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# Differences in Side Effects of Amantadine Hydrochloride and Rimantadine Hydrochloride Relate to Differences in Pharmacokinetics

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In a double-blind, placebo-controlled study, the comparative toxicities and blood concentrations of amantadine hydrochloride and rimantadine hydrochloride were determined. Healthy, working adults ingested either 200 ($n$ = 52) or 300 mg ($n$ = 196) per day in divided doses for 4.5 days. Mean plasma drug concentrations at 4 h after the first dose were lower in rimantadine recipients given 100- (140 versus 300 ng/ml for rimantadine and amantadine, respectively; $P < 10^{-5}$) or 200-mg doses (310 versus 633 ng/ml; $P < 10^{-5}$). The plasma drug concentrations after the first dose correlated significantly with total symptom sources for both amantadine and rimantadine, but the plasma levels of toxic and nontoxic subjects overlapped extensively. At 300-mg/day dosage amantadine was associated more often with adverse central nervous system symptoms (33% of amantadine versus 9% of rimantadine recipients; $P < 0.001$) and sleep disturbance (39 versus 13%; $P < 0.001$), but not gastrointestinal symptoms (19.5 versus 16.0%). However, no differences between the drugs were noted in symptom frequency or scores in volunteers with similar plasma concentrations. Amantadine and rimantadine differ in their pharmacokinetics but not in their potential for side effects at comparable plasma concentrations.

Clinical trials have documented that amantadine hydrochloride (8, 12, 16, 20, 28) and its analog rimantadine hydrochloride (6, 12, 23, 28, 29) are effective drugs for the prophylaxis and treatment of influenza A virus infection. However, widespread use of amantadine has been limited in part by concern about its side effects. Most studies of amantadine prophylaxis have documented minimal toxicity at a dosage of 200 mg/day (16, 20, 22; G. R. Noble, W. E. Jones, H. S. Kaye, A. P. Kendal, W. J. Brown, R. Curtis, P. H. Rossing, and W. F. Dowdle, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 18th, Atlanta, Ga., abstr. no. 484, 1978), but the frequency and severity of side effects increase with increasing dosage (15, 16, 25). Rimantadine has been considered to be better tolerated in humans than amantadine (12), although conflicting results have been reported from studies of their relative toxicities (22; Noble et al., ICAAC 1978, abstr. no. 484).

In a double-blind, placebo-controlled study, Hayden et al. determined the relative toxicities of amantadine and rimantadine in healthy, working adults who took either 200 or 300 mg/day for 4.5 days (11). Although both drugs were well tolerated at the lower dosage, amantadine recipients had a significantly greater frequency and severity of nervous system and sleep complaints at 300 mg/day than did rimantadine (300 mg/day) and placebo recipients. Amantadine recipients also performed less well on an objective psychomotor test that measured sustained attention and problem solving ability.

This study did not examine the reasons for the differences in drug side effects between amantadine and rimantadine. The observed differences in toxicity may have related to differences in drug concentration in the blood or central nervous system (kinetics) or in their intrinsic neuropharmacological activity (dynamics). Blood samples were collected from volunteers during the course of our previously described study (11), and the current study examines the relationship between plasma amantadine and rimantadine concentrations and the occurrence of side effects during drug administration.

## MATERIALS AND METHODS

**Study population.** As previously described (11), 248 healthy adult volunteers from the clerical and managerial staff of the Eastern Regional Office, State Farm Insurance Company, Charlottesville, Va., participated in the study. All subjects had normal renal function as

