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OPIOIDS: MYTHS, MAGIC & MISCONCEPTION
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The opioid class of drugs includes some of the most potent analgesic drugs available in medicine but this drug class has been underutilized in veterinary patients, mostly because of fear of adverse effects. However, the actual incidence of most adverse effects is highly overstated and the benefits of the opioid class should be weighed against the unlikely occurrence of clinically significant adverse effects. Opioids bind to stereospecific presynaptic and postsynaptic opioid receptors, primarily mu and kappa receptors, that are located in the central and peripheral nervous systems. Opioids provide analgesia primarily by decreasing the release of excitatory neurotransmitters presynaptically and inhibition of evoked activity postsynaptically. These effects occur mainly through an increase in potassium conduction (causing hyperpolarization), calcium channel inactivation, or both. Opioids can be used to treat both chronic (**Table 1**) and acute (**Table 2**) pain.

The opioids most commonly used in veterinary medicine fall under the 'full' agonist category (morphine, hydromorphone, fentanyl, oxymorphone, methadone), 'partial' agonist category (buprenorphine) or 'agonist-antagonist' category (butorphanol). Full opioid agonists activate both mu and kappa receptors, thereby providing the most profound analgesia but also the highest likelihood of adverse effects (although it is important to remember here that the adverse effects are not generally clinically significant). In dogs and cats, morphine, hydromorphone, oxymorphone and methadone produce analgesia that begins roughly 1-5 minutes after IV injection or 5-10 minutes after IM injection. The duration of analgesia is approximately 2-4 hours, depending on the dose of the drug and the intensity of the pain. These opioids can be administered by a wide variety of routes. Morphine is the prototypical opioid against which all other opioids are measured. Morphine is a very effective opioid in dogs but less effective in cats as cats don't make one of the intermediate metabolites that is responsible for a portion of the morphine-mediated analgesia. However, it is a myth that morphine is not effective in cats. It is also a myth that morphine cannot be administered IV because it causes histamine release. The drug can indeed cause histamine release if administered rapidly IV, but this is not likely to occur when the drug is administered slowly. Hydromorphone is effective in both dogs and cats. Most opioids (and ketamine) have all been implicated in drug-induced hyperthermia in cats (Posner et al., VAA 2010;37:35-43) but hydromorphone may contribute more than other opioids (Wegner & Robertson, VAA 2007;34(2):132-138). However, it is a misconception that hydromorphone is contraindicated in cats and many cats receive hydromorphone without complications. Oxymorphone is very similar to morphine and hydromorphone but is less popular than the other two opioids because of its higher cost and fluctuating availability. Methadone is the most commonly used full opioid agonist in Europe but is less popular in the US due to its higher cost. Methadone may have some N-methyl-D-aspartate antagonist activity which could lead to anti-hyperalgesic properties. Of the opioids listed here, methadone is the least likely to cause vomiting. Fentanyl is 80x more potent than morphine, is even less likely to cause adverse effects than the opioids just listed, has a short duration of action (20-30 minutes from a single bolus) and is

highly lipid soluble so it is absorbed across the skin. Fentanyl is very effective in both dogs and cats and can be administered as a bolus for a short boost in analgesia or as part of an anesthetic induction protocol, as a constant rate infusion, or as a transdermal patch or transdermal solution. Fentanyl is my favorite opioid in critical patients & cats love fentanyl.

Buprenorphine is a partial agonist at the mu receptors (thus evokes only a 'partial' response) and an antagonist at the kappa receptors, thus the analgesia provided is not as profound as that provided by the full agonist opioids. Buprenorphine has a slow onset of action (10-30 minutes) regardless of the route of administration and a long duration of action (6-8 hours, maybe out to 12 hours if pain is mild). Buprenorphine binds tightly to opioid receptors and is difficult to reverse but, fortunately, reversal is rarely necessary since buprenorphine is the least likely of the listed opioids to cause adverse effects. Buprenorphine is absorbed transmucosally in both dogs and cats but dogs may require a higher dosage than cats. (Abbo et al., Vet Ther.2008;9(2):83-93)

Butorphanol is an agonist at the kappa receptors and an antagonist at the mu receptors. Butorphanol produces moderate sedation and analgesia of about 60 minutes duration in the dog and 90 minutes duration in the cat. This duration is not adequate for most surgical pain.

