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# Pharmacokinetics of amantadine in cats

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This study reports the pharmacokinetics of amantadine in cats, after both i.v. and oral administration. Six healthy adult domestic shorthair female cats were used. Amantadine HCl (5 mg/kg, equivalent to 4 mg/kg amantadine base) was administered either intravenously or orally in a crossover randomized design. Blood samples were collected immediately prior to amantadine administration, and at various times up to 1440 min following intravenous, or up to 2880 min following oral administration. Plasma amantadine concentrations were determined by liquid chromatography–mass spectrometry, and plasma amantadine concentration–time data were fitted to compartmental models. A two-compartment model with elimination from the central compartment best described the disposition of amantadine administered intravenously in cats, and a one-compartment model best described the disposition of oral amantadine in cats. After i.v. administration, the apparent volume of distribution of the central compartment and apparent volume of distribution at steady-state [mean ± SEM (range)], and the clearance and terminal half-life [harmonic mean ± jackknife pseudo-SD (range)] were 1.5 ± 0.3 (0.7–2.5) L/kg, 4.3 ± 0.2 (3.7–5.0) L/kg, 8.2 ± 2.1 (5.9–11.4) mL·min/kg, and 348 ± 49 (307–465) min, respectively. Systemic availability [mean ± SEM (range)] and terminal half-life after oral administration [harmonic mean ± jackknife pseudo-SD (range)] were 130 ± 11 (86–160)% and 324 ± 41 (277–381) min, respectively.

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## INTRODUCTION

Amantadine, an antiviral agent, is used in the treatment of influenza A infections (Van Voris *et al.*, 1981; Dolin *et al.*, 1982). It has also been shown to antagonize *N*-methyl-D-aspartate (NMDA) receptors and is used to treat chronic pain (Hewitt, 2000). NMDA receptors are at least in part responsible for central nervous sensitization to noxious stimulation, and preemptive treatment with NMDA antagonists has been shown to prevent this sensitization (Eide, 2000). Amantadine has anecdotally been combined with opioids in cats to improve analgesia (Robertson, 2008). However, there have been no published studies on the disposition or effects of amantadine in cats. The purpose of this study is to characterize the pharmacokinetics of amantadine in cats, after oral and i.v. administration.

## MATERIALS AND METHODS

### *Animals*

Six healthy adult spayed domestic shorthair female cats weighing 4.1 ± 0.6 kg (mean ± SD) were used in the study. Cats were allowed free access to food and water during the study. The study was approved by the institutional animal care and use committee at the University of California, Davis.

### *Instrumentation and drug administration*

On the day before an experiment, cats were anesthetized with isoflurane in oxygen. A 20-gauge, 10-cm catheter was placed in a jugular vein. A light bandage was placed over the catheter to protect it, and cats were allowed to recover.

On the day of the experiment, a 20-gauge, 4.8-cm catheter was placed in a medial saphenous vein and protected with a light bandage (i.v. studies only). Amantadine HCl (5 mg/kg, equivalent to 4 mg/kg amantadine base; Spectrum Chemicals, Gardena, CA, USA) was administered either orally or intravenously via the medial saphenous catheter. For i.v. administration, amantadine HCl was dissolved in sterile water to a concentration of 5 mg/mL, immediately before administration. The solution was filtered through a 0.2-μm filter. A 10-min constant rate infusion was used, resulting in the administration of 0.5 mg/kg·min of amantadine HCl. For oral administration,

approximately 5 mg/kg of bulk amantadine HCl powder was weighed and placed in gelatin capsules. Capsules were prepared individually for each cat. No excipient was added. All cats received both administrations, and the order of treatments was randomly selected. Two weeks were allowed between treatments. Blood samples (2 mL) were collected from the jugular catheter prior to drug administration and at 5, 15, 30, 60, 120, 240, 480, 960, 1440, and 2880 min following oral administration, or 1, 5, 10, 11, 12, 15, 20, 30, 60, 120, 240, 480, 960 and 1440 min following i.v. administration. Blood samples were transferred to tubes containing ethylenediaminetetraacetic acid, immediately placed on ice, and (within 10 min of collection) centrifuged at 3901 ***g*** for 10 min at 4 °C. The plasma was separated and stored at −20 °C until analysis for amantadine concentration.

