PERIOPERATIVE PAIN MANAGEMENT

MOVING BEYOND BUTORPHANOL

Part 1

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What's the big deal about pain management? Why all the fuss? Who wants to manage more scheduled drugs? Are the drugs safe? Aren't these complicated techniques? Weren't we doing just fine before? To answer these questions we need to review the current understanding of the consequences of pain and the advantages of appropriate analgesia.

Effective pain management is the key to safer anesthesia and better patient outcomes. Balanced analgesia is the key to balanced anesthesia. You can improve your patient's comfort and safety, reduce patient morbidity and mortality, all while improving your bottom line.

The most potent cardiac and respiratory depressants are the induction agents, above all propofol, and the inhalant agents. How can you guarantee that you'll expose your patient to the absolutely highest levels of these most potent cardiac and respiratory depressant agents? Skip the premeds and mask the patient down with sevoflurane or isoflurane. Skip the premeds, induce with propofol, and place on sevoflurane or isoflurane. As contrary as it might sound to some of the corporate sales driven efforts in recent years, one-dimensional anesthesia is not in your patients or your staff's best interests.

Effective analgesic/sedative medications allow you to intubate with much less induction agent and maintain anesthesia with lower sevoflurane or isoflurane levels. This should translate into more stable blood pressures and better patient ventilation. Patient stress, anxiety, and pain are all reduced which, generally, improves patient outcomes. For a small initial investment in the premeds you gain a substantial reduction in the per-patient cost of the expensive agents, propofol and sevoflurane.

By limiting mask and chamber use and reducing inhalant agent requirements you can reduce staff exposure to anesthetic waste gases improving staff morale and reducing the risk of an OSHA citation. OSHA's Anesthetic Gases: Guidelines For Workplace Exposures[1] states that "Employers can be cited for violating the General Duty Clause if there is a recognized hazard and they do not take steps to prevent or abate the hazard." OSHA considers staff exposure above 2 ppm (on a time weighted average) of ANY halogenated agent to be an unacceptable hazard. Despite the availability of inexpensive

[1] Anesthetic gases: guidelines for workplace exposures. US Department of Labor: OSHA. Revised May 18, 2000: http://www.osha.gov/dts/osta/anestheticgases/

waste gas monitoring badges[2], most practices don't even know what their staff exposure levels are. Reducing masking and chamber use goes a long way toward "abating the hazard".

As late as the mid 1980s, complex surgeries were being performed on human neonates not just without analgesics, but also without anesthesia. Neonates were given paralytic drugs and placed on ventilators. The assumption at the time was that anesthetics presented a risk while patient pain did not. It was assumed that these patients possessed poorly developed nervous systems incapable of significant pain response and that, even if pain was perceived, patients this young wouldn't remember the experience.

Studies have long since shown that even the fetal nervous system is capable of meaningful painful response[3]. Early painful experiences have been shown to significantly increase the pain associated with vaccinations 4 and 6 months later[4]. Basically, the pain pathways are capable of "memory". Subsequent painful experiences can be much more unpleasant to the individual. The implications, clearly, are that we should be mindful of patient pain from birth on.

The American Academy of Pediatrics has published a policy statement[5], Prevention and Management of Pain and Stress in the Neonate, which includes the following points:

- Neuroanatomical components and neuroendocrine systems are sufficiently developed to allow transmission of painful stimuli in the neonate.
- Exposure to prolonged or severe pain may increase neonatal morbidity.
- Infants who have experienced pain during the neonatal period respond differently to subsequent painful events.
- Neonates are not easily comforted when analgesia is needed.
- A lack of behavioral responses (including crying and movement) does not necessarily indicate a lack of pain.

