Pharmacokinetics of Buprenorphine Following Intravenous and Oral Transmucosal Administration in Dogs*

Lisa A. Abbo, DVMa
Jeff C. H. Ko, DVM, MS, DACVAa,†
Lara K. Maxwell, DVM, PhD, DACVPb
Raymond E. Galinsky, PharmDc
David E. Moody, PhDd
Brenda M. Johnson, RVT, BSa
Wenfang B. Fang, PhDb

aDepartment of Veterinary Clinical Sciences
School of Veterinary Medicine
Purdue University
West Lafayette, IN 47907

bDepartment of Physiological Sciences
Center for Veterinary Health Sciences
Oklahoma State University
Stillwater, OK 74074

cDepartment of Industrial & Physical Pharmacy
School of Pharmacy and Pharmaceutical Sciences
Purdue University
West Lafayette, IN 47907

dCenter for Human Toxicology
Department of Pharmacology and Toxicology
College of Pharmacy
University of Utah
Salt Lake City, UT 84112

CLINICAL RELEVANCE

Pharmacokinetic analysis of buprenorphine administered to six healthy dogs via the oral transmucosal (OTM) route at doses of 20 and 120 µg/kg was conducted using liquid chromatography–electrospray ionization–tandem mass spectroscopy (LC-ESI-MS/MS). Bioavailability was 38% ± 12% for the 20 µg/kg dose and 47% ± 16% for the 120 µg/kg dose. Maximum plasma concentrations were similar for buprenorphine doses of 20 µg/kg IV and 120 µg/kg OTM. Sedation and salivation were common side effects, but no bradycardia, apnea, or cardiorespiratory depressive effects were seen. When the two OTM dosing rates were normalized to dose, LC-ESI-MS/MS analysis of buprenorphine and its metabolites detected no significant difference ($P > .05$), indicating dose proportionality. The results of this study suggest that OTM buprenorphine may be an alternative for pain management in dogs.

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†Correspondence should be sent to Dr. Ko: phone, 765-496-9329; email, jcko@purdue.edu.
The objectives of this study were to: (1) evaluate the pharmacokinetics of buprenorphine and its metabolites in dogs following doses of 20 µg/kg IV and 20 and 120 µg/kg OTM; (2) compare the pharmacokinetic profiles of 20 and 120 µg/kg doses of OTM buprenorphine; (3) establish the use of the LC-ESI-MS/MS method for measuring concentrations of buprenorphine and its metabolites in dogs; and (4) evaluate administration of buprenorphine at 20 and 120 µg/kg IV and 20 and 120 µg/kg OTM for obvious dose-related side effects.

**MATERIALS AND METHODS**

The Purdue Animal Care and Use Committee approved this study. Eight healthy 2-year-old purpose-bred mixed-breed research dogs weighing 14.1 ± 1.4 kg (mean ± SD) were used. The dogs were individually housed indoors with a 12-hour light–dark cycle in a climate-controlled environment. The dogs were acclimated to their housing for at least 1 month before the start of the study. They were fed a commercial dry diet, and water was available at all times.

Each dog received each of the four treatments in a randomized crossover design. The treatments consisted of buprenorphine (0.3 mg/ml injectable formulation, Abbott Laboratories) administered at two doses and using two routes:

