Double-Blind Controlled Study of Central Nervous System Side Effects of Amantadine, Rimantadine, and Chlorpheniramine

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A total of 52 healthy, adult volunteers were randomly assigned to five treatment groups to be treated twice daily for 4 days with 100 mg of amantadine, 100 mg of rimantadine, 4 mg of chlorpheniramine or placebo alone, or 100 mg of amantadine in combination with chlorpheniramine. The results of tests measuring performance on tasks of attention, reasoning, and memory were unaffected by treatment. Subjective side effects in recipients of amantadine, rimantadine, and chlorpheniramine were comparable and minimal. Side effects appeared to be enhanced in subjects receiving both amantadine and chlorpheniramine.

Amantadine has been shown to have antiviral activity prophylactically and therapeutically against influenza A infection (2, 7, 11, 16, 17) but has not been used widely by physicians. This may be due in part to concern regarding reported central nervous system side effects, such as inability to concentrate, insomnia, and nervousness, which are usually infrequent and minimal (3, 7, 10, 11). Rimantadine, an analog of amantadine, has been shown to have similar antiviral efficacy but reportedly fewer side effects (2, 13, 17; L. P. Van Voris, 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). Recent studies suggest that amantadine has depressive effects on various psychomotor functions, such as the ability to sustain attention and the perception of spatial relationships (3, 12). However, there are limitations in these studies, and the clinical significance of these findings has not been established. Some observers have suggested that, qualitatively, the side effects of amantadine are no more significant than those produced by antihistamine drugs which are well accepted by the public (10). Since amantadine may have anticholinergic effects similar to those of antihistamines which are commonly used to treat the symptoms of influenza, concurrent use might potentiate side effects (4).

To put the significance of these side effects into perspective, we compared the effects of amantadine, rimantadine, and a commonly used antihistamine (chlorpheniramine) on the central nervous system. Side effects studied included subjective complaints and performance on tests of attention, cognition, and memory, which were examined in a controlled, blind study in healthy adults.

MATERIALS AND METHODS

Between October 1979 and January 1980, 52 adult volunteers were recruited from the University of California at Los Angeles (UCLA) student population. The study group included an equal number of men and women whose ages ranged from 18 to 44 years, with a mean of 25 years. Volunteers with a history of seizures, renal disease, or pregnancy or those taking antihistamine drugs or other medications that might mimic or enhance the effects of the study drugs were excluded. Subjects were enrolled after informed consent was obtained.

Medications. Amantadine and rimantadine and their lactose placebo were identical, salmon-colored tablets provided by Endo Laboratories. An antihistamine, chlorpheniramine, and its lactose placebo were identical white tablets prepared by the UCLA Investigation Drug Unit.

Study group assignment. Subjects were randomized in a double-blind manner to drug or placebo groups as follows. The amantadine group was given amantadine (100 mg) and chlorpheniramine placebo every 12 h; the amantadine-chlorpheniramine group was given amantadine (100 mg) and chlorpheniramine (4 mg) every 12 h; the chlorpheniramine group was given chlorpheniramine (4 mg) and an antiviral placebo every 12 h; the rimantadine group was given rimantadine (100 mg) and chlorpheniramine placebo every 12 h; and the placebo group was given an antiviral placebo and a chlorpheniramine placebo every 12 h.

Ten subjects were enrolled in the amantadine, rimantadine, and placebo groups, and 11 subjects were enrolled in the amantadine-chlorpheniramine and chlorpheniramine groups. Subjects were instructed to take one salmon-colored and one white tablet between 8 and 9 a.m. and 8 and 9 p.m. daily for a period of 3 to 4 days, 1 h before or 2 h after meals. All subjects were
Monitoring subjective side effects. Subjects completed a general medical history questionnaire and kept a daily record of possible side effects experienced during the study. These included the following symptoms: central nervous system (inability to concentrate, confusion, euphoria, insomnia, headache, dizziness, fatigue); antihistamine-related (drowsiness, dry mouth); gastrointestinal-related (abdominal pain, diarrhea, vomiting); and skin rash. Subjects graded the severity of the symptoms as follows: 1, mild, if symptoms were just perceptible and there was no interference with daily tasks; 2, moderate, if symptoms were perceptible and tasks were performed with some difficulty; 3, severe, if they caused discomfort or daily tasks were performed with extreme difficulty.

Performance tests. A battery of five tests was used to assess drug effect upon sustained attention, cognition, logical reasoning, and short-term memory. This included the Critical Tracking Test (14), the Children’s Checking Test (9), the Grammatical Transformation Test (1), the Memory for Designs Test (8), and the Symbol Digit Modalities Test (15), which are briefly described below.

