OPIOIDS

Alison Clode, DVM, DACVO
Port City Veterinary Referral Hospital
Portsmouth, NH 03801
New England Equine Medical and Surgical Center
Dover, NH 03820

Opioids (opiates = derived from the opium poppy; opiate-like = synthetic; opiates + opiate-like = opioids) are predominantly used for their beneficial analgesic and sedative effects, however the significant side effects, both peripheral and central, necessitate caution and a thorough understanding of the pharmacology of different opioids to allow safe and effective use in veterinary patients.

Central effects mediated by opioids include analgesia, euphoria, and sedation; decreased respiratory rate and decreased cough reflex; nausea and vomiting; and miosis and truncal rigidity. Peripheral effects include those on the gastrointestinal system (constipation, decreased gastric motility, decreased small intestinal digestion, decreased colonic peristalsis, increased biliary smooth muscle constriction, and increased esophageal reflux), skin (increased itching and sweating, increased flush of face, neck, and thorax), cardiovascular system (decreased blood pressure and heart rate in the face of cardiovascular stress), immune system (decreased activity of natural killer cells), urogenital system (depressed renal function, increased urinary retention, decreased uterine tone), and behavioral restlessness.

Receptor pharmacology

Four general classes of opioid receptors have been identified: mu (μ), delta (δ), kappa (κ), and opioid receptor-like 1 (ORL-1), localized in many tissues within the central nervous system. All are G-protein-linked (7 transmembrane-spanning domains linked to Gα, Gβ, and Gγ subunits), with the response to a particular opioid dependent upon its receptor specificity, affinity for that receptor, and whether it has inherent agonist or antagonist activity.

Following binding of an opioid to an opioid receptor, the Gα subunit dissociated from the Gβγ subunits and exerts effects that ultimately inhibit activity of adenylyl cyclase and decrease cAMP formation. Additionally, increased neuronal K⁺ efflux stimulated by the Gα subunit (leading to hyperpolarization) and decreased Ca²⁺ influx mediated by the Gβγ subunits inhibits tonic neural activity and associated pain transmission. Multiple other intracellular pathways are involved, including utilization of arrestin and activation of MAPK pathway.

Receptor terminology

1. Agonist = bind receptors and activate the receptor; capable of producing maximal effect in dose-dependent manner
2. Antagonist = bind receptors and do not activate the receptor, however block binding of an agonist
3. Partial agonist = bind receptors and exert partial/limited activity; incapable of producing maximal effect, no matter the dose administered
4. Agonist/antagonist = mu antagonist and kappa agonist
5. Endogenous agonists = enkephalins, endorphins, and dynorphins.

- Mu agonism → analgesia, euphoria, bradycardia, hypothermia, urinary retention, emesis, hypoventilation, constipation
- Kappa agonism → minor analgesia, dysphoria, sedation, diuresis
- Delta agonism → hypoventilation, constipation, urinary retention

Efficacy

The effect of opioids is dose-dependent, with increasing doses of pure agonists producing greater effects (both beneficial and adverse), without reaching a ceiling effect. Tolerance can develop by multiple mechanisms.
Opioids in Veterinary Ophthalmology

Morphine
Morphine is a short-acting (initial effect 5-15 min; max effect 30-45 min; half-life 1h) full μ-receptor agonist with κ-agonist activity at high doses. Receptor localization within the canine cornea has identified delta receptors in greater proportion than mu-receptors. Topical morphine (1%) has been evaluated in dogs for analgesic efficacy as well as impact on wound healing, with three times daily administration decreasing blepharospasm and not adversely impacting wound healing in dogs with experimentally-induced corneal ulcers (Stiles, 2003). In dogs and cats with naturally occurring corneal ulcers that received one drop of 1% morphine, no analgesic effect was noted (Thomson, 2013).