- 20 µg/kg IV
- 20 µg/kg OTM
- 120 µg/kg IV
- 120 µg/kg OTM

Analgesic studies in dogs have shown that buprenorphine administered at 20 µg/kg IV or IM is effective in treating pain. However, the pharmacokinetic profile of this dose in dogs has not been reported. Currently, the OTM bioavailability of buprenorphine in dogs is unknown. Also unknown is whether the dose of OTM buprenorphine affects bioavailability in dogs. A specific liquid chromatography–electrospray ionization–tandem mass spectrometry (LC-ESI-MS/MS) method has recently been developed to precisely determine human plasma buprenorphine and its metabolites norbuprenorphine (NorBUP), buprenorphine-3-glucuronide (B-3-G), and norbuprenorphine-3-glucuronide (N-3-G). The use of this assay should provide specific insight on the pharmacokinetic profile of buprenorphine and its metabolites in dogs.
A washout period of 2 weeks was observed between treatments. The OTM doses were selected based on the published studies of a dose of 20 µg/kg IM used clinically to treat pain in dogs and the reported excessively low oral bioavailability of buprenorphine (3% to 6%) at doses of 3.45 to 4.11 mg/kg in two dogs. Therefore, a sixfold higher dose was selected to explore the OTM bioavailability compared with the clinical dose of 20 µg/kg IM. Because of financial considerations associated with the LC-ESI-MS/MS assay, the pharmacokinetic analysis in this study was based on plasma samples from six dogs receiving buprenorphine at 20 µg/kg IV, 20 µg/kg OTM, and 120 µg/kg OTM. Plasma samples from the 120 µg/kg IV group were collected and retained for future comparisons. For the remaining study assessments, all eight dogs were used and treated identically in the four treatment groups, including blood sampling, cardiorespiratory and behavioral observations, and saliva pH measurements. Although cardiorespiratory and behavioral data were collected, only obvious side effects are reported here; the remaining details will be reported in a separate article.

On each study day, food was withheld for 12 hours before anesthesia; water was available at all times. Each dog was facemask-induced with sevoflurane (SevoFlo, Abbott Animal Health, Abbott Park, IL) delivered in 100% oxygen and then orotracheally intubated for maintenance on sevoflurane in oxygen. For all dogs, the neck was clipped over either jugular vein, and the area was aseptically prepared. A single-lumen jugular catheter (Arrow International, Reading, PA) was placed in the jugular vein, sutured in place, and bandaged with 4-inch cotton and elastic bandage material; an intravenous catheter was then placed in the opposite cephalic vein. After both catheters were placed, dogs were allowed to recover from anesthesia. One hour after the end of anesthesia, when dogs were completely recovered, baseline blood samples (time zero) were collected and buprenorphine treatment initiated. OTM buprenorphine was drawn into a syringe and delivered into the dog’s cheek pouch over 1 to 3 minutes to avoid overspill or swallowing by the dogs. IV buprenorphine was administered into the preplaced cephalic catheter as a bolus over 1 minute; the catheter was immediately flushed with saline.

Blood samples were collected at 0 (baseline sample), 1, 6, 15, 30, and 45 minutes (0.017, 0.1, 0.25, 0.5, and 0.75 hour, respectively) and 1, 2, 4, 6, 8, 12, 16, and 20 hours after buprenorphine administration. At each time point, 1 ml of blood was removed from the jugular catheter into a syringe and an additional 3 ml of blood was subsequently removed from the jugular catheter and placed in a heparinized tube. The first 1 ml of blood was returned to the jugular catheter, followed by 9 ml of balanced electrolyte fluids (Normosol-R, Hospira, Lake Forest, IL) to replace the blood volume. Beginning at the 1-hour sample collection, the jugular catheter was flushed with 1 ml of heparinized saline after administration of the replacement fluids to prevent clotting between sampling times. The blood was handled at room temperature and centrifuged immediately. The plasma was removed immediately after centrifugation, placed in a single microcentrifuge plastic container, and stored at −80°C until analysis.

Before each blood sample was collected, heart rate, respiratory rate, and rectal temperature were measured. Physiologic responses to buprenorphine, including salivation, urination, defecation, excitement, interest in food, nausea, and/or regurgitation, were closely observed. For all treatment groups, saliva pH of the oral cavity was measured at baseline and 1 hour after administration of buprenorphine using a pH indicator strip (Color pHast, EMD Chemicals, Gibbstown, NJ).
Plasma Buprenorphine Analysis

Determination of buprenorphine and its metabolites (NorBUP, B-3-G, and N-3-G) was performed using a modification of the LC-ESI-MS/MS method described by Huang et al. One major modification was the replacement of morphine-3-glucuronide as the internal standard with BUP-d₄ and Nor-BUP-d₃ for B-3-G and N-3-G, respectively. The second major modification was to change monitoring of NorBUP to its acetonitrile adduct (the respective transitions for NorBUP acetonitrile adduct and its internal standard were mass:charge ratio [m/z] 455 to 414 and 458 to 417). The instrument used imparts greater sensitivity for this analyte. The method has a lower limit of quantitation (LLOQ) of 0.1 ng/ml for all four analytes.

