Pharmacokinetics of Buccal Mucosal Administration of Fentanyl in a Carboxymethylcellulose Gel Compared with IV Administration in Dogs*

Amy A. Little, DVMa,† Ursula Krotscheck, DVM, DACVSa Dawn M. Boothe, DVM, PhD, DACVIM (Internal Medicine), DACVCPb Hollis N. Erb, DVM, MS, PhDc

aDepartment of Clinical Sciences
bDepartment of Clinical Sciences

Clinical Relevance

The pharmacokinetics of fentanyl administered IV (0.01 mg/kg) and in a carboxymethylcellulose gel (0.05 mg/kg) applied to the buccal mucosa of six healthy adult medium- to large-breed dogs was evaluated. At 5 minutes after transmucosal (TM) administration, serum fentanyl levels above the therapeutic target (0.95 ng/ml) were achieved in all dogs. Except for the longer duration of serum fentanyl concentrations above the therapeutic target associated with TM administration, no significant pharmacokinetic differences were found between IV and TM fentanyl. TM fentanyl may be considered a noninvasive alternative to IV administration with rapid achievement of serum fentanyl concentrations.

Introduction

Fentanyl is a highly efficacious µ-selective short-acting opioid. Oral bioavailability of fentanyl is approximately 30%, which often necessitates parenteral, rather than oral, administration.† Intestinal and hepatic first-pass metabolism are responsible for low oral bioavailability.‡-§ Transdermal patches bypass first-pass

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†Dr. Little’s current address is VCS Veterinary Specialty Center of Seattle, 20115 44th Avenue West, Lynnwood, WA 98036.
metabolism, thereby offering an alternative administration route through which steady-state serum fentanyl concentrations might be maintained over several days. Patches have been used successfully for control of pain in both human and veterinary patients.5–7

The buccal mucosa is an attractive surface for noninvasive drug administration. Compared with skin, which has a thick, avascular, lipophilic, keratinized stratum corneum, the buccal mucosa is thin and highly vascularized; any drugs absorbed pass directly into the systemic circulation, bypassing intestinal and hepatic first-pass metabolism.8,9 The oral cavity is also accessible, making application feasible.

Because of the low oral bioavailability of fentanyl, buccal transmucosal (TM) administration has been actively investigated in human medicine.9 Oral transmucosal fentanyl citrate (OTFC) is given via a “lollipop” delivery device (Oralet and Actiq, Anesta, Salt Lake City, UT).9 More recently, buccal tablet formulations (Fentora, Cephalon, Frazer, PA) have become available.10,11 Both formulations dissolve and/or are consumed over 15 minutes, during which time the oral mucosa is exposed to fentanyl, resulting in systemic absorption.1,9–11 Because canine and human mucosae, including permeability coefficients, are very similar, the assumption that fentanyl can be effectively absorbed through canine buccal mucosa is reasonable.12

TM fentanyl could offer a noninvasive route for fentanyl delivery in veterinary patients, especially those without IV access. The OTFC “lollipop” has been examined in great apes for handling and veterinary care,13 and sublingual administration of buprenorphine is effective in cats as an alternative to injection.14

The purpose of this study was to compare the pharmacokinetics of IV fentanyl (0.01 mg/kg) versus buccal TM administration of fentanyl (0.05 mg/kg) in a pH-modified carboxymethylcellulose (CMC) gel.

### MATERIALS AND METHODS

#### Animals

This study was approved by the Cornell University Institutional Animal Care and Use Committee. In a crossover design, six medium- to large-breed adult dogs (two castrated males and four spayed females; two golden retrievers, one Chesapeake Bay retriever, one Labrador retriever, and two mixed breeds), owned by veterinary students, veterinary technicians, and veterinarians, were enrolled in the study. Each owner gave written informed consent before enrollment.

All dogs were considered normal and healthy based on physical examination (with specific emphasis on the oral cavity), complete blood cell count, and serum biochemistry. The mean ± SD age and weight were 27 ± 10 months and 31 ± 6.8 kg, respectively. No dog received any medications other than heartworm or tick preventives (other than the test drug) or had significant medical history before or during the drug trial.

