Anaesthesia: MAC Reduction Techniques

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“There are no safe anaesthetic agents, there are no safe anaesthetic techniques, there are only safe anaesthetists.”
Robert Smith

Disclaimer: While all care has been taken in compiling the published dose recommendations contained in the text and tables of this handout, veterinarians are strongly advised to check the accuracy of dose rates in addition to always following labelled instructions prior to administrating any of the agents discussed below.

Introduction
General anaesthesia is a state of unconsciousness produced by drug-induced depression of the central nervous system (CNS). In order to produce “general anaesthesia”, a drug or combination of drugs must induce the “four facets of anaesthesia”: - unconsciousness, amnesia, analgesia, and muscle relaxation; however, we still lack the ability to selectively depress those areas of the brain responsible for these functions. Instead, anaesthetic agents produce dose-dependent depression of the entire CNS in-addition to producing both direct and indirect effects on all the major systems of the body – at least to some degree. General anaesthesia also impairs – and in some cases completely obtunds - normal homeostatic reflexes and control systems. This further limits the patient’s ability to recognise, respond to, and compensate for anaesthetic-induced reductions in vital organ function. Put simply, general anaesthesia not only predisposes patients to profound changes in vital organ function but also limits their ability to cope with these insults and “self correct”. Normal, healthy individuals have significant reserves of organ function and are usually tolerant of the physiological stresses of anaesthesia and surgery – as long as the insults are short in duration or moderate in degree. In compromised or critically ill patients however, these same “reserves” of organ function are reduced to a variable degree, impairing the ability of these patients to cope with the “normal” depressant effects of anaesthesia. These patients are intolerant of physiological stresses and insults, irrespective of duration or degree, and are therefore highly vulnerable to the adverse effects of anaesthesia per se.

Inhalants such as isoflurane, halothane and sevoflurane have long been the maintenance agents of choice in small animal anaesthesia, and there is no doubt their use offers many advantages. However some patients – the very young, the very old, the very sick – and some species such as the cat, are often intolerant of inhalant-induced cardiopulmonary depression and may benefit from adjunctive strategies that permit a reduction in vaporizer settings (i.e. MAC reduction). The concept of balanced anaesthesia (combining low doses of multiple agents to produce the four facets of anaesthesia rather than relying on a relatively large dose of a single agent) is not new, but until recently, our ability to implement this idea has been somewhat limited. While the importance of appropriate pain management in veterinary patients is now well recognised, our focus has tended to be on postoperative- rather than intraoperative analgesic techniques. However, intraoperative pain management may prove equally important – particularly in patients who are intolerant of higher vaporizer settings. This lecture will focus on three – relatively easy to implement - MAC reduction strategies: judicious premedication, regional anaesthetic techniques, and the use of adjunctive
intraoperative analgesic agents. Brief notes – including published dose rate recommendations for the various techniques – are given below and will be supplemented by the on-line lecture material.

**MAC: What is it and why is MAC reduction beneficial?**

The potency of an inhalational agent is a measure of that amount which must be delivered to a patient to produce a desired effect i.e. surgical anaesthesia. It is obvious that the dose of an inhalational agent cannot be measured in terms of “mg/kg” - the basis for determining potency of injectable agents. The term "MAC" (minimum alveolar concentration) was first coined in 1963, and has become the standard index of potency for the inhalational agents. MAC is defined as the minimum alveolar concentration of an agent at one atmosphere that produces immobility in 50% of subjects exposed to a supramaximal (i.e. surgical) stimulus. Anaesthetic potency is inversely related to MAC – the smaller the MAC value, the more potent the agent. Halothane is the most potent of the commonly used inhalational agents with a MAC of 0.8. Isoflurane (1.3) and sevoflurane (2.5) are less potent than halothane: isoflurane or sevoflurane vaporizer settings therefore need to be significantly higher than those used for halothane to produce the same "level" of anaesthesia in a given patient under identical circumstances.

MAC is a measure of the ED₅₀ of an inhalational agent i.e. the concentration at which 50% of subjects are at surgical anaesthesia but 50% are not. To prevent movement in 95% of anaesthetized patients it is necessary to administer somewhere in the range of 1.3-1.5 x MAC (i.e. an alveolar concentration of approximately 1.2% halothane (1.5 x 0.8%) or 1.95% isoflurane (1.5 x 1.3%)). MAC is derived in healthy, un-premedicated animals that have been mask-induced with the agent being investigated. Not all patients will require vaporizer settings as high as 1.5 x MAC to ensure surgical anaesthesia – in fact, these settings will be excessive for >50% of the population. Factors such as age, premedication, induction agent, body temperature and patient “well being” all influence MAC. It’s also important to remember “MAC” refers to the alveolar concentration of the agent, not the vaporizer setting or circuit concentration. However, an understanding of anaesthetic delivery systems allows us to make educated guesses about the relationships between inspired and alveolar concentrations of a given agent, while end-tidal gas monitors – which measure the concentration of anaesthetic agent in exhaled gases (a close approximation of alveolar concentration) – are now readily available.

