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Comparative Toxicity of Amantadine Hydrochloride and Rimantadine Hydrochloride in Healthy Adults

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The relative toxicities of amantadine and rimantadine were compared in a double-blind, placebo-controlled study involving healthy adults. In separate studies, drugs were administered at a dosage of 200 mg/day (52 volunteers) or 300 mg/day (196 volunteers) for 4.5 days. Both drugs were well tolerated at the lower dosage. At 300 mg/day amantadine recipients had a greater frequency and severity of central nervous system (nervousness, lightheadedness, difficulty concentrating) and sleep (insomnia, fatigue) complaints compared with rimantadine or placebo recipients. Amantadine recipients also performed less well on an objective test measuring sustained attention and problem-solving ability. Both amantadine and rimantadine recipients reported adverse gastrointestinal symptoms more often than placebo recipients. Because of better tolerance at higher dosage, rimantadine offers more promise than amantadine for treatment of influenza A virus infections.

Clinical trials have documented that amantadine hydrochloride (7, 11, 14, 17, 18, 22; L. P. VanVoris, F. G. Hayden, R. F. Betts, R. G. Douglas, Jr., and W. A. Christmas, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 18th, abstr. no. 483, 1978) and rimantadine hydrochloride (6, 11, 26, 33) are effective prophylactic and therapeutic drugs in influenza A virus infections. Several in vitro (10, 31) and animal (1, 28, 31) models have suggested that rimantadine has greater antiviral activity than amantadine against influenza A viruses. However, the relative effectiveness of the two compounds in human infections has not been fully defined.

Available information regarding the relative toxicities of the two compounds in humans is also inconclusive. Most studies of amantadine prophylaxis with a dose of 200 mg/day have described few side effects (14, 22, 25; G. R. Noble, W. E. Jones, H. S. Kaye, A. P. Kendal, W. J. Brown, Jr., R. Curtis, P. H. Rossing, and W. R. Dowdle, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 18th, abstr. no. 484, 1978). However, recent work found substantial rates of subjective central nervous system (CNS) complaints and possible adverse effects on objective measures of psychomotor performance at this dosage (4). Rimantadine has been considered to be better tolerated in humans (11), but several studies (25; Noble et al., 18th ICAAC, abstr. no. 484) have not confirmed this observation. Optimal antiviral and therapeutic effects in treatment of influenza A virus infections would likely be achieved with administration of higher drug dosages. If lower drug toxicity were confirmed for rimantadine, then it would be an appropriate candidate for future chemotherapy studies in which higher dosages are used.

The present study was undertaken to compare the relative toxicities of equivalent doses of amantadine and rimantadine. Both subjective and objective measures of potential drug side effects were studied at conventional (200 mg/day) and higher (300 mg/day) dosages in healthy adults. Our results indicated that both drugs were well tolerated at the lower dosage, but that rimantadine was significantly better tolerated than amantadine at a dosage of 300 mg/day.

MATERIALS AND METHODS

Study population. Two hundred fifty-one healthy adult volunteers were recruited from the clerical and managerial staff of the Eastern Regional Office, State Farm Insurance Co., Charlottesville, Va. All participants had normal renal function, as determined by serum creatinine measurement. Criteria for exclusion from the study were pregnancy, neuropsychiatric or chronic medical illness, prior untoward reaction to amantadine, or concurrent use of antiepileptic, antihistaminic, decongestant, or psychotropic drugs. To complete appropriate monitoring (see below), groups of 40 to 50 subjects were studied each week over a 6-week period. Informed consent, in a form approved by the University of Virginia Institutional Review Board, was obtained from all participants before the study. The guidelines for human experimentation of the U.S. Department of Health, Education, and Welfare and of the University of Virginia were followed in conducting this study.