#### Sample Collection

All dogs were fasted for at least 8 hours before each trial. Four dogs completed the IV trial first, and two completed the TM trial first. This was based on the dates the dogs were first available for participation. Dogs available trial week 1 received IV fentanyl first, while dogs that were not available until trial week 2 received TM fentanyl first. There was a total of 3 trial weeks. The morning of each study, one side of the ventral neck was shaved and lidocaine gel (Lidocaine Hydrochloride Jelly 2%, Akorn, Buffalo Grove, IL) was applied. After 30 minutes, the area was aseptically prepared and a 19-gauge, 12-inch through-the-needle jugular catheter (Intracath, BD Worldwide, Newark, DE) was placed to the level of the cranial vena cava and secured in place with a wrap. This catheter was used only for collection of blood samples.

For both IV and TM drug administration, samples were collected at time 0 (before drug administration) and at 2, 5, 10, 15, 20, 25, 30,
35, 40, 50, 60, 90, 120, 180, 270, 360, and 480 minutes after administration. The duration of the trial was based on three elimination half-lives of fentanyl as determined in a pilot study. A minimum of 1 week elapsed between the IV and TM trials to ensure drug clearance.

Whole blood (3 ml) was collected into plain glass evacuated tubes. After samples were collected, 3 ml of sterile saline (0.9%) was administered through the catheter to replace the blood removed.

Collected blood was allowed to clot, and serum was harvested within 2 hours after centrifuging samples at 560 × g for 15 minutes. Samples were frozen in polypropylene serum transport tubes (Globe Scientific, Paramus, NJ) and stored at −70°C until sample collection was complete. Samples were shipped overnight on ice to the analytical laboratory (Clinical Pharmacology Laboratory, Auburn University).

Drug Administration

One of the authors (AAL or UK) administered all drugs. They were not blinded to treatment groups during sample collection.

Intravenous Fentanyl

Fentanyl citrate (Hospira, Lake Forest, IL) (50 µg/ml) was administered as an IV bolus at 0.01 mg/kg into a cephalic vein. All injection sites were examined immediately after administration to assure extravasation had not occurred.

Transmucosal Fentanyl

The TM gel was compounded by a licensed pharmacist at Cornell University Hospital for each syringe was mixed, using a syringe adaptor, to yield 3 ml of CMC gel containing an expected 1.66 mg/ml of fentanyl citrate. Sodium hydroxide was added to adjust the pH to 7.4 using a pH meter (pH Testr3, Oaktron Instruments, Vernon Hills, IL). A 0.5-ml aliquot of the gel was frozen at −70°C and the concentration of fentanyl determined by the same clinical pharmacology laboratory as for the serum.

The oral pH of each dog was measured using short-range (pH 6.0–8.0) pH paper (Hydron, Micro Essential Laboratory, Brooklyn, NY), sensitive to 0.5 pH units. For buccal TM administration, the upper lip on one side was elevated and the mucosa dried with a dry gauze sponge. The CMC fentanyl citrate gel (0.05 mg/kg of TM fentanyl) was applied by rubbing it on the buccal mucosa with a gloved hand until the gel was no longer discernible. The mean ± SD volume of gel administered...
was 0.91 ± 0.21 ml. The dogs were allowed to act normally after application, and no attempt was made to deter licking or swallowing. The administration site was evaluated for signs of irritation in each animal after application and until the completion of the TM trial.

Animal Observation

Dogs were supervised throughout the first 2 hours of the IV and TM study periods, and observations of clinical signs typical of opioid administration, including vomiting, nausea, dysphoria, ptyalism, panting, sedation, and recumbency, were recorded at sample collection times. As per hospital policy for small animals with jugular catheters, dogs were never left unattended for more than 10 minutes during the study period. Dogs were offered water as soon as they were able to ambulate without ataxia. The jugular catheter was removed at the completion of the trial. Owners were instructed to evaluate the application site daily for 48 hours and to report any oral irritation or behavior changes.

