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Efficacy and safety of low dosage amantadine hydrochloride as prophylaxis for influenza A

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Summary

The efficacy and safety of prophylactic low dose amantadine hydrochloride was assessed in two double-blind, placebo-controlled, randomized studies. In a study of 476 subjects aged 18 to 55 years, adverse reactions were not significantly different between the group receiving 100 mg/day amantadine and the placebo group but significantly greater in the group given 200 mg/day ($P < 0.009$). The influenza attack rate in this study was too low to assess efficacy. In an experimental challenge study of influenza A/Beth/1/85 in 78 subjects of similar age the prophylactic administration of 50 mg, 100 mg or 200 mg/day doses of amantadine were more effective than placebo in preventing influenza illness ($P < 0.02$, 66, 74 and 82% protection, respectively), and in suppressing viral replication ($P = 0.02$). There was no significant difference between amantadine groups in influenza illness or viral shedding. Compared with the placebo group the 100 and 200 mg amantadine groups showed a significant decrease in infection rate (100 mg: 40% protection: $P = 0.012$; 200 mg: 32% protection: $P = 0.045$) whereas the 50 mg group did not (20% protection: $P = 0.187$). These results suggest that 100 mg/day of amantadine will reduce toxicity but maintain the prophylactic efficacy seen with 200 mg/day.

Low dose amantadine; Influenza A

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Introduction

Amantadine hydrochloride has been shown to be effective prophylaxis for influenza A illness when given at the recommended dose of 200 mg/day (Consensus Development Conference, 1979; Dolin et al., 1982; Monto et al., 1979). However, significant side effects (mostly CNS) associated with the 200 mg/day dose, have resulted in the drug being underutilized. Although several studies have demonstrated that amantadine at 100 mg/day was as effective as 200 mg/day for influenza A prophylaxis each study has methodological problems (Sears and Clements, 1987; Smorondintsev et al., 1970a,b). The conclusions of a study evaluating amantadine use in natural infection (Smorondintsev et al., 1970a) have been criticized because of methods used in subject selection and because of a low rate of influenza infection. Studies using experimental challenge of influenza by Smorondintsev et al. (1970b) and by Sears and Clements (1987) show efficacy of low dose amantadine but do not include a 200 mg/day regimen for comparison. Further data on amantadine pharmacokinetics and its relation to drug toxicity and efficacy are therefore needed (Consensus Development Conference, 1979; Dolin et al., 1982; Aoki et al., 1985; Douglas, 1982).

This paper presents two double-blind, placebo-controlled, randomized studies of prophylactic amantadine: (1) a study of 476 subjects followed during the 1985-86 influenza season, and (2) a study of 78 subjects challenged with influenza A/Beth/1/85 during the summer of 1986. The very low incidence of influenza A infection (5%) in the first study population allowed us to compare adverse experiences of 100 and 200 mg/day of amantadine but did not allow evaluation of efficacy. In the second study the prophylactic efficacy of amantadine doses of 50, 100, and 200 mg was assessed.

Materials and Methods

Study populations

Natural occurring influenza study. Subjects aged 18 to 55 years were recruited from personnel of The Christ Hospital, Cincinnati, Ohio. Subjects were excluded if they had: (a) an abnormal pre-study clinical history and physical examination by study physician, (b) chronic disease, (c) a history of seizures, (d) serious drug allergy, (e) a recent upper respiratory illness, (f) a history of chemical dependence, (g) pregnancy or were breast feeding, or (h) a history of influenza vaccine. Out of 526 subjects, 476 were initially enrolled. Written consent was obtained from all participants before beginning the study.