*Drug analysis*

Amantadine was quantitated in feline plasma by LC-MS[1] analysis of protein-precipitated samples. The calibration standards were prepared as follows: stock solutions were made by dissolving 10.0 mg of amantadine standard (Sigma-Aldrich Co, St Louis, MO, USA) in 10.0 mL of methanol. Working solutions were prepared by dilution of the amantadine stock solution with methanol to amantadine concentrations of 1000, 100, and 1.0 ng/mL. Plasma calibrators were prepared by dilution of the working amantadine solution with feline drug-free plasma to concentrations of 2.5, 5.0, 10, 50, 100, 150, 250, 500, 1000, 2000, 3000, and 4000 ng/mL. Calibration curves and negative control samples were prepared fresh for each quantitative assay. In addition, quality control samples (plasma fortified with analytes at two midpoint concentrations of the standard curve) were routinely included as an additional check of accuracy. The concentration of amantadine in each sample was determined by the internal standard (oxymorphone-D3; Toronto Research Chemicals, Ontario, Canada) method using the peak area ratio and linear regression analysis.

Quantitative analyses were performed on a mass spectrometer (TSQ Quantum Ultra triple quadrupole mass spectrometer; Thermo Scientific, San Jose, CA, USA) equipped with a heated electrospray ionization probe that was kept at 355 °C. All analyses were performed in the positive ionization mode with a spray voltage set at 5000 V. The sheath and auxiliary gas used was nitrogen at 45 and 10 arbitrary units, respectively. The system was operated in the selected reaction monitoring mode with argon as the collision gas at a pressure of 1.5-mTorr. The ion transfer tube was kept at 300 °C while the scan time and width were 0.25 sec and 0.1 *m/z*, respectively. Data were processed using LCQUAN software version 2.6 (Thermo Scientific). The triple quadrupole mass spectrometer was coupled with liquid chromatography (1100 Agilent LC system; Agilent, Santa Clara, CA, USA). Chromatographic separation employed a column (ACE $C_{18}$, 100 × 2.1 mm, 3 μm, column; Mac Mod, Chadds Ford, PA, USA) and a linear gradient of acetonitrile (HPLC grade; Burdick and Jackson, Muskegon, MI, USA) in water with a constant 0.2% formic acid (spectrophotometric grade; Aldrich, St Louis, MO, USA) at a flow rate of 0.35 mL/min. The acetonitrile concentration was held at 1% for 0.5 min and ramped up to 90% over 8.5 min. Prior to analysis, the plasma samples, controls, and calibrators were fortified with 100 ng/mL of oxymorphone-D3. The injection volumes were 10.0 μL.

Detection and quantification employed full-scan LC-MS/MS transitions of initial product ions for amantadine [mass to charge ratio (*m/z*) 152.1]. The response for the major product ions for amantadine (*m/z*, 135.1, 77.1, 93.1, 79.1 and 107.1) was plotted, and peaks at the proper retention time were integrated using LCQUAN. The software was used to generate calibration curves and quantitate the analyte in all samples.

The concentration of amantadine in each sample (e.g., calibrators, quality control, and unknowns) was determined by an internal standard method using the peak area ratio and linear regression analysis. The response for amantadine was linear and gave correlation coefficients ($R^2$) of 0.99 or better. The technique was optimized to provide a limit of quantitation at 2.5 ng/mL for the analyte. The intraday accuracy (percentage of nominal concentration) was 93% and 105% at 50 and 1000 ng/mL, respectively. Intraday precision (percentage relative SD) was 22% and 10% at 50 and 1000 ng/mL, respectively.

*Amantadine concentration in the solution for i.v. administration*

In a separate experiment, the purity and strength of amantadine solutions used for i.v. administration was determined by extracting 0.1-mL aliquots ($n$ = 2) of the product compounded as described in the Instrumentation and Drug Administration section, and comparing concentrations to a amantadine reference standard. Amantadine potency was determined through dilution of the solution and use of a modification of the LC-MS procedure described earlier.