Although they produce general anaesthesia – and therefore by definition must produce some degree of analgesia – the inhalants are relatively poor analgesic agents. Pain is a complex, multidimensional experience involving both a physiologic sensation (i.e. nociception) and an emotional reaction to that sensation (i.e. perception). Perception occurs in the higher centres of the brain and requires a normally functioning cortex. As an anaesthetized patient moves along the continuum of unconsciousness from “near awake” to “near death”, certain functions controlled by the CNS are lost in a specific order: - (1) pain and memory, (2) consciousness, (3) motor coordination, (4) response to external stimuli, (5) muscle tone, (6) protective reflexes (e.g. the gag reflex), (7) normal control of autonomic function, (8) normal control of the cardiovascular and respiratory systems resulting in dysfunction, (9) absolute control of ventilation resulting in respiratory arrest, and (10) absolute control of cardiovascular function resulting in cardiac arrest. Pain perception cannot occur in appropriately anaesthetized patients because the higher centres of the brain are
effectively blocked by the anaesthetic agent(s) – in fact, loss of pain perception occurs in Stage I anaesthesia, prior to the actual loss of consciousness.

So how can the addition of adjunctive analgesic agents benefit a patient who is already rendered incapable of pain perception by the administration of general anaesthetic agents? Although an appropriately anaesthetized patient cannot perceive pain, nociception – the physiological process by which the noxious stimulus is transmitted from the site of injury to the brain – does not require a functioning cortex and continues unabated in the face of general anaesthesia. Anaesthetized patients should always exhibit a small sympathetic response (i.e. tachycardia, hypertension and peripheral vasoconstriction) in the face of a supramaximal stimulus, but in some patients, the depth of anaesthesia required to prevent an excessive sympathetic response and/or purposeful movement in response to the stimulus is associated with profound inhalant-associated cardiopulmonary depression. The addition of adjunctive analgesic agents (e.g. opioids, alpha₂-agonists, and local anaesthetic agents) modulates nociception, reduces the sympathetic response, and by supplementing one of the four essential “facets” of general anaesthesia, allows a reduction in the dose of the primary anaesthetic agent. In addition, adjunctive analgesic agents may also contribute to postoperative analgesia by modifying components of acute pathological pain (e.g. central sensitization).

MAC REDUCTION STRATEGIES

1. Premedication
Premedication offers many benefits including (1) analgesia, (2) calming, sedation or restraint, (3) promoting a smooth induction and recovery, (4) reducing the subsequent dose of induction and maintenance agents, and (5) offsetting potentially adverse drug and physiological effects. Although all drugs have both positive and negative effects, the benefits of judicious premedication – including intraoperative analgesia and subsequent MAC reduction – far outweigh potential disadvantages: premedication should therefore be considered in every patient.

In cats and dogs, “premeds” are usually administered IM or SQ for the sake of convenience, although many of these agents can also be given IV at the lower end of the dose range – the latter method is particularly useful in compromised patients, allowing titration of the desired response. Two or more premeds are often combined to achieve a specific effect (e.g. neuroleptanalgesia) or to counteract undesirable side effects of a single agent (e.g. ketamine-induced muscle rigidity). Strictly speaking, the term “neuroleptanalgesia” refers to a state of hypnosis and analgesia produced by the combination of a neuroleptic agent (i.e. a phenothiazine or a butyrophenone) with an opioid; however, similar effects are seen with all sedative/opioid combinations. Sedative/opioid combinations result in marked synergism, producing analgesia and a degree of sedation (or restraint) greater than that achieved by either agent alone, often accompanied by a significant dose-sparing effect for both induction and maintenance agents. Common neuroleptanalgesic techniques include acepromazine/opioid-, benzodiazepine/opioid-, or alpha₂-agonist/opioid combinations. The agents may be combined at any dose within the recommended dose ranges for each individual drug, although it is important to remember the synergistic effects of these combinations: low doses of each drug are often more than sufficient. Unfortunately, there is no ideal premed, and no premed that is ideal for all situations. Every premed has its own set of advantages and disadvantages that vary according to the circumstances.
under which the drug is employed: appropriate drug choice for a given patient is based on a thorough understanding of these.

