce the likelihood of opioid related adverse events (e.g. excessive sedation) the top up dose of opioid should be appropriate to the requirement for additional analgesia in the individual patient. Based on drug pharmacology, it is advised to supplement TFS will full μ agonist opioids (e.g. methadone (Comfortan®, Dechra Veterinary Products) or fentanyl (Fentadon®, Dechra Veterinary Products)) rather than a partial μ agonist such as buprenorphine. Methadone 0.1-0.2 mg/kg slowly IV is a good starting point to provide additional analgesia, with further incremental doses of methadone (0.1 mg/kg IV) being given if necessary. Note that these dose recommendations are lower than those licensed for dogs on the Comfortan® Specific Product Characteristics (SPC).

TFS has been used with a variety of regional anaesthetic blocks (e.g. epidural anaesthesia / analgesia, femoral and sciatic and brachial plexus blocks) appropriate to the site of surgery. Although multi-modal analgesia techniques are "best practice" and there is no inherent problem with using TFS in combination with local blocks, it is the authors' impression that dogs that receive an effective regional nerve block and TFS may be somewhat "over-

analgesed", particularly in the immediate post-operative period. For this reason, it is prudent to omit morphine (which has a duration of action of up to 24 hours administered epidurally) from epidurals if TFS has been applied and only administer epidural bupivacaine. More robust clinical recommendations on the use of TFS with regional nerve blocks will likely emerge as TFS use increases in veterinary practice.

There is no contraindication to using TFS with NSAID analgesia, and this practice is recommended unless there is a contraindication to NSAID administration in an individual patient.

- **Analgesia:** Field studies prior to licensing indicated that TFS provided analgesia for 96 hours that was equivalent to the comparator analgesic (buprenorphine 20 µg/kg every 6 hours) in dogs undergoing soft tissue and orthopaedic procedures (Linton et al. 2012). Veterinary surgeons using the product in dogs have also found it to provide reliable and efficacious analgesia.
- **Sedation:** A clinical study (Linton et al. 2012) indicated that sedation from TFS was mild and similar to sedation caused by buprenorphine 20 µg/kg IM every 6 hours. A small proportion of dogs may be mild–moderately sedated for up to 36 hours after application and require more careful monitoring over this time period. Opioid related side effects are more likely when there is a relative overdose of opioid compared with the pain challenge, hence only use TFS in dogs when moderate to severe pain is expected for 24-36 hours after surgery.
- **Body temperature:** A proportion (approximately 25%) of dogs remain slightly hypothermic for 24-36 hours after TFS in the peri-operative period (rectal temperatures 36.5-37.5 °C), although it appears difficult to predict which animals will have impaired thermoregulation. It may be that hypothermia is more likely in dogs that are clinically more sedated. It is recommended to monitor rectal temperature closely (at least every 6 hours) for the first 24 hours after application.
- **Appetite:** The clinical impression of the authors and nursing staff working in the authors' institutions is that TFS does not have an adverse effect on appetite and that the majority of dogs start eating quickly after surgery with little evidence of nausea.

Figure 3. Clinical effects of TFS: key facts


**3. TFS and user safety (veterinary staff and dog owners)**
TFS has significant user considerations that must be followed to use the product safely and effectively in veterinary practice. These are summarized briefly below:


**Veterinary staff**
a) **Training:** Due to the unique formulation, only veterinary surgeons who have completed a short online training program provided by Elanco Animal Health may

order TFS from their veterinary wholesaler. Once a veterinary surgeon has been trained, it is their responsibility to train others within the practice (e.g. veterinary surgeons, veterinary nurses, lay staff) about the product.

b) **Product preparation and application:** Personal protective clothing (including gloves and eye goggles) should be worn when drawing up and administering the product, as it is rapidly absorbed across mucous membranes and more slowly across the skin. Humans are particularly susceptible to fentanyl induced respiratory depression so great care needs to be taken to avoid accidental exposure.

c) **Application system:** TFS comes with its own syringes and applicator that reduce the likelihood of product spillage during preparation.

d) **Post application of TFS:** Once the solution has been applied to the back of the neck (dorsal scapula region), the site of application should not be touched for 5 minutes (drying time). After 5 minutes, once the TFS has dried, the site may be touched, but hands should be washed immediately afterwards to prevent any fentanyl residue from being accidentally transferred to the mucous membranes and absorbed systemically; alternatively gloves could be worn to handle the dog. Care during handling (hand washing, gloves) is important for up to 72 hours after TFS application.

e) **Discharge to the owner:** Dogs > 20 kg bodyweight must be hospitalized for at least 48 hours after TFS application. This is because of the greater risk of adverse human events should TFS residues be absorbed systemically when a larger dose has been applied to dogs of greater bodyweight, particularly in small children and other pets (see below).

