Objective—To determine pharmacokinetics of clomipramine and its principle metabolite (desmethylclomipramine) in the plasma of dogs following single-dose and repeated-dose oral administration at various dosages.

Animals—9 male and 9 female Beagles.

Procedures—Clomipramine was administered orally at a dose of 1, 2, or 4 mg/kg to 3 male and 3 female dogs, first as a single dose and then, after an interval of 14 days, twice daily for 10 days. Plasma clomipramine and desmethylclomipramine concentrations were measured by use of a gas chromatography with mass-selection method.

Results—Dose-related accumulation was detected following repeated-dose administration. Accumulation ratios after administration of clomipramine at dosages of 1, 2, and 4 mg/kg twice daily were 1.4, 1.6, and 3.8, respectively, for clomipramine and 2.1, 3.7, and 7.6, respectively, for desmethylclomipramine. Terminal half-life increased slightly (1.6-fold for clomipramine and 1.2-fold for desmethylclomipramine) with repeated-dose administration but remained short in all groups (≤4 hours). Steady state was reached within 4 days in all animals. Ratios of the areas under the concentration versus time curves from time 0 to 12 hours for clomipramine and desmethylclomipramine were 3.9, 3.1, and 1.5 after repeated administration at dosages of 1, 2, and 4 mg/kg every 12 hours, respectively. Areas under the concentration versus time curve, mean residence times, and terminal half-lives were not significantly different between male and female dogs.


Clomipramine hydrochloride is used to treat a wide range of diseases in humans, including anxieties, depression, and stereotypies. It has also been shown to be effective as an aid in the treatment of several behavioral disorders in dogs, including separation anxiety and stereotypies.

In another study, we determined the pharmacokinetics of clomipramine and its major metabolite, desmethylclomipramine, in dogs after single-dose IV administration (4 mg/kg) and single-dose oral administration (2 mg/kg). The kinetics were characterized by a large volume of distribution (3.7 L/kg), reflecting the lipophilic nature of the compound and rapid elimination of clomipramine and desmethylclomipramine ($t_{1/2} ≤ 5$ hours). The rapid disappearance of clomipramine and desmethylclomipramine from plasma in dogs has been shown in other studies, and because of their rapid elimination, minimal accumulation of clomipramine and desmethylclomipramine might be expected during repeated administration of clomipramine to dogs. However, accumulation of clomipramine and desmethylclomipramine in dogs after oral administration of clomipramine at a dosage of 3 mg/kg of body weight every 24 hours for 28 days has been reported. This may be because of reduced clearance of the molecules with repeated application. An accumulation of desmethylclomipramine and, to a lesser extent, clomipramine occurs at the start of treatment in humans with repeated administration of clomipramine. However, the elimination rate of these substances is markedly longer in humans than in dogs.

The purpose of the study reported here was to determine the pharmacokinetics of clomipramine and desmethylclomipramine in the plasma of dogs following single-dose and repeated-dose oral administration at various dosages.

Materials and Methods

Dogs—Eighteen healthy Beagles (9 male, 9 female) between 51 and 60 weeks old and weighing between 10.7 and 14.3 kg were used. Dogs were housed in climate-controlled rooms in groups of 3 and fed a complete dry diet twice daily at approximately 0:30 AM and 3:30 PM. All dogs ate all of the food soon after it was provided. 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 each phase of the study and at the end of the trial. There were not any changes in health status, body weight, feed intake, or results of laboratory tests during the study.

Study design—Dogs were randomly assigned to 1 of 3 groups with 6 dogs (3 male, 3 female) per group. A randomized complete block design was used with blocking on body weight, sex, and litter. The study was conducted in 2 phases. During the first phase, dogs were given a single dose of clomipramine PO (group 1, 1 mg/kg; group 2, 2 mg/kg; group 3, 4 mg/kg) approximately 1 hour after their morning feeding. Venous blood samples (4 to 5 ml) were collected immediately before drug administration (0 hours) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours after. All blood samples were collected in glass tubes containing lithium heparin. After mixing, tubes were centrifuged at 1,600 X g for 10 minutes at
Plasma was collected and stored at −20°C until analyzed; all samples were analyzed within 3 months after collection. The second phase of the study was conducted 14 days after the first. During this phase, dogs were given clomipramine (group 1, 1 mg/kg; group 2, 2 mg/kg; group 3, 4 mg/kg) twice daily for 9 consecutive days (days 14 through 22) and once the morning of the following day (day 23). Throughout this phase, clomipramine was administered at approximately 7:30 AM (1 hour after the morning feeding) and 4:30 PM (1 hour after the afternoon feeding). On days 14, 15, 16, 17, 18, 21, and 22, blood samples were collected immediately before the morning dose of clomipramine was given and 1 hour after the afternoon dose was given. On day 23, blood samples were collected immediately before and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, and 24 hours after the final dose of clomipramine was given.