**Table 1: Published dose recommendations for premedicants with MAC-sparing potential***

<table>
<thead>
<tr>
<th>Agent</th>
<th>Published dose recommendations Dogs</th>
<th>Published dose recommendations Cats</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acepromazine</td>
<td>0.01-0.1 mg/kg (max dose = 3mg) 0.01-0.04 mg/kg preferable</td>
<td>0.01-0.1 mg/kg</td>
<td>IV, IM, SQ</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.1-0.2 mg/kg</td>
<td>0.07-0.2 mg/kg</td>
<td>IV, IM, SQ</td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.1-0.5 mg/kg</td>
<td>0.05-0.5 mg/kg</td>
<td>Slow IV</td>
</tr>
<tr>
<td>Medetomidine</td>
<td>2-40 mcg/kg IV or IM</td>
<td>20-80 mcg/kg IM</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>0.1-2.0 mg/kg</td>
<td>0.1-0.5 mg/kg</td>
<td>IV, IM, SQ</td>
</tr>
<tr>
<td>Methadone</td>
<td>0.1-1.0 mg/kg</td>
<td>0.1-0.6 mg/kg</td>
<td>IV, IM, SQ</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>0.01-0.02 mg/kg</td>
<td>0.005-0.02 mg/kg</td>
<td>IV, IM, SQ</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>0.2-0.4 mg/kg</td>
<td>0.2-0.4 mg/kg</td>
<td>IV, IM, SQ</td>
</tr>
</tbody>
</table>

*Not all agents listed have produced clinically significant reductions in MAC under the conditions studied.

The use of transdermal opioid “patches” (e.g. fentanyl patches) has increased in recent years. Preoperative fentanyl patch application is a successful MAC reduction strategy (18% in cats and 37% in dogs), providing sufficient time has been allowed for the patch to achieve effective plasma fentanyl concentrations prior to induction i.e. at least 7 hr after patch application in cats and 24 hr in dogs. Premedication with NSAIDs has no effect what-so-ever on MAC.

2. **Intraoperative Analgesia: Local Anaesthetic Techniques**

Local anaesthetic agents (LAA) produce reversible blockade of signal transmission along nerve fibres, causing temporary loss of sensory and/or motor function. These agents produce complete – albeit often short-lived – analgesia by blocking nociceptive input from a given area. LAA are voltage-gated sodium (Na\(^+\)) channel blockers, inducing conduction blockade via inhibition of the normal Na\(^+\) ion influx responsible for action potential generation (and propagation) within nerve axons. The blockade is completely reversible, with normal conduction returning as the agent is redistributed and metabolised. Variations in Na\(^+\) channel density and LAA binding affinity between different nerve fibres results in the phenomenon of differential blockade: small fibres (e.g. autonomic and pain) are blocked before larger fibres (e.g. sensory and motor), while myelinated fibres are blocked before non-myelinated fibres of similar diameter. Blockade therefore results in loss of function in the following order: (1) pain sensation, (2) cold sensation, (3) warmth sensation, (4) touch, (5) deep pressure, and finally (6) motor function.

Various agents – including lidocaine, mepivacaine, bupivacaine, and ropivacaine – provide useful and effective analgesia in small animals. Potency, onset of effect and duration of action varies from agent to agent (see Table 2). LAA may be administered topically (e.g. deposited onto the cornea), delivered transdermally, or injected via a number of techniques including (1) local infiltration, (2) perineural injection (i.e. depositing the agent near specific, often major nerves to produce regional blockade of a known area), (3) neuraxial administration (i.e. epidural or subarachnoid injection), (4) intra-articular injection, (5) injection into a body cavity (e.g. interpleural or intraperitoneal injection), (6) injection into an occluded vessel i.e. intravenous regional anaesthesia (IVRA), or (7) delivered intravenously as a constant rate infusion (CRI).
### Table 2: Basic properties of commonly used local anaesthetic agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Onset of action (min)</th>
<th>Duration of effect (min)</th>
<th>Relative potency</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>Intermediate 10-15</td>
<td>Intermediate 60-120</td>
<td>2</td>
<td>Local infiltration, topical, IVRA*, regional blocks**</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>Rapid 5-10</td>
<td>Intermediate 90-180</td>
<td>2</td>
<td>Local infiltration, regional blocks</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Slow 20-30</td>
<td>Long 240-360</td>
<td>8</td>
<td>Local infiltration, regional blocks</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>Rapid 5-10</td>
<td>Long 180-300</td>
<td>8</td>
<td>Local infiltration, regional blocks</td>
</tr>
</tbody>
</table>

* IVRA = intravenous regional anaesthesia  
** = all perineural, neuraxial, intra-articular, and “inter-cavity” techniques.

