

PERIOPERATIVE PAIN MANAGEMENT

MOVING BEYOND BUTORPHANOL

Part 3

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In the previous two installments 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. Intervening before the pain system becomes sensitized is an absolute necessity when your goal is optimal patient benefit. In Part III, we will continue our review of the various drug families and individual agents that may contribute to our perioperative patient analgesic management.

SEDATIVE/TRANQUILIZERS represent an important element in any balanced analgesic strategy. Unchecked, stress adds to the “inflammatory soup” that sensitizes the nerve pathways¹ amplifying the patient’s pain. While not all of these drugs are direct analgesics, they all enhance the patient’s total analgesic benefit².

PHENOTHIAZINE TRANQUILIZERS. ACEPROMAZINE, an alpha antagonist, is an effective, inexpensive drug. Acepromazine is capable of reducing induction and maintenance needs significantly. It possesses anti-arrhythmic and antihistaminic qualities and reduces the incidence of preanesthetic medication related vomiting³. Potential adverse effects, including hypotension, are rarely seen with proper patient selection and appropriate dosing. Hypothermia, from peripheral vasodilation and hypothalamic influence, is best managed by providing effective supplemental heat. The association between acepromazine and seizures is a more tenuous connection than past literature would suggest. In fact, acepromazine may reduce the frequency of seizures in some dogs^{4,5}. But we’ll leave that discussion for another day.

Acepromazine use as a sole agent is not recommended. In general, acepromazine should always be used in combination with an opioid. This combination provides significant analgesic and sedative synergism. For dogs, doses from 0.005 to 0.050 are usually effective when combined with 0.2 mg/kg butorphanol, 0.5 to 1.0 mg/kg morphine, or 0.1 to 0.2 mg/kg hydromorphone. Cats appear somewhat less responsive to the sedative effects of acepromazine making doses from 0.02 to 0.10 more appropriate when combined with 0.2 mg/kg butorphanol or 0.1 mg/kg hydromorphone. Buprenorphine, 0.020 to 0.060 mg/kg, can be substituted for the above opioids but you will see less total sedation.

Lower doses of acepromazine are much more easily managed by creating a vial of 1 mg/ml or 2 mg/ml concentration. To create a 1 mg/ml final concentration, mix 9 ml sterile water with 1 ml (10mg) acepromazine in a sterile vial. To create a 2 mg/ml final concentration, mix 8 ml sterile water with 2 ml

(20mg) acepromazine in a sterile vial. Carefully label and date these vials. Dosing charts are available for this and other drugs at www.vasg.org/support_material.htm.

Acepromazine may be repeated at small doses for those patients experiencing emergence delirium or dysphoria at recovery using 0.005 mg/kg increments. We will occasionally use low dose medetomidine (0.0005 to 0.0010 mg/kg increments slowly IV) for postop agitation in patients previously treated with acepromazine. On the surface this might seem a conflict between alpha agonist and an alpha antagonist. This appears more logical if one considers acepromazine's alpha antagonistic effects to be weighted towards the alpha-1 receptor while medetomidine's agonistic effects are quite selective for the alpha-2 receptor.

Acepromazine use should be avoided in patients less than 12 weeks of age and those exhibiting significant liver dysfunction, particularly those demonstrating elevated bilirubin, hypoalbuminemia, and altered coagulation. Doses should be conservative, if used at all, in the healthy geriatric patient.

This drug has been associated with some concern regarding its use in Boxers. The main concern was based on strains found in England but there are a few reported instances by anesthesiologists in the US. The untoward effect is described as an acute bradycardic collapse that does appear to be responsive to atropine and support.

ALPHA-2 AGONISTS. MEDETOMIDINE (Domitor®) is a very capable sedative analgesic agent. The use of xylazine, a less selective alpha-2 agonist, is not recommended by this author and will not be discussed. Medetomidine benefits include stress reduction, dose related analgesia, muscle relaxation, better maintenance of patient core body temperature, more stable anesthetic planes, a general freedom from respiratory depression, and, unlike xylazine, an anti-arrhythmic benefit⁶. **When medetomidine is included in the preanesthetic medications there is a substantial reduction in patient induction and maintenance agent needs.** As with acepromazine, the potential for unwanted adverse effects is quite low when medetomidine is used appropriately in combination with an opioid. In contrast to acepromazine, medetomidine is a fully reversible agent adding an extra element of flexibility.

Unfortunately, many have experienced medetomidine as a sole agent used at label doses: doses that are as high as 0.150 mg/kg (150 µg/kg). At these higher doses peripheral vasoconstriction is pronounced, marked hypertension is common, and bradycardia is often unsettling. Mucous membranes appear ashen, making it difficult to obtain consistent pulse oximeters readings and indirect blood pressures are hard to evaluate. **In short, the author does not recommend medetomidine use as a sole agent.**

In contrast, medetomidine doses ranging from 0.001 to 0.010 mg/kg in dogs and 0.001 to 0.015 in cats combined with 0.2 mg/kg butorphanol, 0.4 to 0.5 mg/kg nalbuphine, 0.5 to 1.0 mg/kg morphine (0.5 mg/kg for cats), or 0.1 to 0.2 mg/kg hydromorphone (0.1 mg/kg for cats) normally provides an attractive, balanced sedative/analgesic level. Mucous membranes remain pink, heart rates and blood pressures remain in a more "normal" range. Indirect blood pressure monitors and pulse oximeters should function consistently.

