Pharmacokinetics of clomipramine in dogs following single-dose intravenous and oral administration

Jonathan N. King, PhD; Max P. Maurer, PhD; Rolf P. Hotz, Dr vet med; Roland D. Fisch, PhD

Objective—To determine pharmacokinetics of clomipramine and its principle metabolite (desmethylclomipramine) in the plasma of dogs after IV or oral administration of a single dose.

Animals—6 male and 6 female Beagles.

Procedures—Clomipramine was administered IV (2 mg/kg), PO (4 mg/kg) after food was withheld for 15 hours, and PO (4 mg/kg) within 25 minutes after dogs were fed. Plasma clomipramine and desmethylclomipramine concentrations were measured by use of a gas chromatography with mass-selection method.

Results—Time to peak plasma concentrations of clomipramine and desmethylclomipramine following oral administration was 1.2 hours. For clomipramine, after IV administration, elimination half-life was 5 hours, mean residence time was 3 hours, and plasma clearance was 1.4 L/hr/kg. Values for mean residence time and terminal half-life following oral administration were similar to values obtained following IV administration, and systemic bioavailability was approximately 20% for clomipramine and 140% for desmethylclomipramine, indicating fast absorption of clomipramine from the gastrointestinal tract and extensive first-pass metabolism. Administration of clomipramine with food did not alter the area under the concentration versus time curve for desmethylclomipramine but resulted in a 25% increase for clomipramine. Clomipramine and desmethylclomipramine were extensively bound (>96%) to serum proteins. There were no significant differences in area under the concentration versus time curve between male and female dogs.

Conclusions and Clinical Relevance—Results indicate that there should not be any clinically important differences in efficacy regardless of whether clomipramine is administered with or without food. (Am J Vet Res 2000;61:74-79)

Clomipramine hydrochloride has been demonstrated to be effective in a wide range of behavioral disorders in humans, including depression, stereotypies, panic attacks, phobias, chronic pain disorders, and eating disorders. Its broad spectrum of activity and efficacy in people with severe stereotypies or depression are attributed to effects on serotonin and noradrenaline. Clomipramine itself is a potent and selective inhibitor of neuronal serotonin reuptake, and its principle metabolite, desmethylclomipramine, is an inhibitor of neuronal noradrenaline reuptake. In addition, clomipramine and desmethylclomipramine are antagonists of cholinergic muscarinic receptors, which accounts for many of the reported adverse effects in humans.

Clomipramine has been shown to be effective as an aid in the treatment of several behavioral disorders in dogs, including separation anxiety and stereotypies, and the pharmacokinetics of clomipramine in dogs have been studied. For instance, the compound was eliminated rapidly after IV and oral administration of a single dose (5 mg/kg of body weight) of C-labeled clomipramine to 1 dog. Similarly, elimination was rapid after administration of single or multiple doses (3 mg/kg) of clomipramine to 6 dogs. However, samples were collected too infrequently in that study to allow pharmacokinetic variables to be determined optimally.

The purpose of the study reported here was to determine the pharmacokinetics of clomipramine and its principle metabolite (desmethylclomipramine) in the plasma of dogs after IV or oral administration of a single dose. A gas chromatography with mass-selective detection (GC-MS) method was used to measure concentrations of clomipramine and desmethylclomipramine. Extent of protein binding of clomipramine and desmethylclomipramine was assessed by use of an ultrafiltration method.

Materials and Methods

Dogs—Twelve Beagles (6 male and 6 female) between 8 and 8.5 months old and weighing between 10.9 and 17.1 kg were used. Dogs were housed in climate-controlled rooms in groups of 2 and fed a complete diet, consisting of canned dog food, twice daily at approximately 7 AM and 3 PM. Water was available ad libitum. Studies were conducted under a Swiss Federal Permit after approval by an Ethics Committee of the Canton of Fribourg. Physical examinations were performed and feed intake and body weight of the dogs were monitored throughout the study. Complete blood counts and plasma biochemical analyses (including determination of alanine aminotransferase and γ-glutamyltranspeptidase activities) were performed before the start of each of the 3 phases of the study and at the end of the trial. No abnormalities were detected in any dog.

