PERIOPERATIVE PAIN MANAGEMENT

MOVING BEYOND BUTORPHANOL

Part 2

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In Part 1 we reviewed the basic advantages of effective perioperative, multimodal pain control. Analgesics coupled with sedative/tranquilizers provide a more comfortable patient experience, reduce induction and maintenance agent requirements, and generally improve patient morbidity and mortality. Multimodal techniques reduce the dose of each individual drug which, in turn, reduces the potential for adverse drug effects. The pain pathway is a tinderbox. Once in flames, it is difficult to put out. Intervening before the pain system becomes sensitized is an absolute necessity when your goal is optimal patient benefit.

Perioperative pain management planning is most effective, and the outcome is more attractive, when each patient is looked upon as an individual. No single protocol, no single drug dose, could possibly be consistently safe and effective across the broad spectrum that comprises the veterinary patient pool. Advanced anesthesia and pain management is partially an art, not simply a mathematical exercise. Patient variables suggesting that higher drug doses should be considered include younger age, smaller size, excitable nature, and good health. Patient variables suggesting that lower doses be considered or that one should forego a drug family altogether include older age, larger size, calm nature, and poor health. In Part II, current information about the various drug families and individual agents will be discussed.

OPIOIDS remain the most important perioperative drug family. Opioids form the basis upon which perioperative strategies should be based. With few exceptions, these drugs are well tolerated. Their negative effects are easily controlled. They can be delivered by many different routes including intramuscular, transmucosal, IV bolus, IV CRI (constant rate infusion), and orally in some instances. These drugs can provide both sedation and pain relief but these qualities vary significantly between opioids. Significant side effects are not common at appropriate doses. It is critical that the anesthesiologist understand the basic advantages and shortcomings of the more common opioids in order to gain their best overall benefit.

BUTORPHANOL is a kappa agonist with moderate sedative effects capable of providing mild analgesia. Often the sedation outlasts the analgesia. Canine studies have failed to demonstrate analgesia past 45 minutes[1,2]. Feline studies have failed to show analgesia past 90 minutes[3,4]. In fact some studies have failed to show analgesia of any significance in dogs and cats[5,6]. Interestingly, Lascelles & Robertson's research in cats failed to demonstrate a difference in the analgesic intensity or duration as the dose was increased from 0.1 mg/kg to 0.8 mg/kg[4]. A significant number of these healthy cats demonstrated dysphoria when butorphanol was used as a sole agent.

Butorphanol 0.2 to 0.4 mg/kg can be combined with either acepromazine or medetomidine in healthy patients to create an effective preanesthetic or procedural sedation combination. Butorphanol can also be combined with a benzodiazepine, either midazolam or diazepam, to sedate aged and less healthy patients.

Butorphanol is not an effective analgesic when delivered by the oral route as butorphanol undergoes significant first-pass metabolism after oral administration. Couple the low oral bioavailability with butorphanol's short duration of effect and you would have to give a dog at least 1.0 mg/kg every 45 minutes to gain any meaningful analgesia.

A logical companion for butorphanol is buprenorphine. Butorphanol's analgesic onset is rapid but the mild analgesia is of short duration. Buprenorphine's time to peak analgesic effect is quite slow even when given by the IV route but its analgesic duration can be quite long. When administered together, butorphanol's short-term analgesia wanes as buprenorphine is reaching its peak effect.

One additional application for butorphanol is that of a mu antagonist. If a patient is exhibiting undesirable mu agonist effects while on morphine or hydromorphone (dysphoria, excess sedation, or excessive respiratory depression) butorphanol can reduce the unwanted mu agonist effects without total loss of patient analgesia.

In general, butorphanol does NOT give you much bang for the buck. Butorphanol costs about ten times more than morphine, per dose, while providing much more limited analgesia of much shorter duration.