Experimental challenge study. Subjects between the ages of 18 and 40 years were recruited primarily from a college student population. Only subjects with a serum hemagglutination-inhibition antibody (HAI) titer $\leq$ 1:8 for influenza A/Bethesda/1/85(H3N2) were included in the study. Subjects were ineligible if they

had any of the same findings as the exclusion criteria listed above for the natural occurring influenza study. Of 377 subjects that were screened, 164 were susceptible, 51 did not show for physical exam, 19 failed the physical exam, and 14 did not show for the study. This left 81 subjects who were enrolled in the study. Four subjects did not complete the study protocol. Three subjects left the study before receiving influenza challenge: one (200 mg group) was discharged after one dose because of emotionally unstable behavior and two (200 mg group) dropped out after two days of receiving outpatient amantadine. These three subjects were excluded from efficacy analyses. One subject (50 mg group) suffered insomnia and medication was stopped. All subject data were included in safety analyses.

Study design

Natural occurring influenza study. Subjects were randomly assigned (computer-generated code of random numbers) to one of three groups: (1) placebo, (2) amantadine 100 mg/day and (3) amantadine 200 mg/day. There were 159 subjects in groups 1 and 2, and 158 subjects in group 3. Each subject was seen weekly for six weeks and took one capsule from one bottle in the morning and one capsule from the other bottle in the afternoon (placebo and amantadine capsules were identical in appearance).

Capsules were prepared, packaged and coded by E.I. DuPont de Nemours and Co., Inc. of Wilmington, Delaware. Diary cards for recording the dose and time of medication, daily flu symptoms, adverse effects and all concomitant medication were collected weekly. Subjects were asked during the weekly visits for any possible drug related side effects by asking whether they 'felt any different since starting the study drug'. Subject explanations were categorized by choosing the appropriate symptom(s) from a list of recognized adverse effects of amantadine. All symptoms reported by subjects outside of predefined influenza symptoms were recorded as adverse experiences and judged for their relatedness to amantadine toxicity. An unannounced random blood sample was collected from the entire study population to test for compliance.

Subjects were instructed to contact study personnel if acute respiratory illness developed, and encouraged to do so even if illness was mild. Subjects were promptly seen whenever influenza-like illness occurred (fever $\geq$ 100°F and cough for $\geq$ 24 h plus at least two of the following signs and symptoms: headache, malaise, myalgia, sore throat, pain on coughing and anorexia). Any subject that met these criteria was evaluated twice during their illness on two consecutive days for clinical signs and symptoms and for collection of nasal wash to be used for viral isolation.

Experimental challenge study. Subjects were randomly assigned to one of four treatment groups: (1) placebo, (2) amantadine 50 mg once a day, (3) amantadine 100 mg once a day and (4) amantadine 200 mg once a day. Subjects were housed for 13 days in an isolation facility and administered two capsules (100 mg amantadine or placebo) and one tablet (50 mg amantadine or placebo) in the morning

under staff supervision for eight days (three days before viral challenge and five days after challenge).

Capsules and tablets were prepared, packaged and coded by E.I. DuPont de Nemours and Co., Inc. of Wilmington, Delaware. Three days after initiation of study drug regimens, each subject was inoculated intranasally (0.25 ml per nostril) with a dose of $10^{7.15}$ 50% tissue culture infectious doses ($TCID_{50}$) of influenza A/Bethesda/1/85(H3N2) virus (passage history: primary chick kidney cells × 4 and egg allantoic cavity × 2). The challenge virus was provided by Dr. Carol Heilman (N.I.H.). Subjects were prohibited from taking any medications during the study unless approved by the study physicians. All concomitant medications were recorded.

Subjects were interviewed and examined twice daily by the same physician. Signs and symptoms were scored only as present or absent. Oral temperatures and vital signs were recorded four times a day. Temperatures over 100°F, documented within one hour, were used to define fever for the tabulation of influenza illness. Nasal wash for viral assay was collected just prior to viral challenge and daily for nine days after challenge. Blood samples for antibody and amantadine levels were collected as outlined below.

Influenza infection was defined as a 4-fold or greater increase in serum HAI antibody titer to influenza antigen and/or isolation of influenza virus from at least one nasal wash. Influenza illness was considered present when subjects had: (1) a temperature elevation of 100°F (37.8°C) or greater confirmed within 1 h of the time it was initially recorded, and (2) the occurrence of at least two other symptoms characteristic of influenza: myalgia (involvement of more than one muscle group), chills and sweats, rhinitis or pharyngitis or cough observed on at least two consecutive clinical evaluations within one evaluation of documented fever. The diagnosis of influenza illness also required evidence of influenza infection.