TABLE 1. Demographic characteristics of the study population

| Drug | Dose (mg/day) | No. of females/ no. of males | Data for population (mean ± one SD) | | | |
|---|---|---|---|---|---|---|
| | | | Age (yr) | Ht (cm) | Wt (kg) | Serum creatinine (mg/dl) |
| Amantadine | 200 | 12/6 | 35.3 ± 13.3 | 167 ± 10 | 69.0 ± 19.7 | 0.9 ± 0.8 |
| Rimantadine | 200 | 9/8 | 32.5 ± 8.9 | 169 ± 14 | 70.2 ± 18.4 | 0.8 ± 0.3 |
| Placebo | 200 | 12/5 | 33.8 ± 9.7 | 169 ± 8 | 69.3 ± 16.5 | —[a] |
| Amantadine | 300 | 38/29 | 32.6 ± 9.7 | 170 ± 9 | 69.7 ± 13.8 | 0.9 ± 0.2 |
| Rimantadine | 300 | 42/21 | 33.8 ± 9.7 | 168 ± 10 | 68.1 ± 13.5 | 0.8 ± 0.2 |
| Placebo | 300 | 46/20 | 31.6 ± 10.5 | 168 ± 9 | 67.3 ± 13.5 | — |

[a] —, Not done.

determined by serum creatinine measurement.

**Drug administration.** In a randomized, double-blind manner, participants took tablets containing drug or placebo twice daily (7:30 to 8:00 A.M. and 4:00 to 4:30 P.M.) for a total of nine doses. In the first study, 52 subjects received a drug dose of 100 mg twice daily. In the second study, 196 subjects received a daily drug dose of 300 mg, administered as 200 mg in the morning and 100 mg in the afternoon.

At 4 h after the first and ninth doses, 10 ml of venous blood was collected into heparinized tubes for measurement of drug concentrations. Plasma was frozen at −20°C until assays were performed on coded samples at the Stine Laboratory, Newark, Del.

**Evaluation of drug toxicity.** The methods used for symptom measurement and psychomotor testing have been described previously (11). Twenty-one symptoms previously reported to be possible side effects of amantadine were arbitrarily divided into four major categories for analysis: central nervous system (CNS), sleep disturbance, gastrointestinal (GI), and atropinic.

**Drug assay.** Determinations of amantadine hydrochloride concentrations in human plasma were performed with modifications of previously described methods (4). Plasma samples (2 ml) were alkalinized with 5 N NaOH and extracted sequentially with toluene. The pooled toluene extracts were treated with 2 N HCl, and the aqueous phase was collected and retreated with 5 N NaOH and toluene. The toluene phase was subjected to derivatization with pentafluorobenzyl chloride in toluene (1 μg/ml) (18) followed by 5 N NaOH and was then injected directly into a Hewlett Packard model 5730A gas chromatograph column (6 ft [ca. 1.8 m] by 4 mm glass, 10% OV-1 on 80- to 100-mesh chromosorb W) with electron capture detector at 250°C. Standard solutions of amantadine hydrochloride (0.5, 0.1, 0.05, 0.25, and 0.01 μg/ml) prepared in human plasma provided a standard curve for calculation of the amantadine concentrations in unknown samples. The mean ± standard deviation of the slopes of the standard curves was 0.140 ± 0.008 (±5.7%) for 17 replicate assays. At the lower limit of detectability (10 ng/ml), the standard deviation of the assay was ±7.8%, and at 100 ng/ml it was ±2.3%.

For the rimantadine assay, 1 ml of plasma was mixed with an equal volume of 0.1 M $Na_2HPO_4$ buffer (pH 9.1) and applied to Bond-Elut columns (Analytichem International, "CN" columns, catalog no. 613101). After drainage by gravity and then by air pressure, the columns were washed with distilled water. The drug was eluted with five 0.2-ml volumes of methanol, and samples were evaporated to dryness. Derivatization and gas chromatographic procedures were similar to those used for the amantadine samples. The mean ± standard deviation of the slopes of the standard curves was 0.243 ± 0.015 (±6.2%) for 15 replicate assays. The lower limit of detectability was 10 ng/ml. Both the amantadine and rimantadine standard curves were linear throughout the range of plasma concentrations tested.

**Statistical analysis.** Psychomotor test performance and individual and composite symptom scores were examined in relation to drug given, dose (milligrams per kilogram), and measured blood drug levels by multiple regression. Comparisons of plasma drug concentration were made by the two-tailed $t$ test for two independent samples.

