

Comparison of Central Nervous System Adverse Effects of Amantadine and Rimantadine Used as Sequential Prophylaxis of Influenza A in Elderly Nursing Home Patients

Linda A. Keyser, PharmD; Margaret Karl, RPh; Anne N. Nafziger, MD, MHS; Joseph S. Bertino, Jr, PharmD

Background: Amantadine hydrochloride and rimantadine hydrochloride are recommended by the Centers for Disease Control and Prevention for prophylaxis of influenza A. While data suggest that rimantadine is better tolerated, there are no data examining the rate of adverse reactions in elderly patients who receive amantadine vs rimantadine. Our objective was to assess the adverse reaction rate in elderly nursing home patients receiving sequential amantadine and rimantadine for influenza A prophylaxis.

Methods: Data were collected in 156 nursing home patients (70% women; mean \pm SD age, 83.7 \pm 10.1 years) in a single care setting who received sequential therapy with amantadine and rimantadine during the 1997-1998 influenza season. Patients were assessed for central nervous system adverse effects and therapy discontinuation occurring with each agent.

Results: Twenty-nine (18.6%) of the 156 patients experienced an adverse effect when receiving amantadine

compared with 3 patients (1.9%) when rimantadine was given ($P < .01$). Drug use was discontinued due to adverse events in 17.3% ($n = 27$) of the amantadine courses and 1.9% ($n = 3$) of the rimantadine courses ($P < .001$). Confusion was the most frequently observed adverse event (amantadine, 10.6%; rimantadine, 0.6%; $P < .001$). Multivariate logistic regression analysis showed that significant risk factors for central nervous system adverse events included male sex (odds ratio, 3.65), reduced calculated creatinine clearance (odds ratio, 1.78), and use of amantadine (odds ratio, 12.73).

Conclusions: Amantadine use was associated with a significantly higher incidence of central nervous system adverse events than rimantadine use in this elderly population receiving influenza prophylaxis. In addition, the discontinuation rate of amantadine was significantly higher than that with rimantadine.

Arch Intern Med. 2000;160:1485-1488

From the University of Colorado School of Pharmacy, Denver (Dr Keyser), and the Department of Pharmacy Services (Ms Karl and Dr Bertino), the Department of Medicine (Drs Nafziger and Bertino), The Research Institute (Drs Nafziger and Bertino), and the Clinical Pharmacology Research Center (Drs Nafziger and Bertino), Bassett Healthcare, Cooperstown, NY.

INFLUENZA A is a common cause of serious respiratory illness in the elderly population.¹ Among persons aged 65 years and older, rates of hospitalization for influenza range from 200 to more than 1000 per 100 000 population.¹ Immunization with influenza vaccine has been shown to be 50% to 60% effective in preventing hospitalization and pneumonia, 80% effective in preventing death, and 30% to 40% effective in preventing disease in elderly populations. However, because of the limited effectiveness of the vaccine, chemoprophylaxis is often indicated during suspected or confirmed outbreaks.¹

Two antiviral agents are approved for influenza prophylaxis, amantadine hydrochloride and rimantadine hydrochloride. While both agents are effective in the prophylaxis of influenza A, amantadine appears to cause more central nervous system (CNS) adverse effects (AEs)

than rimantadine.¹⁻³ To date, there are no data in elderly nursing home patients on the comparative toxicity of these agents. Since the cost of amantadine is significantly less than that of rimantadine, amantadine continues to have high usage in the nursing home setting. If in fact a high incidence of AEs occurs with amantadine use, this could lead to excessive discontinuation rates and possibly put patients at risk of developing influenza A.

During the 1997-1998 influenza season, residents at a rural Upstate New York nursing home received amantadine and rimantadine sequentially during a suspected and a documented influenza A outbreak. For each agent, we assessed the incidence of CNS AEs in this cohort of patients and attempted to identify risk factors for AEs. In addition, we evaluated the rate of discontinuation of drug secondary to AEs.

