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Topical Review

Adjunctive, Pain-Modifying, Analgesic Drugs

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Outside the realm of nonsteroidal antiinflammatory drug(NSAID) and opioid exist a broad range of medications that exert an analgesic effect, or otherwise modify and protect against pain, by manipulating various targets along the nociceptive pathway. Strength of evidence for dogs and cats can vary widely, and this article will review the available literature that may guide clinical usage in these species.

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Alpha-2 Agonist

Alpha-2 and opioid receptors are colocated on central nociceptors, both drugs serve to close calcium channels presynaptically on the first order neuron in dorsal horn of spinal cord (albeit through different mechanisms) thus hyperpoloarizing the second-order nociceptor, and thus the use of both these drug classes together is highly synergistic for sedation and analgesia. The analgesic and sedating effect have been reported to be similar to those of opioids in dogs,[1] although when used together, synergy of the 2 drugs allows for significant dose reduction of both. Sedation occurs due to blocking of norepinephrine (NE) production. It also blocks NE receptors on blood vessels, resulting in vasoconstriction; the resulting hypertension parasympathetically induces bradycardia, which is extended by a subsequent direct decrease in sympathetic tone, although central perfusion is maintained. It has a versatile if off-label dosing profile where low (5 μg/kg) and even microdoses (0.25-1 μg/kg, resulting in volumes as low as 0.01-0.03 mL even in larger dogs) with opioids are clinically useful and minimize the cardiovascular effects. Be mindful that these lower doses shorten the duration of the drug, and the analgesic effects may wane before the sedative effects. The safety and pain-modifying effect of dexmedetomidine constant rate infusions (CRIs) have been described.[1]

Ketamine

The phencyclidine dissociative anesthetic ketamine exerts a pain-modifying effect predominantly as a potent N-methyl-D-aspartate (NMDA) receptor antagonist. It binds to its receptor inside the NMDA receptor, that is, the ion channel would already have to be open and active for ketamine to exert its effect. However, once bound, it decreases the channel's opening time and frequency, thus reducing Ca^+ influx and dampening secondary intracellular signaling cascades. Hence, it is unlikely (and has not been shown) to be truly analgesic in nature. Rather, subanesthetic ketamine CRI has been convincingly shown to have pain-preventive, anti-hyperalgesic, antiallodynic effects in humans[2-7] and existing studies in dogs appear to support a similar clinical effect[8-10] (not yet studied in a feline surgical model). The International Veterinary Academy of Pain Management has adopted a position that the pain-modifying effects and safety warrant the consideration of subanesthetic ketamine as part of a multimodal approach to transoperative pain management, especially in patients with risk factors that may predispose them to exaggerated or maladaptive pain states.

Intravenous Lidocaine

The mechanisms behind a pain-modifying effect of systemic lidocaine remain an area of investigation but appear to include its ability to enter the nociceptor cell body in the dorsal root ganglion. In humans, the evidence is strong for safety and the beneficial effects of intravenous lidocaine (IVL) on pain after abdominal surgery in humans (although not other surgeries eliciting somatic pain)[11] and possibly horses, including both pain and return of

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bowel function. Systemic, intravenous infusion of lidocaine has also been shown to elicit a sustained effect on neuropathic pain in humans,[12] although this has not been studied in companion animals. It is anesthetic sparing in dogs and cats, but the current evidence for a pain-modifying effect in these species remains inconclusive.[13-18] IVL can still be suggested as a safe and sparing adjunct to opioid and other analgesics for abdominal surgery, trauma, and pancreatitis at a dose of 50 μg/kg/min, in dogs; and this has been used for 24-48 hours.

Some investigators discourage the use of IVL in cats because of negative cardiovascular effects,[19] but, anecdotally, it has been utilized in clinical practice.

Systemic, intravenous infusion of lidocaine may have a specific point of action in the brain.[20]

Note: alpha-2 agonists, systemic lidocaine, and ketamine CRI are sedating and can be profoundly anesthetic sparing especially in combination with opioids.[1] If administered during anesthesia, induction doses and maintenance vaporizers should be adjusted downward accordingly and can often be at 1% or less. The drug concentrations and fluid rates may be adjusted to fit the needs of the individual patients. Rate calculators are available on www.vin.com (Library/Calculators) and www.vasg.org/resources_&_support_material.

