OBJECTIVE
To evaluate the pharmacokinetics of hydrocodone (delivered in combination with acetaminophen) and tramadol in dogs undergoing tibial plateau leveling osteotomy (TPLO).

ANIMALS
50 client-owned dogs.

PROCEDURES
Dogs were randomly assigned to receive tramadol hydrochloride (5 to 7 mg/kg, PO, q 8 h; tramadol group) or hydrocodone bitartrate–acetaminophen (0.5 to 0.6 mg of hydrocodone/kg, PO, q 8 h; hydrocodone group) following TPLO with standard anesthetic and surgical protocols. Blood samples were collected for pharmacokinetic analysis of study drugs and their metabolites over an 8-hour period beginning after the second dose of the study medication.

RESULTS
The terminal half-life, maximum serum concentration, and time to maximum serum concentration for tramadol following naïve pooled modeling were 1.56 hours, 155.6 ng/mL, and 3.90 hours, respectively. Serum concentrations of the tramadol metabolite O-desmethyltramadol (M1) were low. For hydrocodone, maximum serum concentration determined by naïve pooled modeling was 7.90 ng/mL, and time to maximum serum concentration was 3.47 hours. The terminal half-life for hydrocodone was 15.85 hours, but was likely influenced by delayed drug absorption in some dogs and may not have been a robust estimate. Serum concentrations of hydromorphone were low.

CONCLUSIONS AND CLINICAL RELEVANCE
The pharmacokinetics of tramadol and metabolites were similar to those in previous studies. Serum tramadol concentrations varied widely, and concentrations of the active M1 metabolite were low. Metabolism of hydrocodone to hydromorphone in dogs was poor. Further study is warranted to assess variables that affect metabolism and efficacy of these drugs in dogs. (Am J Vet Res 2015;76:763–770)

Tramadol hydrochloride is a synthetic opioid with weak μ-opioid receptor affinity.1 The drug also acts as a serotonin and norepinephrine reuptake inhibitor,1,2 which leads to antinociceptive effects at the spinal level. There are several known metabolites of tramadol in various species, including humans and dogs.1,3 The main metabolites discussed in dogs include O-desmethyltramadol (M1), N-desmethy tramadol (M2), and N,O-didesmethyltramadol (M5). The metabolite M1 has pharmacological effects as a high-affinity μ-opioid receptor agonist in humans,1,3 whereas M2 and M5 are considered inactive metabolites in several species.1 In studies5–7 where circulating M2 and M5 concentrations were assessed in dogs following oral tramadol administration, these were reportedly higher than tramadol or M1 concentrations. Only a few studies5–8 have been conducted to evaluate the pharmacokinetics of tramadol following oral administration in dogs, and to our knowledge, no such studies have included a heterogeneous canine population in a clinical setting.

Hydrocodone bitartrate is also a μ-opioid receptor agonist analgesic and is metabolized in part to hydromorphone in many species, including dogs.9 In recent pharmacokinetic study10 in healthy Greyhounds that received hydrocodone-acetaminophen (0.5 mg of hydrocodone/kg, once), hydrocodone and hydro-
morphine were detected in plasma at concentrations thought to be clinically useful (> 1.6 ng/mL for each through 8 hours after administration).

To our knowledge, the pharmacokinetics of hydrocodone and tramadol has not been evaluated in a heterogenous population of dogs undergoing surgery. The purpose of the study reported here was to determine the pharmacokinetics of hydrocodone (delivered as hydrocodone-acetaminophen) and tramadol administered orally in multiple doses to a heterogenous population of dogs following TPLO. We hypothesized that both drugs would be metabolized to active compounds; that serum concentrations of tramadol would vary widely, with metabolites similar to previously described circulating concentrations in dogs (including low M1 and high M2 and M5 concentrations)\(^1\)\(^2\); and that hydrocodone metabolism would result in serum hydromorphone concentrations > 2 ng/mL, which has been a concentration previously accepted\(^11\)\(^12\) to provide clinical analgesia.

