

PERI-OPERATIVE NSAID USE – INDICATIONS, CONTRAINDICATIONS AND COMPLICATIONS

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Basic overview of provision of clinical pain relief (see figure 1):

There are 4 time periods during which decisions made about the management of patients affect the post-operative pain status of the patient:

- a. Pre-operative
- b. Intra-operative
- c. Immediate ('in hospital') post-operative
- d. At home post-operative

The most important time periods to consider are the pre and intra-operative periods – time periods when post-operative pain can be prevented, or very much reduced, via the concept of pre-emptive analgesia.

When designing the provision of 'post-operative analgesia' [which should in fact be a consideration of pre, intra and post-operative analgesic provision], the 6 basic classes of analgesic drugs that should be currently considered are:

1. Opioids
2. NSAIDs
3. Sodium channel blockers ('local anaesthetics')
4. Alpha-2 adrenoceptor agonists
5. NMDA antagonists
6. Gabapentin-like drugs

It is also very important to remember that pain relief can also be provided at each stage by non-drug therapies. Although the evidence for a beneficial effect is largely lacking in veterinary medicine due to the studies having not been performed, seven general modalities are most often used. The seven therapeutic modalities are used to decrease pain, reduce inflammation, and stimulate normal healing responses in veterinary patients: (1) local hypothermia and hyperthermia, (2) passive range-of-motion activity, (3) massage, (4) therapeutic exercise, (5) hydrotherapy, (6) ultrasound, and (7) electrical stimulation. For more information on the indications and contraindications, along with the methods of action and application for each therapeutic modality commonly used in companion animal rehabilitation, see Lumb & Jones, *Veterinary Anesthesia and Analgesia*, Fourth Edition.¹

The following notes refer to aspects of using NSAIDs in the peri-operative period.

The analgesic efficacy of NSAIDs when treating acute pain is high.² Moreover, NSAIDs are often more efficacious than opioids such as pethidine, butorphanol, and papaveretum in treating acute pain.²⁻⁷ This does not necessarily mean that NSAIDs should be used to the exclusion of opioids for acute pain relief. Their use in combination can be more effective than individual drugs used alone.⁸ NSAIDs do not have sedative or dysphoric effects, allowing better postoperative assessment of pain and the adequacy of analgesia in the patient.

Incidence of adverse effects associated with perioperative use of NSAIDs is probably lower versus chronic use, since extended treatment is not involved and the patient is often younger and without underlying physiologic deficits.

Several aspects of perioperative NSAID use deserve emphasis:

Preemptive use

Pain is more difficult to control once it occurs, so preemptive administration of NSAIDs prior to surgery will maximize and extend their efficacy,^{2,9} reduce the overall analgesic requirement, and ease patient handling. Although preemptive use of NSAIDs tends to increase their efficacy in relieving acute pain, renal effects of NSAID therapy should be clearly understood and considered to ensure safe use (see additional details below).

Balanced analgesia

Using NSAIDs in the context of balanced, or multi-modal, analgesia is preferred because the use of drugs from two or more analgesic classes will alter more than one nociceptive pathway, producing a synergistic effect. Ketoprofen and carprofen, for example, have been shown to provide the best postoperative analgesia when combined with an opioid.^{8,10} Combinations of analgesics also reduce the amount of each drug used, minimizing the risk of side effects associated with each. An example of multi-modal analgesia would be preoperative administration of a parenteral NSAID and a parenteral opioid, followed by intra-operative use of an epidural opioid or intra-articular anesthetic, and concluding with a local anesthetic block of the wound and use of a postoperative oral NSAID for extended analgesia following surgery.

Renal and hemostatic safety

Although preemptive use of NSAIDs tends to increase their efficacy in relieving acute pain, renal effects of NSAID therapy should be clearly understood to ensure safe use. When anesthesia results in hypovolemia, renal perfusion and GFR are maintained by PGs synthesized locally in the kidney by COX. Because the kidneys receive about a fifth of the cardiac output, they are particularly susceptible to ischemic injury. All NSAIDs, including COX-2 inhibitors, can negatively affect kidney function because of their ability to inhibit COX. Thus, it is important for the clinician to ensure the patient has normal renal function and is adequately hydrated when NSAIDs are used preoperatively. In properly hydrated patients without pre-existing renal compromise, it appears that approved veterinary NSAIDs can be safely given as acute therapy with little risk of inducing renal insufficiency. The margin of safety is increased if intra-operative IV fluids are given for surgeries where NSAIDs are used.