In a recent review presented by Dr. Grimm at the 2004 ACVIM meeting, medetomidine and butorphanol were shown to be very effective and safe when used in combination for heavy sedation to restrain canine and feline patients for radiation therapy. The study reviewed 8191 sedation events in dogs averaging 8.9 years and cats averaging 10.8 year of age. Each cat averaged 15 sedative events and each dog averaged 12 events. All patients were undergoing therapy for cancer management. There were no fatalities during this sequence

covering 8 years. Only 2.8% of the patients required alterations in their protocol. Butorphanol was dosed at 0.22 mg/kg and the medetomidine was dosed, on average, at 0.0085 mg/kg for the dogs and 0.017 mg/kg for the cats⁷.

Medetomidine is capable of providing significant dose dependent analgesia. Analgesic duration is about 1 hour at 0.010 mg/kg (10 µg/kg)⁸. Medetomidine may be redosed every hour, slowly IV, to maintain its analgesic and MAC sparing benefit.

Postanesthetic dysphoria and agitation usually responds quite nicely to 0.001 to 0.002 mg/kg medetomidine slowly IV with the residual sedation waning by 1 hour postadministration. Alternatively, a constant rate infusion of 0.0005 to 0.001 mg/kg/hr medetomidine can be of benefit in managing agitated patients over longer periods of time.

There appears to be significant analgesic and sedative synergism between medetomidine and the opioids. As stated above, when transitioning to medetomidine based protocols, you should anticipate a significant reduction in the amount of induction agent and maintenance agent needed. Dosing to effect is a necessity.

BENZODIAZEPINES include midazolam and diazepam. These tranquilizers are, as a group, poorly effective as sole agents, especially in healthy energetic pets. They are useful in combination with opioids, acepromazine and medetomidine. Benzodiazepines are capable of providing muscle relaxation, induction agent reduction and inhalant MAC reduction, and, possibly, patient amnesia. The benzodiazepines are relatively free of unwanted side effects. One often forgotten advantage of the benzodiazepines is their reversibility; flumazenil (Romazicon®) is the benzodiazepine antagonist.

Midazolam (Versed®) is a water-soluble agent while diazepam is only available in a propylene glycol solution. As such, midazolam mixes well with most agents and it is rapidly absorbed from the IM injection route while diazepam precipitates when mixed with most agents (ketamine being the most important exception) and it is more painful and less consistently absorbed when given IM. For all practical purposes the two drugs have comparably dosing.

Benzodiazepines, 0.1 to 0.4 mg/kg, in combination with a mu agonist often provide an effective preanesthetic combination of analgesia and mild sedation for aged and depressed patients as this combination has minimal impact on the patient's cardiovascular and respiratory function. This is not, however, an effective combination for energetic, healthy patients. Acepromazine or medetomidine should be added to the opioid/benzodiazepine base to more effectively manage younger and healthier patients.

Midazolam and diazepam may be given at 0.2 to 0.4 mg/kg IV just prior to propofol administration to smooth the induction process and significantly reduce the patient's propofol requirement. Expense considerations favor the use of diazepam for this application. The addition of 0.5 mg/kg ketamine to the benzodiazepine further reduces propofol need while reducing the likelihood of propofol induced hypotension and apnea without creating any of the typical concerns associated with higher dose ketamine use⁹.

Benzodiazepines are the preferred agents delivered IV immediately prior to etomidate inductions. Etomidate is considered to be the most attractive induction agent for patients with cardiovascular instability, particularly those with serious myocardial disease. Diazepam and midazolam given at 0.2 to 0.4 mg/kg IV prior to the etomidate helps minimize the retching and muscle tremors that may otherwise occur with that agent.

Benzodiazepines may also be used as an intermittent bolus or as a constant rate infusion to help minimize inhalant agent levels while maintain anesthetic depth for those patients poorly tolerant of inhalant agents.

NMDA ANTAGONISTS helps to prevent sensitization of the central nervous system, reducing the exaggerated pain response that is otherwise a potential development after any significant traumatic or surgical event¹⁰. NMDA antagonists enhance opioid analgesia and they help to combat the opioid tolerance that may occur when opioids are given for long periods of time.