**Materials and Methods**

**Animals**

Fifty client-owned dogs weighing > 10 kg and admitted to Kansas State University Veterinary Health Center for unilateral TPLO as treatment for cranial cruciate ligament rupture were enrolled in the study, which was performed with approval from the university’s IACUC and in accordance with applicable animal use regulations. Written informed consent was obtained from owners prior to enrollment of dogs in the study. Clinical data from these dogs were included in a pharmacodynamic study, which was conducted simultaneously by our research group.\(^13\)

Any NSAIDs were required to have been discontinued ≥ 24 hours prior to preoperative examination for study enrollment. All dogs were randomly assigned\(^13\) to receive either hydrocodone bitartrate-acetaminophen\(^2\) (hydrocodone group) or tramadol hydrochloride\(^2\) (tramadol group) at predetermined time points after surgery.

**Anesthesia and surgery**

Morphine (0.3 to 0.5 mg/kg, SC) was administered with acepromazine (0.01 to 0.06 mg/kg, SC) or midazolam (0.2 mg/kg, SC) prior to induction of anesthesia with propofol (2 to 7 mg/kg, IV, to effect). Anesthesia was maintained with isoflurane delivered via endotracheal tube with 30 mL of oxygen/kg/min. Perioperative decisions regarding treatment were made by the clinician responsible for the case; patients were removed from the study if changes to the predetermined protocol were needed. The TPLO was performed as described elsewhere.\(^13\)\(^14\) All dogs received an intra-articular injection of 0.5% bupivacaine (0.5 to 1.5 mg/kg) in the affected joint prior to the end of the surgery. All patients were monitored after surgery. Morphine (0.25 to 0.5 mg/kg, SC, once) was administered immediately following surgery or up to 4 hours after extubation from the surgical procedure, depending on postoperative recovery progress.\(^13\)

**Administration of study drugs**

Patients were judged to be awake, alert, and able to swallow and stand without difficulty before the first dose of study drug was given; thus, the timing of the first dose varied among dogs. Oral administration of the assigned test medication (hydrocodone-acetaminophen\(^2\) [0.5 to 0.6 mg of hydrocodone/kg] or tramadol\(^2\) [5 to 7 mg/kg]) continued at 8-hour intervals until discharge from the hospital. Postoperative administration of morphine did not affect the timing of oral drug administration, but the study treatments were not commenced before the end of the 4-hour time period for injectable morphine administration.

**Blood sample collection and rescue analgesia protocol**

For pharmacokinetic analysis, approximately 2 to 3 mL of venous blood was collected by venipuncture from a jugular or peripheral (cephalic or saphenous) vein by a surgical staff member at predetermined times following the second dose of study medication. Samples were transferred into nonheparinized tubes and centrifuged. The serum was collected and stored in polypropylene vials at −80°C until the serum drug concentrations were determined.

The IACUC-approved study protocol allowed for collection of up to 5 blood samples/patient (1 sample at each of 5 time points) after surgery. Pharmacokinetic analysis was performed with a series of blood samples obtained at collection times staggered across the study population at 0, 15, 30, and 45 minutes and 1, 2, 4, 6, and 8 hours after the second oral dose of the study analgesic (start of the pharmacokinetic study). Prior to each blood sample collection, each patient was evaluated for signs of pain by a trained investigator (MEB) using a modified Glasgow composite measure pain scale\(^15\) as part of the concurrent study.\(^13\)

Briefly, a score ≥ 6 for mobile dogs (range of possible scores, 0 to 24) or ≥ 5 for dogs in which mobility could not be assessed (range of possible scores, 0 to 20) required intervention with rescue analgesic treatment (morphine, 0.25 to 0.5 mg/kg, SC). An additional 2- to 3-mL venous blood sample was obtained at time of rescue intervention (before rescue morphine administration) to determine serum drug concentration at time of treatment failure. These patients were not excluded from further study drug administration, blood sample collection, and pharmacokinetic analysis, regardless of when rescue drug treatment was given.

