Pain Medications and How They Work

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Briefly, pain is a subjective experience with two complementary, but unpleasant aspects: one is a localized sensation in a particular body part; the other is a mechanical quality of varying severity commonly associated with behaviors directed at relieving or terminating the experience. Pain begins with specific receptors. Differing species will have varying numbers of receptors based on their evolutionary development and CNS physiology. Receptors are nerve endings, present in most body tissues, that respond in relation to pain by damaging or potentially damaging stimuli. Second, the messages initiated by these noxious stimuli are transmitted by specific, identified nerves to the spinal cord at the dorsal horn. The sensitive nerve ending in the tissue and the nerve attached to it together form a unit called the primary afferent nociceptor. The primary afferent nociceptor contacts second-order pain-transmission neurons in the spinal cord. The second-order cells relay the message through well-defined pathways to higher centers, including the brain stem reticular formation, thalamus, somatosensory cortex, and limbic system. It is thought that the processes underlying pain perception involve primarily the thalamus and cortex.

Opioids

Opioid drugs work by binding to varying opioid receptors in the brain, spinal cord, and more newly discovered peripheral areas of the body. They reduce the sending of pain messages to the brain and reduce (not eliminate) feelings of pain. Chronic use can lead to tolerance and even dependence like other addictive medications. New evidence in human and animals models is showing systemic inflammatory processes, making us have to re-evaluate the dose regiments to our patients of this still gold standard acute pain management drug classification. Opioids will have varying effects and potency on differing species and patient to patient. Opioids are generally safe for even the most critical patients at appropriate dosing.

Non-steroidal anti-inflammatories (NSAIDS)

This is a critical drug class that groups together medications that provide analgesia by processes of anti-inflammatory effects and antipyretic effects. This drug class is an ever evolving group with medications that have varying effects acting through inhibition of prostaglandin synthesis secondary to their inhibition of the enzyme cyclooxygenase (COX). This results in suppression of inflammation, and thus analgesia. Most NSAIDs not only inhibit prostaglandins at sites of inflammation, but systemically. Prostaglandins serve important functions in other parts of the body (kidneys and GI), a factor that accounts for some of the toxicity of these agents. The most frequent complications associated with NSAID usage are those involving the gastrointestinal tract and the creation of ulcers after administration. Studies on NSAIDS use the negative side effects on the gastrointestinal track as standard in safety testing. The evolution of NSAIDS has developed more specific (COX1, COX2) acting medications with improved safety and anti-inflammatory effects. NSAIDs that inhibit COX1, with increases up to 3 times with tissue injury were the first generation with more detrimental side effects on GI tissue. COX2 NSAIDS are more pain relieving by way of inhibiting the isoform synthesized by macrophages and inflammatory cells with tissue injury, which is the more pain stimulating concern able to produce severe inflammation and hyperalgesia.

NSAIDS do have positive synergy with other analgesics, such as opioids, and can actually help reduce the dose of opioids to achieve the same level of pain without the NSAID synergistic effect.

More and more evidence is supporting the use of certain NSAIDS pre-operatively, affectively alleviating the inflammation process BEFORE it starts for hydrated, elective and healthy patients over 6 weeks of age. It is critical renal infarct is avoided to reduce potential negative side effects.

Grapiprant is a member of a new piprant chemical class being developed by Arantana that works through a

specific targeted mechanism. Specificity at the EP4 prostaglandin receptor. Instead of inhibiting the cyclooxygenase enzymes, grapiprant has a specific target, at the EP4 prostaglandin receptor. What is particularly unique about this mechanism is grapiprant does not affect the function of the other prostaglandin pathways that are necessary to support normal kidney function, platelet function and other important physiological processes.

