Recognition of pain in animals and provision of appropriate analgesia are becoming increasingly important issues in veterinary medicine. Recognition of pain in certain small mammals, such as rabbits and rodents, can be challenging because many small mammals are prey species and have evolved to hide signs of illness and pain.

Once pain is detected, numerous analgesics are available to treat affected animals; however, the usefulness of many analgesics is limited by associated adverse effects, difficulty of administration, or high cost. Few analgesics have been evaluated in small mammals.

Although tramadol has routinely been used for the relief of moderate to severe pain in humans for the last 2 decades, its use in veterinary medicine is relatively new. Tramadol is a centrally acting analgesic that has agonist activity at opioid \( \mu \)-receptors and also inhibits reuptake of norepinephrine and serotonin. Numerous metabolites of tramadol have been identified, including M1 through M5; however, to the authors’ knowledge, M1 (O-desmethyltramadol) is the only metabolite that has analgesic properties. Although tramadol has adverse effects similar to those of other commonly used opioids, little sedation or respiratory depression has been associated with administration of tramadol in humans. Also unlike several commonly used opioids, tramadol is not a controlled drug, is inexpensive, and can be administered orally.

Few studies have been designed to investigate the analgesic effects and metabolism of tramadol in nonhuman animals, but recommended dosages based on pharmacokinetic studies are available for cats and dogs. One study

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**Pharmacokinetics of orally administered tramadol in domestic rabbits**

*Oryctolagus cuniculus*

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**Objective**—To determine the pharmacokinetics of an orally administered dose of tramadol in domestic rabbits (*Oryctolagus cuniculus*).

**Animals**—6 healthy adult sexually intact female New Zealand White rabbits.

**Procedures**—Physical examinations and plasma biochemical analyses were performed to ensure rabbits were healthy prior to the experiment. Rabbits were anesthetized with isoflurane, and IV catheters were placed in a medial saphenous or jugular vein for collection of blood samples. One blood sample was collected before treatment with tramadol. Rabbits were allowed to recover from anesthesia a minimum of 1 hour before treatment. Then, tramadol (11 mg/kg, PO) was administered once, and blood samples were collected at various time points up to 360 minutes after administration. Blood samples were analyzed with high-performance liquid chromatography to determine plasma concentrations of tramadol and its major metabolite (O-desmethyltramadol).

**Results**—No adverse effects were detected after oral administration of tramadol to rabbits. Mean ± SD half-life of tramadol after administration was 145.4 ± 81.0 minutes; mean ± SD maximum plasma concentration was 135.3 ± 89.1 ng/mL.

**Conclusions and Clinical Relevance**—Although the dose of tramadol required to provide analgesia in rabbits is unknown, the dose administered in the study reported here did not reach a plasma concentration of tramadol or O-desmethyltramadol that would provide sufficient analgesia in humans for clinically acceptable periods. Many factors may influence absorption of orally administered tramadol in rabbits. (Am J Vet Res 2008;69:979–982)

**ABBREVIATIONS**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>AUC(_{0–120})</td>
<td>Area under the plasma concentration–time curve from time 0 to 120 minutes after drug administration</td>
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<tr>
<td>AUC(_{0–}\infty)</td>
<td>Area under the plasma concentration–time curve from time 0 to infinity</td>
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<tr>
<td>AUMC(_{0–}\infty)</td>
<td>Area under the first moment time curve from 0 to infinity</td>
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<tr>
<td>C(_{\text{max}})</td>
<td>Maximum plasma concentration</td>
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<tr>
<td>HPLC</td>
<td>High-performance liquid chromatography</td>
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<td>( T_{\text{max}} )</td>
<td>Time to reach maximum plasma concentration</td>
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revealed that tramadol provided analgesia approximately equal to that of morphine in dogs with no adverse effects. Results of another study indicated that epidurally administered tramadol provided adequate relief for perineal and lumbosacral pain in horses. Respiratory depression associated with IV administration of tramadol has been reported in cats, and abuse of tramadol in the racehorse industry has been reported. The purpose of the study reported here was to determine the pharmacokinetics of an orally administered dose of tramadol in domestic rabbits (Oryctolagus cuniculus).

Materials and Methods

Animals—The experimental protocol was approved by the Institutional Animal Care and Use Committee of the University of Tennessee. Six adult sexually intact female New Zealand White rabbits were used. Body weights of rabbits ranged from 3.2 to 4.6 kg (mean ± SD body weight, 3.8 ± 0.38 kg). All rabbits were separately housed in a temperature-controlled environment and were allowed to acclimate 2 weeks prior to treatment. Rabbits had free access to water, a pelleted diet, and timothy hay. Fresh greens were also provided 2 to 4 times weekly. Food was removed 8 to 10 hours before treatment. Physical examinations and plasma biochemical analyses were performed on all rabbits within 72 hours before treatment to ensure rabbits were healthy.

