Plasma concentrations and behavioral, antinociceptive, and physiologic effects of methadone after intravenous and oral transmucosal administration in cats

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Objective—To determine plasma concentrations and behavioral, antinociceptive, and physiologic effects of methadone administered via IV and oral transmucosal (OTM) routes in cats.

Animals—8 healthy adult cats.

Procedures—Methadone was administered via IV (0.3 mg/kg) and OTM (0.6 mg/kg) routes to each cat in a balanced crossover design. On the days of drug administration, jugular catheters were placed in all cats under anesthesia; a cephalic catheter was also placed in cats that received methadone IV. Baseline measurements were obtained ≥90 minutes after extubation, and methadone was administered via the predetermined route. Heart and respiratory rates were measured; sedation, behavior, and antinociception were evaluated, and blood samples were collected for methadone concentration analysis at predetermined intervals for 24 hours after methadone administration. Data were summarized and evaluated statistically.

Results—Plasma concentrations of methadone were detected rapidly after administration via either route. Peak concentration was detected 2 hours after OTM administration and 10 minutes after IV administration. Mean ± SD peak concentration was lower after OTM administration (81.2 ± 14.5 ng/mL) than after IV administration (112.9 ± 28.5 ng/mL). Sedation was greater and lasted longer after OTM administration. Antinociceptive effects were detected 10 minutes after administration in both groups; these persisted ≥2 hours after IV administration and ≥4 hours after OTM administration.

Conclusions and Clinical Relevance—Despite lower mean peak plasma concentrations, duration of antinociceptive effects of methadone was longer after OTM administration than after IV administration. Methadone administered via either route may be useful for perioperative pain management in cats. (Am J Vet Res 2011;72:764–771)

Pain in cats has been inadequately managed because of a lack of licensed drugs for treatment of pain in this species and concerns related to adverse effects, particularly the deficiency of certain hepatic uridine di-phosphate-glucuronyltransferase isoforms, which predisposes cats to adverse effects of some drugs.1 The use of opioids in cats has been limited because these treatments have been associated with excitement,2,3 despite reports4,5 that suggest opioid administration results in signs of analgesia and euphoria (ie, purring, rolling, rubbing, and kneading with forepaws) when used appropriately in cats with signs of pain.

To date, the analgesic effects of several opioids, including morphine, buprenorphine, hydromorphone, oxymorphone, and butorphanol, have been evaluated in cats6–11; however, the use of methadone, a synthetic opioid, in this species has received less attention. Early reports12,13 indicated that this drug may potentially be useful as an analgesic, likely because of its unique pharmacological properties; methadone binds to μ opioid

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ABBREVIATIONS

DIVAS Dynamic interactive visual analog scale
HR Heart rate
LOQ Limit of quantification
OTM Oral transmucosal
SDS Simple descriptive scale
TP Total plasma protein
peptide receptors and also has antagonist activity at N-methyl-D-aspartate receptors. Antagonism of N-methyl-D-aspartate receptors is reported to mitigate spinal facilitation of pain. Additionally, unlike other µ opioid peptide receptor agonist opioids, methadone inhibits the reuptake of serotonin and norepinephrine and promotes the blockade of nicotinic cholinergic receptors.

These are additional mechanisms thought to play important adjunct roles in methadone-mediated analgesia. In cats, administration of methadone IM or SC was reported to result in a rapid onset of analgesia after surgery but to vary markedly in duration of effect. Mild sedation was reported by some authors, whereas others did not detect this effect.

The OTM route has some advantages over other routes of drug administration because it is simple, painless, and generally well tolerated. Additionally, if drug characteristics are favorable, there is a potential for rapid absorption, and first-pass elimination by the liver may be minimized. The high acid dissociation constant of methadone and the alkaline environment of the cat’s mouth collectively make it likely that methadone administered OTM has a high bioavailability, suggesting that methadone administered OTM may potentially be useful for pain management in cats.

The purpose of the study reported here was to measure plasma drug concentrations and compare behavioral, antinociceptive, and physiologic effects of methadone after IV and OTM administration in conscious cats.