## RESULTS

**Plasma drug concentrations.** Table 1 gives demographic data and Table 2 the concentra-

TABLE 2. Plasma concentrations of amantadine and rimantadine

| Drug | Initial dose (mg) | Daily dose (mg) | Plasma level[a] (ng/ml) | |
|---|---|---|---|---|
| | | | First | Second |
| Amantadine | 100 | 200 | 300 ± 98[b] | 723 ± 366[c] |
| Rimantadine | 100 | 200 | 140 ± 68 | 442 ± 149 |
| Amantadine | 200 | 300 | 633 ± 145[b] | 1,405 ± 437[b] |
| Rimantadine | 200 | 300 | 301 ± 75 | 913 ± 270 |

[a] First plasma level was obtained at 4 h after initial dose. Second plasma level was obtained 4 h after ninth drug dose.

[b] $P < 0.00001$, statistical analysis by $t$ test for amantadine versus rimantadine at same dose.

[c] $P = 0.006$.

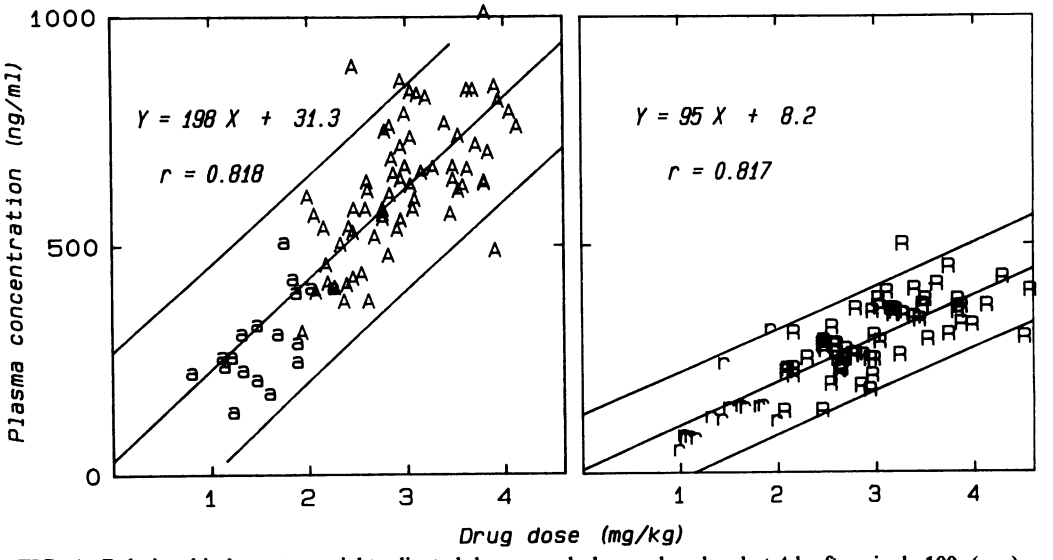


FIG. 1. Relationship between weight-adjusted dosage and plasma drug level at 4 h after single 100- (a, r) or 200-mg (A, R) doses of amantadine hydrochloride (a, A) or rimantadine hydrochloride (r, R). The correlation coefficient for amantadine was 0.818 ($P < 10^{-5}$) and for rimantadine it was 0.817 ($P < 10^{-5}$).

tions of amantadine and rimantadine in the plasma of each of the four drug and two placebo groups. At 4 h after the first doses of amantadine or rimantadine, the average plasma concentrations of either drug doubled (2.1-fold) when the dosage was doubled from 100 to 200 mg. After either single 100- or 200-mg doses, the mean rimantadine concentrations were 47% of the amantadine levels at each dose. Similarly, the plasma rimantadine concentrations 4 h after the ninth dose averaged 61 and 65% of the amantadine concentrations in volunteers receiving either 200 or 300 mg/day, respectively.

Dose correlated with drug levels for both amantadine ($r = 0.818$, $P < 0.0001$) and rimantadine ($r = 0.815$, $P < 0.00001$) (Fig. 1). At equivalent dosages of 2, 3, or 4 mg/kg, the rimantadine plasma concentrations averaged 44 to 46% of the corresponding amantadine concentrations. The second blood level was less highly correlated with daily dose for both amantadine ($r = 0.654$) and rimantadine ($r = 0.802$).