**Dog owners and other animals**

TFS has potential risks for human health for up to 72 hours after application; therefore, within this time window certain precautions are advised (Fig. 4).

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1. Give the owner an information leaflet (supplied by Elanco Animal Health) that warns about the human safety aspects of TFS, particularly with respect to systemic absorption of fentanyl should the dog be handled (at the site of application). The leaflet should indicate at what time (and date) (filled in by the veterinary surgeon) children can have contact with the dog

2. Advise the owners not to let children weighing 15 kg or less touch dogs treated with TFS for 72 hours post application.

3. Other dogs and cats should not come into contact with the site of application on the treated dog.

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Figure 4. Considerations for dog owners and other animals when a treated dog is discharged home

**4. Reversal of TFS?**

The major disadvantage with any long acting product is that once the drug has been applied it cannot be removed! Clinical data to date suggest that the likelihood of adverse events is low if TFS is used according to the SPC. It is VERY important to differentiate between effects of anaesthesia *per se* (i.e. mild sedation, slow respiratory rate with normal $SpO_2$ in dogs breathing room air, or mild hypothermia (temperature 36.0-37.5 °C)) from respiratory depression and hypothermia exacerbated by TFS. It is sensible to consider a step-wise approach to provision of supportive therapy before administering a μ opioid antagonist such as naloxone. For example, should sedation and hypothermia be identified then supportive care such as use of warming devices, regular turning of the patient and bladder management until the sedation and hypothermia wane is sufficient in the majority of animals. Pharmacological reversal of the effects of a μ agonist can also be achieved by the administration of buprenorphine (a partial μ agonist) or butorphanol (a μ antagonist, κ (kappa) agonist). Both buprenorphine and butorphanol may offset some of the unwanted effects of full μ opioid agonists, whilst providing analgesia. Starting doses of either buprenorphine at 5μg/kg or butorphanol at 0.1mg/kg - with both drugs being diluted with 0.9% NaCl to facilitate slow administration - can be titrated slowly IV to effect to antagonize adverse effects of fentanyl, and these doses can be repeated if no response is seen immediately following the first dose; if 10 μg/kg buprenorphine or 0.2mg/kg butorphanol have been given and the adverse effects (e.g. respiratory depression) persist, consideration should be given to investigating whether the problem may actually be related to some other factor in the animal rather than the fentanyl. The use of buprenorphine or butorphanol for antagonism of fentanyl is 'off licence'. Should it be decided that it is necessary to administer naloxone (no veterinary licence), the starting dose recommended for this drug on the SPC for Recuvyra® is 0.1mg/kg IV, although - being a pure opioid antagonist - use of naloxone is likely to remove all analgesia from the patient, and this needs to be carefully considered and alternative analgesic methods implemented (e.g. local anaesthetic blocks) before naloxone is given; in a situation of this nature, it would be sensible to seek specialist advice, either through a referral centre with a European Specialist in Veterinary Anaesthesia and Analgesia or from Elanco Animal Health 24 hour technical support service. Due to the prolonged action of TFS, it is very likely that multiple doses or a CRI of the appropriate reversal agent (buprenorphine, butorphanol or nalaoxone) would be required (see below).

**Should adverse events attributable to TFS occur, what practical steps should be taken? (Fig. 5)**

1. Plasma fentanyl concentration peaks 13 hours after TFS application, therefore adverse events are most likely in the first 24 hours.
2. Confirm that the presenting signs are likely attributable to an opioid overdose.

3. Is supportive therapy (e.g. maintain normothermia, regular turning to manage recumbency, bladder management if the dog is unable to be taken outside to toilet, apply topical lubricant to the corneas) all that is necessary?

4. If additional intervention is needed consider pharmacological reversal of fentanyl with butorphanol or buprenorphine (see above)

5. Administration of naloxone (a Mu opioid antagonist) is only indicated when severe opioid adverse effects are noted (see Fig. 6). Naloxone has a short duration of action (30-60 minutes). Although the SPC for Recuvyra® recommends a dose of naloxone of 0.1mg/kg IV if reversal is required, this may be excessive in some dogs and result in complete removal of all analgesia; it may be more appropriate to commence with a lower dose in an attempt to remove the undesired side effect of the TFS but maintain some opioid analgesia if possible. A single test dose (160 µg/kg IM or 0.04-0.1 mg/kg IV) can be given to ascertain whether the clinical signs shown by the dog are caused by opioid overdose (Freise et al. 2012).

6. If naloxone is effective, starting a naloxone intravenous continuous rate infusion (0.02 mg/kg/hour) for approximately 6 hours is recommended, followed by careful reassessment of the dog 1-3 hours after stopping the CRI to determine whether clinical signs of opioid overdose recur and - if so - the naloxone CRI must be extended. Administration of naloxone will reverse **all** Mu opioid agonist analgesia, including endogenous opioid peptides, therefore consider naloxone **only** when supportive measures to abate clinical signs of opioid overdose are inadequate.