Drug administration. Identically appearing tablets containing 100 mg of amantadine hydrochloride, rimantadine hydrochloride, or inert placebo material were provided by Endo Laboratories, E. I. du Pont de Nemours & Co., Wilmington, Del. In a randomized, double-blind manner, participants took drug- or placebo-containing tablets twice daily (7:30 to 8:00 a.m. and 4:00 to 4:30 p.m.) for 4.5 days, Monday through Friday morning (total of nine doses). Tablets were taken under the direct supervision of a project nurse to assure compliance. In the first study, 52 subjects received a drug dose of 200 mg/day (n = 18 amantadine, 17 rimantadine, and 17 placebo). In the second study, 199 subjects received a daily drug dose of 300 mg, which was administered as 200 mg in the morning and 100 mg in the afternoon (n = 68 amantadine, 64 rimantadine, and 67 placebo).

Subjective evaluation of drug side effects. Subjects were interviewed daily by a project nurse about symptoms in the preceding 24-h period. Subjects were interviewed both Friday afternoon and the next Monday about symptoms occurring on Friday through Saturday. Thirty symptoms, including 23 which had been previously reported to be possible side effects of amantadine administration, were considered. For analysis, items were arbitrarily divided into four major symptom categories: CNS, sleep, gastrointestinal (GI), and atropinic. CNS symptoms included lightheadedness or dizziness, depression, confusion, difficulty concentrating, nervousness or anxiousness, irritability, hallucinations, and headache. Symptoms of sleep disturbance were insomnia and excess fatigue; GI symptoms were loss of appetite, nausea, vomiting, diarrhea, and constipation; and atropinic symptoms were dry mouth, blurred vision, difficulty voiding, and difficulty swallowing. Subsequent analysis of symptom scores for CNS, sleep, and GI complaints showed that the percentage of variance accounted for between groups was low (r^2 = 0.01 to 0.15), which confirmed that little overlap existed between the symptom groups. Also included were amantadine side effects that have been rarely reported with short-term administration (swelling of legs, shortness of breath, skin rash, and slurred speech) and seven dummy items.

Subjects were asked to grade symptom severity as follows: absent (0); mild (1+), noticeable; moderate (2+), troublesome, but able to do usual activities; or marked (3+), definite effect on ability to do usual activities. Symptom scores were recorded for each symptom on each day of drug administration. A total symptom score was generated for each subject by adding his or her scores for each of the 23 symptoms on each day of drug administration. In addition, cumulative and daily symptom scores for categories of related symptoms (see above) were calculated by adding individual symptom scores on each study day.

On the final day of drug administration subjects were asked to rate overall drug acceptability as good, fair, poor, or unacceptable and to assess whether drug administration was associated with an adverse effect on their work.

Objective evaluation of drug side effects. Objective tests of psychomotor performance were undertaken to assess more subtle effects of amantadine and rimantadine on attention, memory, and motor proficiency. All subjects who agreed to participate in this phase of testing were included (total of 89). Tests were administered twice, once during the week before and again on the 3rd, 4th, or 5th day of drug administration. This battery of tests required approximately 15 min for completion.

The trail making test part B (3, 19) consists of 25 circles, numbered 1 to 13 and lettered A to L, which the subject is required to connect as rapidly as possible by alternating between these two sequences, i.e., 1, A, 2, B, 3, C, etc. The total time from start to completion is recorded. This test has been found to measure problem solving, sustained attention, and the ability to attend and concentrate on more than one aspect of a situation simultaneously.

The digit span subtest of the Wechsler Adult Intelligence Scale (32) requires oral repetition of progressive series of numbers enunciated by the experimenter at the rate of one digit/s. The subject is asked to repeat digits forward and backward, and a total combined score is collected. This test is a measure of immediate recall, attention, and concentration.

The maze test (21) is a pencil maze test in which blind alleys have been eliminated and the maze board placed in the semiupright position in the subject's midline. The subject is then required to go through the maze with an electric pencil attached to a time clock, and the cumulative time (in seconds) of contact with the side walls is recorded, first for the dominant hand and then for the nondominant hand. This test is a measure of gross motor and hand-eye motor coordination.

The resting steadiness test (21), which measures fine motor steadiness, requires the subject to fit an electronic stylus into a series of holes which get progressively smaller. A cumulative score of side contact is recorded in seconds for the dominant hand and then the nondominant hand.

The reaction time test (Lafayette Instrument Co., Lafayette, Ind.) is a four-choice reaction task in which the subject is required to respond by pressing the appropriate button below one of four signal lights. The average response time is recorded. This test measures reaction speed and accuracy.