Experimental procedures—A tramadol suspension was prepared by pharmacy staff at the College of Veterinary Medicine as described and validated. Briefly, crushed 50-mg tablets of tramadol were mixed with a suspension vehicle. The suspension was refrigerated for up to 72 hours prior to the experiment. To facilitate placement of an IV catheter for collection of blood specimens, anesthesia was induced in each rabbit with isoflurane. An IV catheter was inserted into a medial saphenous or jugular vein of or jugular vein, and a pretreatment blood sample (baseline) was collected into 3-mL glass tubes that contained lithium heparin as an anticoagulant. Rabbits were allowed to recover from anesthesia for a minimum of 1 hour, then the tramadol solution was orally administered to each at a dosage of 11 mg/kg via a 3-mL syringe (time 0). Blood samples were collected via catheters at 10, 20, 30, 45, 60, 90, 120, 180, 240, 300, and 360 minutes after treatment by removing an initial 1 mL of blood, collecting 1.2 mL of blood for analysis, replacing the initial 1 mL of blood, and then flushing the catheter with 0.5 to 1.0 mL of saline (0.9% NaCl) solution or heparinized saline solution. In the event of catheter failure (blockage or migration out of vein), blood samples were removed from a peripheral vessel such as a lateral saphenous vein, cephalic vein, central ear artery, or marginal ear vein. Rabbits were monitored throughout the experiment for adverse effects associated with tramadol administration (eg, respiratory depression, bradycardia, and decreased physical activity). Catheters were removed after the final blood sample was collected or when catheters failed.

Plasma sample analysis—Plasma was separated and stored at −80°C pending analysis. Thawed plasma samples were analyzed for concentrations of tramadol and O-desmethy tramadol by use of reverse-phase HPLC with fluorescence detection. The HPLC system consisted of a separations module, a fluorescence detector, and a computer equipped with chromatography system software. Tramadol and O-desmethyltramadol were extracted from plasma samples by use of a liquid extraction method. Brieﬂy, tubes containing plasma samples were vortex-mixed, then 350 µL of plasma was transferred to another test tube containing 100 µL of internal standard (butorphanol [50 µg/mL]). Seventy microliters of 29.7% ammonium hydroxide solution was added, after which 1.5 mL of mixture of ethyl acetate and hexane (ratio of 40:60) was added. Tubes were placed on a tube rocker for 15 minutes and then centrifuged for 20 minutes at 1,000 X g. The organic layer was transferred to a clean tube and evaporated to dryness under a steady stream of nitrogen gas. Samples were reconstituted in 350 µL of mobile-phase solvent, which consisted of 0.01M potassium phosphate buffer (pH, 2.9) and 0.1% triethylamine mixed with acetonitrile at a ratio of 92:8. 25 µL of reconstituted sample was analyzed. Compounds were separated on an HPLC column (4.6 × 250 mm, 5 µm) with a guard column. The flow rate was 1.1 mL/min, and the column temperature was approximately 22°C. Fluorescence was measured at an excitation of 202 nm and an emission of 296 nm.

Untreated, pooled rabbit plasma was mixed with tramadol and metabolites to yield a linear range of concentrations from 5 through 1,500 ng/mL, and these concentrations were used to produce standard curves for plasma analysis. Calibration samples were prepared exactly as were plasma samples. Mean percentage recoveries ranged from 78% to 94% for tramadol and its metabolites, respectively. Intra-assay variability was < 11% for all compounds. Interassay variability was < 10% for respective compounds.

Pharmacokinetic analysis—Pharmacokinetic characteristics of tramadol and the O-desmethy tramadol metabolite were calculated by use of a computer software program. Values for elimination rate constant, plasma half-life, Cmax, Tmax, AUC0–t, AUC0–t and AUMC0–t were calculated by use of noncompartmental analysis. The AUC and AUMC were calculated by use of the linear rule. Mean residence time was calculated as AUMC0–t/AUC0–t.

Results

No adverse effects were detected in rabbits after a dose (11 mg/kg) of tramadol was administered orally. The plasma concentration time profile was determined (Figure 1). Concentrations of tramadol, O-desmethy tramadol, and other metabolites were undetectable in all baseline plasma samples obtained prior to administration of tramadol.

Values of terminal half-life, T1/2, and Cmax for an orally administered dose of tramadol in rabbits were 143.4 ± 81 minutes, 26.7 ± 16.0 minutes, and 135.3 ± 89.1 ng/mL, respectively. Values of T1/2 and Cmax for O-desmethy tramadol after treatment were 45.8 ± 14.6 minutes and 135.3 ± 89.1 ng/mL, respectively (Table 1). The terminal half-life of O-desmethy tramadol after treatment varied greatly.
Discussion

In the study reported here, pharmacokinetic properties of tramadol were measured after oral administration of a dose of tramadol (11 mg/kg) to 6 healthy domestic rabbits (Oryctolagus cuniculus). Time of tramadol administration was designated as time 0. Tramadol and O-desmethyltramadol were not detected in baseline plasma samples obtained before tramadol administration.

