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Safety and Prophylactic Efficacy of Low-Dose Rimantadine in Adults during an Influenza A Epidemic

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A placebo-controlled, double-blind study to evaluate the safety and prophylactic efficacy of a low dose (100 mg) of rimantadine hydrochloride against naturally occurring influenza in adults was conducted at two sites. After the onset of the influenza season, volunteers (ages, 18 to 55 years) were assigned randomly to receive rimantadine or placebo daily. Subjects were monitored for adverse effects and evidence of influenza virus infection weekly for six weeks. Only 10 (8.7%) of 114 rimantadine recipients and 5 (4.4%) of 114 placebo control recipients reported one or more mild to moderate adverse symptoms, most of which were related to the gastrointestinal or central nervous system. Compared with placebo, low-dose rimantadine was highly effective in the prevention of influenza A virus infection (20 of 110 versus 7 of 112 participants; $P < 0.01$) and influenza illness (7 of 110 versus 1 of 112 participants; $P = 0.04$). Influenza A/Leningrad/87-like (H3N2) virus was recovered from the nasopharynxes of only five placebo recipients. These findings indicate that low-dose rimantadine is well tolerated and highly effective for the prevention of influenza A illness in healthy adults.

Influenza viruses continue to be a major source of epidemic respiratory disease that results in significant morbidity and mortality worldwide. Each year approximately 25 million to 75 million cases of influenza A virus illness occur, with the highest attack rates being in children and young adults (1). Elderly people and people with chronic heart or lung disease are at high risk for hospitalization and death (2, 3, 12). Immunization is recommended for individuals at risk for serious influenza and those who are likely to transmit influenza virus (e.g., physicians, nurses, and other health care providers) to high-risk individuals (6, 7), but the efficacies of licensed influenza vaccines for those at risk for serious influenza have been variable (7, 8). Amantadine hydrochloride, a licensed antiviral agent, has been shown to be approximately 70 to 90% effective in preventing illness caused by influenza A viruses in controlled trials (1, 9). Yet, the drug is underused for influenza prevention, in part because of concern about drug toxicity. Central nervous system symptoms occurred in approximately 5 to 10% of recipients of a 200-mg daily dose (15). These and other side effects appear to occur more frequently in elderly people who receive the 200-mg dose (15). For this reason, there is need for an effective antiinfluenza drug with fewer side effects.

Controlled studies have shown that rimantadine hydrochloride, a structural analog of amantadine, when administered in comparable doses, is as effective as amantadine in preventing influenza A virus infection and illness (10). Moreover, a 200-mg daily dose of rimantadine appears to be associated with fewer central nervous system side effects than 200 mg of amantadine does, even though rimantadine has a longer half-life (15).

Recent findings (16) that 100 mg of amantadine is highly effective in restricting virus replication and preventing influenza A virus infection and illness in adults prompted us to conduct a placebo-controlled, double-blind randomized study to determine the tolerability and prophylactic efficacy of rimantadine administered in a daily dosage of 100 mg to young adults during an epidemic of influenza A (H3N2) virus. Our findings suggested that a 100-mg dose of rimantadine is both highly effective for prophylaxis and well tolerated.

MATERIALS AND METHODS

Population. Study protocols were approved by the Human Subjects Research Committee of Children's Hospital Research Foundation, Columbus, Ohio, and the Joint Committee on Clinical Investigations of the Johns Hopkins University School of Medicine and the Johns Hopkins Hospital, Baltimore, Md. Two hundred twenty-eight healthy adult volunteers (ages, 18 to 55 years) were recruited from the Baltimore ($n = 115$) and Columbus ($n = 113$) communities. The health status of each volunteer was determined by history, physical examination, and clinical laboratory tests, including a urinalysis; a complete blood count; and serum urea nitrogen, creatinine, albumin, total protein, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase. Volunteers were excluded from participation in the study if they had a history of seizures, vaccination against influenza A virus, or allergy to amantadine or rimantadine or if they were taking medications that might interfere with the study. Each volunteer gave written, informed consent.

Experimental design. The study was conducted in a double-blind manner between 8 February and 14 April 1988. The rimantadine and identical-appearing placebo capsules were prepared, packaged, and coded by Hoffmann-La Roche Inc., Nutley, N.J. The study was initiated immediately after documentation of the presence of influenza A virus in the

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community at each study site. Subjects were assigned randomly, according to a computer-generated code, to receive either 100 mg of rimantadine or a placebo capsule daily for 6 weeks.

