FOUNDATIONS

Pathophysiology and Management of Surgical and Chronic Oral Pain in Dogs and Cats

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Pain involves a myriad of physiochemical responses leading to the perception of an unpleasant sensation arising from tissue damage. An understanding of the terminology and basic neurophysiology involved with the pain process is helpful in preventing and treating discomfort in our patients. A general understanding of the concepts of nociception, peripheral sensitization, and central sensitization will allow decisions to be made on the choices of analgesic agents in each individual patient based upon the type, duration, and severity of the pain. Using preemptive pain management with a multimodal approach provides the most consistent and predictable results. Analgesic protocols should be closely scrutinized on an individual basis with careful patient pain assessment during the postoperative period. Chronic pain mechanisms, particularly significant in cancer pain and stomatitis, require aggressive and perhaps unique approaches to ensure maximum patient comfort.

Nociception

Nociception is defined as the processing of a noxious stimulus resulting in the perception of pain by the brain (Fig. 1).[1] The components of nociception include transduction, transmission, and modulation.[2] Transduction is the conversion of a noxious stimulus (mechanical, chemical, or thermal) into electrical energy by a peripheral nociceptor (free afferent nerve ending). Transmission involves impulse propagation from the site of oral injury primarily through the trigeminal afferent nerves. Nerve fibers involved include A-delta (fast) fibers responsible for the initial sharp pain, C (slow) fibers that cause the secondary dull, throbbing pain, and, A-beta (tactile) fibers that have a lower threshold of stimulation. Modulation in the oral cavity occurs when neurons from these fibers synapse with nociceptive-specific and wide dynamic range neurons in the nucleus caudalis located in the medulla.[3] This brain tissue is very similar to that of the spinal cord dorsal horn that modulates pain from areas other than the oral cavity.[3] Located within the excitatory synapse, neuropeptides such as glutamate and substance P facilitate the pain signals by binding to their receptors on these neurons.[2] At the same time, endogenous (opioid, serotonergic, and noradrenergic) descending analgesic systems serve to dampen the nociceptive response.[2]

Peripheral Sensitization

Surgical manipulation of tissues within the oral cavity results in a greatly enhanced nociceptor response to any additional stimulus postoperatively. This enhanced response is termed peripheral sensitization (hyperalgesia).[4] Primary hyperalgesia occurs when peripheral hyperalgesia develops at the site of injury. ATP, potassium ions, hydrogen ions, prostaglandins, bradykinin, and nerve growth factors are all released by the damaged tissue

Figure 1

Diagram showing nociceptive pathways involving transduction, transmission, and modulation resulting in the perception of a painful surgical stimulus.

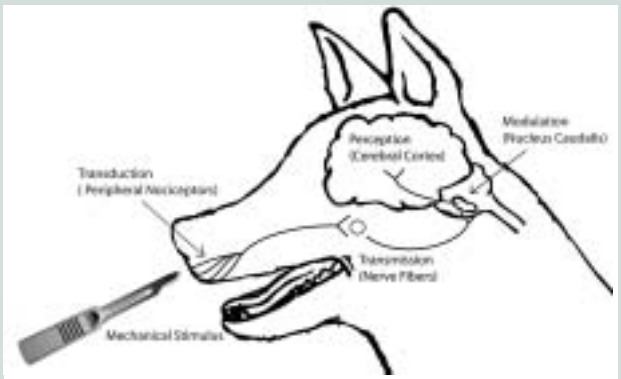
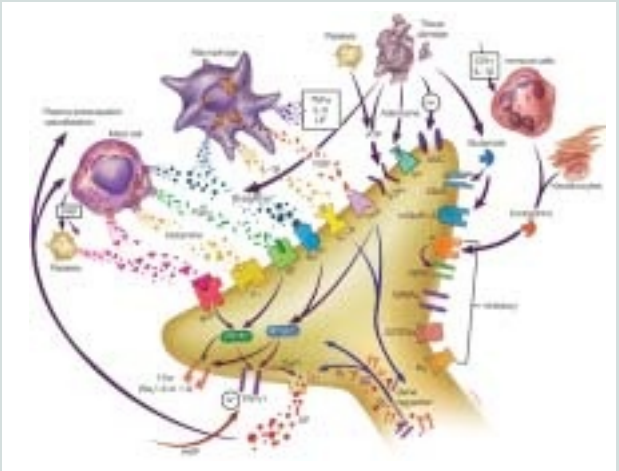


Figure 2

Diagram showing the complex interaction of inflammatory mediators involved with peripheral sensitization. Chemicals released directly from damaged tissue and inflammatory cells in response to inflammation sensitize peripheral nerve terminals.

Elsevier 2006, McMahon and Koltzenburg: Wall and Melzack's *Textbook of Pain*, 5th ed, www.textbookofpain.com



(Fig. 2).[2] Inflammatory cells including lymphocytes, monocytes, macrophages, and mast cells are attracted to the site. They release cytokines that amplify and potentiate inflammation. Histamine, a cytokine, enhances vasodilation resulting in plasma extravasation into surrounding tissues. As a result this "sensitizing soup" of substances extends into normal tissue producing secondary hyperalgesia. At this point, normal non-noxious stimuli such as touch can produce pain at and around the site of injury (allodynia).

