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COMPARISON OF AMANTADINE AND RIMANTADINE FOR PREVENTION OF TYPE A (RUSSIAN) INFLUENZA*

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The efficacies of 200 mg daily doses of amantadine and of rimantadine for prevention of infection and illness due to influenza A/USSR/77 (H1N1) virus were compared in a double-blind, placebo-controlled study on a college campus. Frequencies of symptoms that might have been side effects of the drugs were not significantly different from those in placebo recipients. Analyses indicated that the trial was initiated late in the epidemic and that an age-related protective effect against A/USSR virus existed; seroconversion frequencies were 52/139 (37%) among 18–19-year-olds, 33/130 (25%) among 20–21-year-olds, and 5/39 (12.8%) among 22–24-year-olds. Among initially antibody-negative ($<1:4$ in complement fixing and neutralizing tests and $<1:8$ in hemagglutination inhibition tests) 18–19-year-old students, amantadine was associated with significantly fewer seroconversions ($P = 0.01$) and both less infection and milder illness than occurred in placebo recipients ($P<0.05$). Although rimantadine was not accompanied by reduction in frequency of seroconversions in the same age group, illness frequency and severity among seroconverters were significantly reduced when compared to placebo recipients ($P<0.01$). Amantadine and rimantadine appear suitable for use in young adults. Although other studies have suggested greater effectiveness of rimantadine than of amantadine against influenza, no evidence for this was seen in the present study which used both drugs at the same dose.

influenza amantadine rimantadine effectiveness of antiviral humans

INTRODUCTION

Amantadine hydrochloride (1-adamantanamine hydrochloride) and rimantadine hydrochloride (α-methyl-1-adamantane methylamine hydrochloride) are cyclic amines with antiviral activity in vitro and in vivo against strains of type A influenza virus [2, 3, 6–8, 10–12, 14–21]. Both amantadine and rimantadine have been effective in humans when used to prevent or treat infections with several type A viruses [2, 3, 6–8, 10–12, 15, 18, 20, 21]. In most human studies, amantadine was used at a dose of 200 mg daily and rimantadine at 300 mg daily.

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Extensive testing in the Soviet Union has suggested that rimantadine is more effective for prevention and treatment of type A influenza and is better tolerated than amantadine (ref. 21; and Zlydnikov, D.M., personal communication). Tolerance to both drugs appears good, although diverse side effects have been reported [7, 8, 11, 13].

The present study was designed to compare the efficacy of amantadine and rimantadine in preventing H1N1 influenza in a population of young adult university students. Since rimantadine has been reported to be more active in vitro and in laboratory animals at comparable doses [7, 16], identical dosages of 200 mg/day of each drug were used.

MATERIALS AND METHODS

Clinical procedures

Participants in the study were 18–24-year-old students at Texas A & M University, who were free of acute illness at the beginning of the study and for the preceding week, who had no chronic illness, and who were non-pregnant if female. Informed consent was obtained prior to participation.

The study was conducted in a double-blind fashion. A pre-study serum sample was obtained from all participants, and, in a random manner, they were then issued amantadine, rimantadine, or placebo. After a period of 6 weeks, tablets were discontinued and a repeat serum specimen obtained then and two weeks later. Weekly illness and symptom reports were obtained by postcard. Per this postcard the subject was simply asked whether or not illness was present or had occurred in the past week and to list prominent symptoms in a blank space provided on the card. For analysis of data, all non-respiratory symptoms were assumed to be possibly related to drug. Students had been apprised in the written consent of symptoms that might occur from influenza and of symptoms reportedly caused by the study drugs.

444 students began the study, and 308 (70%) provided all illness reports and at least two of the blood specimens. Students not completing the study were equally distributed among the three groups.

Drugs

Amantadine hydrochloride, rimantadine hydrochloride, and placebo were provided by E.I. duPont de Nemours and Company as identical appearing 100 mg tablets. Medication was taken orally in the morning and evening without supervision. Participants were given drug, packaged in 14 tablet amounts, along with postca.ds for weekly reports. Weekly reports included a report of the number of tablets taken; 90–95% of scheduled drug was reported as taken each week. As a further assessment of compliance, an unannounced, random blood sample was taken from 54 volunteers at the end of the second week. Sixteen of the 54 proved to be in the amantadine group; the remainder were in

the rimantadine or placebo groups. D.C. Rakestraw of the E.I. duPont Company kindly agreed to perform serum amantadine levels on those in the amantadine group; an assay for rimantadine was not available. Amantadine was detected in all 16 samples from subjects taking amantadine. Concentrations varied between 0.27 and 1.39 μg/ml, but the interval between the last dose and the blood donation was not recorded.

