ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Aug. 1985, p. 216–221
0066-4804/85/080216-06$02.00/0

Vol. 28, No. 2

# Comparative Single-Dose Pharmacokinetics of Amantadine Hydrochloride and Rimantadine Hydrochloride in Young and Elderly Adults

FREDERICK G. HAYDEN,[1,2]* ANIL MINOCHA,[1] DANIEL A. SPYKER,[1] AND HOWARD E. HOFFMAN[3]

*Departments of Internal Medicine[1] and Pathology,[2] University of Virginia School of Medicine, Charlottesville, Virginia 22908, and Pharmaceuticals-Biomedical Products Department, E. I. DuPont de Nemours and Company, Newark, Delaware 19714[3]*

Received 10 February 1985/Accepted 1 May 1985

**The single-dose pharmacokinetics of amantadine hydrochloride and rimantadine hydrochloride were compared in a randomized, two-period, crossover study involving six young (≤35 years) and six elderly (≥60 years) adults. Subjects ingested single 200-mg oral doses after an overnight fast, and serial plasma (0 to 96 h), nasal mucus (0 to 8 h), and urine (0 to 24 h) samples were collected for assay of drug concentration by electron capture gas chromatography. For both groups combined, rimantadine differed significantly from amantadine in peak plasma concentration (mean ± standard deviation, 0.25 ± 0.06 versus 0.65 ± 0.22 μg/ml), plasma elimination half-life (36.5 ± 15 versus 16.7 ± 7.7 h), and percentage of administered dose excreted unchanged in urine (0.6 ± 0.8 versus 45.7 ± 15.7%). No significant age-related differences were noted for rimantadine. Urinary excretion (0 to 24 h) of rimantadine and its hydroxylated metabolites averaged 19% of the administered dose. The maximum nasal mucus drug concentration was similar for both drugs (0.42 ± 0.25 versus 0.45 ± 0.32 μg/g), and the ratio of maximum nasal mucus to plasma concentration was over twofold higher after rimantadine than after amantadine. These findings may in part explain the clinical effectiveness of rimantadine in influenza A virus infections at dosages that have lower toxicity than those of amantadine.**

The adamantane compounds, amantadine hydrochloride and rimantadine hydrochloride, have well-documented prophylactic and therapeutic efficacy in influenza A virus infections (5, 21). Limited in vitro and animal model results suggest that rimantadine has greater influenza A virus-inhibitory activity than amantadine (7, 15, 19). More importantly, clinical studies have found that at equivalent oral dosages of 200 mg (5) or 300 mg (8) per day rimantadine is associated with significantly fewer central nervous system side effects than amantadine. The differences in side effect rates observed between the two drugs appear to be related to differences in plasma concentrations (8). Whereas amantadine pharmacokinetics have received extensive study (1–4, 9, 17), the pharmacokinetics of oral rimantadine have not been delineated. Limited results in healthy adults indicate that rimantadine is associated with significantly lower plasma concentrations after single or multiple doses (8) and has a longer plasma half-life and lower urinary excretion than amantadine (20). In addition, the pharmacokinetics of these drugs have not been defined in the elderly, one of the target populations for the prevention of influenza A virus infections.

The current study was conducted to determine the comparative single-dose pharmacokinetics of amantadine and rimantadine in both young and elderly adults. This study also incorported collection of nasal mucus samples to determine concentrations of these drugs in respiratory secretions after systemic administration.

## MATERIALS AND METHODS

**Study design.** This study was a randomized, open-label, two-treatment, crossover study in which rimantadine and amantadine were administered to both elderly and young adults. Healthy male volunteers between the ages of 18 and 35 years and adults aged 60 years or older were recruited for participation. All subjects gave written informed consent in a form approved by the University of Virginia Human Investigation Committee. Persons with laboratory evidence of renal or hepatic dysfunction, significant medical illness, or concurrent alcohol use were excluded from participation. A medical history and physical examination were performed within 1 week of the first drug administration. The participants were housed on the University of Virginia Clinical Research Center for the first day of each drug administration.

**Drug administration.** Amantadine and rimantadine tablets containing 100 mg were provided by DuPont Pharmaceuticals, E. I. DuPont de Nemours and Co., Wilmington, Del. After an overnight fast, rimantadine or amantadine was administered to the subjects as a single 200-mg oral dose. Subjects remained in an upright position for the first hour after drug administration, and no food was permitted for 4 h. Participants ate meals at approximately 4 and 8 h after drug administration. The intake of water was unrestricted throughout the study. After an initial 12-h stay on the Clinical Research Center, participants were allowed to leave the facility on an unrestricted diet and to return at appropriate times for specimen collection. A minimum washout interval of 1 week was present between the two sampling periods.