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i) **Severe respiratory depression associated with a slow respiratory rate or inadequate respiratory effort.** A definitive diagnosis is made on detection of an elevated blood carbon dioxide tension (measured by blood gas analysis) or elevated end tidal carbon dioxide concentration (> 55 mmHg measured by nasal catheter and side stream capnometry in an otherwise conscious dog), or inability to maintain adequate oxygenation on room air in a dog with otherwise normal cardiorespiratory function (pulse oximeter $SpO_2$ < 95%).

ii) **Severe sedation** not associated with recovery from anaesthesia (i.e. an adequate time period for recovery from anaesthetic drugs has been allowed and the dog is normothermic).

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**Figure 5. Clinical signs of fentanyl overdose where opioid antagonism might be indicated**

**Should you stock naloxone in your practice if you intend to use TFS?**

Clinical data and user experience suggests that the risk of fentanyl overdose and requirement for naloxone is extremely low in dogs treated with TFS; however it is sensible to keep

naloxone in stock when using TFS or any other opioid. If naloxone is not available, then administration of butorphanol or buprenorphine (as described above) can be considered.

**Common misconceptions about opioid administration in cats and dogs**

- **Opioids & cats:** Although attitudes towards the use of opioids in cats are changing, there still exists a reluctance to use full Mu agonists in this species due to concerns about opioid excitement and mania. Opioids have the potential to cause excitation in all animals if inappropriately high doses are given to animals that do not require them. However if clinical doses are used sensibly either sedation or no effects on mentation are expected. If unwanted excitation should occur in cats or dogs this can be managed effectively by the administration of long acting sedative agents such as acepromazine, or if severe, propofol or alfaxalone can be given intravenously to provide immediate sedation.

- **Opioids cannot be redosed:** Unlike NSAIDs, opioids can and should be given to effect in order to provide adequate analgesia. It is sensible to approach opioid administration in a step wise manner, and only give repeat doses after assessment of the patient and determination of whether further analgesia is required. The capability to adjust the dose of opioid depending on the individual requirements of the patients is a feature that makes opioids a very versatile class of analgesics.

- **Respiratory depression may occur after opioid administration:** With the exception of the administration of fentanyl, alfentanil and sufentanil to anaesthetised animals respiratory depression following administration of clinical doses of opioids is unlikely. However heavy sedation caused by administration of morphine or methadone to sick patients, particularly brachycephalic breeds, may contribute to respiratory depression caused by obstruction of the upper respiratory tract. In brachycephalic animals it is prudent to monitor the depth of sedation with repeated morphine or methadone administration for post-operative analgesia and decrease the dose or frequency of dosing if depth of sedation is increasing.

- **Opioids cannot be combined with other classes of analgesic drugs:** Opioids are used most effectively as part of a multi-modal analgesia technique in combination with other classes of analgesic drugs. Dose adjustment depends on the nature of the total analgesia regimen that is being provided and the duration of action of concurrent analgesia techniques.
    - There is no need to reduce the dose of systemic opioid to account for morphine given epidurally. However, animals given epidural morphine will usually require a lower dose of systemic opioid, or it may allow administration of buprenorphine rather than morphine or methadone.
    - Generally co-administration of a NSAID will not influence the dose of opioid given, however more effective analgesia will be provided by the combination.

- A continuous rate infusion of morphine is commonly combined with a continuous rate infusion of ketamine and lidocaine in animals with severe pain (MLK mixture). No studies have evaluated optimal dosing of these drugs in combination, and it is likely that co-administration of multiple drugs will alter the pharmacokinetics of the drugs compared to when they are given in isolation. Clinical judgement should be used to adjust dose rates according to the status of the patient.
- Use of local analgesic techniques, such as maxillary and mandibular nerve blocks for dental procedures or a brachial plexus block for lower forelimb surgery should not necessarily alter opioid dose rates. The requirement for systemic opioid analgesia will depend on clinical assessment of the patient, the dose or dosing interval may be reduced if analgesia appears adequate.

**Conclusions**

Opioids are a diverse group of drugs that play a major role in the provision of peri-operative analgesia in dogs and cats. Rationale selection of an opioid depends on the required analgesic efficacy, duration of action, and the other classes of analgesic drugs or techniques that will be administered to an individual animal. Clinically relevant side effects resulting from opioid administration are relatively uncommon and can usually be managed symptomatically without the requirement for naloxone.