Data analysis. Parametric (chi square) and nonparametric (Wilcoxon signed rank) statistical tests and several other types of analysis were used to compare groups for symptom scores and performance measures. For symptom scale analysis, the Hotelling T^2 statistic was used first to test for equality of treatment group means on total and grouped symptom scores across the predrug and the five drug treatment days. The statistical package for the social sciences programs for discriminant analysis and univariate analysis of variance were then used to test the equivalence of these group means on each variable (5, 23). Then the Duncan new multiple-range test was used to evaluate the differences in which the F ratio was significant for a specific dependent variable (16). Analysis of covariance was initially used to test the equivalence of group means for posttreatment psychomotor test scores in order to control for pretreatment psychomotor test performance (23).

RESULTS

Study population. Fifty-two volunteers participated in the low-drug-dose portion of the

study, and 199 participated in the high-dose portion. The mean (± standard deviation [SD]) age was 32.1 (±10.1) years, with a range of 18 to 65 years. Males comprised 35% of the participants. The treatment groups did not differ significantly with respect to mean age, sex distribution, height, or weight.

Three participants in the high-dose portion did not complete the protocol and were not included in the subsequent analysis. One amantadine recipient had disabling lightheadedness and difficulty concentrating that impaired his activities as a computer programer. One rimantadine recipient decided not to participate after the first two drug doses, but had no specific complaints. One placebo recipient developed an upper respiratory illness for which she took decongestants and antihistamines.

Total symptom scores. Total symptom scores for the 5 days of drug administration were generally low in subjects receiving the 200-mg/day dose. Less than 10% of amantadine or rimantadine-treated subjects had minimally elevated scores, defined as ≥4, or moderately elevated scores, defined as ≥8. In contrast, the total symptom scores in those receiving the 300-mg/day drug dose ranged widely in all treatment groups (Fig. 1). Moderately elevated scores were observed in 49% of amantadine recipients, as compared with 21% of rimantadine recipients ($P < 0.001$ versus amantadine)or 6% of placebo recipient ($P < 0.001$ versus amantadine, $P < 0.03$ versus rimantadine). Markedly elevated scores, defined as ≥16, were found in 21% of amantadine recipients, as contrasted with 6% of rimantadine recipients ($P < 0.004$ versus amantadine) and none of those receiving placebo ($P < 0.001$ versus amantadine, P = not significant versus rimantadine).

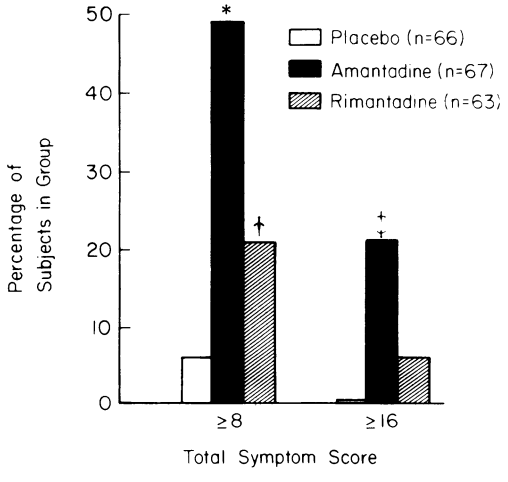

FIG. 1. *Proportion of subjects with moderately (≥8) and markedly (≥16) elevated total symptom scores for 4.5 days of drug administration. Participants received amantadine or rimantadine at 300 mg/day or placebo; see text for details of symptom analysis. Statistical analysis with chi-square test: *, $P < 0.001$ versus rimantadine or placebo recipients; †, $P < 0.03$ versus placebo recipients; ‡, $P < 0.001$ versus placebo recipients and $P < 0.004$ versus rimantadine recipients.*

Type and duration of symptoms. The frequency, severity, and time course of individual symptoms and groups of related symptoms were analyzed to more fully characterize differences between the groups. Table 1 lists the proportion of subjects in each group who reported symptoms of moderate or marked severity on any day of drug administration. This analysis focuses on those individuals who graded their symptoms as troublesome (score of 2+) or disabling (score of 3+) and excludes those who reported only mild symptoms (score of 1+). The number of subjects receiving lower drug doses was small, and no significant differences were observed between the groups. At the 300-mg/day dose, 61% of amantadine recipients ($P < 0.001$ versus placebo or rimantadine recipients), in contrast to 20% of placebo recipients and 29% of rimantadine recipients, reported that one or more symptoms were troublesome or adversely affected their usual activities.