Virologic and serologic procedures

Throat swab specimens for virus isolation tests were immediately rinsed in veal infusion broth (VIB) which was stored at -70°C until tested for virus. Viral isolation tests were performed in rhesus monkey kidney tissue culture, and hemadsorption-positive cultures were identified using indirect immunofluorescence [1].

Hemagglutination inhibition (HI) and complement fixation (CF) assays for antibody were performed in microtiter plates, as previously described, using whole A/USSR/90/77 virus and RNP antigen, respectively [4]. Tests for serum-neutralizing antibody were performed in microtiter plates, using Madin–Darby canine kidney tissue cultures as previously described [5].

RESULTS

The A/USSR epidemic

Random cultures were obtained from students reporting to the student respiratory disease clinic with febrile respiratory disease; A/USSR virus was isolated during week 7 of 1978, and the study was initiated two weeks later. Retrospective surveillance of respiratory disease clinic visits subsequently indicated that the study was initiated during the peak of clinic visits. Nevertheless, through the first three weeks of drug administration, isolates of A/USSR virus were obtained.

Drug side effects

Students were encouraged to report all symptoms that might be related to drug. Reports of drowsiness, headache, and diarrhea were infrequent and equally distributed in each drug category, whereas other symptoms were primarily associated with amantadine or rimantadine. During the first week, 3% of students reported nausea, vomiting, dizziness, nervousness, trembling, or insomnia. During the remaining weeks, 1–2% reported potential side effects each week. The total number of students with one or more complaints was 12 with placebo, 18 with amantadine, and 24 with rimantadine. Although not significantly different from placebo, symptoms with increased frequency for the two drugs were nausea and vomiting for rimantadine, insomnia for amantadine, and dizziness for both drugs.

Twelve students (2.7%) discontinued drug because of occurrence of some of the side

effects described above; six were taking amantadine, two were taking rimantadine, and four were taking placebo.

Infection and illness

Seroconversion to A/USSR virus occurred in 90/308 (29%) students (Table 1), but there were no differences in frequency of seroconversions among the three drug categories. Because of the possibility that drug was started too late to detect an effect, the relationship between seroconversion and illness occurrence was assessed. Illness with cough was significantly more commonly associated with seroconversion than was absence of illness, and the seroconversion frequency in those with illness without cough was intermediate (Table 1). This indicated that A/USSR virus was active in the study group during the observation period. Nevertheless, the high frequency of seroconversions without an illness (40/182) and the high frequency of illnesses without a seroconversion (76/126) suggested that many A/USSR infections occurred prior to initiation of the study and that other causes of illnesses were also active during the study period.

In an attempt to identify subpopulations exhibiting an influence of drug, results were further evaluated by age and initial antibody. Seroconversion frequencies were highest among 18–19-year-olds (52/139, 37%), intermediate among 20–21-year-olds (33/130, 25%), and lowest among 22–24-year-olds (5/39, 12.8%). Because of the apparent age-related protective effect and low frequency of seroconversions in the 22–24-year-old age group, this group was not further evaluated.

No differences according to age or drug category were noted for 18–21-year-old students who had antibody in the initial serum specimen. A lower frequency of seroconversions, however, occurred among the antibody-negative 18–21-year-olds given amantadine than among those given placebo (12/61 vs. 21/60, $P = 0.06$). When divided into two

TABLE 1

Seroconversion[a] frequencies to A/USSR influenza virus according to drug category and illness occurrences

Group	Frequency Ab rise according to reported illness			Ab rise total group	
	None	Ill without cough	Ill with cough		
Placebo	12/55	8/22	12/22	32/99 (32%)	$P>0.10$
Amantadine	13/65	7/25	8/17	28/107 (26%)	$P>0.10$
Rimantadine	15/62	7/22	8/18	30/102 (29%)	
Total group	40/182 (22%)	22/69 (32%)	28/57 (49%)	90/308 (29%)	
	$P = 0.10$	$P = 0.05$			
	$P<0.001$				

[a] Fourfold or greater rise in titer of complement fixing, hemagglutination inhibiting, or neutralizing antibody.

age groups, it was noted that the apparent protective effect was among 18- and 19-year-olds ($P = 0.01$) (Table 2). Thus, 65% fewer seroconversions occurred among those with the highest attack rate (18–19-year-olds). Although the numbers are small, illness with cough was also reduced among 18–19-year-olds given amantadine (Table 2).