Materials and Methods

Animals—Eight healthy adult (1- to 2-year-old) neutered mixed-breed cats, including 4 females and 4 males, with a mean ± SEM body weight of 5.91 ± 0.45 kg, were used in this study. Cats were housed as a group, with fresh water and commercial dry cat food available ad libitum. Before the study began, cats were handled for familiarization with study personnel, procedures (including nociceptive devices), and environment, which was located adjacent to their group housing. On the days of drug administration, cats were individually housed but interacted frequently with study personnel.

The study was approved by the Institutional Animal Care and Use Committee of Colorado State University.

Experimental protocol—A balanced crossover design was used in which methadone was administered IV (0.3 mg/kg) and OTM (0.6 mg/kg) to each cat, with a minimum of 10 days in between the 2 treatments. Thus, 4 of 8 cats were assigned to receive either treatment first and were assigned to the IV or OTM group on each treatment day according to the method of drug administration. Before methadone was administered OTM, oral cavity pH was measured by use of pH paper placed in contact with the buccal mucosa.

On the days of drug administration, cats were anesthetized by use of a chamber, mask, or both with 3% isoflurane in oxygen (5 L/min) delivered via a standard small animal circle breathing system until orotracheal intubation could be performed with a cuffed tube. During anesthesia, HR and rhythm were monitored by use of an ECG, and systolic arterial blood pressure was monitored by use of an ultrasonic Doppler flow detector.

A 16-gauge catheter was aseptically placed in a jugular vein by use of an over-the-wire technique and secured with 2-0 monofilament nylon-polyamide suture and a bandage to facilitate subsequent blood sample collection for analysis of plasma drug concentrations. Cats in the IV group also had a 22-gauge catheter s aseptically inserted into a cephalic vein for administration of methadone. The cephalic catheter was removed approximately 1 hour after drug administration. Isoflurane administration was discontinued after catheter placement, and cats were continuously monitored during recovery. Total anesthesia time (from administration of isoflurane until extubation) was recorded.

A minimum of 90 minutes after extubation, catheter patency was verified, baseline blood samples were collected, and methadone was administered. For OTM administration, 0.6 mg of methadone/kg was delivered between the lateral gingival surface and buccal mucosa with a 1-mL syringe. For IV administration, 0.3 mg of methadone/kg was delivered as a bolus via the cephalic catheter followed by a 2-mL heparinized saline flush. The volume of blood collected during each experiment was adjusted for each individual cat so that < 10% of its total blood volume (67 mL/kg) was removed over the duration of each experiment. On the basis of body weight of cats in the study, this was between 2 and 2.5 mL/sample. A similar volume (2 to 2.5 mL) of heparinized saline (0.9% NaCl solution + U of heparin/mL) was administered after each sample collection to flush and maintain patency of the catheter. Blood samples were obtained immediately prior to drug administration (ie, baseline) and at 5, 10, 20, and 30 minutes and 1, 2, 4, 6, 12, and 24 hours after drug administration. Blood was transferred to tubes containing lithium heparin that were refrigerated and centrifuged (1,016 X g) for 10 minutes at 4°C. Plasma was separated and stored at –70°C until analysis. Packed cell volume and TP were evaluated in samples obtained prior to and 1, 6, and 24 hours after drug administration. For determination of PCV, a microcapillary centrifuge was used. Total plasma protein was measured by use of a refractometer.

Heart rate, respiratory rate, sedation, behavior, and response to noxious or nonnoxious stimuli were assessed by a single observer (THF) at baseline and at 10 and 30 minutes and 1, 2, 4, 6, 8, 12, and 24 hours after methadone administration. Heart rate and respiratory rate were determined by means of auscultation and observation of thoracic excursions, respectively, each for a minimum of 15 seconds. Rectal temperature was measured just prior to and at 1 and 6 hours after methadone administration. Temperature was the last variable recorded at each time point because of the potential for thermometer insertion to influence the cat’s behavior.