**Sample collection.** Venous blood samples were collected into heparinized tubes from indwelling catheters just before the dose and at 1, 2, 3, 4, 6, 8, 12, 24, 48, 72, and 96 h after drug administration. The plasma was separated by centrifugation and frozen at −20°C. Urine was collected from the time of drug administration (0 h) to 24 h after administration, and a 50-ml sample of the collection was frozen for later analysis. Nasal mucus samples were collected before drug

* Corresponding author.

TABLE 1. Demographic characteristics of subjects

| Subject no. | Sex | Ht (cm) | Wt (kg) | Age (yr) | LBW[a] (kg) | Serum creatinine (mg/dl) | CorCcr[b] (mg/ml) |
|---|---|---|---|---|---|---|---|
| Young | | | | | | | |
| 1 | M | 163 | 68.2 | 19 | 62.2 | 1.0 | 121 |
| 2 | M | 183 | 75.0 | 23 | 75.0 | 0.9 | 130 |
| 3 | M | 180 | 60.0 | 26 | 60.0 | 0.9 | 126 |
| 4 | M | 183 | 95.9 | 29 | 79.2 | 1.2 | 92 |
| 5 | M | 180 | 86.0 | 30 | 77.5 | 1.1 | 99 |
| 6 | M | 185 | 89.5 | 35 | 83.2 | 0.9 | 116 |
| Mean | | 180 | 79.1 | 27 | 72.8 | 1.0 | 114 |
| SD | | 6 | 13.7 | 6 | 9.5 | 0.1 | 15 |
| Elderly | | | | | | | |
| 7 | F | 152 | 68.0 | 60 | 58.0 | 0.7 | 97 |
| 8 | M | 180 | 79.5 | 63 | 79.5 | 1.2 | 64 |
| 9 | F | 157 | 60.9 | 63 | 60.9 | 0.7 | 94 |
| 10 | M | 183 | 80.9 | 63 | 80.9 | 1.1 | 70 |
| 11 | F | 168 | 75.9 | 65 | 70.1 | 0.8 | 80 |
| 12 | M | 171 | 80.9 | 65 | 73.3 | 1.0 | 75 |
| 13 | F | 160 | 68.0 | 67 | 65.2 | 0.9 | 69 |
| 14 | F | 168 | 72.3 | 67 | 70.2 | 0.9 | 69 |
| 15 | M | 178 | 86.4 | 68 | 78.1 | 0.8 | 90 |
| 16 | M | 180 | 84.0 | 70 | 79.0 | 1.1 | 63 |
| Mean | | 170 | 74.7 | 65[c] | 71.5 | 0.9 | 77[c] |
| SD | | 11 | 9.7 | 3 | 8.1 | 0.2 | 13 |

[a] Lean body weight calculated from age, height, and sex (18).
[b] Calculated creatinine clearance corrected for age and sex (18).
[c] $P < 0.01$, young versus elderly, two-tailed $t$ test.

administration and at 1, 4, and 8 h after the dose. Mucus specimens were collected by previously described methods (14), in which 3 to 5 drops of water was sniffed into the nares and allowed to dwell for 60 s, and then mucus was forcefully blown into preweighed plastic containers. This technique has been shown to provide respiratory secretion samples that are significantly more concentrated than conventional nasal washes (14).

**Drug assay.** Amantadine and rimantadine concentrations were measured in plasma, urine, and nasal secretions by previously described electron capture gas chromatography assays (8). Briefly, rimantadine and amantadine were extracted from plasma and nasal mucus samples with disposable extraction columns, derivatized with pentafluorobenzoyl chloride, and analyzed by gas chromatography with an electron capture detector. A lower limit for detectability for these assays is approximately 5 ng/ml. Plasma concentrations from clinical specimens were determined by use of the best-fit line from standards prepared from predose plasma of each subject. Nasal mucus samples collected from healthy adults were used to prepare the standard curves for the assay of drug concentrations in nasal mucus.

For measurement of rimantadine in urine, 1 ml of urine was added to 5 ml of 5 N NaOH, 15 ml of hexane, and 15 mg of NaCl. The mixture was agitated on a wrist-action shaker for 30 min and centrifuged to separate the phases, and the hexane layer was removed. The extraction was repeated, the hexane layers were combined, and the solvent was removed by a stream of air. To the dried residues, 1 ml of toluene containing amantadine (as internal standard) at 0.5 μg/ml, about 20 mg of $Na_2SO_4$, and 20 mg of pentafluorobenzoyl chloride were added and shaken for 30 min at 55°C. To stop the reaction, 5 ml of 5 N NaOH was added to each tube, and shaking was resumed for 15 min. The tubes were centrifuged, and the toluene layer was removed for analysis by gas chromatography as described above. The method was found to be linear for rimantadine from 50 to 1,000 ng/ml. The recovery of rimantadine added to urine was approximately 62%. The variation averaged 11.4% for replicate assays.

