Pharmacokinetics, bioavailability, and hemodynamic effects of trazodone after intravenous and oral administration of a single dose to dogs

Ariane R. Jay, DVM; Ursula Krotscheck, DVM; Elizabeth Parsley; Lisa Benson; Ariel Kravitz; Abby Mulligan; Jharon Silva, PhD; Hussni Mohammed, PhD; Wayne S. Schwark, DVM, PhD

Objective—To determine the pharmacokinetics and hemodynamic effects of trazodone after IV and oral administration in dogs and bioavailability after oral administration.

Animals—6 adult Beagles.

Procedures—Dogs received trazodone HCl (8 mg/kg) orally and IV in a randomized controlled crossover design. Blood samples were collected at various times after administration. Heart rates and indirectly measured blood pressures of dogs and plasma concentrations and pharmacokinetics of trazodone were determined.

Results—Following IV administration, the mean ± SD elimination half-life, apparent volume of distribution, and plasma total body clearance were 169 ± 53 minutes, 2.53 ± 0.47 L/kg, and 11.15 ± 3.56 mL/min/kg, respectively. Following oral administration, the mean ± SD elimination half-life and absolute bioavailability were 166 ± 47 minutes and 84.6 ± 13.2%, respectively. Maximum plasma concentration following oral administration was 1.3 ± 0.5 µg/mL, and time to maximum plasma concentration was 445 ± 271 minutes. After IV administration, all dogs immediately developed transient tachycardia (184.3 ± 8.0 beats/min), and 3 of 6 dogs developed aggression. Increase in heart rate was significantly associated with increase in plasma drug concentration following IV administration.

Conclusions and Clinical Relevance—Results of this study indicated oral administration of trazodone resulted in acceptable absolute bioavailability, with substantial variability in time to maximum plasma concentration. Individualized approaches in dosing intervals may be necessary for dogs receiving oral trazodone. An orally administered dose of 8 mg/kg was well tolerated in dogs; IV administration of a dose of 8 mg/kg caused substantial adverse effects, including tachycardia and behavior disinhibition. (Am J Vet Res 2013;74:1450–1456)
amount of information is known about its pharmacokinetic or pharmacodynamic parameters in dogs; dosage protocols have typically been extrapolated from data for humans. In humans, trazodone is initially administered in low amounts (25 to 30 mg/d), and the amount is gradually increased to effect (maximum amount, 600 mg/d); therapeutic plasma concentrations range from 1.7 to 19.5 µg/mL (mean, 7.25 mg/kg). Plasma concentrations of trazodone were not determined for dogs in this study. A therapeutic plasma concentration range of trazodone has not been reported for dogs, to the authors’ knowledge. With the exception of a study performed in 1970 in which dogs received a single oral dose of trazodone at doses of 20 and 50 mg/kg, no other pharmacokinetic data for that drug in dogs have been reported. The purpose of the study reported here was to determine the pharmacokinetics of trazodone following oral and IV administration at clinically relevant doses, determine bioavailability after oral administration, and determine effects on hemodynamic variables after oral and IV administration.

Materials and Methods

Animals—Six adult sexually intact male Beagles were included in the study. The dogs were determined to be healthy on the basis of results of physical examination, CBC, and serum biochemical analyses performed at the beginning of the study. Mean ± SD body weight and age of the dogs were 12.1 ± 0.6 kg and 70.7 ± 0.8 months, respectively. The study protocol was approved by the Institutional Animal Care and Use Committee at Cornell University.