KETAMINE is the most commonly utilized veterinary NMDA antagonist. As the sole agent, at anesthetic doses, its analgesic uses are limited. It is most effective when utilized at subanesthetic doses as a constant rate infusion to antagonize the NMDA receptors in the dorsal horn of the spinal cord. Given at typical analgesic adjunct doses, ketamine is unlikely to affect cardiovascular, CNS, or ophthalmologic concerns significantly, especially when administered after an opioid to blunt potential sympathetic stimulation. Constant rate analgesic infusions can be delivered prior to, during, and after painful events. A more detailed discussion of CRIs will follow later in this review series.

AMANTADINE is an antiviral drug that has also demonstrated NMDA antagonistic properties. It is a useful addition to long-term outpatient pain management when given at 3 to 5 mg/kg PO once daily. It is available as a 100 mg capsule and a 10 mg/ml liquid.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS have become a popular perioperative pain management choice perhaps, in part, due to the fact that they are not controlled by the DEA. NSAIDs act at both the peripheral level, where they inhibit the inflammatory response, and the central nervous system level combining to reduce both peripheral and centrally mediated sensitization and hyperalgesia. There are many “new generation” NSAIDs. The individual characteristics vary as to the variety of available preparations, the frequency of administration, cost, and applicability to cats versus dogs. NSAIDs have become increasing “selective” or “preferential” in their ability to focus on the COX-2 and lipoxygenase pathways. But, as has recently been shown on the human side of the medicine fence, increasing selectivity is not without risks.

It is important to recognize that the COX-2 pathway has its beneficial (constitutive) qualities especially with respect to the healing of GI injuries¹¹ and in the maintenance of renal blood flow^{12,13,14,15}. It is this constitutive aspect of COX-2 oriented agents that raises concerns regarding their preoperative use. Although there are studies available that suggest a lack of adverse effects when NSAIDs are given perioperatively to healthy dogs^{16,17}, it might seem prudent to limit their use to the postoperative period when hypovolemia, hypotension, and GI surgical trauma has been fully assessed and addressed. When NSAIDs are used preoperatively patient blood pressures should be attentively monitored and meticulously maintained within the acceptable range. See: http://www.vasg.org/blood_pressure_management.htm for blood pressure management information. NSAID adverse affects on bone healing do not appear to be overly concerning and certainly should not preempt short-term use in the immediate postoperative orthopedic period.

There is a broad range of NSAIDs available for use in dogs. There is no single NSAID that is considered the class leader, as any given patient may respond and tolerate one better than another. Therapeutic trials are the best determinant of NSAID choice for a given patient. In general one should try to match a perioperative

injectable with subsequent oral medications as switching from one NSAID to another has potential for adverse consequences, especially when moving from a less selective agent to a more selective COX-2 agent. Carprofen (Rimadyl®), etodolac (Etogesic®), deracoxib (Deramaxx®), tepoxalin (Zubrin®), firocoxib (Previcox®), and meloxicam (Metacam®) are all approved for canine use in the USA.

Conversely, there is only one approved NSAID approved for use in cats in the USA; meloxicam injectable is the sole NSAID approved for use in cats as a single injection at 0.3 mg/kg. There is substantial support, though off-label, for the cautious use of meloxicam at 0.1 mg/kg on day 1 then 0.05 mg/kg PO up to 4 days followed by 0.025 to 0.05 mg/kg PO every 48 to 72 hours. Long-term use must be applied very cautiously with careful dosing accuracy and tight owner/patient monitoring as cats have substantially longer NSAID half-lives than dogs creating significant risks if excessive doses or dose frequency are used. All drops are not created equally (just ask a drip set). Use a Tb or insulin syringe without the needle for greatest oral liquid dosing accuracy.

NSAIDs alone may provide adequate analgesia for only the most minor surgeries. For perioperative purposes, NSAIDs effectiveness is enhanced significantly when they are preceded by, or combined with, an opioid analgesic in conjunction with an effective sedative/tranquilizer as outlines above (remember, butorphanol does not count as a significant opioid analgesic). **With appropriate preemptive analgesia presurgically**, NSAIDs may be adequate as a sole **postoperative** agent for mild to moderate surgical pain such as that associated with spays and neuters in young healthy dogs and cats. NSAIDs should be teamed with ongoing opioid analgesics (buprenorphine TM in cats, fentanyl patch, tramadol) and, possibly, an NMDA antagonist like amantadine when managing moderate to severe pain like that associated with declaws, mature spays, orthopedics, thoracic surgery, and similar pain level procedures.

In summary, NSAIDs are most attractive when used in a multimodal pain management strategy that includes an opioid and an NMDA antagonist. NSAID use should be reserved for healthy patients free of significant disease. Special cautions exist for patients that have pre-existing renal or hepatic dysfunction, dehydration/hypovolemia/hypotension, coagulopathies, ongoing corticosteroid therapy, GI disease, or pregnancy. NSAIDs use should be limited to a single dose when used after cesarean sections in nursing animals.

When used for more than a few days, patient monitoring should include periodic hepatic and renal assessments to include ALTs and urine specific gravities at a minimum. Testing is preferred prior to use, at 2 weeks, 3 months, then every 3 to 6 months thereafter depending on patient status and clinical history.

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