To assess sedation, an SDS and a DIVAS were used. To implement use of these scales, cats were observed, then approached, spoken to, and petted. The SDS was used to evaluate sedation on a scale of 0 to 4 as follows: 0, euphoric behavior (meowing, purring, rolling, rubbing, kneading with forepaws); 1, rising and moving to the enclosure door to investigate activity; purring, meowing; 2, resting in sternal recumbency but appar-
ently listening and responding with head movement without rising; 3, apparently sleeping but responding by opening the eyes and raising the head; and 4, sleeping with no response to a single handclap. The DIVAS consisted of a horizontal 100-mm line on which 0 mm corresponded to normal behavior and consciousness and 100 mm corresponded to unconsciousness. A mark was placed on the line to indicate the degree of sedation. Because use of the scales did not fully capture additional behavioral responses in the same manner as those described for euphoria, other notable behaviors were also recorded.

Food and water were offered 1 hour after drug administration. Feeding behavior, water consumption, urination, and defecation were recorded. After drug administration, changes in salivation, drooling, vomiting, and other physical changes, such as mydriasis and third eyelid protrusion, were also recorded.

Two mechanical nociceptive devices were used sequentially to determine the response to noxious stimulus before and after methadone administration. The first was a custom C clamp outfitted with a calibrated 1-cm² force transducer connected to an electronic recorder capable of recording the pressure (ie, force) at which the cat first responded. The device was used to manually apply force in a dorso palmar direction across either metacarpus. The second, an algometer with a 1-cm² circular tip, was manually applied to the lateral surface of either antebrachium, midway between the elbow and carpus. The algometer was externally calibrated and, similar to the C clamp, recorded the force at which the first response was detected. Responses included the cat turning its head toward the stimulus, moving away from the stimulus, vocalizing, or attempting to bite. The stimulations were immediately stopped when a response was detected. To prevent tissue damage if cats did not react, cutoff values were preset for the C clamp (20 kg/cm²) and algometer (5 kg/cm²). These cutoff values were similar to or lower than those used previously in other species in our laboratory; in those studies, no evidence of tissue damage or discomfort was detected.

Methadone and fentanyl standard solutions were prepared in acetonitrile. Methadone was extracted from plasma by adding 300 µL of acetonitrile to 100 µL of sample plasma, vortexing for 10 minutes, and centrifuging at 18,000 × g for 10 minutes. An aliquot of 10 µL of the supernatant was injected into the liquid chromatography–tandem mass spectroscop system for analysis.

Statistical analysis—Data analysis was performed by use of statistical software. A randomized block design with repeated measures was used. The blocking effect was cat, the repeated measures effect was time, and treatment was the between-cat effect. Comparisons between antinociceptive responses before and after anesthesia (used to establish the baseline for antinociceptive effects) were analyzed by use of a randomized block design. For repeated-measures ANOVA, post hoc pairwise comparisons between treatments at each time and between times for each treatment were performed by use of Student t tests. Because residuals for DIVAS, C clamp, and plasma methadone concentration values were skewed, log (y + 1) transformation was used. For algometer, C clamp, and DIVAS data, analysis was performed only for the intermediate times because baseline and 4 of the 7-hour responses were nearly all zeros. Because we used the LOQ for plasma methadone concentration, baseline data for this variable did not react, cutoff values were preset for the C clamp, recorded the force at which the first response was detected. To prevent tissue damage if cats did not react, cutoff values were preset for the C clamp (20 kg/cm²) and algometer (5 kg/cm²). These cutoff values were similar to or lower than those used previously in other species in our laboratory; in those studies, no evidence of tissue damage or discomfort was detected.

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oral cavity before methadone administration was 8.8 \pm 3.2 minutes for cats assigned to receive methadone via IV and OTM routes, respectively. Mean pH of the oral cavity before methadone administration was 8.8 \pm 0.1. All cats urinated, defecated, and had apparently normal appetites during the study period after methadone administration via either route. None of the cats vomited during the study period. Except for 1 cat that began to salivate and tried to escape when methadone first came into contact with the oral mucosa, administration via the OTM route was without incident. However, an increase in salivation (drooling) was detected from 1 to 60 minutes after OTM methadone administration in 7 of 8 cats. In 3, 1, and 2 cats, the duration was 2, 7, and 20 minutes, respectively. One cat drooled intermittently for 60 minutes after methadone administration. Licking of nose and lips was observed in 5 of 8 cats in the IV group and in 1 of 8 cats in the OTM group after administration of methadone. The duration of this behavior ranged from 1 to 10 minutes after the drug was given.

