

## Pharmacokinetics and Metabolism of Rimantadine Hydrochloride in Mice and Dogs

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We studied the pharmacokinetics and metabolism of rimantadine hydrochloride (rimantadine) following single-dose oral and intravenous administration in mice and dogs. Absorption of the compound in mice was rapid. Maximum concentrations in plasma occurred at less than 0.5 h after oral administration, and the elimination half-life was 1.5 h. Peak concentrations in plasma following oral administration were markedly disproportional to the dose (274 ng/ml at 10 mg/kg, but 2,013 ng/ml at 40 mg/kg). The bioavailability after an oral dose of 40 mg/kg was 58.6%. Clearance was 4.3 liters/h per kg, and the volume of distribution was 7.6 liters/kg at 40 mg/kg. In contrast to the results observed in mice, absorption of the compound in dogs was slow. Maximum concentrations in plasma occurred at 1.7 h after oral administration, and the elimination half-life was 3.3 h. A further difference was that peak concentrations in plasma were approximately proportional to the dose. Following administration of a single oral dose of 5, 10, or 20 mg/kg, maximum concentrations in plasma were 275, 800, and 1,950 ng/ml, respectively. The bioavailability after an oral dose of 5 mg/kg was 99.4%. The clearance was 3.7 liters/h per kg, and the volume of distribution was 13.8 liters/kg at 5 mg/kg. Mass balance studies in mice, using [*methyl*-<sup>14</sup>C]rimantadine, indicated that 98.7% of the administered dose could be recovered in 96 h. Less than 5% of the dose was recovered as the parent drug in dog urine within 48 h. Finally, gas chromatography-mass spectrometry studies, done with mouse plasma, identified the presence of two rimantadine metabolites. These appeared to be ring-substituted isomers of hydroxyrimantadine.

Rimantadine hydrochloride (rimantadine), which is chemically related to the anti-influenza A drug amantadine hydrochloride (amantadine, Symmetrel), has been reported to be effective against influenza A in human studies and in mouse model systems (2, 7, 11). It is being used in the USSR for both prophylaxis and therapy of influenza A infections (12).

The pharmacokinetics and metabolism of rimantadine in humans have been reported (F. G. Hayden and H. E. Hoffman, *Abstr. 14th Annu. UCLA Symp., J. Cell. Biochem.*, suppl. 96, p. 276, 1985; L. P. Van Voris, J. Bartram, H. E. Hoffman, L. M. Shalaby, J. C. Gaylord, L. S. Davis, and F. G. Hayden, *Program Abstr. 23rd Intersci. Conf. Antimicrob. Agents Chemother.*, abstr. no. 684, 1983) for healthy subjects, but no animal studies have been reported. We have studied rimantadine kinetics and metabolism in mice (mice are used for most influenza model infections) and in dogs.

### MATERIALS AND METHODS

**Rimantadine assay.** (i) **Plasma.** The rimantadine level in plasma was analyzed as previously described (3), with modifications for measuring the levels in urine, feces, and tissues.

A 1-ml sample of plasma was extracted by using cyano Bond Elut disposable extraction columns (Analytichem International). The extracted rimantadine was derivatized with pentafluorobenzoyl chloride (PFB) (Aldrich Chemical Co., Inc.), yielding the pentafluorobenzoyl derivative of rimanta-

dine, which was then analyzed by gas chromatography (HP 5880A; Hewlett-Packard Co.) with an electron capture detector (6). PFB-amantadine was used as the internal standard and was prepared in house. The oven temperature was programmed for 240°C for 5 min, followed by a temperature gradient of 5°C/min for 6 min, to 270°C. The 6-ft (1.83-m) column was packed with 10% OV-1 (Ohio Valley Specialty Chemical, Inc.) on Chromasorb W (Hewlett-Packard Co.). The method was linear between 10 and 10,000 ng/ml in plasma-free solutions. The limit of detection was 5 ng/ml. However, linearity in biological solutions, such as plasma or tissue extracts, was restricted to a narrower range and was determined for each analysis. Samples were assayed only in the linear portion of the curve. Absolute recovery from plasma ranged from 54% at 50 ng/ml to 72% at 1,000 ng/ml. Reproducibility was 7% relative standard deviation. Rimantadine in plasma was stable when stored at -20°C for 5 weeks.