**Data analysis.** Data for each patient were entered via microcomputer terminal, stored directly on disk files, verified, and thereafter manipulated only by the pharmacokinetic and statistical programs.

The multiple plasma drug concentrations were fit to the two-compartment linear model with exponential absorption where elimination occurs from the central compartment (22). A lag between the drug adminstration and the beginning of the absorption was permitted. Since intravenous data were not available, we could not separate out absorption fraction and were actually fitting the ratio of fraction absorbed and the volume of distribution ($F_a/V_d$).

TABLE 2. Pharmacokinetic parameters in young adults[a]

| Drug | Subject no. | Lag (h) | $T_{ab}$ (h) | $T_{alpha}$ (h) | $T_{beta}$ (h) | Cl (μg/ml) | $V_c$ (liters) | $V_{dss}$ (liters) | AUC (μg/ml per h) | $C_{max}$ (μg/ml) | $T_{max}$ (h) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Amantadine | 1 | 0.6 | 1.3 | 0.5 | 8.5 | 0.57 | 191 | 393 | 5.8 | 0.38 | 3.2 |
| | 2 | 0.4 | 0.4 | 0.2 | 14.6 | 0.44 | 194 | 538 | 7.6 | 0.40 | 1.2 |
| | 3 | 0.4 | 0.7 | 0.2 | 10.9 | 0.31 | 217 | 289 | 10.8 | 0.58 | 3.0 |
| | 4 | 0.7 | 0.2 | 0.3 | 25.4 | 0.21 | 401 | 461 | 15.9 | 0.43 | 1.6 |
| | 5 | 0.1 | 0.2 | 1.0 | 10.9 | 0.31 | 233 | 285 | 10.7 | 0.74 | 1.0 |
| | 6 | 0.4 | 1.1 | 1.2 | 15.8 | 0.33 | 173 | 399 | 10.0 | 0.56 | 2.6 |
| | Mean | 0.4 | 0.6 | 0.6 | 14.4 | 0.36 | 235 | 394 | 10.2 | 0.51 | 2.1 |
| | SD | 0.2 | 0.5 | 0.4 | 6.0 | 0.13 | 84 | 98 | 3.4 | 0.14 | 1.0 |
| Rimantadine | 1 | 0.3 | 2.1 | 7.3 | 64.0 | 0.18 | 383 | 812 | 18.6 | 0.32 | 5.8 |
| | 2 | 0.8 | 0.5 | 0.7 | 30.4 | 0.33 | 312 | 829 | 10.2 | 0.34 | 2.0 |
| | 3 | 0.0 | 1.8 | 0.4 | 32.2 | 0.36 | 375 | 984 | 9.3 | 0.17 | 6.6 |
| | 4 | 0.9 | 0.3 | 7.1 | 50.7 | 0.45 | 784 | 1,550 | 7.4 | 0.23 | 2.4 |
| | 5 | 0.8 | 1.2 | 1.2 | 21.7 | 0.47 | 492 | 836 | 7.2 | 0.22 | 4.0 |
| | 6 | 0.9 | 1.9 | 0.4 | 20.2 | 0.53 | 352 | 901 | 6.2 | 0.17 | 6.6 |
| | Mean | 0.6 | 1.3 | 2.9 | 36.5 | 0.39 | 450 | 986 | 9.8 | 0.24 | 4.6 |
| | SD | 0.4 | 0.8 | 3.4 | 17.3 | 0.13 | 174 | 284 | 4.5 | 0.07 | 2.1 |
| *P* value | | 0.64 | 0.09 | 0.13 | 0.01 | 0.74 | 0.02 | 0.001 | 0.88 | 0.002 | 0.02 |

[a] Abbreviations: Lag, absorption lag; $T_{ab}$, absorption half-life; $T_{alpha}$, distribution half-life; $T_{beta}$, elimination half-life; Cl, total body clearance; $V_c$, central volume of distribution; $V_{dss}$, steady-state volume of distribution; AUC, area under plasma concentration time curve; $C_{max}$, maximum concentration; $T_{max}$, time to maximum concentration.