For each phase of the study, clomipramine was administered as the hydrochloride salt as 5, 20, and 80 mg disposable tablets containing a meat flavor. In all cases, the exact dose (within 10% on a mg/kg basis) was given by administering a combination of whole and partial tablets.

Measurement of plasma clomipramine and desmethylclomipramine concentrations—Plasma clomipramine and desmethylclomipramine concentrations were measured simultaneously by use of a gas chromatography with mass-selective detection (GC-MS) method, as described.[4,18] Coefficients of variation for within- and between-assay precision (5 runs) were < 15% for clomipramine (range, 5.7 to 570 nmol/L) and desmethylclomipramine (range, 5.9 to 594 nmol/L) concentration. The lower limit of quantification was 5.7 nmol/L for clomipramine and 5.9 nmol/L for desmethylclomipramine; concentrations less than the lower limits of quantification were designated as 0.

Pharmacokinetic calculations—The rate constant of the terminal (λz) phase of the concentration versus time curve was calculated by linear least-squares regression analysis, using a computer program and a minimum of 4 data points greater than the limit of quantification.

Pharmacokinetic parameters, including maximal concentration (Cmax), time to reach Cmax (Tmax), and half-life of the terminal phase (t1/2z), were calculated, using standard formulas.[17] Area under the plasma concentration versus time curve from time of administration to time of the last value greater than the limit of quantification (AUC0–∞) and area under the plasma concentration versus time curve from time of administration to 12 hours after administration (AUC0–12) were calculated by use of the linear trapezoid rule. Area under the plasma concentration versus time curve from time of administration to infinity (AUC0–∞) was calculated as AUC0–12 + C0/λz. Mean residence time (MRT) following single-dose administration was calculated as AUMC0–∞/AUC0–∞, where AUMC0–∞ was area under the first moment curve. For data obtained after repeated-dose administration, MRT at steady state (MRTss) was calculated from the following equation[19]:

\[
\text{MRTss} = \frac{\text{AUMC}_{0-\infty} + \tau \times \text{AUC}_{\tau-\infty}}{\text{AUC}_{0-\tau}}
\]

where \(\tau\) = the dosing interval (12 hours). The accumulation ratio (R) of clomipramine and desmethylclomipramine was calculated as the ratio of the area under the concentration versus time curve at steady state after repeated-dose administration (ie, after the 19th dose) to the area under the concentration versus time curve after administration of a single dose[20]:

\[
R = \frac{\text{AUC}_{0-\infty}}{\text{AUC}_{0-1}(1)}
\]

Time to reach steady state was estimated from concentrations obtained for samples collected on consecutive days during the second phase of the study. These concentrations were used as estimates of the trough and peak concentrations. Anticipated accumulation was calculated from measured terminal half-lives, using the following equation[20]:

\[
R = \frac{1}{1 - e^{-\lambda t}}
\]

Statistical analyses—Values of pharmacokinetic variables were expressed as medians, except for half-lives, which were expressed as harmonic means. Values obtained for AUC0–12, AUC0–∞, MRT, and R were log transformed to provide approximations of normal distributions. Differences between AUC0–12, MRT, and R after single- and repeated-dose administration of clomipramine and differences between AUC0–∞ after single-dose administration and AUC0–12 after repeated-dose administration were tested for significance by use of paired t tests.[4] Effect of dose and sex on MRT, R, and dose-normalized AUC0–12 were evaluated by use of ANOVA. The correlation between AUC0–12 after single- and repeated-dose administration was tested by calculating the Pearson correlation coefficient. Differences in half-lives between groups were tested by use of nonparametric tests, because data for half-lives did not appear to be robust. The Wilcoxon signed rank test[4] was used to compare values for each dog after single- and repeated-dose administration, and the Kruskal-Wallis test[4] was used to test for effects of sex and dose. All statistical tests were performed as two-tailed tests. Values of P < 0.05 were considered significant.

Results

After single-dose and repeated-dose administration of clomipramine, peak concentrations of clomipramine (median Tmax ≤ 3 hours) and desmethylclomipramine (median Tmax ≤ 3.5 hours) were rapidly attained (Tables 1 and 2), and concentrations of both compounds declined rapidly (t1/2z ≤ 4 hours).