Surveillance. Each volunteer maintained a daily record of the time of drug ingestion and any symptoms or side effects that occurred. To assess drug toxicity, subjects were questioned weekly about the development of symptoms, particularly those related to the gastrointestinal and central nervous systems. Adverse effects were classified as probably being related to the study drug if the onset of the event and administration of the study drug were temporally related and no other etiology was found. Adverse events temporally associated with the study drug for which an alternative etiology was more likely were considered possibly related. Blood tests, including complete blood count, blood urea nitrogen, alanine aminotransferase, and urinalysis, were performed prior to treatment and on the last day of treatment. Each volunteer reported in person to a central site and was questioned at least once a week regarding the development of fever and respiratory symptoms. All subjects were asked to report influenzalike illness as soon as it developed, and each ill volunteer was examined on the first or second day of illness. A volunteer was considered to have an influenzalike illness if he or she had a febrile respiratory illness (development of fever [oral temperature, ≥38.0°C] plus generalized myalgia, sore throat, cough, or rhinorrhea or an afebrile respiratory illness), development of at least two respiratory symptoms for 2 days, plus a systemic symptom, such as myalgia or malaise. An illness was attributed to influenza A virus when it was confirmed by virus isolation, a serum antibody response, or both.

Sampling and laboratory studies. A nasal wash specimen or nasopharyngeal swab was taken from each ill participant for virus culture on the first or second day of illness. Each sample was mixed in veal broth transport medium, and 0.1 ml of sample was inoculated onto African green monkey cell lines (samples in Columbus) or Madin-Darby canine kidney tissue culture (samples in Baltimore). Influenza A virus isolates were identified by hemadsorption of chicken or guinea pig erythrocytes by using an indirect fluorescent-antibody method with polyclonal chicken antisera (Wellcome Diagnostics, Research Triangle Park, N.C.) to type the isolates, a hemagglutination inhibition (HAI) assay with chicken erythrocytes, or both.

To confirm influenza A virus infection serologically, blood was collected from all participants at the beginning and end of the study. Paired serum specimens were tested in Baltimore by an HAI assay by using influenza A/Leningrad/87 (H3N2) and influenza A/Los Angeles/87 (H3N2) viruses, which were both closely antigenically related to the viruses that circulated in both communities. These viruses were kindly provided by Brian R. Murphy (National Institute of Allergy and Infectious Diseases, Bethesda, Md.). Influenza A virus infection was confirmed by virus isolation, a fourfold or greater rise in the HAI antibody titer in serum, or both.

Statistical analysis. Data for participants who received any doses of test drug were considered evaluable for side effects. Data for four rimantadine and two placebo recipients who received less than 36 doses and who withdrew from the study prematurely were included in the analysis for side effects but not that for efficacy. Student's t test, the two-tailed chi-square test with the Yates correction, and the Fisher exact test were performed when appropriate. The reduction in the rate of illness in rimantadine recipients (the efficacy rate) was calculated as follows: [(rate of illness in placebo control groups − rate of illness in rimantadine group) × 100]/rate of illness in placebo control group.

TABLE 1. Characteristics of the study population

Treatment	No. of:		Mean age (yr)	Pretreatment geometric mean HAI antibody titer
	Males	Females		
Rimantadine (n = 114)	30	84	31.3	1:44
Placebo (n = 114)	28	86	31.4	1:50

RESULTS

A total of 58 men and 170 women participated in the study. The demographic characteristics (gender, age, race) of the participants from Columbus and Baltimore were similar, but their pretreatment geometric mean HAI assay titers to influenza A/Leningrad/87 (H3N2) virus differed (Columbus volunteers, 1:36; Baltimore volunteers, 1:61, $P < 0.01$). Because there was no statistically significant difference in the mean HAI assay titers or other characteristics of the rimantadine and placebo groups at either site, we pooled the data from the study groups from the two sites for analysis. Each pooled group was comparable with regard to gender, mean age, race, and geometric mean influenza HAI assay titers (Table 1). The number of rimantadine and placebo recipients who used concomitant medications (mainly oral contraceptives, analgesics, and antihistamines) was also similar.

Rimantadine was as well tolerated as the placebo was (Table 2). Only 10 (8.7%) of the 114 rimantadine-treated subjects and 5 (4.4%) of 114 placebo recipients reported one or more clinically adverse experiences; most were mild or moderate. The most frequently reported adverse experiences in both groups were related to the gastrointestinal and central nervous systems. The rate of headache and fatigue was similar for both groups. Gastrointestinal symptoms (most notably nausea) occurred more often in volunteers who received rimantadine, but nausea was reduced by taking the drug shortly before or after a meal. Laboratory test

TABLE 2. Symptoms in volunteers who indicated adverse effects during treatment

Symptoms	No. (%) of volunteers			
	Rimantadine (n = 114)		Placebo (n = 114)	
	Possibly related[a]	Probably related[b]	Possibly related	Probably related
Headache	2 (1.8)	0	2 (1.8)	0
Insomnia	1 (0.9)	0	0	0
Dry mouth	1 (0.9)	0	0	0
Nausea	3 (2.6)	3 (2.6)	0	3 (2.6)
Fatigue	1 (0.9)	0	1 (0.9)	0
Total no. of adverse experiences	8	3	3	3
Total no. of subjects with adverse experiences	7 (6.1)	3 (2.6)	2 (1.8)	3 (2.6)

[a] Symptoms related to administration of the study drug for which another etiology was more likely were considered possibly related to treatment.

