# Clinical Pharmacology of Methadone in Dogs and Cats

Pharmacology · https://anesthesiabraintrust.org/docs/clinical-pharmacology-of-methadone-in-dogs-and-cats/

## Pharmacokinetics and Mechanism of Action

Methadone is a synthetic opioid that functions as a full μ-opioid receptor agonist. Unlike morphine, methadone also acts as an N-methyl-D-aspartate (NMDA) receptor antagonist and inhibits the reuptake of serotonin and norepinephrine, contributing to its analgesic efficacy. In dogs, methadone has a bioavailability of approximately 75% after intramuscular administration, with peak plasma concentrations occurring within 1-2 hours. The elimination half-life in dogs ranges from 2-4 hours, while in cats it is slightly longer at 3-6 hours. Methadone undergoes hepatic metabolism primarily via N-demethylation and is excreted through both renal and fecal routes. The drug exhibits stereoselective pharmacokinetics, with the R-enantiomer being responsible for most of the opioid effects and having a longer half-life than the S-enantiomer.

Methadone's lipophilic properties allow for good penetration of the blood-brain barrier, resulting in rapid onset of analgesia. The drug exhibits pronounced first-pass metabolism similar to other opioids. Ketoconazole can inhibit metabolism of methadone resulting in less first-pass metabolism contributing to more predictable effects when administered orally, though oral administration is less common in veterinary medicine than human medicine. Protein binding of methadone is high (approximately 85-90%) in both dogs and cats, which affects its distribution and duration of action.

## Clinical Uses in Veterinary Medicine

Methadone serves several functions in small animal practice. As an analgesic, it is primarily used for moderate to severe pain management in both perioperative and chronic pain settings. The recommended dosages range from 0.1-0.3 mg/kg in dogs and 0.1-0.3 mg/kg in cats, administered intravenously, intramuscularly, or subcutaneously every 4-6 hours as needed.

In perioperative pain management, methadone is valuable as both a preemptive analgesic and for postoperative pain control. Studies have shown that preoperative administration reduces the minimum alveolar concentration (MAC) of inhalant anesthetics by 30-45%, allowing for decreased anesthetic requirements. This property makes methadone particularly useful for patients with cardiovascular compromise, where minimizing inhalant effects is beneficial.

For chronic pain conditions, particularly those with a neuropathic component, methadone's dual mechanism as an opioid agonist and NMDA antagonist provides advantages over single-mechanism opioids. This dual action makes it particularly interesting for managing cancer pain and chronic osteoarthritis in geriatric patients.

Methadone is also employed in anesthetic protocols as part of balanced anesthesia, often combined with sedatives like acepromazine or α2-agonists, and benzodiazepines. Additionally, methadone has applications in emergency medicine for trauma patients requiring immediate pain control and sedation.

## Side Effects and Adverse Reactions

Like all opioids, methadone carries potential adverse effects that require monitoring. Respiratory depression is dose-dependent and more pronounced in dogs than cats. This effect is potentiated when combined with other sedatives or anesthetics. At clinical doses, the respiratory effects are typically mild to moderate, though they can be more significant at higher doses or in compromised patients.

Gastrointestinal effects include decreased motility, constipation, and occasionally vomiting, particularly in cats. These effects result from methadone's action on μ-receptors in the gastrointestinal tract and chemoreceptor trigger zone. Methadone may cause bradycardia, though this effect is generally less pronounced than with other μ-agonists like morphine.

Dysphoria and behavioral changes can occur, particularly in cats, manifested as vocalization, restlessness, or agitation. These effects are more common with higher doses and can be managed by reducing the dose or administering a tranquilizer. Hyperthermia has been reported in cats receiving methadone, requiring careful monitoring of body temperature in this species.

Histamine release with methadone administration is minimal compared to morphine, resulting in fewer instances of pruritus or urticaria. This makes methadone a good choice for patients with

previous hypersensitivity reactions to other opioids. Urinary retention can occur but is less common than with other μ-agonists.

Prolonged use may lead to tolerance and physical dependence, though this is rarely a concern in the context of veterinary medicine where treatment courses are typically short. Nonetheless, gradual dose reduction is recommended when discontinuing long-term therapy.

## Comparison with Other Opioids

When compared to other opioids, methadone offers several advantages. Unlike morphine, methadone causes minimal histamine release, making it safer for patients with mast cell tumors or a history of hypersensitivity reactions. Its NMDA antagonist activity may provide some efficacy for neuropathic pain compared to pure μ-agonists like morphine or hydromorphone.

Compared to buprenorphine, methadone provides more potent analgesia for severe pain due to its full μ-agonist properties. However, buprenorphine has a longer duration of action (6-8 hours) and potentially fewer side effects, making it preferable for mild to moderate pain cases or in cats where compliance with repeated administration may be challenging.

Unlike butorphanol, which is a κ-agonist/μ-antagonist with a ceiling effect, methadone doesn't have an analgesic ceiling and can be titrated for more severe pain. However, butorphanol may provide better sedation with fewer side effects for minor procedures.

The main disadvantages of methadone include its controlled substance classification, which creates prescribing and storage restrictions, and its potential for human abuse. Additionally, its availability may be limited in some veterinary practices due to these regulatory constraints. The cost of methadone is generally higher than morphine but comparable to or lower than newer synthetic opioids.

## References


1. KuKanich B, Wiese AJ. Opioids. In: Grimm KA, Lamont LA, Tranquilli WJ, et al., eds. Veterinary Anesthesia and Analgesia. 5th ed. Wiley Blackwell; 2015:207-226.
2. Bley CR, Neiger-Aeschbacher G, Busato A, Schatzmann U. Comparison of perioperative racemic methadone, levo-methadone and dextromoramide in cats using indicators of post-operative pain. Vet Anaesth Analg. 2004;31(3):175-182.

3. Ingvast-Larsson C, Holmberg M, Bondesson U, Gustafsson M, Larsson P. Clinical pharmacology of methadone in dogs. Vet Anaesth Analg. 2010;37(1):48-56.
4. Plumb DC. Plumb's Veterinary Drug Handbook. 9th ed. Wiley-Blackwell; 2018:749-752.
5. Credie RG, Teixeira Neto FJ, Ferreira TH, et al. Effects of methadone on the minimum alveolar concentration of isoflurane in dogs. Vet Anaesth Analg. 2010;37(3):240-249.
6. Maiante AA, Teixeira Neto FJ, Beier SL, Corrente JE, Pedroso CE. Comparison of the cardio-respiratory effects of methadone and morphine in conscious dogs. J Vet Pharmacol Ther. 2009;32(4):317-328.
7. Simon BT, Steagall PV. The present and future of opioid analgesics in small animal practice. J Vet Pharmacol Ther. 2017;40(4):315-326.
8. Kästner SB. A2-agonists in sheep: a review. Vet Anaesth Analg. 2006;33(2):79-96.