Procedures—Each dog received 100 mg of trazodone HCl (mean ± SD dose, 8.26 ± 0.26 mg/kg) orally and a dose of 8 mg/kg IV in a randomized controlled crossover design. A minimum washout period of 7 days was allowed between treatments. Water was provided to the dogs ad libitum during the study. Their daily intake of food was provided once during the morning of each treatment day. The dogs were fed approximately 1 hour prior to drug administration. Trazodone tablets were administered orally following 30 mL of water to ensure tablets were completely swallowed. Trazodone HCl injectable solution (5 mg/mL) was prepared on each day of administration by use of United States Pharmacopeia trazodone HCl powder. Trazodone HCl powder was dissolved in sterile saline (0.9% NaCl) solution and passed through a 0.2-µm filter into a sterile vial. The sterile solution was then stored at –80°C until assays were performed within 30 minutes after collection. Plasma was harvested and then stored at –80°C until assays were performed within 30 days after collection.

Sample collection—For each dog, 19-gauge catheters were aseptically placed in a jugular vein with manual restraint during the morning of the treatment day to facilitate blood sample collection. Blood samples (3 mL) were collected from each dog 5 minutes prior to drug administration (0 minutes) and 5, 15, 30, 60, 120, 240, 480, 720, 1,080, and 1,440 minutes after IV administration of trazodone or 5 minutes prior to drug administration (0 minutes) and 30, 60, 120, 240, 480, 720, 1,080, and 1,440 minutes after oral administration of that drug. Blood samples were placed into collection tubes containing lithium heparin and kept on ice. Within 30 minutes after collection, samples were centrifuged at 1,000 × g for 10 minutes. Plasma was harvested and then stored at –80°C until assays were performed within 30 days after collection.

Clinical data collection—On each treatment day, 2 dogs received trazodone IV, 2 dogs received trazodone orally, and 2 dogs received no drug (these dogs were negative control animals for the clinical data collection period). Heart rate, respiratory rate, and indirectly measured mean, systolic, and diastolic arterial blood pressures were recorded 5 minutes prior to drug administration (0 minutes) and 5, 15, 30, 60, 120, 240, 480, and 720 minutes after drug administration. Heart rate was also measured immediately after completion of IV drug administration (5 minutes after the start of administration). Heart rate was determined via auscultation and simultaneous palpation of pulse. Blood pressure was determined indirectly with a commercially available oscillometric blood pressure measurement device intended for veterinary use. Cuff size was selected such that the width of the cuff was approximately 40% of the circumference of the distal aspect of the hind limb. Animals were gently restrained in lateral recumbency, and a cuff was placed on the right hind limb. Blood pressure values obtained with an accurate pulse wave and pulse rate were recorded. Dogs were housed individually in runs to which they had been acclimated.

Analysis of plasma concentrations of trazodone—Quantitative analysis of plasma trazodone concentrations was performed at a commercial laboratory by means of UPLC. This UPLC system was validated for use with human blood, plasma, serum, and urine samples. To account for possible differences between human and canine plasma, a matrix matching experiment was conducted. Briefly, blank plasma samples (ie, samples without trazodone) obtained from 5 of the study dogs were divided into 3 aliquots, yielding a total of 15 samples. One sample per animal was kept blank, and the other 2 were spiked with known amounts of reference standard trazodone at various concentrations. The chromatography results for blank samples were evaluated at the expected trazodone retention time. Trazodone concentrations for spiked samples were determined, and the accuracy of the assay was measured. Acceptable accuracy for the assay was set at ± 20% of the expected amount.
Pharmacokinetic analysis—Plasma trazodone concentration-versus-time data after IV and oral administration for each dog were plotted on linear and semilogarithmic graphs for analysis. The data were administered for each dog were plotted on linear and concentration-versus-time data after IV and oral administration for each dog. Two levels of control were run in each analytic batch. This UPLC method had a lower limit of quantitation of 0.050 µg/mL and between-run coefficients of variation of 9.62% and 7.63% at 0.08 g of trazodone/mL, respectively.