Central Sensitization

When peripheral sensitization remains untreated, wide dynamic range neurons of the nucleus caudalis produce central sensitization, also termed "windup."[2,3] A complex interaction of numerous chemicals increases the sensitivity of these neurons enhancing the frequency and intensity of the pain signal to the brain. Glutamate is responsible, in part, by binding to the NMDA receptor on the wide dynamic range neuron and is one of the primary chemicals involved in central hypersensitization (Fig. 3).[2] Administering drugs to preferentially bind to the NMDA receptor in the nucleus caudalis is an effective way to manage central sensitization associated with oral pain states.

Preemptive Analgesia

Preemptive analgesia refers to the administration of analgesic medications prior to a painful stimulus to decrease subsequent pain. The practice of drug administration prior to the introduction of a painful stimulus is more effective than giving the same drug after the stimulus is induced. Pain states, once established, especially when central sensitization is involved become difficult to control emphasizing the importance of providing pain management in the preoperative period.[2] Feline lymphocytic, plasmacytic gingivitis/stomatitis (LPGS), refractory stomatitis in dogs, oral cancer, and other chronic painful conditions should all receive special consideration for preoperative pain management. Failure to provide preemptive analgesia makes postoperative pain management extremely difficult requiring additional hospitalization, administration of injectable rather than oral analgesics, and assisted alimentation (Fig. 4).

Multimodal Analgesia

Multimodal pain management refers to the use of two or more analgesics in combination to control patient pain. Often this approach allows for a decrease in dose for each of the agents making the combination safer than a higher dose of a single agent. The multimodal approach also allows clinicians to use different analgesics to block pain in different portions of the nociceptive pathway (Table 1). It should be noted that the local anesthetics block pain in all three pathways of nociception.

Environmental Comfort

Adjunctive environmental manipulation becomes important to providing maximal comfort for painful patients especially when surgical pain is managed. Temperature monitoring is

Figure 3

Diagram of modulation in the oral cavity demonstrating peripheral nerves synapsing with nociceptive-specific and wide dynamic range neurons in the nucleus caudalis located in the medulla. Within the synapse, excitatory neuropeptides like glutamate and substance P amplify the pain signals by binding to their receptors on these neurons. At the same time, endogenous opioids, serotonin, and norepinephrine are among the compounds released from higher centers in an attempt to decrease the pain response.

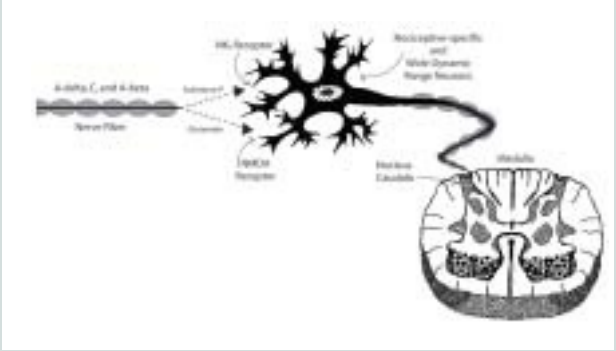
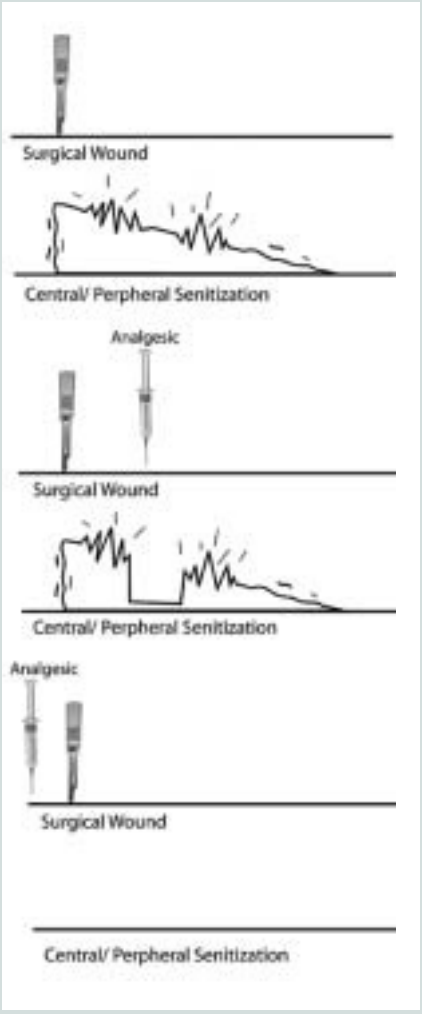


Figure 4

Diagram representing the effects of no analgesic therapy, intraoperative analgesic therapy, and preemptive analgesic therapy on central and peripheral sensitization.



particularly important in oral surgery. Small patients subject to cooling spray from ultrasonic and high-speed instrument devices become hypothermic quickly. Warm intravenous fluids and safe external warming devices maximize patient comfort postoperatively, and minimize intraoperative hypothermia. Dry warm towels and blankets provide comfortable padding for recovery and hospitalization. Species and individual patient separation within the hospital decreases stress. Minimizing noise allows painful patients to rest more comfortably. Patient contact in the form of verbal and tactile interaction is comforting in many whereas some patients recover better with passive observation. Soothing music is also considered beneficial.