Tramadol does have some opioid effects and is also a norepinephrine and serotonin reuptake inhibitor. In the dog, the bioavailability of tramadol is highly variable (65+/-38%), little to no intermediate metabolite is produced (the intermediate metabolite is responsible for most of the analgesia provided by tramadol) and the drug is cleared quickly (4x faster than in humans) (KuKanich & Papich, J Vet Pharmacol Ther, 2004;27(4):239-246). Thus, tramadol SHOULD NOT BE USED ALONE for moderate to severe pain in the dog. However, tramadol is very useful as part of a multimodal protocol. Tramadol bioavailability is less variable in the cat but can cause profound dysphoria. The taste of tramadol is extremely bad and the drug has to be well-disguised to get patients to take it.

MAGIC, MYTHS AND MISCONCEPTIONS:
Magic: Most of the opioids are very potent analgesic drugs.
Magic: The opioids can be administered by a wide variety of routes including IV (as boluses or infusions), IM, SQ, PO, transdermally, intra-articularly and perineurally as part of local block.
Myth: The adverse effects of opioids preclude their use in many patients. Not true! The primary adverse effects of the opioids include nausea, vomiting, slowing of GI motility, constipation, dysphoria, pruritis and respiratory depression. The actual incidence of clinically significant adverse effects is highly overstated. Nausea and vomiting are common but short-lived and not likely to occur in painful patients. Thus, patients premedicated with opioids are likely to vomit but patients treated with opioids post-operatively or post-trauma are highly unlikely to vomit. Slowing of gastrointestinal (GI) motility may occur, but slowed motility is not the same as ileus and the occurrence of ileus is rare. Furthermore, moderate to profound pain causes sympathetic overdrive, which can itself cause slowing of GI motility. Constipation may occur with opioids used for chronic pain but unlikely to occur with acute use. If using opioids for chronic pain, increase the fiber in the patient's diet.
Myth: Opioids cause profound respiratory depression. Not true! In animals, the respiratory depression caused by opioids is minimal and is generally related to the degree of sedation and

to the adverse effects of concurrently administered drugs. Thus, respiratory depression may occur in patients under general anesthesia since the inhalants are also respiratory depressants. However, the dose-sparing effects of the opioids will allow a reduction in the dose of isoflurane, which is a more potent respiratory depressant than the opioids. In conscious patients, the respiratory depression is rarely clinically significant.

Misconception: Dysphoria is common in patients receiving opioids. In actuality, dysphoria is generally caused by high dosages of opioids and, because we don't commonly use opioids that aggressively in veterinary medicine, break through pain is more likely than dysphoria to occur in our patients. Dysphoria, if it does occur, is easily controlled with sedatives.

Myth: Opioids cannot be used in horses and cats because they cause profound excitement. Not true! Nonpainful horses and cats can experience excitement but excitement is extremely uncommon in painful patients. Since much of the research was done in nonpainful patients, the literature is replete with frightening reports of cat and horse excitement following opioid administration. In truth, cats and horses respond very well to post-operative or post-trauma opioids. And opioids can be administered with a tranquilizer to alleviate excitement.

Magic: Opioids (especially fentanyl) cause minimal to no cardiovascular effects. They should be used for sedation and analgesia in patients with cardiovascular disease or instability. They also cause a decrease in the dose of inhalants, which decreases the incidence of inhalant-mediated dose-dependent cardiovascular depression.

