Evaluation of Transdermal Morphine and Fentanyl Pluronic Lecithin Organogel Administration in Dogs*

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CLINICAL RELEVANCE

Transdermal administration of morphine and fentanyl using a pluronic lecithin organogel was evaluated in dogs. IV administration of morphine and fentanyl resulted in therapeutic serum drug concentrations. Following transdermal administration, however, median serum drug concentrations were never above the limit of quantitation for morphine or fentanyl. These findings indicate that use of a pluronic lecithin organogel for transdermal administration of morphine or fentanyl cannot be justified.

INTRODUCTION

The use of transdermal delivery systems (TDDS) is increasing in both human and veterinary medicine, as evidenced by the increasing visibility of this subject in journals such as the International Journal of Pharmaceutical Compounding. The most commonly used TDDS are patches, ointments, and gels designed to deliver a drug systemically after being applied topically. The transdermal fentanyl patch (Duragesic, Janssen Pharmaceutica) has been documented to be safe and effective in dogs and cats, although absorption varies greatly among individuals.1–5 The success of this patch in animals, coupled with the “ease” appeal of transdermal administration, probably contributes to the increasing popularity of TDDS. Transdermal drug delivery offers other potential advantages, including avoiding the first-pass hepatic metabolism, flexibility of drug application to different sites, avoiding the changing environment of the gastrointestinal tract, improved client compliance (particularly for owners of fractious veterinary patients),...
avoiding oral administration in vomiting patients, and avoiding side effects, such as vomiting and nausea associated with oral administration of some drugs.\textsuperscript{6,7} Disadvantages of TDDS include local skin reaction or irritation to the medication or its vehicle, potential oral ingestion or removal by the patient, and potential exposure of the pet owner to the drug.\textsuperscript{6,7}

The majority of gels offered for use in veterinary medicine are compounded in a pluronic lecithin organogel (PLO gel).\textsuperscript{7} These water-based gels are easily prepared, theoretically can host a wide variety of drugs compared with other TDDS,\textsuperscript{8} and are reported to be stable.\textsuperscript{9} The finished PLO gel consists of a phospholipid liposomal microemulsion prepared from a water (pluronic copolymer) and a lipid (lecithin, generally of soy origin) phase. The drug to be delivered is first wetted and then dissolved in the phase (lipid or water) in which it is most soluble. Subsequent rapid mixing of the two phases (e.g., between two syringes) generates shear forces, causing the formation of flexible cylindrical reverse micelles containing the drug.\textsuperscript{9} Presumably, the phospholipid tails of the micelles interact with the lipids in the stratum corneum, causing its rearrangement and thus facilitating drug penetration between the epidermal cells into the systemic circulation.\textsuperscript{8,10} The rate of drug movement across the stratum corneum is directly proportional to the concentration gradient of dissolved (diffusible) drug and the thickness of the lipophilic stratum corneum.\textsuperscript{11,12} The partitioning of a drug between the skin and the reservoir favors a more lipophilic drug because skin acts as an organic phase.\textsuperscript{13}

Little scientific evidence supports the ability of a PLO gel to systemically deliver drug. The purpose of this study was to evaluate the ability of a PLO gel system to deliver analgesic drugs in dogs. Two drugs of similar molecular weight but differing lipophilicity were selected: morphine and fentanyl. The molecular weight of morphine is 337 D, whereas that of fentanyl is 286 D (18% smaller).\textsuperscript{14} The octanol–water coefficients for morphine and fentanyl are 0.7 and 717, respectively, indicating that fentanyl is significantly more lipophilic than morphine.\textsuperscript{14} The authors hypothesize that therapeutic serum concentrations will be achieved for both fentanyl and morphine using the PLO gel as described.

\textbf{MATERIALS AND METHODS}

\textbf{Animals}

The experimental protocol was approved by the Texas A&M University Lab Animal Care Committee. Nine adult hound dogs (five males and four females) weighing 21.1 to 38.9 kg (mean ± SD: 30.2 ± 5.6 kg) were housed singly in standard indoor runs. All dogs were fed a commercial dry dog food diet (Adult Canine Maintenance, Science Diet, Hill’s Pet Nutrition) once daily. Tap water was available ad libitum. One to 2 hours before each study period, a complete blood count and chemistry panel were performed on each dog. Every dog was fasted for 24 hours before each study.