Local Anesthetics

Regional and local nerve block techniques commonly utilized to provide analgesia in veterinary patients are detailed in texts and manuscripts and therefore will not be described here.[6-9] These techniques are aimed at providing profound and complete analgesia to the targeted tissue, and can also decrease the concentration of the inhalant anesthetic.[6] A lower concentration of inhalant anesthetic decreases complications from hypotension, bradycardia, and hypoventilation.[8]

Lidocaine[a] and bupivacaine[b] are two widely employed local anesthetic agents. The short duration of lidocaine (1 to 2-hours) and the delayed time to onset of action of bupivacaine are limiting factors in their use as individual agents.[10] Combining the two can negate these limitations providing lidocaine's short onset of action with bupivacaine's extended duration of effect (8-hours).[10] A maximum of 6 sites are needed for complete regional blockade of all four quadrants. Calculations for each agent are based on patient size (kgs) and the number of anticipated regional sites blocked (Tables 2-6).

Research in humans has shown that combining local analgesics with opioids provides extended duration of action. In one study the addition, of morphine[c] or buprenorphine[d] to a regional brachial plexus block for limb amputation provided nearly a two-fold increase in duration of effect compared with patients receiving only bupivacaine[b].[11] Another study using a similar model demonstrated that the addition of buprenorphined to the regional block provided significant increases in duration

Table 1

Drug classes affecting varying portions of the nociceptive pathway. Note that the local anesthetics affect all three portions of the pathway.

Transduction (Peripheral Sensitization Inhibition)	Transmission (Impulse Conduction Inhibition)	Modulation (Central Sensitization Inhibition)
Local anesthetics	Local Anesthetics	Local Anesthetics
Opiods	Alpha2 Agonists	Alpha2 Agonists
NSAIDs		Opiods
Corticosteroids		Tricyclic Antidepressants'
		Cholinesterase Inhibitors
		NMDA Antagoinists
		NSAIDs
		Anticonvulsants

Table 2

Recommended volumes of regional anesthetics for dogs and cats < 4 kg. Sterile saline is added to adjust the volume to accommodate infusion of all four quadrants if necessary. The author recommends following this recommendation and discarding the unused portion of the mixture if infiltration of all four quadrants is not needed to minimize volume calculation error.

Weight (kg)	Maximum Volume (ml) Lidocaine 2.0%	Maximum Volume (ml) Bupivicaine 0.5%	Sterile Saline (ml)	Volume Per Site(ml)
1	0.05	0.20	0.75	0.20
1.5	0.05	0.30	0.45	0.20
2	0.10	0.40	0.50	0.25
2.5	0.10	0.50	0.40	0.25
3	0.15	0.60	0.35	0.25
3.5	0.20	0.70	0.10	0.25

Table 3

Recommended volumes of regional anesthetics for dogs and cats ≥ 4 kg for anticipated infiltration of 1 regional site.

Weight (kg)	Maximum Volume (ml) Lidocaine 2.0%	Maximum Volume (ml) Bupivacaine 0.5%	Volume Per Site(ml)
4-6	0.05	0.20	0.25
6-15	0.06	0.24	0.30
16-20	0.08	0.32	0.40
20-25	0.12	0.48	0.60
26-30	0.15	0.65	0.80
31-35	0.20	0.80	1.00
36-40	0.25	0.95	1.20
41-45	0.30	1.10	1.40
46-50	0.35	1.25	1.60

Table 4

Recommended volumes of regional anesthetics for dogs and cats ≥ 4 kg for anticipated infiltration of 2 regional sites.

Weight (kg)	Maximum Volume (ml) Lidocaine 2.0%	Maximum Volume (ml) Bupivacaine 0.5%	Volume Per Site(ml)
4-6	0.10	0.40	0.25
6-15	0.12	0.48	0.30
16-20	0.16	0.64	0.40
20-25	0.25	0.95	0.60
26-30	0.30	1.30	0.80
31-35	0.40	1.60	1.00
36-40	0.50	1.90	1.20
41-45	0.60	2.20	1.40
46-50	0.70	2.50	1.60

Table 5

Recommended volumes of regional anesthetics for dogs and cats > 4 kg for anticipated infiltration of 3 regional sites.

Weight (kg)	Maximum Volume (ml) Lidocaine 2.0%	Maximum Volume (ml) Bupivacaine 0.5%	Volume Per Site(ml)
4-6	0.15	0.60	0.25
6-15	0.20	0.70	0.30
16-20	0.25	0.95	0.40
20-25	0.35	1.45	0.60
26-30	0.45	1.95	0.80
31-35	0.60	2.40	1.00
36-40	0.75	2.85	1.20
41-45	0.90	3.30	1.40
46-50	1.00	3.80	1.60

Table 6

Recommended volumes of regional anesthetics for dogs and cats > 4 kg or greater for anticipated infiltration of 4 regional sites.