[b] Symptoms related to administration of the study drug for which no other etiology was obvious were considered probably related to treatment.

TABLE 3. Protective effect of 100 g of rimantadine hydrochloride compared with that of placebo against naturally occurring influenza A (H3N2) wild-type virus

Treatment	No. (%) of volunteers:			
	Shedding influenza A virus	Infected with influenza A virus[a]	With illness caused by influenza A virus	With any influenzalike illness[b]
Rimantadine (n = 112)	0	7 (6.2)[c]	1 (0.9)[d]	19 (16.9)
Placebo (n = 110)	5 (5.5)	20 (18.1)[c]	7 (6.4)[d]	21 (19.1)

[a] Infection was documented by isolation of influenza A virus, seroconversion, or both.
[b] Influenzalike illness was defined as respiratory illness with or without fever (oral temperature, ≥38°C).
[c] $P < 0.01$ (two-tailed chi-square test).
[d] $P = 0.04$ (two-tailed Fisher exact test).

results after treatment were seldom abnormal for either group. The only abnormalities detected were liver enzyme levels less than or equal to twice the normal level in two rimantadine recipients and one placebo recipient and clinically insignificant hematologic abnormalities. With the exception of more frequent reporting of nausea in participants from Columbus, safety and tolerance data were similar for participants at the two sites.

A total of 7 rimantadine recipients and 20 placebo recipients developed influenza A virus infection, as documented by isolation of influenza A virus, a fourfold or greater rise in HAI antibody titer to influenza A (H3N2) virus in serum, or both (7 of 112 versus 20 of 110 participants, respectively; chi-square test, $P < 0.01$) (Table 3). Influenza A/Leningrad/87-like (H3N2) virus was recovered from five placebo recipients (three in Baltimore and two in Columbus) but was not recovered from any of the rimantadine recipients.

Altogether, 19 rimantadine recipients and 21 placebo recipients developed a respiratory illness during the study, but influenza A virus infection was documented in only 15 ill volunteers (Table 3). A total of 3 illnesses were due to influenza B virus, but no causative agent in 22 other illnesses was found. Rimantadine recipients developed influenza A illness significantly less often than did placebo recipients (1 of 112 versus 7 of 110 recipients, respectively; Fisher exact test, $P < 0.04$) (Table 3). The efficacy of rimantadine was 86% for prevention of influenza illness and 66% for prevention of influenza A virus infection. Illness and efficacy data were similar for participants at both sites.

DISCUSSION

Rimantadine hydrochloride, a derivative of the cyclic amine amantadine hydrochloride, is more active in vitro against influenza A strains on a molar basis than amantadine is (19, 20). Moreover, in clinical trials, rimantadine, given as 200 mg daily or 100 mg twice daily, appeared to be as effective as amantadine for the treatment of and prophylaxis against influenza A virus illness (10, 19, 21, 23), but it caused fewer side effects (10, 19, 21). Even though the 200-mg dose of rimantadine is generally as well tolerated as the placebo is, 4 to 11% of healthy adults may experience drug-related central nervous system adverse effects, such as insomnia, difficulty in concentrating and headache, and gastrointestinal symptoms such as nausea and vomiting (1, 10). Apparently, adverse effects related to rimantadine and amantadine are dose dependent (19).

In a previous study in adults, we found that the 100-mg dose of amantadine is not associated with gastrointestinal or central nervous system toxicity (16). Moreover, the level of amantadine achieved in blood was high enough to provide a high level of protection against influenza illness induced by experimental challenge with wild-type influenza A H1N1 virus (16). These encouraging results prompted us to conduct a placebo-controlled trial in adults to determine the tolerability of a 100-mg regimen of rimantadine given daily for 6 weeks and its protective efficacy against naturally occurring influenza A virus illness and infection. Our double-blind, placebo-controlled study demonstrated that daily administration of low-dose rimantadine was as well tolerated as placebo was and was highly effective in preventing influenza A virus infection and illness. The 100-mg regimen reduced the rate of influenza A virus illness in our study population (efficacy rate, 86%) and that of influenza A virus infection (efficacy rate, 67%) when compared with the placebo. Studies conducted in the USSR have reported similar efficacies for the 100-mg regimen of rimantadine (17, 24). These prophylactic efficacy rates are also comparable to those for the conventional 200-mg dose observed in placebo-controlled studies in adults given rimantadine for 4 to 6 weeks (10, 18; R. Dolin, R. F. Betts, J. J. Treanor, S. M. Erb, D. H. O'Brien, F. K. Roth, P. Miller, and P. Duffy, Program Abstr. 23rd Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 691, 1983).