Institutional Review Committee. Both studies were approved by the Institutional Review Committee of The Christ Hospital. Written informed consent was obtained from all subjects. Subjects from both studies were paid an approved fixed sum of money after completing their respective study protocol.

Laboratory procedures

Serology. Sera for antibody were evaluated using a standard hemagglutination inhibition assay (Palmer et al., 1975). During the study of naturally occurring influenza, sera were collected at the beginning and at the end of the six week study period and evaluated for HAI antibody to the three prevalent strains for 1985–86: A/Chile/1/83(H1N1); A/Philippines/1/82(H3N2); and B/USSR/100/83. For the challenge study paired sera obtained prior to challenge and 28 days afterward were assayed against the challenge strain of influenza A/Bethesda/1/85(H3N2). Statistical comparisons of titers were made by comparing log transformations of titers. Titers of $< 1:8$ were treated as 1:4.

Viral assays. Nasal wash specimens were inoculated onto MDCK continuous cell line and hemadsorbed with guinea pig erythrocytes at 3–4, 10 and 14 days post-inoculation for detection of influenza virus (Palmer et al., 1975). One hemadsorption positive specimen from each patient was confirmed as influenza A by IFA (as per protocol of Influenza Branch of the Centers for Disease Control, Atlanta, Georgia). End point titrations of positive specimens were performed on MDCK cells as previously described (Hsiung and Fong, 1982; Lennette, 1980).

Drug assays. Serum for amantadine levels was collected: (a) just prior to initial administration of study medication, (b) 2 h after the first dose, (c) 4 h after the third dose just prior to challenge, (d) 2 h after the seventh dose and (e) just prior to the last dose. Amantadine levels in serum were kindly measured by Dr. Howard Hoffman of Stine-Haskell Laboratory in Newark, Del. by standard methods (Hayden et al., 1983). All pre-study and placebo drug levels were below detectable levels. In order to avoid making statistical comparisons to zero values in the placebo group, a value of 25 ng/ml was assigned (level of assay sensitivity).

Statistical analysis

One-way analysis of variance (ANOVA) and the chi-square test were used to test for differences among treatment groups. The challenge study was performed with the assumption of influenza infection rates of >90% for the placebo group, <30% for the 50 and 100 mg groups and <20% for the 200 mg group. The study sample size was chosen to assure a 99% power to detect a significant difference at the 0.05 level between groups using a two tailed test. Statistical tests included comparisons of each active dose versus placebo, comparison of combined active groups versus placebo and a comparison among the three active dose groups. These comparisons were of interest 'a priori', therefore no adjustment for multiplicity was done. Since the small sample size did not provide sufficient power to find differences between the three amantadine groups these two groups were combined for comparison with placebo.

Results

Naturally occurring influenza study

Compliance with amantadine and placebo dosage regimens was measured in two ways, tablet counts and random blood sampling for amantadine. Of the total 84 allotted tablets, the minimum number taken was 69 and the maximum 92. In the 200 mg amantadine group, 66% of subjects took less than the total allotted 84 tablets compared to 49% of subjects in the 100 mg amantadine group and 58% of subjects in the placebo group. Random blood sampling was done on 48 subjects. All 30 samples from the amantadine groups were positive for drug and all 18 samples from the placebo group were negative for drug.