Pharmacokinetic analysis—Plasma trazodone concentration-versus-time data after IV and oral administration for each dog were plotted on linear and semilogarithmic graphs for analysis. The data were evaluated by means of noncompartmental analysis with commercially available software. That software resolved the concentration-versus-time curves into a series of exponential terms corresponding to the elimination and distribution phases (IV administration) and absorption and elimination phases (oral administration) for the time that the drug was in the blood. These exponential terms were used to calculate parameters on the basis of established pharmacokinetic calculations. The program assumed the disposition phases of the drug followed apparent first-order rate processes, as evidenced by linearity of the terminal portion of the semilog plots. Area under the curve data were computed on the basis of the trapezoidal rule. Parameters evaluated after oral administration included elimination half-life, area under the concentration-versus-time curve from zero to infinity, and mean residence time. Maximum plasma concentration and Tmax were recorded directly from the data. For IV administration, additional parameters estimated included apparent volume of distribution and total body clearance. Absolute bioavailability was calculated with the following equation:

\[ F = \frac{(\text{AUC}_{\text{PO}} \times \text{Dose}_\text{PO})}{(\text{AUC}_{\text{IV}} \times \text{Dose}_\text{IV})} \times 100\% \]

where \( F \) is absolute bioavailability; \( \text{AUC}_{\text{PO}} \) and \( \text{AUC}_{\text{IV}} \) are area under the concentration-versus-time curve after oral and IV administration, respectively; and DosePO and DoseIV are the doses administered via IV and oral routes, respectively.

Statistical analysis—All statistical analyses were performed with a commercially available statistical software program. Continuous data were tested for normality with a Shapiro-Wilk test. The effect of route of administration (IV vs oral administration of trazodone or no drug [control]) on heart rate, systolic arterial blood pressure, and mean arterial blood pressure was assessed in a linear regression model controlling for time, time squared, and drug concentration. Values of \( P < 0.05 \) were considered significant. Only significant \( P \) values were reported. All parametric parameters were reported as mean ± SD values unless otherwise specified.

Results

Pharmacokinetics—All pharmacokinetic data were normally distributed. Data for 5 dogs were used in the pharmacokinetic analysis for oral administration of trazodone because not enough data points were available for analysis for one of the dogs (trazodone concentrations were lower than the lower limit of quantitation of the assay at most times). Following IV administration of trazodone to dogs, the mean ± SD elimination half-life, apparent volume of distribution, and systemic clearance were 169 ± 53 minutes, 2.534 ± 0.472 L/kg, and 11.15 ± 3.56 mL/min/kg, respectively. Following IV administration, the mean ± SD area under the concentration-versus-time curve from zero to infinity was 791 ± 295 µg·min/kg and the residence time was 238 ± 79 minutes. Following oral administration, the mean ± SD elimination half-life and systemic bioavailability were 166 ± 47 minutes, and 84.6 ± 13.2%, respectively. Following oral administration of the drug, the mean ± SD Tmax was 443 ± 271 minutes, the Cmax was 1.3 ± 0.5 µg/mL, the area under the concentration-versus-time curve from zero to infinity was 743 ± 205 µg·min/kg, and the mean residence time was 544 ± 242 minutes.

The mean ± SD plasma trazodone concentrations following IV (8 mg/kg) and oral (mean ± SD dose, 8.26 ± 0.26 mg/kg) administration were summarized (Figures 1 and 2). Following oral administration, 5 of 6 dogs achieved Cmax for trazodone between 8 and 12 hours, whereas Cmax was achieved for 1 dog at 30 minutes. All dogs had plasma trazodone concentrations > 130 ng/mL; plasma trazodone concentrations were maintained at such concentration for 4 hours in 2 of 6 dogs, for 10 hours in 1 of 6 dogs, for 14 hours in 2 of 6 dogs, and for 20 hours in 1 of 6 dogs. Trazodone was not detectable in plasma samples of 5 of 6 dogs at 24 hours following both IV and oral administration.