TABLE 3. Pharmacokinetic parameters in elderly adults[a]

| Drug | Subject no. | Lag (h) | $T_{ab}$ (h) | $T_{alpha}$ (h) | $T_{beta}$ (h) | Cl (μg/ml) | $V_c$ (liters) | $V_{dss}$ (liters) | AUC (μg/ml per h) | $C_{max}$ (μg/ml) | $T_{max}$ (h) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Amantadine | 8 | 0.1 | 1.7 | 0.8 | 19.0 | 0.19 | 281 | 308 | 17.6 | 0.51 | 6.4 |
| | 10 | 0.0 | 0.4 | 11.9 | 29.5 | 0.11 | 184 | 221 | 30.3 | 1.00 | 2.0 |
| | 11 | 0.1 | 0.3 | 0.4 | 15.3 | 0.24 | 175 | 311 | 13.9 | 0.71 | 1.0 |
| | 12 | 0.0 | 0.4 | 0.4 | 9.8 | 0.25 | 143 | 206 | 13.4 | 0.90 | 1.4 |
| | 14 | 0.0 | 0.2 | 0.5 | 10.3 | 0.25 | 149 | 219 | 13.3 | 1.00 | 0.8 |
| | 15 | 0.3 | 0.4 | 2.1 | 30.2 | 0.19 | 224 | 463 | 17.2 | 0.67 | 1.8 |
| | Mean | 0.1 | 0.6 | 2.7 | 19.0 | 0.21 | 192 | 288 | 17.6 | 0.80 | 2.2 |
| | SD | 0.1 | 0.5 | 4.5 | 9.1 | 0.54 | 52 | 97 | 6.5 | 0.20 | 2.1 |
| Rimantadine | 7 | 0.5 | 5.1 | 5.3 | 19.3 | 0.30 | 274 | 387 | 11.1 | 0.33 | 10.0 |
| | 8 | 0.8 | 1.0 | 1.6 | 37.6 | 0.31 | 902 | 1,007 | 10.7 | 0.18 | 5.4 |
| | 9 | 0.8 | 1.1 | 0.9 | 21.6 | 0.55 | 599 | 997 | 6.1 | 0.18 | 3.8 |
| | 10 | 0.9 | 1.0 | 0.4 | 22.9 | 0.46 | 391 | 887 | 7.3 | 0.20 | 3.4 |
| | 11 | 0.9 | 0.4 | 8.1 | 52.8 | 0.22 | 700 | 940 | 15.1 | 0.26 | 2.8 |
| | 12 | 0.9 | 0.4 | 1.1 | 27.4 | 0.32 | 561 | 740 | 10.5 | 0.28 | 2.8 |
| | 13 | 0.6 | 1.8 | 3.0 | 30.8 | 0.39 | 417 | 889 | 8.5 | 0.27 | 4.8 |
| | 14 | 1.0 | 0.7 | 0.9 | 45.1 | 0.19 | 465 | 734 | 17.5 | 0.28 | 3.2 |
| | 15 | 1.0 | 0.0 | 8.5 | 62.2 | 0.20 | 726 | 995 | 16.9 | 0.27 | 1.4 |
| | 16 | 0.8 | 0.5 | 1.4 | 45.1 | 0.30 | 695 | 1,138 | 11.2 | 0.21 | 2.8 |
| | Mean | 0.8 | 1.2 | 3.1 | 36.5 | 0.32 | 573 | 871 | 11.5 | 0.25 | 4.0 |
| | SD | 0.2 | 1.5 | 3.1 | 14.5 | 0.12 | 189 | 210 | 3.9 | 0.05 | 2.4 |
| P value | | <0.01 | 0.33 | 0.81 | 0.01 | 0.03 | 0.001 | <0.001 | 0.03 | <0.01 | 0.14 |

[a] Abbreviations are in footnote *a* of Table 2.

The data were fit by using a Pascal version of the Marquardt-Levenberg algorithm (10) for nonlinear least-squares estimation of parameters adapted from the initial program in BASIC by Horwitz and Homer. Peck and Barret compared a microcomputer version of this algorithm to standard mainframe programs (NONLIN, BMD) on a variety of problems and found comparable or better accuracy and precision in all sample problems (12). For each patient the absorption lag, $K_e$, $K_{12}$, $K_{21}$, and $V_c$ were found (22). From the kinetic model, the volume of distribution at steady state ($V_{dss}$), total drug clearance, area under the plasma concentration-time curve (AUC), maximum plasma concentration ($C_{max}$), and time to maximum plasma concentration ($T_{max}$) were calculated according to standard definitions (22).

Individual kinetic plots of measured levels and kinetic fit were generated for each case. Patient parameters and calculated kinetic parameters were compared by standard analysis of variance. Other parametric or nonparametric statistical tests for paired samples were employed as indicated.

## RESULTS

**Participants.** The demographic characteristic of the subjects are shown in Table 1. Six healthy elderly adults (ages 60 to 70 years; two women, four men) and six young adult men (ages 19 to 35 years) partipicated in both phases of this study. In addition, four elderly adults (ages 63 to 70 years; three women, 1 man) participated in the rimantadine phase only. The elderly subjects were similar to the young adults in regard to height, weight, and serum creatinine, but had significantly lower calculated creatinine clearance corrected for age and sex (Table 1).

No clinically significant side effects occurred during the course of this study. One 68-year-old male experienced 2 h of mild dizziness shortly after ingesting rimantadine; he did not report any symptoms after receiving amantadine. One 19-year-old male reported a headache of moderate intensity lasting for 14 h on the day of rimantadine ingestion.