TABLE 1

Natural occurring influenza study: adverse experiences by body system in 476 subjects followed for six weeks during the 1985–1986 influenza season [number (percent) of subjects reporting at least one adverse experience with possible relation to amantadine]

	Placebo	Amantadine 100 mg	Amantadine 200 mg
Total No. of subjects at risk	159	159	158
Total No. (%) of subjects with adverse experiences	49 (31%)	47 (30%)	71 (45%)[a]
Central nervous	25 (15%)	23 (14%)	47 (30%)[a]
Gastrointestinal	12 (8%)	12 (8%)	17 (11%)
Cardiovascular	1 (0.6%)	1 (0.6%)	1 (0.6%)
Whole body[b]	24 (15%)	16 (10%)	21 (13%)

[a]Significantly different compared to placebo ($P = 0.009$) and the 100 mg group ($P = 0.005$). Compared to placebo, CNS symptoms that contributed ($P = 0.001$) included sleep abnormalities ($P = 0.023$), nervousness ($P = 0.048$) and dizziness ($P = 0.167$).
[b]Includes asthenia, myalgia, fatigue and headache.

Study subjects (hospital employees) were asked to report any drug related side effects during their weekly study visits. All reported symptoms outside of predefined influenza symptoms were recorded as adverse experiences. The total number of patients with adverse experiences (Table 1) did not differ between the placebo (31%) and 100 mg treatment groups (30%). The high percentage of reported adverse effects in the placebo group may have occurred because hospital employees were more likely to report minor symptoms as adverse experiences at their weekly interview. A significantly greater number of total adverse experiences ($P = 0.009$) and CNS related adverse experiences (sleep disturbances, nervousness and dizziness) ($P < 0.001$) were observed in the amantadine 200 mg group compared to the placebo group. In addition, the individual symptoms of dry nose and dry mouth were significantly greater ($P \leq 0.005$) in the 200 mg treatment group compared to the other two groups. Of the 476 subjects entered in the study, only three withdrew because of an adverse experience: one in the placebo group and two in the 200 mg group. One subject was dropped from the 100 mg and one from the 200 mg group because of pregnancy documented after initiation of the study. Both women delivered healthy children.

Of the 158 subjects in the placebo group, only eight (5%) were confirmed to be infected with influenza A or B. This rate was far below the pre-study estimated infection rate of 30% used in calculating the size of the study needed to make valid statistical comparisons (450 subjects assured 80% power to detect a significant difference at the 0.05 level between the amantadine group and placebo using a two-tailed test). The diagnosis of influenza A was made in eight cases, four by isolation only, three by seroconversion and one by both methods. Five subjects were infected in the placebo groups, two subjects in the 100 mg group and one subject in the 200 mg amantadine group.

TABLE 2

Challenge study: protective effect of three different doses of amantadine HCl compared with placebo in 78 subjects challenged with $10^{7.15}$ $TCID_{50}$ of influenza A/Beth/1/85(H3N2)

Treatment group	No. of subjects	Number infected[a]	*P* value[b]	No. ill[c]	*P* value[b]
Placebo	19	18 (95%)		11 (58%)	
Amantadine 50 mg/day	20	16 (80%)	0.187	4 (20%)	0.017
Amantadine 100 mg/day	20	12 (60%)	0.012	3 (15%)	0.005
Amantadine 200 mg/day	19	13 (68%)	0.045	2 (11%)	0.003

[a]Influenza infection is defined as virus isolation, antibody response, or both.
[b]*P* values (Fisher exact test) refer to comparison of each amantadine group to placebo.
[c]Influenza illness is defined as fever > 100°F and two influenza symptoms (see Materials and Methods).

Experimental challenge study

Demographic data. There were no significant differences among treatment groups for age, sex, race, height, weight, pre-study body temperature, blood pressure, pulse, physical and laboratory examination. A history of asthma and other pulmonary disorders were found in three of 20 subjects in the amantadine 50 mg/day group and in none of the other groups ($P = 0.029$).

Influenza illness

Influenza illness (Table 2) was found in 11 of 19 (58%) placebo subjects, 4 of 20 (20%) subjects given 50 mg/day amantadine, 3 of 20 (15%) subjects given 100 mg/day amantadine and in 2 of 19 (11%) subjects given 200 mg/day amantadine (compared with placebo: $P = 0.017$, 0.006, and 0.003, respectively). Compared with the placebo group, 200 mg of amantadine reduced the rate of influenza illness by 82%, 100 mg by 74%, and 50 mg by 66%. The three groups receiving amantadine did not differ significantly from each other in their overall rates of influenza illness ($P = 0.713$). The occurrence of influenza illness in subjects with detectable HAI antibody at the beginning of the study (titer = 1:8) did not differ among the four groups.