Dose linearity of the kinetics of clomipramine and desmethyloclopramine was tested by examining AUC0–12. Following single-dose administration of clomipramine, the dose response of AUC0–12 for clomipramine and desmethyloclopramine was linear. The ratio of median AUC0–12 in response to administration of 1, 2, and 4 mg/kg doses was 1:2.6:2.6 for clomipramine (Table 1) and 1:2.7:4.8 for desmethyloclopramine (Table 2). However, following repeated-dose administration of clomipramine, the dose response of AUC0–12 for clomipramine and desmethyloclopramine was not linear (P = 0.01). The ratio of median AUC0–12 in response to administration of 1, 2, and 4 mg/kg twice daily was 1:3.1:8.1 for clomipramine (Table 1) and 1:4.2:22.1 for desmethyloclopramine (Table 2).
clomipramine, male dogs had significantly higher dose-normalized AUC_{0-12} values for desmethylclomipramine than female dogs (ratio of median values, 3.3) but did not have significantly higher dose-normalized AUC_{0-12} values for clomipramine (ratio of median values, 2.5; \( P = 0.06 \)). There were no significant differences in AUC_{0-12} between male and female dogs following repeated-dose administration of clomipramine.

Values of AUC_{0-12} for clomipramine and desmethylclomipramine were significantly greater after repeated-dose administration than after single-dose administration; therefore, R values were > 1. The extent of accumulation of these compounds increased as dosage of clomipramine increased, but the extent of accumulation was greater for desmethylclomipramine than for clomipramine. Median R values after administration of clomipramine at dosages of 1, 2, and 4 mg/kg twice daily were 1.4, 1.6, and 3.8, respectively, for clomipramine and 2.1, 3.7, and 7.6, respectively, for desmethylclomipramine. Dosage of clomipramine had a significant effect on R values for desmethylclomipramine (\( P = 0.01 \)) but not for clomipramine (\( P = 0.07 \)). If accumulation was only controlled by the terminal half-life (harmonic mean, \( \leq 4 \) hours for clomipramine and desmethylclomipramine), R values \( \leq 1.14 \) would be expected with a dosing interval of 12 hours.

Extent of accumulation of clomipramine and desmethylclomipramine was not significantly different between male and female dogs. Median R values for male and female dogs were 1.8 and 2.6, respectively, for clomipramine (\( P = 0.09 \)) and 3.5 and 5.2, respectively, for desmethylclomipramine. Dosage of clomipramine had a significant effect on R values for desmethylclomipramine (\( P = 0.07 \)) but not for clomipramine (\( P = 0.07 \)). If accumulation was only controlled by the terminal half-life (harmonic mean, \( \leq 4 \) hours for clomipramine and desmethylclomipramine), R values \( \leq 1.14 \) would be expected with a dosing interval of 12 hours.

Table 1—Pharmacokinetics of clomipramine in plasma of dogs following single-dose (1, 2, or 4 mg/kg) and repeated-dose (1, 2, or 4 mg/kg, twice daily for 10 d) oral administration

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dosage</th>
<th>Median Range</th>
<th>Median Range</th>
<th>Median Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mg/kg</td>
<td>2 mg/kg</td>
<td>4 mg/kg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Single-dose administration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max} (nmol/L)</td>
<td>123</td>
<td>25–398</td>
<td>269</td>
<td>65–388</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>1.3</td>
<td>1–3</td>
<td>1.5</td>
<td>1–2.5</td>
</tr>
<tr>
<td>t_{1/2}α (h)</td>
<td>1.8*</td>
<td>1.0–2.2</td>
<td>1.8*</td>
<td>1.2–3.6</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>2.9</td>
<td>2.2–3.7</td>
<td>3.5</td>
<td>2.5–4.1</td>
</tr>
<tr>
<td>AUC_{0-12} (nmol×h/L)</td>
<td>358</td>
<td>61–1,591</td>
<td>945</td>
<td>199–1,525</td>
</tr>
<tr>
<td>AUC_{0-∞} (nmol×h/L)</td>
<td>378</td>
<td>85–1,809</td>
<td>1,081</td>
<td>212–1,891</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1,092</td>
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<tr>
<td>Repeated-dose administration</td>
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<td></td>
<td></td>
<td>426–1,506</td>
</tr>
<tr>
<td>C_{max} (nmol/L)</td>
<td>93</td>
<td>77–139</td>
<td>202</td>
<td>184–338</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>2</td>
<td>1–3</td>
<td>2.5</td>
<td>1.5–4</td>
</tr>
<tr>
<td>t_{1/2}α (h)</td>
<td>2.1*</td>
<td>1.6–3.1</td>
<td>2.8*</td>
<td>2.0–3.8</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>4.0</td>
<td>3.6–5.8</td>
<td>5.5</td>
<td>4.1–7.0</td>
</tr>
<tr>
<td>AUC_{0-12} (nmol×h/L)</td>
<td>361</td>
<td>348–502</td>
<td>1,119</td>
<td>780–1,545</td>
</tr>
<tr>
<td>AUC_{0-∞} (nmol×h/L)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>R</td>
<td>1.4</td>
<td>0.3–5.7</td>
<td>1.6</td>
<td>0.8–3.9</td>
</tr>
</tbody>
</table>

