Multimodal Approach to Pain Management: Layering for Safety and Efficacy

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The framework of effective pain management systems rests solidly on the foundation of recognition, assessment, preemption, and using multiple modalities. Multiple modalities allow for intervention at several different points of the nociceptive pathway, increasing effectiveness and minimizing the need for high or protracted doses of any one particular drug. It is well-established in human medicine, for example, that the use of adjunct medications will minimize the use of PCA (patient-controlled analgesia) opioids with a resultant decreased incidence of adverse effects such as nausea and constipation (1, 2, 3, 4).

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAID'S)

Their primary mode of action is to inhibit cyclooxygenase 2 (COX2), the enzyme that is expressed at the site of inflammation and results in the production of pro-inflammatory and vasoactive prostaglandins. Also, through poorly understood mechanisms, possibly by modulating multiple gene expression pathways (5), it may inhibit central perception of pain. Several superior products are now labeled for use in dogs (and some in cats), making them among the most popular of pain management medications in veterinary medicine. All seem to be effective, and head to head studies now emerging may help to reveal objective differences if they are present. The main limitation of all NSAID's revolves around the potential for adverse effects, since both COX 1 and COX 2 enzymes may be constitutive, that is, consistently present and crucial to the production of cyto-protective prostaglandins (COX1 especially in the gastro-intestinal (GI) tract and renal tubules and COX2 in the renal tubules). Thus the primary adverse effects of non-selective NSAID's may include GI erosion/ulceration and nephrotoxicity. COX1-sparing NSAID's should have a dramatically diminished GI toxicity profile, but will maintain their risk for nephrotoxicity. Rarely and on an idiosyncratic basis, hepatotoxicity may occur. The GI and renal adverse effects can be expected to occur most commonly in higher risk patients, e.g.: hypovolemia, hypotension (including anesthetic procedures especially those not supported by intravenous fluids), pre-existing GI or renal disease, over usage, and the inappropriate combination with other NSAID's, corticosteroids, or other highly protein-bound drugs. Notable in adverse drug interactions is the client use of aspirin in their pets, which may be unbeknown to the clinician unless specifically queried in a thorough history. The relative roles and molecular dynamics of COX1, COX2, and a possible new variant COX3, is still being elucidated and the "final word" on the optimal COX-selective or –sparing effect in order to maximize effectiveness and to limit toxicity, is yet to be heard.

NSAID's, and the merits of using them in cases of chronic inflammatory conditions, e.g. osteoarthritis, are familiar and well-established. However, their long-term use may increase the chances of adverse effects. In general, a 5-day washout between NSAID's is recommended, and 10 days specifically for aspirin and meloxicam. Where possible, the use of other modalities may allow lower NSAID doses which may in turn increase the safety profile. In all cases of NSAID use, the practitioner must consistently educate clients regarding the potential adverse effects of this class of drug. More than ¾ of individuals reporting adverse NSAID events to the FDA hotline feel that their veterinarian did not inform them adequately of possible side effects, and/or failed to give

the client the drug information sheets provided by the pharmaceutical company (6).

A special word regarding the long-term use of NSAID in cats: In 2010 the American Academy of Feline Practitioners) AAFP and ISFM (International Society of Feline Medicine) released Consensus Guidelines on the long-term use of this class of drug in cats (7). The reader is referred to this manuscript in its entirety, but the authoring panel suggests the following points: withholding NSAID in cats with chronic pain may fulfill the "First, Do No Harm" paradigm but fails to recognize the harm of undermanaged chronic pain; and that NSAID's may be used long-term as a management tool with proper patient selection, monitoring, and seeking the lowest effective dose. Unfortunately, the "Black Box" placed on the label of the drug meloxicam in the U.S. complicates the use of this product in cats.

Acetaminophen appears to have weak COX-1 and COX-2 inhibition, but may inhibit a centrally-expressed COX-3 and a partial COX1 (PCOX-1) enzymes, mediating an analgesic effect by dulling the pain sensory system (8). Acetaminophen is contraindicated in cats and in patients with liver disease, and should be used with caution, especially chronically, in dogs due to limited experience and diminished metabolism when compared to humans (9).