\textbf{Pluronic Lecithin Organogel Preparation}

All PLO gels were made in accordance with procedures currently being used in training facilities such as the Professional Compounding Centers of America (Houston, TX) within 24 hours of the study.\textsuperscript{15} The lipid phase was composed of granular soy lecithin (Gallipot, St.
Paul, MN) intended to dissolve lipid-soluble drugs as well as to increase the stratum corneum permeability. Isopropyl palmitate (Gallipot) was included as a penetration enhancer and solvent, and sorbic acid (Gallipot) was added as a preservative. The water phase consisted of purified water as a solvent, pluronic F127 (Poloxamer 407, Gallipot) as a surfactant, and the preservative potassium sorbate (2,4-hexadienoic acid and potassium salt; Gallipot). Morphine sulfate (Spectrum Chemicals & Laboratory Products, New Brunswick, NJ) was evaluated at a PLO gel concentration of 50 mg/ml; fentanyl citrate (Sigma-Aldrich, St. Louis, MO) was evaluated at PLO gel concentrations of 5 and 20 mg/ml.

Commercially available premixed phases were used to make the gel. Lipoil (Gallipot) served as the lipid phase, and Polox 20% (Gallipot) served as the water phase. Each drug was added and mixed with the phase more consistent with its lipid solubility; fentanyl was dissolved in the lipid phase and morphine in the water phase. The amount of drug added to each gel was based on calculated dosages for each animal. The phases were mixed by passing the contents of the two phases between the syringes until the mixture was homogenous. For each medicated gel, a 1-ml aliquot was set aside for analysis to verify the calculated concentration.

### Dosage and Application of TDDS

For each opioid, two dogs in each group received the recommended dose of the commercially available preparation IV. These dogs served as positive controls and were intended to document that the methods and procedures, including drug analysis, were appropriate (Table 1). Transdermal morphine was studied at two dosages (1 and 2 mg/kg) in a 50 mg/ml morphine PLO gel, and fentanyl was studied at 0.88 mg/kg using two gel concentrations (5 and 20 mg/ml). The determination of PLO gel drug concentration was based on dosage and estimated amount of PLO gel that could be administered easily by an owner. The site of gel administration in each dog was inspected before each study to ensure the site was free of long hair and debris. Long hair was carefully trimmed with clippers immediately before the study. Each gel was rubbed onto the skin until no visible gel remained.

The study groups were as follows:

- **Group M1** (n = 2)—Morphine sulfate administered IV at 0.3 mg/kg (0.14 mg/lb)
- **Group M2** (n = 6)—Morphine sulfate as a transdermal PLO gel (20 mg/ml) at 1 (n = 2) to 2 (n = 4) mg/kg (0.5 to 1.0 mg/lb) applied to the inguinal region (n = 4) or in the ear pinna (n = 2)

<table>
<thead>
<tr>
<th>Drug/Group</th>
<th>Route</th>
<th>Mean Dose (mg/kg)</th>
<th>Gel Concentration (mg/ml)</th>
<th>Volume (ml)</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1 (n = 2)</td>
<td>IV</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M2 (n = 6)</td>
<td>TD</td>
<td>1.67</td>
<td>50</td>
<td>0.6–1.3</td>
<td>Inguinal region and pinna</td>
</tr>
<tr>
<td><strong>Fentanyl</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F1 (n = 2)</td>
<td>IV</td>
<td>0.015</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F2 (n = 6)</td>
<td>TD</td>
<td>0.88</td>
<td>5 and 20</td>
<td>1.3–6.9</td>
<td>Inguinal region</td>
</tr>
</tbody>
</table>

IV = intravenous, TD = transdermal.
• **Group F1** (n = 2)—Fentanyl citrate administered IV at 0.01 to 0.02 mg/kg (0.005 to 0.01 mg/lb)

• **Group F2** (n = 6)—Fentanyl citrate as a transdermal PLO gel (5 and 20 mg/ml) at 0.88 mg/kg (0.4 mg/lb) applied to the inguinal region

At least 2 weeks of washout time was allowed between each study.