Study design—Each dog received the 3 following treatments in a balanced, randomized, three-way crossover design with a 2-week interval between each phase: clomipramine (2 mg of the HCl salt/kg) IV approximately 1 hour after feeding, clomipramine (4 mg of the HCl salt/kg) PO 6 to 22 minutes after feeding, and clomipramine (4 mg of the HCl salt/kg) PO prior to the morning feeding (approx 13 hours after dogs had last been fed; dogs were fed 2 to 3 hours after clomipramine administration).

The dose administered PO (4 mg/kg) was at the upper end of the dose range used clinically in dogs. In a preliminary
study, bolus IV injection of clomipramine at a dose of 4 mg/kg caused transient weakness in dogs. Therefore, a slightly lower dose (2 mg/kg) was chosen for IV administration. For oral administration, 5 and 20 mg tablets were used. In all cases, the exact dose was given by administering a combination of whole and partial tablets. For IV administration, an aqueous solution containing 25 mg of clomipramine/ml was used.

Cephalic vein blood samples were collected 1 hour prior to administration of clomipramine and 3, 25, 45, and 65 minutes and 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, and 30 hours after IV administration and 30, 70, 120, 160, and 200 minutes and 4, 5, 6, 8, 10, 12, 16, 24, and 30 hours after oral administration. Blood samples were immediately placed in prechilled 5 ml administration and 30, 70, 120, 160, and 200 minutes and 4, 5, 6, 8, 10, 12, 16, 24, and 30 hours after IV administration. Blood samples were immediately placed in prechilled 5 ml glass tubes containing lithium heparin, and tubes were stored on ice for a maximum of 30 minutes. Samples were centrifuged at 1,800 × g for 20 min at 4 C, and plasma was collected and stored at ~20 C until analyzed. All samples were analyzed within 3 months after collection.

**Measurement of plasma clomipramine and desmethylclomipramine concentrations**—Plasma clomipramine and desmethylclomipramine concentrations were measured simultaneously by use of a GC-MS method. Briefly, after addition of known amounts of deuterium-labeled internal standards of clomipramine and desmethylclomipramine to give final concentrations of 637 and 259 nmol/L, respectively, clomipramine and desmethylclomipramine were derivatized with pentafluoropropionic anhydride. Gas chromatography was performed with a 12 m × 0.2 mm × 0.33 μm column and a mass-selective detector. Standard curves were prepared, using plasma from untreated dogs to which clomipramine and desmethylclomipramine had been added to give concentrations ranging from 5.7 to 570 nmol/L for clomipramine and 5.9 to 594 nmol/L for desmethylclomipramine. Standard curves for both compounds were linear over the stated range. Coefficients of variation for within- and between- assay precision (5 runs) were < 15% for clomipramine and desmethylclomipramine concentrations. The lower limit of quantification was 5.7 nmol/L for clomipramine and 5.9 nmol/L for desmethylclomipramine; concentrations less than the lower limit of quantification were designated as 0.

**Pharmacokinetic calculations**—Two or 3 phases were observed in the plasma concentration versus time curves after IV administration of clomipramine. Concentrations of clomipramine and desmethylclomipramine corresponded to the following equation:

\[ C = C_0 e^{-\lambda t} \]

where C is plasma concentration and \( C_0 \) is the coefficient and \( \lambda \) is the rate constant of the ith phase. The rate constant and coefficient of the terminal (\( \lambda_t \) and \( C_t \)) phase were calculated by linear least-squares regression analysis of the semilogarithmic concentration versus time data, using a computer program and a minimum of 4 data points greater than the limit of quantification. Rate constants and coefficients of the preceding second (\( \lambda_2 \)) and first (\( \lambda_1 \)) phases were determined by the method of residuals. The extrapolated concentration at time 0 (\( C_0 \)) was estimated from the regression analysis.

Pharmacokinetic parameters were calculated using standard formulas. Half-life of the ith phase (\( t_{1/2,i} \)) was calculated as \( \ln2/\lambda_i \). Area under the concentration vs time curve from time of administration to time of the last value greater than the limit of quantification (AUC(0→∞)) was calculated by use of the linear trapezoidal rule. Area under the concentration vs time curve from time of administration to infinity (AUC(0→∞)) was calculated as AUC(0→∞) + C(0→∞). Systemic plasma clearance (CL) was calculated as Dose/AUC(0→∞). Mean residence time (MRT) was calculated as AUMC(0→∞)/AUC(0→∞), where AUMC(0→∞) was area under the first moment curve. Apparent volume at steady state (Vss) was calculated as Dose × AUMC(0→∞)/(AUC(0→∞)). Apparent volume of the central compartment (Vc) was calculated as Dose/CL.