Sample Analysis

Samples were analyzed using a commercial 125I radioimmunoassay kit (Coat-a-Count Fentanyl, DPC Diagnostics Product Corp., Los Angeles, CA) for quantitative measurement of fentanyl. This method has been validated in canine serum, is highly specific for fentanyl, and does not detect fentanyl metabolites.16 The lower limit of detection is 0.08 ng/ml of serum fentanyl. The lower limit of quantification was 0.1 ng/ml, and the upper limit was 8.5 ng/ml. Any serum concentration exceeding this level was measured by dilution, using similarly diluted control samples to assure predictability. Laboratory workers were blinded to whether the samples were from the IV or TM trial.

Fentanyl concentrations were measured in unknown samples by comparing them with samples of canine serum to which known concentrations of fentanyl had been added. The calibration curve was validated based on three controls that spanned the breadth of the standard curve. The coefficient of variation for control samples was <15% for all controls except the lowest, for which ≤20% was accepted. All samples, including the gel, were run in duplicate.

Pharmacokinetic Analysis

Noncompartmental pharmacokinetic analysis used the concentration versus time data for both IV and TM fentanyl delivery in each dog. Area under the curve (AUC) and its first moment (AUMC) were calculated to infinity using computer-assisted regression with a log-linear trapezoidal model (WinNonlin, Pharsight, Mountain View, CA). Pharmacokinetic parameters determined included maximum concentration (Cmax), time of maximum concentration (Tmax), elimination half-life (t1/2el), mean residence time to infinity (MRT), rate constant associated with the terminal elimination phase (k0), and extrapolated concentration at time 0 (C0). The AUC above the therapeutic target (AUC high) and time above the therapeutic target of 0.95 ng/ml (time high) were calculated to assess duration of time above an analgesic serum level of fentanyl (0.95 ng/ml), which has previously been identified as an analgesic fentanyl serum concentration in dogs.6

Model independent parameters included absolute bioavailability (%F), MRT, and clearance (Cl) and were calculated as follows:

\[
%F = \frac{AUC_{IM} \times Dose_{IV}}{AUC_{IV} \times Dose_{IM}}
\]

\[
MRT = \frac{AUMC}{AUC}
\]

\[
Cl = \frac{Dose}{AUC}
\]
Apparent volume of distribution at steady state (Vdss), the volume in which the amount of drug would need to be uniformly distributed to produce the observed blood concentration, was calculated for IV fentanyl as follows:

\[ V_{dss} = \text{MRT} \times \text{Cl} \]

Mean absorption time (MAT) was calculated by subtracting the MRTIV from MRTTM.

**Statistical Analysis**

Normality of within-dog differences in pharmacokinetic parameters was determined using the Shapiro-Wilk test. Normally distributed parameters were reported as mean ± SD and were compared between routes of administration using a two-sided paired t-test. An exception was made for t1/2el, which was reported as harmonic mean and pseudostandard deviation. The significance level was \( P < .05 \). Median and range were reported for non-normally distributed data.

**RESULTS**

All six dogs completed the IV and TM trials. The oral pH of all dogs was 7.

Subjective clinical effects from the IV and TM delivery of fentanyl were similar in timing and magnitude. Sedation was evident with either route 2 to 10 minutes after drug administration. Additional signs included panting and whining in all dogs and ptyalism in three of six dogs. Two of six dogs exhibited ptyalism after both IV and TM administration. Clinical signs abated 90 to 120 minutes after administration via either route. Recumbency was preferred in all dogs except two (both of which exhibited ptyalism after IV and TM administration) after IV administration. Neither vomiting nor dysphoria was noted. The behavior of each dog was considered normal at the end of each 8-hour study period.

The final concentration of the gel was 1.76 mg/ml. Buccal TM administration did not appear to cause any adverse oral effect, including mucosal irritation, during the 48 hours of monitoring after administration. The mean ± SD volume of gel (0.91 ± 0.21 ml) was easily administered, in part due to its viscosity, with the gel being unidentifiable within 1 minute after application.

All pharmacokinetic parameters data, except \( T_{\text{max}} \), were normally distributed (Table 1).

