ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, July 1984, p. 101–103
0066-4804/84/070101-03$02.00/0

Vol. 26, No. 1

Safety of Prolonged Administration of Rimantadine Hydrochloride in the Prophylaxis of Influenza A Virus Infections in Nursing Homes

PETER A. PATRIARCA,[1]* NANCY A. KATER,[1] ALAN P. KENDAL,[1] DENNIS J. BREGMAN,[1] JOHN D. SMITH,[2] AND R. KEITH SIKES[2]

Division of Viral Diseases, Center for Infectious Diseases, Centers for Disease Control, Atlanta, Georgia 30333,[1] and Georgia Department of Human Resources, Atlanta, Georgia 30334[2]

Received 8 November 1983/Accepted 13 April 1984

We evaluated the safety of rimantadine hydrochloride (RH) prophylaxis in a double-blind, placebo-controlled trial in three nursing homes during a community epidemic of influenza A (H3N2). Although daily monitoring of the 35 participants revealed an association between RH administration (100 mg twice a day) and the development of nausea and anxiety ($P < 0.05$), these and other potential side effects were transient and were rarely considered to be clinically significant. Serum RH levels measured at the end of the trial (mean, 1,159 ng/ml) were nearly three times higher than those measured previously in younger individuals, suggesting that lower dosages may be indicated for the elderly.

The elderly and persons with certain chronic medical conditions have been shown to be at great risk of death or other serious complications after type A influenza infection (1, 4, 7, 8). Influenza vaccine can often provide adequate protection for many of these individuals, but because new strains of influenza A continually emerge, antiviral agents may also be useful under some circumstances.

Amantadine hydrochloride prevents 70 to 90% of influenza type A infections (10), but associated central nervous system side effects raise concerns about its use in the elderly (8). Rimantadine hydrochloride (RH; investigational in the United States), an analog of amantadine, has been shown to be as effective as amantadine in preventing influenza A infections in young, healthy volunteers but with significantly fewer side effects (3). To provide a preliminary evaluation of the safety of RH for elderly, chronically ill individuals, we conducted a double-blind, placebo-controlled trial in three nursing homes during an influenza A (H3N2) epidemic in the community.

(This work was presented in part at the 23rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Las Vegas, Nevada, 1983.)

Candidates for the study were selected from a total population of 405 residents; 298 were considered ineligible for a variety of reasons; these ineligible residents included 119 who had medical conditions that might increase the severity of side effects or require careful adjustments in the dosage of RH based on information available for its analog, amantadine (2). Such conditions included renal impairment (serum creatinine, >2 mg/dl), liver disease, acute congestive heart failure, seizure disorders, psychosis, severe pitting edema, orthostatic hypotension, and conditions requiring central nervous system stimulants. Written informed consent was obtained from 35 (33%) of the remaining 107 patients and their families before the entry of these consenting patients into the study, which had been approved by the Centers for Disease Control, the Georgia Department of Human Resources, and the National Institute of Allergy and Infectious Diseases. The 35 participants, all of whom had been vaccinated the previous autumn, were randomly assigned to receive either RH (100 mg twice a day) or placebo. Serum specimens were collected before the trial began and 3 to 4 h after the last dose of medication.

A sensitive adverse-reaction monitoring system was established to increase the chances of detecting small but statistically significant differences between the study groups. Nursing staff at the three homes, who were most familiar with the residents and their medical conditions, were trained by the investigators to evaluate all participants for 15 signs and symptoms that could represent potential adverse reactions (Table 1) and to record these observations daily.

The 35 participants ranged in age from 68 to 102 years; 18 received rimantadine and 17 received placebo. There were no significant differences between the two study groups in age, sex, race, underlying medical conditions, concurrent medications, or level of required nursing care. The trial began in early January 1983, shortly after the first influenza A (H3N2) viruses were isolated from patients in the community, and ended on 6 April, when influenza activity declined to sporadic levels. Although laboratory-proven infections were also documented at all three nursing homes during this interval, only two of the participants, both of whom had received placebo, were affected. The mean duration of chemoprophylaxis for those residents who completed the trial was 80 ± 4.9 (standard deviation) days.