Before samples from this study were analyzed, intra-run accuracy and precision in the canine plasma matrix were validated from analysis of three concentrations of quality controls (QCs; n = 5/concentration) prepared in pooled canine plasma and the LLOQ (n = 1 for each of six different matrix sources) in a single analytic batch. The canine plasma used for this experiment and other calibrators and QCs was from a commercial source (BioChemmed, Winchester, VA). Calibrators (from 0.1 to 50 ng/mL) were also prepared in canine plasma. For the intra-run precision and accuracy experiment, LLOQ samples had a mean result within 18.0% of target and a percent coefficient of variation (%CV) within 14.7%. The results of other QCs were within 8.0% of target, with %CVs within 6.7%. Canine plasma calibrators and canine plasma QCs were used for all analyses; a total of 23 QCs were run, and their mean results were within 11.8% of target, with %CVs within 11.8%. All samples were run in duplicate.

During sample analysis, only results within the calibration range were used. Those less than the LLOQ were reported as <LLOQ and converted to zero for pharmacokinetic analysis. Any sample with a concentration greater than the upper calibrator was reanalyzed after dilution.

Pharmacokinetic and Statistical Analysis

The concentration versus time data for buprenorphine and its metabolites were analyzed by both compartmental and noncompartmental methods. The data obtained after IV buprenorphine administration were weighted by the reciprocal of the buprenorphine concentration. The two- and three-compartment models using WinNonlin (Pharsight, Mountain View, CA) were fit to the data. The most appropriate model was chosen using Akaike’s information criterion. Standard compartmental equations were then used to estimate the pharmacokinetic parameters for each dog. OTM data were analyzed noncompartmentally. The maximum plasma concentration (C_{max}) and time to C_{max} (T_{max}) were estimated directly from the buprenorphine and metabolite concentration data. The area under the plasma concentration versus time curve (AUC) was determined as the sum of linear trapezoids to the last quantifiable analyte concentration (AUC_{t}), and the AUC extrapolated to infinity (AUC_{∞}) was calculated using the estimated elimination rate. Bioavailability (F) of both doses of OTM buprenorphine was calculated by normalizing the AUC_{∞} to dose and using the formula F (%) = (AUC_{∞}/AUC_{dose}) × 100.

The calculation of bioavailability following ex-
travascular drug administration using the ratio of \( \text{AUC}_{\text{extravascular}} : \text{AUC}_{\text{intravascular}} \) assumes that the total body clearance of the drug is constant between the two doses. Because this assumption is not always met, as in the case of saturable elimination, dose proportionality between doses must be assumed or tested. In this study, the pharmacokinetics of two different dose rates of OTM buprenorphine (20 and 120 µg/kg) were determined to test dose proportionality. Since the dose-normalized AUC and \( C_{\text{max}} \) did not differ significantly from one another, the pharmacokinetics appear to be dose proportional between doses of 20 and 120 µg/kg in dogs. This supports the use of a single IV dose for determination of bioavailability from both OTM dose rates.

The AUC and \( C_{\text{max}} \) from the two OTM dosing rates were normalized to the dose and compared for dose proportionality using a paired difference \( t \)-test. The significance level was set at \( P < .05 \).