Approximately one-third of amantadine recipients reported one or more adverse CNS symptoms, which was a significantly higher proportion than in placebo or rimantadine recipients. The most commonly reported complaints in amantadine recipients were nervousness (15%), lightheadedness (13%), or difficulty concentrating (10.5%). Headache was an infrequent complaint in all groups (less than 3%). Nearly two-fifths of amantadine recipients had substantial degrees of sleep disturbance, and this was a significantly higher proportion than in either of the other groups. Both amantadine and rimantadine recipients reported adverse GI complaints in a significantly higher frequency than did placebo recipients. The most commonly reported symptoms in drug recipients were loss of appetite (8%) or nausea (8.5%). Very few subjects reported atropinic side effects.

The proportions of volunteers with moderate or marked side effects in the two placebo control groups were not significantly different ($\chi^2 = 1.89$, $P > 0.1$), and therefore the data for the two drug doses were compared. A significantly higher proportion of subjects receiving amantadine at 300 mg/day had one or more adverse side effects (61 versus 11%, $P < 0.001$), specifically CNS symptoms (33 versus 0%, $P < 0.02$) or sleep disturbance (39 versus 11%, $P < 0.05$), compared with those receiving amantadine at

TABLE 1. *Comparative frequency of moderate and marked side effects in volunteers receiving amantadine at 300 mg/day, rimantadine at 300 mg/day or placebo*[a]

Type of symptom	% of subjects with symptoms		
	Placebo (n = 66)	Amantadine, 300 mg/day (n = 67)	Rimantadine, 300 mg/day (n = 63)
Any	20	61[b]	29
CNS	9	33[b]	9
Sleep	7.5	39[b]	13
GI	3	19.5[c]	16[d]
Atropinic	0	1.5	1.5

[a] See text for description of symptom classification and scoring.
[b] $P < 0.001$ compared with placebo or rimantadine (300 mg/day) recipients.
[c] $P < 0.01$ compared with placebo recipients.
[d] $P < 0.02$ compared with placebo recipients.

200 mg/day. No significant differences were found between the high- and low-dose rimantadine recipients.

The time course of symptoms is depicted in Fig. 2. The mean symptom scores for complaints related to the CNS, sleep, or GI tract are listed for the day before and each day during drug administration. None of the treatment groups were found to differ before drug administration. Amantadine-treated subjects reported an excess of symptoms within 24 h of drug administration and had significantly higher mean symptom scores for CNS, sleep, and GI complaints on each day of drug administration compared with placebo-treated subjects. The severity of complaints, as reflected in the mean score on each day, appeared to plateau on the 2nd day of drug administration and decrease on the 4th and 5th days despite continued amantadine ingestion. Compared with the 3rd day, the mean score for sleep complaints of amantadine recipients was significantly lower on the 4th (P = 0.05, Wilcoxon signed ranks test) and 5th days (P = 0.001) of drug administration. Rimantadine recipients had significantly lower mean scores for CNS complaints than amantadine recipients on the 1st and 3rd through 5th days and for sleep complaints on the 1st and 2nd days. Although rimantadine recipients tended to have higher symptoms scores than placebo recipients, the rimantadine group scores differed significantly from placebo only for CNS complaints on day 4. Similarly, mean cumulative scores did not differ significantly between rimantadine and placebo for CNS or sleep complaints. Rimantadine-treated subjects had a pattern of GI complaints similar to that of amantadine-treated subjects, and the rimantadine group scores were significantly higher than placebo group scores on days 1 through 4 of drug administration. All symptomatic participants reported that side effects stopped within 1 to 2 days after cessation of drug administration.