The resultant peaks on the chromatograms indicated that the method was highly specific. Retention times were reproducible regardless of the biological fluids, and there was no interference from other substances in the extracts. Retention times for principal peaks were as follows: internal standard, 4.3 min; rimantadine, 6.6 min; metabolite M-1, 9.9 min; and metabolite M-2, 12.2 min.

(ii) **Mouse lung assay.** Individual lungs were each homogenized in 3 ml of 5 N NaOH. A 1-ml sample of the resulting homogenate was added to 5 ml of 5 N NaOH-50 mg of NaCl-15 ml of hexane. After 30 min on a wrist action shaker and

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centrifugation to separate the phases, the hexane layer was removed and evaporated to dryness. The residue was dissolved in 1 ml of toluene and derivatized as with the plasma extracts. Recovery of rimantadine from mouse lungs was 42%.

(iii) **Standard curves.** Standards were prepared in each biological fluid analyzed, i.e., mouse, rat, and dog plasma; lung extracts; and dog and mouse urine. A standard curve was prepared from the peak height ratios by linear regression analysis, and concentrations were computed from the regression equation. Four to six points were used in each regression analysis.

(iv)  **$\beta$ -Glucuronidase hydrolysis.** Glucuronide conjugation was determined by using  $\beta$ -glucuronidase supplied by Sigma Chemical Co. (kit 325). The enzyme, at a final concentration of 10 U/ml of urine, was incubated with dog urine for 2 h at 37°C.  $\beta$ -Glucuronidase activity was monitored by hydrolyzing phenolphthalein glucuronic acid. After incubation, the urine samples were extracted as described above.

(v) **Urine assay.** A 1-ml sample of urine was placed in 5 ml of 5 N NaOH and extracted as described for the mouse lung assay.

**[<sup>14</sup>C]rimantadine methods.** [<sup>14</sup>C]rimantadine (specific activity, 5.34 mCi/mmol), prepared by Du Pont, NEN Research Products, was labeled at the methyl group. Its radiochemical purity was 98%.

**Virus preparation.** Influenza virus A/Bangkok/1/79 (H3N2) was prepared by serial passage in CD-1 mice inoculated intranasally with 50  $\mu$ l of an appropriately diluted stock preparation. At about 36 h postinfection, lungs were surgically excised under aseptic conditions and homogenized in phosphate-buffered saline containing bovine serum albumin (0.2%), penicillin (100 IU/ml), and kanamycin (25  $\mu$ g/ml). The homogenate was frozen and thawed three times and clarified by centrifugation. The supernatant was collected and stored frozen at -70°C in 1-ml aliquots.

CD-1 female mice (Sendai virus free), 20 to 30 days of age and weighing an average of 15 g, were each infected intranasally, under light anesthesia, with 50  $\mu$ l of influenza virus A/Bangkok/1/79 (H3N2) at dilutions of 10<sup>-3.8</sup>, 10<sup>-4.8</sup>, and 10<sup>-5.8</sup>, respectively, with 12 mice per dilution level. Virus dilutions were made in phosphate-buffered saline (pH 7.2), as described above. The virus preparation yielded a 50% lethal dose of 10<sup>-5.24</sup> and a 90% lethal dose of 10<sup>-4.25</sup>.

**Sample preparation for liquid scintillation counting.** (i) **Radiometric assay.** Samples were counted in a Packard Prias scintillation spectrometer with Atomlight (Du Pont, NEN) as the scintillation fluid.