The addition of epinephrine/adrenaline (5 micrograms/ml or 1:200,000) to local anaesthetic solutions results in local vasoconstriction and therefore a more prolonged duration of effect due to decreases in local perfusion and reduced uptake and redistribution of the agent. However, epinephrine-containing solutions are contraindicated in distal sites (e.g. ears, digits and the tail) where reduced perfusion may lead to ischaemic injury. Commercial mixtures of LAA with adrenaline are available. Alternatively, this concentration can be prepared by adding 0.1 ml of a 1:1000 solution of adrenaline to 20 ml of LAA. While generally considered very safe, known complications accompany the use of LAA including (1) injection related problems (e.g. infection, haematoma formation and nerve laceration/injury), and (2) various drug-associated toxicities.

**Local anaesthetic agents: Toxicity**

Like all drugs, LAA have both positive and negative effects. Various LAA toxicities are well documented, including: (1) seizures and CNS dysfunction, (2) cardiovascular collapse, (3) allergic reactions, (4) methaemoglobinaemia, and (5) localized tissue reactions. CNS dysfunction and cardiovascular collapse are the most common (and clinically dramatic) complications, but are generally not fatal if recognised early and treated appropriately. These problems usually arise as a result of overdose or accidental IV administration: preventative strategies include careful dose calculation, dose-reducing strategies, and use of appropriate injection technique (see below). Signs of CNS toxicity include (1) drowsiness, (2) agitation, (3) respiratory depression, and (4) fine muscle tremors progressing to grand mal seizures; and are usually seen at doses lower than those resulting in cardiovascular collapse. Cardiovascular effects include (1) myocardial depression (with reductions in electrical excitability, HR and contractility), (2) ventricular arrhythmias, (3) peripheral vasodilation, and (4) arterial hypotension: these effects may be profound and arise from both direct (myocardial and peripheral vascular effects) and indirect (CNS toxicity and autonomic blockade) actions. Needless-to-say, anaesthesia masks many of these signs: respiratory arrest, hypotension and/or cardiovascular collapse may be the first indicators of a problem. Species vary in their susceptibility to toxicosis: cats seem particularly susceptible to lidocaine toxicosis. Treatment involves (1) immediately ceasing further administration of the LAA, (2) administering anti-convulsant agents to control seizures (e.g. benzodiazepines or thiobarbiturates), and (3) symptomatic therapy including IV fluid therapy (volume expansion), the use of positive inotropes, and ventilatory support. Acidosis and hypoxia potentiate the CNS and cardiovascular toxic effects: some experts therefore recommend delivery of bicarbonate and O₂ administration to offset this.
Local anaesthetic blocks: Administration guidelines

Basic rules governing proper administration of LAA include: (1) always use sterile solutions and injection equipment, (2) clip and/or clean the skin over the injection site appropriately, (3) use the smallest gauge needles practicable and change these as they become dull, (4) avoid injection into inflamed tissues, (5) align the needle with the nerve trunk if possible, (6) always calculate the maximal allowable dose for a given patient, (7) always aspirate prior to injecting the LAA to ensure the needle has not penetrated a vessel, and (8) inject agents slowly.

Table 3: Commonly used local anaesthetic agents: toxic doses

<table>
<thead>
<tr>
<th>Agent</th>
<th>Clinically useful concentrations*</th>
<th>Published dose recommendations - MAXIMUM doses</th>
<th>Reported toxic doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>1-2%**</td>
<td>5 mg/kg in dogs</td>
<td>&gt;12 mg/kg in dogs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3 mg/kg in cats</td>
<td>&gt; 6 mg/kg in cats</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>2%</td>
<td>5 mg/kg in dogs</td>
<td>20-30 mg/kg</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>0.25-0.75% (0.5%)</td>
<td>2 mg/kg in cats and dogs</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>0.5%</td>
<td>3 mg/kg in dogs</td>
<td>5 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 mg/kg in cats</td>
<td></td>
</tr>
</tbody>
</table>

* Agents can be diluted to a maximum of 50:50 with normal saline (0.9% NaCl)
** Many local anaesthetic solutions are acidic and sting on administration. Lidocaine may be particularly painful at clinically useful concentrations. Patient tolerance may be improved by (1) raising the pH of the solution by combining with sodium bicarbonate (1 mEq/ml solution), in a 1:9/NaHCO₃:2% lidocaine ratio, by volume, (2) warming the solution, and (3) always injecting slowly.