Amantadine at all doses significantly ($P < 0.05$) suppressed respiratory symptoms (rhinorrhea + pharyngitis + cough) on days 2 through 6 post-challenge (Fig. 1A) and systemic symptoms (fever + myalgia + chills and sweats) on days 2 and 3 post-challenge (Fig. 1B).

Influenza infection

Influenza infection was detected in 18 of 19 (95%) placebo subjects, 16 of 20 subjects (80%) given 50 mg/day ($P = 0.187$), 12 of 20 subjects (60%) given 100

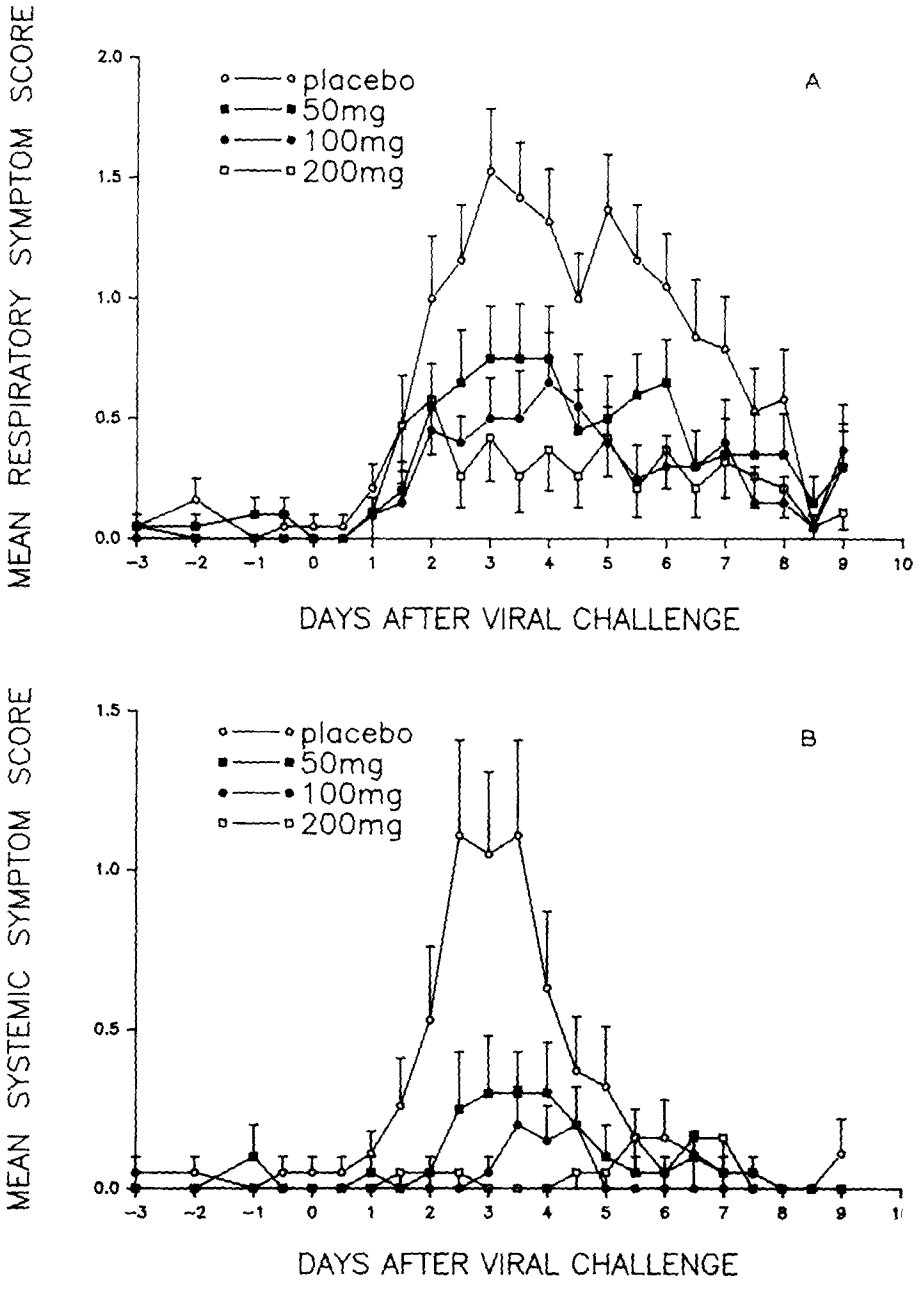

Fig. 1. (A) The mean and standard error of the total respiratory symptom score (rhinorrhea, s
throat plus cough) for all subjects of each amantadine dosage group per bi-daily clinical evaluation.
The mean and standard error of the total systemic symptom score (fever, myalgia plus chills and swe
for all subjects of each amantadine dosage group per bi-daily clinical evaluation.

mg/day (P = 0.012) and 13 of 19 subjects (68%) given 200 mg/day (P = 0.045) (Table 2). The three groups receiving amantadine did not differ significantly from each other in their overall rates of influenza infection (P = 0.386).

Virus shedding