## RESULTS

### Pharmacokinetics

Pharmacokinetic data generated after administration of buprenorphine are presented in Tables 1 and 2. The mean plasma concentrations of buprenorphine versus time after IV and OTM administration are shown in Figures 1 through 3. The three assayed metabolites of buprenorphine were quantifiable for only a short duration in all but the high-dose OTM group. The number of time points with quantifiable analytes was as follows (range, mean):

- **20 µg/kg IV**
  - NorBUP: 4 to 7, 5.3
  - B-3-G: 1 to 7, 3.7
  - N-3-G: 0 to 6, 2.2
- **20 µg/kg OTM**
  - NorBUP: 3 to 6, 4.8
  - B-3-G: 0 to 1, 0.2
  - N-3-G: 0 to 6, 3.0

Therefore, only the metabolite data from the 120 µg/kg OTM treatment group are reported.

A three-compartment model best described the IV data, and buprenorphine could be quantified up to the 16th hour after administration for all six dogs assayed (Figure 1). After OTM administration, plasma concentration of buprenorphine quickly increased over time.

### Table 1. Pharmacokinetic Parameters* for Buprenorphine after a Single Intravenous Dose at 20 µg/kg in Six Dogs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (ng/ml)</td>
<td>0.7 ± 0.3</td>
</tr>
<tr>
<td>B (ng/ml)</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>C (ng/ml)</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (ng/ml)</td>
<td>19.0 ± 4.9</td>
</tr>
<tr>
<td>( V_c ) (L/kg)</td>
<td>1.0 ± 0.3</td>
</tr>
<tr>
<td>( V_{\text{diso}} ) (L/kg)</td>
<td>9.5 ± 1.9</td>
</tr>
<tr>
<td>Cl (ml/min/kg)</td>
<td>24 ± 5</td>
</tr>
<tr>
<td>( t_{1/2\alpha} ) (hr)</td>
<td>0.05 ± 0.03</td>
</tr>
<tr>
<td>( t_{1/2\beta} ) (hr)</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>( k_{10} ) (hr(^{-1}))</td>
<td>9.4 ± 3</td>
</tr>
<tr>
<td>( k_{12} ) (hr(^{-1}))</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>( k_{31} ) (hr(^{-1}))</td>
<td>6.4 ± 5.3</td>
</tr>
<tr>
<td>( k_{31} ) (hr(^{-1}))</td>
<td>5.8 ± 3.5</td>
</tr>
<tr>
<td>( k_{31} ) (hr(^{-1}))</td>
<td>1.1 ± 0.5</td>
</tr>
<tr>
<td>( k_{31} ) (hr(^{-1}))</td>
<td>0.13 ± 0.06</td>
</tr>
<tr>
<td>( \text{AUC}_t ) (ng × hr/ml)</td>
<td>13.5 ± 2.5</td>
</tr>
<tr>
<td>( \text{AUC}_\infty ) (ng × hr/ml)</td>
<td>15.3 ± 2.7</td>
</tr>
<tr>
<td>MRT (hr)</td>
<td>6.7 ± 1.4</td>
</tr>
</tbody>
</table>

*Values are expressed as the mean (or harmonic mean) ± SD.

\( A = \) coefficient of rapid distribution phase (coefficients have been normalized to dose); \( B = \) coefficient of slow distribution phase; \( C = \) coefficient of elimination phase; \( C_{\text{max}} = \) maximum plasma concentration; \( V_c = \) apparent volume of the central compartment; \( V_{\text{diso}} = \) apparent volume of distribution at steady state; \( Cl = \) total body clearance; \( t_{1/2\alpha} = \) rapid distributional half-life; \( t_{1/2\beta} = \) slow distributional half-life; \( t_{1/2\gamma} = \) elimination half-life; \( k = \) intercompartmental rate transfer term; \( \text{AUC}_t = \) area under the plasma drug concentration versus time curve to last quantifiable analyte concentration; \( \text{AUC}_\infty = \) \( \text{AUC} \) extrapolated to infinity; \( \text{MRT} = \) mean residence time.
any of the treatment groups at any time during the study. Sedation and salivation were two of the most common side effects observed following both IV and OTM administration of 20 and 120 µg/kg of buprenorphine. There were no other significant behavioral side effects, such as dysphoria, observed in any of the treatment groups. The baseline pH of the dogs’ saliva in this study was 9 to 10. Administration of buprenorphine via the OTM route did not change the saliva pH, as it remained in the same 9 to 10 range at 1 hour after administration of OTM buprenorphine. All dogs recovered well at the end of study.