*Pharmacokinetic analysis*

Nonlinear least squares regression (WinNonlin 6.1; Pharsight, Cary, NC, USA) was performed on plasma amantadine concentrations after i.v. administration or oral administration. Dosing for the pharmacokinetic analysis was based on amantadine HCl, i.e., uncorrected for the difference in molecular weight between the HCl salt and amantadine base. One-, two-, and three-compartment models with zero-order input in, and first-order elimination from, the central compartment (where appropriate) were fitted to the i.v. data. Data were weighted by the reciprocal of the predicted plasma concentration. One- and two-compartment models with lag time, and with first-order absorption in and elimination from the central compartment were fitted to the oral data. Data were weighted by the reciprocal of the predicted plasma concentration squared. Observation of the residuals plot and use of Akaike's information criterion were used to select which model fitted the data

[1]Liquid chromatography–mass spectrometry

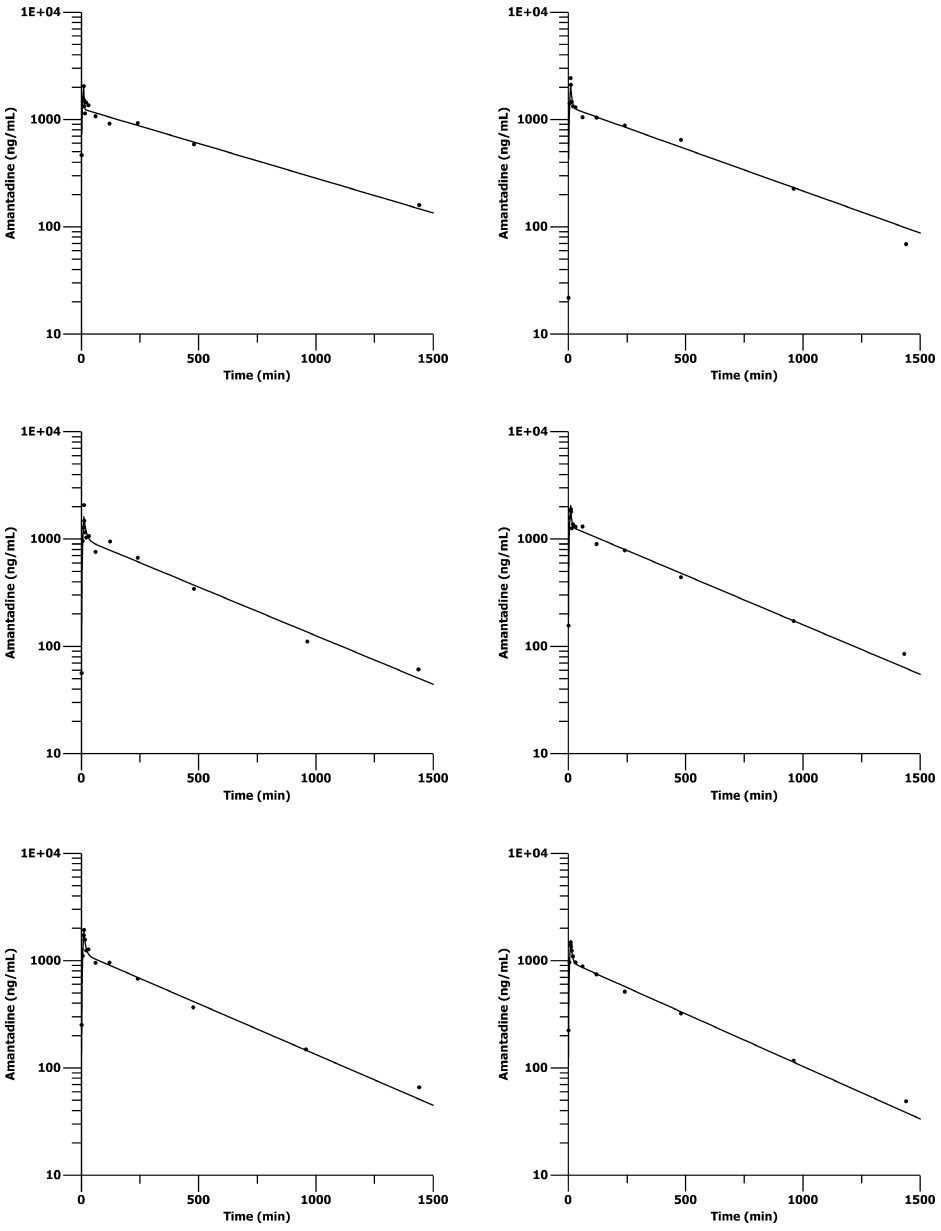


**Fig. 1.** Observed (circles) and predicted (line, two-compartment model) plasma amantadine concentrations following a 10-min i.v. constant rate infusion of amantadine (0.5 mg/kg·min) in six cats.

best (Yamaoka *et al.*, 1978; Gibaldi & Perrier, 1982). $F$[2] was calculated from the ratio of the areas under the plasma amantadine curve after oral and i.v. administration:

$$F(\%) = \frac{\mathrm{AUC_{oral}}}{\mathrm{AUC_{i.v.}}} \times 100$$

Parameters estimated by the compartmental model were $V_c$[3], $V_2$[4], Cl[5], and Cld[6] for i.v. administration, and $V$[7]$/F$, $K_{01}$[8], Cl$/F$ and $t_{lag}$[9] for oral administration. These parameters were then used to calculate other pharmacokinetic parameters for each cat, using standard pharmacokinetic equations (Gabrielsson & Weiner, 2006). Parameters for oral administration were corrected for systemic availability where appropriate.

Normal distribution of pharmacokinetic parameters was verified using the Shapiro–Wilk test. Data are presented as weighted mean ± SEM (range), and half-lives and clearances are reported as harmonic mean ± jackknife pseudo-SD (range) unless specified otherwise (Lam *et al.*, 1985). To improve the precision of the mean estimates, individual parameters used to calculate means were weighted by the reciprocal of the variance obtained by the nonlinear regression procedure (Cooper & Weekes, 1983).