**Correlation of side effects and plasma drug concentration.** Total symptom scores correlated significantly but weakly with the plasma drug concentrations in both amantadine and rimantadine recipients. The relationship between the total symptom score and the plasma drug concentration measured after the first dose proved to be the best single predictor of the total symptom score and was more highly correlated with the total symptom score ($r = 0.258$ for amantadine, $r = 0.355$ for rimantadine) than the corresponding second plasma concentration ($r = 0.162$ and 0.270, respectively) or an average of the two plasma concentrations (Fig. 2). The correlation between group scores of related symptoms (CNS, sleep, GI) and plasma drug concentration was lower for both amantadine ($r = 0.255$, 0.177, and 0.150) and rimantadine ($r = 0.335$, 0.217, and 0.282) than that of the total score. No substantial correlation was found between total or grouped symptom scores and age, sex, height, weight, serum creatinine, or creatinine clearance derived from a nomogram ($r = 0.01$ to 0.020). The daily dose corrected for weight did correlate weakly with the total symptom score for both amantadine ($r = 0.22$) and rimantadine ($r = 0.19$) recipients.

To determine predictive factors for the occurrence of more serious side effects, we compared the plasma drug concentration in volunteers who experienced pronounced side effects on any day of drug administration with that in volunteers not reporting adverse drug effects. The proportions of volunteers with moderate or marked side effects in the two placebo control groups were not significantly different (chi-square, 1.89; $P > 0.1$), and therefore the data for the two drug doses were combined for analysis (Fig. 3).

At the 300-mg/day dose, 61% of amantadine recipients, compared with 20% of placebo and 29% of rimantadine recipients, reported that one or more symptoms were troublesome or impaired their usual activities ($P < 0.001$). Specifically, 33% of amantadine-treated subjects experienced one or more adverse CNS symptoms compared with 9% of the placebo- or rimantadine-treated subjects ($P < 0.001$). Similarly, 39% of amantadine ($P < 0.001$ versus placebo and

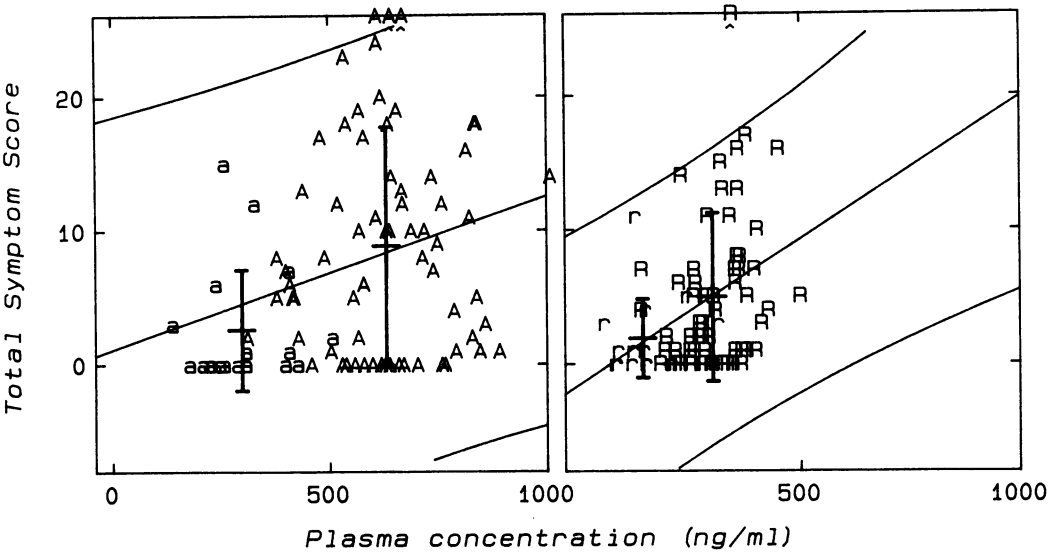


FIG. 2. Relationship between initial plasma concentrations of amantadine (A, a) and rimantadine (R, r) measured 4 h after single 100- or 200-mg doses and total symptom scores during 4.5 days of drug administration at 200 (a, r) or 300 (A, R) mg/day. The mean ± one standard deviation for total symptom scores for the 200- and 300-mg/day dosages are shown, as are the mean ± 95% interval in symptom scores. The correlation coefficient for amantadine was 0.258 ($P = 0.016$), and for rimantadine it was 0.355 ($P = 0.002$).

rimantadine), 13% of rimantadine, and 7.5% of placebo recipients reported sleep disturbance. Few subjects (1.5% of either drug group) reported atropinic side effects, but 19.5% of amantadine and 16% of rimantadine recipients, in contrast to 3% of placebo recipients ($P < 0.02$ versus either drug), had adverse GI symptoms.