**Non Steroidal Anti-Inflammatory Drugs**

Non-steroidal anti-inflammatory drugs (NSAIDs) are recognized to be effective anti-hyperalgesic drugs; they do not elevate pain threshold in normal animals but will normalize the exaggerated pain behaviour (hyperalgesia) that is observed after tissue injury or inflammation. As such NSAIDs form an important component of multi-modal analgesia strategies for the management of acute and chronic pain

**Key benefits of using NSAIDs for pain management include:**
- Action at both the site of tissue damage and centrally in the spinal cord and brain to reduce or prevent hyperalgesia
- Reduce inflammation at the site of tissue damage
- Have a long duration of action; most NSAIDs provide analgesia for approximately 24 hours after a single dose
- Do not cause sedation; which is particularly advantageous for animals in the home environment
- Can be dispensed to owners for administration at home

There are a number of different NSAIDs that are currently licensed for use in cats and dogs, however understanding the differences in clinical pharmacology between these NSAIDs can be challenging. The aim of this article is to highlight the clinical relevance of any pharmacological differences in terms of the clinical effects of the drugs, particularly with respect to NSAID related side effects in cats and dogs

**Central and peripheral mechanisms of action of NSAIDs**

The mechanism of action of all NSAIDs is primarily through inhibition of cyclo-oxygenase enzymes to decrease the synthesis of prostaglandins that are key mediators of inflammation and play a pivotal role in the pain pathway (Svensson & Yaksh 2002). Critically, at the site of tissue damage and inflammation, prostaglandins are important sensitizers of nociceptors, which is a key step in the development of primary hyperalgesia. This usually manifests as increased pain responses to noxious mechanical and thermal stimuli and causes increased pain sensitivity, for example at the site of surgery.

COX enzymes are also induced in the spinal cord and brain in response to peripheral inflammation, leading to synthesis of prostaglandins in the central nervous system that are important in the upregulation of nociceptive pathways. NSAIDs therefore also act centrally to reduce prostaglandin synthesis, thereby preventing or reducing secondary hyperalgesia. It is secondary hyperalgesia that causes the increased sensitivity to mechanical stimulation (e.g. palpation) around a wound, a cardinal feature of acute and chronic inflammatory pain. The central action of NSAIDs can also reduce or prevent the onset of allodynia (when stimuli such as touch that would not normally cause pain become painful), both at the site of tissue damage and in the surrounding area.

**COX-selectivity**

Until recently COX-selectivity was the "buzz word" surrounding NSAIDs, with a drive to develop NSAIDs that were highly selective for the COX-2 enzyme, with relatively little inhibition of COX-1. This reflected increased understanding of the mechanisms responsible for NSAID related side effects. In brief, it was considered that prostaglandins synthesized via the COX-1 pathway were important for normal organ function, whereas COX-2 enzyme was induced in the periphery and CNS as a response to tissue damage and prostaglandins synthesized via the COX-2 pathway were important mediators of inflammation and pain. Although to some extent this dogma still holds true, there is now much greater understanding about the relative roles of COX-1 and COX-2 mediated prostaglandins in both normal organ function and the pain pathways. COX-2 mediated prostaglandins are known to be vital for maintenance of normal kidney physiology and play a role in the healing of some tissues, particularly the gastro-intestinal system. Some COX-1 mediated prostaglandins are thought to play a role in the pain pathway.

NSAIDs licensed for use in both cats and dogs are either COX-2 preferential (e.g. carprofen or meloxicam) or COX-2 specific, termed coxibs (e.g. robenacoxib). Coxibs have the least inhibitory effects on the COX-1 enzyme. COX selectivity is often described in terms of the ratio of inhibition of the COX-1 and COX-2 enzymes, however it is important to interpret ratios with caution. Assays are often carried out *in vitro* using blood from a non target species, and therefore the reported selectivity may not apply to the relevant species (e.g. dog or cat).

**Does COX selectivity confer safety benefits?**

**Gastrointestinal system**
In human studies, drugs with greater selectivity for the COX-2 enzyme compared to COX-1 cause less gastrointestinal side effects than non-selective NSAIDs (Hawkey et al. 2000). This is because prostaglandins synthesized by the COX-1 enzyme are particularly important for the maintenance of normal physiology in the gastro-intestinal system, particularly the upper GI tract. Comparable large scale studies have not been carried out in cats and dogs, although field trials comparing a newer selective NSAID (robenacoxib) vs. meloxicam confirmed this trend in dogs receiving chronic NSAID treatment for OA (EPAR Onsior). It is reasonable to assume that COX-2 preferential and coxibs confer some safety in terms of a reduced likelihood of GI related side effects compared to non-selective NSAIDs, although differences in the relative GI safety of coxibs compared to COX preferential NSAIDs remain to be elucidated fully.

**Renal function**
In contrast to the GI system, COX-2 selectivity appears to be less important as a determinant of the relative renal safety of NSAIDs (Rosset et al. 1999) as COX-2 mediated prostaglandins are essential for normal renal physiology, particularly the maintenance of adequate renal blood flow during periods of hypotension. Inhibition of renal prostaglandin synthesis in animals that are hypotensive can result in renal ischaemia and acute renal failure, a risk that must be considered around the time of anaesthesia and surgery when hypotensioncan occur.