(ii) **Standards.** Using the external standard system, we determined counting efficiencies with graded quenched standards programmed into the Prias counter. The radioactivity in the test sample was measured as counts per minute, corrected for quenching, and reported as disintegrations per minute.

(iii) **Plasma, urine, and cage wash.** A measured volume of plasma, urine, or liquid used for washing the cages was placed into a scintillation vial containing 7 ml of Atomlight and counted in the liquid scintillation counter.

(iv) **Feces.** Feces samples (50 to 500 mg) were oxidized in a Packard Tri-Carb sample oxidizer, and the <sup>14</sup>CO<sub>2</sub> was trapped in Carbosorb (Packard) absorbent with Permafluor (Packard) as the scintillant. All samples were counted in triplicate when possible, and control and spiked [<sup>14</sup>C]rimantadine standards were run concurrently with the experimental samples. The mean <sup>14</sup>C recoveries from feces spiked

with known amounts of labeled rimantadine and subjected to combustion were 94.3%.

**Animal treatments.** (i) **Mice.** Groups of six nonfasted female mice (mean weight, 22 g) were dosed perorally with 10 or 40 mg of rimantadine per kg, formulated in saline at 1 mg/ml. An additional group received 40 mg/kg intravenously. Blood was drawn by intracardiac puncture into heparin-containing tubes and pooled, and plasma was prepared. Blood samples were taken at 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, and 24 h after dosing.

To determine the effects of virus infection on the pharmacokinetics of rimantadine, mice (five per time interval) were infected intranasally with influenza virus A/Bangkok/1/79 (H3N2), as above, at a virus dilution of 10<sup>-4.8</sup>, and dosed orally with the drug (40 mg/kg) at 72 h postinfection. Uninfected control mice simultaneously received the same oral doses of rimantadine. At 0, 0.25, 0.5, 1, 2, 4, 6, 8, 12, 16, 24, and 48 h after drug dosing, blood was collected, pooled, and then centrifuged to separate the plasma. The lungs were excised at the same time points, and all samples were frozen until assayed.

(ii) **Dogs.** Female beagles were dosed with rimantadine at 5, 10, and 20 mg/kg perorally and 5 mg/kg intravenously. Rimantadine was formulated in water at 5 mg/ml for peroral dosing and in sterile saline for intravenous dosing. The dogs were fasted overnight and treated with drug in the morning. Blood was collected from the jugular vein at 0.5, 1, 2, 4, 6, 8, 10, 12, 16, and 24 h in sodium heparin-containing tubes. All samples from dogs were assayed separately.

(iii) **Material balance study in mice.** [<sup>14</sup>C]rimantadine was dissolved in water (1 mg/ml) at a specific activity of 3.2  $\mu$ Ci/mg. Three groups of two Charles River CD female mice each were given a single oral dose of 40 mg of [<sup>14</sup>C]rimantadine per kg and placed into metabolism chambers. Groups 1 and 3 received a total dose of 4.86  $\mu$ Ci, and group 2 received 5  $\mu$ Ci. Urine and feces were collected at 24-h intervals during the study. Samples (1 ml) of the urine and cage-washing liquid were counted in triplicate. Fecal samples were oxidized prior to liquid scintillation counting.

**Mass spectrometry.** The gas chromatography separations were made on a 15-m J&W DB-1, 0.25-mm (inner diameter) capillary column which was directly interfaced to a Finnigan model 4500 mass spectrometer. The column temperature was programmed from 200 to 260°C at 10°C/min. Mouse plasma extract, containing rimantadine and its metabolites, was reacted with PFB and dissolved in toluene. The derivatized sample was initially analyzed by capillary gas chromatography-mass spectrometry in the electron impact mode, and to enhance the molecular (M<sup>+</sup>) ion, the gas chromatography-mass spectrometry was rerun with chemical ionization.