Following oral administration of clomipramine, maximal concentration (Cmax), time to reach Cmax (Tmax), t1/2, AUC(0→∞), AUC(0→t), and MRT were calculated. The fraction of the administered oral dose available systemically (F) was calculated from the following equation:

\[ F = \frac{AUC_{oral}(0→∞) \times Dose_{oral}}{AUC_{oral}(IV) \times Dose_{oral}} \]

Values of F were determined for clomipramine and desmethylclomipramine and for the sum of the molar concentrations of clomipramine and desmethylclomipramine.

**Measurement of protein binding**—Extent of binding of clomipramine and desmethylclomipramine by serum proteins was estimated by use of the ultrafiltration method. Serum was used to avoid any possible interaction with anticoagulants. Duplicate solutions of clomipramine (0.29, 2.9, 14.2, and 28.5 nmol/L) and desmethylclomipramine (0.15, 1.5, 14.8, and 29.6 nmol/L) were prepared in serum obtained from healthy dogs that had never received clomipramine. An aliquot (1 mL) of each of the samples was ultrafiltered, using a micropartition system that had been equilibrated at 37 C for ≥ 10 minutes. Concentrations of clomipramine and desmethylclomipramine in the serum and ultrafiltrate were determined by use of the GC-MS method. Free percentage of the compounds was calculated by dividing concentration in the ultrafiltrate by concentration in the sample before ultrafiltration. Bound percentage was calculated by subtracting free percentage from 100.

**Statistical analyses**—Values of pharmacokinetic variables were expressed as median, except for half-life values, which were expressed as harmonic means. Ratios of values obtained for AUC(0→∞), Cmax, and MRT were calculated by dividing concentration in the ultrafiltrate by concentration in the sample before ultrafiltration. Bound percentage was tested by means of ANOVA. As treatment sequence was not found to have a significant effect, bioequivalence calculations were determined, using pooled data for all dogs and using data for each sex separately. Bioequivalence was evaluated by use of a Bayesian bioequivalence test approach, with equivalence limits of 80 to 125% (0.80 to 1.25) for the ratio of values obtained when dogs were fed versus values obtained when dogs were not fed. Differences in Tmax and half-life values between groups were tested by use of a Wilcoxon rank sum test, because half-life data appeared nonrobust, and Tmax values were derived from few time points. All tests were performed as two-tailed tests. Values of P < 0.05 were considered significant.

**Results**

Results for 1 dog suggested that a portion of the clomipramine intended for IV administration was given extravascularly. Therefore, data obtained for this dog after IV administration of clomipramine were not included in the analyses. Terminal half-lives (\( \lambda_t \) phase) could not be modeled optimally in all dogs, especially for desmethylclomipramine. Furthermore, after IV administration of clomipramine, the contribution of the extrapolated part of the AUC(0→∞) (i.e., the portion from the last recorded concentration to infinity, \( C_t/\lambda_t \)) was large (mean, 19.1%; range, 9 to 37%; n = 11) for
Table 1—Pharmacokinetics of clomipramine and its metabolite desmethylclomipramine in plasma of dogs following IV administration of a single dose of clomipramine (2 mg/kg)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clomipramine</th>
<th>Desmethylclomipramine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No. of dogs</td>
</tr>
</tbody>
</table>