**Drug concentrations**

Serum drug concentrations were determined by means of liquid chromatography with triple quadrupole mass spectrometry according to published methods.\(^7\)\(^10\) Standard curves for serum tramadol and its primary metabolites in dogs (M1, M2, and M5) were linear for concentrations from 1 to 500 ng/mL and were
accepted if the measured concentrations were within 15% of the actual concentrations. Accuracy (measured concentration/actual concentration) of the assay for tramadol was 102%, 103%, and 95% and the coefficient of variation was 5%, 1%, and 3% on replicates of 5 at 1, 10, and 500 ng/mL, respectively. Accuracy of the assay for M1 was 103%, 97%, and 104% and the coefficient of variation was 5%, 4%, and 3% on replicates of 5 at 1, 10, and 500 ng/mL, respectively. Accuracy of the assay for M2 was 94%, 100%, and 96% and the coefficient of variation was 10%, 4%, and 4% on replicates of 5 at 1, 10, and 500 ng/mL, respectively. Accuracy of the assay for M5 was 101%, 92%, and 108% and the coefficient of variation was 5%, 4%, and 4% on replicates of 5 at 1, 10, and 500 ng/mL, respectively.

Standard curves for serum hydrocodone and hydromorphone were linear for concentrations from 1 to 100 ng/mL and were accepted if the measured concentrations were within 15% of the actual concentrations. Accuracy of the assay for hydrocodone was 97%, 102%, and 106% and the coefficient of variation was 2%, 4%, and 5% on replicates of 5 at 1, 10, and 100 ng/mL, respectively. Accuracy of the assay for hydromorphone was 106%, 98%, and 104% and the coefficient of variation was 1%, 2%, and 5% on replicates of 5 at 1, 10, and 100 ng/mL, respectively.

**Pharmacokinetic analysis**

Naïve pooled pharmacokinetic analysis was performed with computer software in a 1-compartment first-order model with absorption, no lag time, and first-order elimination. Uniform weighting was used. Pharmacokinetic modeling was performed for the second dose; therefore, all parameters were relative to the second dose. Population pharmacokinetic modeling of tramadol was performed with computer software in a 1-compartment first-order model with absorption, no lag time, and first-order elimination. Model equations for the primary model parameters were as follows:

\[
V_F = V_F_\theta \cdot (V_F_\eta)
\]
\[
K_{01} = K_{01_\theta} \cdot (K_{01_\eta})
\]
\[
K_{10} = K_{10_\theta} \cdot (K_{10_\eta})
\]

where \(V_F\), \(V_F_\eta\), and \(V_F_\theta\) are volume of distribution per fraction of the dose absorbed, the \(V_F\) fixed effect, and the \(V_F\) random effect, respectively; \(K_{01}\), \(K_{01_\eta}\), and \(K_{01_\theta}\) are the absorption rate constant, the \(K_{01}\) fixed effect, and the \(K_{01}\) random effect, respectively; \(K_{10}\), \(K_{10_\eta}\), and \(K_{10_\theta}\) are the elimination rate constant, the \(K_{10}\) fixed effect, and the \(K_{10}\) random effect, respectively; and \(\theta\) is base of the natural logarithm.

**Results**

Two dogs (1 in each treatment group) were removed from the study because of changes in the anesthetic protocol or resistance to handling in the postoperative period. Most of the remaining dogs were mixed breeds (n = 16) or Labrador Retrievers (11). The study population also included Golden Retrievers (n = 4); Rottweilers, Boxers, and German Shepherd Dogs (2 each); and German Shorthair Pointer, Chesapeake Bay Retriever, English Pointer, Great Dane, Great Pyrenees, Doberman Pinscher, English Springer Spaniel, Giant Schnauzer, Siberian Husky, Saint Bernard, and Viszla (1 each). Mean ± SD age (5.3 ± 2.6 years vs 4.8 ± 2.2 years, respectively) and body weight (34.4 ± 7.85 kg vs 37.5 ± 11.79 kg, respectively) did not differ significantly between the hydrocodone and tramadol groups. The mean ± SD dose of hydrocodone