The Critical Tracking Test is a visual compensatory test used to measure the effects of drugs or stress upon the ability to sustain maximum attention (14). To diminish the possibility of a practice effect, each subject was required to participate in two separate practice sessions of repetitive trials until a constant level of performance was achieved. An average of 120 trials were performed before initial testing.

The Children’s Checking Test is a vigilance test designed to measure sustained attention over a period of 20 min (9).

The effect of the drug on logical reasoning was assessed by the Grammatical Transformation Test (1).

The Memory for Designs Test assesses recent memory and spatial relationships, whereas the Symbol Digit Modalities test, given in written and oral forms, measures recent memory (8, 15).

The battery was administered during a 1-h session. Subjects received the first test battery before medication; the tests were repeated after the study drugs had been taken for at least 50 h, and not more than 1 h after the last dose of medication.

Data analysis. A composite symptom score for subjective side effects within symptom categories was calculated by adding daily scores for each subject during the treatment period. The paired t test was used in the analysis of scores on performance tests within groups. A one-way analysis of variance was used to compare demographic data, group mean scores, and differences in group mean scores among treatment groups (5).

RESULTS

Subjective side effects. There was no significant difference among treatment groups with respect to age or sex of the subjects. Mild symptoms occurred with approximately equal frequency in all groups and therefore were excluded from further analysis. Table 1 shows the frequency and cumulative scores of moderate or severe symptoms which were most commonly reported within each treatment group. The frequency of reported symptoms was low in the amantadine and placebo groups. Antihistamine-like side effects, such as drowsiness and dry mouth, were less frequent and severe in the amantadine group than in the chlorpheniramine group. However, moderate to severe inability to concentrate, dizziness, and fatigue were reported more frequently by subjects who received the combination of amantadine and chlorpheniramine. Two subjects who received this combination reported additional symptoms of confusion and distorted depth perception as well as nausea and chills.

Subtle side effects. There were no significant differences between the group mean scores on the second practice trial and the pretreatment trial of the Critical Tracking Test among all treatment groups. This result showed that the practice effect on this test was diminished or abolished.

Table 2 shows the differences between group mean scores obtained before and during treatment within each group. Mean scores decreased

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>No. of subjects experiencing side effects in group treated with:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amantadine (10)</td>
</tr>
<tr>
<td>Decreased concentration</td>
<td>1 (6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

*a Numbers in parentheses represent the total symptom score (moderate complaint, 2; severe complaint, 3). Total scores within symptom categories for each treatment group represent the sum of the total daily moderate and severe complaints during the treatment period (4 days).

*b Moderate to severe side effects are included.

*c Total number of subjects in the group.
DISCUSSION

This study supports the general acceptability of both amantadine and rimantadine as safe prophylactic and therapeutic agents, since subjective complaints were minimal and comparable to those associated with treatment with chlorpheniramine or a placebo. Since amantadine and antihistamines may have similar central nervous system and anticholinergic effects, it is not surprising that these symptoms were enhanced when the drugs were used in combination (4).

The effects of amantadine or rimantadine on higher central nervous system functions, such as memory and attention, become more important when considering its use for prophylaxis of large populations. Our data show that neither of these drugs had a significant effect upon performance of tasks which involved attention, cognition, and memory. Peckinpaugh et al. (12) reported a suggestive but insignificant decrease in spatial perception and an increased reaction time in naval recruits receiving 200 mg of amantadine. Bryson et al. (2) used the same test battery as that used in the present study and reported depressed performance on the Critical Tracking Test and Children’s Checking Test. The study had several limitations, however, due to the crossover design, with an imbalance of treatment sequence groups and a practice effect observed on the Critical Tracking Test. In the present study, this practice effect was abolished or minimized by multiple trials before testing. Our data is in agreement with a report by Hayden et al. (6), who found that no significant effects of amantadine or rimantadine on psychomotor function occurred at a dosage of 200 mg, but that performance of attentional tasks was decreased when the dose was increased to 300 mg daily. We found that, although the combination of amantadine and chlorpheniramine enhanced
subjective complaints, performance of psychomotor functions was not significantly affected.

The practical use of amantadine and rimantadine depends upon low toxicity and high efficacy in the treatment and prophylaxis of influenza A infection. Our data suggest that these antiviral agents have minimal side effects which are comparable to those of a common antihistamine and do not significantly affect higher central nervous system functions. However, physicians should be aware of the possibility of potentiation of side effects when amantadine and antihistamines are used in combination.

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LITERATURE CITED