The plasma drug concentrations (mean ±1 standard deviation) in the 47 amantadine recipients reporting one or more adverse symptoms (610 ± 149 ng/ml) were higher than those in the 38 unimpaired amantadine recipients (524 ± 216 ng/ml; $P = 0.038$) (Fig. 3). Similar trends toward differences in plasma amantadine concentrations were observed in those reporting adverse CNS symptoms or sleep disturbance, but not in those

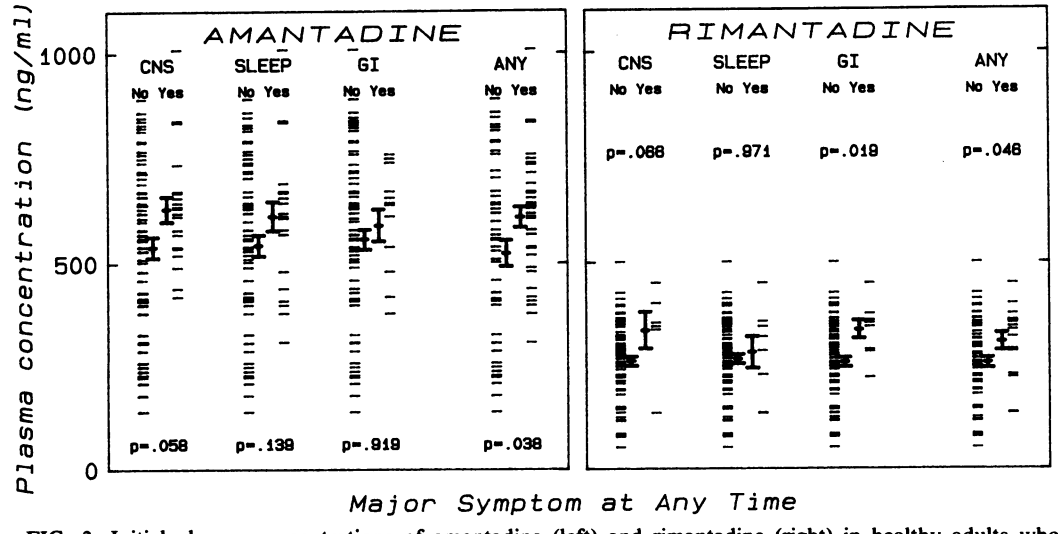


FIG. 3. Initial plasma concentrations of amantadine (left) and rimantadine (right) in healthy adults who developed moderate or marked (score = 2 or 3) CNS, sleep disturbance (sleep), GI, or any combination of these symptoms and in those without symptoms (score = 0 or 1). Plasma samples were collected at 4 h after the first dose. Statistical analysis by two-tailed $t$ test.

TABLE 3. Relationship between occurrence of moderate or marked side effects in amantadine and rimantadine recipients and plasma drug concentration after 4.5 days of drug administration

| Symptom type | Drug | No. of volunteers with adverse symptoms/total at plasma drug concn (ng/ml): | | | | |
|---|---|---|---|---|---|---|
| | | ≤500 | 501–1,000 | 1,001–1,500 | 1,501–2,000 | >2,000 |
| CNS | Amantadine | 0/5 | 2/20 | 8/32 | 7/19 | 3/8 |
| | Rimantadine | 0/12 | 2/48 | 4/17 | 0/2 | 0/0 |
| Sleep | Amantadine | 0/5 | 5/20 | 10/32 | 5/19 | 3/8 |
| | Rimantadine | 0/12 | 6/48 | 2/17 | 0/2 | 0/0 |
| GI | Amantadine | 0/5 | 4/20 | 4/32 | 4/19 | 0/8 |
| | Rimantadine | 0/12 | 5/48 | 2/17 | 1/2 | 0/0 |