**Pharmacokinetic data.** Statistically significant differences were found between the two drugs in the elimination half-lives, peak plasma concentrations, and the volume of distribution in both young (Table 2) and elderly (Table 3) adults. In the elderly (Table 3), rimantadine was also associated with a significantly longer absorption lag and smaller area under the plasma concentration-time curve compared with amantadine. For all subjects combined, rimantadine was associated with approximately 2 times longer absorption half-life and 2.5 times larger central volume of distribution compared with amantadine. Peak plasma rimantadine concentrations averaged 31 and 47% of amantadine levels in the elderly and young subjects, respectively, and appeared in about twice the time (Fig. 1). Despite the difference in the plasma elimination half-life, the total body clearance of the two drugs was comparable.

A comparison of the results between the young and the elderly subjects did not reveal any significant differences for rimantadine. Younger subjects ingesting amantadine, however, tended to have a smaller steady-state volume of distribution (mean 27% less) than the elderly ($P = 0.08$), and the total body clearance averaged 1.7 times than that of the elderly ($P = 0.01$). After administration of amantadine, elderly subjects averaged 1.5 times higher peak plasma concentrations ($P = 0.01$) and 1.7 times greater area under the curve values ($P = 0.03$) than young adults. No significant differences in the elimination half-life was found.

Mean steady-state peak and trough plasma concentrations were estimated by using the means of the kinetic parameters for the elderly subjects. Assuming a single-dose regimen of a 200 mg per day, the steady-state peak and trough concentrations were 0.49 and 0.28 μg/ml, respectively, for rimantadine and 1.00 and 0.35 μg/ml, respectively, for amantadine.

**Urinary excretion.** The proportion (mean ± standard deviation) of the administered dose that was recovered in urine (0 to 24 h) as the parent drug represented 51.7 ± 20.4% of the amantadine dose in the young adults and 39.7 ± 6.3% in the elderly. In contrast, only 0.8 ± 1.1% of the administered rimantadine dose was recovered in the urine of young adults, and 0.5 ± 0.4% was recovered in the elderly. At least three rimantadine metabolites were also excreted in the urine.

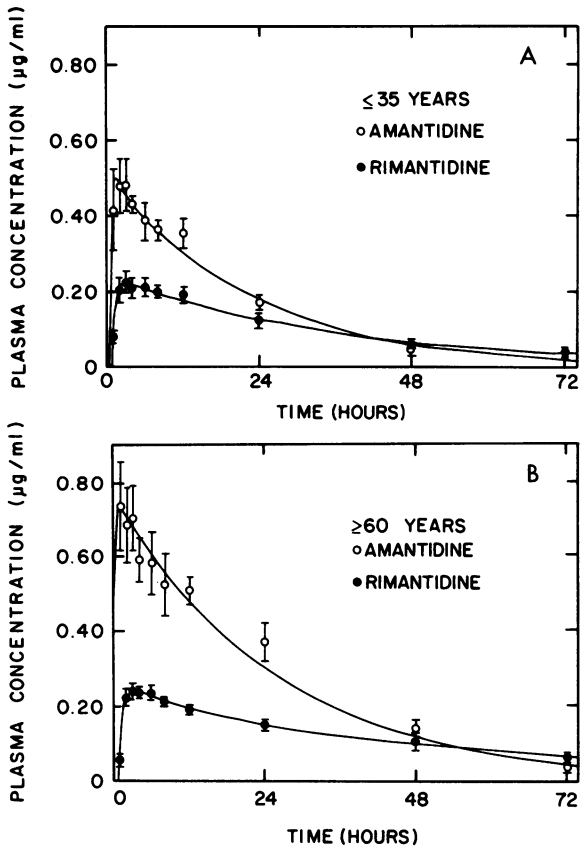


FIG. 1. Plasma amantadine and rimantadine concentrations (mean ± standard error of the mean) in young (≤35 years) (A) and elderly (≥60 years) (B) adults after single 200-mg oral doses. The line represents the best fit to the two-compartment linear model through use of a standard nonlinear least-squares method (12).

Preliminary mass spectrometry analysis found these metabolites to be the ortho-, para-, and metahydroxylated metabolites of rimantadine (L. P. Van Voris, J. Bartram, H. E. Hoffman, L. M. Shalaloy, J. C. Gaylord, L. S. Davis, and F. G. Hayden, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 24th, Las Vegas, Nev., 1984). The total urinary recovery of rimantadine and its hydroxylated metabolites (mean ± standard deviation) was 19.7 ± 17.5% of the administered dose in elderly subjects and 17.8 ± 7.3% in young subjects.