NALBUPHINE possesses similar qualities to butorphanol and can be used in similar situations. The sedative effects are minimal when used alone but it is an effective component for procedural sedation or for initial preanesthetic sedation and analgesia; the sedation is somewhat less intense than, and the duration of effect 10 to 15 minutes less than, that of butorphanol containing combinations. Like butorphanol, nalbuphine provides mild analgesia of short duration. Nalbuphine can be dosed similar to butorphanol at 0.2 to 0.4 mg/kg up to 1.0 mg/kg in combination with acepromazine, medetomidine, or midazolam. See www.vasg.org/13_week_old_m.htm for videos demonstrating the differences between nalbuphine/medetomidine and butorphanol/medetomidine combinations in cats.

Like butorphanol, nalbuphine can be used to antagonize unwanted mu agonist effects without total loss of patient analgesia. Unlike butorphanol, **nalbuphine is not a scheduled drug** reducing the paper trail burden of the practice.

BUPRENORPHINE is a considerably more capable analgesic. While it is usually classified as a partial mu agonist, detailed research reveals complex interactions at the mu, delta, kappa, and ORL-1 receptors[7,8,9]. Buprenorphine is capable of providing analgesia for mild to moderate pain and, as newer animal research suggests, may be capable of handling more severe pain at higher doses than are currently being recommended[8]. There is considerable debate about the effect of dose on the analgesic intensity and the duration of effect.

In general, **higher doses are expected to provide a longer duration of effect**. Sheilah Robertson's work at the University of Florida supports that premise but no one has yet clearly defined the exact relationship between dose and duration. Table 1 below sums up a reasonable dose range including approximate durations of analgesic effect.

Increasing buprenorphine's dose increases the analgesic intensity but only to a point. Buprenorphine's dose/effect analgesia can be characterized as a bell shaped curve with higher doses, at a variable point

depending on the pain model studied, exerting a diminution of the analgesic intensity[8]. It appears that the dose at which you may see a reduction in analgesia is at or well above 0.1 mg/kg[8,10, 11].

Buprenorphine is remarkably free of adverse effects. Sedation, vomiting, and respiratory depression are rarely seen with buprenorphine. This lack of consistent sedation makes the drug unattractive as a solo opioid in a preanesthetic medication strategy for healthy patients.

Buprenorphine has a delayed onset, even when given IV, that needs to be taken into account for best effect. Given IV, peak effect occurs in about 30 minutes. Given IM, peak effect occurs in 45 to 60 minutes[12]. Data from Dr. Robertson's feline hydromorphone studies have shown SQ administration to be the least effective route, even in healthy cats[13]. Therefore, subcutaneous administration is not recommended.

Transmucosal (TM) absorption has been shown to be an effective route of administration in cats[14]. It appears to be as effective as IV administration. The alkaline pH of the cat's oral cavity favors the un-ionized form of the drug enhancing the drug's absorption. Placing the drug inside the cheek pouch or sublingually is easier than conventional oral drug administration. Coupled with the potential for long-term analgesia at proper dose, TM buprenorphine is an extremely attractive home analgesic medication for cats. Transmucosal administration should not be confused with oral (PO) delivery. **Buprenorphine is not effective when combined with a liquid and administered orally**. The enterohepatic first-pass effect removes 90+% of the drug before it can reach systemic circulation rendering that route impractical[15].

To date, no canine oral mucosal absorption studies have been performed leaving the details of that question unanswered. Oral mucosal absorption undoubtedly does occur in dogs but the bioavailability percentage is not yet known. We know that the transmucosal bioavailability in humans is 30% to 50% (possibly as high as 75%)[16]. Human pH is neutral to slightly acidic while canine saliva is slightly alkaline. It is likely that TM buprenorphine bioavailability in dogs is similar, if not superior, to that in humans. Adjusting the drug dose to compensate for the reduced bioavailability makes TM buprenorphine theoretically useful in dogs but expensive.