**Effects on haemostasis**
COX-2 selectivity is also relevant when the effects of NSAIDs on haemostasis are considered. Thromboxane $A_2$ is produced by platelets via the COX-1 pathway and promotes vasoconstriction and platelet aggregation. NSAIDs may reduce the efficacy of blood clotting through inhibition of COX-1 enzyme, the magnitude of this effect is related to the degree of COX-1 inhibition. Coxibs should have less potential to prolong haemostasis than COX-2 preferential NSAIDS, although in animals with normal platelet function and blood clotting, the clinical significance of this difference is likely to be minimal.

**Tissue selectivity**

The limitations of COX-2 enzyme selectivity to reduce the risk of side effects associated with NSAID administration has led to the development of a new strategy to increase NSAID safety: tissue selectivity. In terms of NSAIDs, tissue selectivity can be defined as the combined effect of 2 properties:

- Accumulation at the site of inflammation
- Short plasma half life

The aim of these combined pharmacological properties is to limit the exposure time of organs that are vulnerable to NSAID related side effects to the drug, thereby reducing the risk of side effects in these organs.

### 1) Accumulation at the site of inflammation

Some NSAIDs will preferentially accumulate at sites of inflammation in the body and are slowly eliminated from the inflammatory exudate. This results in a long lasting inhibition of prostaglandin synthesis in the inflamed tissue while the effects on prostaglandin synthesis in normal healthy tissue is limited (Brune & Furst 2007).

The preferential uptake of NSAIDs by inflamed tissues occurs because of two pharmacokinetic properties of traditional NSAIDs; they are highly protein bound in the circulation and because they are weak acids.

**Protein binding:** Plasma proteins are large charged molecules that are unable to leave the circulation to penetrate capillary beds in peripheral tissues and most body organs because the pores between vascular endothelial cells are too small. Therefore binding of NSAID molecules to plasma proteins tends to promote maintenance of the NSAID in the systemic circulation. However there are some exceptions to this general rule:

- One of the cardinal features of inflammation is that the permeability of the vascular endothelial cells increases, the blood vessels become "leaky". This allows proteins to leave the circulation in inflamed tissue, which manifests as swelling. As a consequence, NSAIDs are also able to leave the circulation at sites of tissue damage and inflammation, allowing them to exert a therapeutic action in these tissues.
- In some body organs, particularly the liver and kidney, the pores between vascular endothelial cells are larger than in other tissues. This is due to the role of these organs in the metabolism and excretion of substances, including drugs. Therefore unlike most other normal tissues and organs, in the liver and kidney, NSAIDs are able to accumulate. The potential for NSAIDs to accumulate in these organs, combined with the fact that prostaglandins are essential for their function, leads to the risk of NSAID related side effects.

**Some NSAIDs are weak acids:** Once NSAIDs have left the circulation through the leaky blood vessel walls at sites of inflammation, it is important that NSAIDs remain at the site of inflammation. It is the weakly acidic nature of some NSAIDs that encourages persistence of the NSAID in inflamed tissues through a phenomenon termed "ion trapping".

The low pH in inflamed extracellular fluid results in predominance of the uncharged form of the NSAID molecule which allows it to be taken up by the cells where they can exert their therapeutic effect. Once in the cells the molecules revert back to being charged because the intracellular environment has a neutral pH.

Thus the NSAID molecules remain trapped in cells in inflamed tissue, ensuring a long duration of analgesia (up to 24 hours) following administration of a single dose.

Therefore it is the ability to accumulate at site of inflammation of traditional acidic NSAIDs that encourages a long duration of analgesia following a single dose.

**2) Short Plasma half-life** Ability to accumulate at the sites of inflammation alone does not significantly alleviate the risk of NSAID related side effects, because NSAIDs are also able to leave the circulation in side effect organs such as the liver and kidney.

However, if a NSAID has a short residence time in plasma **and** accumulates in sites of inflammation, these combined properties limit the total exposure time of vulnerable side effect organs such as the kidney, gastro-intestinal system, liver, vascular endothelium and blood platelets to the drug following a single dose. In effect, the NSAID is able to provide a long duration of analgesia, while the total time that prostaglandin synthesis in normal organs is inhibited is minimized. This should, in theory, ensure a profound and long lasting anti-hyperalgesic action, while reducing the risk of NSAID related side effects.

**Tissue Selectivity and Robenacoxib**

Robenacoxib, a NSAID licensed for cats and dogs has protein binding over 99% and the shortest plasma-half life of all veterinary licensed NSAIDs - approximately 1-2 hours (Jung et al. 2009, Giraudel et al. 2009). The accumulation in inflamed tissues and joints has been published in both cats and dogs (Pelligand et al. 2012, Silber et al. 2010).