**Nasal mucus drug concentrations.** Table 4 lists the relationship between plasma and nasal mucus drug concentrations during the 8-h period after drug ingestion. As described above, plasma amantadine concentrations rose more rapidly and peaked at significantly higher levels than rimantadine concentrations, averaging over twofold higher than rimantadine values at 4 or 8 h (Fig. 1). Plasma and nasal mucus concentrations were very low in rimantadine recipients at 1 h. Whereas plasma concentrations declined between 4 and 8 h after ingestion of either drug (Fig. 1), nasal mucus concentrations of both amantadine and rimantadine tended to rise through 8 h after drug administration (Table 4). Although nasal mucus concentrations showed considerable variability, no differences were observed in mean concentrations between the drugs at 4 or 8 h after drug administration. The ratio of nasal mucus to plasma concentrations approached unity at 8 h after amantadine ingestion. The ratios observed after rimantadine administration were significantly higher at 4 and 8 h than after amantadine, and the mean ratio of nasal mucus to plasma exceeded unity at 8 h after drug ingestion. The maximum nasal mucus concentrations (mean ± standard deviation) of rimantadine (0.42 ± 0.25 μg/g) were similar to those of amantadine (0.45 ± 0.32 μg/g) and were higher than the maximum measured plasma concentrations of rimantadine (0.25 ± 0.05 μg/ml) ($P < 0.05$, paired $t$ test).

## DISCUSSION

This study was the first to determine the comparative pharmacokinetics of amantadine and rimantadine in the same patient population. An earlier study of the comparative toxicities of the two drugs found highly significant differences in plasma concentrations after single or multiple doses (8). The results of the current study confirm that rimantadine and amantadine differ significantly in a number of pharmacokinetic parameters. Peak rimantadine concentrations averaged 47% of amantadine levels in young adults and 31% in elderly subjects. The time to peak plasma concentration also tended to be longer after rimantadine than amantadine, which suggests a slower rate of absorption for rimantadine. The elimination half-life and volume of distribution of rimantadine averaged over twofold greater than amantadine, although wide interindividual variations existed in pharmacokinetic parameters for both drugs.

The reasons for the lower plasma concentrations of rimantadine are not certain. Both amantadine and rimantadine have similar chemical structures, are water soluble (≥50 g/liter of water), and were formulated in the same fashion for this study. In the current study the subjects were fasting and other drugs were avoided, to prevent interaction of rimantadine with other substances in the gastrointestinal tract. Differences in drug stability or solubility at the pH of gastrointestinal fluids, inactivation or transformation by gut enzymes or flora, or variable drug absorption from the intestine are possible explanations for the observed differ-

TABLE 4. Relationship between plasma and nasal mucus drug concentrations after single 200-mg oral dosages[a]

| Drug ($n$ = 12) | Time after dose (h) | Drug concn in: | | Ratio of nasal mucus/plasma concn |
|---|---|---|---|---|
| | | Plasma (μg/ml) | Nasal mucus (μg/g) | |
| Amantadine | 1 | 0.58 (0.32)[b] | 0.15 (0.16)[c] | 0.31 (0.33) |
| | 4 | 0.51 (0.13)[b] | 0.28 (0.26) | 0.59 (0.61)[d] |
| | 8[e] | 0.45 (0.17)[b] | 0.39 (0.34) | 0.95 (0.86)[f] |
| | Maximum | 0.72 (0.21)[b] | 0.45 (0.32) | 0.71 (0.62)[g] |
| Rimantadine | 1 | 0.07 (0.04) | 0.02 (0.05) | 0.22 (0.51) |
| | 4[e] | 0.24 (0.05) | 0.26 (0.25) | 1.05 (0.92) |
| | 8 | 0.20 (0.03) | 0.34 (0.21) | 1.75 (1.10) |
| | Maximum | 0.25 (0.05) | 0.42 (0.25) | 1.73 (1.04) |

[a] Values are listed as mean (standard deviation). Maximum values represent highest measured concentrations between 1 and 8 h after the dose for both plasma and nasal mucus.

[b] $P < 0.001$, amantadine versus rimantadine (1, 4, or 8 h or maximum), two-tailed paired $t$ test.

[c] $P < 0.02$, amantadine versus rimantadine (1 h).

[d] $P = 0.02$, amantadine versus rimantadine (4 h), Wilcoxon matched pairs, signed ranks test.

[e] $n = 11$.

[f] $P = 0.05$, amantadine versus rimantadine (8 h).

[g] $P < 0.02$, amantadine versus rimantadine (maximum).

ences in peak plasma drug concentrations. However, in recent studies in six young adults ingesting single 200-mg doses of $^{14}$C-labeled rimantadine, it was found that an average of 92% of the radioactivity was recovered in urine collections continued for 360 h (H. E. Hoffman, unpublished observations). These results indicate that the oral bioavailability of rimantadine is high and comparable to that reported for amantadine (4). In the current study, the low concentrations of rimantadine in plasma could be due to postabsorbtive biotransformation in the liver or to a volume of distribution that is larger than that of amantadine (Tables 2 and 3). Unfortunatley, no intravenous formulation of either amantadine or rimantadine is available for studies to examine these possibilities.