PATIENTS AND METHODS

This was a retrospective cohort study to assess the AEs of antiviral administration given as prophylaxis for influenza A. The study population included 167 residents of an Otsego County, New York, long-term care facility for the elderly. All residents received influenza vaccine in October to November 1997. In January 1998, an influenza A outbreak occurred in the community and several residents of the nursing home developed symptoms consistent with influenza infection. Cultures were obtained; however, none were positive. A planned 24-day course of amantadine for prophylaxis was begun for all residents. Dosage adjustment (**Table 1**) was done using creatinine clearance (ClCr) calculated with the following equation⁴:

$$\text{ClCr} = [(140 - \text{Age})(\text{Ideal Body Weight})] / (72 \times \text{Scr})$$

(multiplied by 0.85 for women),

where ClCr is given in milliliters per minute per 1.73 square meters, Scr indicates serum creatinine in milligrams per deciliter, and weight in kilograms. In February 1998, approximately 1 week after completion of the amantadine course, a confirmed influenza A (via positive cultures) outbreak occurred in the nursing home. At this time, the New York State Department of Health mandated that all patients receive rimantadine hydrochloride, 100 mg/d, for 28 days.

Nursing staff were in-serviced by a pharmacist before the initiation of antiviral therapy. The regular nursing staff at the facility collected detailed information on the clinical course of each patient during both the amantadine and rimantadine treatment periods. All CNS AEs (including new-onset agitation, aggression, confusion, decreased coordination, hallucinations, lethargy, paranoia, seizures, and tremors) were carefully documented. Patients were assessed daily for CNS AEs (while receiving therapy) with the information (presence or absence of CNS AEs and a description of such) recorded in the patient chart.

Data collected for this study included age, sex, weight, height, current CNS disease states (eg, history of seizures, stroke, and transient ischemic attack), dose of amantadine and rimantadine, duration of antiviral therapy, concurrent CNS active medications, reason for drug discontinuation before the planned course of therapy was completed, and all noted CNS AEs.

Only patients who received both of the antiviral agents were included in the analysis. Data were analyzed using SAS version 6.08 software.⁵ The McNemar test was used for categorical variables. The paired *t* test was used to examine duration of therapy. Multivariate stepwise logistic regression analysis was used (using the demographic, underlying disease, and concurrent CNS drug therapy data) to evaluate risk factors for AEs and for early discontinuation of therapy. When significant risk factors were found by logistic regression analysis, interaction terms were examined. $P \leq .05$ was considered significant. Data are presented as mean \pm SD.

Table 1. Dosing Scheme for Amantadine Use in Study Patients

Calculated Creatinine Clearance*	Maintenance Dosage
≥ 0.83 (≥ 50) (Patients <65 years old)	100 mg twice a day
≥ 0.83 (≥ 50) (Patients ≥ 65 years old)	100 mg/d
0.50-0.82 (30-49)	200 mg on day 1 then 100 mg/d
0.25-0.49 (15-29)	200 mg on day 1 then 100 mg every other day
<0.25 (<15) (and patients receiving hemodialysis)	200 mg every 7 d

*Given in units of milliliters per second per 1.73 square meters (milliliters per minute per 1.73 square meters).

RESULTS

Of a total of 167 patients at the nursing facility, 156 patients received amantadine therapy followed by rimantadine therapy. Eleven patients died, either during amantadine therapy or between the time of drug therapies. Of the patients who died during amantadine therapy, none had positive cultures for influenza A. **Table 2** gives the demographic data on the 156 patients included in the analysis.

The average duration of therapy in all patients was 20.6 ± 6.7 days for amantadine and 26.3 ± 5.3 days for rimantadine ($P = .21$). Duration of therapy in patients who experienced CNS toxic effects was 10.9 ± 4.4 days in the amantadine group and 16.3 ± 10.6 in the rimantadine group. For patients who did not have toxic reactions, duration of therapy for amantadine was 22.6 ± 5.1 days and for rimantadine, 26.5 ± 5 days ($P \leq .05$ vs patients with toxic effects for each drug).

Table 3 outlines the concurrent CNS conditions and CNS active medications for the 156 patients. One hundred five (67%) of the residents were receiving 1 CNS active medication. Forty-one (26%) of the residents were taking multiple CNS medications. No additional CNS active medications were noted to be used during the study period (ie, opioids, antihistamines, antiemetics). There was no change in concurrent CNS conditions or use of CNS active medications during the amantadine or rimantadine treatment periods.