Tramadol

In humans, tramadol is known to exert its pain-modifying effect through 2 metabolites: one enhances inhibitory neurotransmitters (serotonin or NE) and the other (0-desmethyltramadol or "M1") metabolite is a weak opioid (1/100th the μ-receptor affinity of morphine). However, tramadol has a very short half-life (1.7 hours) in dogs,[21] and it appears that dogs produce very little of the M1 opioid metabolite.[22-24] Nevertheless, pharmacodynamic studies in dogs have demonstrated the anesthetic-sparing[25,26] and pain-modifying effects of *parenteral* (IV, SC, Epidural) tramadol[27-32]; however, convincing evidence for a pain-modifying effect of *oral* tramadol remains elusive at this time, and indeed some skepticism is warranted.[33] In addition to the lack of demonstrable opioid activity in dogs, pharmacokinetic (PK) studies in dogs reveal that not only are plasma levels much lower following oral administration than in humans, sequential dosing for several days leads to dramatic reductions of those plasma levels[33,34] (suggesting saturation of gastrointestinal [GI] active transport sites, increased metabolism, more robust first-pass effect, or a combination). A study of oral tramadol did report a statistically significant increase of mechanical threshold levels, but at a relatively high dose (10 mg/kg) and only at the 5- and 6-hour point,[24] and it should be pointed out that this is not a clinical pain study. Another study did find oral tramadol effective as *part* of a multimodal analgesic protocol to control cancer pain,[35] but others found it (not unsurprisingly) inferior as a solo agent to multimodal analgesic approaches to control postoperative pain.[36,37] Another study found that tramadol improved the condition in dogs with osteoarthritis (OA) by subjective outcome measures, but the placebo group showed improvement as well, and objective data (gait analysis) did not reveal statistical differences between tramadol and placebo groups.[33] An unpublished abstract on the effectiveness of tramadol administered once daily in canine OA may be encouraging,[38] but this study has not passed peer review. In contradistinction to dogs, cats do produce the μ-agonist M1 metabolite,[39] and a pain-modifying effect has been demonstrated in a both a thermal threshold[40] and clinical surgical model[41] and in a case series of use of oral tramadol in a flavored compounded form[42] (the drug is otherwise quite bitter).

The short half-life of the drug and its metabolites in the dog suggests a treatment regime of up to every 6 hours, but there are no dose-titration data in dogs and cats. Dosing has been suggested at 3-5 mg/kg, but due to unfavorable PK in the dog, KuKanich suggests up to 10 mg/kg; it is not known whether this would contribute to increased incidence or severity of adverse events. Safety and toxicity data in both dogs and cats are also lacking. Adverse events listed for humans include GI upset, sedation, increased GI bleeding (from serotonin-mediated diminished platelet function), hypertension (from NE-mediated vasoconstriction), seizure potentiation, and the possibility of increased risk of erosion and ulceration when combined with NSAIDs. In August of 2014, the FDA announced that tramadol would become a Schedule IV drug in the United States.

Gabapentin

Gabapentin is an anticonvulsant with analgesic properties that appear to be predominantly derived from downregulation of voltage-dependent calcium channels,[43] but other mechanisms probably exist as well (while structurally similar to γ-aminobutyric acid, it is not a direct agonist, although it may have indirect effects on γ-aminobutyric acid metabolism such as increasing intracellular stores). Because of its effectiveness and tolerability, it is in widespread use for humans with neuropathic and other maladaptive pain conditions,[44-48] and this suggests, along with published case reports in dogs and cats,[49-51,55,56] a strong rationale for the utilization of gabapentin in analogous conditions experienced by dogs and cats. The utility of gabapentin for OA is demonstrable in rodent models.[52,53] A canine study suggests a disease-modifying effect in experimental OA,[54] but no clinical studies have been published investigating gabapentin in canine OA. In cats, an unpublished study is reported to demonstrate a benefit of gabapentin in naturally occurring OA,[57] in addition to a case series of chronic musculoskeletal pain.[58]

Systematic reviews in humans support safety and benefit of transoperative oral gabapentin for postsurgical pain.[59-63] The evidence in dogs and cats for efficacy in acute pain currently is disappointing,[64-67] but 1 case series uses gabapentin in cats with acute traumatic musculoskeletal injuries.[58] PK studies in dogs reveal that it may have a half-life of 3-4 hours in dogs,[68] suggesting a thrice-a-day administration schedule, although anecdotally twice a day appears to be useful. The primary adverse effect in dogs appears to be somnolescence (as in humans), which usually spontaneously resolves over a few days acclimation time. For chronic pain dosing, a general consensus is that doses are initiated at 3 mg/kg and gradually tapered upward as the patient can tolerate to a target dose range of 20 mg/kg or higher. In the perioperative setting, dose based on the experience in humans is approximately 10 mg/kg.

Amantadine

Amantadine exerts a pain-modifying effect as an NMDA receptor antagonist[69] and remains a research focus for chronic pain (but not specifically OA) in humans.[70] A study demonstrates its utility as an adjunct to NSAIDs in dogs with refractory OA.[71] Toxicity and kinetic studies have been performed in humans[72] and cats[73] but not in dogs. Amantadine dosing range is 3-5 mg/kg orally once to twice daily.

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) exert their analgesic activity by enhancing synaptic NE and serotonin (inhibitory transmitters) in the dorsal horn of the spinal cord, although they have other effects including antihistaminic, anticholinergic, NMDA receptor