Plasma concentrations of methadone in cats were determined after the drug was administered via IV and OTM routes (Table 1; Figure 1). These values peaked at 10 minutes and 2 hours in the IV and OTM groups, respectively. Twenty-four hours after administration, methadone concentrations were significantly lower than those measured at 12 hours, regardless of the route of drug delivery; however, these values were higher than baseline values. Plasma concentrations of methadone were significantly lower at 2, 5, 10, 20, and 30 minutes after administration in the OTM group, compared with values in the IV group. Changes in PCV and TP over time were recorded (Table 2). No significant difference was detected between the 2 groups.

Heart rate 30 minutes after methadone administration was significantly lower in cats of the IV group, compared with that in cats of the OTM group (Table 3). In cats of the IV group, HR was significantly decreased from baseline at 10 and 30 minutes after drug administration; no differences were found over time in the OTM group. Although respiratory rates were similar between groups, a significant decrease from baseline was observed from 10 minutes through 6 hours after drug administration in the IV group and at 4 hours in the OTM group. No differences were detected in body temperature within or between groups.

The degree and duration of sedation after methadone administration varied in cats of both groups (Figure 2). After drug administration, cats in the OTM group had significantly higher DIVAS scores at 30 minutes and 1 hour and higher SDS scores at 30 minutes, compared with scores for cats in the IV group. Onset of sedation was also variable and occurred between 1 and 5 minutes in 6 of 8 cats in the IV group and between 2 and 10 minutes in 7 of 8 cats in the OTM group. Three of 8 and 1 of 8 cats in the IV and OTM groups, respectively, had third eyelid protrusion, but this did not seem to be related to their degree of sedation.

Following a period of sedation, euphoric behavior that ranged in duration from 2 to 6 hours after drug administration was observed in 6 of 8 cats in the IV group. The remaining 2 cats had more affectonate behavior (eg, rubbing up against the handler, rolling over when touched) than was known to be typical for them. In the OTM group, 7 of 8 cats had signs of euphoria for 6 to 12 hours after methadone administration. However, prior to the onset of euphoria, 2 cats in the OTM group were sensitive to noise, and 1 of these 2 had apprehensive behaviors (ie, appeared apprehensive and did not like to be touched) immediately after drug administration. The noise sensitivity lasted 30 minutes in 1 cat and 1 hour in the other, which also had the described apprehensive
Behaviors for that same amount of time. Marked mydriasis was observed in all cats in both groups within 1 to 2 minutes after methadone administration. Duration of mydriasis was 8 hours in 5 of 8 cats in the IV group and 3 of 8 cats in the OTM group and was 12 hours in the remaining cats in each group.

The cats tolerated application of noxious devices and had no signs of injury or change in activity after the effects of methadone were no longer discernable. Significantly higher antinociception scores were recorded via algometer at 10 minutes and 1 hour after drug administration in the IV group, compared with scores in the OTM group (Figure 3). For cats in the IV group, these antinociception scores were significantly increased from 10 minutes to 4 hours after drug administration, and antinociception scores recorded via C clamp were significantly increased from 10 minutes to 2 hours, compared with baseline values. In the OTM group, significant increases were detected in antinociception scores recorded via algometer from 10 minutes to 6 hours and in antinociception scores recorded via C clamp at 10 and 30 minutes and 4 hours. From 1 to 4 hours after methadone administration, 3 of 8 cats in the IV group and 5 of 8 cats in the OTM group had such marked euphoric behaviors that applying the stimulus and interpreting the response were challenging.

### Discussion

The study reported here evaluated selected behavioral, antinociceptive, and physiologic effects of methadone administered via IV and OTM routes in cats. Plasma concentrations of methadone were evaluated to begin to define the relationships of methadone concentration and effect, although pharmacokinetic properties of the drug were not determined in this study.