**DISCUSSION**

The bioavailability of oral opioids is generally poor in dogs. For example, bioavailability of both extended-release and traditional tablet formulations of morphine is 5% to 17% in

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**TABLE 2. Pharmacokinetic Parameters* for Buprenorphine (Bup) and Its Metabolites (NorBUP, B-3-G, N-3-G) after a Single Oral Transmucosal (OTM) Dose of Buprenorphine at 20 and 120 µg/kg in Six Dogs**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>20 µg/kg OTM</th>
<th>120 µg/kg OTM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bup</td>
<td>Bup</td>
</tr>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/ml)</td>
<td>2.2 ± 0.3</td>
<td>19.5 ± 9.6</td>
</tr>
<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; (hr)</td>
<td>0.7 ± 0.2</td>
<td>0.5 ± 0.3</td>
</tr>
<tr>
<td>T&lt;sub&gt;last&lt;/sub&gt; (hr)</td>
<td>8 ± 2.5</td>
<td>20 ± 0</td>
</tr>
<tr>
<td>Terminal t&lt;sub&gt;1/2&lt;/sub&gt; (hr)</td>
<td>7.1± 1.2</td>
<td>8.7± 1.7</td>
</tr>
<tr>
<td>MRT (hr)</td>
<td>5.3 ± 0.2</td>
<td>6.4 ± 0.7</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;C&lt;/sub&gt; (ng/hr/ml)</td>
<td>4.2 ± 0.8</td>
<td>38.2 ± 14.1</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;∞&lt;/sub&gt; (ng/hr/ml)</td>
<td>5.3 ± 0.7</td>
<td>48.1 ± 15.0</td>
</tr>
<tr>
<td>F (%)</td>
<td>38 ± 12</td>
<td>47 ± 16</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;t(terminal)/AUC&lt;sub&gt;t(bup)</td>
<td>0.22 ± 0.12</td>
<td></td>
</tr>
<tr>
<td>AUC&lt;sub&gt;t(terminal)/AUC&lt;sub&gt;t(bup)</td>
<td>0.10 ± 0.05</td>
<td>0.09 ± 0.15</td>
</tr>
</tbody>
</table>

*Values are expressed as the mean (or †harmonic mean) ± SD.

C<sub>max</sub> = maximum observed plasma concentration; T<sub>max</sub> = time to C<sub>max</sub>; T<sub>last</sub> = time of last quantifiable plasma analyte concentration; terminal t<sub>1/2</sub> = terminal phase half-life; MRT = mean residence time; AUC<sub>C</sub> = area under the plasma drug concentration versus time curve to last quantifiable analyte concentration; AUC<sub>∞</sub> = AUC extrapolated to infinity; F = bioavailability.
dogs, presumably a result of the extensive hepatic and extra-hepatic first-pass extraction of morphine. Similarly, the bioavailability of oral buprenorphine has been shown to be only 3% to 6% in dogs. In contrast, our results showed that the injectable formulation of buprenorphine (0.3 mg/ml) administered OTM had a bioavailability of 38% ± 12% at a dose of 20 µg/kg and 47% ± 16% at 120 µg/kg. This is in agreement with human studies in which OTM bioavailability ranged from 28% to 55%. A recent study demonstrated that a sublingual spray of buprenorphine at a dose of approximately 30 µg/kg resulted in a bioavailability of 22% in four dogs. The formulation of the alcohol-based buprenorphine spray was different from that used in the study reported here, which could account for the differences in results between the two studies. Nevertheless, the results of the current study together with the sublingual spray study demonstrate that a higher bioavailability can be achieved in dogs with OTM administration than the reported 3% to 6% achieved via the oral–gastric route. In addition, the current results demonstrated that the OTM bioavailability was similar in the two treatment groups, despite the sixfold difference in doses. However, as expected, the duration of effect with

**Figure 1.** Mean (±SD) plasma concentration of buprenorphine versus time after a single 20 µg/kg dose administered IV to six healthy dogs.