Dental blocks: brief notes

Recommended dental blocks for cats and dogs are as follows. For more detailed descriptions of the blocks, please see specific references in the reference list. Relevant diagrams are provided on the last page of this handout. When performing these blocks, always calculate maximum doses of LAA carefully and then divide this dose between the various sites to minimise the risks of inadvertent toxicity. Recommended volumes of LAA for administration at multiple sites in small animals are (1) 0.1 mL per site in very tiny patients, (2) 0.1-0.3 mL per site in cats, and (3) 0.1-0.5 mL/site in dogs. If these volumes exceed dosing recommendations, consider diluting the agent up to a maximum of 50:50 with sterile 0.9% NaCl. Avoid inserting needle tips deeply into the various foramina to minimise the risks of nerve laceration. Instead, entry of LAA into foramina is encouraged by (1) placing pressure over the needle tip and opening of the foramen with your thumb during injection, (2) injecting the agent slowly, and (3) tilting the patient’s head during injection to encourage gravity flow. Dental blocks should be performed using the smallest gauge needles practicable e.g. 25-27 g.

1. **Infraorbital (IO) block:** This block produces ipsilateral analgesia of soft tissues rostral to the IO foramen but variable analgesia of the maxillary incisors in dogs. The block is performed via percutaneous or intraoral injection at the level of the IO foramen (dorsal to the caudal root of the 3rd upper premolar in dogs, or dorsal to the 2nd upper premolar in cats. Do NOT extend the needle tip beyond the medial canthus of the eye. Take extra care with cats and brachycephalics as the IO foramen is very shallow and poor technique may result in puncture of the globe or retrobulbar haemorrhage with proptosis.
2. **Maxillary nerve block**: Successful blockade produces ipsilateral analgesia of entire upper jaw, including the teeth. The block is performed via percutaneous injection (with the needle introduced at 90° to the skin) ventral to the zygomatic arch and just caudal to the lateral canthus of the eye. Walk the needle tip rostrally if the needle encounters the ramus of the mandible. An alternative, *intra-oral* approach for blocking the maxillary nerve is described in the article by Reuss-Lamky (see reference list). Animals need to be positioned in dorsal recumbency with the mouth opened widely. In dogs, the block is performed by inserting a small gauge needle just caudal to, and centre with, the last maxillary molar. The needle is advanced dorsally to a point level with or just beyond the root tips of the last molar and the agent injected slowly after aspirating initially. In cats, the block is said to be performed by inserting a small gauge needle at the base of the V-shaped notch or divot, near the soft palate junction at the roof of the mouth, just medial to the caudal root tips of the upper 4th premolar.

3. **Mental nerve block**: This block produces ipsilateral analgesia of the lower incisors and soft tissues rostral to the foramen. The block is performed via percutaneous or *intraoral* injection at the level of the mental foramen (caudoventral to the lower canine and ventral to the rostral root of the lower 2nd premolar). The foramen can be difficult to palpate in cats and small dogs. The injection site in this instance is on the line formed by the junction of the lower and middle thirds of the mandible at the level of the diastema between the 1st and 2nd premolars.

4. **Mandibular nerve block (inferior alveolar)**: This block produces reliable analgesia of the entire hemi-mandible. The block is performed via percutaneous injection at the opening of the mandibular/inferior alveolar foramen on the ventromedial aspect of the mandible at the level of the mandibular notch. Assist the direction of the needle tip by palpating the foramen *intra-orally* while making the injection, and attempt to keep the needle-tip “hard against” the mandible to minimize the chances of accidental blockade of the lingual nerve (blockade of which can result in postoperative self trauma to the tongue due to residual paraesthesia).

In all cases, a block of reasonably rapid onset but prolonged duration of action can be achieved by combining 1.0 mg/kg 2% lidocaine and 0.25 mg/kg 0.5% bupivacaine (i.e. 0.5 ml of each per 10 kg LBW) to create a solution that is then divided between the various sites.