Methadone doses used in the present study were selected on the basis of reports of other studies in cats. The IV group and 5 of 8 cats in the OTM group had such marked euphoric behaviors that applying the stimulus and interpreting the response were challenging.
After OTM administration than after IV administration, plasma drug concentrations also increased more slowly despite the fact that the dose given to cats in the OTM group was lower than those detected after IV administration, plasma drug concentrations after OTM administration following administration via other routes. Low values of systemic bioavailability have been associated with swallowing buprenorphine intended for OTM administration in humans. Because, to the authors’ knowledge, this was the first study to include OTM administration of methadone in cats, we tried to ensure that efficacy was not influenced by drug dose. The high acid dissociation constant and lipid solubility of methadone make it well suited for absorption from the buccal mucosa in cats. However, in the present study, peak plasma drug concentrations after OTM administration were lower than those detected after IV administration, despite the fact that the dose given to cats in the OTM group was twice that given to cats in the IV group. Plasma drug concentrations also increased more slowly after OTM administration than after IV administration, consistent with slower absorption of the drug as is reported in humans administered opioids via the sublingual route. Reabsorption from the gastrointestinal tract has also been suggested as a reason for later peaks in plasma concentrations of other drugs such as propranolol administered via the OTM route in humans, compared with the time to peak plasma concentrations following administration via other routes.

To the authors’ knowledge, no other study has reported plasma concentrations of methadone in cats. In horses, plasma drug concentrations were detected for 12 hours after administration of 0.1, 0.2, and 0.4 mg of methadone/kg, PO, when an LOQ of 2 ng/mL was used for analysis. In a study in Greyhounds, the mean ± SE plasma concentration of methadone decreased to 3.78 ± 0.82 ng/mL, approaching the LOQ of 2 ng/mL at 6 hours after administration of a dose of 0.5 mg/kg, IV. On the basis of these earlier studies, we elected to discontinue sample collection for plasma concentration analysis at 24 hours with the assumption that this would include an adequate period for drug concentrations to return to baseline. However, in cats of the present study, plasma methadone concentrations well above the LOQ could be detected even at 24 hours after administration via the IV and OTM routes (18.0 ± 1.5 ng/mL and 25.4 ± 3.9 ng/mL, respectively). Further investigation may be beneficial in determining reasons for this apparent difference in drug disposition among various species. Although we removed <10% of total blood volume in each cat and cats were allowed free access to food and water throughout most of the study period, we detected significant decreases in PCV and TP from baseline values; the values were still within normal limits for the species. These decreases were likely attributable to collection of blood samples and hemodilution caused by administration of heparinized saline solution used to flush the catheter.

Heart rate was decreased from baseline by 18% and 15% at 10 and 30 minutes, respectively, after methadone administration in cats of the IV group only. Although HR remained within or slightly above the reference interval for cats (168 to 221 beats/min) in this study, an 18% reduction may be relevant in a critically ill patient or one with a lower starting value. The largest decrease in HR corresponded with the highest plasma drug concentrations in cats of the IV group. No changes in HR have been reported following methadone administered IM or SC (0.3 and 0.6 mg/kg, respectively) in cats. This information is consistent with findings for the OTM group in the present study and likely a result of the gradual rise in plasma drug concentrations when methadone is given via routes other than IV.