*Harmonic mean.

\( n = 6 \) dogs/group (3 males and 3 females). NA = Not applicable. C_{max} = Maximum concentration. T_{max} = Time to reach C_{max}. t_{1/2}α = Half-life of the terminal phase. MRT = Mean residence time. AUC_{0-12} = Area under the plasma concentration versus time curve between 0 and 12 hours. AUC_{0-∞} = Area under the plasma concentration versus time curve between 0 and infinity. R = Accumulation ratio.

There was evidence that the pharmacokinetics of clomipramine and desmethylclomipramine changed with repeated-dose administration of clomipramine, because AUC_{0-12} values after repeated-dose administration were significantly greater than AUC_{0-12} values after single-dose administration. Median values for the ratio of AUC_{0-12} after repeated-dose administration to AUC_{0-∞} after single-dose administration for the 1, 2, and 4 mg/kg doses of clomipramine were 1.3, 1.4, and 3.4, respectively, for clomipramine and 0.9, 2.8, and 6.3, respectively, for desmethylclomipramine.

Ratios of AUC_{0-12} for clomipramine to AUC_{0-12} for desmethylclomipramine following repeated-dose administration were less than ratios of AUC_{0-∞} for clomipramine to AUC_{0-∞} for desmethylclomipramine following single-dose administration. Median values for these ratios after repeated-dose administration of clomipramine at dosages of 1, 2, and 4 mg/kg were 3.9 (range, 2.1 to 5.3), 3.1 (1.2 to 3.5), and 1.5 (1.2 to 2.3), respectively, whereas median ratios after single-dose administration of clomipramine at doses of 1, 2, and 4 mg/kg were 5.8 (2.1 to 5.3), 6.9 (2.4 to 7.0), and 2.9 (1.7 to 4.4), respectively. Median ratio for all dogs (\( n = 18 \)) was 3.9 (1.7 to 7.0) after single-dose administration and 2.6 (1.2 to 5.3) after repeated-dose administration.

Plasma concentrations before and 1 hour after administration of clomipramine on days 14, 15, 16, 17, 18, 21, and 22 were used to estimate time to reach steady-state concentrations. Time at which steady-state concentration was achieved, defined as the earliest time at which concentration at a particular time point was greater than or equal to concentrations at subsequent time points, ranged from 1 to 4 days for clomipramine and desmethylclomipramine.

Regardless of whether clomipramine was administered as a single dose or as repeated doses, MRT of clomipramine increased significantly as dosage of clomipramine increased. When clomipramine was administered as repeated doses, MRT of desmethyl-
Clomipramine and desmethylclomipramine peaked quickly after oral administration of clomipramine (Tmax ≤ 3.5 hours) and declined rapidly (t1/2z ≤ 4 hours). The half-life for desmethyldalomipramine was not a true elimination half-life, as concentration of desmethyldalomipramine is a function of its metabolic transformation from clomipramine, as well as its elimination rate. Because measured terminal half-lives of clomipramine and desmethyldalomipramine were similar, we can conclude that the elimination rate of desmethyldalomipramine is the same or faster than that of clomipramine in dogs.