Virus was isolated on at least one occasion, from the nasal wash of 54 volunteers, 95% of placebo controls and 61% of subjects receiving amantadine (P = 0.021). Nasal washes were free of detectable virus in seven (35%) subjects of the 50 mg group, nine (45%) of the 100 mg group, and seven (37%) subjects of the 200 mg group (P = 0.789). In those subjects who shed virus, duration of viral shedding ranged up to nine days in all the groups. The mean duration of viral shedding was 6.5 days for the placebo group, 5.3 days for the 50 mg/day group, 5.7 days for the 100 mg/day group and 5.5 days for the 200 mg/day group (P = 0.15 for placebo vs. all amantadine groups).

The placebo group had significantly higher ($P < 0.05$) mean viral titers than any amantadine group on each of days 1 through 6 post-challenge (a negative viral titer was designated as zero for statistical comparisons). Thereafter, the four study groups were not significantly different (Fig. 2). There was no significant difference among the amantadine groups. Virus shedding did not increase after amantadine was discontinued.

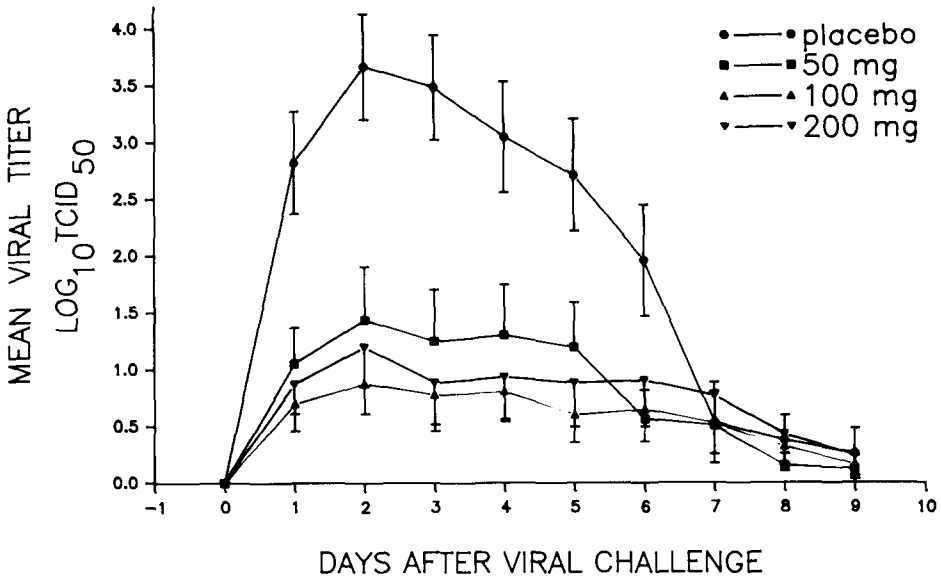

Fig. 2. Mean and standard error of viral titers for all subjects of each amantadine dosage group per day.