**TABLE 1. Mean (±SD) Pharmacokinetic Parameters for IV (0.01 mg/kg) and TM (0.05 mg/kg) Fentanyl Administration in Dogs**

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>( C_{\text{max}} ) (ng/ml)</th>
<th>( T_{\text{max}} ) (min)*</th>
<th>AUC (ng × min/ml)</th>
<th>AUC High (ng × min/ml)</th>
<th>Time High (min)</th>
<th>( t_{1/2el} ) (min)</th>
<th>MRT (min)</th>
<th>( K_{el} ) (min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV</td>
<td>NA</td>
<td>NA</td>
<td>666 ± 275</td>
<td>234 ±133</td>
<td>169 ± 95</td>
<td>164 ± 73</td>
<td>239 ± 76</td>
<td>0.0042 ± 0.0018</td>
</tr>
<tr>
<td>TM</td>
<td>9.3 ± 2.0 (5–35)</td>
<td>858 ± 157</td>
<td>432 ± 116</td>
<td>236 ± 87</td>
<td>128 ± 50</td>
<td>176 ± 62</td>
<td>0.0054 ± 0.0021</td>
<td></td>
</tr>
</tbody>
</table>

*Results stated as median (range).
†Results stated as harmonic mean (pseudostandard deviation).

\( C_{\text{max}} \) = maximum serum concentration; \( T_{\text{max}} \) = time of maximum concentration; AUC = area under the curve; AUC high = AUC above 0.95 ng/ml; time high = time during which serum concentrations were above 0.95 ng/ml; \( t_{1/2el} \) = elimination half-life; MRT = mean residence time; \( k_{el} \) = rate constant associated with the terminal elimination phase; NA = not applicable.
The mean ± SD C₀ of fentanyl immediately after IV administration was 10.0 ± 2.8 ng/ml. Other relevant kinetics (mean ± SD) for fentanyl after IV administration included a $t_{1/2d}$ of 164.0 ± 72.7 minutes, $V_{dss}$ of 3.80 ± 1.2 L/kg, and $Cl$ at 17.4 ± ml/min × kg. Fentanyl concentrations (mean ± SD) were above the recommended therapeutic target for 169 ± 95 minutes after IV administration (Figure 1).

TM fentanyl resulted in serum fentanyl concentrations within 2 minutes of administration, with all dogs having serum levels above the therapeutic target at 5 minutes. The mean ± SD $C_{max}$ measured was 9.3 ± 2.0 ng/ml at $T_{max}$ (median, 10 minutes; range, 5–35 minutes). The mean ± SD absolute TM bioavailability was 29% ± 10% (Table 2). Fentanyl concentrations were above the recommended target for 236 ± 87 minutes after TM administration (Figure 1).

The only significant difference in pharmacokinetic parameters between IV and TM administration was in the time above the therapeutic target of 0.95 ng/ml ($P = .03$). Non-significant pharmacokinetic differences were $AUC (P = .13)$, $AUC_{high} (P = .07)$, $t_{1/2d} (P = .28)$, $MRT (P = .15)$, and $k_{el} (P = .19)$.

**DISCUSSION**

Noninvasive routes of drug administration are attractive in both veterinary and human medicine. The characteristics of fentanyl that allow transdermal administration are the same for TM administration. These include fentanyl’s small molecular weight (336.5 g/mol) and lipophilic nature (octanol:water partition coefficient, 717:1) and that fentanyl is a weak base (pKa 8.4); in addition, and of particular interest in TM administration, fentanyl is tasteless and non-bitter.8,9,17,18 An added benefit for TM administration is that fentanyl is absorbed through the buccal mucosa, directly entering the systemic circulation and bypassing intestinal and hepatic first-pass metabolism.2–4

In humans, one of the most effective uses of TM fentanyl is in the treatment of break-
through pain in cancer patients. TM fentanyl averts the need for emergency center visits, parenteral opioids, and hospitalization.\textsuperscript{19} Pain relief is faster in onset and more effective compared with other medications used for breakthrough pain episodes, such as morphine.\textsuperscript{20} An advantage of TM fentanyl is that dosages can be titrated to the patient, which is especially important in opioid-tolerant patients.\textsuperscript{10,19–21}