Table 4 shows the comparative CNS AEs seen during amantadine and rimantadine therapy. Significant differences were seen in the total number of patients with CNS-related AEs and those requiring drug discontinuation in the amantadine vs the rimantadine treatment periods ($P < .001$). Significant differences were seen in rates of confusion ($P < .001$) during the treatment periods. No falls were reported in either group during either treatment phase. In addition, no hospitalizations or aspiration pneumonia episodes resulted from CNS AEs.

Table 5 gives the results of the multivariate analyses of risk factors for CNS AEs and for drug discontinuation due to CNS AEs. Male sex and antiviral agent used were the most important risk factors for both CNS AEs and for drug discontinuation due to CNS AEs. In addition, reduced creatinine clearance was a risk factor for

Table 2. Characteristics of 156 Nursing Home Patients Treated With Amantadine and Rimantadine During the Study Period

Characteristic	Value*
Age, y	83.7 ± 10.1
Sex, % of patients	
Male	30
Female	70
Serum creatinine, μmol/L (mg/dL)	91.7 ± 83.3 (1.1 ± 1.0)
Total body weight, kg	61.8 ± 14.7
Ideal body weight, kg	56.1 ± 10.2
ClCr†	0.68 ± 0.32 (41.1 ± 19.3)

*Data are given as mean ± SD, except for sex.

†ClCr indicates calculated creatinine clearance (given in units of milliliters per second per 1.73 square meters [milliliters per minute per 1.73 square meters]).

Table 3. Percentage of Elderly Nursing Home Population With Concurrent CNS Conditions or Receiving CNS Active Medications*

Variable	% of Study Population
CNS conditions	
Dementia, unknown cause	32.7
Cerebrovascular disease	15.7
Alzheimer disease	9.0
Seizure disorder	7.7
Mental retardation	2.6
Transient ischemic attack	0.3
Receiving CNS active medications	
Antihypertensive agents	46.4
Anticonvulsant agents	15.2
SSRIs	17.3
Antipsychotic agents	13.5
Tricyclic antidepressants	12.2
Benzodiazepines	6.4
Histamine ₂ blockers	5.1
Antiparkinson agents	2.6

*CNS indicates central nervous system; SSRIs, selective serotonin reuptake inhibitors.

CNS AEs. No interaction terms were significant for either of the 2 logistic regression analyses.

Since the presumed influenza outbreak during the amantadine treatment phase was never proved by culture, no comparative efficacy data could be gathered from this analysis.

COMMENT

While immunization against influenza remains the primary method of prevention, chemoprophylaxis with amantadine or rimantadine is recommended in high-risk elderly patients during influenza outbreaks.¹ It is known that amantadine has a high AE rate in elderly patients. No comparative CNS toxicity data of amantadine to rimantadine (in the same persons) were available prior to this study. High rates of CNS AEs (18.6%) were seen in the amantadine treatment period compared with the

Table 4. Percentage of Study Population (N = 156) Manifesting Adverse CNS Effects With Amantadine or Rimantadine Therapy*

Adverse Effect†	% of Patients			Odds Ratio (95% CI)
	Amantadine	Rimantadine	P‡	
Patients with any AE	18.6	1.9	.01	2.63 (1.20-4.06)
Drug D/C due to AE	17.3	1.9	.01	2.57 (1.13-4.01)
Agitation	4.5	1.3	.05	...
Aggression	0.6	0.6	.56	...
Confusion	10.3	0.6	.001	2.77 (0.75-4.79)
Decreased coordination	0.6	0.6	.50	...
Hallucinations	3.9	0	.35	...
Lethargy	1.3	0.6	.15	...
Paranoia	0.6	0.6	.31	...
Seizures	1.3	0	.15	...
Tremors	1.9	0	.08	...

*CNS indicates central nervous system; AE, adverse effects; CI, confidence interval; D/C, discontinuation; and ellipses, not applicable.

†No falls were reported in any patient.

‡P value for amantadine compared with rimantadine using the McNemar test.