**Figure 2.** Mean (±SD) plasma concentration of buprenorphine versus time after a single 20 µg/kg dose administered via the oral transmucosal (OTM) route to six healthy dogs.
saliva pH presented interesting results. One study found that the bioavailability of the buprenorphine tablet was approximately 50% of that of liquid buprenorphine and was not affected by saliva pH. Another study found that increased saliva pH correlated with decreased recovery from saliva, and bioavailability of sublingual buprenorphine in human volunteers was approximately 30%. Sublingual exposure times ranged from 3 to 5 minutes, with equivalent results. The effect of exposure time on sublingual absorption and subsequent bioavailability was also evaluated in a separate human study, with no difference in the percentage of buprenorphine absorbed across the oral mucous membrane noted between the 2.5- and 10-minute holding times.

In the current study, the dogs’ saliva pH was measured before and 1 hour after OTM buprenorphine administration. Saliva pH did not change with OTM buprenorphine administration, remaining at 9 to 10 at 1 hour after administration. Because buprenorphine is a weak base (having a pKₐ of 8.24), saliva pH plays a role in OTM absorption. In the alkaline saliva environment of these dogs, buprenorphine would be primarily non-ionized, enhancing its lipophilicity and thereby facilitating the absorption of buprenorphine molecules across the oral–buccal–lingual mucosa membrane lipid bilayers and, thus, entry into the bloodstream.

Studies have shown that buprenorphine absorption can be successfully achieved through nonspecific placement of buprenorphine either on or beneath the tongue or into the cheek.

**Figure 3:** Mean (±SD) plasma concentration of buprenorphine and its metabolites versus time after a single 120 µg/kg dose administered via the oral transmucosal (OTM) route to six healthy dogs.

Metabolites of Buprenorphine Were Most Quantifiable in the High-Dose OTM Group

<table>
<thead>
<tr>
<th>Plasma Analyte Concentration (ng/ml)</th>
<th>0.1</th>
<th>1</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Buprenorphine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Norbuprenorphine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Buprenorphine-3-glucuronide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Norbuprenorphine-3-glucuronide</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Figure 3.** Mean (±SD) plasma concentration of buprenorphine and its metabolites versus time after a single 120 µg/kg dose administered via the oral transmucosal (OTM) route to six healthy dogs.
Our study demonstrated that buprenorphine can be successfully absorbed into the bloodstream via a nonspecific cheek pouch delivery method.

7.5 ± 4.2 minutes after 20 µg/kg OTM and 1 ± 0 minute after 120 µg/kg OTM and reached T_{max} at 0.7 ± 0.2 hour (42 ± 12 minutes) and 0.5 ± 0.3 hour (30 ± 12 minutes), respectively. Based on these results, our study demonstrated that buprenorphine can be successfully absorbed into the bloodstream via a nonspecific cheek pouch delivery method. This claim is further supported by T_{max} values that are in agreement with those previously reported (33.6 ± 7.8 minutes) in the buprenorphine sublingual spray study in dogs.\(^2\) The C_{max} of buprenorphine after 20 µg/kg OTM was 2.2 ± 0.3 ng/ml in the current study, which is similar to the C_{max} of 1.87 ng/ml reported after administration of 30 µg/kg buprenorphine as a sublingual spray.\(^2\)

In the current study, although the C_{max} achieved after administration of 20 µg/kg OTM is lower than that achieved with the same dose IV, it is interesting to note that C_{max} of the 20 µg/kg IV and 120 µg/kg OTM doses are nearly identical. This finding is important because most clinical analgesic studies in dogs\(^4\)-\(^{10}\) use 10 to 30 µg/kg of buprenorphine administered parenterally for pain management. The C_{max} of 120 µg/kg OTM in the current study provides a platform for future plasma buprenorphine concentration–analgesia comparison studies in dogs. The results of the current study indicate that by using a buprenorphine dose of 120 µg/kg OTM in dogs, it is possible to achieve a buprenorphine plasma concentration similar to that achieved with a dose of 20 µg/kg IV.