Therefore robenacoxib has some unique properties compared to other NSAIDs with a veterinary license. It is a coxib and it is tissue selective (including a short plasma-half life). The combination of these properties harnesses the two key strategies that have been developed to increase the safety of NSAIDs in a single drug.

**Other strategies to increase the safety of NSAID administration in cats and dogs**

Despite the advances in NSAID development, the risk of adverse effects must always be considered when deciding whether NSAID administration is appropriate for an individual patient. The following strategies are recommended to reduce the likelihood of NSAID related adverse effects when used for the management of acute and chronic pain.

1. Do not administer NSAIDs to animals that are hypotensive for example due to blood loss, dehydration caused by vomiting or diarrhoea or severe cardiovascular disease.
2. Do not administer NSAIDs to animals with acute renal failure, and avoid NSAIDs in the peri-operative period in animals with chronic kidney disease (CKD). NSAIDs may be administered to animals with stable CKD however they should always be used cautiously in this patient population and should only be administered once the patient is normotensive and able to maintain a normal fluid balance.
3. Avoid NSAIDs in animals with disturbances of haemostasis, consider both the risks of both decreased blood clotting and thromboemboli formation, dependent on the NSAID administered.
4. Do not administer NSAIDs to animals with gastro-intestinal ulceration or vomiting or diarrhoea.
5. Educate owners about the potential side effects of NSAID administration and when not to administer the dose of NSAIDs in the home environment (e.g. if the animal stops eating). Ensure owners are told not to increase the NSAID dose or administer NSAIDs licensed in man instead of the prescribed drug.

**Conclusion**

NSAIDs have significantly enhanced our capability to manage pain in small animals and are a key component of analgesic strategies, particularly for the management of chronic pain. In order to reduce the risk of NSAID related side effects, drug development has focussed on two pharmacological properties of NSAIDs; selectivity for the COX-2 enzyme and tissue selectivity.

The newer NSAIDs are coxibs, with high selectivity for the COX-2 enzyme so that COX-1 function is largely unchanged at clinical doses. This property is likely to reduce the prevalence of GI related side effects compared to NSAIDs with a lower specificity for the COX-2 enzyme. Tissue selectivity, whereby preferential concentration of the drug at the site of tissue inflammation is combined with a short plasma half life, may also reduce the risk of NSAID related side effects by reducing the total time that normal tissues and body organs are exposed to the drug following a single dose. Robenacoxib is the only NSAID with Marketing Authorisation for administration to cats and dogs that is both a coxib (and is therefore highly selective for the COX-2 enzyme) and tissue selective. The combination of both of these

pharmacological approaches to decrease the prevalence of NSAID related side effects in single drug (robenacoxib) may be advantageous for veterinary patients.

**Local anaesthetics**

Local anaesthetic techniques are widely used in human anaesthesia. They can alleviate the need for general anaesthesia and also be used to provide effective "pre-emptive" analgesia by blocking the transfer of peripheral nociceptive information to the spinal cord.

Currently local anaesthetic techniques are often neglected as part of small animal anaesthetic and analgesic regimens. However use of a local technique can reduce the dose of other anaesthetic drugs required for maintenance of anaesthesia and contributes to a multi-modal analgesic technique. Use of specific nerve blocks to prevent the relay of nociceptive information from the site of injury to the spinal cord can also provide pre-emptive analgesia, and prevent or reduce the development of central sensitization.

**Mechanism of Action and Pharmacology of Local Anaesthetic Agents**

Local anaesthetics reversibly block conduction of action potentials in nerves by causing changes in the nerve membrane that prevent depolarisation and thus block nerve propagation, termed "membrane stabilization".

An action potential is a brief fluctuation in membrane potential caused by the rapid opening and closing of voltage-gated ion channels. In resting mode, nerve fibres are polarized, with higher concentrations of sodium ions outside than inside the cell, and the reverse for potassium ions.  The sodium and potassium channels are closed. Depolarisation is caused by the sodium channels opening, allowing the influx of sodium ions from the outside to inside the cell. Local anaesthetics prevent the sodium channels from opening so that depolarization and therefore action potential transmission is obtunded.

**Physiochemical characteristics of different local anaesthetic drugs:**

Most injectable local anaesthetics have a three-part structure consisting of a tertiary amine attached to a substituted aromatic ring by an intermediate chain. Local anaesthetics can be classified according to whether the intermediate chain contains either an ester or amide group. In current clinical practice esters have been largely superseded by amides.

- Ester linkages are unstable and are broken down by hydrolysis in solution and in the plasma by pseudocholinesterase.  They have a short half-life and cannot be sterilized by heat. Ester local anaesthetics include cocaine, procaine and amethocaine. Procaine with adrenaline is the only local anaesthetic preparation licensed for use in cattle in the UK.

- Amide linkage is more stable and the drug in solution can withstand heat sterilization and pH changes. Amide local anaesthetics are liver metabolised. Examples of amides include lidocaine, bupivacaine and mepivicaine.