Further analysis considered possible factors in the development or reporting of symptoms during drug administration. No substantial correlation was found between total or group symptom scores and age, sex, height, or weight (r^2 = 0.00 to 0.06).

Volunteer assessment. All subjects in the 200-mg/day dose study rated drug acceptability as good or fair and reported that work performance during drug administration was not impaired. However, 21% of those receiving amantadine at 300 mg/day rated their drug as poor or unacceptable ($0.05 < P < 0.1$ versus amantadine,

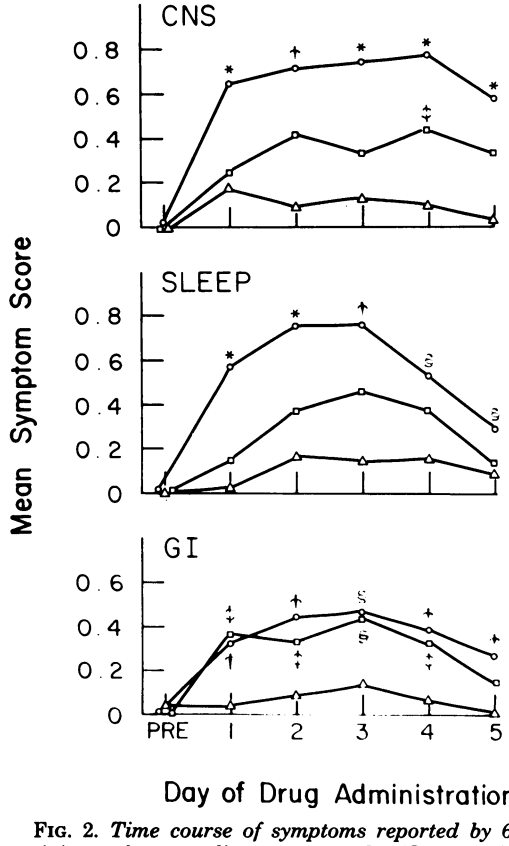

FIG. 2. *Time course of symptoms reported by 67 recipients of amantadine at 300 mg/day* (○), *63 recipients of rimantadine at 300 mg/day* (□), *and 66 recipients of placebo* (△). *Points are mean symptom scores for CNS, sleep, and GI complaints. See text for details of symptom analysis. Symbols:* *, $P < 0.01$ *for amantadine group versus rimantadine or placebo groups;* †, $P < 0.01$ *for amantadine group versus placebo group;* ‡, $P < 0.01$ *for rimantadine group versus placebo group;* §, $P < 0.05$ *for amantadine or rimantadine group versus placebo group.*

200 mg/day), as compared with 6% of those receiving rimantadine at 300 mg/day ($P < 0.04$) and one placebo recipient ($P < 0.001$). Similarly, 30% of amantadine recipients considered that their work performance was impaired during drug administration ($P < 0.02$ versus amantadine, 200 mg/day), as contrasted with 3% of rimantadine recipients ($P < 0.001$) and no placebo recipients ($P < 0.001$).

Performance studies. The 89 participants who underwent psychomotor testing were comparable to the overall study group in regard to age, sex distribution, height, and weight. In addition, the subgroups of test participants were similar to each other in regard to these factors, as well as occupation and educational status. The testing day during drug administration (3rd, 4th, or 5th) did not significantly relate to test performance. No significant differences were found in performance measures of low-dose drug recipients, but the group sizes were small (placebo, 6, amantadine, 11, and rimantadine, 8 subjects). Table 2 lists the results of performance studies for those individuals receiving a 300-mg/day drug dose. Using analysis of covariance to control for pretreatment performance, no significant differences were found among the drug groups for the maze, digit span, resting steadiness, or reaction time test. However, amantadine recipients performed significantly less well on the Trails B test than did rimantadine or placebo recipients ($P < 0.01$). This performance did not result from a decline in functioning from predrug testing levels, but reflected a significant lack of expected improvement due to practice for the amantadine group as compared with the other two groups.