| C0 (nmol/L) | 3,297.0 | 2,453–4,023 | 11 | NA | NA |
| C1 (nmol/L) | 1,778.0 | 763–2,524 | 10 | NA | NA |
| C2 (nmol/L) | 1,505.0 | 912–2,831 | 11 | 76.2 | 25.7–1,523 |
| C3 (nmol/L) | 79.3 | 20.1–929 | 11 | 36.5 | 10.4–99.3 |
| λ1 (h−1) | 2.6 | 0.60–5.1 | 10 | NA | NA |
| λ2 (h−1) | 0.53 | 0.40–1.9 | 11 | 0.87 | 0.51–5.9 |
| λ3 (h−1) | 0.10 | 0.07–0.40 | 11 | 0.26 | 0.07–0.41 |
| t1/2,1 (h) | 0.23* | 0.14–1.2 | 10 | NA | NA |
| t1/2,2 (h) | 1.1* | 0.37–1.7 | 11 | 0.45* | 0.12–1.4 |
| t1/2,3 (h) | 5.9* | 1.7–10.3 | 11 | 2.9* | 1.7–9.9 |
| AUC0−∞ (nmol×h/L) | 4,158.0 | 3,147–5,135 | 11 | 166.0 | 68.0–232 |
| AUC0−t (nmol×h/L) | 4,242.0 | 3,179–5,321 | 11 | 227.0 | 98.1–284 |
| CL (L/h/kg) | 1.4 | 1.1–1.9 | 11 | NA | NA |
| Vc (L/kg) | 3.7 | 2.6–5.6 | 11 | NA | NA |
| Vss (L/kg) | 1.7 | 1.4–2.3 | 11 | NA | NA |
| MRT (h) | 3.0 | 1.8–3.3 | 11 | 3.5 | 2.6–10.8 |

*Values are harmonic mean.
NA = Not applicable. C0 = Extrapolated concentration at time 0. C1 = Coefficient and rate constant of the ith phase. λi = Half-life of the ith phase. AUC0−∞ = Area under the plasma concentration versus time curve between time 0 and the last measured concentration. AUC0−t = Area under the plasma concentration versus time curve between time 0 and infinity. CL = Systemic plasma clearance. Vss = Apparent volume of distribution at steady state. Vc = Apparent volume of the central compartment. MRT = Mean residence time.

Table 2—Pharmacokinetics of clomipramine and desmethylclomipramine in plasma of 12 dogs following oral administration of a single dose of clomipramine (4 mg/kg) after food was withheld for 15 hours (unfed) and < 25 minutes after dogs were fed

<table>
<thead>
<tr>
<th>Variable</th>
<th>Unfed</th>
<th>Fed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
</tbody>
</table>

| Cmax (nmol/L) | 405.0 | 136–883 | 534.0 | 219–1,074 |
| Tmax (h) | 1.2 | 1.2–2 | 1.2 | 0.5–2 |
| t1/2,1 (h) | 5.0* | 2.9–20.8 | 1.0* | 1.8–8.9 |
| AUC0−∞ (nmol×h/L) | 1,280.0 | 483–2,038 | 1,381.0 | 854–2,484 |
| AUC0−t (nmol×h/L) | 1,374.0 | 550–2,068 | 1,452.0 | 903–2,548 |
| F (%) | 16.1 | 8.7–26.0 | 19.8 | 12.5–31.5 |

Desmethylclomipramine

| Cmax (nmol/L) | 142.0 | 54–331 | 180.0 | 53–257 |
| Tmax (h) | 1.2 | 1.2–2 | 1.2 | 0.5–2 |
| t1/2,1 (h) | 2.1* | 1.4–7.4 | 1.9* | 1.6–3.2 |
| AUC0−∞ (nmol×h/L) | 439.0 | 175–695 | 467.0 | 280–776 |
| AUC0−t (nmol×h/L) | 447.0 | 195–902 | 458.0 | 237–703 |
| F (%) | 138.0 | 36.9–199 | 142.0 | 87.1–170 |

Sum of clomipramine and desmethylclomipramine

| AUC0−∞ (nmol×h/L) | 1,867.0 | 728–2,929 | 1,851.0 | 1,076–3,266 |
| AUC0−t (nmol×h/L) | 1,759.0 | 768–2,955 | 1,913.0 | 1,125–3,336 |
| F (%) | 21.3 | 11.8–35.2 | 26.5 | 16.8–38.7 |

Cmax = Maximal concentration. Tmax = Time to reach Cmax. F = Fraction of the oral administered dose available systemically. See Table 1 for remainder of key.