Weight (kg)	Maximum Volume (ml) Lidocaine 2.0%	Maximum Volume (ml) Bupivacaine 0.5%	Volume Per Site(ml)
4-6	0.20	0.80	0.25
6-15	0.25	0.95	0.30
16-20	0.30	1.30	0.40
20-25	0.50	1.90	0.60
26-30	0.70	2.50	0.80
31-35	0.80	3.20	1.00
36-40	1.00	3.80	1.20
41-45	1.20	4.40	1.40
46-50	1.30	5.10	1.60

compared to giving the buprenorphine[d] intramuscularly.[12]

Although very uncommon, patients receiving local anesthetics for oral surgery have been known to traumatize their tongues during mastication in the postoperative period. Patient positioning in sternal recumbency precludes the tongue deviation expected when a patient is laterally recumbent. Observation and proper recovery assistance during this period will aid in avoiding this complication.

Opiods

The opiods currently provide the most effective pain control of any systemic agent. Opioid receptors are found in the central and peripheral nervous systems as well as various cells throughout the body. Stimulation of opiod receptor subtypes by drugs in this class produces variable clinical effects characteristic of that particular receptor (Table 7). Opioids possess specific characteristics that dictate their activity at a given receptor (Tables 8 and 9). Finally receptor affinity refers to an individual opioid's ability to bind preferentially to a given receptor. The following classes of opioids are listed in decreasing order of receptor affinity: antagonist > partial agonist/mixed agonist; antagonist > agonist. Understanding these relationships can help the practitioner choose the correct combination of agents based upon the species and the degree and duration of the anticipated pain.

Research in the field of pain physiology has changed considerably in recent years. Our understanding of opiod receptor physiology has been dramatically improved with our ability to clone the mu, kappa, and delta opioid receptors. Researchers use this knowledge to produce "knockout" mice that do not possess specific opioid receptor genes. It is widely thought that stimulation of the mu opiod receptor plays the most significant role of all receptors in the generation of analgesia.

Morphine[c] is the prototype in the opiod category and is the drug of choice for severe acute pain in dogs. The literature suggests that cats have classically experienced more of the sigma effects of morphine (Table 7).[13] Recent studies suggest that the dysphoric effects were likely due to excessively high doses and that opioids actually convey euphoric effects in cats when used at

Table 7

Variable clinical effects produced by the stimulation of opiod receptor subtypes.

Opioid Receptor Subtypes

- □ Supraspinal, spinal, and peripheral analgesia; minimal to mild sedation; respiratory depression; bradycardia; ileus; urine retention; temperatore reduction
- κ Supraspinal, spinal (?), and peripheral analgesia; minimal sedation, respiratory depression, and bradycardia
- δ Supraspinal, spinal, and peripheral analgesia; minimal sedation, respiratory depression, and bradycardia; ileus, urine retention; temperature reduction
- σ Excitement-delirium, tachycardia, hypertension

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Table 8

Definitions of opiod receptor activity with examples of common agents in each class.

Pure Agonist = Produces an optimal effect by binding to a given receptor.
Morphine, hydromorphone, fentanyl.

Partial Agonist = Binds to the opiate receptor and produces a less profound effect than a pure agonist.
Buprenorphine, butorphanol.

Antagonist = Causes no effect at the opiate receptor
Naloxone, naltrexone.

Agonist/Antagonist = Binds to more than one receptor and produces an effect on one and no effect on another.
Nalbuphine, nalorphine.

Table 9

Receptor activity of common opiods.

	Selectivity for Opioid Receptor Subtypes			
Drug	□	κ	δ	σ
Agonists				
Morphine	+++	++	++	–
Meperidine	++	+	++	–
Methadone	+++	+	++	–
Codeine	+	+	+	–
Oxymorphone	+++	+	+	–
Fentanyl	++++	–	+	–
Partial/Mixed Agonists				
Butorpanol	++	(++)	–	++
Pentazocine	+	(++)	+	++
Nalbuphine	+	(++)	(++)	+
Buprenorphine	(+++)	–	–	–
Antagonists				
Naloxone	+++	++	++	–
Naltrexone	+++	++	++	–
Atypical Opioid				
Tramadol	+	?	?	–

+, Mild effect; ++, moderate effect; +++ pronounced effect; ++++, very pronounced effect; ( ), partial agonist effects; ?, unknown; –, little or no effect

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lower doses.[14,15] In the author's experience, dysphoria and excitation tend to occur in the postoperative period after preoperative administration of morphine in cats. Therefore, consideration must be given to the combination of agents administered in the preoperative, induction, and intraoperative periods to avoid exacerbation of dysphoria and excitation in the postoperative period.

Opioids may cause hyperthermia in cats, necessitating careful core temperature monitoring.[16] Significant hyperthermia may be treated with reversal of the opioid. Butorphanol[e] and nalbuphine[f] are agonists at the kappa receptor. When used as mu antagonists to reverse morphine, they provide some analgesia compared to naloxone[g], an antagonist at the mu, kappa, and gamma receptors.