Test performance on the Trails B test had no substantial correlation with the age, sex, occupation, or educational status of the participants ($r^2 = 0.0$ to 0.07). Subjective complaints during drug administration did not appear to correlate with performance on this measure. The nine amantadine recipients who reported moderate or marked CNS side effects (see Table 1) and who also underwent psychomotor testing had a mean (±SD) score on the Trails B test of 77.9 (18.1), compared with a score of 70.0 (24.4) for 14 amantadine recipients who did not report CNS symptoms (P = not significant).

DISCUSSION

Previous studies which have considered the relative toxicities of amantadine and rimantadine have yielded inconclusive and somewhat contradictory results. In a crossover-designed chemoprophylaxis trial involving 162 military recruits, Peckinpaugh et al. compared daily doses of 200 mg of amantadine and 300 mg of rimantadine (25). Although the frequency of CNS complaints in the drug recipients did not differ significantly from that in placebo recipients, rimantadine administration was associated with a trend toward greater frequency of GI complaints and weight loss, observable tremor, and insomnia compared with placebo. In contrast, amantadine recipients tended to report a heightened sense of well-being. In a prophylaxis study involving 548 students who received equivalent 200-mg/day drug doses for 16 days, Noble et al. (18th ICAAC, abstr. no. 484) found that rimantadine recipients tended to report a higher frequency of nervousness (11%) than did aman-

TABLE 2. *Comparative performance in motor proficiency and adaptive ability tests of 23 volunteers receiving amantadine at 300 mg per day, 20 volunteers receiving rimantadine at 300 mg per day, and 21 receiving placebo*[a]

Test parameter[b]	Mean (SD) result during drug administration		
	Amantadine	Rimantadine	Placebo
MDS	0.33 (0.35)	0.27 (0.42)	0.26 (0.31)
MNDS	0.45 (0.52)	0.61 (0.58)	0.49 (0.61)
TrB	73.09 (22.05)[c]	56.05 (16.31)	55.00 (14.91)
DTOT	10.56 (2.08)	11.60 (1.79)	10.76 (1.89)
RDS	0.68 (2.41)	0.11 (0.25)	0.33 (0.99)
RNDS	0.31 (0.60)	0.30 (0.55)	0.72 (1.33)
REAC	0.59 (0.06)	0.62 (0.09)	0.61 (0.10)

[a] See text for explanation of performance studies. Each subject was tested before and again during drug administration. Statistical evaluation by F test of analysis of covariance controlling for base-line performance and the Duncan new multiple-range test.

[b] MDS, Maze test dominant hand, seconds of side contact; MNDS, maze test nondominant hand; TrB, Trails B test, seconds to complete test; DTOT, total number of digits repeated; RDS, resting steadiness test dominant hand, seconds of side contact; RNDS, resting steadiness test nondominant hand; REAC, reaction time test, seconds to complete test.

[c] $P < 0.01$ versus rimantadine or placebo recipients.

tadine (6%) or placebo (6%) recipients. A recent study of 54 college students used amantadine or rimantadine at 200 mg/day for treatment of documented A/USSR/77/H1N1 infection (VanVoris et al., 18th ICAAC, abstr. no. 483). On the 5th day of drug administration, the frequency of minor CNS complaints (difficulty concentrating, lightheadedness) was significantly higher in amantadine recipients (33%) than in rimantadine recipients (0%).

The discrepant results in these studies may relate to such problems as comparison of nonequivalent drug dosages, uncertain drug compliance, self-reporting of subjective complaints, and lack of objective measures of possible drug side effects. The present study was designed to overcome these limitations.

In the present study, both amantadine and rimantadine appeared to be well tolerated at a dosage of 200 mg/day on a short-term basis. When administered at dosages of 300 mg/day, rimantadine was better tolerated than amantadine. At this dosage of amantadine, healthy, working adults reported significantly more frequent and prominent side effects related to the CNS and sleep disturbance than did rimantadine or placebo recipients. Over one-half (35 of 67) of amantadine recipients experienced troublesome CNS or sleep side effects, a frequency nearly threefold higher than in rimantadine recipients. In contrast to previous work which suggested a higher proportion of GI side effects with rimantadine (25), the present study found that approximately one-fifth of each drug group had troublesome GI symptoms. Overall, 39% (26 of 67) of amantadine recipients felt that their drug was of low acceptability or adversely affected their work performance, in contrast to 8% (5 of 63) of rimantadine recipients and one placebo recipient.

