Buprenorphine

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Buprenorphine hydrochloride is a Schedule III, partial μ-opioid agonist and a synthetic derivative of thebaine. Structurally, it is similar to morphine. Because of its lipophilic nature, buprenorphine binds to the μ-opioid receptor slowly but with a high affinity; therefore, buprenorphine has a slow onset and long duration of action. Despite its high affinity for the μ-receptor, buprenorphine has only partial activity; therefore, it provides moderate analgesia and variable sedation and is associated with few adverse effects.

The most commonly used buprenorphine formulations in veterinary medicine are those with a 6- to 12-hour duration of effect and those with potentially longer durations of action. Of the latter, there are 2 types: 1) sustained-release preparations, in which drug release from the subcutaneous space is gradual because of the addition of a proprietary sustained release compound (eg, DL-lactide-co-caprolactone) and 2) high-concentration preparations.

Pain management protocols involving buprenorphine should tailor dose regimens to patient status and pain level rather than using predetermined dosing intervals.

Indications

In veterinary medicine, buprenorphine is used primarily as an analgesic for relieving mild-to-moderate pain in dogs and cats following surgical procedures such as routine ovariohysterectomy, castration, and simple orthopedic procedures. Buprenorphine has been shown to have analgesic properties similar to morphine after elective arthrotomy in healthy dogs without also causing excessive sedation.[1]

Studies investigating the analgesic effects of buprenorphine have shown that the addition of an NSAID greatly enhances overall pain control[2,3]; hence, the current recommendation is to combine buprenorphine with an NSAID for surgical pain management in healthy patients. Buprenorphine should not be considered the opioid of choice for surgical procedures involving severe pain.

Buprenorphine has also gained popularity for use in combination with dexmedetomidine, ketamine, tiletamine/zolazepam, and other sedative or anesthetic drugs in shelter animal medicine and clinical practice. Examples of injectable anesthetic combinations using buprenorphine postoperatively included dexmedetomidine-ketamine-buprenorphine, midazolam-dexmedetomidine-buprenorphine, dexmedetomidine-tiletamine/zolazepam-butorphanol, and dexmedetomidine-ketamine-butorphanol.[4]

Buprenorphine is considered safe for use in cats with hypertrophic cardiomyopathy, especially as a premedication combined with dexmedetomidine.

Pharmacokinetics & Dosing

Results of pharmacokinetic and pharmacodynamic studies of buprenorphine use in dogs and cats vary with regard to the drug's effective plasma level and half-life; however, dosing tends to follow 2 to 3 times per day compartmental models. In cats, some pharmacokinetic and pharmacodynamic studies of IV and IM buprenorphine have demonstrated a negative hysteresis, indicating that buprenorphine's effective plasma levels are not necessarily associated with the drug's antinociceptive effects.[3] In dogs, buprenorphine is metabolized predominantly in the liver, with the major route of elimination being biliary excretion into the feces.

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Recommended dosing for both species is 0.01 to 0.04 mg/kg (higher doses for sustained-release and high-concentration formulations) q6-12h IV, IM, or SC. However, pain management protocols involving buprenorphine should tailor dose regimens to patient status and pain level rather than using predetermined dosing intervals.

A new subcutaneous, long-acting buprenorphine product, Simbadol (abbottanimalhealth.com), has been approved for use as a once-daily analgesic in cats for up to 3 days. According to the product information insert, the analgesic effects of Simbadol appear about 1 hour after administration and last 24 to 28 hours.[5] Another product, Buprenorphine SR (wildpharm.com), is a sustained-release formulation that provides analgesia for 72 hours.

Oral transmucosal administration of buprenorphine at 0.02 to 0.04 mg/kg is common, especially in cats and dogs. Pharmacokinetic studies of oral transmucosal buprenorphine have shown effective plasma levels and antinociceptive capabilities comparable to those with IV administration.[6] Some evidence demonstrates that preoperative oral transmucosal buprenorphine (0.02 mg/kg) in dogs can be as effective as IV buprenorphine for pain control following elective ovariohysterectomy.[7] Oral buprenorphine (0.02 mg/kg) combined with oral dexmedetomidine (0.04 mg/kg) does not reach plasma levels similar to IM administration; however, levels of sedation and antinociception are similar.[8] IV or IM buprenorphine is recommended over oral buprenorphine for the treatment of acute pain.[3]

Contraindications & Drug Interactions

One of the advantages of using buprenorphine at clinical doses is that there are few adverse effects in dogs and cats. Buprenorphine can cause clinically insignificant cardiovascular changes, such as mild bradycardia and hypotension. Buprenorphine has minimal respiratory depressant effects and is not associated with clinically significant hyperthermia in cats; conversely, larger doses have caused a greater degree of antinociception in cats exposed to thermal stimulation. Larger doses of buprenorphine are not associated with an increased level of sedation or adverse effects.[9]

Advantages & Disadvantages

Buprenorphine has some advantages over full μ-opioid agonists. It provides moderate analgesic effects without excessive sedation and with less potential for adverse responses that are common to μ-opioid agonists (eg, potential bradycardia, mild respiratory depression). Oral buprenorphine is a viable option for long-term pain management in dogs and cats. Combining buprenorphine with an NSAID is a simple way to provide analgesia for routine procedures that involve mild to moderate pain. Buprenorphine has the advantage of providing good analgesia in cats without the necessity of multiple-dose regimens.

Compared with full μ-opioid agonists, buprenorphine has some distinct disadvantages. One major drawback is the drug's high affinity for the μ-opioid receptor, which inhibits the effects of full μ-opioid agonists used concurrently. A 2006 study demonstrated that when buprenorphine was administered with sufentanil to dogs undergoing routine ovariohysterectomy, a significantly greater amount of the pure μ-agonist was required to provide analgesia compared with dogs receiving sufentanil alone.[10] The study authors recommended withholding buprenorphine therapy for at least 6 to 8 hours before administering anesthesia when incorporating a pure μ-receptor agonist.

Another disadvantage of buprenorphine, compared with some full μ-opioids such as hydromorphone and morphine, is cost. Although the prices of many μ-opioid agonists have increased over the past few years, buprenorphine is more expensive than hydromorphone and morphine. Currently, the cost of buprenorphine is comparable to that of methadone.

Conclusion

Buprenorphine has many unique characteristics that distinguish it from other μ-opioid agonists with significant clinical advantages. Although its onset of action is slow, buprenorphine has a long duration of action with good to moderate analgesia and few side effects. Buprenorphine can be administered via multiple routes and is effective in both dogs and cats. Recently introduced buprenorphine products provide uniform pain control with infrequent administration. Buprenorphine has stood the test of time in veterinary medicine and should be considered a major component of clinical pain management protocols. ■ cb

References

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