In this study, we found moderately high variability in plasma concentrations of clomipramine and desmethyldalomipramine among dogs (maximum AUC0-12, or AUC0-∞ were 3 to 4 times the minimum values). Similar wide between-subject variation in concentrations of clomipramine and desmethyldalomipramine has been reported for dogs and humans.8,10,11,14,20 The most important cause of this variation in humans is genetically controlled differences in rate of biotransformation.26 Also, we observed that concentrations of clomipramine were higher than those for desmethyldalomipramine in dogs, as has been reported for other studies.8,10 This is an important difference from pharmacokinetics in humans, in whom desmethyldalomipramine concentrations are higher.11-13

Pharmacokinetics of clomipramine in dogs were unconventional in at least 3 aspects. First, repeated-dose administration of clomipramine led to increases in plasma concentrations of clomipramine and desmethyldalomipramine that were larger than expected from half-life values. Extent of accumulation of desmethyldalomipramine was greater than extent of bioaccumulation of clomipramine. Similar findings were reported after administration of clomipramine to dogs at a dosage of 3 mg/kg every 24 hours.26 Second, values of AUC after single-dose administration were poorly correlated with values obtained after repeated-dose administration. Third, pharmacokinetics of clomipramine and desmethyldalomipramine were not necessarily linearly related to dosage of clomipramine. Mean residence times

Discussion
In this study, as in other trials,8,10 concentrations of clomipramine and desmethyldalomipramine peaked significantly as dosage of clomipramine increased. Sex of the dog did not have an effect on MRT of clomipramine or desmethyldalomipramine in either phase of the study.

Mean residence times of clomipramine and desmethyldalomipramine were significantly longer after repeated-dose administration than after single-dose administration for all 3 dosages used. Median ratios of MRT after repeated-dose administration to MRT after single-dose administration were 1.5 (range, 0.9 to 2.1) for clomipramine and 1.5 (1.1 to 2.6) for desmethyldalomipramine. Neither sex nor dosage had a significant effect on ratio of MRT after repeated-dose administration to MRT after single-dose administration.

The terminal half-lives of clomipramine and desmethyldalomipramine were short (< twofold) but significant increase in terminal half-lives of clomipramine and desmethyldalomipramine. Sex did not have a significant effect on terminal half-lives of clomipramine or desmethyldalomipramine after single-dose or repeated-dose administration of clomipramine.

Plasma half-life of clomipramine, but not of desmethyldalomipramine, was significantly longer with repeated-dose administration, compared with single-dose administration. Harmonic mean values for all dosages after single-dose and repeated-dose administration were 1.9 hours (range, 1.0 to 3.8 hours) and 2.8 hours (1.6 to 3.0 hours), respectively, for clomipramine and 2.9 hours (2.1 to 4.7 hours) and 3.0 hours (1.8 to 4.5 hours), respectively, for desmethyldalomipramine. Median values for the ratio of the terminal half-life after repeated-dose administration to terminal half-life after single-dose administration were 1.6 for clomipramine and 1.2 for desmethyldalomipramine.

Table 2—Pharmacokinetics of desmethyldalomipramine in plasma of dogs following single-dose (1, 2, or 4 mg/kg) and repeated-dose (1, 2, or 4 mg/kg twice daily for 10 days) oral administration of clomipramine

<table>
<thead>
<tr>
<th>Variable</th>
<th>Single-dose administration</th>
<th>Repeated-dose administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (nmol/L)</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>Tmax (h)</td>
<td>2.3</td>
<td>5.1</td>
</tr>
<tr>
<td>t1/2z (h)</td>
<td>2.2*</td>
<td>3.4*</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>3.4</td>
<td>6.5</td>
</tr>
<tr>
<td>Λ0-12 (nmol×h/L)</td>
<td>59</td>
<td>92</td>
</tr>
<tr>
<td>Λ∞ (nmol×h/L)</td>
<td>110</td>
<td>NA</td>
</tr>
</tbody>
</table>

See Table 1 for key.

In this study, as in other trials,8,10 concentrations of clomipramine and desmethyldalomipramine peaked quickly after oral administration of clomipramine (Tmax ≤ 3.5 hours) and declined rapidly (t1/2z ≤ 4 hours). The half-life for desmethyldalomipramine was not a true elimination half-life, as concentration of desmethyldalomipramine is a function of its metabolic transformation from clomipramine, as well as its elimination rate.8 Because measured terminal half-lives of clomipramine and desmethyldalomipramine were similar, we can conclude that the elimination rate of desmethyldalomipramine is the same or faster than that of clomipramine in dogs.