"Because the anatomic structures and neurophysiologic mechanisms mediating pain are remarkably similar in human beings and animals, it is appropriate to assume that a stimulus that is painful to people…is indeed painful to that animal."[6]

Pain management is most effective when instituted prior to the painful event as illustrated by the figure below. As the pain pathways become sensitized the amount of medication needed to control patient pain increases. Patient stress further aggravates the sensitization

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[2] Assay Technology. 1-800-833-1258. Monitor badge order# X574 ($195.00/5 prepaid monitors)
[3] Anand KJ, Hickey PR **Pain** and its effects in the human neonate and fetus. *N Engl J Med.* 1987; 317:1321-1329
[4] Taddio A, Goldbach M, Ipp M, Stevens B, Koren G Effect of neonatal circumcision on **pain** response during vaccination in boys. *Lancet.* 1995; 345:291-292
[5] American Academy of Pediatrics: Prevention and Management of Pain and Stress in the Neonate. Pediatrics Vol. 105 No. 2 February 2000, pp. 454-461
[6] Lamont LA Feline perioperative pain management. Veterinary Clinics of North America: Small Animal Practice- 2002 7 (Vol. 32, Issue 4) 747-763

process. Consideration should be given to patient stress at admissions. Early administration of a sedative/analgesic combination greatly enhances patient comfort, staff safety, and staff sanity. Laboratory samples can be drawn and catheters placed more easily. Should a significant delay occur prior to induction, and additional dose, or partial dose, of the initial medications can be easily given.

Typically, preanesthetic medications are based on an opioid with one or two additional drugs to enhance sedation and analgesia. Butorphanol and nalbuphine are mixed opioid agonist-antagonists with primary kappa agonistic activity providing mild analgesia of short duration as well as mild sedation. Buprenorphine is a partial mu opioid agonist capable of providing moderate analgesia of long duration at appropriate doses but free of significant sedative effect. The pure mu opioid agonists include fentanyl, hydromorphone, morphine, oxymorphone and methadone. The mu agonists are the most cost-effective opioids capable of providing dose related analgesia and sedation of moderate duration. Opioids can be delivered IM or IV as intermittent analgesics, as constant rate infusions (CRI), transmucosally (buprenorphine in cats), transdermally (fentanyl patch), and, to a more limited degree, orally.

The benzodiazepines include midazolam and diazepam. They are not very attractive as solo agents in healthy patients as some patients become more difficult to manage when only given a benzodiazepine. These agents are most effective when given with either an opioid alone or in combination with either acepromazine or medetomidine. Midazolam is more ideal for premedication purposes than diazepam as its water solubility facilitates rapid drug absorption from the IM route. One additional potential advantage of midazolam is the possibility that the patient may experience a few hours of amnesia, which is a common effect when given to human patients. The benzodiazepines are relatively free of serious unwanted adverse effects. One additional advantage of the benzodiazepines is their reversibility. Flumazenil (Romazicon®) is the benzodiazepine antagonist.

The phenothiazine acepromazine is an attractive analgesic adjunct. Acepromazine is an inexpensive alpha antagonist with predominant activity at the alpha-1 receptor. It is capable of producing significant hypotension but, as with most drugs, this is dose dependent. Its synergism with the opioids allows for good sedative effect at doses that should be free of any negative consequence. 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. There is also an historic concern that acepromazine use can increase seizure potential and should not be used in patients prone to seizures. Most anesthesiologists consider the connection between acepromazine and seizures to be a bit tenuous.

Alpha-2 agonists can be attractive perioperative analgesic sedatives. Medetomidine's greater alpha-2/alpha-1 receptor selectivity and its antiarrhythmic qualities make it more attractive than xylazine. The University of Illinois recently completed a study involving

over 8000 medetomidine (Domitor®) based heavy sedation events in dogs and cats for radiation therapy[7]. The cats averaged 10.8 years of age and 15 treatments; the dogs averaged 8.9 years of age and 12 treatments. Only 2.8% of these patients required a change to a different chemical restraint protocol. There were no deaths attributed to this routine. Alpha-2 agonists are reversible agents. Atipamezole (Antisedan®) is a much more attractive antagonist than yohimbine (Yobine®). The alpha-2/alpha-1 receptor specificity of atipamazole is about 200 times that of yohimbine while its receptor affinity is 100 times that of yohimbine[8].

NSAIDs should be used cautiously in the preoperative period. Unless blood pressure is being consistently monitored and maintained, NSAIDs present a significant renal risk as the COX-2 enzyme plays a constitutive role in maintaining renal perfusion. COX-2 also plays a constitutive role in the gastrointestinal healing process. COX-1 inhibition (ketoprofen) is associated with increased risk from hemorrhage. Although important and effective analgesics, many feel that the NSAIDs are best reserved for the postoperative period in normotensive NSAID tolerant patients undergoing non-GI surgery.