Magic: The adverse effects of opioids are reversible. If the patient doesn't respond well, administer an opioid antagonist. However, the analgesia will also be reversed so other analgesic drug classes should be used. Also, butorphanol is an agonist-antagonist and can be used to reverse the mu-mediated effects while allowing the kappa-mediated effects to remain. Kappa-receptor mediated analgesia is not as potent as mu-receptor mediated analgesia so, again, analgesia may need to be provided using other drug classes.

Misconception: Tolerance (or 'desensitization of antinociceptive mechanisms') to opioid effects is a common problem. Actually, tolerance can occur but is not likely with the low dosages and infrequent administration of opioids commonly used in veterinary medicine. Tolerance is more likely with long-term opioid use for treatment of chronic pain. The likelihood of tolerance can be decreased if opioids are used at low dosages in a multimodal protocol.

Myth: Opioid-induced hyperalgesia (or 'sensitization of pronociceptive mechanisms') is a common problem. Again, not likely, in fact even less likely than development of tolerance, with the dosages/dosing intervals commonly used in veterinary medicine. Difficult to differentiate from tolerance.

Myth: Naloxone provides analgesia. Potentially a misconception rather than a myth since there is some evidence that naloxone MIGHT play a role in analgesia in some circumstances - but it requires a dose of picog/kg (we use mg/kg) and the right pain syndrome to work. Definitely works as an antagonist so best just to use it for reversal.

TABLE 1 – OPIOIDS USED TO TREAT CHRONIC PAIN

Drug	Dog Dosage	Cat Dosage	Comments
NOTE: Chronic use of opioids may cause constipation.			
Tramadol	2-5 mg/kg PO BID-TID	1-4 mg/kg PO BID-TID?	Tramadol is an 'opioid like' drug that has other mechanisms of action. The pharmacokinetics in the dog are somewhat erratic so the drug is best used as multimodal therapy with NSAIDs or other analgesic drugs.
Oral morphine (10,15,30 mg tablets)	0.5-2 mg/kg PO TID- QID	0.25-0.5 mg/kg PO TID-QID (liquid most commonly used in cats)	Higher doses may induce sedation or dysphoria. Nausea & vomiting may also occur but a tolerance to these effects generally develops within 2 weeks.
Sustained release oral morphine (15, 30, 60, 100, 200mg tablets)	0.5-2 mg/kg PO BID- QID (not really 'sustained release' in dogs)	Difficult to dose due to size of tablets (tablets should not be scored).	Higher doses may induce sedation or dysphoria. Increase the dosing frequency prior to increasing dose if duration is not long enough
Codeine	1-2 mg/kg PO q8-12 hr	Not commonly used	More potent and more consistent than tramadol. Class II opioid
Codeine (30 or 60 mg) plus acetaminophen (300 mg)	1-2mg/kg codeine PO q 8-12 hr with acetaminophen <10 mg/kg/dose	**Acetaminophen TOXIC TO CATS - DO NOT USE**	Multimodal therapy improves analgesia over either drug used alone.
Hydrocodone	0.25mg/kg q4-6hrs	Not used	Efficacy unknown
Transdermal fentanyl patch	3-5 microg/kg/hr on skin	3-5 microg/kg/hr	Available in 25, 50, 75, 100 microg/hr patches. Addition of NSAID may improve consistency of analgesia.
Transdermal fentanyl solution	2.7 mg/kg on skin	Not approved	50 mg/ml solution applied topically; one dose = analgesia for 4 days.
Buprenorphine (0.3 mg/ml injectable)	0.01-0.02 mg/kg SC, IM, IV	0.01-0.02 mg/kg SC, IM, IV or transmucosal	Used primarily for chronic pain in cats, maybe useful for very small dogs. Expensive in larger dogs.