TM fentanyl provides rapid achievement of analgesia without injections, which is of particular benefit in patients without IV access. Potential TM fentanyl indications in humans—reduction in pain and anxiety associated with invasive procedures (nonsurgical or surgical), postoperative pain management, painful bandage changes, and rehabilitation therapy—should be relevant to canine patients. In a small study, bandage changes took less time and the nurses had better cooperation in pediatric burn patients receiving OTFC versus oral morphine.\textsuperscript{22,23} Even relatively simple procedures (e.g., catheter placement, positioning for radiographs, physical examinations) may be facilitated by fentanyl administration. Fentanyl’s short duration of action was noted to allow rapid onset with limited unnecessary sedation time, inappetence related to sedation, and adverse effects.\textsuperscript{22,23}

In the current study, TM administration resulted in rapid detection of fentanyl in serum. Within 2 minutes, serum fentanyl concentrations were above the serum target level in five of six dogs, with $T_{\text{max}}$ occurring at a median of 10 minutes (range, 5–35 minutes). This rapid achievement of serum fentanyl levels above a therapeutic serum level of 0.95 ng/ml (first 10 minutes) is consistent with buccal mucosal, rather than intestinal, absorption and is seen in human studies of OTFC, buccal tablets, and oral fentanyl solutions using IV formulations or compounded from fentanyl powder.\textsuperscript{10,17,24} Depending on the formulation, studies in humans in which fentanyl is consumed over 15 minutes have shown a $T_{\text{max}}$ of 22 to 56 minutes.\textsuperscript{1,10,25–27} The rapid achievement of serum concentrations above the therapeutic target, combined with clinical signs of opioid administration, makes the TM route an attractive option for rapid analgesic effect in dogs.

In this study, fentanyl pharmacokinetics did not differ between IV and TM administration except in the time above the therapeutic target of 0.95 ng/ml ($P = .03$), which supports findings described in humans and dogs.\textsuperscript{1,17} This indicates that TM administration may result in a longer duration of pain relief. The pharmacokinetics similarly support the TM route as an alternative to IV administration in dogs.

It is important to note that this study focused on the pharmacokinetics of fentanyl and that signs of opioid administration were subjectively evaluated. Analgesic fentanyl serum concentrations can be quite variable and in humans are estimated between 0.2 and 2 ng/ml.\textsuperscript{5,28} This variability, as well as individual sensitivity to opioids, requires analgesia to be assessed based on analgesia achieved and not solely on serum concentrations of fentanyl. Pharmacodynamic studies on the efficacy and analgesia produced after TM administration are needed.

| TABLE 2. Absolute Bioavailability (%F) of TM Fentanyl in Individual Dogs |
|----------------|---|
| Dog | (%F) |
| Dog 1 | 29 |
| Dog 2 | 16 |
| Dog 3 | 37 |
| Dog 4 | 24 |
| Dog 5 | 22 |
| Dog 6 | 41 |
| Mean ± SD | 29 ± 10 |
The TM dose of 0.05 mg/kg used in the current study represents a fivefold increase over the administered IV dose. This was based on an anticipated decrease in bioavailability with TM delivery, as has been demonstrated in children, in which OTFC bioavailability is approximately 30%.29 A similarly reduced bioavailability in dogs has been demonstrated in a pilot study.15 The fivefold difference between TM and IV doses represents increased exposure to fentanyl after TM administration compared with IV administration. This could affect the time above the therapeutic target of 0.95 ng/ml by two possible mechanisms: absorption of the swallowed fentanyl or continued buccal mucosal absorption.