In general, preanesthetic medications should be given by the IM or IV route. Sheilah Robertson's absorption studies, performed on healthy cats, have shown such variable absorption from the SQ route that it should no longer be considered a primary route of administration for preanesthetic medications.

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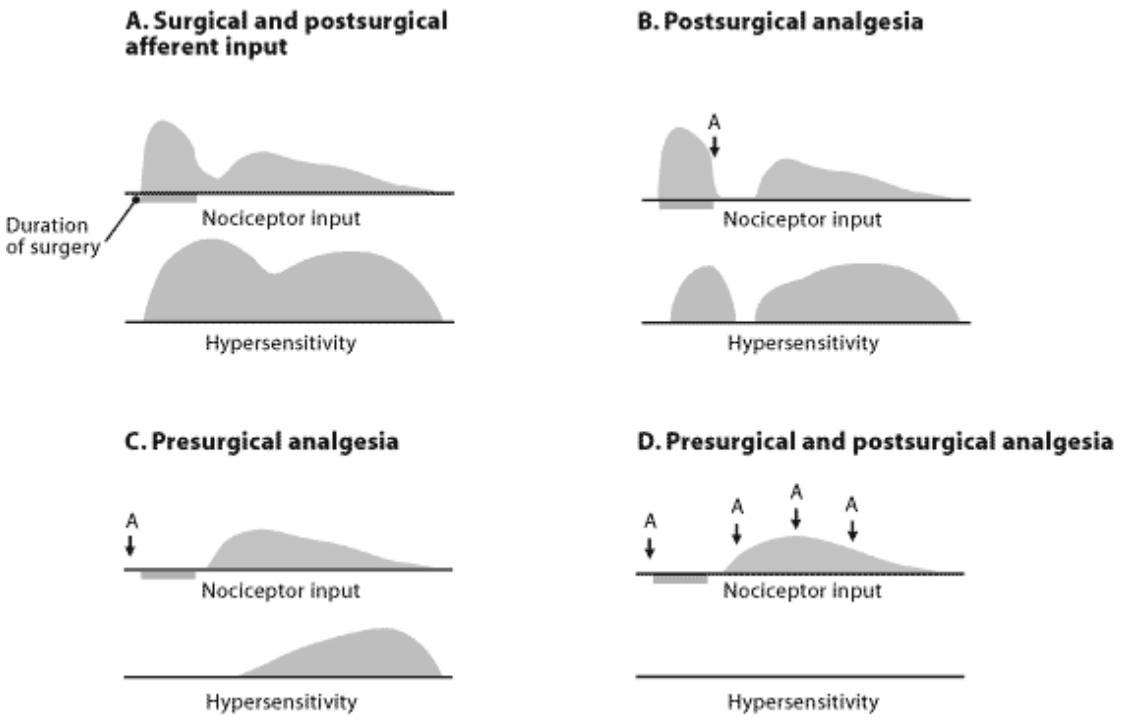
7 Grimm JB, deLorimier LP, Grimm KA. Medetomidine-butorphanol-glycopyrrolate sedation for radiation therapy: an eight-year study [abstract]. In: Proceedings of the Veterinary Midwest Anesthesia and Analgesia Conference. Columbus: The Ohio State University; 2004. p. 18.

[8] Virtanen R, Savola JM, Saano V. Highly selective and specific antagonism of central and peripheral alpha 2-adrenoceptors by atipamezole. Arch Int Pharmacodyn Ther. 1989 Jan-Feb;297:190-204.



Schematic of preemptive analgesia with an emphasis on preventing sensitization of the nervous system throughout the perioperative period. A typical experience without intervention is shown in A, which depicts pain from the initial surgery and the hypersensitivity that subsequently develops. In B, analgesia (A) administered after sensitization may decrease pain somewhat but has little long-term benefit. Analgesia administered before surgery limits the pain from that stimulus and decreases subsequent hypersensitivity, as shown in C. However, the most effective preemptive analgesic regimen is initiated before surgery and continued throughout the postoperative period, as illustrated in D. Although timing of the intervention is important, it must also be capable of preventing sensitization of the nervous system.

Gottschalk A, Smith DS. New concepts in acute pain therapy: preemptive analgesia. Am Fam Physician. 2001 May 15;63(10):1979-84.