Nalbuphine
As a kappa-receptor agonist, nalbuphine produces mild to moderate analgesia; while as a mu-receptor antagonist, it avoids the euphoria and coinciding risk of dependency that occurs with mu-agonists. Evaluation of 1% topical nalbuphine versus oral tramadol and saline control in dogs with experimentally-induced corneal ulcers demonstrated no beneficial analgesic effect of three-times daily nalbuphine (nor of tramadol), however no adverse effect on wound healing was present (Clark, 2011). Evaluation of three-times daily 0.8% topical nalbuphine in dogs following phacoemulsification demonstrated no difference in overall pain score between treated and untreated dogs, however markers interpreted to be more specific to corneal pain were decreased in treated dogs (Lee, 2013). In normal horses without corneal wounds, a single administration of nalbuphine 1% did not decrease corneal sensitivity (Wotman, 2010).

Tramadol
The analgesic effects of tramadol are mediated by mu-, kappa-, and delta-receptors, with additional effects mediated by inhibition of norepinephrine and serotonin reuptake and enhanced serotonin release. Evaluation in dogs with experimentally-induced corneal ulcers demonstrated no beneficial effect of tramadol at a dosage of 4 mg/kg every 8 hours (Clark, 2011). Evaluation in dogs following enucleation, with dogs receiving either carprofen and tramadol 2 hours pre-operatively and again 12 hours later found a significantly greater proportion of tramadol-treated dogs required rescue analgesia than did those receiving carprofen (6/21 versus 1/22, respectively (Delgado, 2014).

Naltrexone
Opioid growth factor (OGF), an endogenous opioid with its corresponding receptor (OGFr), are present in the canine cornea, and activation of the receptor leads to inhibition of cell growth, which may have significant implications in wound healing. Thus, use of naltrexone topically has been evaluated as an OGFr antagonist, with the goal being to improve corneal sensation and other protective ocular effects in dogs experiencing adverse effects of decreased corneal sensation (such as brachycephalic breeds or diabetic dogs). Treatment with 0.3% naltrexone in normal dogs once daily for 7 days produced no change in STT1, STT2, corneal sensitivity, IOP, or TFBUT, nor did it produce any signs of ocular irritation (Arnold 2014).

Opioids in Veterinary Medicine

Fentanyl
Fentanyl is a short-acting full μ-receptor agonist (30 min – 2 hour duration), with greater potency than morphine. It is poorly bioavailable following oral administration, and SQ and IM administration require large volumes, thus its use is predominantly via IV or transdermal (patch or solution) routes. Transdermal patches utilized for humans can be applied to dogs, requiring 24 hours to reach therapeutic effects, with duration of action around 48 hours. A transdermal solution is available that is indicated for application 4 hours prior to surgery, with duration of effect of 4 days. The absorption is variable, thus post-application monitoring is indicated. Thorough training in appropriate use of the product is indicated.

Sufentanil, alfentanil, remifentanil
All three are fentanyl derivatives in IV preparations with short duration of action.
Methadone
Methadone is a μ-receptor agonist with potency comparable to morphine, and also has NMDA-antagonist effects. Oral administration is limited in animals due to poor bioavailability. Synergism with other μ-receptor agonists may occur.

Meperidine
Meperidine is a μ-receptor agonist with serotonergic effects, as well as negative inotropic and anti-muscarinic effects. As with most other opioids, oral bioavailability is poor. Duration of action is less than 2 hours in dogs, and administration may lead to histamine release in dogs.

Hydrocodone
Hydrocodone is a μ-receptor agonist that is metabolized to a variable degree to hydromorphone following oral administration. Predominantly used as an antitussive in dogs, analgesic effects are poorly characterized in veterinary species.

Codeine
Codeine is a μ-receptor agonist with limited oral bioavailability in dogs.