Pharmacokinetics following IV administration—
Following IV administration of clomipramine, 3 distinct phases were observed in the clomipramine concentration versus time curves for 10 dogs. Two distinct phases were observed for the remaining dog, and the fastest
There was no sign of secondary (delayed) peaks indicative of enterohepatic recycling in the clomipramine concentration versus time curves. Desmethylclomipramine was 17.5 (range, 14.5 to 35.1). Harmonic mean “apparent” half-lives for the 2 dogs, and 2 distinct phases were observed for the other clomipramine concentration versus time curves for 2 distinct phase was observed in the desmethyl clomipramine steady state was high (median, 3.7 L/kg). Volume of distribution of clomipramine at 3.0 hours), and plasma clearance was rapid (median, 1.4 L/h/kg).

Following IV administration of clomipramine, 1 distinct phase was observed in the desmethylclomipramine concentration versus time curves for 2 dogs, and 2 distinct phases were observed for the other 9 dogs. Harmonic mean “apparent” half-lives for the 2 phases (λ₂, λ₃) were 0.45 and 2.9 hours, respectively (Table 1). Mean residence time was low (median, 3.0 hours), and plasma clearance was rapid (median, 1.4 L/h/kg). Volume of distribution of clomipramine at steady state was high (median, 3.7 L/kg).

Following IV administration of clomipramine, 1 distinct phase was observed in the desmethylclomipramine concentration versus time curves for 2 dogs, and 2 distinct phases were observed for the other 9 dogs. Harmonic mean “apparent” half-lives for the 2 phases (λ₁, λ₂) were 0.23, 1.1, and 5.0 hours, respectively (Table 1). Median ratio of the AUC∞ for clomipramine versus the AUC∞ for desmethylclomipramine was 0.45 and 2.9 hours, respectively (Table 1). For desmethylclomipramine, measured half-lives were not true estimates of the distribution and elimination phases, because the observed profiles were influenced by the continuous generation of desmethylclomipramine via metabolism from clomipramine. Desmethylclomipramine concentrations were low, compared with clomipramine concentrations, after IV administration of clomipramine (Fig 1). Median ratio of the AUC∞ for clomipramine versus the AUC∞ for desmethylclomipramine was 17.5 (range, 14.5 to 35.1). There was no sign of secondary (delayed) peaks indicative of enterohepatic recycling in the clomipramine concentration versus time and desmethylclomipramine concentration versus time curves.

**Pharmacokinetics following oral administration**—Regardless of whether dogs were fed or unfed, peak plasma concentrations of clomipramine and desmethylclomipramine were rapidly achieved (median Tmax, 1.2 hours; Table 2; Figs 2 and 3). In addition, values for MRT and t½z, following oral administration were similar to values obtained following IV administration, indicating that clomipramine was rapidly absorbed and transformed to desmethylclomipramine. Desmethylclomipramine concentrations were higher after oral administration of clomipramine than after IV administration. Following oral administration of clomipramine, median ratio of the AUC∞ for clomipramine versus the AUC∞ for desmethylclomipramine was 2.6 (range, 1.8 to 6.6) when dogs were not fed prior to clomipramine administration and 3.2 (range, 2.0 to 5.2) when dogs were fed.

Median systemic bioavailabilities after oral administration of clomipramine to unfed and fed dogs were 16.1 and 19.8%, respectively, for clomipramine; 138 and 142%, respectively, for desmethylclomipranime; and 21.3 and 26.5%, respectively, for the sum of the molar concentrations of clomipramine and desmethylclomipramine.

**Effect of feeding**—Effect of feeding on pharmacokinetics of clomipramine and desmethylclomipramine were examined by comparing values obtained for AUC∞, Cmax, t½z, and Tmax when dogs were fed with values obtained when dogs were not fed (Table 2). Values for AUC∞ and Cmax were significantly higher for clomipramine when dogs were fed, but not for desmethylclomipramine. Geometric mean ratios of AUC∞ when dogs were fed to AUC∞ when dogs were not fed were 1.25 (95% CI, 1.10 to 1.41) for clomipramine and 1.08 (95% CI, 0.87 to 1.34) for desmethylclomipramine. Geometric mean ratios of Cmax when dogs were fed to Cmax when dogs were not fed were 1.55 (95% CI, 1.20 to 2.0) for clomipramine and 1.15 (95% CI, 0.85 to 1.35) for desmethylclomipramine. Values for t½z and Tmax obtained when dogs were fed were not significantly different from values obtained when dogs were not fed.