Combining buprenorphine with other opioids presents a variety of debatable consequences. **Combining buprenorphine with a kappa agonist like butorphanol or nalbuphine** might seem counterintuitive but it is a combination that the author supports for procedures producing mild to moderate pain. Buprenorphine is primarily a partial mu agonist with the available studies supporting opposing opinions about kappa receptor agonism/antagonism depending on the species and the study; more recent studies support an agonistic kappa effect in animals[17,18]. Butorphanol is a kappa agonist with mu antagonistic properties. When the two drugs are given together, butorphanol provides an immediate sedative and analgesic benefit, but one of short duration. Butorphanol's analgesia wanes about the same time that buprenorphine reaches its peak analgesic effect. Combining buprenorphine with a mu agonist might also seem to present a conflict, possibly reducing the mu agonist's analgesic benefit (partial agonists are generally regarded as less efficacious analgesics than mu agonists with potential to antagonize mu agonist effects). Fortunately, mu agonists form an additive, if not synergistic, analgesic benefit for patients previously treated with therapeutic doses of buprenorphine[9,19].

Buprenorphine is also an attractive epidural agent as it is preservative-free and it has compared favorably to preservative free (PF) morphine in canine trials[20]. One additional buprenorphine benefit is gained when buprenorphine is added to local anesthetic blocks. Human studies have shown that 0.003 mg/kg

buprenorphine added to lidocaine and bupivacaine local blocks will effectively double the duration of analgesic benefit[21]. Buprenorphine's shortcoming is its cost.

THE MU AGONISTS include morphine, hydromorphone, oxymorphone, methadone, and fentanyl. Inconsistent availability and higher cost has made it more difficult to maintain oxymorphone in the analgesic inventory. Methadone is significantly more expensive in the United States than other areas of the world making its use unattractive. Morphine, hydromorphone, and fentanyl serve as the core opioids in most advanced practices. Of the mu agonists, morphine and hydromorphone are the most attractive cost-effective analgesics.

Mu agonists have no ceiling effect. Higher doses produce stronger effects, wanted and unwanted. Adverse effects include vomiting, defecation, respiratory depression, dysphoria, and bradycardia. There are significant differences between opioid induced human concerns and veterinary concerns. Vomiting may persist with ongoing mu agonist use in people but it is usually limited to a single episode in dogs and cats. Transient nausea is a small penalty for superior analgesia. Often a full stomach is emptied or a foreign body revealed that could have been tomorrow's GI obstruction. To be fair, vomiting should be avoided if an upper GI obstruction is suspected, an esophageal foreign body is present, or increased intracranial pressure is a concern. Defecation provides a ready sample for parasitic evaluation.

Respiratory depression is a considerable concern in human medicine but is rarely of great clinical concern in veterinary patients (the exception being higher doses of fentanyl). Dysphoria can usually be managed by including low doses of acepromazine, medetomidine, or a benzodiazepine. Dysphoria may also be managed by the administration of buprenorphine, nalbuphine, or butorphanol, reducing dysphoric effect without losing all analgesic benefit. Bradycardia is the easiest of all to manage. ***IF*** the bradycardia produces clinically significant effects (i.e. a concerning drop in patient blood pressure), anticholinergics should easily rectify the situation.

A reduction in opioid dosing is not necessarily the best way to address concerns about opioid adverse effects. For instance, Sheilah Robertson's work has shown that hydromorphone doses below 0.1 mg/kg fail to generate consistent analgesia of adequate duration in cats. Paradoxically, opioid-induced hyperalgesia can occur at very low opioid doses[22].

There are some exciting future possibilities for opioid applications. One area of particular promise involves the combination of ultra-low dose antagonists like naltrexone with mu agonists and monoamine reuptake inhibitors. The net effect is enhanced analgesia while reducing the potential for opioid tolerance and dependency[23,24,25].

For a comparative overview of the opioids, see Tables 1, 2, & 3 below.

MORPHINE remains one of the most attractive opioid agents. It is the most cost-effective and versatile mu agonist. Morphine may be administered by intermittent injection, included in constant rate infusions (CRIs), added to local blocks for extended analgesic duration[21], and included in epidural injections.

Morphine mania is a dated reference to research conducted on cats at extreme doses far above those used clinically in cats today. At appropriate doses, morphine is a very useful feline analgesic. The cat's uniquely limited glucuronyl transferase capability reduces the total morphine related benefit as the active morphine

metabolite, morphine-6-glucuronide, is produced in lower quantity. The IV administration of morphine also carries a caution. Rapid IV infusions can trigger histamine release resulting in a transient negative effect on blood pressure. This is rarely of great clinical concern, but can generally be avoided all together by slowing the rate of administration.