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**Figure 1**—Actual (circles) and predicted (line) serum concentrations of tramadol in 24 of 25 client-owned dogs that received tramadol hydrochloride (mean ± SD dose, 5.85 ± 0.61 mg/kg) orally at 8-hour intervals after TPOLO. All dogs received morphine (0.25 to 0.5 mg/kg, SC) between 0 and 4 hours after surgery. The first dose of tramadol was given when dogs had recovered sufficiently to safely receive oral medication. Blood sample collection commenced following administration of the second dose of tramadol and was performed at 0, 15, 30, and 45 minutes and 1, 2, 4, 6, and 8 hours after this treatment. Owing to study protocol restrictions, each dog had up to 5 samples (≤1/time point) collected for the study. One dog in the group was removed from the study prior to sample collection. Time shown in the graph reflects time after the second dose of the drug.

**Figure 2**—Actual (circles) and predicted (line) serum concentrations of the tramadol metabolite M1 in the same 24 dogs as in Figure 1. See Figure 1 for remainder of key.
The serum concentration-time profiles of tramadol (population pharmacokinetic model) and metabolites M1 and M5 (naïve pooled pharmacokinetic model) after tramadol administration were shown graphically (Figures 1 and 2). The metabolite M2 was not modeled because serum concentrations continued to increase throughout the 8-hour sample collection interval. Associated pharmacokinetic parameters for tramadol (population and naïve pooled models) and metabolites M1 and M5 (naïve pooled model) were summarized (Tables 1 and 2). Mean concentrations of the tramadol, the active metabolite M1, and inactive metabolites M2 and M5 were illustrated (Figure 3). Inactive M2 and M5 metabolite concentrations far exceeded concentrations of the active M1 metabolite. The values predicted by population pharmacokinetic modeling were similar to those predicted by naïve-pooled pharmacokinetic modeling for tramadol, despite the different methods of analysis. On the basis of naïve-pooled results for tramadol, the t\textsubscript{1/2}, Cmax, and Tmax were approximately 4.67 hours, 4.6 ng/mL, and 2.82 hours, respectively. The inactive metabolite, M2, was found in high concentrations with no elimination or terminal phase noted; therefore, pharmacokinetic modeling was not performed.

A population pharmacokinetic model could be fit to the data of the parent compound tramadol after oral administration (Table 1). The mean t\textsubscript{1/2}, Cmax, and Tmax were approximately 1.58 hours (range, 0.78 to 3.93 hours), 195.0 ng/mL (range, 46.8 to 613.0 ng/mL), and 3.54 hours (range, 1.77 to 6.96 hours), respectively.

The serum concentration-time profile of hydrocodone after administration was graphed (Figure 4). The associated naïve pooled pharmacokinetic parameters of hydrocodone were summarized (Table 3). A population pharmacokinetic model could not be fit to the hydrocodone data. The hydromorphone metabolite was too infrequently measured to appropriately assess pharmacokinetic modeling.

Table 1—Predicted pharmacokinetic parameters for tramadol as determined by population pharmacokinetic and naïve pooled modeling following oral administration of the drug (mean ± SD dose, 5.85 ± 0.61 mg/kg) to 24 client-owned dogs after TPLO.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD (range)</th>
<th>Median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V/F (L/kg)</td>
<td>5.4 (4.4–5.4)</td>
<td>5.4 ± 0.4</td>
</tr>
<tr>
<td>K\textsubscript{s} (h\textsuperscript{-1})</td>
<td>0.2046 ± 0.1145 (0.0548–0.7611)</td>
<td>0.131 ± 0.0444</td>
</tr>
<tr>
<td>K\textsubscript{u} (h\textsuperscript{-1})</td>
<td>0.5579 ± 0.5657 (0.1762–0.8866)</td>
<td>0.444 ± 0.1145</td>
</tr>
<tr>
<td>AUC (h•ng/mL)</td>
<td>2.115 ± 1.926 (943–4811)</td>
<td>1.983 ± 1.606</td>
</tr>
<tr>
<td>Absorption half-life (h)</td>
<td>6.11 ± 6.05 (0.91–12.65)</td>
<td>5.30 ± 5.06</td>
</tr>
<tr>
<td>t\textsubscript{1/2} (h)</td>
<td>1.58 ± 1.23 (0.78–3.93)</td>
<td>1.56 ± 1.38</td>
</tr>
<tr>
<td>Cl/F (mL/min/kg)</td>
<td>150.92 ± 151.0 (46.8–613.0)</td>
<td>135.6 ± 135.0</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>3.54 ± 3.27 (1.77–6.96)</td>
<td>3.90 ± 3.74</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>195.0 ± 151.0 (46.8–613.0)</td>
<td>135.6 ± 135.0</td>
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</table>