The metabolic fate of rimantadine was only partially determined in this study. Urinary excretion of the parent drug and ortho-, para-, and metahydroxy metabolites accounted for approximately one-fifth of the administered dose. However, considerable variability existed in the proportion of the dose recovered in the 24-h urine sample (range, 5.5 to 49%). No metabolites of rimantadine were identified in plasma specimens with the electron capture gas chromatography method of assay. Further work is needed to determine the antiviral activity and potential toxicity of rimantadine metabolites.

As previously described in elderly subjects ingesting amantadine (1), we found fluctuations in the plasma concentration profile for amantadine, and less often for rimantadine, over the 96-h period of measurement. In many instances these oscillations appeared to temporally relate to the ingestion of food. This suggests that either the drug had been incompletely absorbed earlier or, more likely, that the drugs were undergoing enterohepatic recycling, since this pattern was seen more than once over the 96-h period. Pederson and Miller have proposed a similar model for the effect of fasting and feeding on enterohepatic recycling of cimetidine (13).

This study was the first to examine the pharmacokinetics of rimantadine in the elderly, one of the target populations for prevention and treatment of influenza A virus infections. In contrast to the age-related differences in amantadine pharmacokinetics found in this and earlier studies (1), no significant differences were detected in the parameters measured between elderly and young adults after administration of rimantadine. Using the means of the pharmacokinetic parameters for the elderly, the steady-state peak and trough concentrations of rimantadine could be estimated to be 0.49 and 0.28 μg/ml, respectively, in older adults ingesting 200 mg per day. These values underestimate peak concentrations (mean ± standard deviation, 1.16 ± 0.56 μg/ml), which have been reported in elderly nursing home subjects taking rimantadine (200 mg/day) for approximately 10 weeks (11). This discrepancy may be in part attributed to differences in the patient populations, since the subjects in the current study represented a small number of ambulatory elderly adults with well-preserved renal function. Alternatively, substantial differences may exist between the single-dose and multiple-dose pharmacokinetics of rimantadine, so that assumptions based on single-dose studies may not accurately predict steady-state conditions. Studies of the multidose pharmacokinetics of rimantadine are needed in the elderly and other target groups for rimantadine use.

The differences observed in drug concentrations in nasal secretions are of particular interest, since these may more closely predict intracellular drug concentrations in the respiratory mucosa than plasma concentrations. Previous studies by Aoki et al. (3) could not define a positive dose-response relationship between steady-state plasma amantadine concentrations and protection against experimental influenza A virus infection. Animal studies and anecdotal information from humans has suggested that amantadine may be concentrated in pulmonary tissues (4, 6). In the current study, the results observed with amantadine confirm an earlier report (16), in which the authors used nasal washings to conclude that amantadine appeared in nasal secretions at levels similar to those found in serum. In the current study we used an improved method of collection of nasal mucus (14) and found that despite nearly threefold-lower plasma concentrations, rimantadine nasal mucus concentrations were similar to those observed with amantadine and that the ratio of nasal mucus to plasma concentration was significantly higher for rimantadine. The results of this study suggest that rimantadine may be concentrated in respiratory secretions. For both drugs nasal mucus concentrations continued to rise through the 8-h observation period, at a time when plasma concentrations were declining, and exceeded concentrations that have been shown to be inhibitory for influenza A viruses in vitro (7). Although further studies are needed to assess the accumulation of rimantadine in respiratory secretions after multiple drug doses, these findings may in part explain the clinical efficacy of rimantadine in the therapy (21) and prophylaxis (5) of influenza A virus infections at doses that yield significantly lower plasma concentrations than those of amantadine.

## ACKNOWLEDGMENTS

This study was conducted on the Clinical Research Center, University of Virginia Medical Center. Support was provided in part by a grant from E. I. DuPont de Nemours and Co. and by Public Health Service grant RR00847 from the National Institutes of Health.

We thank Lisa D. Keenan, Kevin Keenan, Janet Michie, and the Clinical Research Center nursing staff for help in conducting this study and Margaret Belew for help in manuscript preparation.