[2]Systemic availability
[3]Apparent volume of the central compartment
[4]Apparent volume of the peripheral compartment
[5]Clearance
[6]Distribution clearance
[7]Apparent volume of distribution
[8]Absorption rate constant
[9]Lag time

## RESULTS

A two-compartment model best described the disposition of amantadine following i.v. administration (Fig. 1). The apparent volume of the central compartment, the apparent volume of distribution at steady-state, the clearance, and the terminal half-life were 1.5 ± 0.3 (0.7–2.5), 4.3 ± 0.2 (3.7–5.0) L/kg, 8.2 ± 2.1 (5.9–11.4) mL·min/kg, and 348 ± 49 (307–465) min, respectively (Table 1).

Actual oral dose (mean ± SD) was 5.08 ± 0.06 mg/kg. A one-compartment model best described the disposition of amantadine following oral administration (Fig. 2). Systemic availability and terminal half-life after oral administration were 130 ± 11 (86–160)% and 324 ± 41 (277–381) min, respectively (Table 1). Time to reach maximum concentration after oral administration and maximum concentration were 118 (89–306) min and 1141 ± 133 (838–1639) ng/mL, respectively (Table 1).

Amantadine concentration in solutions prepared following the procedure used for preparation of the i.v. solutions was 4.8 mg/mL.

## DISCUSSION

The disposition of amantadine in cats is characterized by a large volume of distribution and a moderate clearance, resulting in a relatively long terminal half-life. According to discussions on the Veterinary Information Network, practitioners are increasingly using amantadine as an analgesic adjunct in cats, usually in combination with low doses of opioids. However, no data have been published on the disposition of amantadine in cats, making dosing recommendations difficult. This study describes the pharmacokinetics of amantadine in cats after i.v. and oral administration. With this information, complementary pharmacodynamic studies can be conducted to examine whether or not amantadine is an effective agent to help improve analgesia if given with low doses of opioids. In turn, these pharmacodynamic studies may establish effective plasma concentrations and data in the study presented here could then be used to determine adequate dose, as well as dosing interval.