**Sample Collection and Handling**

Blood samples were collected via either an external jugular catheter placed 1 hour before the study or a femoral venous access port that had been placed at least 4 months before the current study as part of a previous unrelated study. Before the gel was applied, a blood sample was collected and designated as time 0 minutes. After the gel was applied, 3-ml blood samples were collected in blood tubes without added anticoagulants at 2, 5, 10, 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, and 420 minutes for morphine and 2.5, 5, 7.5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 75, 90, 105, 120, 135, 150, 165, and 180 minutes for fentanyl. Samples were centrifuged at 2,500 rpm (560 g) for 15 minutes. Harvested serum was frozen within 2 hours at –4°C until the time of sample analysis. Each animal was observed throughout the study to prevent inadvertent oral ingestion of the transdermally applied drug. Clinical effects typical of opioids, including vomiting, ptalism, sedation, and lateral recumbency, were recorded throughout the study.

**Sample Analysis**

Serum and gel samples were analyzed using a commercial $^{125}$I radioimmunoassay kit for the quantitative measurement of fentanyl or morphine (Coat-a-Count Fentanyl or Coat-a-Count Morphine, respectively, DPC Diagnostics Products, Los Angeles, CA). According to the package inserts, the fentanyl kit does not discriminate between the parent drug and its metabolites whereas the morphine kit detects only morphine with essentially no cross-reactivity with major metabolites. The lower limits of detection for morphine and fentanyl as delineated by the manufacturer were 0.5 and 0.08 ng/ml, respectively. Each assay was validated in dog serum by comparing unknown samples to a standard curve generated by the addition of known amounts of each drug to canine serum. The lower limits of quantification for morphine and fentanyl in canine serum were 10 and 0.5 ng/ml, respectively. The coefficient of variation for three controls that spanned the detection range was less than 15% for high controls and 20% or less for low controls.

For studies in which sufficient drug concentration versus time curve data were available, standard pharmacokinetic analysis was implemented by noncompartmental analysis using a log-linear trapezoidal rule (WinNonlin, Pharsight, Mountain View, CA) to infinity. Absolute bioavailability was calculated from the formula

$$F = \frac{\text{AUC}_{\text{gel}} \times D_{\text{IV}}}{\text{AUC}_{\text{IV}} \times D_{\text{gel}}} \times 100$$

where $\text{AUC}$ is the area under the curve and $D$ is the dose. For all studies, including those for which data were insufficient to allow pharmacokinetic analysis, median peak drug concentrations ($C_{\text{max}}$) and the time that the peak occurred ($T_{\text{max}}$) were reported (Table 2).

**RESULTS**

All animals tolerated the PLO gels with no evidence of skin irritation at the site of application. Applying small volumes of gel was easier because a smaller area of application could be used to achieve visual disappearance of the gel. Gel concentrations were verified to be accurate.
Morphine

The median $C_{\text{max}}$ following IV administration of morphine was 141.45 ng/ml (range: 141.1–188.5 ng/ml; Table 2, Figure 1). The median half-life was 123.3 minutes (range: 87.2–159.5 minutes; Table 2). Clinical signs of morphine administration, such as vomiting, sedation, and lateral recumbency, were evident in all dogs that received morphine IV. Regardless of dose or administration site, few blood samples collected after application of the transdermal gel contained sufficient morphine to allow drug quantification, and therefore pharmacokinetic modeling was not possible for any transdermal morphine trial. Median $C_{\text{max}}$ for group M2 was 1.65 ng/ml (range: 0.067–4.2 ng/ml; Table 2, Figure 1). All transdermal concentrations were above the lower limit of detection but below the (accurately) quantifiable concentration. Variation of serum morphine concentrations from time 0 minutes (baseline) was minimal. Clinical signs associated with opioid administration, such as salivation, nausea, vomiting, and sedation, did not occur in any dog after transdermal morphine administration.