reporting GI side effects (Fig. 3). In rimantadine recipients, the plasma drug concentrations in subjects reporting one or more adverse symptoms (309 ± 90 ng/ml) were slightly higher than those in the unaffected volunteers (256 ± 98 ng/ml; $P = 0.046$). A significant difference in plasma concentration was present between the volunteers with and without adverse GI symptoms (339 ± 65 versus 259 ± 98 ng/ml; $P = 0.018$), although only eight volunteers were affected.

**Predictive value of plasma drug concentration.** Almost all of the drug recipients with more pronounced CNS, sleep, or GI side effects had plasma drug concentrations greater than 300 ng/ml at 4 h after the first drug dose (Fig. 3). However, considerable overlap existed between the plasma concentrations of affected and unaffected volunteers. For example, 37 of 75 (51%) amantadine and 20 of 30 (67%) rimantadine recipients with initial plasma concentrations greater than 300 ng/ml were unaffected.

The mean (range) plasma concentrations of the 10 amantadine recipients who had marked CNS symptoms or sleep disturbance (individual symptom score = 3) was 650 (400 to 1,010) ng/ml. The corresponding values for the five rimantadine recipients with marked symptoms were 334 (228 to 450) ng/ml. The blood levels in these volunteers, who represented the most symptomatic individuals, overlapped those of unaffected volunteers. Similarly, the plasma concentrations found after the ninth amantadine dose were 1,346 (904 to 1,700) ng/ml in the 10 recipients with marked CNS symptoms compared with 1,212 (225 to 2,552) in the other 47 amantadine recipients (Table 3).

**Drug toxicity at equivalent plasma concentrations.** To assess the intrinsic neurological and GI toxicity of the two drugs, we analyzed the effect of the drug (amantadine versus rimantadine) on the symptom scores after correcting for the effect of plasma drug concentration by multivariate analysis. No significant drug effect was found on total ($P = 0.98$), CNS ($P = 0.77$), sleep ($P = 1.00$), or GI ($P = 0.14$) symptom scores. Similarly, in groups of amantadine and rimantadine recipients matched for initial plasma drug concentrations (range, 300 to 450 ng/ml; Fig. 3), the ratios of affected to total drug recipients were similar for CNS (2 of 16 for amantadine versus 5 of 29 for rimantadine), sleep (5 of 16 versus 4 of 29; $P = 0.31$), or GI (3 of 16 versus 6 of 29) symptoms. Similarly, no significant differences in this ratio existed between amantadine and rimantadine when the plasma drug levels after 4.5 days of administration were considered (Table 3).

**Performance studies.** At the higher dosage (300 mg/day), the 23 amantadine recipients performed less well on the Trials B test, a measure of sustained attention and problem solving ability (5, 17), than did the 20 rimantadine or 21 placebo recipients (11).

However, test performance during drug administration did not correlate significantly with plasma drug level (first sample) for either amantadine ($r = 0.162$) or rimantadine ($r = 0.078$).

## DISCUSSION

The current study is the first prospective, placebo-controlled, blind trial to assess the relationship between plasma amantadine or rimantadine concentration and the occurrence of side effects. We found significant but low correlations between the plasma concentration of either drug and the occurrence of side effects. Cases of amantadine toxicity have been reported after ingestion of massive doses or in renal failure patients with high plasma amantadine concentrations (1,800 to 4,400 ng/ml) (3, 7, 14; T. S. Ing, A. C. Rahn, K. F. W. Armbruster, J. H. Oyama, and H. L. Klawan, letter, N. Engl. J. Med. **291**:1257, 1974). Reversible agitation and aggressive behavior were reported in elderly patients with depression who received 300 mg of amantadine per day and presented with steady-state plasma concentrations of 680 to 1,010 μg/ml (24). Studies of drug-induced parkinsonism have found a positive correlation between plasma amantadine levels and improvement in extrapyramidal symptoms (9, 21).