**Pharmacokinetic calculations.** All pharmacokinetic parameters were determined with the RS-1 computer program (BBN Research Systems, Cambridge, Mass.). The area under the concentration-time curve from zero to infinity (AUC<sub>0-∞</sub>) was calculated by summing the area to the last measured time point (C<sub>last</sub>) determined by the linear trapezoidal rule, and the extrapolated area was determined by C<sub>last</sub>/k<sub>el</sub>, where k<sub>el</sub> is the elimination rate constant and was determined from the slope of the terminal portion of the ln concentration-time curve. The half-life (t<sub>1/2</sub>) was 0.693/k<sub>el</sub>. The clearance (CL) was D/AUC, and the volume of distribution (V) was CL/k<sub>el</sub>.

TABLE 1. Pharmacokinetics of rimantadine in mice<sup>a</sup>

Route	Dose (mg/kg)	C <sub>max</sub> (ng/ml)	T <sub>max</sub> (h)	AUC (ng · h/ml)	t <sub>1/2</sub> (h)	CL (liters/h per kg)	V (liters/kg)	F (%)
Oral	10	274	0.5	555	1.253			
	40	2,013	0.5	5,421	2.063			58.6
i.v. <sup>b</sup>	40		0.5	9,247	1.224	4.3	7.6	

<sup>a</sup> Plasma was pooled from six mice per period.

<sup>b</sup> i.v., Intravenous.

## RESULTS

**Mouse pharmacokinetics.** Plasma pharmacokinetic data for mice are summarized in Table 1. Oral absorption was rapid, with the maximum concentration in plasma (C<sub>max</sub>) occurring at 30 min, the earliest time point measured (Fig. 1). The elimination half-life (t<sub>1/2</sub>) was between 1 and 2 h. V was 7.6 liters/kg, which suggests extensive distribution of the drug into tissues. CL was 4.3 liters/h per kg. The increase in AUC values was not proportional to the dose. The bioavailability of rimantadine in mice after oral administration of 40 mg/kg was 58.6%.

**Influenza A virus-infected mice.** In a separate study, normal and influenza virus-infected mice were compared (Table 2). Peak levels in both plasma and lungs decreased in infected mice, and the peak time in the lungs increased from 0.25 to 2.0 h, whereas it remained the same in plasma. Thus, infection both decreases and delays the uptake of rimantadine in the lungs. However, AUC values for lungs from infected and noninfected mice were not different (Table 2), nor were the AUC<sub>lung</sub>/AUC<sub>plasma</sub> ratios. The ratio for normal mice, 45.7, is similar to that for infected mice, 48.5, suggesting that the virus infection does not alter the total impact of rimantadine during the period studied.

TABLE 2. Pharmacokinetic parameters in mouse plasma and lungs from uninfected and influenza A virus-infected mice given a single oral dose of 40 mg/kg

Specimen	n <sup>a</sup>	k <sub>el</sub> (h <sup>-1</sup> )	t <sub>1/2</sub> (h)	AUC (ng · h/ml)	C <sub>max</sub> (ng/ml)	T <sub>max</sub> (h)
<b>Plasma</b>						
Uninfected	6	0.324	2.1	7,631	2,169	0.25
Infected	5	0.299	2.3	6,667	1,436	0.25
<b>Lung</b>						
Uninfected	6	0.385	1.8	348,546	74,251	0.25 (2.0) <sup>b</sup>
Infected	5	0.156	4.4	323,457	45,436	2.00

<sup>a</sup> n, Number of mice per period.

<sup>b</sup> A second C<sub>max</sub> occurred at 2 h.