OPIOIDS

Opioid receptors are distributed ubiquitously throughout the body and can be found in most central and peripheral tissues. Several different opioid receptor types and subtypes have been isolated, each with a variant effect; activation of an opioid receptor inhibits presynaptic release and postsynaptic response to excitatory neurotransmitters. The proposed mechanism includes opioid receptor coupling with the membrane-associated G protein; this leads to decreased intracellular formation of cAMP which diminishes calcium channel phosphorylation (closing off the channel) and opens potassium channels enhancing potassium influx. The resulting effect is hyperpolarization of the neuron and blockade of Substance P release. Nociceptive transmission is thus greatly impeded (10).

Similarly, a number of different opioid drugs are available which vary in their relative potency and receptor affinity, and a complete discussion of their similarities and differences are available in a number of resources. Briefly, however, of the pure mu agonists, of which morphine remains the prototype in widest use, has no ceiling effect on analgesia or respiratory depression, elicits histamine release, and causes vomiting at low doses (higher doses, IV doses, and chronic use do not elicit vomiting, presumptively by interaction with mu receptors in the antiemetic center) (11). Cats lack glucoronate metabolism, resulting in minimal production of the analgesic M6G metabolite (12), therefore morphine may not be the ideal opioid for use in this species. Oxymorphone (Numorphan®) and hydromorphone (Dilaudid®) do not elicit histamine release (therefore may be a wiser choice in cases with hypovolemia e.g. trauma, dehydration), and nausea may be less pronounced, but they have a much shorter duration of action than morphine. Hydromorphone in particular has been implicated in episodes of hyperthermia in cats (13). Fentanyl in a transdermal patch (Duragesic®) remains useful in veterinary medicine though a number of studies have demonstrated wide kinetic variability in veterinary patients due to species, body condition score, body temperature, surgical procedure, placement of the patch, etc. (14, 15).

Buprenorphine is a partial mu agonist with a greater affinity for the mu receptor than pure mu agonists e.g. morphine, hydromorphone, fentanyl. Thus theoretically, buprenorphine would displace morphine (or hydromorphone, fentanyl) if competing for the mu receptor simultaneously. However in a rodent model, this antagonistic effect was seen only when buprenorphine was given at higher doses and before morphine or hydromorphone; and interestingly when buprenorphine was administered concurrently with pure-mu agonists, the mu-opioid analgesic effect was either additive or synergistic. (16). A great benefit of the drug in veterinary medicine is that its pKa (8.4) closely matches the pH of the feline oral mucosa (9.0), which allows for nearly complete absorption when given buccally in that species (17) with kinetics nearly identical to IV and IM administration (18), and eliciting very little sedation. Butorphanol is a mu agonist and a kappa agonist; its very short duration of action in the dog (approx. 30-40 min) makes it a poor choice for an analgesic in this species, though used parenterally it has utility as an adjunct with other medications such as alpha-2 agonists.

Opioids for all their effectiveness may create clinical challenges as well. In the acute setting, opioid-induced dysphoria, hyperalgesia, and respiratory depression may be encountered. Recognition and having strategies for counteracting

their signs will minimize the complications that they may present (19).