Our study considered drug plasma concentrations at only one time point after dosing, and it is

possible that more frequent measurements would have uncovered a higher correlation between symptoms and plasma concentrations. The amantadine concentrations we observed corresponded closely to the average peak concentrations reported after single or multiple doses in earlier studies (2, 21, 27). Recent studies of rimantadine pharmacokinetics found mean (range) peak plasma concentration of 256 (189 to 351) ng/ml after a single 200-mg dose (L. P. Van Voris, unpublished data). These concentrations were similar to those observed in the present study. However, we cannot be certain that peak plasma concentrations for either drug were reached before the 4-h postdose time of sampling. This could have contributed to substantial variability in individual drug concentration-effect relationships.

Our study involved young and middle-aged adults with normal renal function and no recognized confounding illness or drug intake. Under these circumstances we found considerable interindividual variation in the frequency and severity of symptoms at similar plasma drug concentrations or during administration of similar weight-adjusted dosages. Despite the overall correlations between symptom occurrence and plasma drug concentration (or drug dosage), we could not readily define clinically useful guidelines for dose adjustment in this population. However, amantadine at 300 mg/day was associated with significant increases in the frequency and severity of side effects compared with lower doses and with rimantadine (11), as well as with plasma levels associated with the occurrence of neurotoxicity by other studies (14, 24).

Several lines of evidence suggest that amantadine and rimantadine differ in their intrinsic neuropharmacological activity (dynamics). Whereas amantadine has proven useful in the amelioration of parkinsonian symptoms, rimantadine has been ineffective in limited testing (25). However, blood concentrations were not reported in that study, and our results suggest that the failure of oral rimantadine in the treatment of parkinsonian symptoms could be related to subtherapeutic drug levels. In dopamine-primed dogs, amantadine causes a dose-related pressor response (10), whereas rimantadine results in a depressor response (R. P. Grelak, P. Clark, J. M. Stump, and V. G. Vernier, Pharmacologist 12:235, 1970).

In the current study we attempted to indirectly assess whether the drugs differed in their potential for causing CNS toxicity by comparing side effects at comparable plasma concentrations. Although we did not measure brain or cerebrospinal fluid concentrations, we found that amantadine and rimantadine did not differ in the frequency or severity of their side effects at similar plasma concentrations.

This observation may have important implications for the use of these drugs in the prophylaxis or therapy of influenza A virus infections. If the antiviral activity of these drugs also relates to the corresponding plasma concentrations, then higher dosages of rimantadine than amantadine may be necessary to achieve comparable antiviral and clinical effects. For example, Van Voris and co-workers (28) found that the rates of defervescence and symptomatic improvement and the frequency of virus shedding after 2 days of drug therapy tended to be better with amantadine than with equivalent dosages (200 mg/day) of rimantadine in the treatment of naturally occurring A/USSR/90/77 influenza virus infection. Although we did not directly study higher rimantadine dosages in the current study, its apparent advantage of fewer and lesser side effects at equivalent dosages (11) may be entirely attributable to its differences in pharmacokinetics and associated lower plasma concentrations compared with amantadine.

At equivalent dosages of 200 or 300 mg/day, amantadine plasma concentrations averaged approximately twofold higher than the corresponding rimantadine concentrations. We found plasma amantadine concentrations to be similar to those reported from studies involving small numbers of normal adults (2, 13, 27). No corresponding information has been published for rimantadine. Aoki et al. (2) found almost complete and dose-independent oral bioavailability with amantadine at dosages up to 300 mg/day, but this has not been studied for rimantadine. Further studies will be necessary to define the differences between amantadine and rimantadine pharmacokinetics.

In summary, we found that equivalent dosages of 200 or 300 mg/day produced plasma amantadine levels greater than rimantadine levels; that significant but low correlations existed between plasma amantadine and rimantadine levels and the occurrence of symptoms in healthy adults, although considerable interindividual variation existed in the occurrence of side effects at similar plasma drug concentrations or drug dosages; and that amantadine and rimantadine appear to differ in their pharmacokinetics but not in their potential for side effects at comparable plasma concentrations.

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