Antibody response

Increases in HAI antibody titers (≥ 4-fold) following viral challenge were seen in 13 (68%) of 19 placebo subjects and in 23 (39%) subjects receiving amantadine ($P = 0.03$). Eight (40%) of the 50 mg group, 6 (30%) of the 100 mg group and 9 (47%) subjects of the 200 mg group had ≥ four-fold increases in their HAI titer ($P = 0.10$).

Serum amantadine levels

Mean serum amantadine levels were significantly different between groups at each time ($P < 0.001$) increasing approximately 2-fold for each dose increase (Table 3). Amantadine levels increased from 2 h after the first dose to 4 h after the third dose ($P < 0.001$) by which time a steady state was reached. Peak levels obtained just prior to influenza virus challenge were not significantly different from peak levels for the same group five days after challenge. Trough levels were significantly less than peak drug levels ($P < 0.001$).

Amantadine blood levels were not significantly different between infected and uninfected subjects ($P > 0.69$). When differences in amantadine levels were examined within each dose group significant differences between infected and uninfected subjects were found only for blood levels obtained after the first 50 mg dose ($P = 0.03$). Amantadine blood levels were also not significantly lower in subjects with illness compared to subjects without illness ($P > 0.36$).

Adverse experiences

The proportion of subjects with at least one adverse experience judged as possibly or probably related to amantadine ranged from 50% in the placebo group to 80% in the amantadine 100 mg/day group. Adverse experiences were mostly mild, transitory, of short duration and resolved spontaneously. The majority of adverse experiences were related to the central nervous system and gastrointestinal systems. There were no significant differences in the percent of subjects with at least one adverse experience between the treatment groups pre-challenge ($P = 0.42$),

TABLE 3

Serum amantadine levels at four times during study isolation (ng/ml)

Study group	2 h after dose 1 Mean ± SD	4 h after dose 4 Mean ± SD	2 h after dose 7 Mean ± SD	10 min before dose 8 Mean ± SD
Placebo	25 ± 0	25 ± 0	25 ± 0	25 ± 0
Amantadine 50 mg/day	152 ± 88	237 ± 96	197 ± 90	77 ± 52
Amantadine 100 mg/day	250 ± 104	419 ± 138	476 ± 161	184 ± 79
Amantadine 200 mg/day	604 ± 195	857 ± 234	946 ± 411	404 ± 209

post-challenge ($P = 0.20$) or over the entire duration of the study ($P = 0.27$). The number of subjects reporting at least one central nervous system related adverse experience was also not significantly different between the four treatment groups during the entire duration of the study. However, the number of CNS adverse experiences was found to significantly correlate with amantadine blood levels obtained prior to challenge 2 h after the first dose ($P = 0.035$). Amantadine blood levels were higher in subjects reporting more CNS adverse experiences (none: 292 ± 213 ng/ml; one: 337 ± 257 ng/ml; two: 335 ± 209 ng/ml; three to four: 583 ± 296 ng/ml).

Only four adverse experiences were rated as severe. The investigator stopped the treatment of one subject in the amantadine 50 mg/day group after five days of dosing because of severe insomnia associated with fatigue, dry mouth, headache and nervousness. The amantadine blood level in this subject prior to discontinuation was 294, within the range expected for this dose group. The other three adverse reactions rated as severe included two complaints of headache (one placebo and one 100 mg subject), and a complaint of dream abnormality from a subject in the 100 mg group.

Discussion

Amantadine hydrochloride has been shown to be effective for prophylaxis against and treatment of influenza A illness when used at a dose of 200 mg per day but is infrequently prescribed because of drug toxicity (Dolin et al., 1982; Monto et al., 1979; Muldoon et al., 1976; Payler and Purdham, 1984; Rose, 1983; Van Voris et al., 1981). Central nervous symptoms occur in 5 to 13% of recipients receiving the 200 mg/day (Couch et al., 1986; Hayden et al., 1983; Horadem et al., 1981). The toxicity associated with amantadine may be related to the dose (Douglas, 1982) although studies investigating both the safety and efficacy of the drug at different doses have not been performed. These two double-blind, randomized and placebo-controlled studies permit analysis of both safety and efficacy for different doses of amantadine.