A number of oral mu-agonists are available, and opioid tolerance or resistance is a common sequel of chronic use. As effectiveness diminishes and dose requirements escalate, undesirable adverse effects become more likely (most commonly reported in humans by far is constipation; but abnormal pain sensitivity, hormonal changes, and immune modulation are also reported though their mechanisms are not fully established) (20), and the practitioner must also always be vigilant regarding drug diversion. Historically, opioid use in chronic pain has been most commonly reserved for palliative care and breakthrough pain (BTP), often of cancer patients. However, as opioid interaction with a variety of non-opioid receptors (e.g. N-Methyl-D-aspartate (NMDA), alpha-2-adrenergic) has become more evident, the role of opioids is being redefined for their utility in a multi-modal approach to chronic pain conditions (21), including osteoarthritis (22). Hydrocodone, codeine (alone and in combination with acetaminophen), and sustained-released forms of oral opioids include morphine (MSContin®), oxycodone (Oxycontin®), and oxymorphone (Opana ER®) are all available by prescription (23), though pharmacokinetics and pharmacodynamics in dogs and cats is less well established. Rectal suppository opioid formulations may also be prescribed, but appear to provide little advantage in bioavailability over the oral route in the dog (24). Buprenorphine is a partial mu-agonist well-absorbed across the buccal mucosa in cats and has been used as an adjunct in the management of chronic pain in this species. A sustained-released version of buprenorphine has recently become available.

TRAMADOL

Tramadol has also become a popular adjunct to chronic pain management in humans (25, 26) with one hundredth of the affinity for the mu receptor compared to morphine but a much better analgesic effect than this would predict. This is likely due to the combined effect of a highly active M1 metabolite and serotonin (an inhibitory neurotransmitter) agonism. However recent work demonstrates that it appears to have a very short half-life (1.7 hours) in the dog (27), so for full effectiveness it may need to be given as often as every 6 hours, which may or may not be an obstacle for short-term administration. A sustained-released version of oral tramadol seems to offer no advantage in this regard (28). Furthermore, conversion to the active mu agonist M1 metabolite appears to be minimal in the dog (29), indicating most of its activity in this species may be derived from its serotoninergic and noradrenergic activity. Pharmacodynamic and toxicity data is severely lacking in dogs and cats, however one unpublished study on the effectiveness of tramadol administered once daily in canine osteoarthritis appears encouraging (30). Tramadol should not be used with other serotoninergic medications such as tricyclic antidepressants, (Serotonin and Norepinephrine Reuptake Inhibitors) SNRI's, and amitraz-containing compounds.

ALPHA- 2-AGONISTS

Medetomidine and dexmedetomidine binds opioid-like receptors on C- and A-delta fibers, especially in the central nervous system. Binding pre-synaptically, norepinephrine production is reduced and sedation occurs; binding post-synaptically, analgesia is produced, and is profoundly synergistic with opioids. It also blocks norepinephrine receptors on blood vessels, resulting in vasoconstriction; the resulting hypertension parasympathetically induces bradycardia, which is extended by a subsequent direct decrease in sympathetic tone. However, central perfusion is maintained and the author has found a wide use for these alpha-2 agonists in acute and peri-operative setting, though only in combination with opioids and at doses much lower than suggested by the manufacturer. One particularly novel and user-friendly utility is IV micro-doses intra- and post-operatively, 0.25 – 1.0 μg/kg. This may result in intravenous volumes of only 0.01 – 0.03 ml in even the largest of dogs.

KETAMINE

A phencyclidine dissociative anesthetic, the evidence is building for its pre-emptive and preventive effects when given at sub-anesthetic doses in an intravenous constant rate infusion. Ketamine binds to a phencyclidine receptor inside the NMDA receptor, i.e. the calcium 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+ ion influx and dampening secondary intracellular signaling cascades. Hence it is unlikely (and has not been shown) to be truly analgesic in nature. Rather, it appears to be protective against hyperalgesia and central hypersensitization in the post-operative setting (31), including in the dog (32).

LOCAL ANESTHETICS

Local anesthetics were once a mainstay of pain management in veterinary medicine, and may now be one of the most under-utilized modalities. Local anesthetics exert their effect by closing sodium channels on nociceptors, thereby disallowing depolarization of the cell (33). Other local beneficial effects include: broad anti-inflammatory effects (reduced production of eicosanoids, thromboxane, leukotriene, histamine, and inflammatory cytokines; and scavenging of oxygen free radicals) and even antimicrobial, antifungal and antiviral effects (34, 35). Overdose of local anesthetics can be fatal, and so observation of reported dose rates and careful calculation should allow their safe use. A commonly held misconception is that local anesthetics impair wound healing – although they can powerfully inhibit the inflammatory component of cellular tissue influx, there is no evidence to support impaired wound healing. Lidocaine if administered IV at high doses tends to elicit CNS adverse events, and the more lipophilic bupivacaine can be cardiotoxic and therefore should never be administered IV. The duration of activity can reportedly be doubled with small amounts of an opioid, either morphine or buprenorphine (36, 37).