Rimantadine is under consideration for licensure for prophylactic use by the Food and Drug Administration. Based on our findings, the 100-mg dose of rimantadine, like low-dose amantadine, could be advocated for short-term prophylaxis during influenza A virus outbreaks. The Immunization Practices Advisory Committee recommends chemoprophylaxis for high-risk adult patients who have not previously received influenza vaccine during epidemics when the influenza vaccine might be ineffective because of antigenic drift in the influenza virus and to supplement protection in patients who may be expected to mount a poor antibody response to vaccination (1, 6).

Naturally occurring influenza A virus strains appear to be susceptible to rimantadine (5). It may be prudent, however, to reexamine the recommendations for chemoprophylaxis in view of recent evidence of the emergence of rimantadine-resistant strains of influenza A virus that have the potential for transmission and for causing disease in household contacts of treated patients (14). During a study in a family setting, rimantadine-resistant strains of influenza A virus were recovered from eight index patients and five household contacts treated with rimantadine (14). Furthermore, the rimantadine-resistant strains appeared to have spread to six contacts with secondary illnesses in family settings (14). In a different study, investigators have attributed the failure of amantadine prophylaxis during an outbreak of influenza A virus illness in a nursing home to the emergence and transmission of drug-resistant strains of virus (E. E. Mast, J. P. Davis, M. W. Harmon, N. H. Arden, R. Circo, and G. E. Tyszka, 29th ICAAC, abstr. no. 65, 1989). In treatment studies in children, rimantadine-resistant strains of influenza A H3N2 virus have also been recovered from up to 45% of children with influenza who were treated for 7 days (13). The studies involving concomitant use of amantadine for treatment and chemoprophylaxis have demonstrated the emergence of drug-resistant strains that appear to be genetically stable and that can cause typical disease even in birds that receive the drug (4, 22). These findings in humans and avian models suggest that rapid selection and apparent transmis-

sion of rimantadine (or amantadine)-resistant influenza A viruses can occur when there is exposure of contacts to treated individuals in a closed environment (14). As yet, there is no evidence from avian studies or clinical trials that suggests that illnesses caused by resistant strains are more severe than those caused by drug-susceptible wild-type strains (14). Nevertheless, it may be prudent to isolate patients with influenza who are receiving antiviral treatment to reduce the likelihood of transmission of drug-resistant strains of influenza A virus (14). There is also evidence from studies in birds that suggests that the combined use of immunization and chemoprophylaxis reduces the mortality caused by transmission of amantadine-resistant strains of influenza A virus (22).

It is not known whether drug resistance occurs during mass chemoprophylaxis (without treatment of ill patients). Amantadine appeared to be highly effective for prophylaxis against influenza A H3N2 virus in a study in a family setting in which the household contacts, but not the index patients, received amantadine (11). In the present study, we did not recover influenza A virus from the rimantadine recipients, whereas five placebo controls did shed influenza A/Leningrad/87-like (H3N2) virus. Our volunteers differed from those in most studies in family settings in which the antiinfluenza drug was ineffective: they were not in close contact with each other, nor were they exposed to patients with influenza who were treated. It is therefore possible that chemoprophylaxis was effective in our study because the naturally occurring strains of influenza A virus that infected our volunteers were susceptible to rimantadine. Antiviral drugs like amantadine and rimantadine that restrict virus replication should lessen the likelihood of transmission of influenza A virus and should prevent illness if they are used appropriately so that drug resistance does not develop. Short-term prophylaxis might be warranted during influenza A virus outbreaks for the following high-risk individuals: first, those who have not received influenza vaccine previously with the provision that individuals who are hospitalized or in closed populations who become ill should be isolated to reduce the possibility of the nosocomial spread of drug-resistant strains and, second, those who have been vaccinated but who may not mount a protective level of antibody because of antigenic drift in the epidemic strain of influenza A virus. Combined treatment and prophylaxis in closed settings should be avoided. Additional studies are needed to assess the ratio of benefit (protection against severe complications of influenza) to risk (selection of drug-resistant strains of influenza A virus capable of causing illness) for chemoprophylaxis with low-dose rimantadine for high-risk patients.

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