As noted in previous studies (14, 15, 24), we found that amantadine-associated side effects were time and dose related. Jackson et al. found that approximately 20% of students receiving 200 mg of amantadine per day reported adverse effects and that this proportion increased to 40% at a 400-mg/day dose (15). In the present study, significant increases in the incidence of adverse CNS and sleep side effects were observed in amantadine recipients when the dosage was increased from 200 to 300 mg/day. However, comparisons between the low- and high-dose drug recipients must be interpreted cautiously, because all volunteers were carefully informed about potential side effects and high-dose recipients were aware that they were receiving higher drug doses than used in the first study. This possibility was reflected in the trend toward a higher complaint rate in the high-dose placebo group compared with the low-dose group. Most reactions occurred early in the course of drug administration. Symptoms tended to decrease despite continued drug administration and were promptly reversed after cessation of drug.

Several previous studies have assessed the possible effects of amantadine on psychomotor function. Peckinpaugh et al. found no obvious drug effects on military recruits' performance in academic tests or recent memory tasks (25). Amantadine administration (200 mg/day) was associated with a trend toward improved performance on reaction time tests but impaired performance in tests of spatial relations. Bryson et al. studied small numbers of college students receiving 200 mg of amantadine per day for influenza chemoprophylaxis and found no demonstrable effect on recent memory function or sense of spatial relations, but found that amantadine administration may be associated with impaired performance on tests of maximal and sustained attention (4).

The present study found no evidence for impaired performance on standard tests of psychomotor function in small numbers of subjects who received amantadine or rimantadine at 200 mg/day on a short-term basis. However, a higher amantadine dose was associated with significantly decreased performance, relative to placebo or rimantadine administration, on the Trails B test, a task designed to measure sustained attention, mental flexibility, and problem-solving ability. The extent of impairment was substantial and fell between the mean (±SD) retest values which have been observed for young healthy male subjects (51.28 ± 12.29) and for elderly subjects with cerebrovascular disease (158.66 ± 11.12) (19). The presence of subjective CNS side effects during drug administration was not predictive of impaired performance on this test. Other measures of reaction time, coordination, motor steadiness, or memory were not adversely affected. Similar tests have demonstrated impaired sustained concentration, motor coordination, steadiness, and reaction time in patients with high serum levels of anticonvulsant medication compared with those with nontoxic levels (12, 20).

The reasons for differences in drug side effects between amantadine and rimantadine are unclear. The compounds are structurally quite similar and differ only in the side chain of the 10-carbon ring (1). The observed differences may relate to their intrinsic neuropharmacological activity. Although amantadine has proven to be a useful drug for control of Parkinson's disease, rimantadine is reportedly not effective in this condition (29). In dopamine-primed dogs, amantadine causes a dose-related pressor response,

possibly mediated through release of dopamine and other catecholamines from neuronal storage sites (9). In contrast, rimantadine results in a depressor response in the same model (R. P. Grelak, P. Clark, J. M. Stump, and V. G. Vernier, Pharmacologist **12**:235, 1970). Whether these drugs differ in other pharmacological features, such as blood or brain concentrations after oral administration, has not been reported.

The dose-related amantadine toxicity found in the present study might not be of clinical importance in chemoprophylaxis of influenza A virus infections, in which lower dosages are used. However, considerable variations in amantadine kinetics exist between individuals, so that wide ranges of steady-state serum levels may be found (2, 8, 27). Persons with diminished renal function (13) and those with slower clearance of amantadine (2, 8) may be at increased risk of drug accumulation and toxicity even at conventional doses. Previous work has shown that short-term (5 days) administration of amantadine or rimantadine at 200 mg/day is associated with therapeutic effects in uncomplicated influenza (VanVoris et al., 18th ICAAC, abstr. no. 483). Increased drug dosages might provide greater antiviral and therapeutic effects in treatment of established infections, but CNS toxicity appears to be a limiting factor in use of higher amantadine doses. Because of better tolerance at increased dosage, rimantadine offers more promise than amantadine for treatment of influenza A virus infections.

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