N-methyl-D-aspartate receptor (NMDA)
NMDA is a receptor for the excitatory neurotransmitter glutamate, which is released with noxious peripheral stimuli. The activation of these receptors is associated with hyperalgesia, neuropathic pain, and reduced functionality of opioid receptors. Increased spinal neuron sensitization, leading to hyperalgesia and neuropathic pain are a result of a heightened level of pain and can develop very quickly. When this occurs opioid receptors can become less sensitive leaving opioids less or totally ineffective and can lead to prolonged tolerance. Common NMDA medications include Amantidine, Methadone and Ketamine. All work to antagonize, or inhibit the action of the NMDA receptor.

Alpha-2 agonists
Dexmedetomidine (DxMd) is probably the most widely used alpha-2 in small animal practice today. Binding to alpha-2 adrenaline receptors in the central nervous system and the peripheral nervous system inhibits the release of norepinephrine and impedes transmission of further nerve impulses, which provides the dual effect of sedation and analgesia. Alpha- 2 agonists cause vasoconstriction by directly inhibiting K(ATP) channels. Constriction of these vessels increases the pressure, which in turn the heart senses and will decrease to the point of what might be considered severe bradycardia.

Dexdomitor is a purified derivative of the old formulation known at Domitor. Domitor contained the active molecule, medetomidine and the inactive levomedetomidine, which only added to the negative effects associated with Domitor, such as stress on the liver for clearance. DxMd is a highly selective alpha$_2$ agonist, ~1000 times more selective than Xylazine, which was formerly a common small animal sedative, used mostly for large animals and inducing feline emesis. The value of this medication is invaluable in many different ways other than sedation. Dexmedetomidine also has moderate analgesic properties, comparable to the analgesic effects of buprenorphine. It is important to note that while an animal is sedate and the analgesic properties are in effect, the analgesic effects will diminish before the sedation. Therefore it is recommended give pain medication well before the sedation wears off. The medication also has the added benefit of opioid potentiation, thereby reducing the total amount of opioids one will need. DxMd has a ceiling effect, meaning giving more will not depress the patient further, but only add to the time the patient is sedated. DxMd can be given IM, IV and PO (in cats). Dexmedetomidine can also be given at micro doses as a CRI and added to local anesthetics to prolong their effects.

Local Anesthetics
Many of us are familiar with the common sodium channel blockers lidocaine and bupivacaine, among others. When the fast voltage gated sodium channel is blocked by this drug group the membrane of the postsynaptic neuron will not depolarize and so fail to transmit an action potential leading to its anesthetic effect. Sodium channel blockers are the only pain medication that offer complete pain relief and are now recommended to be given for any elective tissue trauma, such as surgery. Adding adjuncts such as steroids, DxMd and opioids have all shown to extend the efficacy of local blocks to vary degrees and are being more and more encouraged.

Neurotoxins
While most people think of neurotoxins as a bad thing the saying “everything in moderation” comes to mind. Practitioners and researchers in the human world have been using various types of neurotoxins derived from shellfish, snakes, fish and bacteria in various forms of pain relief systemically and locally. Saxitoxin, a shellfish derivative had success in multiple human studies for significantly increasing local anesthesia (~72hrs). In canine bone cancer studies substance-p saporin was used to target pain-transmitting neurons after injection into the spinal

cord and provided excellent pain relief compared to more traditional methods.

Magnesium

Magnesium (Mg) is a common cation in the body playing a fundamental role in many cellular functions. Mg possesses calcium antagonistic properties and is involved in transmembrane ion fluxes and regulates neuronal activity. Mg is also an antagonist of the NMDA receptors as the magnesium ion blocks the central canal of the ionic receptor inhibiting calcium influx and preventing neuronal depolarization. With these physiological principles Mg has gained interest again as a non-narcotic analgesic systemically and epidurally. Human studies have reported conflicting reports of analgesic effects of systemic administration intraoperatively. Multiple studies including veterinary studies do show reduction of intra- and post- operative opioid requirements during soft tissue surgery, orthopedic surgery and thoracotomy. Additionally a study in dogs showed analgesia after an epidural of Mg with no motor deficits, but no potentiation of morphine antinociception like seen in systemic combination. Further studies are needed to determine onset and half-life of the technique.

References available upon request.