Opioids, in particular morphine[c], cause vomiting in a significant number of patients. Intravenous administration appears to decrease the incidence of vomiting, however morphine must be given slowly IV to minimize histamine release. Hydromorphone[h] is an excellent analgesic and can be used as an alternative to morphine[c] in cats. Intravenous administration of hydromorphone in cats provides quicker onset, increased intensity, and longer duration with a decreased incidence of

vomiting than IM or SQ administration.[17]

Patients that have received oral surgery may be difficult to medicate due to discomfort upon manipulation of the head and oral cavity. Fentanyl[i] is available in transdermal patches and is a viable addition to the options for postoperative pain management for oral surgery cases. The onset of effect in dogs and cats is 18 to 24-hours and 6 to 12-hours, respectively.[18] If the patch can not be placed in a time period to achieve adequate immediate postoperative blood levels, the analgesic protocol must include agents to adequately fill that void before onset of effect.

Butorphanol is a mu antagonist possessing minimal effect for control of somatic pain. It is relatively expensive and has a short half-life requiring frequent dosing. These limitations make it a poor choice for management of oral pain.

Buprenorphine is a partial agonist at the mu receptor and therefore has less profound analgesic properties compared with pure agonists. It is a safe and effective analgesic and has proven especially convenient for use in cats sublingually and transdermally for mild to moderate pain.

Cox-2 Selective NSAIDs

Prostaglandins are produced by the breakdown of arachidonic acid by cyclooxygenase (Cox) enzymes that are released from various cell types at the site of tissue injury. Cytokines and growth factors that develop at the site contribute to induction of further prostaglandin production. Prostaglandins are considered a major component of the inflammatory cascade and contribute significantly to sensitize afferent neurons to noxious chemical, thermal, and mechanical stimuli.[19,20] Research suggests that prostaglandins not only play a role at the site of inflammation and in the spinal cord.[21] Peripheral inflammation and nerve injury results in upregulation of cyclooxygenase enzyme expression in the spinal cord.[22] Therefore, agents that prevent the production of prostaglandins may be used to decrease this phenomenon especially when given preoperatively prior to the mechanical induction of inflammation.

The non-steroidal anti-inflammatory drugs (NSAIDs), which inhibit Cox enzymes, are the most widely used and effective drugs for the treatment of pain and hyperalgesia associated with inflammation.[23] With the recent development of cyclooxygenase-2 (Cox-2) selective NSAIDs, side effects previously common with earlier NSAID's have decreased significantly. Although NSAIDs alone can be effective in some cases to control postoperative pain the multimodal approach may offer additional safety and efficacy.[24] Combining an NSAID with an opioid has been shown in humans to have an opiod sparing effect in the range of 20-30 %.[25] To the author's knowledge, no Cox-2 selective NSAID approved for use in veterinary medicine has been shown to demonstrate significant advantages over another.

5-Lox Selective NSAIDs

Leucotrienes are produced by the breakdown of arachidonic acid by 5-lipoxygenase (5-Lox) and have a major role in the inflammatory process. Leucotrienes and prostaglandins work synergistically to potentiate the inflammatory cascade. Inhibition of the Cox-2 and 5-Lox pathways could theoretically enhance the anti-inflammatory effects of NSAIDs.[26] An NSAID approved for use in veterinary medicine that demonstrates both Cox-2 and 5-Lox inhibition has not been shown to demonstrate significant advantages over Cox-2 inhibition alone.[?R]

Alpha^2 Agonists

Mechanisms associated with the action of Alpha^2 agonists involve guanine nucleotide binding proteins (G proteins) acting as modulators of intracellular second messenger systems to produce a complex cascade of events that result in a barrage of both beneficial and detrimental physiologic effects. Among these are sedation, analgesia, increased systemic vascular resistance, bradycardia, respiratory depression, and vomition.[27] Many of the negative effects of zylazine[j], the prototypical drug in this class, have been minimized with the introduction of the alpha-2 agonist medetomidine[k]. Combined with opioids, this agent in doses of 5 to 20 μ/kg provides effective sedation and analgesia. However, due to the physiologic effects of this agent, it should not be used without blood pressure, end tidal CO_2, SPO2, and EKG monitoring. Doses above this value contribute considerably to the adverse side effects associated with this agent. The alpha-2 agonist reversal agent atipamezole[l] should be a part of the drug inventory to administer in the face of patient compromise.

The administration of anticholinergics in the preoperative period with medetomidine to offset bradycardia is controversial. Some believe that the initial reflex tachycardia associated with atropine[m] combined with the increased cardiac afterload associated with increased systemic vascular resistance may result in cardiac compromise. A full review of medetomidine is beyond the purpose of this manuscript and references should be consulted prior to its use.

N-methly-D-aspartate (NMDA) Receptor Antagoinsts

NMDA receptor antagonists can be used to inhibit or attenuate central sensitization.[28] Agents in this class act by competitively binding to the NMDA receptor and preventing glutamate and aspartate receptor activation and subsequent pain transmission. Ketamine[m] is a drug that produces antagonism at the NMDA receptor in microdoses in conjunction with a constant rate infusion.