In the study of naturally occurring influenza, a significantly greater number of total adverse experiences, CNS related adverse experiences and dry nose and mouth were found in the group receiving amantadine at 200 mg/day compared to the 100 mg/day group or the placebo group but no significant differences between the 100 mg/day and placebo groups were found. The smaller challenge study did not detect significant differences in adverse experiences among the amantadine dosage groups. The first study more accurately determined amantadine toxicity because of larger numbers per dosage group and because it permitted analysis of adverse effects of amantadine in the absence of symptoms of influenza that may be confused with amantadine adverse effects. It therefore appears that amantadine at 100 mg/day will reduce the toxicity associated with therapy.

In the challenge study we found that prophylactic amantadine HCl at any of the three doses tested (50, 100, and 200 mg/day) was significantly more effective than

placebo in preventing influenza illness but comparable to each other. Similarly, the three amantadine doses reduced symptoms and viral shedding nearly equivalently. Systemic symptoms were significantly less ($P < 0.05$) for two to three days after influenza challenge and respiratory symptoms from two through six days after challenge with each of the amantadine doses compared to placebo. Mean viral titers were also significantly higher in the placebo group compared to any of the three amantadine groups on study day 5 through 10. Thus, although the 50 mg dose was the least effective in reducing symptoms and viral shedding, the difference never reached significance. We did not observe a rebound in virus shedding or in clinical illness after discontinuing amantadine, in contrast to findings of others using rimantadine in children (Hall et al., 1987). The reasons for the difference are not clear.

Infection rates were also similar among all three amantadine groups and significantly decreased for the 100 mg and 200 mg groups compared to placebo but not significantly decreased when the 50 mg group was compared to placebo. This data combined with the analysis of symptom scores and viral shedding suggests that 50 mg may be less effective prophylaxis.

Several studies have evaluated the prophylactic effectiveness of low dose amantadine (Sears and Clements, 1987; Smorondintsev et al., 1970a,b; Payler and Purdham, 1984; Rose, 1983; Van Voris et al., 1981) but none allowed comparison of amantadine efficacy at different doses. Most recently Sears and Clements (1987) challenged subjects with H1N1 influenza A and reported a 78% protective efficacy for the 100 mg dose regimen. This study lacked a 200 mg group and the calculation of efficacy included subjects without fever in the diagnosis of influenza illness. Such a definition is not comparable with definitions of influenza illness commonly used in naturally occurring influenza studies. Two studies reported by Smorondintsev et al. (1970a; 1970b) had methodological problems including arbitrary exclusion of 20% of subjects from the analysis (Smorondintsev et al., 1970a) and lack of randomization after pre-inoculation screening, lack of viral isolation and a low rate of serologic conversion (Smorondintsev et al., 1970b). Two other studies done in English boarding schools by Payler et al. (1984) and Rose (1983) also had methodological problems including lack of a placebo group and a history for previous vaccination. Although our study has allowed comparison of amantadine efficacy at different doses, it is still not clear whether the effect of amantadine on influenza is a direct linear dose response relationship or a threshold relationship.

In summary, our studies suggest that amantadine at 100 and 200 mg/day is equally efficacious and that the lower dose is less toxic. The 50 mg/day dose may not be as effective although the number of subjects evaluated was too small to reveal significant differences. Recently it has been suggested that lower doses of amantadine be used for people over 65 because of decreased renal function (Centers for Disease Control, 1986). Amantadine at 100 mg/day may be appropriate for use in prophylaxis against influenza A for individuals younger than 65 years of age and older than 18 years of age. However, field trials with lower doses of amantadine are necessary to determine whether the 100 mg/day regimen is effective against naturally occurring influenza illness.

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