Topical anesthetics such as prilocaine/lidocaine cream (EMLA®) is described for use in dogs and cats for minor procedures including the simplest but still uncomfortable procedures such as venipuncture. The lidocaine 5% patch (Lidoderm®) are intended for post-herpetic neuralgia (Shingles) and the pharmacokinetics of this product has been investigated in dogs and cats, with minimal systemic absorption noted (38, 39) and can be used for post-operative pain control.

Other local-regional techniques include:

- Line block, splash block
- En bloc Infiltrative
- Regional Nerve Blocks
  - dental
  - intercostal
  - brachial plexus; paravertebral
- Diffusion Catheter
- Intra-articular
- Retrobulbar
- Epidural
- Intrapleural, Intra-abdominal

OTHER PAIN-MODIFYING ANALGESIC DRUGS

Gabapentin

Gabapentin is labeled for use as an anti-convulsant drug but is in widespread human use for its analgesic properties. Its interaction with the alpha-2-delta subunit of the voltage gated calcium channel has it made it popular in human medicine since its introduction in 1994 for many chronic and neuropathic pain conditions (40-44). Pharmacokinetic studies in dogs reveal that it may have a half-life of 3-4 hours (45), suggesting a three times a day administration (TID) schedule which may be difficult to sustain long-term; no veterinary studies are currently published on its use. However, anecdotally, twice a day (BID) administration does appear to achieve a clinical effect in dogs. Interestingly, in a rat model there is recent evidence that a gabapentin-like analog may have reduced the development of experimental osteoarthritis (46). The primary adverse effect in dogs appears to be somnolescence (as in humans) which usually spontaneously resolve over a few days acclimation, and can be mitigated by beginning at quite low doses and increasing upwards. Evidence in the human literature also supports a utility in the perioperative period (47).

Amantadine

NMDA receptor antagonism remains a research focus for chronic pain in humans (48), but no clinical studies report on its use for osteoarthritis. Amantadine is an anti-viral (influenza-A) compound use in humans as for treatment of Parkinson's disease due to its dopaminergic effects, and is reported to exert an analgesic effect through NMDA receptor antagonism (49). One study in dogs with osteoarthritis demonstrated greater improvement over 12 weeks of treatment with amantadine with meloxicam, compared to meloxicam alone (50). Toxicity and kinetic studies have been performed in humans (51), but not in dogs. Anecdotally in dogs and cats, diarrhea is commonly noted and agitation less frequently.

TRICYCLIC ANTIDEPRESSANTS (TCA), SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITORS (SNRI) AND OTHERS:

TCA's exert their analgesic activity by blocking norepinephrine and serotonin (5-HT) reuptake in the dorsal horn synaptic cleft of inhibitory neurons that have descended from

the medulla oblongata and mesencephalon; this allows these inhibitory neurotransmitters to exert a prolonged and more pronounced effect. Since depression (pain-related and otherwise) is also mediated through NE and serotonin, patients may have benefit of TCA's from these co-existing but distinct mechanisms. Other additional effects include interaction with NMDA activity and sodium channel blockade. As a class, TCA's are a first-line medication for neuropathic pain in humans (52), and amitriptyline is the most commonly used TCA in both humans (primarily for diabetic neuropathy) (53) and animals (primarily for chronic feline interstitial cystitis (54)). It has a balanced norepinephrine and serotonin effect, and thus is among the more sedating, anti-cholinergic, and effective of various TCA's (55).