Clinical effects—Three of 6 dogs developed marked signs of aggression, including growling and attempting to bite, within 0 to 5 minutes after IV administration of trazodone; this was considered abnormal behavior for all of the dogs in the study. All dogs became briefly ataxic following IV administration of trazodone; ataxia progressed to sternal recumbency of approximately 5 minutes’ duration in 5 of the 6 dogs. All dogs developed transient tachycardia (mean ± SD heart rate, 184.3 ± 8.0 beats/min) of 2 to 5 minutes
duration during IV administration of trazodone. Two dogs developed transient signs of nausea, including hypersalivation and licking of lips (1 after oral administration and 1 after IV administration). No other adverse effects were noticed. All continuous data were normally distributed. Heart rates, systolic arterial blood pressures, and mean arterial blood pressures for each evaluation time were summarized (Figures 3–5). Heart rate was strongly correlated with plasma concentration of trazodone (regression coefficient = 8.201; $P < 0.001$). Systolic arterial blood pressure and mean arterial blood pressure were not significantly correlated with route of drug administration, time, or plasma drug concentration.

Discussion

Trazodone has actions by means of unique and multifunctional pharmacological mechanisms. It is an antagonist of 5-HT2A and 5-HT2B receptors, a partial agonist of 5-HT1A receptors, and a serotonin reuptake inhibitor. The concurrent blockade of some serotonin receptors and activation of others as a result of increased amounts of serotonin in neuronal synapses is thought to cause the antidepressant and anxiolytic effects of trazodone. Additionally, trazodone antagonizes $\alpha$-adrenergic and histamine H1 receptors and blocks T-type calcium channels; these effects may cause potential adverse cardiovascular effects. Few data...
are available regarding trazodone metabolism in dogs, although that topic has been extensively studied for humans. In humans, trazodone undergoes extensive hepatic metabolism and is primarily metabolized by the cytochrome p450 enzymes CYP3A4 and CYP2D6, the latter of which has a high amount of genetic variability. Greater than 75% of orally administered trazodone is excreted renally as metabolites, and < 1% of the unmetabolized drug is excreted in the urine. Approximately 20% of the parent compound is metabolized to the pharmacologically active metabolite meta-chlorophenylpiperazine. Meta-chlorophenylpiperazine is a potent serotoninergic agonist and may be responsible for some of the clinical effects of trazodone. For humans, there are various indications for administration of trazodone including treatment of depression, anxiety disorders, insomnia, certain causes of pain, and cognitive dysfunction. In dogs, however, reported clinical use of trazodone is limited to chronic management of behavioral disorders, including storm phobias and separation anxiety, and it is typically administered in combination with conventional psychoactive medications. Its broad spectrum of pharmacological action and clinical applications in humans suggests that trazodone may have similar versatility for treatment of companion animals. In our institution, trazodone is administered orally for acute and chronic anxiolysis in dogs after surgery. Given the increasing popularity of trazodone among veterinary clinicians, determination of the pharmacokinetics, safety, and clinical effects of the drug are warranted.