Table 2—Predicted pharmacokinetic parameters after naïve pooled modeling for tramadol metabolites M1 and M5 in samples from the same 24 dogs as in Table 1.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>M1</th>
<th>M5</th>
</tr>
</thead>
<tbody>
<tr>
<td>V/F (L/kg)</td>
<td>742.51 ± 742.51</td>
<td>53.00 ± 53.00</td>
</tr>
<tr>
<td>K\textsubscript{s} (h\textsuperscript{-1})</td>
<td>0.696 ± 0.148</td>
<td>0.238 ± 0.192</td>
</tr>
<tr>
<td>K\textsubscript{u} (h\textsuperscript{-1})</td>
<td>0.148 ± 0.148</td>
<td>0.192 ± 0.192</td>
</tr>
<tr>
<td>AUC (h•ng/mL)</td>
<td>47.00 ± 47.00</td>
<td>510.00 ± 510.00</td>
</tr>
<tr>
<td>Appearance half-life (h)</td>
<td>1.00 ± 1.00</td>
<td>2.91 ± 2.91</td>
</tr>
<tr>
<td>Cl/F (mL/min/kg)</td>
<td>1835.80 ± 1835.80</td>
<td>169.70 ± 169.70</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>2.82 ± 2.82</td>
<td>4.67 ± 4.67</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>4.60 ± 4.60</td>
<td>39.90 ± 39.90</td>
</tr>
</tbody>
</table>

See Table 1 for key.
Because hydrocodone is commonly supplied in combination with other drugs such as homatropine and acetaminophen, it would be inadvisable to prescribe it at the dose used in the study by Findlay et al.16 At higher dosages, acetaminophen would have described its analgesic effects. If used with caution, however, it may be beneficial in certain settings.

Discussion

The present report described investigation of the pharmacokinetics of hydrocodone (delivered as hydrocodone bitartrate–acetaminophen) and of tramadol hydrochloride following oral administration to a diverse group of dogs that underwent a routine surgical procedure in a veterinary teaching hospital. Pharmacokinetic studies5–10 of hydrocodone and tramadol have previously been performed in healthy research dogs, which may not have been representative of the true clinical population of dogs. The first report8 on the metabolism of hydrocodone in several species, including 2 dogs, indicated that hydrocodone was metabolized to hydromorphone via O-demethylation when administered SC at a dose near 1.0 mg/kg. In addition, analgesic activities of the O-demethylated metabolites, including hydromorphone, were found to be significantly greater (2- to 7-fold difference) than that of hydrocodone; thus, these metabolites are likely to be an important factor in effectiveness of hydrocodone for analgesia in domestic species.9 Findlay et al16 examined the bioavailability and metabolism of hydrocodone administered orally at a dose equivalent to 3.1 mg of hydrocodone bitartrate/kg in a crossover study of 2 male Beagles from which food had been withheld for 16 hours prior to drug administration. The absolute bioavailability of hydrocodone in those 2 dogs was 44% and 34%, and plasma concentrations of free hydromorphone ranged from 17 to 24 ng/mL.16 Those concentrations were proportionally higher than the concentrations achieved in the clinical population of dogs in the present study; hydromorphone was infrequently detected in this study, with quantifiable concentrations found in only 3 dogs. With the exception of those 3 dogs, the approximate concentration of hydromorphone detected in the remaining samples in our study was ≤ 1.1 ng/mL throughout the 8-hour period after the second dose of hydrocodone (approx 0.5 mg of hydrocodone bitartrate/kg). The dose administered in the study by Findlay et al16 was nearly 6 times that given in the present study; and it is possible that use of a higher dose may influence serum hydromorphone concentrations and alter the metabolite profile by saturating other pathways shunting metabolism to produce detectable hydromorphone.