Clinical manifestations compatible with RH toxicity were reported in 14 RH recipients (78%) and 13 placebo recipients (76%). Potential side effects were reported throughout the trial (Fig. 1); there was no definite temporal relationship between the appearance of any sign or symptom and the duration of prophylaxis (by the exponential and log-normal distributions). A significantly greater proportion of the RH group developed anxiety, nausea, or both compared with the placebo group (Table 1); there was also a significantly greater number of days in which anxiety, nausea, confusion, depression, or vomiting were reported (Table 1). However, most of these and other potential side effects lasted <9 days (Fig. 1) and were seldom so severe that they interfered with the daily activities or care of the residents (see exceptions below).

Of the RH group, two members withdrew after days 5 and 9 because of insomnia, anxiety, or both, which resolved over the next 3 days. A third member with an underlying idiopathic seizure disorder (not recorded in medical records available when the study began) suffered a generalized

* Corresponding author.

TABLE 1. Signs and symptoms compatible with adverse reactions to rimantadine prophylaxis trial at Atlanta area nursing homes

Sign or symptom[a]	No. of patients[b] (%) treated with:		Total no. of episodes[c] per 100 patient-days of observation		Total no. of days present per 100 patient-days of observation		Median duration of each episode[c] in days (range)	
	Rimantadine	Placebo	Rimantadine	Placebo	Rimantadine	Placebo	Rimantadine	Placebo
Anxiety	9[d] (50)	3 (18)	1.27	0.46	4.26[e]	2.46	3.0 (1–8)	2.0 (1–21)
Confusion	2 (11)	4 (24)	0.71	0.54	5.41[e]	1.77	2.0 (1–32)	1.5 (1–15)
Depression	4 (22)	1 (6)	0.71	0.31	5.77[e]	3.16	5.5 (2–42)	3.0 (3–21)
Insomnia	3 (17)	2 (12)	0.80	0.31	1.33	0.54	2.0 (1–3)	1.0 (1–3)
Fatigue	6 (33)	6 (35)	1.24	1.39	8.43	9.54	3.0 (1–23)	2.5 (1–47)
Dizziness	2 (11)	2 (12)	0.18	0.15	0.27	0.15	1.5 (1–2)	1.0 (1)
Anorexia	6 (33)	5 (29)	1.51	1.08	6.57	4.62	1.5 (1–13)	1.0 (1–21)
Nausea	6[d] (33)	1 (6)	0.62[e]	0.08	1.42[e]	0.08	3.5 (1–8)	1.0 (1)
Vomiting	2 (11)	1 (6)	0.18	0.08	0.62[e]	0.08	1.0 (1–6)	1.0 (1)
Weight loss ≥5%	3 (17)	2 (12)						

[a] Participants were also monitored for the development of psychosis, hallucinations, urinary retention, postural hypotension, and congestive heart failure, but no episodes were reported in either group.
[b] Number per group: rimantadine, 18; placebo, 17.
[c] Defined as 1 day or a series of consecutive days in which the sign or symptom was observed.
[d] Significantly higher compared with the placebo group ($P < 0.05$; Fisher's exact test [one-tailed]).
[e] Significantly higher compared with the placebo group ($P < 0.05$; chi-square test).

convulsion of undetermined etiology after 10 days of RH prophylaxis. Of the remaining 14 members, 3 later withdrew for reasons unrelated to side effects, as did 2 of 17 placebo recipients.

Serum specimens from 14 RH recipients, obtained 3 to 4 h after the last dose, showed drug levels ranging from 634 to 2,602 ng/ml (kindly measured by H. E. Hoffman, E. I. du Pont de Nemours & Co., Inc., Newark, Del.). The mean level (1,159 ± 563 [standard deviation]) was nearly three times higher than those measured in young adults who had been on the same regimen for 5 days (H. E. Hoffman, personal communication). There was no correlation between serum RH concentration and the presence or duration of side effects, the age of the resident, or the category of underlying disease.