**Dog plasma pharmacokinetics.** Plasma pharmacokinetic data for dogs are shown in Table 3. The t<sub>1/2</sub>s were 2.9, 3.4, and 3.7 h for oral administration of 5, 10, and 20 mg/kg, respectively, and 2.6 h for a 5-mg/kg intravenous dose. As found for mice, the increase in AUC values for dogs was not proportional to the dose. The bioavailability after a 5-mg/kg oral dose was 99.5%, nearly twice that found in mice (58.6%) after a 10-mg/kg dose. The values for the time to maximum concentration of drug (T<sub>max</sub>) were 1 h at 5 mg/kg and 2 h at 10 and 20 mg/kg. C<sub>max</sub> increased with increasing dose, but the increase was not proportional to the dose. CL was 3.7 liters/h per kg, similar to that for mice, and V was 13.8 liters/kg.

**Metabolism studies.** Mouse plasma extracts contained two metabolites: M-1, with a retention time of 9.9 min, and M-2, with a retention time of 12.2 min. Both rimantadine and M-1 were observed at the earliest time sampled (0.5 h). M-1 and M-2 were also found in mouse urine.

Concentrations of M-1 and rimantadine in mouse lungs

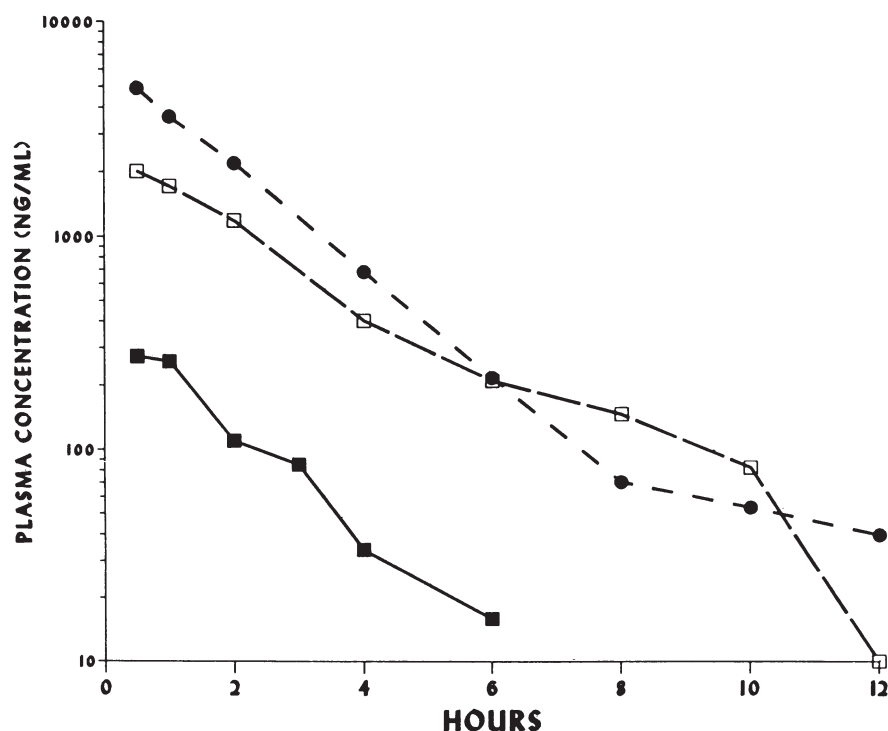


FIG. 1. Concentration of rimantadine in uninfected mouse plasma after a single dose. Groups of six nonfasted female mice, weighing 20 to 23 g, were dosed at 10 mg/kg peroral (■), 40 mg/kg peroral (□), and 40 mg/kg intravenously (●) and bled by cardiac puncture into heparinized tubes. The serum was pooled. The mean variation of the method for replicate samples was 7% (coefficient of variation).

TABLE 3. Pharmacokinetics of rimantadine in dogs

Route	Dose (mg/kg)	$n^a$	$k_{el}$ ( $h^{-1}$ )	$t_{1/2}$ (h)	AUC (ng · h/ml) ( $\pm$ SD)	$C_{max}$ (ng/ml) ( $\pm$ SD)	$T_{max}$ (h)	CL (liter/h per kg)	V (liter/kg)	F (%)
Oral	5	3	0.242	2.86	1,353 (236)	275 (47)	1.0			99.4
	10	2	0.202	3.43	4,066 (263)	788 (16)	2.0			
	20	1	0.190	3.65	11,520	1,950	2.0			
i.v. <sup>b</sup>	5	3	0.267	2.60	1,361 (94)			3.7	13.8	

<sup>a</sup>  $n$ , Number of animals per dose level used. Samples from each dog were assayed separately.