**Epidural anaesthesia: brief notes**

In dogs and cats, epidural injection is usually performed at the lumbosacral space (i.e. L7/S1). The space is identified by palpation after positioning the patient in either sternal or lateral recumbency with the hind limbs drawn cranially – practice in both positions is essential. Palpable landmarks include the wings of the ilium, and the dorsal spinal processes of L6, L7 and the fused sacrum. The dorsal spinal process of L7 may be difficult to palpate in large or obese individuals, as it is considerably shorter than that of L6. Sterile technique is essential i.e. surgical clip and prep of the area, and the use of sterile gloves, spinal needles (22-20 g, 25-55 mm) and solutions. The spinal needle is inserted perpendicular to the skin and the tip walked cranially if bone is encountered. Entry into the space is identified using the “hanging drop” technique or via a test dose of 1 ml of air or sterile 0.9% NaCl. A bloody tap (i.e. puncture of a vertebral sinus) requires repositioning of the needle. However, in the face of dural sac puncture (i.e. CSF flows from
the needle hub), choices are repositioning of the needle or administration of half the calculated dose as long as the agent(s) is preservative-free: agents containing preservatives should *never* be administered subdurally.

### Table 4: Agents and doses for epidural administration in dogs: Published recommendations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Epidural dose</th>
<th>Onset of action (min)</th>
<th>Duration of effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>4-5 mg/kg</td>
<td>5-10</td>
<td>45-90 min</td>
</tr>
<tr>
<td></td>
<td>1 ml/4.5-7.5 kg LBW*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>1-1.5 mg/kg</td>
<td>20</td>
<td>120-360 min (2-6 hr)</td>
</tr>
<tr>
<td></td>
<td>1 ml/4.5-7.5 kg LBW</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>1-1.5 mg/kg</td>
<td>7-20</td>
<td>115-140 min</td>
</tr>
<tr>
<td>Morphine**#^</td>
<td>0.05-0.15 mg/kg</td>
<td>30-60</td>
<td>10-24 hr</td>
</tr>
<tr>
<td></td>
<td>in 0.2 ml/kg 0.9% NaCl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buprenorphine^</td>
<td>0.005-0.015 mg/kg</td>
<td>60</td>
<td>6-24 hr</td>
</tr>
<tr>
<td></td>
<td>in 0.2 ml/kg 0.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* LBW = lean body weight, further reduce doses by 25% in paediatric, geriatric and pregnant patients
** Use preservative-free morphine. Some references report minimal neurotoxicity in people following administration of morphine containing the preservatives methylparaben or sodium metabisulphite, but these preservatives should *never* be injected subdurally.
# This dose of morphine may also be “diluted in” the recommended volume of lidocaine or bupivacaine (rather than 0.9% NaCl) and administered as a combination. This combination results in excellent intraoperative anaesthesia and long-lived postoperative analgesia.
^ Epidural morphine or buprenorphine alone does not result in significant MAC reduction in cats.

**Note:** Total volume of injectate should approximate 0.2 ml/kg but should *not* exceed 6 ml in total in any dog.

3. **Intraoperative Adjunctive Analgesic Agents**

Supplemental or adjunctive analgesic agents – i.e. opioids, alpha₂-agonists, lidocaine and ketamine – may be administered intraoperatively as a single bolus, as repeat “top-up” doses, or continuously as constant rate infusions (CRI). In many cases, a single slow IV bolus of morphine (e.g. 0.1-0.3 mg/kg – use lower end in cats) or fentanyl (e.g. 2.0-10 mcg/kg in dogs or 1.0-3.0 mcg/kg in cats) given prior to an expected painful stimulus may offset the need to increase vaporizer settings and provide an adequate period of additional intraoperative analgesia. However, many compromised patients are intolerant of normal vaporizer settings, and may benefit from the constant “background” of analgesia and subsequent MAC reduction provided by continuous administration of an adjunctive agent.

CRI results in more stable and effective analgesia in comparison to intermittent IM or IV administration, and minimises the disadvantages of intermittent delivery including (1) slow onset of effect, (2) plasma drug concentration “peaks and troughs”, and (3) a higher overall drug burden (CRI usually results in less total drug delivery over time compared to intermittent “bolus” dosing).
### Table 5: Published dose recommendations for adjunctive analgesic CRIs