In summary, we report a statistically significant associa-

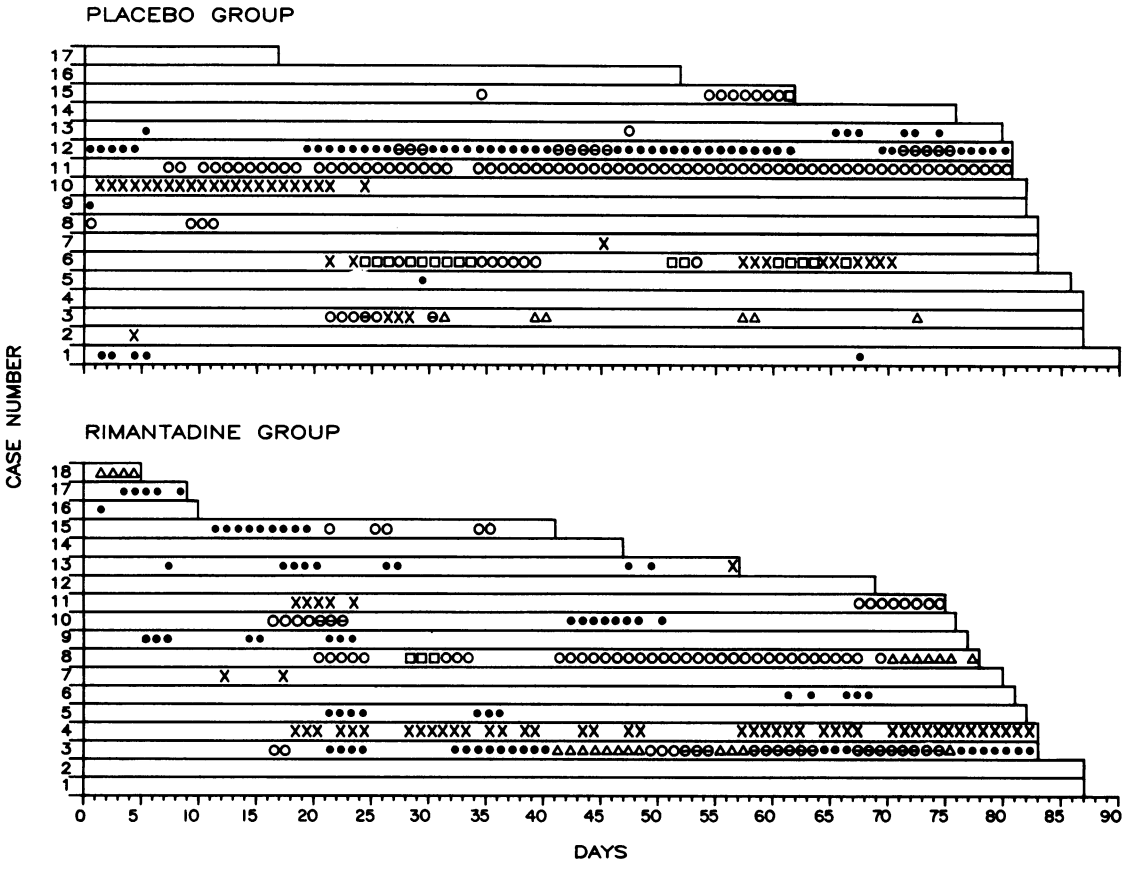

FIG. 1. Possible central nervous system involvement, gastrointestinal illness, or other side effects by day of therapy. Symbols: ●, central nervous system; X, gastrointestinal illness; ○, other; ⊖, central nervous system plus other; □, gastrointestinal illness plus other; △, central nervous system, gastrointestinal illness, plus other.