Fentanyl

After IV administration, all dogs exhibited clinical signs consistent with opioid administration, including lateral recumbency, ptyalism, and sedation. Because the first dog exhibited profound clinical signs after receiving 0.02 mg/kg, the second dog was given only half the planned dose. The median $C_{\text{max}}$ was 2.17 ng/ml (range: 1.5–2.8 mg/ml; Table 2, Figure 2). As with morphine, few blood samples contained quantifiable fentanyl after any transdermal PLO gel application (Figure 2). The median $C_{\text{max}}$ for group F2 was 0.51 ng/ml (range: 0.41–2.3 ng/ml). Half-lives could not be determined because modeling (or even peak-
could have served as a positive control to indicate whether the PLO gel prevents transdermal movement of the drugs. Assay problems are unlikely because achievement of therapeutic concentrations was documented after IV administration of both drugs. Additionally, both the fentanyl and the morphine assays have been validated in canine serum.19,20

The epidermis, specifically the stratum corneum, is the rate-limiting step to transdermal drug penetration in humans.11 It is estimated that the relative ratio of transdermal absorption at various anatomic sites correlates with the thickness and lipid content of the stratum corneum.21 A similar correlation may exist in dogs. For PLO gels, the generally accepted theory is that drugs are absorbed through the intercellular lipid, not the cells.8,10 Because the stratum corneum presents a lipid barrier, the greatest flow rate through the stratum corneum occurs with highly lipophilic and low-molecular-weight (<500 D) drugs.22 The rate of trans-

**Figure 1.** Results for IV and transdermal (TD) morphine administration. Lower limit of quantitation is 10 ng/ml. Therapeutic target for morphine is 10 ng/ml. All results are reported as medians.
Dermal flux also changes inversely with the thickness of the epidermis and is proportionate to the surface area of skin to which the drug is exposed. After the drug has traversed the lipid matrix of the stratum corneum, it must diffuse through the remaining underlying epidermal layers and dermis, which have an aqueous environment. Thus, affinity for both lipid and aqueous environments is required for effective transdermal absorption of drugs. The aqueous solubility and octanol–water distribution of a drug are the major determinants of its lipophilicity. Fentanyl has an octanol–water coefficient of 717, whereas morphine's is 0.7, emphasizing the difference in potential transdermal absorption. Other factors important to transdermal absorption include drug stability, use of a solvent carrier or vehicle, use of a penetration enhancer, and the type of delivery device. Although drug absorption through hair follicles and sweat glands does occur, its effect in humans is negligible. Since dogs have much less widely distributed sweat glands, this potential absorptive effect is probably even less likely. Traumatic shaving of the area to which the drug is applied in humans seems to enhance transdermal absorption. Because of this, the authors chose not to closely shave the dogs in this study to avoid traumatizing the inguinal skin. Absorption of drug across traumatized skin would not reflect the true efficacy of the TDDS.

One goal of this study was to identify a dose of transdermal opioid that would generate systemic concentrations within a therapeutic range. However, the therapeutic concentration of morphine in dogs has thus far been indeterminable because of individual variability of morphine serum concentrations necessary to achieve analgesia. Human studies suggest a therapeutic concentration goal of 9 to 65 ng/ml. For fentanyl, a targeted therapeutic concentration of 0.95 ng/ml has been recommended in dogs.

For morphine, the minimal recommended therapeutic goal in humans was not achieved in
any dog after transdermal delivery (6.67 times the IV dose). As with morphine, no dog achieved consistent therapeutic concentrations of fentanyl after transdermal delivery at 44 to 88 times the IV dose. Serum fentanyl concentrations did surpass the therapeutic target at 165 and 180 minutes (2.3 and 1.05 ng/ml, respectively) in one dog (dose: 5 mg/ml gel applied to the inguinal region) and in a second dog (1.1 ng/ml after administration of the 20 mg/ml gel to the inguinal region) at one time point (165 minutes). The late onset of detectable drug may suggest that the upper skin layers serve as a depot for fentanyl, much as they do for the transdermal fentanyl patch in humans.\textsuperscript{30–35} However, neither dog in which low or high concentration fentanyl PLO gel.