The antitussive dextromethorphan[o] and the antiviral agent amantidine[p] are two orally administered NMDA receptor antagonists that are currently used in veterinary medicine for the treatment of chronic pain and to minimize central sensitization.[29] Neither drug is a particularly good analgesic when administered alone, yet they appear to help alleviate chronic pain states in combination with opioids and NSAIDs. Available in 100 mg capsules and a 10 mg/ml liquid, amantidine is administered once daily at a dose of 3 to 5 mg/kg for dogs and cats.[29] Dextromethorphan[o] is found in Vick's Forumla 44 cough syrup and Robitussin DM capsules. A dose of 2.0 mg/kg has been determined safe for treatment of dogs with allergic dermatitis.[30] It has been used in cats at lower doses however it is not palatable to cats and therefore not well tolerated in this species.

Table 10

Sample CRI protocol and nerve block calculations for a feline patient undergoing four quadrant extractions. Lidocaine can safely be added to the CRI at recommended doses in canine patients.

CRI

Loading Dose for morphine = 0.50 mg/kg IM

Loading dose for ketamine = 0.25 mg/kg IV

CRI formulation = 500 ml LRS + 30 mg ketamine + 30 mg morphine (Morphine will lose potency if exposed to light, therefore cover the fluid bag to protect it).

Run at 2 ml/kg/hour = 0.12 mg/kg/hour of each drug.

Intraoperative fluid rates of 10 ml/kg/hour are obtained by adding a second line of LRS at 8 ml/kg/hour.

Regional Nerve Block

Lidocaine + bupivacaine (refer to Tables 2-6) + morphine at 0.5 mg/kg or a volume equal to the regional mixture whichever is less.

Example for a feline patient that weighs 4 kg: Using Table 6 for four anticipated sites = lidocaine 2% = 0.2 ml + bupivacaine 0.5%

Serotonin/Norepinephrine Reuptake Inhibitors

Tramadol[q] acts centrally to alleviate pain by its action on reuptake inhibition of two inhibitory neurotransmitters; serotonin and norepinephrine. Although not an opiod, it is thought to possess weak mu agonist characteristics. It is available in 50 mg tablets and dosed at 2.5 to 10 mg/kg SID-TID in dogs and cats.[29] Tramadol has been evaluated in the canine as a preemptive agent with morphine and has proven safe at a dose of 2.0 mg/kg.[31] It is currently used for chronic and postoperative pain management in a multimodal approach with opiods and NSAIDs. Tramadol should not be used concurrently with tricyclic antidepressants, selective serotonin reuptake inhibitors, or monoamine oxidase inihibitors due to the risk of serotonin syndrome.

Constant Rate Infusions (CRI)

Oral surgery in canine and feline patients often requires extended periods of anesthesia necessitating optimal anesthetic management. A safe and effective mode of pain management for the oral surgery patient is intravenous constant rate infusion utilizing a multimodal approach to affect various levels of the nociceptive pathway.

The administration of opioids in various veterinary species has been studied and has been shown to be both safe and effective in decreasing MAC.[32-34] Lidocaine acts to decrease central hypersensitivity in significant pain states, and when given with opiods has a sparing effect on those agents.[35] In a recent study, dogs undergoing limb amputation that received ketamine[n] infusions had significantly lower pain scores 12 and 18-hours after surgery and were significantly more active on postoperative day 3 than dogs that did not receive ketamine.[36] Furthermore, the combination of morphine, lidocaine, and ketamine delivered as a low dose CRI provides significant decreases in required isoflurane MAC in dogs.[37] No adverse hemodynamic effects were experienced. Medetomidine has been used as a CRI in veterinary patients however a recent study warned of adverse hemodynamic effects of this drug when used in this manner noting that further investigation needs to be done before its use can be advocated.[38]

Detailed spreadsheets[l] may be used for calculation of rates, volumes and loading doses for CRI in dogs and cats utilizing morphine, lidocaine, and ketamine (Fig. 5 and Table 10).

Chronic Pain

The pathophysiology of chronic pain involves the complex mechanisms of peripheral and central sensitization. Significant pain states arise frequently in oral disease since the pathology is often hidden from casual owner observation and many patients that suffer from chronic pain do not become anorectic. Feline LPGS, canine stomatitis, chronic ulcerative paradental stomatitis (CUPS), untreated oral trauma, and some types of oral cancer are common examples of chronic oral pain states.

In the presence of persistent central and peripheral sensitization, traditional perioperative and postoperative pain management fall considerably short of their desired effect. In general, more aggressive treatment protocols must be designed in order to effectively manage postoperative pain in chronic conditions. A unique approach to managing chronic pain termed the "analgesic reverse pyramid" protocol shows considerable promise.[2] With this approach, immediate intense multimodal analgesic management is employed utilizing agents targeted to different portions of the nociceptive pathway. The chronic pain is targeted aggressively from the initiation of pain management and then tapered as desired based upon patient observation contrasted to the traditional approach of adding analgesics from different classes if the initial response was less than desired.