The seroconversion frequency was similar among those given placebo and rimantadine, but only one illness with cough occurred among 18- and 19-year-olds who took rimantadine. Comparison of frequencies of 18- and 19-year-old students with no seroconversion, seroconversion without illness, illness without cough, and illness with cough for amantadine and placebo revealed a statistically significant difference in favor of less infection and milder infection-related illness among students taking amantadine. (Distributions were 26, 2, 2, 1 for amantadine and 15, 6, 2, 5 for placebo, respectively – see Table 2 for derivation – Wilcoxon, $Z = 2.11$, $P<0.05$.) A similar comparison for rimantadine and placebo was not statistically significant (distribution for rimantadine was 17, 11, 6, 1); however, when only illness among seroconverters was compared, illness tended to be less common and severe among those given rimantadine (Wilcoxon, $Z = 3.2$, $P<0.01$).

DISCUSSION

The present study was designed to compare the protective effects of similar dosages of amantadine and rimantadine for influenza caused by A/USSR (H1N1) virus. The results of concurrent tabulation of respiratory disease visits to the health center by other students from the study population suggested that the study was initiated late in the epidemic. Thus, a definitive comparison of the two drugs for preventive effectiveness was not possible. Nevertheless, because A/USSR was isolated from students on campus during the study period, and influenza-like illnesses among study participants was significantly

TABLE 2

Seroconversion[a] frequencies to A/USSR influenza virus among antibody negative students[b] according to age of student, drug category, and illness occurrence

Age	Group	Frequency Ab rise according to illness occurring			Ab rise total group	
		None	Ill without cough	Ill with cough		
18–19	Placebo	6/15	2/5	5/8	13/28	$P = 0.01$
	Amantadine	2/20	2/6	1/5	5/31	$P>0.10$
	Rimantadine	11/20	6/11	1/4	18/35	
20–21	Placebo	2/17	3/9	3/6	8/32	$P>0.10$
	Amantadine	3/19	2/7	2/4	7/30	$P>0.10$
	Rimantadine	2/17	1/4	3/7	6/28	

[a] Fourfold or greater rise in complement fixing, hemagglutination inhibiting, or neutralizing antibody.

[b] Initial serum lacked antibody at 1 : 4 in CF and neutralization tests and 1 : 8 in HI.

related to seroconversion, it should be possible to compare relative efectiveness of th two drugs.

A statistically significant protective effect against infection with influenza A/USSR (H1N1) virus was detected for younger students taking amantadine. Although the numbers were small and not statistically significant, fewer influenza like illnesses occurred among these same students. Similar comparisons for rimantadine did not provide evidence of a protective effect against infection, although fewer influenzal illnesses occurred also in this group. Thus, given the same opportunity, rimantadine was not more effective for prevention of A/USSR infection and illness than amantadine; in fact, amantadine appeared somewhat more effective than rimantadine.

Reports of comparative effectiveness of amantadine and rimantadine in vitro against type A H2N2 viruses and in ferret and mouse studies with an H1N1 and an H2N2 virus, respectively, indicated that rimantadine was more active than amantadine at the same dosage [7, 16]. Similarly, Soviet investigators have indicated that rimantadine was more active in humans for prophylaxis than amantadine for H2N2 and H3N2 infection and illness (ref. 21; and Zlydnikov, D.M., personal communication). No direct comparative studies of the two drugs have been reported for prophylaxis of naturally occurring infection and illness in humans; however, a comparative study of treatment indicated a somewhat greater effectiveness for rimantadine at 300 mg/day than for amantadine at a 200 mg/day dosage [20]. Rimantadine is reported to be well tolerated at the 300 mg/day dose level, so it is possible that equal or greater protection would have occurred in the present study if the high dosage had been used. Amantadine, however, is acknowledged as clearly more toxic at the 300 mg/day dosage and probably not usable for prophylaxis at that dose.

Only 2.4% of students ceased drug because of side effects, and a third of these were taking placebo. The students who visited the health center with reports of side effects did so in the first 48 h of the study. This is reported as the period when side reactions are most likely to occur [9]. Thus, although possibly underestimated in frequency, drug-related side effects were relatively minor in these young adults.

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