In this study, we found moderately high variability in plasma concentrations of clomipramine and desmethyldalomipramine among dogs (maximum AUC0-12, or AUC0-∞ were 3 to 4 times the minimum values). Similar wide between-subject variation in concentrations of clomipramine and desmethyldalomipramine has been reported for dogs and humans.8,10,11,14,20 The most important cause of this variation in humans is genetically controlled differences in rate of biotransformation.26 Also, we observed that concentrations of clomipramine were higher than those for desmethyldalomipramine in dogs, as has been reported for other studies.8,10 This is an important difference from pharmacokinetics in humans, in whom desmethyldalomipramine concentrations are higher.11-13

Pharmacokinetics of clomipramine in dogs were unconventional in at least 3 aspects. First, repeated-dose administration of clomipramine led to increases in plasma concentrations of clomipramine and desmethyldalomipramine that were larger than expected from half-life values. Extent of accumulation of desmethyldalomipramine was greater than extent of bioaccumulation of clomipramine. Similar findings were reported after administration of clomipramine to dogs at a dosage of 3 mg/kg every 24 hours.26 Second, values of AUC after single-dose administration were poorly correlated with values obtained after repeated-dose administration. Third, pharmacokinetics of clomipramine and desmethyldalomipramine were not necessarily linearly related to dosage of clomipramine. Mean residence times
and terminal half-lives of clomipramine and desmethylclomipramine increased as dosage of clomipramine increased. Although with single-dose administration of clomipramine, AUC\textsubscript{0-12} increased in a linear fashion as dose increased, with repeated-dose administration, there was a disproportional increase in AUC\textsubscript{0-12} for desmethylclomipramine and, to lesser extent, for clomipramine as dosage increased. Therefore, the extent of accumulation was related to dosage of clomipramine. This may suggest that the principle elimination steps for clomipramine and desmethylclomipramine are saturable or the molecules themselves inhibit these reactions, as has been suggested for rats\textsuperscript{21,22} and humans.\textsuperscript{23,24} The larger accumulation of desmethylclomipramine, as compared with that of clomipramine, may be explained by mutual competitive inhibition.\textsuperscript{21,22} It is important to point out that the observed accumulation of clomipramine and desmethylclomipramine in our dogs was complete within the first 4 days of treatment.

Although males had significantly greater dose-normalized AUC\textsubscript{0-12} values for desmethylclomipramine following single-dose administration of clomipramine than females, other differences between sexes were not observed. Therefore, we conclude that, as in another study\textsuperscript{9}, there were no biologically relevant differences between male and female dogs.

The limitations of this study must be fully appreciated. Clomipramine is a centrally acting agent, and although some authors have described a correlation between plasma clomipramine and desmethylclomipramine concentrations and clinical efficacy in humans,\textsuperscript{13,20} most studies have shown no relation.\textsuperscript{13,20} However, many of the adverse effects of clomipramine in humans are mediated peripherally and, therefore, would probably be correlated to some extent with plasma drug concentrations.

Even though the terminal half-lives of clomipramine and desmethylclomipramine in dogs are short (≤ 4 hours), it does not follow that clomipramine needs to be given frequently in dogs. The current recommendation to administer clomipramine once or twice daily is consistent with the known central actions of the drug.\textsuperscript{1} In addition, the fact that steady-state plasma concentrations of clomipramine and desmethylclomipramine are rapidly attained in dogs (within 4 days) does not necessarily mean that the onset of clinical efficacy will be equally as fast. In humans, maximal effects of clomipramine on depression, panic disorders, and stereotypies can take several weeks to appear.\textsuperscript{2} This delay may be attributable to the time needed to reach steady-state conditions in the brain. In addition, inhibition of noradrenaline and serotonin reuptake may not be sufficient by itself to induce clinical effects. Rather, reuptake inhibition may induce secondary effects, such as down-regulation of postsynaptic receptors, that in turn are responsible for the clinical effects of clomipramine.\textsuperscript{2}

In humans, clomipramine is commonly associated with nonserious but annoying adverse effects such as dry mouth and skin but, in rare instances, may produce serious adverse effects, such as cardiac arrhythmias and urinary stasis.\textsuperscript{1,2} Most of these adverse effects are attributed to peripheral anticholinergic effects of the drug.\textsuperscript{23,24} Clinical experience suggests that clomipramine produces adverse effects less frequently in dogs than in people,\textsuperscript{3} possibly because the shorter terminal half-lives of clomipramine and desmethylclomipramine in dogs, compared with humans,\textsuperscript{3} result in more rapid elimination of the compounds from peripheral sites. Also, the ratio of clomipramine to desmethylclomipramine is higher in dogs (approx 3:1) than in humans (1:2.5)\textsuperscript{12,13,35} and clomipramine acts predominately on serotonin, whereas desmethylclomipramine is responsible for most of the anticholinergic properties of the drug.\textsuperscript{25}

References