A short (10-min) constant rate infusion, rather than a bolus, was used for i.v. administration of amantadine. Infusions are preferred for drugs with narrow therapeutic index. Because the potential toxicity after i.v. administration of amantadine in cats has not been studied, an infusion was selected. Short infusions allow better characterization of initial disposition than longer infusions.

In this study, a two-compartment model best describes the disposition of amantadine after i.v. administration, while a one-compartment model best describes the disposition of amantadine after oral administration. Although both distribution and elimination phases are detected with i.v. administration, only the elimination phase can be observed after oral administration. This is likely due to the absorption phase, which may have masked the distribution phase.

**Table 1.** Pharmacokinetic parameters [mean ± SEM (range)] for amantadine following a 10-min i.v. infusion (0.5 mg·kg/min) or oral administration (5.1 mg/kg) in six cats

| Parameter | i.v. | Oral |
|---|---|---|
| $F$% | n/a | 130 ± 11 (86–160) |
| $V_c$ (L/kg) | 1.5 ± 0.3 (0.7–2.5) | 4.5 ± 2.8 (3.4–5.3) |
| $V_c/F$ (L/kg) | n/a | 2.9 ± 0.3 (2.4–4.3) |
| $V_2$ (L/kg) | 2.6 ± 0.2 (2.1–3.2) | n/a |
| Cl [(mL/min)/kg]† | 8.2 ± 2.1 (5.9–11.4) | 8.3 ± 2.0 (6.1–11.5) |
| Cl/$F$ [(mL/min)/kg]† | n/a | 7.1 ± 1.4 (5.8–9.4) |
| Cld [(mL/min)/kg]† | 183 ± 65 (127–398) | n/a |
| $K_{01}$ (/min) | n/a | 0.016 ± 0.008 (0.006–0.055) |
| $t_{lag}$ (min) | n/a | 24 ± 3 (12–29) |
| $A$ (ng/mL) | 1569 (1014–5846)* | n/a |
| $B$ (ng/mL) | 1095 ± 61 (975–1319) | n/a |
| $\alpha$ (/min) | 0.18 (0.11–0.70)* | n/a |
| $\beta$ (/min) | 0.002 ± 0.0001 (0.001–0.002) | n/a |
| $t_{1/2\alpha}$ (min)† | 2.7 ± 3.1 (1.0–6.4) | n/a |
| $t_{1/2\beta}$ (min)† | 348 ± 49 (307–465) | n/a |
| $K_{10}$ (/min) | 0.005 (0.004–0.008)* | 0.002 ± 0.0001 (0.002–0.003) |
| $K_{12}$ (/min) | 0.096 (0.051–0.565)* | n/a |
| $K_{21}$ (/min) | 0.081 ± 0.010 (0.054–0.124) | n/a |
| $K_{01}$ $t_{1/2}$ (min) | n/a | 24.4 (12.7–119.1)* |
| $K_{10}$ $t_{1/2}$ (min)† | 131 ± 43 (83–168) | 324 ± 41 (277–381) |
| $V_{ss}$ (L/kg) | 4.3 ± 0.2 (3.7–5.0) | n/a |
| AUC (ng*h/mL) | 8228 ± 1047 (7329–14119) | 11521 ± 956 (9027–14493) |
| $t_{max}$ (min) | n/a | 118 (89–306)* |
| $C_{max}$ (ng/mL) | 1715 ± 100 (1548–2109) | 1142 ± 133 (838–1639) |

$F$, systemic availability; $t_{1/2\alpha}$, distribution half-life; $t_{1/2\beta}$, elimination half-life; $K_{01}$, $K_{10}$, $K_{12}$, $K_{21}$, rate constants; $t_{lag}$, lag time; $V_c$, apparent volume of the central compartment; $V_2$, apparent volume of the peripheral compartment; $V_{ss}$, apparent volume of distribution at steady-state; Cl, clearance; Cld, distribution clearance; AUC, area under the plasma concentration–time curve to the last observation; $t_{max}$, time to reach maximum concentration; $C_{max}$, maximal plasma concentration. *Value reported is the median (range), because the parameter was not normally distributed. †Parameter reported as harmonic mean ± jackknife pseudo-SD (range).