Serotonin and norepinephrine reuptake inhibitors come in various degrees of selectivity for one or the other of these inhibitory neurotransmitters. Most of them are on the market as anti-depressants, revealing the shared pathways and well-established co-morbidity of depression and chronic pain. Newer selective serotonin reuptake inhibitors (SSRI's) and selective serotonin norepinephrine reuptake inhibitors (SSNRI's) such as milnacipran (Savella®) and duloxetine (Cymbalta®) have been developed for chronic pain states such as fibromyalgia and diabetic neuropathy respectively, with the latter having more strict serotonin (i.e. norepinephrine-sparing) activity and therefore reportedly with diminished adverse effects. The clinical use of these drugs or earlier versions such as fluoxetine (Prozac®) in animals has not been documented but some studies do suggest efficacy for osteoarthritis in humans (56).

SSRI's, SNRI's and TCA's should not be used together or with other serotoninergic medications and compounds such as tramadol and amitraz.

DISEASE-MODIFYING OSTEOARTHRITIC AGENTS (DMOAA)

DMOAA's are products that are not FDA-approved medications or are not known to have a primary analgesic mechanism of action, or both, but which seem to have a positive influence on patients with osteoarthritis. The polysulfated glycosaminoglycans exert their action by inhibiting collagenase and promoting the formation of fibrocartilage, which should have the dual effect of improving the clinical status of the patient as well as slowing the course of osteoarthritis. While some studies have demonstrated that the combination of glucosamine and chondroitin (neither used alone) exerts a positive structure-modifying effect on the cartilage (57), large randomized controlled trials in humans have failed to demonstrate improvement in pain when compared to placebo. There are several veterinary oral products available, either alone or in combination with other compounds that have independently been found to have disease- and/or pain-modifying effects: soybean avocado unsuponifiables (58), S-adenosylmethionine (59), methylsulfonylmethane (60), among others. However the strongest evidence can be found with Adequan®, an FDA-approved polysulfated glycosaminoglycan (PSGAG) drug with demonstrable effects (61). Adequan® may be administered (off-label) via a subcutaneous route with similar bio-availability as the IM route, allowing it to be dispensed for the owner to give at home. This decreases considerably the cost and inconvenience to the owner, which in turn adds greatly to compliance. The author also uses it regularly (off-label) in cats.

Microlactin is an oral byproduct of the milk from hyper-immunized cows exerts its action by unknown mechanisms, but there is evidence of its suitability for use in patients with chronic osteoarthritis (62).

CANCER PAIN

Neoplasia remains a special subset of patients suffering from chronic pain, with osteosarcoma as the prototype in dogs. Certainly soft-tissue inflammation, necrosis, nerve compression and lymphatic obstruction are all indirect contributors to cancer pain. With osteosarcoma, pathology to the periosteum is a direct contributor to the pain associated with this type of cancer. Tumors may also secrete a number of bioactive molecules which sustain and enhance the nociceptive pathways in ways distinct from other sorts of chronic inflammatory conditions. Lastly, our therapeutic interventions may elicit pain as well. For this reason, it is important to access the practitioners' entire pain-modulating arsenal, and where possible, at the higher end of tolerated doses (e.g. tramadol, gabapentin). The anti-neoplastic effects of certain NSAID's in humans (63) and in dogs (64) have been well-established and appear to be mediated through the inhibition of up-regulated and over-expressed COX2 enzymes in some neoplasms of these species (65). It is unknown across what spectrum of other NSAID's, species, and neoplasms this effect might occur; in fact most of the neoplasms evaluated in cats have little if any COX2 expression (66). However, NSAID's in can-