<sup>b</sup> i.v., Intravenous.

were measured after oral dosing. Peak concentrations of rimantadine were observed at 0.5 h, whereas M-1 concentrations peaked at 2 h after dosing. A plot of the concentrations of rimantadine and M-1 in lung tissues is shown in Fig. 2. Metabolite M-2 in mouse lungs was not determined quantitatively owing to poor chromatographic resolution but was found in mouse and rat plasma and human, mouse, and dog urine with a retention time of about 12 min.

Dog urine (0 to 24 h) (see Table 5) and plasma also contained an abundance of M-1 and M-2 after a single oral 10-mg/kg dose. The M-1 concentration in dog plasma peaked at 2 h and reached approximately one-half the  $C_{max}$  of rimantadine. The pharmacokinetics of the metabolites were not analyzed owing to the absence of pure compound and the resultant inability to develop suitable methods.

**Structural elucidation of metabolites by gas chromatography-mass spectrometry.** Rimantadine metabolites in mouse plasma were identified by mass spectrometry as rimantadine having a hydroxyl group on the adamantane ring. The metabolites were separated from other components on a

capillary gas chromatograph, and the fragmentation patterns were investigated by both electron impact and chemical ionization mass spectrometry. Comparison of the chemical ionization mass spectra for both rimantadine and the metabolite indicated a gain of 16 mass units on the adamantane ring of the metabolite. This suggested the presence of a hydroxyl group. The spectral data suggested that the isolated rimantadine PFB metabolite had a molecular weight of 389 and made up of the structure shown in Fig. 3.

Preparation of the trimethylsilyl derivatives for both PFB rimantadine and the metabolite confirmed that the hydroxyl group is on the adamantane ring of the metabolite. Our studies of human urine extracts showed that there are three isomers of hydroxyrimantadine: the 1-, 2-, and 3-hydroxyrimantadines (Van Voris et al., 23rd ICAAC).

**Material balance in mice and dogs.** Most of the radioactivity (69.4%) excreted by mice after 24 h was found in the urine, with only 1.7% excreted in feces (Table 4). During the next 24 h, 13.8% was excreted in urine, while only 1.1% was