Applications for morphine include:

- Intermittent injections as a preanesthetic medication or for ongoing pain management
  - Cats 0.1 to 0.5 mg/kg
  - Dogs 0.5 to 1.0 mg/kg
- CRI delivery at rates of 0.12 to 0.36 mg/kg/hr
  - Commonly given with lidocaine and ketamine for a multimodal infusion in cats and dogs helping to avoid the peaks and valleys associated with intermittent injections
- The inclusion of 0.075 mg/kg morphine with bupivacaine effectively doubles the duration of analgesia from local blocks including intra-articular blocks[21]
- Preservative free morphine remains the most attractive epidural opioid at 0.1 to 0.2 mg/kg.

Morphine is one of the more attractive opioids when significant canine liver dysfunction exists. It is protein bound to a lesser extent than most opioids preserving a more predictable dose-effect relationship. Also, its route of metabolism in canines, glucuronidation, is usually well preserved in liver disease.

HYDROMORPHONE vies with morphine for cost-effectiveness and versatility. It may also be administered by intermittent injection, included in constant rate infusions (CRIs), added to local blocks for extended analgesic duration, and included in epidural injections. Unlike morphine, hydromorphone is not associated with histamine release.

Hydromorphone is a more effective analgesic than morphine for feline patients. Robertson's work has shown that the most ideal dose for cats is 0.1 mg/kg. That dose provides excellent analgesia but **you will see a transient hyperthermia in a significant number of these feline patients**. Temperatures may reach 103^0 F to 106^0 F degrees, last a few hours, then self-resolves. In some cases patient temperature will exceed 107^0 F. The usual timeframe is 2 to 6 hours post administration. When used in a balanced combination with a sedative like medetomidine hyperthermia is much less likely and usually of lower magnitude. Should body temperature exceed 104^0 F, 0.020 mg/kg buprenorphine should be administered IV to allow body temperature to return to the euthermic range.

Dogs are dosed from 0.1 to 0.2 mg/kg. Vomiting, as a one-time event at initial administration, is not uncommon. As with oxymorphone, dogs often pant on hydromorphone making hydromorphone less attractive when sedating patients for chest radiographs.

Applications for hydromorphone include:

- Intermittent injections as a preanesthetic medication or for ongoing pain management.
  - Cats 0.1 mg/kg.
  - Dogs 0.1 to 0.2 mg/kg.
- CRI delivery at rates of 0.025 to 0.075 mg/kg/hr.
  - Commonly given with lidocaine and ketamine for a multimodal infusion in cats and dogs helping to avoid the peaks and valleys associated with intermittent injections.

- The inclusion of 0.015 mg/kg hydromorphone with bupivacaine effectively doubles the duration of analgesia from local blocks including intra-articular blocks.
- Hydromorphone is also an attractive epidural opioid at 0.04 to 0.1 mg/kg with saline q.s. to a total volume of 0.1 to 0.2 ml/kg.

FENTANYL use is greatly influenced by its short duration of effect. The short durations makes it generally less attractive as a preanesthetic medication or for intermittent bolus administration on an ongoing basis. Fentanyl is also unattractive as an epidural agent; it is absorbed into systemic circulation almost as fast as if administered by the IM route. The short duration of effect becomes an advantage when the drug is administered by constant rate infusion making the CRI more responsive. It is also well suited to intraoperative IV bolus administration at key painful points in the procedure. Fentanyl, at high dose rates, can be combined with midazolam to provide total intravenous anesthesia (TIVA). This is a challenging form of anesthesia best reserved for the advanced setting.

Fentanyl has more potential to cause respiratory depression than the other mu agonists. At higher doses patient ETCO2 monitoring becomes a critical element as pulse oximeter readings may remain in the high 90s while the ETCO2 may be well above 100 mmHg. This is not normally a concern at standard analgesic CRI dose rates.