To date, bioavailability studies on buprenorphine in companion animals have been limited to cats.\(^7\),\(^{16}\) These studies employed immunoassay methods that measure a combined total of buprenorphine immunoequivalents (the combined measurement of buprenorphine and a percentage of metabolites based on their respective cross-reactivity with the antibody used). The methodology for measuring the plasma concentration of buprenorphine in this canine study is different; the LC-ESI-MS/MS is more selective at distinguishing between the parent buprenorphine compound and the metabolites.\(^{11}\) This provides two advantages over the previous studies.\(^7\),\(^{16}\) First, bioavailability was determined based on the specific measurement of buprenorphine, and second, some extent of buprenorphine metabolism in dogs was measured. The calculated bioavailability in
these dogs after OTM administration was much lower than that previously reported in cats, in which bioavailability exceeding 100% was estimated after OTM administration. This drastic difference in OTM bioavailability was more likely attributed to the assay selectivity of the LC-ESI-MS/MS versus the radioimmunoassay rather than species variation. This is based on a sibling study in cats using OTM buprenorphine dosages and assay method identical to those used in this study, which yielded bioavailability of 40% to 50%, not 100% as reported in the other studies.7,16

The three main metabolites of buprenorphine detected in humans, NorBUP, B-3-G, and N-3-G, were also detected in this study. Examination of the plasma metabolic ratios (AUC_{metal}:AUC_{buprenorphine}) from the data presented here and that presented by Huang et al11 provides evidence that buprenorphine was less extensively metabolized in dogs than in humans. The respective metabolic ratios for dogs and humans11 are NorBUP:buprenorphine, 0.09 (dogs) and 2.73 (humans); B-3-G: buprenorphine, 0.08 and 0.79; and N-3-G: buprenorphine, 0.19 and 9.84. In humans, buprenorphine dealkylation to NorBUP is the primary route of oxidative metabolism, but hydroxylation of the alkyl hydroxyl chain and the aromatic rings has also been described.19,20 It is possible that buprenorphine is also extensively metabolized in dogs but at other sites, such as the hydroxylation sites identified in humans. These buprenorphine metabolites may play a different role in the clinical efficacy and in the differing durations of action between dogs and humans. NorBUP has been shown to be an active metabolite.21 In a study in mice, NorBUP has a higher efficacy than buprenorphine at the µ receptor but has less potency.21 At this time, the clinical implication of these active metabolites in dogs is unknown and requires further investigation.

CONCLUSION

The results of this study demonstrated that (1) bioavailabilities of 38% ± 12% and 47% ± 16% were achieved in dogs after doses of 20 and 120 µg/kg OTM buprenorphine, respectively; (2) OTM buprenorphine bioavailability was not significantly different with a sixfold increase in dose rate; (3) similar C_{max} can be achieved with buprenorphine at doses of 20 µg/kg IV and 120 µg/kg OTM; (4) sedation and salivation were common side effects; (5) canine saliva pH was 9 to 10 and did not change after OTM buprenorphine administration; (6) no bradycardia, apnea, or delayed cardiorespiratory depressive effects were observed after either IV or OTM buprenorphine at doses up to 120 µg/kg in dogs; (7) LC-ESI-MS/MS can be used to measure buprenorphine and its metabolites in dogs; and (8) buprenorphine is less extensively metabolized to produce NorBUP and the glucuronide metabolites of buprenorphine and NorBUP in dogs than in humans.

REFERENCES