tion between RH administration and the development of nausea and anxiety in selected elderly patients. This finding and the observation that the most troublesome side effects appeared during the first 10 days of prophylaxis are consistent with those results reported in controlled trials involving young, healthy subjects in both the Soviet Union (9) and the United States (3, 5, 16, 11, 12), and suggest, in spite of the small number of participants, that our monitoring system had sufficient specificity and sensitivity to detect bona fide adverse reactions. Nevertheless, we also found that such reactions were transient and only seldom considered clinically important, providing preliminary evidence that RH can be relatively well tolerated in selected elderly patients. On the basis of our preliminary observation that serum RH levels may be significantly higher in the elderly compared with younger persons, additional pharmacokinetic studies appear desirable to determine whether lower dosages should be prescribed for this age group. If so, an even lower risk of side effects might be expected, based on an earlier study in young adults (6). Larger trials will be needed to evaluate the safety of rimantadine in patients with medical conditions for which they were excluded in the present study and to help clarify the epidemiological and clinical circumstances in which the drug might prove to be most beneficial.

We thank the Georgia Health Care Association and the administrators, nursing staff, and attending physicians of the Wesley Woods, Snellville, and Christian City convalescent centers for their cooperation and assistance; Gary R. Noble for advice; and Tommi Munro, Alice Reed, Ruth Ann Tucker, Faye Cowart, and Teresa Ratajczak for laboratory support.

LITERATURE CITED

1. **Alling, D. W., W. C. Blackwelder, and C. H. Stuart-Harris.** 1981. A study of excess mortality during influenza epidemics in the United States, 1968-1976. Am. J. Epidemiol. **113**:30–43.
2. **American Medical Association.** 1983. Agents used to treat viral infections, p. 1451–1464. *In* J. C. Ballin (ed.), AMA drug evaluations. American Medical Association, Chicago.
3. **Dolin, R., R. C. Reichman, H. P. Madore, R. Maynard, P. N. Linton, and J. Webber-Jones.** 1982. A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. N. Engl. J. Med. **307**:580–584.
4. **Eickhoff, T. C., I. L. Sherman, and R. E. Serfling.** 1961. Observations on excess mortality associated with epidemic influenza. J. Am. Med. Assoc. **176**:776–782.
5. **Hayden, F. G., J. M. Gwaltney, Jr., R. L. Van de Castle, K. F. Adams, and B. Giordani.** 1981. Comparative toxicity of amantadine hydrochloride and rimantadine hydrochloride in healthy adults. Antimicrob. Agents Chemother. **19**:226–233.
6. **Hayden, F. G., H. E. Hoffman, and D. A. Spyker.** 1983. Differences in side effects of amantadine hydrochloride and rimantadine hydrochloride relate to differences in pharmacokinetics. Antimicrob. Agents Chemother. **23**:458–464.
7. **Housworth, J., and A. D. Langmuir.** 1974. Excess mortality from epidemic influenza. 1957-1966. Am. J. Epidemiol. **100**:40–48.
8. **Immunization Practices Advisory Committee.** 1983. Influenza vaccines 1983-1984. Morbid. Mortal. Weekly Rep. **32**:333–337.
9. **Karpukhin, G. I., E. G. Shvetsova, and A. M. Malysheva.** 1979. Results of long-term study of the efficacy of emergency prophylaxis of influenza by means of rimantadine. Epidemiological observations, p. 91–122. *In* G. I. Karpukhin (ed.), The problems of influenza and acute respiratory diseases. Medicina, Leningrad.
10. **National Institute of Allergy and Infectious Diseases.** 1980. Amantadine: does it have a role in the prevention and treatment of influenza A. A National Institutes of Health Consensus Development Conference. Ann. Intern. Med. **92**:256–258.
11. **Quarles, J. M., R. B. Couch, T. R. Cate, and C. B. Goswick,** 1981. Comparison of amantadine and rimantadine for prevention of type A (Russian) influenza. Antiviral Res. **1**:149–155.
12. **Van Voris, L. P., R. F. Betts, F. G. Hayden, W. A. Christmas, and R. G. Douglas.** 1981. Successful treatment of naturally occurring influenza A/USSR/77 H1N1. J. Am. Med. Assoc. **245**:1128–1131.