**Protein binding**—Clomipramine was not detected in ultrafiltrates from any of the serum samples, and measured concentrations in serum samples were 0.33, 3.6, 17.1, and 34.2 nmol/L. Extent of protein binding was, therefore, calculated as >99.5% for concentrations ≥0.17 nmol/L and >99.5% for concentrations ≥3.6 nmol/L. Recovery rates were >80%.

Desmethylclomipramine was detected in ultrafiltrate samples only from serum samples with concentrations ≥19.5 nmol/L, and measured concentrations in serum samples were 0.17, 1.8, 19.5, and 37.9 nmol/L. Extent of protein binding was, therefore, calculated as >95% for the lowest concentration (0.17 nmol/L) and >99.5% for concentrations ≥1.8 nmol/L. Recovery rates were >87%.

**Discussion**

Results of this study indicate that, in certain aspects, the pharmacokinetics of clomipramine in dogs are simi-
lar to the pharmacokinetics in humans. \(^3,15,16\) In both species, clomipramine is rapidly absorbed from the gastrointestinal tract after oral administration, but bioavailability is incomplete, presumably because of substantial first-pass metabolism. In addition, there is moderately high variability in plasma concentrations after administration, extensive binding to plasma proteins, and a large volume of distribution. However, important differences appear to exist between pharmacokinetics in dogs and humans. Clomipramine and desmethyclomipramine are eliminated more rapidly from plasma in dogs, and the ratio of the concentration of clomipramine to the concentration of desmethyclomipramine is higher.

The principle limitation of this study was our inability to assess reliably the terminal half-life of desmethyclomipramine in all dogs and the resulting unreliability of calculated variables such as \(\text{AUC}_{\infty}\) and MRT. For desmethyclomipramine, the calculated \(t_{1/2}\) is a function of the concentration of the molecule and generation via metabolism from clomipramine. For this reason, the \(t_{1/2}\) of desmethyclomipramine should not be shorter than that for clomipramine. The fact that this occurred frequently in our results is evidence that half-lives were not determined accurately in all dogs.

Peak plasma concentrations of clomipramine and desmethyclomipramine were attained rapidly after oral administration of clomipramine. In addition, values for MRT and \(t_{1/2}\) following oral administration were similar to values obtained following IV administration, and systemic bioavailability, calculated by comparing \(\text{AUC}_{\text{oral}}\) following oral administration with \(\text{AUC}_{\text{IV}}\) following IV administration, was approximately 20% for clomipramine and 140% for desmethyclomipramine. Taken together, these results are consistent with fast absorption of clomipramine from the gastrointestinal tract and extensive, rapid first-pass metabolism.\(^13,17\) Demethylation to desmethyclomipramine is the major metabolic pathway for clomipramine in humans, but hydroxylation and N-oxidation and subsequent conjugation are also important.\(^8\) Studies involving administration of radiolabeled clomipramine to dogs suggest that there is complete absorption of the drug from the gastrointestinal tract in dogs, which is as expected given the drug's high lipid solubility.\(^8,18\) Excretion of clomipramine has been reported to be predominately (approx 80%) via the biliary route in dogs;\(^5\) nevertheless, we did not find any evidence of enterohepatic recycling.

Determining the bioavailability of clomipramine is problematic, because both clomipramine and desmethyclomipramine are biologically active, and the 2 compounds act on different neurotransmitter systems. Bioavailability can, therefore, be calculated only for clomipramine itself (16 to 20% in the present study) or for the sum of the concentrations of clomipramine and desmethyclomipramine (21 to 26% in the present study).\(^9\) However, the discrepancy between results of these 2 methods was small in our study. This may be explained by the fact that values of \(\text{AUC}_{\text{oral}}\) for desmethyclomipramine were smaller than those for clomipramine. Nevertheless, all of these values could be underestimates of the true bioavailability, as results of a related study indicated that clearance of clomipramine and desmethyclomipramine are reduced at higher concentrations.\(^19\) Correction of the bioavailability for differences in half-life between IV and oral administration was not valid in our study, as it increased the coefficient of variation for F values and half-lives were not significantly different between IV and oral administration.\(^20\)