<table>
<thead>
<tr>
<th>Agent</th>
<th>Published dose rates</th>
<th>Loading dose rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>Dogs: 1.0-10.0 mcg/kg/hr (1.0-5.0 mcg/kg/hr is often sufficient)</td>
<td>Dogs: 2.0-5.0 mcg/kg IV</td>
</tr>
<tr>
<td></td>
<td>Cats: 1.0-5.0 mcg/kg/hr</td>
<td>Cats: 1.0-3.0 mcg/kg IV</td>
</tr>
<tr>
<td>Morphine</td>
<td>Dogs: 0.1-0.2 mg/kg/hr (0.1 mg/kg/hr often sufficient)</td>
<td>Dog: 0.3-0.5 mg/kg slow IV</td>
</tr>
<tr>
<td></td>
<td>Cats: 0.03-0.1 mg/kg/hr</td>
<td>Cat: 0.1 mg/kg slow IV/IM</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Dogs: 10-50 mcg/kg/min (0.6-3.0 mg/kg/hr)</td>
<td>Dogs: 1.0 mg/kg IV</td>
</tr>
<tr>
<td></td>
<td>Cats: <strong>Not recommended during anaesthesia</strong></td>
<td></td>
</tr>
<tr>
<td>Medetomidine</td>
<td>Dogs: 0.5-3.0 mcg/kg/hr</td>
<td>Dogs: 0.0-1.0 mcg/kg IV</td>
</tr>
<tr>
<td></td>
<td>1.0 mcg/kg/hr recommended during anaesthesia</td>
<td></td>
</tr>
<tr>
<td>Ketamine</td>
<td>2.0-20.0 mcg/kg/min (0.12-1.2 mg/kg/hr)</td>
<td>0.25-0.5 mg/kg IV</td>
</tr>
</tbody>
</table>

(i) **Opioid CRIs**

Opioid CRIs offers many advantages for intraoperative pain management including ease of administration and rapid adjustment of effective dose. Although several agents have been evaluated for their effectiveness, fentanyl or morphine CRIs are used most commonly in cats and dogs. Fentanyl’s pharmacokinetic profile (i.e. rapid onset of effect, short duration of action and short context-sensitive half time) makes it an ideal agent for delivery via CRI. Adjustments in delivery rate produce rapid changes in plasma fentanyl concentrations, allowing accurate titration of a desired response. MAC reduction is significant; however, many patients will experience marked bradycardia following clinically useful doses (although ABP is usually well maintained). Fentanyl can be delivered undiluted via a syringe pump or diluted to varying concentrations in LRS or 0.9% NaCl. It is still a relatively expensive agent in Australasia.

Morphine is a particularly appealing CRI agent due to its low cost, ready availability, and capacity to be diluted in commonly available IV fluids such as LRS or normal saline (0.9% NaCl). Morphine-associated histamine release may present a possible disadvantage of this strategy in animals with limited cardiovascular reserve or depressed sympathoadrenal function. Histamine release following the administration of morphine is a well-documented phenomenon. Histamine release is thought to depend on the dose, rate and route of morphine administration: rapid delivery of large IV boluses results in the greatest increase in plasma histamine concentrations while IM administration produces no appreciable change. The correlation between plasma histamine levels and consistent haemodynamic changes is controversial. While a study of five healthy dogs documented measurable increases in plasma histamine concentrations with morphine CRIs at doses ranging from 0.17 to 0.43 mg/kg/hr, cardiovascular function did not differ significantly compared to controls.

(ii) **Lidocaine CRIs**

Systemically administered lidocaine has also been investigated as an analgesic adjunct. The analgesic effects of systemic lidocaine are well documented in the human literature, and oral lidocaine is used commonly for the relief of neuropathic pain in people. Several studies have investigated the use of lidocaine infusions in dogs. Lidocaine CRIs have been shown to reduce MAC in healthy, isoflurane-anaesthetized dogs, and were not associated with adverse haemodynamic effects when administered at doses of 50 up to 200 μg/kg/min. A pilot
study investigating the potential analgesic effects of a CRI of lidocaine in dogs undergoing intraocular surgery, reported apparent post-operative comfort for up to 24 hours in 50% of the dogs receiving IV lidocaine intraoperatively. The infusion was started 15 minutes prior to commencing surgery and was discontinued at the conclusion of anaesthesia. Although dogs remained comfortable over the 24-hour study period, residual plasma lidocaine concentrations were undetectable two hours after extubation, suggesting a possible pre-emptive analgesic effect in these individuals.

The effects of lidocaine CRIs have also been examined in isoflurane-anaesthetized cats. Although infusions were shown to reduce MAC (and, incidentally, result in better preservation of mean ABP than isoflurane alone), the plasma concentrations necessary to achieve clinically significant MAC reduction were associated with significantly worse cardiovascular function overall (including reductions in heart rate, cardiac output, stroke volume, haemoglobin saturation and oxygen delivery) than an equipotent dose of isoflurane. Individual sensitivity/toxicosis was documented in the same study with one cat developing severe cardiovascular depression (necessitating resuscitation) at relatively modest plasma lidocaine concentrations. Lidocaine CRIs have been recommended in cats experiencing severe pain. However, published studies documenting the efficacy of this technique in cats are lacking, while one study investigating the effects of systemic lidocaine on thermal thresholds was unable to document any evidence of analgesia under the conditions studied.