Figure 4—Actual (circles) and predicted (line) serum concentrations of hydrocodone in 24 of 25 client-owned dogs that received hydrocodone bitartrate–acetaminophen (mean ± SD dose, 0.51 ± 0.04 mg of hydrocodone/kg) orally at 8-hour intervals after TPLO. All dogs received morphine (0.25 to 0.3 mg/kg, SC) between 0 and 4 hours after surgery. The first dose of hydrocodone was given when dogs had recovered sufficiently to safely receive oral medication. Blood sample collection began following administration of the second dose of hydrocodone and was performed at 0, 15, 30, and 45 minutes and 1, 2, 4, 6, and 8 hours after this treatment. Each dog had up to 5 samples (≤ 1/time point) collected for the study. One dog in the group was removed from the study prior to sample collection. Time shown in the graph reflects time after the second dose of the drug.

Table 3—Predicted pharmacokinetic parameters for hydrocodone as determined by naïve pooled modeling following oral administration (mean ± SD dose, 0.51 ± 0.04 mg of hydrocodone/kg) to 24 client-owned dogs after TPLO.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>V/F (L/kg)</td>
<td>33.82</td>
</tr>
<tr>
<td>K1a (h–1)</td>
<td>0.921</td>
</tr>
<tr>
<td>K2a (h–1)</td>
<td>0.0437</td>
</tr>
<tr>
<td>AUC (h·ng/mL)</td>
<td>211.00</td>
</tr>
<tr>
<td>Absorption half-life (h)</td>
<td>0.75</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>15.85</td>
</tr>
<tr>
<td>Cmax (mL/min/kg)</td>
<td>24.70</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>3.47</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>7.90</td>
</tr>
</tbody>
</table>

See Table 1 for key.
after a single oral dose of hydrocodone bitartrate-acetaminophen (providing approx 0.5 mg of hydrocodone/kg) in 6 healthy Greyhounds; both hydrocodone and hydromorphone were detected in plasma, and a 6- to 8-hour dosing schedule was recommended. In that study, the mean Cmax of hydrocodone was 11.73 ng/mL with a Tmax of 0.74 hours, and the mean Cmax of hydromorphone was 5.2 ng/mL with a Tmax of 1.37 hours. Although serum hydromorphone concentrations in dogs of the present study were too low to determine pharmacokinetic parameters, it is worth noting that the mean Cmax of hydrocodone in the present study was 7.9 ng/mL with a mean Tmax of 3.47 hours. Although the Cmax values were comparable, the Tmax in the present study may have been influenced by recent anesthesia, rescue morphine administration in some dogs, and delays in gastrointestinal transit time in the heterogenous population of dogs that underwent orthopedic surgery.

Li et al. evaluated the metabolite profile of hydrocodone administered to dogs (number and breed not indicated) at a dose of 60 or 120 mg/d for a period of 13 weeks (body weight, dose in mg/kg, and dosing frequency were not described). Norhydrocodone and N-oxide metabolites of hydrocodone were the predominant metabolites. Hydromorphone and hydromorphone glucuronide were identified as minor metabolites.

Breed-specific differences in hydrocodone metabolism may occur in dogs. Previous pharmacokinetic studies of hydrocodone and tramadol in this species included small numbers of unanesthetized, healthy dogs that were evaluated after food withholding; these were homogenous groups of purpose-bred Beagles, mixed-breed dogs, or Greyhounds. Although no dogs were excluded on the basis of breed in the present study, no Beagles or Greyhounds were enrolled because none underwent TPLO at our facility during the study period. Despite this limitation, the breeds in this study represented a population of dogs in need of postoperative analgesic treatment following a routine surgical procedure at our hospital.