The physiochemical characteristics of individual local anaesthetics also determine properties such as potency and duration of action.

- **Lipid solubility is the main determinant of potency**.  The higher the lipid/water partition coefficient, the more potent the drug is likely to be.

- **Protein binding determines the duration of effect**, presumably because highly bound drugs stay in the lipoprotein of nerve membranes longer.

- The pKa of a local anaesthetic determines the ratio of ionised to unionised drug when it is injected into the body. The higher the pKa, the less of the unionised base is present at body pH. Only unionised drug can penetrate the nerve membranes, therefore **the pKa will affect the speed of the onset** of the drug. The lower the pKa, the faster the onset.

| Agent | Potency | Lipid solubility | pKa | Prot binding | Onset | Duration Min |
|---|---|---|---|---|---|---|
| Procaine | | 1 | 8.9 | 6% | Slow | 60 – 90 |
| Lidocaine | 2 | 3.6 | 7.7 | 65% | Fast | 90 – 200 |
| Mepivicaine | 2 | 2 | 7.6 | 75% | Fast | 120 - 240 |
| Bupivacaine | 8 | 30 | 8.1 | 95% | Medium | 180 - 600 |
| Ropivacaine | | | 8.1 | 95% | | |
| Levobupivacaine | | | | | | |

**Sensitivity of nerve fibers to local anaesthetics**

Nerve fibres are either myelinated (A and B) with subdivisions into $\alpha$ $\beta$ $\gamma$ $\delta$ or non-myelinated (C). They have somatic motor and somatic sensory functions. B-fibers are part of the autonomic nervous system and are the smallest and slowest conducting fibers.

**Myelinated fibers**

Nodes of Ranvier are present in all myelinated fibers, and the internodal distance decreases with increasing nerve diameter.  Local anaesthetics must prevent depolarization in three to four adjacent nodes to produce a block. Larger nerve fibres have longer internodal distances so that they are more difficult to block effectively by the injection of local anaesthetic. Higher concentrations of local anaesthetics are required higher. Motor nerves are myelinated and generally of large diameter, so in theory they less sensitive to local anaesthetic blockade than

the smaller diameter, myelinated A$\delta$ sensory nerve fibers. However the pharmacology of local anaesthetics is more complex than once thought. Myelination, surface area to volume ratio and frequency of nerve firing all influence the susceptibility of different nerve fibers to blockade by local anaesthetics.

**Unmyelinated fibers**

C fibres are unmyelinated and are both somatic and autonomic. Somatic C –fibres subserve pain and temperature transmission. Unmyelinated fibers are generally considered to be more susceptible to local anaesthetic blockade because a smaller length of nerve fiber membrane must be blocked in order to prevent action potential transmission.

The difference in sensitivity of motor and sensory nerve fibers to local anaesthetics is advantageous, since a concurrent motor nerve block is usually undesirable. Administration of low doses of local anaesthetics may allow some differentiation between sensory and motor fiber blockade, such that motor function is unimpaired whilst analgesia is produced. However clinically, complete sparing of motor function while still producing analgesia is currently not possible with the local anaesthetic drugs available.

**Characteristics of Local Anaesthetic Agents**
**Lidocaine**
- Extremely stable in solution
- Short period of onset (5-10 mins)
- Intense but short duration of action (1.5-2 hours)
- Addition of adrenaline – doubles time for absorption –prolongs duration of effect

**Mepivicaine**
- Slightly less toxic than lidocaine
- Useful equine lameness diagnosis – less post injection oedema
- Longer duration of action than lidocaine (2-3 hours)

**Bupivacaine**
- Very stable compound. Slower rate of onset than lidocaine, but of much longer duration of action (onset: 20-30 minutes, duration of action: 6-8 hours)
- Four times more potent than lidocaine
- Bupivacaine shows good motor/sensory separation and does not require the addition of adrenaline to prolong its effects or reduce its systemic accumulation
- Greater potential for cardio toxicity compared to lidocaine, do not give IV.

**Stereoisomerisms**

Many local anaesthetics contain an asymmetric carbon atom that can exist in two ((S (levo) and R (dextro)) forms. The S isomers (Ropivacaine and Levo bupivacaine) appear to have a lower affinity for the Na$^+$ channel and S isomers have a lower cardiac toxicity profile.