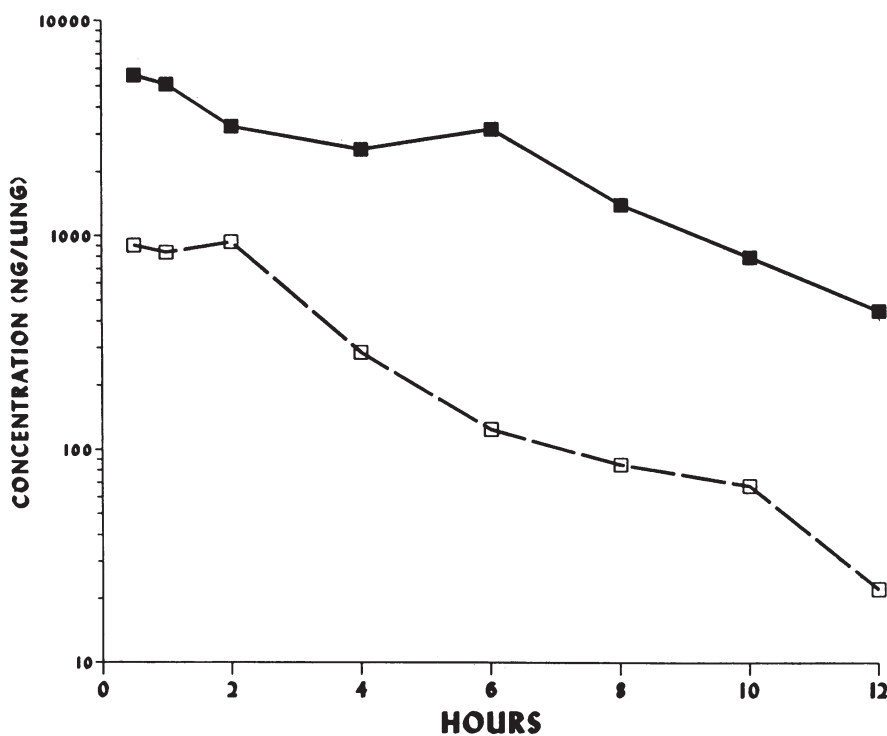


FIG. 2. Concentration of rimantadine and metabolite M-1 in mouse lungs after a single oral dose of 40 mg/kg. Each point represents the mean of rimantadine (■) or M-1 (□) levels in extracts from two lungs collected at 0.5, 1, 2, 4, 6, 8, 10, and 12 h after dosing. The rimantadine high-pressure liquid chromatography retention time was 7.0 min, and that of M-1 was 9.1 min.

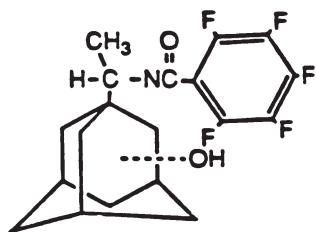


FIG. 3. Structure of isolated rimantadine PFB metabolite.

found in feces. The total percentages of the dose after 96 h were 89.4% in urine and 3.7% in feces.

Dog urine was analyzed for rimantadine and metabolites M-1 and M-2 (Table 5). High-pressure liquid chromatography analysis of the metabolites gives estimates only, based on the assumption that the absorption spectra were similar to those of rimantadine. The amounts of intact rimantadine were less than 2% in the first 24 h, regardless of dose, and less than 1% in the second 24 h. The major excretion product was M-1. The discrepancy between the dogs receiving 10 mg/kg is unexplainable. Approximately 50% of the recovered drug was M-1, while M-2 accounted for 10% or less. The total percentages of the 10-mg/kg dose recovered were 69.4% for dog 75 and 58% for dog 76. At 20 mg/kg, 61.6% was recovered. All values increased 20% following  $\beta$ -glucuronidase hydrolysis. The data in Table 5 were collected after enzyme hydrolysis.

### DISCUSSION

In both mice and dogs, absorption of rimantadine was rapid. No significant differences in  $t_{1/2}$  were noted. The differences observed in bioavailability between mice and dogs were not directly comparable owing to differences in dose. It is probable that bioavailability is not constant with dose; this should be studied.

Infection of mice with influenza A virus 72 h prior to oral administration of rimantadine significantly altered the drug disposition from that in uninfected mice. Reduction in the uptake of rimantadine by lung tissue from infected mice has been previously reported (4), and our results confirm this finding (Table 2). The rimantadine concentrations in plasma and lungs at the time of peak concentration in virus-infected mice were approximately one-half those in uninfected mice. The lung elimination half-life lengthened from 1.8 h in uninfected mice to 4.4 h in infected mice. The net effect of these changes, however, resulted in equivalent AUC values. Although rimantadine concentrations in lungs were not determined, Schulman demonstrated that doses of 25 mg of rimantadine per kg dramatically reduced lung lesions and virus titers in mice (8). Studies of virus titers in lungs versus drug concentrations in lungs and plasma would be of interest.