We observed moderately large variability among dogs in regard to plasma concentrations of clomipramine and desmethyclomipramine, and maximum recorded \(\text{AUC}_{\infty}\) values were three- to fourfold minimum values. Similar between-subject variation in clomipramine concentrations in humans has been reported,\(^15,21\) but this variation is smaller than that observed with other tricyclic antidepressants such as amitriptyline and imipramine.\(^21\) The most important cause of this variability in humans is genetically controlled differences in the rate of biotransformation mediated by various cytochrome P450 enzymes.\(^16,21\) In this study, \(C_{\text{max}}\) values were higher in female than in male dogs, but \(\text{AUC}_{\text{oral}}\), \(T_{\text{max}}\), and half lives for clomipramine and desmethyclomipramine were not significantly different between male and female dogs. Therefore, we conclude that there are not any clinically relevant sex differences in the pharmacokinetics of clomipramine in dogs.

As in other species, \(V_{ss}\) of clomipramine in dogs was large (3.7 L/kg). In rats, radiolabeled clomipramine was distributed extensively into tissues such as lungs, kidneys, liver, and the brain, resulting in low plasma concentrations.\(^8,24\) This pattern of distribution is typical for lipophilic bases such as clomipramine.\(^8\) We could not determine the volume of distribution of desmethyclomipramine in this study, but it is likely to be somewhat lower than that of clomipramine, because desmethyclomipramine is a more polar molecule. We also found that clomipramine and desmethyclomipramine were extensively protein bound (> 96%) in dogs, as they are in humans.\(^15,21\) Drugs that are highly bound to plasma proteins may interact with other agents. However, the extensive protein binding of clomipramine is not responsible for any known drug interaction in humans, because the binding sites on plasma proteins are not shared with any other known class of drug.\(^18\)

We observed 2 important differences between pharmacokinetics of clomipramine in dogs and reported pharmacokinetics in humans. First, the terminal half-lives of clomipramine and desmethyclomipramine were short (≤ 5 hours) in dogs, whereas values of 18 to 34 and 36 to 50 hours have been reported for humans.\(^15,21\) These differences may be explained by the smaller volume of distribution and faster clearance of clomipramine in dogs versus humans. In addition, \(T_{\text{max}}\) values were shorter in dogs (approx 1 hour), compared with values of 2 to 5 hours (clomipramine) and 4 to 8 hours (desmethyclomipramine) reported for humans.\(^15,21\) Second, the ratio of clomipramine to desmethyclomipramine concentrations (assessed by comparing \(\text{AUC}_{\text{oral}}\) values) was higher in dogs (approx 3:1) than the reported ratio of 1.25 for humans.\(^15,21\) This possibly is because in humans, elimination of desmethyclomipramine is slower than elimination of clomipramine, whereas in dogs, elimination of desmethyclomipramine is equal to or faster than elimination of clomipramine.\(^15,21\)
than in humans. The higher clomipramine:desmethylclomipramine concentration ratio may explain why clomipramine is associated with a lower incidence of adverse anticholinergic effects in dogs than in humans. In addition, the faster elimination of clomipramine and desmethylclomipramine in dogs may reduce the potential for adverse effects. In theory, the ratio of serotonin effects versus noradrenergic and cholinergic effects in dogs could be optimized by administering clomipramine IV rather than PO.

Compared with administration when dogs had not been fed for 15 hours, administration of clomipramine shortly after dogs were fed resulted in moderately higher clomipramine concentrations (25% higher AUC_{0-∞}) but no difference in desmethylclomipramine concentrations. This increase, however, was small, compared with the variability among dogs (up to 400%). Therefore, we expect that there will not be any clinically important differences in efficacy regardless of whether clomipramine is administered with or without food. Bioavailability of other tricyclic antidepressants in humans generally is not altered by administration with food, although an increase in bioavailability has been reported for imipramine. The increased bioavailability of clomipramine, but not of desmethylclomipramine, in dogs when clomipramine was administered with food may be explained by a reduction in first-pass metabolism because of the postprandial increase in hepatic blood flow. Our estimate of the clearance of clomipramine in dogs (1.4 L/h/kg) is similar to the hepatic blood flow in this species (approx 2 L/h/kg). This, combined with the known extensive biliary excretion and high first-pass metabolism of clomipramine in dogs, indicates that the hepatic extraction rate of this drug is very high in dogs, and its pharmacokinetics should be highly sensitive to changes in hepatic blood flow.

References