Decreased respiratory rates were also detected in cats that received methadone IV. This is likely the result of changes from atypically high baseline values in these cats. After methadone administration, respiratory rate values remained within the normal range reported for cats in both the IV and OTM groups (40 to 50 breaths/min and 43 to 53 breaths/min, respectively). This is consistent with the observations of other investigators who reported the absence of changes in respiratory rates following methadone administration to cats. Although sedation was not formally assessed until 10 minutes after drug administration, cats in both groups appeared sedated very soon after drug administration. The DIVAS and SDS scores at 10 minutes supported this observation; analysis of DIVAS and SDS scores also indicated that sedation was of a significantly longer duration in cats of the OTM group (up
to 1 hour) than in cats of the IV group (10 minutes). Whereas sedation coincided with the peak in plasma methadone concentrations in the IV group, onset of sedation in the OTM group occurred prior to the measured peak in plasma drug concentration. This suggests that despite lower plasma concentrations, methadone distributed rapidly to the effect site and, as a result of presumed association with receptors, resulted in measurable responses. A similar rapid onset of action has been reported with use of levo-methadone (0.3 mg/kg, SC) in cats.18 Opioid administration can produce sedation in dogs and cats28,29; however, this effect in cats is usually nonexistent or mild, compared with the effect in dogs.16-18,30,31 Therefore, it is interesting that in the present study, marked sedation was observed in most cats, albeit for a short duration.

Interestingly, while plasma drug concentrations peaked between 2 and 4 hours after drug administration in the OTM group of the present study, SDS scores for sedation decreased because of euphoric behavior. Euphoria is commonly reported following opioid administration in cats and is often accompanied by mydriasis,2,3,6,10,11,17,18 which may be mediated by the release of catecholamines from the adrenal gland.32 In the present study, marked mydriasis was observed in cats in both groups for 8 to 12 hours after methadone administration but did not appear to result in adverse effects. Interestingly, the onset of mydriasis was detected almost immediately after drug administration in both groups and most often coincided in the early period with sedation and later with signs of euphoria (eg, purring, kneading, and rubbing against objects). Signs of dysphoria (eg, excitement, anxiety, restlessness, hissing, clawing, and biting) were not observed following administration of methadone via either route in the study reported here. This is consistent with results from other studies10,16,17 in which a similar dose of racemic methadone was administered in cats.

As with sedation, antinociceptive onset seemed to be related to plasma methadone concentrations in cats of the IV group; however, the peak antinociceptive effect was observed prior to detection of peak plasma concentrations in the OTM group. The mechanical nociceptive devices used in this study have not been previously used in cats to our knowledge. However, results of the present study suggest that both mechanical devices, when applied by 1 evaluator, induce consistent and repeatable responses at baseline; methadone administration resulted in an increased nociceptive threshold, which then gradually returned to baseline values. Duration and magnitude of analgesia did not appear to correspond to plasma drug concentration. For example, in cats of the OTM group, a significant antinociceptive effect was seen at 10 minutes after methadone administration when mean plasma concentrations of the drug was 37.1 ± 17.8 ng/mL, whereas at 12 hours, a methadone concentration of 43.4 ± 19.4 ng/mL was not associated with significant antinociception. Modeling pharmacokinetic and pharmacodynamic activity of the drug would allow a better assessment of whether plasma drug concentrations can be used to assess antinociceptive effects in cats. In human patients, the mean minimum effective analgesic plasma concentration of methadone is 59.2 ng/mL.33 However, the range of plasma methadone concentrations (22 to 89 ng/mL) reported prior to recommending administration of additional analgesics is broad.33

It has been suggested that genetic polymorphisms in enzymes may account for variations in metabolism, analgesic efficacy, and adverse effects of methadone among humans.13 Similar diversity in responses to methadone administration was identified in cats of the present study; mean antinociceptive effects lasted 2 and 4 hours in IV and OTM groups, respectively, but some cats had detectable antinociceptive effects for up to 8 hours, and others had these effects for only 1 to 2 hours. One cat did not appear to have any analgesia after either IV or OTM administration of methadone. This type of variation in response to administration of methadone and other opioids has been observed previously in cats.16,18,19,30-33 While sex, genetics, and testing modalities may all influence results of analgesic testing, it is also possible that euphoric behaviors interfered with our ability to properly apply the stimulus and to interpret the responses. Similar challenges were previously reported in a study11 of buprenorphine administration in cats.

Despite individual variations in response, our results suggest that, at the described doses, IV and OTM administration of methadone were associated with antinociceptive effects and behavioral changes (sedation and euphoria) but had little to no influence on measured physiologic parameters. Plasma drug concentrations did not consistently parallel analgesic or sedative effects.

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