Additionally, O-desmethyltramadol in rabbits had a much shorter half-life, a lower \( C_{\text{max}} \), and an earlier \( T_{\text{max}} \), compared with those reported for humans (\( T_{\text{max}} \), 62.4 minutes; \( C_{\text{max}} \), 1,402.8 ng/mL; and \( T_{\text{max}} \), 138 minutes).\(^7\) On the other hand, orally administered tramadol in rabbits had a much shorter half-life, a lower \( C_{\text{max}} \), and an earlier \( T_{\text{max}} \), compared with respective values in humans (half-life, 102.6 minutes; \( C_{\text{max}} \), 1,402.8 ng/mL; and \( T_{\text{max}} \), 144 minutes).\(^7\) Additionally, O-desmethyltramadol in rabbits had a similar \( T_{\text{max}} \) (45.8 minutes) and lower \( C_{\text{max}} \) (35.7 ng/mL) after tramadol was orally administered, compared with respective values in dogs (\( T_{\text{max}} \), 30 minutes; \( C_{\text{max}} \), 449.1 ng/mL), and much lower values, compared with those reported for humans (\( T_{\text{max}} \), 144 minutes; \( C_{\text{max}} \), 110 ng/mL).\(^6\) Slower gastric emptying and transit time in rabbits may account for interspecies differences in pharmacokinetic values.

After oral administration of tramadol to rabbits, the half-life of O-desmethyltramadol varied among rabbits (34 to 519 minutes). Consequently, data regarding the \( \text{AUC}_{0,120} \) was reported because all rabbits had measurable concentrations up to 120 minutes.

Plasma concentrations of tramadol and O-desmethyltramadol associated with analgesia in rabbits are unknown; however, plasma concentrations between 298 ng/mL to 590 ng/mL for tramadol and 39.6 to 84 ng/mL for O-desmethyltramadol are associated with postsurgical analgesia in humans.\(^3,\)\(^5\) Oral administration of 11 mg of tramadol/kg achieved plasma concentrations of O-desmethyltramadol associated with analgesia in humans for only approximately 45 minutes in 2 rabbits in our study (data not shown). Human therapeutic concentrations of tramadol were not reached in any rabbit after treatment. Additionally, variable concentrations of other metabolites were detected, but it is unknown whether these metabolites provide analgesia in rabbits.

The variability in and low values for plasma concentrations of tramadol and O-desmethyltramadol that we detected may have been attributable to many factors, including administration of an incomplete dose, differences in absorption rates among rabbits, existence of food in the stomach, influence of the hepatic first-pass effect, and altered motility of the gastrointestinal tract. In many studies of the pharmacokinetics of drugs in rabbits, investigators have used a tube to deliver medications directly into the stomach; however, we used a syringe inserted into the mouth to administer the tramadol suspension to the rabbits in our study, which is the means by which rabbits are typically medicated in clinical practice.\(^16\)\(^-\)\(^18\) Because of the method of administration, some rabbits may not have ingested the full dose of tramadol. Withholding of food from rabbits without placing a muzzle to prevent coprophagy may have also resulted in variable amounts of ingesta in the stomach and incomplete gastric emptying. However, because of the prolonged gastric emptying time of rabbits, muzzles may not have ensured complete emptying of the stomach. Food and roughage may alter the absorption of some orally administered medications in horses,\(^9\) and withholding of food from rabbits may also alter gastrointestinal motility. Finally, rabbits were anesthetized the day before or the day of treatment for insertion of IV catheters. Typically, rabbits were anesthetized for no more than 20 to 30 minutes; however, this period may have been sufficient to alter gastrointestinal motility. In clinical practice, rabbits that receive tramadol for pain have likely been anesthetized for diagnostic testing or surgery. In that way, we believe that the treatment protocol we used simulated clinical conditions.

Current recommended dosages of tramadol for dogs and cats range from 1 to 4 mg/kg, PO, every 6 to 12 hours.\(^7\) Oral administration of tramadol in excess of 11 mg/kg would be required to provide analgesia to rabbits. Additional studies are needed to assess the pharmacokinetics of higher doses and repeated administration as well as the pharmacodynamics of tramadol in rabbits. The disposition of tramadol was only evaluated in sexually intact female rabbits in the present study; but differences in pharmacokinetics may exist between males and females. Therefore, future studies should also include male rabbits. Furthermore, additional studies are needed to determine which metabolites are active in domestic rabbits.
a. Tramadol hydrochloride, 50-mg tablets, Caraco Pharmaceutical Laboratories Ltd, Detroit, Mich.
b. Ora-Blend SF, Paddock Laboratories Inc, Minneapolis, Minn.
c. Iso Flo, Abbott Laboratories, North Chicago, Ill.
d. Monoject, Kendall, Mansfield, Mass.
e. 2695 separations module, Waters Corp, Milford, Mass.
f. 2475 fluorescence detector, Waters Corp, Milford, Mass.
g. Empower, version 2, Waters Corp, Milford, Mass.
h. US Pharmacopeia, Rockville, Md.
k. Gruenthal, Aachen, Germany.
l. WinNonlin, version 4.1, Pharsight Corp, Mountain View, Calif.

References