Results of this study are not supported by a previous evaluation of PLO drug delivery in cats. In an unblinded, noncontrolled study, long-term transdermal administration of methimazole prepared as a 50-mg/ml PLO gel applied on the pinna of hyperthyroid cats decreased the total thyroxine in nine of 10 cats.\textsuperscript{38} These results contrast with those of a subsequent study that evaluated serum methimazole levels in cats after single IV, oral, and transdermal administration. Transdermal absorption was poor and variable, with only two of six cats achieving detectable serum levels, one of which achieved nearly 100% transdermal bioavailability relative to the oral route.\textsuperscript{39} Methimazole

\textbf{Neither dog in which therapeutic fentanyl concentrations were achieved showed clinical signs consistent with opioid administration.}

therapeutic concentrations were achieved showed clinical signs consistent with opioid administration. Subsequent samples revealed declining concentrations, suggesting lack of persistence of drug levels. Because the PLO gel is being marketed as an alternative to oral drug administration, the duration of this study was based on previous studies evaluating oral administration of these drugs.\textsuperscript{36,37} Other possible explanations for the achievement of transient therapeutic concentrations include oral ingestion of the gel and subsequent bioavailability and/or detection of fentanyl metabolites. Fentanyl was studied at low and high PLO gel concentrations (5 and 20 mg/ml) to determine the effect, if any, drug concentration has on the ability of the PLO gel to systemically deliver a drug that has been shown to cross intact skin in other delivery systems. There was no difference evident in the results of animals receiving the

is characterized by a much smaller molecular weight (114 D) compared with the opioids, but its partition coefficient is not known. Its smaller molecular weight may facilitate transdermal delivery, but such delivery has not been observed consistently. Repeated administration of penetration enhancers such as lecithin can lead to low-grade inflammation and exfoliation of the stratum corneum, both of which may enhance drug absorption.\textsuperscript{40,41} PLO gel has been evaluated in human medicine, but no in vivo pharmacokinetic studies are currently available. Several human studies have evaluated the use of PLO gel for administration of NSAIDs, hormones, and other drugs.\textsuperscript{8,42–45} One ex vivo study demonstrated a 10-fold increased flow of broxaterol and scopalamine across intact human breast skin in Franz diffusion cells with a PLO gel versus an aqueous solution.\textsuperscript{8} Another study found de-
creased lateral epicondylar pain in subjects who received local diclofenac PLO gel versus placebo administration via PLO gel. Serum diclofenac levels were not evaluated. Failure of PLO gels to deliver opioid systematically in dogs is not unexpected. The stratum corneum is approximately 48 cell layers thick in dogs, whereas human stratum corneum is only 10 to 20 cell layers thick. Application of the PLO gel to the abdomen may be more successful than application to the pinna; the thicknesses of the canine stratum corneum in these areas are 12.2 ± 2.12 and 15.09 ± 1.83 µm, respectively. The application of the PLO gel to the pinna was evaluated in this study for several reasons: the animal is less likely to ingest the drug, necessitating less owner observation after application, and absorption through the pinna in cats has been documented. Based on physiochemical characteristics previously discussed, fentanyl should have been more likely than morphine to reach systemic concentrations following transdermal delivery, particularly when administered at 44 to 88 times the IV dose (compared with only three to six times the IV dose for morphine).

■ CONCLUSION

Future areas of research should focus on long-term transdermal administration of drugs, evaluation of different drugs, and evaluation of histologic changes in the dermis and epidermis after long-term PLO gel administration. The authors conclude that fentanyl and morphine PLO gels as used in this study are not effective and are not recommended for use. In the authors’ opinions, use of PLO gel as a drug delivery system should be recommended only for drugs in which efficacy and safety data have been established. Most drugs currently being administered via a PLO gel system have no scientific data supporting their use in this manner. Further evaluations of PLO gels are currently under way with one of the authors (D. M. B.) and at other academic veterinary institutions.

■ REFERENCES