Terminal half-life of amantadine in cats was similar after i.v. and oral administration (5.8 and 5.4 h, respectively). This is similar to values reported in dogs and monkeys (5 h), but significantly lower than in humans (9–15 h) (Bleidner *et al.*, 1965; Greenblatt *et al.*, 1977; Horadam *et al.*, 1981; Hayden *et al.*, 1985). Volume of distribution after i.v. and oral administration is similar between cats (4.3 and 4.5 L/kg, respectively) and humans (3.0 L/kg) (Hayden *et al.*, 1985). The large volume of distribution seen is likely due to amantadine having a pKa of 9.0 and being very lipid soluble at physiological pH, thus being able to be distributed across tissues and transported through the blood–brain barrier (Spector, 1988).

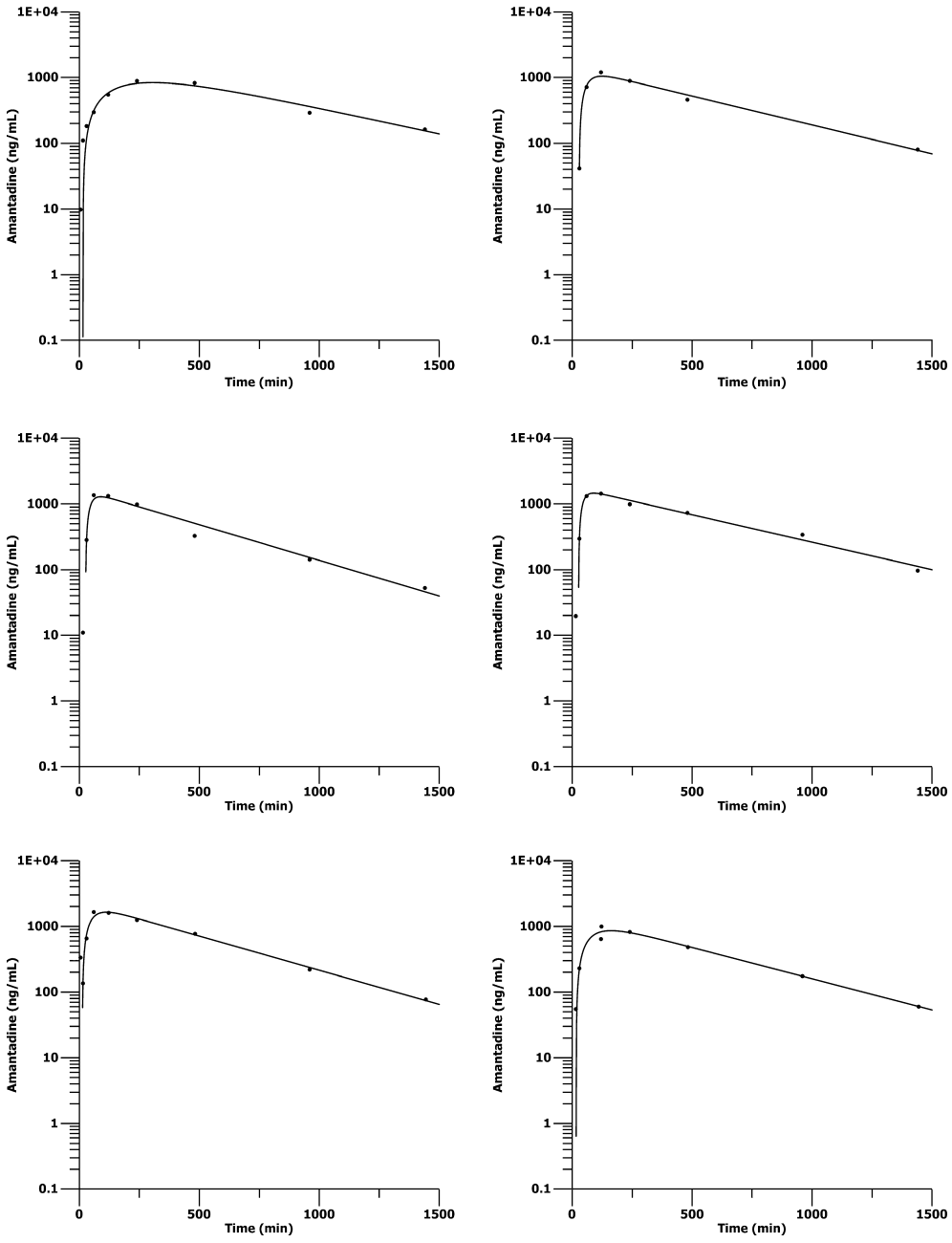


**Fig. 2.** Observed (circles) and predicted (line, one-compartment model) plasma amantadine concentrations following oral administration of amantadine (5.1 mg/kg) in six cats.

Time to reach maximum concentration after oral administration ranged from 1.5–5 h and is consistent with values reported in humans (1–4 h) (Bleidner *et al.*, 1965; Hayden *et al.*, 1985), suggesting a similar absorption half-life between humans (0.6 h) (Hayden *et al.*, 1985) and cats (0.41 h). Clearance is moderate and was similar following i.v. and oral administration (8.2 and 8.3 mL·min/kg, respectively). Clearance in cats is about twice that in humans (4.5 mL·min/kg) (Aoki *et al.*, 1979). This is likely reflecting the effect of body size on clearance. Indeed, because clearance depends on blood flow and metabolic functions, which both scale allometrically to $Mb^{3/4}$ (Schmidt-Nielsen, 1984a,b), where Mb is body mass, it could be theorized that clearance is expected to scale to the same function of Mb rather than to body weight. Considering 5 kg cats and 70 kg humans, total clearance would be 42.5 and 315 mL/min in cats and humans, respectively. Indexing these values to $Mb^{0.75}$ instead of Mb results in values of 12.7 and 13 mL·min/$kg^{0.75}$ in cats and humans.

Systemic availability was calculated to be 130%. Assumptions made for the calculation of systemic availability include that clearance is the same for i.v. and oral administration. This was likely the case in this study, because the same individuals were used for both routes of administration, and estimates of