A population pharmacokinetic model could not be fit to the hydrocodone data in the present study. The lack of a model fit may have been attributable to various factors, including the sampling protocol (which was limited to 8 hours), the total number of samples, the variability of the data, the limited number of dogs in the study, or the effects of anesthesia and other analgesics on hydrocodone pharmacokinetics. Further studies including a larger number of dogs with a longer or more frequent blood-sampling protocol may be able to better fit a population pharmacokinetic model for hydrocodone following oral administration to dogs.

The t1/2 of hydrocodone assessed by naïve-pooled pharmacokinetic modeling in the present study was 15.85 hours. This estimate may not reflect the true t1/2 of hydrocodone in dogs and must be interpreted cautiously. To robustly estimate this parameter, samples should be collected for a period at least 3 times the t1/2; in this study, that criterion would have required collection of samples over approximately 48 hours during the terminal portion of the curve. Because samples were only collected during an 8-hour dosing interval, the estimate for the t1/2 may not have been robust. Further studies assessing accumulation of hydrocodone over 48 to 72 hours would better assess whether the t1/2 is truly 15.85 hours in clinical canine patients.

The mechanisms of action for tramadol in humans are generally believed to be related to its CYP2D6-dependent metabolism to O-desmethyltramadol (M1). Other metabolites, including N-desmethyltramadol (M2) and N,O-didesmethyltramadol (M5), have been identified in dogs following tramadol administration but are considered either inactive or unable to cross the blood-brain barrier in several species, including humans and hamsters. In humans, variability in the pharmacokinetic properties of tramadol is wide, and this can partly be attributed to polymorphisms in the CYP2D6 gene. In a 1996 study by Poulsen et al., human patients were characterized as extensive or poor metabolizers of tramadol on the basis of serum M1 concentrations following oral administration of the drug. The serum concentration of M1 over a 10-hour period after tramadol administration ranged from 10 to 100 ng/mL in extensive metabolizers, whereas in poor metabolizers, serum concentrations of M1 were below or near the detection limit of 3 ng/mL. In dogs that received oral formulations of tramadol at doses up to 10 mg/kg, reported circulating concentrations of M2, M5, and the parent tramadol ranged from approximately 160 to 660 ng/mL, 140 to 300 ng/mL, and 80 to 450 ng/mL, respectively, whereas the same study identified very low concentrations of M1 (geometric mean of 5.7 ng/mL or up to a maximum concentration of 13.8 ng/mL). KuKanich and Papich reported higher concentrations of M1 (a Cmax of approx 450 ng/mL) in 2004. That study was conducted prior to the commercial availability of reference standards for M2 and M5. It is likely that the high-performance liquid chromatography assay used in that study was not specific for M1 and either M2 or M5 coeluted with M1, which resulted in biased and reportedly high M1 concentrations.

The population pharmacokinetics of the parent tramadol compound in the present study also suggested variability for its metabolism in dogs. The Cmax of tramadol in the present study after a second oral dose of 5.85 ± 0.61 mg/kg ranged from 46.8 to 613.0 ng/mL. This up to 12-fold variation in tramadol concentrations may have been attributable to interindividual differences in drug bioavailability or recent anesthesia. It is possible that dogs, like humans, have genetic mutations affecting the enzyme responsible for tramadol metabolism, resulting in some dogs having a low, intermediate, or high bioavailability of tramadol after oral administration. Further investigations are needed to evaluate differences in genotype
or expression of the CYP enzyme responsible for tramadol metabolism in dogs, and a study comparing results of IV versus oral tramadol administration in a heterogeneous group of dogs should be performed to determine the actual variability in bioavailability of tramadol following oral administration in a clinical population of patients.