Feline patients with LPGS are particularly painful. Utilizing multimodal, preemptive, and analgesic reverse pyramid concepts, the author initiates pain management for these patients 24-hours prior to initiation of the surgical stimulus for caudal mouth extractions. Meloxicam[r] is instituted to minimize the inflammatory peripheral sensitization experienced in these patients.

Figure 5

Spreadsheet showing calculation of rates, volumes, and loading doses for CRIs in dogs and cats utilizing morphine, lidocaine, and ketamine.

IV FLUID BAG BASED CRI INFUSIONS

Kilogram based calculations

Patient Wt.	5	kgs
IV Bag Size	125	ml
Fluid Rate	2	ml/kg/hr

	Drug dose rate		Total drug		Drug Volume		Drug/ml fluids	
Morphine	0.12	mg/kg/hr	7.50	mg	0.50	ml	0.060	mg/ml
Lidocaine	1.50	mg/kg/hr	93.75	mg	4.69	ml	0.750	mg/ml
Ketamine	0.60	mg/kg/hr	37.50	mg	0.38	ml	0.300	mg/ml

Drug CRI Dose Range

MORPHINE - 0.12 to 0.36 mg/kg/hr (2 to 6 ug/kg/min).

LIDOCAINE - 0.6 to 1.5 mg/kg/hr (10 to 25 ug/kg/minute).

Dogs can be given a max. dose of 3.0 mg/kg/hr (50 ug/kg/min)

Cats should be limited to a max. dose of 1.5 mg/kg/hr (25 ug/kg/min)

KETAMINE - 0.12 to 1.2 mg/kg/hr (2 to 20 ug/kg/minute).

Loading Doses

MORPHINE - 0.5 mg/kg IM (or very slowly IV)

At 0.5 mg/kg this patients needs a loading dose of: 0.17 ml

LIDOCAINE - 0.5 to 1 mg/kg IV

At 0.25 mg/kg this patients needs a loading dose of: 0.06 ml

At 1.0 mg/kg this patients needs a loading dose of: 0.25 ml

CATS - Limit cats to 0.25 mg/kg loading dose

DOGS - 1.0 mg/kg is the normal loading dose

KETAMINE - 0.25 to 0.50 mg/kg IV bolus

At 0.25 mg/kg this patients needs a loading dose of: 0.01 ml

Drug Concentrations

MORPHINE - 15 mg/ml

LIDOCAINE - 20 mg/ml

KETAMINE - 100 mg/ml

Loading doses and a subsequent CRI of ketamine and morphine are commonly administered. Hydromorphone and fentanyl are alternative opiods that are particularly effective as well.

CRI is continued in the intraoperative and postoperative period. Postoperative analgesics consisting of buprenorphine (transmucosal or transdermal) or a fentanyl transdermal patch and meloxicam are continued for up to 4-days. If a fentanyl patch is used, it is placed such that the onset of therapeutic serum levels coincides with the initiation of the surgical procedure. Regional nerve blocks are always performed preoperatively following achievement of a surgical plane of anesthesia (Table 10).

Lidocaine serves as an additional CRI agent in canine patients in the sample protocol (Table 10). A loading dose of 1.0 mg/kg IV is administered followed by 12.5 ml of lidocaine 2 % added to the morphine/ketamine CRI mixture previously described and is administered at the previously recommended rate of 2 ml/kg/hour. Due to the narrow spectrum between therapeutic and toxic doses of lidocaine in feline patients in addition to its routine inclusion in the regional nerve blocks, lidocaine cannot be advocated as a CRI agent for oral surgery in this species.

Chronic pain may not always be eliminated by surgical means. Many cases of oral neoplasia remain undetected until feasible surgical margins for complete resection no longer exist. Management of patients with oral cancer involves a thorough historical and clinical evaluation utilizing knowledge of pain behaviors and incorporation of pain scoring. Excellent descriptions of pain evaluation in companion animals have been published.[39,40]

Oral cancer pain represents a special category of chronic pain that can prove particularly difficult to manage. The elucidation of the pathophysiology of cancer pain is paramount to researchers in the quest for novel therapeutic agents in this field. Clinicians aware of the mechanisms involved can choose agents that stand the best chance at minimizing patient discomfort.

The excitability of nociceptors are altered as a result of the production of compounds produced by tumors and cells involved with tumors including macrophages, neutrophils, and T-lymphocytes.[41] These compounds include prostaglandins, endothelins, interleukins, and tumor necrosis factor alpha (Fig. 6). Drugs used to block the actions of these compounds may play an important role in management of cancer pain.