**Ropivacaine**

- pKa of 8.1, with high protein binding capacity of up to 95% providing for a long duration of action.
- Single S enantiomer with lipid solubility intermediate between lidocaine and bupivacaine
- Intrinsic vasoconstrictor properties so no adrenaline needs to be added
- Ropivacaine is less arrhythmogenic and less cardio-depressive than equivalent doses of bupivacaine
- Motor and sensory block of shorter duration than bupivacaine
- Motor block slower onset, less dense, more rapid resolution making it an ideal drug for sensory and motor block separation

**Levo-bupivacaine**

- Levo bupivicaine is a long acting amide local anaesthetic that is the S (-) isomer of racaemic bupivacaine
- Produces a longer sensory block due to greater vasoconstriction
- When compared to ropivacaine in animals, levo bupivacaine had similar pronounced nerve blocking effects, depending on the concentration and model
- Similar cardiovascular effects to ropivacaine in animals
- Levo bupivacaine is contraindicated for IVRA (Intravenous regional Anaesthesia)
- Levo bupivicaine should be used with caution in patients with impaired cardiovascular function or liver disease or reduced liver blood flow
- Levo bupivacaine is less cardiotoxic than bupivacaine

**Systemic Toxicity Of Local Anaesthetic Drugs**

Cats are considered to be more susceptible than dogs to toxicity, but problems are uncommon if appropriate doses are given.

| Drug | Maximum dose for infiltration |
|---|---|
| **Lidocaine** | 12 mg/kg (dogs) |
| | 6 mg/kg (cats) |
| **Lidocaine + adrenaline** | 7 mg/kg |
| **Bupivacaine** | 2 mg/kg |

When performing intercostal or intra-pleural injections of local anaesthetics reduce dose by 50%.

**Systemic toxicity depends on:**
- Site of injection: Vascular sites lead to rapid absorption and this will contribute the peak plasma concentration attained after injection. Reduce dose when injected into areas with a good blood supply.
- Drug used (bupivicaine > lidocaine)
- Speed of injection: only important when given IV
- Addition of adrenaline: Local vasoconstriction, resulting in slow absorption with reduction in peak concentration of up to 20 – 50%

**Cardiovascular Effects of Local Anaesthetics**
- Due to a combination of slowing of conduction in the myocardium, myocardial depression and peripheral vasodilation, hypotension, bradycardia and cardiac arrest can occur.

**Central Nervous System Effects of Local Anaesthetics**
These agents are lipid soluble and of low molecular weight and therefore cross the blood-brain-barrier readily. At sub toxic dose, local anaesthetics can act as anticonvulsants, sedatives and analgesics. At higher concentrations they cause convulsions and generalized CNS depression occurs.

**Local toxicity caused by local anaesthetics**
Can cause local vasodilation (depends on whether the preparation contains adrenaline)
Vascular damage if penetrate a blood vessel (care in animals with reduce blood clotting due to the risk of a haematoma)
Nerve damage (if injected directly into a nerve fiber)

**Reducing the risk of toxicity following the administration of local anaesthetics**
- Care during injection: use a small needle that will cause minimal tissue damage
- Calculate the safe maximal dose of local anaesthetic depending on bodyweight
- Draw up the drug using an appropriately sized syringe to ensure accuracy
- Dilute the local anaesthetic with NaCl 0.9% to provide additional volume for infiltration techniques
- Draw back before injecting the local anaesthetic in order to prevent inadvertent intravascular injection

## References

BRUNE K & FURST DE (2007). Rheumatology 2007, 1-9.

FREISE, K.J., NEWBOUND, G.C., TUDAN, C. & CLARK T.P. (2012). J Vet Pharmacol Ther 35 Suppl 2, 45-51

GIRAUDEL JM, KING J, JEUNESSE EC, LEES P, TOUTAIN PL (2009). J Vet Pharmacol Ther 32, 18-30.

HAWKEY CJ, SIMON T, BEAULIEU A ET AL. (2000). Arthritis Rheum 43, 370-377.

JUNG M, LEES P, SEEWALD W, KING J (2009). J Vet Pharmacol Ther 32, 41-48.

LASCELLES BD, MCFARLAND JM, SWANN H (2005). Vet Ther 6, 237-51.

LINTON, D.D., WILSON, M.G., NEWBOUND, G.C., FREISE, K.J. & CLARK T.P. (2012). J Vet Pharmacol Ther. 35 Suppl 2, 53-64.

MCADAM BF, CATELLA-LAWSON F, MARDINI IA et al. (1999). Proc Natl Acad Sci USA 96, 272-277.

ROSSET J, MAILLARD M, NUSSBERGER J ET AL. (1999). Clin Pharmacol Ther 66, 76-84.

SVENSSON CI & YAKSH TL (2002). Annu Rev Pharmacol Toxicol. 42, 553-583.

TEGEDER I, NIEDERBERGER E, ISRAR E et al. (2001). FASEB J 15, 595-597.

EPAR Onsior: p24 http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/veterinary/000127/WC500067756.pdf

PELLIGAND L, KING J N, TOUTAIN P L, ELLIOTT J AND LEES P (2012). J Vet Pharmacol Ther 35, 19-32.

SILBER H E, BURGENER C, LETELLIER M, PEYROU M, JUNG M, KING J N, GRUET P AND GIRAUDEL J M (2010). Pharmaceutical Research 27:2633-45.