Platelet coagulation and clotting activity is regulated by COX-1 synthesis of thromboxane, while anti-thrombotic activity is regulated by COX-2 synthesis of prostacyclin. Because prolonged bleeding is a potential risk with NSAIDs such as aspirin and ketoprofen that inhibit COX-1, they should be avoided pre-operatively (although there is some debate as to whether or not ketoprofen causes significant bleeding perioperatively). When carefully evaluated, the NSAIDs approved for use do variably affect aspects of clotting function,¹¹ and although this is probably not clinically relevant in healthy individuals, it may become important in individuals with clotting disorders (hypo or hyper-coaguable).

Risk factors for NSAID-related toxicity

NSAIDs should be used with caution or not at all in animals with a history of NSAID-associated adverse reactions:

- Patients with renal or hepatic insufficiency, dehydration, or hypotension
- Conditions associated with low effective circulating volume (congestive heart failure, ascites, use of diuretics)
- Clotting disorders
- Evidence of gastric ulceration (e.g., melena) or GI disorders of any kind
- Trauma cases until adequate fluid intake and absence of internal hemorrhage and shock have been assured (however, the use of injectable NSAIDs for trauma patients is an extremely valuable therapeutic tool in providing pain relief)
- Pregnant animals, due to the homeostatic role of COX-2 in reproductive function

Switching between NSAIDs in the peri-operative period

Recent reports highlight the potential side effects from rapidly switching from one NSAID to another, such as might occur in the peri-operative period.^{12,13} However, a small experimental study found no adverse effects when evaluating switching between two approved NSAIDs.¹⁴

1. Dunning D, Lascelles BD. Rehabilitation and palliative analgesia. In: Tranquilli WJ, Thurmon JC, Grimm KA, eds. *Lumb & Jones Veterinary Anesthesia*, 4th ed. Ames, Iowa: Blackwell Publishing; 2007:697-704.
2. Lascelles BD, Cripps PJ, Jones A, et al. 1998. Efficacy and kinetics of carprofen, administered preoperatively or postoperatively, for the prevention of pain in dogs undergoing ovariohysterectomy. *Vet Surg* 27:568-582.
3. Lascelles BD, Butterworth SJ, Waterman AE. 1994. Postoperative analgesic and sedative effects of carprofen and pethidine in dogs. *Vet Rec* 134:187-191.
4. Lascelles BD, Cripps P, Mirchandani S, et al. 1995. Carprofen as an analgesic for postoperative pain in cats: dose titration and assessment of efficacy in comparison to pethidine hydrochloride. *J Small Anim Pract* 36:535-541.
5. Nolan A, Reid J. 1993. Comparison of the postoperative analgesic and sedative effects of carprofen and papaveretum in the dog. *Vet Rec* 133:240-242.
6. Slingsby LS, Murison PJ, Goossens L, et al. 2006. A comparison between pre-operative carprofen and a long-acting sufentanil formulation for analgesia after ovariohysterectomy in dogs. *Vet Anaesth Analg* 33:313-327.
7. Slingsby LS, Waterman-Pearson AE. 1998. Comparison of pethidine, buprenorphine and ketoprofen for postoperative analgesia after ovariohysterectomy in the cat. *Vet Rec* 143:185-189.
8. Slingsby LS, Waterman-Pearson AE. 2001. Analgesic effects in dogs of carprofen and pethidine together compared with the effects of either drug alone. *Vet Rec* 148:441-444.
9. Welsh EM, Nolan AM, Reid J. 1997. Beneficial effects of administering carprofen before surgery in dogs. *Vet Rec* 141:251-253.
10. Pibarot P, Dupuis J, Grisneaux E, et al. 1997. Comparison of ketoprofen, oxymorphone hydrochloride, and butorphanol in the treatment of postoperative pain in dogs. *J Am Vet Med Assoc* 211:438-444.
11. Brainard BM, Meredith CP, Callan MB, et al. 2007. Changes in platelet function, hemostasis, and prostaglandin expression after treatment with nonsteroidal anti-inflammatory drugs with various cyclooxygenase selectivities in dogs. *Am J Vet Res* 68:251-257.
12. Lascelles BD, Blikslager AT, Fox SM, et al. 2005. Gastrointestinal tract perforation in dogs treated with a selective cyclooxygenase-2 inhibitor: 29 cases (2002-2003). *J Am Vet Med Assoc* 227:1112-1117.
13. Enberg TB, Braun LD, Kuzma AB. 2006. Gastrointestinal perforation in five dogs associated with the administration of meloxicam. *Journal of Veterinary Emergency and Critical Care* 16:34-43.
14. Dowers KL, Uhrig SR, Mama KR, et al. 2006. Effect of short-term sequential administration of nonsteroidal anti-inflammatory drugs on the stomach and proximal portion of the duodenum in healthy dogs. *Am J Vet Res* 67:1794-1801.