(iii) Ketamine CRIs
The potential for ketamine (a non-competitive NMDA antagonist) to block spinal NMDA receptors involved in the phenomenon of central sensitisation, has prompted several investigations into the ability of ketamine to prevent or treat pain in cats and dogs. The analgesic effects of sub-anaesthetic doses of ketamine have been known for more than 35 years and appear to persist well beyond ketamine’s expected duration of action. Ketamine is not considered a suitable “primary” analgesic agent but may augment other analgesic therapies (e.g. opioids). Potential benefits of ketamine as an ancillary agent for intraoperative pain control include minimal cardiopulmonary depression (particularly when administered at the low doses associated with analgesia), and a possible pre-emptive analgesic effect. Despite these promising features, studies investigating the use of ketamine as an adjunctive analgesic agent in cats and dogs have yielded variable, sometimes conflicting, results. In isoflurane anaesthetized cats, a ketamine CRI was shown to significantly reduce MAC and increase heart rate and ABP in comparison to controls, but recoveries were so prolonged that the authors felt the technique unacceptable. A single preoperative dose of ketamine (2.5 mg/kg IM) provided measurable but short-lived analgesia in dogs undergoing ovariohysterectomy, and was reportedly more effective than when the same dose was administered immediately upon recovery. However, appreciable analgesia was only seen at 12 and 18 hours postoperatively in dogs undergoing forelimb amputation that received a preoperative bolus of ketamine in-addition to intra- and post-operative ketamine CRIs, while a single dose of ketamine (2 mg/kg IV) actually decreased thermal thresholds (i.e. increased pain sensitivity) in conscious cats.
Although the effects of alpha2-agonists as partial- or total intravenous anaesthetic adjuncts have been well investigated in horses, few studies have examined the intraoperative effects of CRI of these agents in anaesthetized cats or dogs. Two studies have investigated the cardiopulmonary and MAC-sparing effects of a CRI of dexmedetomidine – the dextrorotatory, active enantiomer of the racemic mixture medetomidine – in isoflurane anaesthetized dogs. The first study (Pascoe et al, 2006) reported significant MAC reduction (approximately 60%) in dogs receiving a CRI of 3 mcg/kg/hr. However, the more recent study (Uilenreef et al, 2008) – performed in ASA I or II dogs undergoing orthopaedic or soft tissue procedures – judged a CRI of 1 mcg/kg/hr preceded by an IV loading dose of 5 mcg/kg of dexmedetomidine to be more favourable in terms of overall cardiovascular stability (including adequacy of peripheral oxygen delivery), while still producing clinically useful reductions in MAC. It is important to note that these studies were performed in fit, healthy dogs: the effects of alpha2-agonist CRIs in compromised patients during anaesthesia have not been reported.

Combination CRIs
Combination CRIs e.g. MLK – a combination of morphine, lidocaine and ketamine – have also been promoted as effective analgesic options for pain management in dogs. There are few studies documenting the safety or efficacy of these techniques in either research or clinical veterinary patients. One paper examining the isoflurane MAC-reducing potential of MLK in comparison to CRIs of each of the individual constituents, failed to document any adverse haemodynamic effects when this combination was administered to healthy dogs. However, while MLK resulted in a significantly greater reduction in MAC (45%) than either ketamine or lidocaine, the reduction was no different following lone administration of morphine at the concentration contained in the MLK combination i.e. there was no demonstrable benefit of the MLK combination over and above lone administration of a morphine CRI. MLK is created by adding 12 mg morphine, 150 mg lidocaine and 30 mg ketamine to 500 ml of LRS or 0.9% NaCl and delivering the combination at a rate of 10 ml/kg/hr. This equates to morphine 4 mcg/kg/min (i.e. 0.24 mg/kg/hr), lidocaine 50 mcg/kg/min (i.e. 3 mg/kg/hr) and ketamine 10 mcg/kg/min (i.e. 0.6 mg/kg/hr).

References

References for specific techniques

APPENDIX – Dental block sites in the cat and the dog.

Upper jaw blocks

1. Site for infraorbital block (yellow oval).

Lower jaw blocks

1. Site for mental nerve block (yellow oval).

Please note:

1. Small mental foramen in the cat (yellow circle).