The fentanyl patch has become popular due to the allure of constant analgesia and ease of administration. While they are nice additions to the analgesic pharmacy, their ability to supply adequate analgesia is limited by many factors. There is an inherent variability in the fentanyl absorption from patient to patient and even from patch to patch in the same patient. In one feline study, 2 of 6 cats failed to develop ***any*** detectable fentanyl plasma levels when their patch was initially applied[26]. The hypothermia associated with an anesthetic procedure can drop the fentanyl absorption to zero[27] while lying with the patch on a supplemental heat source may increase blood plasma levels. It is important to note that, in studies, the 100 mcg patch provided no better analgesia than the 50 mcg patch; two 50 mcg patches, rather than one 100 mcg patch, are recommended for larger canine patients[28]. One additional caution; cats may experience hyperthermia and dysphoria while on the patch which may force its removal.

Applications for fentanyl include:

- Intermittent injections at 0.002 to 0.005 mg/kg for painful points during a surgery to gain better patient control especially for patients poorly tolerant of higher inhalant levels.
- CRI delivery at rates of 0.001 to 0.005 mg/kg/hr.
    - Commonly given with lidocaine and ketamine for a multimodal infusion in cats and dogs helping to avoid the peaks and valleys associated with intermittent injections.
- Fentanyl patch placed long enough ahead of surgery to aid in patient analgesia
    - Dog – preplace 24 hours before surgery[28,29]
    - Cats – preplace 8 to 12 hours before surgery
    - Do not assume the patch will be adequate analgesia for all patients

Table 1							
Drug	Dose mg/kg	Duration	Sedation	Analgesia	Classification	Schedule	Cost
Nalbuphine	0.2 to 1.0	¾ - 1 hr	-	+	Kappa agonist	Nonscheduled	High
Butorphanol	0.2 to 0.4	Dogs ¾ hr Cats 1.5 hr	++	+	Kappa agonist	Schedule III	High
Buprenorphine	0.005 0.010 0.020 0.030 0.040–0.060	3 to 4 hr 4 to 6 hr 6 to 8 hr 8 to 10 hr 10 to 12^{+} hr	-	++	Partial mu agonist	Schedule III	High
Fentanyl	0.002 to 0.010	½ to ¾ hr	+++	+++	Mu agonist	Schedule II	Low
Hydromorphone	0.1 to 0.2	3 to 6 hr	+++	+++	Mu agonist	Schedule II	Low
Methadone	0.5 to 1.0	3 to 6 hr	+++	+++	Mu agonist	Schedule II	High
Morphine	0.5 to 1.0	3 to 6 hr	+++	+++	Mu agonist	Schedule II	Low
Oxymorphone	0.05 to 0.1	3 to 6 hr	+++	+++	Mu agonist	Schedule II	Mod.

Table 2						
Drug	Vomiting	Dysphoria	Resp. depression	Bradycardia	Histamine release	
Nalbuphine	-	-	-	-	-	
Butorphanol	-	+	-	-	-	
Buprenorphine	-	-	-	-	-	
Fentanyl	+	++	++	++	-	
Hydromorphone	+++	++	+	++	-	
Methadone	+++	++	+	++	-	
Morphine	+++	++	+	++	+	
Oxymorphone	+	++	+	++	-	

Table 3				
Drug & Dose	Approx. Duration	Cost per dose 20 kg patient	Cost per 24 hours 20 kg patient	Pain Level
Nalbuphine 0.4 mg/kg	1 hour	$ 1.78	$ 42.72	Very Mild
Butorphanol 0.2 mg/kg	1 hour	$ 1.92	$ 46.08	Very Mild
Buprenorphine 0.030 mg/kg	8 hours	$ 5.97	$ 17.91	Mild-moderate
Oxymorphone – 0.05 mg/kg	4 hours	$ 2.47	$ 14.82	Mild-severe
Fentanyl – 0.0025 mg/kg	1/2 hour	$ 0.21	$ 10.08	Mild-severe
Hydromorphone – 0.1 mg/kg	4 hours	$ 0.47	$ 2.82	Mild-severe
Methadone – 0.5 mg/kg	4 hours	$ 4.28	$ 25.68	Mild-severe
Morphine – 0.5 mg/kg	4 hours	$ 0.10	$ 0.60	Mild-severe

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