Results of other studies indicate that trazodone is rapidly and nearly completely absorbed after oral administration to humans; peak plasma concentrations are attained within 30 to 120 minutes after administration of immediate-release tablets. Other authors found that the Cmax increases and the Tmax decreases for trazodone during fasting conditions. However, because absorption is irregular in fasting subjects and improved after food intake, it is recommended that trazodone be administered with food. In the present study, the mean ± SD Tmax of trazodone after oral administration was 443 ± 271 minutes. Peak plasma concentrations were attained within 8 to 12 hours after administration for 5 of the 6 dogs and within 30 minutes for 1 dog. Potential reasons for the longer trazodone Tmax in dogs, compared with that in humans, include differences in gastric residence time and gastrointestinal metabolism between species and variation among individual animals. Given that the gastric residence time for fed dogs (686 ± 352 minutes) is much longer than that for fed humans (143 ± 131 minutes), we suggest that a difference in gastric residence time is a possible explanation for the disparity in trazodone Tmax values between these species. We theorized that variations in feeding behavior may have caused the wide range of Tmax values determined for dogs in the present study, considering that dogs were fed once on the morning of each treatment day and allowed access to that meal throughout the day. Because all of the dogs had similar trazodone pharmacokinetics after IV administration, it was unlikely that differences in enzyme metabolism and organ function among dogs caused variations in Tmax detected after oral administration. Other authors reported that mean gastric residence time for Beagles from which food had been withheld was 25 minutes, whereas that for the same dogs that were fed was 686 minutes. If Tmax is related to gastric residence time, then dogs that finished their meals quickly may have had a substantially longer Tmax than those that did not. The dog in this study with the shortest Tmax also had the highest Cmax. Unfortunately, the feeding behaviors of each dog were not recorded. Other authors reported a Tmax of 2.5 hours for trazodone in dogs from which food had been withheld; that value was substantially shorter than the value determined for dogs in the present study, further suggesting that food withholding may increase the rate of absorption of orally administered trazodone in dogs. Those other authors also reported a Cmax of 2.5 µg/mL for dogs that received trazodone orally at a dose of 20 mg/kg and a Cmax of 4.8 µg/mL for dogs that received a dose of 50 mg/kg. Findings of the present study supported the suggestion of those other authors that trazodone has linear first-order kinetics in dogs for doses ranging from 8 to 50 mg/kg, considering that the mean Cmax for trazodone after oral administration to dogs in the present study was 1.3 µg/mL. The mean ± SD oral bioavailability of trazodone in dogs in the present study was 84.6 ± 13.2%, which was slightly higher than the value reported for humans (65% to 80%). Results of a study in which fed humans received 100 mg of trazodone orally (dose range, 1.3 to 2 mg/kg) indicated a mean ± SD Cmax of 1.47 ± 0.16 µg/mL. In contrast, the mean ± SD Cmax of trazodone in dogs in the present study was 1.3 ± 0.5 µg/mL after oral administration (approx dose, 8 mg/kg); this finding suggested that dogs may require an orally administered trazodone dose approximately 4 times as high as the dose for humans to achieve similar blood concentrations.

Plasma concentrations of trazodone in human patients that receive the drug orally at doses that provide antidepressive effects range between 130 ng/mL and 2 µg/mL. All dogs in the present study had plasma trazodone concentrations within that range following oral administration of a single dose; 4 of the 6 dogs had plasma trazodone concentrations > 130 ng/mL within 4 hours after administration for a duration of at least 10 hours. No dogs had plasma trazodone concentrations > 2 µg/mL. However, that concentration range may not be applicable for treatment of dogs. To the authors’ knowledge, a trazodone dose range specific for anxiolysis in human patients has not been reported. The authors of the present study attempted to characterize responses of dogs to treatment (anxiolysis) and determine an effective dose range on the basis of results determined with an anxiety scoring system developed for the quantification of separation anxiety behavior in shelter dogs. We were unable to identify anxiolysis in dogs because baseline scores did not indicate anxiety in dogs in the study. Other authors reported that 72% of owners felt that trazodone use resulted in satisfactory behavioral calming in their dogs; owners typically observed effects within 1 to 2 hours after administration. However, all dogs in that study were concurrently receiving other psychoactive medications, and a satisfactory response was defined as client-reported efficacy or continued treatment for at least 3 months.
Furthermore, plasma drug concentrations of trazodone were not measured in that study, so the true contribution of trazodone administration to the findings could not be determined. Mild sedation and anxiolysis in dogs in the present study was subjectively detected after trazodone administration by one of the authors (ARI), who observed dogs continuously for 24 hours after each treatment. This finding was characterized as an increased amount of time in recumbency and a decreased amount of vocalization of dogs. However, because the dogs became excitabile whenever additional personnel entered the research facility, these effects were not detected by blinded scorers. A blinded placebo-controlled clinical trial including anxious patients after surgery in which plasma drug concentrations are monitored may be the best study design for detection of anxiolysis.

