**HOW OPIOIDS WORK**

Activation of mu-opioid receptors inhibits presynaptic release and postsynaptic response to excitatory neurotransmitters, closing calcium channels and opening potassium channels. The result is greatly impeded pain transmission.

We've recently discovered that glial cells, once thought to play only a minor supporting role in the spinal cord, are actually highly active in the pain process—enlarging, migrating, and wrapping themselves around nociceptor synapses in the face of peripheral injury.2 They possess many types of receptors including opioid receptors. Therefore, they have the potential to both create and sustain a pain state and can result in a seemingly paradoxical hyperalgesia in some patients treated with opioids.3

**OPIOID OPTIONS**

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Practitioners have three general categories to choose from—pure mu agonists; partial mu agonists and agonist-antagonists; and mu antagonists. Below is an overview of the indications for each.

**Pure mu agonists: "Strong" opioids**

**Morphine.** Federally regulated since World War I, morphine has lost none of its potency or utility in the intervening near 100 years. It has no ceiling effect on analgesia, histamine release, or respiratory depression, meaning that higher dosing can increase the analgesic effect as well as respiratory depression. It consistently results in transient nausea and vomiting (especially at low doses given subcutaneously or intramuscularly to nonpainful patients, for example, as a premedicant), which for many clinicians is actually a persuasive reason for its use preoperatively. Since cats are unable to produce the primary M6G analgesic metabolite,4 morphine may not be ideal for use in this species; however, many clinicians report satisfactory use of morphine in cats (perhaps there are other mu-agonist metabolites in this species).

**Oxymorphone and hydromorphone.** These two opioids are shorter-acting than morphine, a feature some clinicians think makes them more versatile than morphine. They do not elicit histamine release, making them superior to morphine for trauma patients. Nausea, while still predictable, seems to be somewhat milder than that elicited by morphine. While all opioids can induce a transient hyperthermia in cats, hydromorphone appears to be implicated more often than other pure mu agonists.5

**Methadone.** Easily available and commonly used in Europe, injectable methadone may become an attractive alternative to other pure mu agonists here in the United States. It elicits minimal nausea and no histamine release, has NMDA-R blocking activity,6 and is nicely sedating in addition to its analgesic effects. Its effectiveness has been demonstrated in dogs and cats.7,8

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**Fentanyl.** This short-acting mu agonist is far more potent than morphine. It is most often administered as an intravenous constant-rate infusion in veterinary medicine, and its short action allows for a great deal of flexibility in managing a patient since the rate can be fine-tuned based on patient response and needs. The transdermal patch (Duragesic—Janssen Pharmaceutica) formulation is less popular in veterinary medicine than it once was (it still is commonly prescribed for its labeled indication in humans for breakthrough cancer pain) because of the highly unpredictable dosing and effects that are based on numerous variables such as species, body condition score, and body temperature, as well as where and how (and how well) the patch is placed. Additionally, there are serious public health concerns surrounding accidental contact or ingestion by people, especially infants and children—a number of deaths have been recorded since this product has been on the market.

**Partial mu agonists and agonist-antagonists: "Weak" opioids**

**Buprenorphine.** Although it is a partial mu agonist, buprenorphine has a far greater affinity for mu receptors than morphine does and will, therefore, displace a pure mu agonist if both are present. There is a ceiling effect to this drug, providing a level of safety, but also a bell-shaped response curve (there may be some mu antagonism at higher doses). In addition, onset time and duration appear to be highly variable and may be dose-dependent.9 One of the chief benefits of buprenorphine is that in cats it results in minimal sedation and is nearly completely absorbed transmucosally, making it a convenient option for this species. This method of administration results in similar effects as with either intravenous or intramuscular injection.8,10 About 40% to 50% is transmucosally absorbed in dogs, so higher doses than those used in cats are needed when administering it via this route.11

**Butorphanol.** Butorphanol is a mu antagonist, kappa agonist (the latter promotes the production of inhibitory neurotransmitters such as GABA). It has a short duration in dogs,12 with reported minimal analgesia and no anesthetic-sparing effect in a canine tail-clamp model,13 making it a poor choice for prolonged or pronounced analgesia in this species. However, it has a ceiling effect (thus, is safe) and when given parenterally, it has a synergistic effect with other medications such as alpha2 agonists.

**Mu antagonists: Reversal agents**

**Naloxone.** Naloxone has been used as an opioid reversal agent in cases of overdose or severe adverse effects. However, this reversal may be better accomplished with the use of a partial mu agonist such as buprenorphine or an antagonist-agonist such as butorphanol. This approach allows the adverse effects to diminish while maintaining analgesia. In people, ultra-low doses of naloxone have even been used to increase the analgesia provided by buprenorphine.14

**ADVERSE EFFECTS**

In the acute setting, pure mu agonists can cause respiratory depression; however, the degree of the problem appears to be less than it is in humans and it is usually confined in dogs and cats to high doses and when given intravenously. Any opioid can result in dysphoria, but the behavior (often vocalizing) can be difficult to distinguish from pain. Attempting to console or distract an animal may aid in distinguishing between dysphoria and pain. A rule of thumb is that dysphoric animals are difficult to calm out of their agitated state, and administration of additional opioids does not help this situation, while animals in pain can usually be temporarily distracted or calmed. In humans, pure mu agonists are also known to induce hyperalgesia in some patients, and this counterintuitive phenomenon may also occur occasionally in a dog or cat.

In veterinary medicine, unlike in human medicine, opioids are uncommonly used—and arguably underused—in patients with chronic pain. As opioids gain ground as effective analgesics for chronic pain, adverse effects commonly seen in human patients might also become apparent in dogs and cats. Constipation, abnormal pain sensitivity, and effects on gastrointestinal motility may need to be addressed in veterinary patients. With judicious use of opioids in dogs and cats, veterinarians probably do not have to be concerned about dependence issues in these patients; however, it is a sad fact that clinicians have to be alert to the possibility of drug diversion for human consumption.

Remember, a multimodal approach to pain therapy is the most effective way to avoid adverse events, reduce drug dose requirements, and maximize a patient's quality of life.

**WHAT'S ON THE HORIZON?**

Tapentadol is the first new class of analgesic drug for humans to hit the market in 25 years and has shown some utility in animal models.15 It is a mu agonist and norepinephrine reuptake inhibitor.

A sustained-release injectable buprenorphine is already on the market,16 although it is not an FDA-approved drug. Good evidence supports the use of other sustained-release opioids such as liposome-encapsulated hydromorphone,17,18 but a commercial version is not on the horizon. However, several companies are pursuing long-acting opioid preparations or delivery mechanisms, and it is the expectation that the FDA will approve one or more in the not-too-distant future.

Novel peripherally acting mu-opioid receptor antagonists (PAMORAs) are being developed. When administered with an oral opioid, these drugs will permit central analgesia, while blocking their effect on gastrointestinal motility.19,20

Several current drugs are being evaluated for their antiglial activity and may be available for use with opioids in the near future.21

Perhaps most intriguing is the investigation into genomics—how a specific opioid will act in a specific patient. With that information, medication choices and doses can be better tailored to the patient.22