cer pain would seem to exert a positive benefit if only by its anti-inflammatory and analgesic effect. Bisphosphonates are compounds which may palliatively alleviate asteosarcoma-related pain by decreasing osteoclast activity and inhibiting calcium and phosphorus dissolution, with pamidronate in most common use for dogs (67, 68). Infusions are given approximately once every three weeks in patients whose owners elect to forgo surgery and chemotherapy. Anecdotally, 60% of dogs will be responsive within a week, and about half of those will be durable i.e. > 4 months; it appears most effective when administered as part of multi-modal therapy (69). Nephrotoxicosis is reported to be a limiting adverse effect. Oral opioids were once considered to be generally poorly absorbed, short-acting, and prone to tolerance and adverse effects. While their long-term use in animals is currently limited, methadone and newer extended-release and transmucosal opioids, as well as novel opioid combinations which minimize constipation may have a role in palliative care and break-through cancer pain (see above). Recent studies in a rat model suggest pain resulting from bone neoplasia is better attenuated by systemically-administered delta- (rather than mu) opioids (70).

NON-PHARMACOLOGIC MODALITIES

As with acute pain, no discussion of chronic pain or disability management is complete without including interventions that have little to do with drugs or medications. Examples of such interventions include practices such as cryotherapy applied to surgical sites post-operatively and thermotherapy to chronic pain areas. Weight loss is considered crucial due to the systemic effects of pro-inflammatory cytokines known to emanate from adipose tissue, and studies in dogs show substantial improvement in lameness associated with osteoarthritis from weight loss alone (71). Commercial diets have been formulated with joint health specifically in mind (e.g. Hill's J/D, Purina JM, Eukanuba Senior Plus), utilizing high doses of omega-3 fatty acids. Omega-3 polyunsaturated fatty acids exert their action through competitive inhibition of pro-inflammatory prostaglandin production. Thirty three percent of Americans who use complementary modalities cite pain as the reason for doing so, and omega-3 PUFA's remain one of the more well-studied modalities. Recent evidence in humans strongly suggests that omega-3 PUFA's are an attractive adjunct for treatment of inflammatory joint pain (72) and at least one of the diets above have demonstrated objective improvement in force-plate analysis and a NSAID-sparing effect (73, 74).

Providing environmental enrichment and promoting simple activity may minimize chronic discomfort, as human studies have shown that patients who avoid activity suffer the greatest physical disability and distress (75). Exercise physiotherapy includes a broad range of techniques, some of which can be taught for home use or performed in a primary care setting, and others which are best accomplished by referral to a physical rehabilitation clinic with appropriate equipment and certified personnel. For example, transcutaneous and percutaneous electrical nerve stimulation (ENS) is a validated technique in humans (76), and a recent study in dogs demonstrated that a dietetic program accompanied by referral for intensive physiotherapy provided for improved weight loss and limb function (measured by force plate analysis) when compared to an at-home program (though this latter set of patients also improved over baseline) (77). Other biophysical modalities in common use include photobiomodulation (therapeutic laser), therapeutic ultrasound, extra-corporeal shockwave therapy, pulsed electromagnetic field, and others. Each of these modalities has various degrees of evidence supporting its possible anti-nociceptive utility.

ACUPUNCTURE

The National Institute of Health published a consensus statement acknowledging efficacy of acupuncture in dental pain, and supporting it as an adjunct treatment in a wide variety of other painful conditions (78). The role of placebo effect in acupuncture is difficult to determine in humans, much less animals. One recent set of studies illuminated that patient expectations of acupuncture positively correlated with treatment outcomes (79). However, similar effects can be expected with most any non-blinded treatment modality, and in the author's experience with very basic acupuncture techniques, approx. seventy five percent of clients attribute enough of a positive effect to the acupuncture to continue it on an intermediate- to extended course.

REGENERATIVE MEDICINE AND GENOMICS

The holy grail of chronic pain management utilizes techniques which leverage the body's own immunomodulating and healing capacities. Regenerative medicine modalities such as stem cell transplantation, platelet rich plasma

(PRP), and bio-scaffolding are receiving a lot of attention in both human and veterinary medicine for many chronic pain and other degenerative disorders, though these fields are in their infancy and there is much to be learned about their potential utility. Genomics – manipulating gene expression and transcription – is even further into the future but may provide the greatest promise of all to abate the "death spiral" of chronic pain and disability.

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