Adverse effects detected in dogs following oral administration of trazodone include gagging, vomiting, colitis, sedation, increased appetite, increased excitement, and behavior disinhibition. The only adverse effect detected after oral administration of trazodone to dogs in the present study was hypersalivation (1 dog). However, all dogs developed transient tachycardia and ataxia, and 3 of 6 dogs became briefly aggressive following IV administration of the drug. Many of the adverse effects of trazodone in humans (particularly panic, anxiety, dysphoria, and psychosis) are thought to be attributable to meta-chlorophenylpiperazine. The anxiogenic properties of meta-chlorophenylpiperazine are attributed to stimulation of 5-HT2C receptors, which can be decreased by selective 5-HT2C antagonists. In humans, plasma concentrations of meta-chlorophenylpiperazine are approximately 10% to 30% of the plasma concentrations of trazodone, and meta-chlorophenylpiperazine can induce a clinical response when administered orally at low doses. The marked aggression, anxiety, tachycardia, and ataxia observed following IV administration of trazodone to dogs in the present study may have been secondary to high circulating concentrations of meta-chlorophenylpiperazine, although concentrations of this metabolite were not measured. Results of other studies indicate trazodone is cardiodepressive in dogs; however, this finding is for anesthetized dogs, which may complicate interpretation of the results. Results of another study indicate anesthetized dogs have a significant and dose-dependent decrease in mean arterial blood pressure and heart rate after IV administration of trazodone. Results of the present study did not indicate cardiovascular depression in any dogs after trazodone administration; instead, results indicated high drug concentrations were correlated with high heart rates following IV administration. Unfortunately, because of logistical limitations of the study, blood pressure monitoring and behavior scoring were not performed at 5 minutes after drug administration. The tachycardia detected in dogs at that time could have been a physiologic response to hypotension. However, considering that hypotension was not detected in dogs at any time during the study period (including the 15-minute posttreatment time), the authors believe this was unlikely.

There were several limitations of the present study. The low number of dogs included could have resulted in low power; however, we attempted to address this limitation by using a randomized crossover design (each dog was its own control animal). Heart rate and indirectly measured blood pressure are indirect indices of hemodynamic physiology. Additional measurements such as direct arterial blood pressure and continuous ECG (via Holter monitoring) may have provided useful data, and such methods should be considered for future studies. Although the standard addition protocol used to compensate for matrix effects of canine plasma with the UPLC protocol previously validated for samples obtained from humans yielded adequate results with a lower limit of quantitation of 0.050 µg/mL, the process was laborious and required large amounts of sample. This assay interference effect was likely attributable to analyte signal suppression by coeluting substances in canine plasma, such as phospholipids, carbohydrates, and endogenous metabolites (eg, bilirubin), or an interaction between trazodone and the matrix (canine plasma). Development of a canine-specific assay for measurement of trazodone concentrations is indicated.

Results of the present study suggested that trazodone was well tolerated by dogs at oral doses of approximately 8 mg/kg; no clinically important adverse cardiovascular effects were observed after drug administration by that route. The findings of aggression, tachycardia, and ataxia detected during IV administration of the drug suggested that behavior disinhibition was a serious adverse effect of high plasma trazodone concentrations. Given the serious adverse effects detected after IV administration of trazodone to dogs in the present study, a substantial reduction in the dose is strongly recommended when injecting the drug via a parenteral route, and limited use during the peri-anesthetic period may be indicated. Trazodone may be most clinically useful as an oral formulation administered after complete recovery from anesthesia in patients after surgery. Although the time to maximum plasma concentration was variable following oral administration, other pharmacokinetic parameters for IV and oral administration were similar among dogs in the study and absolute bioavailability after oral administration was high. Further studies are warranted to better quantify clinical effects of trazodone in dogs, determine corresponding effective plasma concentrations and dosages of that drug in dogs, and determine differences in pharmacokinetics for fed dogs versus dogs from which food has been withheld.

References