clearance, volume of distribution, and terminal half-life were similar following i.v. and oral administration. Systemic availability after oral administration is not expected to be >100%; the very high availability found in this study may be related to uptake by the lung, as has been reported in mice (Bleidner *et al.*, 1965). Amantadine has also been found in nasal secretions in humans (Hayden *et al.*, 1985). This suggests that a significant first-pass effect may exist following i.v. administration, because the whole amount of drug transits through the lung before reaching the sampling site. High systemic availability following oral administration may therefore be related to a violation of the common assumption that the totality of the dose is available after i.v. administration. If uptake by the lung is a significant factor, oral administration is expected to decrease its impact, because with the absorption phase after oral administration, the concentration gradient for uptake in the lung is much reduced. This would explain why the area under the curve following i.v. administration is smaller than following oral administration, resulting in a calculated systemic availability >100%. Finally, doses for both the i.v. and oral studies were determined by weighing the desired amount of amantadine powder; for the i.v. administration, amantadine was furthermore diluted in water. Each of these steps may have introduced small errors in dosing, which may account for some of the higher than expected systemic availability following oral administration. Amantadine concentration in solutions prepared identically as those used for i.v. administration was 4% lower than expected, according to measurements obtained by mass spectrometry. However, this difference does not account for the high systemic availability; correcting the calculation of systemic availability for a difference in dose of that magnitude between the oral and i.v. studies results in a weighted mean ± SE systemic availability of 123 ± 11%. Published pharmacokinetic studies have reported that amantadine is completely absorbed in dogs (Bleidner *et al.*, 1965) and that systemic availability is high in humans (Aoki *et al.*, 1979; Hayden *et al.*, 1985). Amantadine is excreted unchanged in mice, but is metabolized to some degree in dogs and monkeys (Bleidner *et al.*, 1965). In humans, the main metabolite of amantadine is *N*-acetylamantadine (Koppel & Tenczer, 1985). In the study reported here, metabolism of amantadine in cats was not investigated.

## ACKNOWLEDGMENTS

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