All pre-operative analgesics should be given at a time and at a dose to provide preemptive analgesia at the time surgery starts

Pain management in the immediate post-operative period is facilitated by good preemptive analgesia earlier on. Intensive pain management at this time decreases the length and severity of post-operative pain over the following days. This immediate post-operative pain management should be started before the animals becomes painful – i.e. it should be preemptive

MONITOR PAIN MANAGEMENT AT HOME. INVOLVE AND EMPOWER THE OWNER TO ENSURE OPTIMUM PAIN RELIEF, AND MINIMAL SIDE EFFECTS

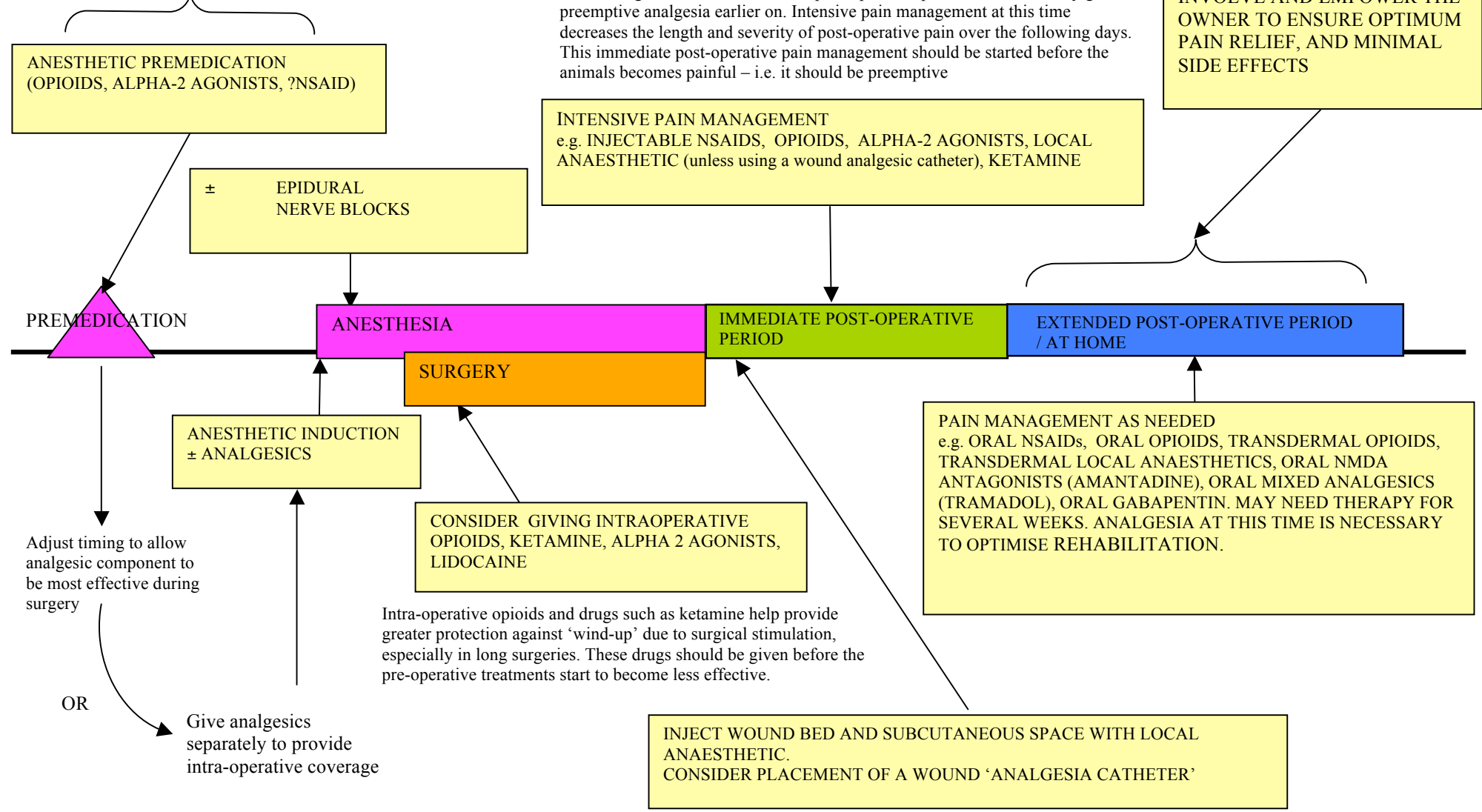


Fig 1: Principles of provision of multimodal peri-operative analgesia