Certain tumors and macrophages associated with tumors produce prostaglandins and express high levels of Cox-2 enzymes.[42,43] As previously discussed, Cox-2 inhibitors are used to treat pain from inflammation, however there is also evidence that Cox-2 expression plays a role in angiogenesis and cancer growth.[44,45] Certain peptides called endothelins also possess properties that block angiogenesis and tumor proliferation.[46,47] In addition the severity of pain in human patients with prostate cancer and plasma levels of endothelins have been shown to be directly correlated.[48] Drugs that block the production of prostaglandins and endothelins are currently approved in humans for other applications and hold promise for decreasing associated pain and proliferation of certain tumors.[41]

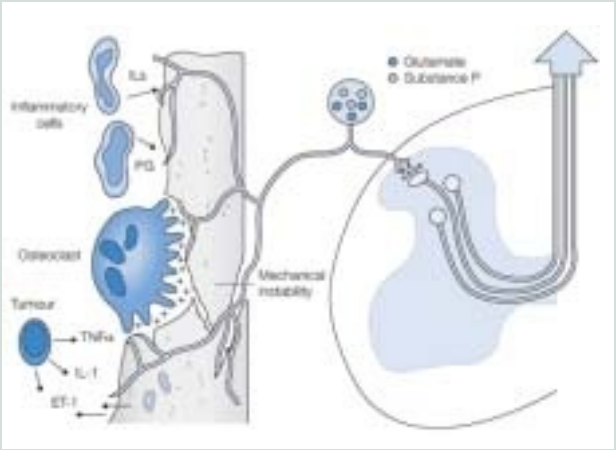
As tumors proliferate, cell turnover and death result in apoptosis and the release of protons which result in an acidic tissue environment.[49] This decline in tissue pH is accentuated by the acidic environment maintained as the mechanism for osteoclast induced bone destruction.[50] This becomes important with the discovery of acid-sensing ion channels (ASIC) expressed by nociceptors that are excited by a decrease in pH which in turn could play a role in the generation of cancer pain. Certain bisphosphonates and osteoprotegerin have been show to decrease osteoclast-induced cancer pain by facilitating apoptosis of osteoclasts.[41] The future development of agents that block the ASIC may prove viable as analgesics in cancer pain.

Tumor derived proteolytic enzymes induce neuropathic pain by their direct effect on sensory and sympathetic nerve fibers.[41] Pain resulting from the direct injury of nerves represents a therapeutic dilemma for clinicians in human medicine. Pain of neuropathic origin is one of the most severe and difficult to treat.

Figure 6

The excitability of nociceptors are altered as a result of the production of compounds produced by tumors and cells involved with tumors including macrophages, neutrophils and T-lymphocytes. These compounds include prostaglandins, endothelins interleukins and tumor necrosis factor alpha. Osteoclasts destroy bone facilitating neuron sensitizing drops in pH. Cells of inflammation are also involved all contributing to central sensitization or "windup."

Elsevier 2006, McMahon and Koltzenburg: Wall and Melzack's *Textbook of Pain*, 5th ed, www.textbookofpain.com



Gabapentin[s] is an anticonvulsant that is used currently to treat neuropathic pain and may also show promise in treating cancer pain.[51]

Studies in cancer pain physiology suggest that central sensitization plays a role in the severity and maintenance of cancer pain.[41] The NMDA receptor antagonist ketamine has been used successfully to treat cancer pain in humans.[52] Studies show that dextromethorphan and amantidine are also successful at treating cancer pain in humans.[53-55]

Knowledge of the pathophysiology of pain, multimodal strategies, preemptive management concepts, and analgesic actions help clinicians choose proper protocols for patients based on species, oral pathology, and individual variability in tolerance. Studies in veterinary species in the field of pain management are lacking. Fortunately organizations like the International Veterinary Academy of Pain Management[3] and the Veterinary Anesthesia Support Group[1] utilize current studies and incorporate clinical experience to publish useful information to help clinicians deliver the most timely techniques and protocols. Research in the dynamic field of pain management holds promise for the development of future agents that specifically antagonize pain receptors, alter ion channels, and block the actions of chemokines and cytokines. As practitioners of veterinary dentistry, we must challenge ourselves to remain current with pain management literature in order to continually provide optimal patient analgesia.

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[a] Lidocaine Hydrochloride 2 %, Phoenix Scientific Corp, St Joseph, MP

[b] Bupivacaine 0.5 %, Abbott Laboratories, N Chicago, IL

[c] Morphine sulfate 15mg/ml, Baxter Animal Health Care Corp, Deerfield, IL

[d] Buprenex, Reckitt & Colman, Wayne, NJ

[e] Torbugesic, Fort Dodge Animal Health, Fort Dodge, IA

[f] Nalbuphine, Hospira, Lake Forest, IL

[g] Naloxone, Abbott Laboratories, Abbott Park, IL

[h] Hydromorphone, Baxter, Deerfield, IL

[i] Duragesic, ALZA Corp, Mountain View, CA

[j] Xylazine HCI injection, Fermenta Animal Health Co., Kansas City, MO

[k] Domitor, Orion Corp, Espoo, Finland

[l] Anteseden Orion Corp, Espoo, Finland

[m] Atropine sulfate, Phoenix Parmaceuticals, Inc., Belmont, CA

[n] Ketaset, Fort Dodge Animal Health, Fort Dodge, IA

[o] Vick's Forumula 44D Hygiene and Helathcare Limited , Maharashta, India

[p] Amantidine, Alliance Pharmaceuticals, Wilshire, UK

[q] Tramadol hydrochloride, Caraco Pharmaceutical, Detroit MI

[r] Metacam, Boehringer Ingelheim Vetmedica Inc, St. Joseph, MO

[s] Gabapentin, Pfizer Inc., New York, NY

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