Buprenorphine
Buprenorphine is a μ-receptor partial agonist with 25x greater potency than morphine. While potency is greater, efficacy in acute pain is lesser than that in morphine, however potency in chronic pain may be greater. Buprenorphine has much greater affinity at μ-receptors, therefore may act as an antagonist of morphine and other full μ-receptor agonists, depending upon relative doses, timing of doses, species being treated, and nature of pain condition. While IV, IM, and SC routes are available, oral transmucosal is an additional option in cats.

Butorphanol
Butorphanol is a μ-receptor antagonist to partial μ-receptor agonist, and a κ-receptor agonist. Oral bioavailability is low, thus analgesia is minimal with oral administration (however antitussive and sedative effects may occur).

Nalbuphine
Nalbuphine is a μ-receptor antagonist and κ-receptor agonist with lesser analgesic effects than other opioids.

Tramadol
Mechanisms of action of tramadol, which is metabolized to a μ-receptor agonist, include inhibition of serotonin and norepinephrine reuptake. The majority of the analgesic effect of tramadol depends upon its metabolism to O-desmethyltramadol (M1), which occurs minimally in animals (relative to humans). Due to is serotonin reuptake inhibition, combination with meperidine, tricyclic antidepressants, and selective serotonin reuptake inhibitors is contraindicated due to the risk of development of serotonin syndrome.

Naloxone
Naloxone is an opioid antagonist, with greater efficacy as a μ-receptor antagonist than as a δ- or κ-receptor antagonist. Dosing by titration to effect is appropriate due to potential reversal of analgesic effects of opioid if high doses are administered initially.

Naltrexone
Naltrexone is a μ-, κ-, and δ-receptor antagonist that is most frequently employed in reversal of opioids in wildlife.
Side effects

Respiratory depression
- Dose-dependent
- Unlikely to be clinically significant in conscious animal
- Mediated by supra-spinal $\mu$-receptors

Antitussive
- Mediated by $\mu$- and $\kappa$-receptors in medulla oblongata
- Not associated with respiratory depression

Cardiovascular
- Bradycardia
- Centrally-mediated increased PS activity
- Histamine release from mast cells mediated by high dose bolus morphine in dogs may lead to hypotension, tachycardia, bronchospasm (1 mg/kg IV or higher)

Nausea/emetic/anti-emetic
- Dependent upon opioid, dose, and route
- Activation of dopamine receptors in chemoreceptor trigger zone $\rightarrow$ emesis
- $\delta$-receptors involved in emetic effects
- $\mu$- and $\kappa$-receptors involved in anti-emetic effects
- SQ or IM more likely to lead to emesis than IV injection

Pupil diameter changes
- Miosis: dogs, rabbits, rats
- Increased PS outflow from Edinger-Westphal nucleus $\rightarrow$ miosis
- Mydriasis: cats, horses, ruminants
- Peripheral sympathetic stimulation $\rightarrow$ mydriasis
- Possible central stimulation of Edinger-Westphal nucleus $\rightarrow$ mydriasis

GI motility
- Inhibition of NT that impact motility: acetylcholine, serotonin, vasoactive intestinal peptide, nitric oxide
- Peripheral ($\delta$-receptors) and central ($\mu$- and $\kappa$-receptors) mechanisms
- Decrease propulsive contractions, increased non-propulsive contractions, decreased GI fluid secretions

Urinary tract effects
- Epidural or intrathecal $\rightarrow$ urine retention due to decreased contraction of detrusor muscles, increased tone of urinary sphincter
- May decrease urine production

Thermoregulation
- Alteration of thermoregulatory set point in hypothalamus
- Hypothermia (dogs, rabbits, birds)
- Hyperthermia (cats, horses, swine, goats, cattle)

Immune system effects
- Immunostimulatory and immunosuppressive effects
- Drug, dose, duration dependent
Minimum alveolar concentration-reducing effects

- Species, dose, and opioid receptor dependent
- Full \( \mu \)-receptor agonists produce greatest effects
- Most significant in dogs, versus horses or cats

References