TABLE 4. [ $^{14}$ C]rimantadine mouse material balance study

Collection interval (h)	Mean % administered dose $\pm$ SD in:	
	Urine	Feces
0-24	69.4 $\pm$ 5.0	1.7 $\pm$ 0.5
24-48	13.8 $\pm$ 1.0	1.1 $\pm$ 0.2
48-72	4.3 $\pm$ 3.0	0.3 $\pm$ 0.2
72-96 <sup>a</sup>	1.9 $\pm$ 1.0	0.6 $\pm$ 0.7

<sup>a</sup> At 96 h, the cage wash activity was 5.6  $\pm$  0.1%. Total recovery was 98.7%.

TABLE 5. Recovery of total rimantadine and metabolites in the urine<sup>a</sup> of dogs given single oral doses of rimantadine

Collection interval (h) and substance	% of dose in:		
	Dog 75 <sup>b</sup>	Dog 76 <sup>b</sup>	Dog 74 <sup>c</sup>
0-24			
Rimantadine	1.6	1.2	1.8
M-1	15.9	43.7	46.6
M-2	2.4	10.0	6.5
24-48			
Rimantadine	0.8	0.3	0.1
M-1	39.9	2.3	5.3
M-2	8.8	0.5	1.3

<sup>a</sup> Urine was treated with  $\beta$ -glucuronidase for 2 h at 37°C before extraction (see text).

<sup>b</sup> Dose was 10 mg/kg.

<sup>c</sup> Dose was 20 mg/kg.

After administration of one oral dose of [ $^{14}$ C]rimantadine to mice, 89.4% of the radioactivity was found in the urine and 3.7% was found in the feces. Most of the radioactivity was excreted during the first 24 h, and only 1.9% of the dose was recovered during the period from 72 to 96 h.

Dogs receiving oral doses of 10 or 20 mg/kg excreted very little intact rimantadine. The main excretion product was M-1, which made up about half of the administered dose; M-2 was about 10%, and rimantadine was less than 5%. Only 58 to 69% of administered drug was recovered in 48 h in the three dogs. This may in part be due to further metabolism of M-1 and M-2 into smaller, as yet unidentified products. Further, until standards of M-1 and M-2 can be prepared and analyzed, quantification of these remains only an estimate.

The metabolites identified in mouse and dog urine, M-1 and M-2, are ring-hydroxylated derivatives of rimantadine. Other investigators have noted ring hydroxylation of adamantane derivatives in vivo. Wesemann et al. (10) demonstrated the presence of a ring-hydroxylated metabolite of 1-amino-3,5-dimethyladamantane in the rat. Spiers and Chatfield (9), studying a novel adamantane derivative, *N*-methyl-1-(2-phenyladamant-1-yl)-2-aminopropane hydrochloride, in humans, determined that two isomers of a ring-hydroxylated metabolite were excreted. The ring position of hydroxylation was not determined. Less than 1% of the dose was excreted unchanged. Approximately 30% of the dose was excreted as conjugated hydroxyl metabolites.

The metabolism of amantadine is less clear. Recent studies by Koppel and Denzer (5) have shown small quantities of eight metabolites recovered from a patient under a therapeutic dosing regimen. A major metabolic pathway was *N* acetylation, with several other unusual metabolic pathways observed. However, no metabolites were detected with a hydroxylated adamantane ring system.

Differences between the metabolism and kinetics of rimantadine and amantadine are noteworthy. For both, >90% is excreted in the urine, with trace amounts in the feces. However, the percentage of unchanged amantadine found in mouse urine was 63% (9), several times that found for intact rimantadine. In humans, amantadine is excreted largely unchanged in urine, whereas less than 10% of rimantadine is excreted intact (Van Voris et al., 23rd ICAAC) in urine.

Little has been reported about the concentration of either drug in lung tissue. Bleidner et al. (1) reported the  $C_{max}$  in mouse lungs at 0.25 h to be 59  $\mu$ g/g following a single oral dose of 25 mg/kg. The concentration of amantadine in blood was 4  $\mu$ g/ml. The ratio  $C_{max, lung} / C_{max, blood}$  of 15 was half the

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