With OTFC it is estimated that 25% of fentanyl is absorbed via the buccal mucosa, with the remaining 75% being swallowed.1 Only 25% of the swallowed fentanyl is absorbed into the systemic circulation because of losses from gastrointestinal and hepatic metabolism.1,3 The swallowed fentanyl could possibly be absorbed over a longer period and, combined with the higher dose, potentially result in prolonged higher serum concentrations. Graphically, no visible peak corresponding to absorption in the stomach and intestines is seen in humans, suggesting continuous absorption over time.1

Continued absorption of fentanyl from the buccal mucosa is also a possible cause for the sustained time above the target serum concentration. Human and canine studies have shown that a fentanyl tissue depot (as found in skin) in the buccal mucosa is unlikely even at total doses of OTFC up to 1,600 mg/person.1,30 One human study did demonstrate that the buccal mucosa may act as a depot when a high-dose (1,080 µg) fentanyl tablet was administered.25 Based on the corresponding t1/2 el between TM and IV administration in the current study, a buccal fentanyl reservoir is not suspected but cannot be completely ruled out as a contributor to the prolonged time above the therapeutic target.1,30

Absolute bioavailability of TM fentanyl in dogs was 29% (±10%), similar to the 33% seen in children consuming OTFC.29 Children tended to consume the lollipop more quickly than adults, thereby swallowing more fentanyl.29 In the current study, no attempt was made to deter dogs from licking or swallowing the fentanyl gel, possibly limiting the time the

Results indicate that TM administration may result in a longer duration of pain relief.

Potential improvements to the gel and application process include adjusting the pH of the gel toward the pKa (because TM fentanyl absorption is pH dependent17,24), extending the
time the lip was held in position after administration, applying the gel to a larger surface area of buccal mucosa, and applying the gel to the sublingual mucosa. The feasibility of sublingual absorption and increasing the contact time is limited because of access and the inability to prevent licking and swallowing in a clinical setting.

After IV administration, serum concentration varied between dogs, as seen in the SD in Figure 1. The \( C_0 \), based on the data sets, was a mean ± SD of 10.0 ± 2.8 ng/ml. This amount of variation in the SD of the serum concentration versus time curve is not unusual and has been described in other pharmacokinetic studies of fentanyl. The \( C_0 \), in particular, is extrapolated data and hence has the potential to be incorrect; however, each animal has inter-individual variability in drug redistribution and metabolism.

Although the primary goal of this study was to describe the pharmacokinetics of fentanyl when administered TM versus IV, certain pharmacodynamic features consistent with opioid administration were noted and reported. The authors who noted behavior and collected the blood samples were not blinded to the route of administration. Blinding to the routes of administration would have added more power to the observations.

Fentanyl is a potent opioid, and human deaths do occur by accidental overdoses; unfortunately, many overdoses and deaths are from illicit abuse. Abuse can be via a nonmedical application of injectable or transdermal fentanyl or when fentanyl is extracted from patches and/or mixed with other drugs and alcohol. Caution and monitoring would be necessary when prescribing TM fentanyl because of the considerable dosage in a small volume. Supervised in-hospital use and administration are essential for safety and to limit illicit use.

To evaluate fentanyl for TM application, using the commercially available injectable fentanyl citrate (50 \( \mu g/ml \)) was not feasible. Based on the mean weight of dogs, an average volume of 30 ml of fentanyl would be used per dog; also, TM absorption could have been hindered by other components in the injectable product. Compounding is allowed when there is no approved drug for the needed dosing regimen. The compounding was done by a licensed pharmacist in a quantity only for this study. The fentanyl powder could be acquired only for research purposes and met USP standards.

Compounded products are not manufactured under Goods Manufacturing Process conditions, nor are they regulated by the FDA. Thus compounded products have not been studied or tested for efficacy, purity, safety, stability, and adverse affects. Compounded products should be used only when legal and necessary (no commercially available product) and when there are studies indicating efficacy.

This study makes no attempt to recommend dosages. Further studies to assess the pharmacokinetics of different gel formulations and pharmacodynamics are needed before dosage and use recommendations can be made.

**CONCLUSION**

The pharmacokinetics of 0.05 mg/kg of fentanyl, when administered in the CMC gel as described, are not significantly different than those of 0.01 mg/kg fentanyl IV. More studies are necessary to determine optimal fentanyl gel formulations, pH, pharmacodynamics, and clinical effects. Administration of the gel is technically easy, and the dogs in the study tolerated the application process. TM administration quickly reached and maintained therapeutic fentanyl concentrations and, as described in this study, is a possible alternative to IV administration in dogs.
REFERENCES