The concentrations of M1 following IV and rectal administration of tramadol at 4 mg/kg in healthy Beagles were 10 to 21 ng/mL and 7 to 28 ng/mL, respectively. At a similar dose given orally to healthy Beagles, the Cmax of M1 was as high as 54 ng/mL. Administration of tramadol orally at approximately 10 mg/kg resulted in Cmax values of M1 as low as 5.7 ng/mL. These previous reports are consistent with results of the present study, in which the active metabolite M1 concentrations were exceptionally low and not likely contributing to analgesia. Similar metabolite profiles for the inactive metabolites M2 and M5 were identified in this study, and these were consistent with previous pharmacokinetic results in healthy, unanesthetized dogs that received tramadol following food withholding. Taken together, these findings support that any analgesic activity of tramadol is independent of M1 activity in dogs.

The t1/2 of the parent tramadol compound in our study was consistent with findings in dogs in previous studies. It is important for clinicians to recognize the importance of the t1/2, as it may be used to make recommendations of a 6-hour oral dosing interval for tramadol in dogs. In the present study, however, samples were collected only during the 8-hour dosing interval, and strong recommendations for dosing intervals cannot be made without future studies using shorter dosing intervals.

The flexibility in the timing of postoperative morphine administration (0 to 4 hours after surgery) in our study reflected the individual variation in characteristics of recovery from surgery and anesthesia. The authors and the university’s IACUC strongly believed that 1 dose of parenteral morphine during this time period was necessary for these dogs that were not receiving caudal epidural analgesic administration. This dose of morphine did not influence the timing of oral study drug administration and did not interfere with the measurement of tramadol, tramadol metabolites, hydrocodone, and hydromorphone.

Additional blood samples were collected at time of rescue analgesic intervention as determined by pain scoring with the modified Glasgow composite measure pain scale. This was done to assess the concentration of drug at the time of perceived treatment failure. On the basis of the median serum drug concentrations at the time of intervention, little can be said about the relationship between concentration and clinical efficacy of the study drugs. Both tramadol and hydrocodone concentrations at the time of intervention were well within the concentration range for dogs in this study that did not receive rescue analgesia. The concentrations of active metabolites M1 and hydromorphone also did not appear related to whether rescue drug treatment was needed. This discrepancy was likely contributed to by several factors, such as the scoring system’s lack of sensitivity in detecting pain, differences in how dogs interacted with the assessor, and intraobserver variability, as well as actual differences among dogs in the degree of pain experienced, pain tolerance, and response to the drug treatment.

It is possible that several mechanisms may have influenced production and detection of active metabolites of tramadol and hydrocodone in dogs of this study. First, dogs enrolled in the study had received other drugs, including premedicants and inhalation anesthetics for general anesthesia. Anesthesia was a uniform variable across patients; however, response to these drugs may have varied. This potential biological variability among patients could have affected the variability of tramadol concentrations and measurable amounts of active metabolites. Concurrent treatment with other drugs, previous NSAID use, or acetaminophen in combination with opioid drugs may have altered drug metabolism in such a way that metabolites were no longer produced via routine metabolic pathways, although these effects have not been fully documented. Even though routine screening of patients was performed to rule out systemically unhealthy animals, it is also possible, but unlikely, that undetected systemic diseases including chronic inflammation from cranial cruciate ligament rupture influenced the normal metabolism of orally administered study drugs.

Other limitations of the present study included the enrollment of only 50 dogs (25/drug). If larger numbers of dogs were used, some individual characteristics allowing better prediction of pharmacokinetics may have been identified (eg, breed, age, and sex).

In accordance with IACUC requirements for study approval, each dog could have only 5 blood samples collected in the postoperative period. Despite the limited number of samples obtained, naïve pooled pharmacokinetic models were able to be fit to the data for tramadol, hydrocodone, M1, and M5, and a population pharmacokinetic model could be fit to the tramadol data. Further studies with larger sample numbers may result in better model fits for hydrocodone and tramadol metabolites.

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Footnotes

a. Hydrocodone bitartrate (5 mg and 10 mg)—acetaminophen (325 mg), Qualitest Pharmaceuticals, Huntsville, Ala.
b. Tramadol hydrochloride (50 mg), Amneal Pharmaceuticals LLC, Paterson, NJ.

c. WinNonLin, version 5.2, Pharsight Inc, Cary, NC.

d. WinNonMix, version 2.0, Pharsight Inc, Cary, NC.

References