TABLE 2 – OPIOIDS USED TO TREAT ACUTE PAIN

Drug	Dog Dosage	Cat Dosage	Comments
Morphine bolus	0.25-1.0 mg/kg IM, IV, SQ (0.25 for geriatrics, 0.5 soft tissue, 1.0 orthopedics)	0.1-0.25 mg/kg IV or IM	Administer slowly if using IV route. More likely to cause excitement in cats if administered IV.
Morphine infusion	LD 0.5 mg/kg IM (or 0.25 mg/kg SLOWLY IV); CRI 0.12-0.3 mg/kg/hr	LD 0.10 mg/kg IM or SLOWLY IV; CRI 0.03-0.07 mg/kg/hr	May cause excitement in cats and sedation in dogs but not likely at these dosages.
Morphine epidural or intra-articular	0.1 mg/kg	0.1 mg/kg	Dilute to a total volume of 1 ml/4.5 kg body weight with local anesthetic or saline
Hydromorphone bolus	0.1-0.2 mg/kg IM, IV, SQ	0.1 mg/kg IM, IV, SQ	May cause hyperthermia in cats.
Hydromorphone infusion	LD 0.05-0.1 mg/kg IV; CRI 0.01-0.05 mg/kg/hr	LD 0.025 mg/kg IV; CRI 0.01 mg/kg/hr	May cause excitement in cats and sedation in dogs but not likely at these dosages.
Methadone bolus	0.3 -0.5 mg/kg IV, IM, SQ	0.3 -0.5 mg/kg IV, IM, SQ	May have some anti-hyperalgesic effects
Methadone infusion	LD 0.1-0.2 mg/kg IV; CRI 0.12 mg/kg/hr	LD 0.1-0.2 mg/kg IV; CRI 0.12 mg/kg/hr	May cause excitement in cats and sedation in dogs but not likely at these dosages.
Fentanyl bolus	0.001-0.005 mg/kg IV, IM SQ	0.001-0.005 mg/kg IV, IM, SQ	Provides profound analgesia for 20-30 minutes.
Fentanyl infusion	LD 0.001-0.003 mg/kg IM or IV; CRI 2-10 microg/ kg/hr post-op; 5-40 microg /kg/hr intra-op	LD 0.001-0.003 mg/kg IM or IV; CRI 2-5 microg/ kg/hr post-op; 5-20 microg/ kg/hr intra-op	Very potent opioid. Minimal adverse effects.
Transdermal fentanyl patch	3-5 microg/kg/hr on skin	3-5 microg/kg/hr	25, 50, 75, 100 microg/hr patches. Use with NSAIDs to improve analgesic consistency.
Transdermal fentanyl solution	2.6 mg/kg on skin	Not approved	50 mg/ml solution applied topically; one dose=analgesia for 4 days.
Buprenorphine	0.01-0.03 mg/kg IV, IM, SQ	0.01-0.03 mg/kg IV, IM, SQ or transmucosal	Partial agonist so not as potent as full agonists. Long duration of action (6-8 hrs, MAYBE to 12 hrs).
Butorphanol bolus	0.1-0.4 mg/kg IV, IM, SQ	0.1-0.4 mg/kg IV, IM, SQ	Only moderately potent & has ceiling effect - use as part of multimodal protocol.
Butorphanol	LD 0.1 mg/kg IV;	LD 0.1 mg/kg IV;	Only moderately potent & has

infusion	CRI 0.1-0.2 mg/kg/hr	CRI 0.1-0.2 mg/kg/hr	ceiling effect - use as part of multimodal protocol.
Tramadol	2-5 mg/kg PO BID-TID	1-4 mg/kg PO BID-TID? (Unknown)	In dog: Highly variable bioavailability, no intermediate metabolite (which provides most of the analgesia in humans), cleared very quickly – thus, NOT appropriate for moderate to severe pain unless used with other drugs.
Codeine	1-2 mg/kg PO q8-12 hr	Not commonly used	More potent and more consistent than tramadol. Class II opioid
Codeine plus acetaminophen	1-2mg/kg codeine PO q8-12 hr with acetaminophen <10 mg/kg/dose	**Acetaminophen TOXIC TO CATS - DO NOT USE**	Multimodal therapy improves analgesia over either drug used alone. Better than tramadol for moderate to severe pain but not as potent as morphine or fentanyl.