Table 5. Multivariate Analyses of Risk Factors for CNS Adverse Effects and for Drug Discontinuation Due to CNS Adverse Effects*

Variable	Odds Ratio (95% CI)	P
Risk Factors for CNS Adverse Effects With Drug Use		
Male sex	3.65 (2.82-4.48)	.002
ClCr	1.78 (1.24-2.32)	.04
Use of amantadine	12.73 (11.50-13.96)	<.001
Risk Factors for Drug Discontinuation Due to CNS Adverse Effects		
Male sex	2.36 (1.56-3.16)	.04
Use of amantadine	11.0 (9.78-12.22)	<.001

*CNS indicates central nervous system; CI, confidence interval; and ClCr, calculated creatinine clearance.

rimantadine treatment period (1.9%; $P < .01$). Risk factors for CNS AEs include male sex, use of amantadine, and reduced calculated creatinine clearance. Clinically, it is commonplace to use an equation and serum creatinine level to calculate creatinine clearance to dose drugs. Since a calculated creatinine clearance was used, it is possible that the equation may have overestimated actual creatinine clearance. Thus, patients with poor renal function may have gotten a comparatively large dose of amantadine. Drug discontinuation was deemed necessary due to CNS AEs in 17.3% of the patients receiving amantadine vs 1.9% of those receiving rimantadine ($P < .01$). It is not surprising that risk factors for drug discontinuation were the same as for occurrence of AEs (male sex and use of amantadine). While amantadine and rimantadine are equally efficacious in preventing influenza A,^{1,6} early discontinuation due to AEs may potentially put a patient or patient population at risk for developing influenza.

Small studies in healthy volunteers have not shown a difference in CNS AEs with the use of amantadine vs rimantadine.⁷ However, other larger studies have shown that amantadine is associated with a higher rate of CNS

AEs than rimantadine. Dolin et al⁶ found amantadine CNS AE rates to be 13% vs 6% and 4%, respectively, in young adults receiving rimantadine or placebo for influenza A prophylaxis. Data from Hayden et al⁸ suggest that the AEs seen with each of these antiviral agents relate to plasma concentrations. We did not measure plasma concentrations of these agents in this study.

The limitations of our trial include retrospective data collection and sequential vs randomized method of administration of the agents. Patients were cared for by the same individuals during both treatment periods. Data were extracted from the nursing progress notes by one investigator and in all cases when the drug was discontinued there was accurate documentation for the reasons for discontinuation. In addition, we are not able to determine the cost implications of the higher incidence of CNS AEs with amantadine vs rimantadine.

CONCLUSIONS

Our data indicate that amantadine causes significantly more CNS AEs in elderly nursing home patients than does rimantadine. In addition, these AEs often lead to discontinuation of amantadine therapy, possibly putting the patient at risk for influenza infection and its attendant morbidity. A pharmacoeconomic analysis could be useful in deciding which agent to use in the elderly patient. However, based on AE rates, rimantadine may be the drug of choice in elderly patients who need chemoprophylaxis for influenza A.

Accepted for publication September 22, 1999.

Presented at the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, Calif, September 26, 1998.

We would like to thank the nursing staff of the Otsego County Nursing Home (The Meadows), Cooperstown, NY, for their documentation efforts.

Reprints: Joseph S. Bertino, Jr, PharmD, Clinical Pharmacy Services, Co-Director, Clinical Pharmacology Research Center, Bassett Healthcare, 1 Atwell Rd, Cooperstown, NY 13326 (e-mail: jbertino@iex.net).

REFERENCES

1. Advisory Committee on Immunization Practices. Prevention and control of influenza. *MMWR Morb Mortal Wkly Rep*. 1998;47(RR-6):1-26.
2. Guay DRP. Amantadine and rimantadine prophylaxis of influenza A in nursing homes. *Drugs Aging*. 1994;5:8-19.
3. Tominack RL, Hayden FG. Rimantadine hydrochloride and amantadine hydrochloride use in influenza A virus infections. *Infect Dis Clin North Am*. 1987;1:459-479.
4. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.
5. *SAS User's Guide*. Cary, NC: SAS Institute; 1985.
6. Dolin R, Reichman RD, Madore HP, Maynard R, Linton PN, Webber-Jones J. A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. *N Engl J Med*. 1982;307:580-584.
7. Millett VM, Dreisbach M, Bryson YJ. Double-blind controlled study of central nervous system side effects of amantadine, rimantadine and chlorpheniramine. *Antimicrob Agents Chemother*. 1982;21:1-4.
8. Hayden FG, Hoffman HE, Spyker DA. Differences in side effects of amantadine hydrochloride and rimantadine hydrochloride relate to differences in pharmacokinetics. *Antimicrob Agents Chemother*. 1983;23:458-464.