## LITERATURE CITED

1. **Aoki, F. Y., and D. S. Sitar.** 1985. Amantadine kinetics in healthy elderly men: implications of influenza prevention. Clin. Pharmacol. Ther. **37**:137–144.
2. **Aoki, F. Y., D. S. Sitar, and R. I. Ogilvie.** 1979. Amantadine kinetics in healthy young subjects after long-term dosing. Clin. Pharmacol. Ther. **26**:729–736.
3. **Aoki, F. Y., H. G. Stiver, D. S. Sitar, A. Boudreault, and R. I. Ogilvie.** 1985. Prophylactic amantadine dose and plasma concentration-effect relationships in healthy adults. Clin. Pharmacol. Ther. **37**:128–136.
4. **Bleidner, W. E., J. B. Harmon, W. E. Hewes, T. E. Lynes, and E. C. Hermann.** 1965. Absorption, distribution and excretion of amantadine hydrochloride. J. Pharmacol. Exp. Ther. **150**: 484–490.
5. **Dolin, R., R. C. Reichman, H. P. Madore, R. Maynard, P. N. Linton, and J. Webber-Jones.** 1982. A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. N. Engl. J. Med. **307**:580–584.
6. **Fishaut, M., and S. R. Mostow.** 1980. Amantadine for severe influenza A pneumonia in infancy. Am. J. Dis. Child. **134**: 321–322.
7. **Hayden, F. G., K. M. Cote, and R. G. Douglas, Jr.** 1980. Plaque inhibition assay for drug susceptibility testing of influenza viruses. Antimicrob. Agents Chemother. **17**:865–870.
8. **Hayden, F. G., H. E. Hoffman, and D. A. Spyker.** 1983. Differences in side effects of amantadine hydrochloride and rimantadine hydrochloride relate to differences in pharmacokinetics. Antimicrob. Agents Chemother. **23**:458–464.
9. **Horadam, V. W., J. G. Sharp, J. D. Smilack, B. H. McAnalley,**

**J. C. Garriott, M. K. Stephens, R. C. Prati, and D. C. Brater.** 1981. Pharmacokinetics of amantadine hydrochloride in subjects with normal and impaired renal function. Ann. Intern. Med. **94**:454–458.

10. **Marquardt, D. W.** 1963. An algorithm for least squares estimation of nonlinear parameters. J. Soc. Indust. Appl. Math. **11**:431–441.
11. **Patriarca, P. A., N. A. Kater, A. P. Kendal, D. J. Bregman, J. D. Smith, and R. K. Sikes.** 1984. Safety of prolonged administration of rimantadine hydrochloride in the prophylaxis of influenza A virus infections in nursing homes. Antimicrob. Agents Chemother. **26**:101–103.
12. **Peck, C. C., and B. B. Barret.** 1979. Nonlinear least-squares regression programs for microcomputers. J. Pharmacol. Biopharm. **7**:537–541.
13. **Pederson, P. V., and R. Miller.** 1980. Pharmacokinetics and bioavailability of cimetidine in humans. J. Pharm. Sci. **69**: 2394–2398.
14. **Powell, K. R., R. Shorr, J. D. Cherry, and J. O. Hendley.** 1977. Improved method for collection of nasal mucus. J. Infect. Dis. **136**:109–111.
15. **Schulman, J. L.** 1968. Effect of 1-amantanamine hydrochloride (amantadine HCl) and methyl-1-adamatanethylamine hydrochloride (rimantadine HCl) on transmission of influenza virus infection in mice (33222). Exp. Biol. Med. **128**:1173–1178.
16. **Smith, C. B., R. H. Purcell, and R. M. Chanock.** 1967. Effect of amantadine hydrochloride on parainfluenza type 1 virus infections in adult volunteers. Am. Rev. Respir. Dis. **95**:689–690.
17. **Soung, L. S., T. S. Ing, J. T. Daugirdas, M. J. Wu, V. C. Gandhi, P. T. Ivanovich, J. E. Hann, and S. W. Viol.** 1980. Amantadine hydrochloride pharmacokinetics in hemodialysis patients. Ann. Intern. Med. **93**:46–49.
18. **Spyker, D. A., and R. L. Guerrant.** 1981. Dosage nomograms for aminoglycoside antibiotics. Hospital Formulary **16**:132–139.
19. **Tsunoda, A., H. F. Maassab, K. W. Cochran, and W. C. Eveland.** 1966. Antiviral activity of α-methyl-1-adamantanemethylamine hydrochloride, p. 553–560. Antimicrob. Agents Chemother. 1965.
20. **Van Voris, L. P., J. Bartram, and F. G. Hayden.** 1984. Pharmacokinetics of amantadine and rimantadine, p. 421–423. *In* D. Schlessinger (ed.), Microbiology–1984. American Society for Microbiology, Washington, D.C.
21. **Van Voris, L. P., R. F. Betts, F. G. Hayden, W. A. Christmas, and R. G. Douglas, Jr.** 1981. Successful treatment of naturally occurring influenza A/USSR/77 H1N1. J. Am. Med. Assoc. **245**:1128–1131.
22. **Wagner, J. G.** 1975. Fundamentals of clinical pharmacokinetics. Drug Intelligence Publications, Hamilton, Ill.