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A Comparison of Acetaminophen and Rimantadine in the Treatment of Influenza A Infection in Children

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Rimantadine was compared with acetaminophen in a double-blind randomly assigned therapeutic trial in 63 children presenting with influenzal symptoms. Forty-nine of the children were proven to have influenza A by culture on presentation. Forty-three of the cultures, 88%, were influenza A/H1N1 strains. Both drugs were well tolerated. Rimantadine lowered the amount of virus shed in the first 2 days after initiation of therapy. Clinical resolution of illness was not different between the two therapeutic modalities. In individuals who shed virus for 4 days, strains recovered on the last day were relatively resistant to rimantadine.

Key words: antiviral, A/H1N1, A/H3N2

INTRODUCTION

Rimantadine is a drug of demonstrated value in the prophylaxis of influenza A infections in adults (Dolin et al, 1982). It is potentially a valuable drug in the treatment of influenza A infections. Its congener, amantadine, is a licensed antiviral drug that has not gained widespread acceptance in spite of demonstrated prophylactic and therapeutic effectiveness. This lack of acceptance is in part because of a low but definable frequency of transitory neurologic complications, most frequently insomnia and inability to concentrate (NIHCDC, 1980; Dolin, 1979; Wright et al, 1976; Bryson et al, 1980). Rimantadine, in placebo controlled trials, appears to be as effective as amantadine in the prophylaxis of influenza A infections and has no greater risk of neurologic complications than placebo (Dolin et al, 1982; LaMontagne and Galasso, 1978; Couch and Jackson, 1976). This study determines the therapeutic efficacy and adverse effects of rimantadine in the treatment of ambulatory children with acute influenza A infection compared to standard symptomatic therapy with acetaminophen.

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MATERIALS AND METHODS

Children in a general pediatric practice presenting with typical influenza illness of less than 48 hours duration were enrolled in the study. Eligible children were 1 to 12 years of age and had no underlying chronic diseases. Oral and written parental and participant (over 7 years of age) consent was obtained after the proposal was approved by the Vanderbilt Committee for the Protection of Human Subjects.

After a physical examination and a review of the presenting illness, the children were randomly assigned in a double-blind fashion to one of two treatment groups: 1) rimantadine (E.I. duPont de Nemours, Wilmington, Delaware) (6.6 mg/kg/day given orally every 12 hours up to a maximum daily dose of 200 mg) plus a placebo for acetaminophen; or 2) acetaminophen (McNeil Consumer Products Company, Fort Washington, Pennsylvania) (10 mgm/kg/day given orally every 6 hours up to a maximum of 360 mgm/day) plus a placebo for rimantadine. Placebos for both drugs were used since the timing and dosage of acetaminophen and rimantadine differed. The drugs were administered for a total of 5 days. All drugs left over at the end of the study period, including placebos, were collected, measured for volume, and then compared with the amounts prescribed and reportedly given each subject.

At the initial visit, the mother was given a clinical thermometer, instructed in its use and requested to take the child's oral temperature at 7 A.M. and 12, 4, 8, and 11 P.M. daily. On the subsequent 4 days, a nurse visited the child in the home to obtain a history of symptoms in the prior 24 hours, perform a physical examination, and collect a nasal wash, using a 1-ounce tapered bulb (eye-ear syringe) (Hall and Douglas, 1975). Two to 5 ml of saline were instilled and collected from each nostril by a single squeeze of the bulb. The nasal washes were inoculated unfrozen on a canine kidney cell line (MDCK) for isolation and identification of influenza.

A plaque titration of virus in the original nasal wash was done (Meguro et al, 1979; Hayden et al, 1980). Rimantadine sensitivity was evaluated using a plaque reduction assay and also a reduction in hemagglutinin yield during a single cycle infection (Scholtissek and Faulkner, 1979). Concentrations up to 25 μg/ml of rimantadine in the assay were utilized; higher concentrations were toxic to the cell sheet. Blood for serology was not collected.

For analysis of illness scores (0–3 points) based on severity of each individual sign or symptom were grouped into four symptom complexes: respiratory (cough, coryza, sore throat, hoarseness), systemic (headache, anorexia, malaise), gastrointestinal (nausea, vomiting, abdominal pain), and side effects possibly attributable to rimantadine (insomnia, irritability, behavior changes) in order to derive a symptom score for each illness. Individual symptoms most typically associated with influenza — cough, coryza, headache, and malaise — were examined in a similar manner. Data analysis was completed before the code was broken, using Fishers' Exact two-tailed tests, mean, geometric mean, frequency distribution, and chi square analysis.

RESULTS

During a 2-week period between 3/14–3/31/83, sixty-three children were enrolled in the study. Thirteen children were between 1–3 years, 23 were 4 to 6 years, 16 were 7 to 9 years, and 11 children were 10 to 12 years old. Thirty-four children received acetaminophen and twenty-nine children received rimantadine. Subject com-

pliance was similar in the two treatment groups. Three children in the rimantadine group did not complete the full dosage regimen because of nausea [2] or a suspected allergic rash [1]. Five were considered noncompliant because they took less than 75% of the prescribed amount. Similarly, two children in the acetaminophen group discontinued their regimen because of nausea [1] and persistent fever [1], and five children took less than 75% of their drug.

Of 63 children enrolled, influenza A was isolated from 49. The predominant serotype was H1N1 (43 children). Six isolates were H3N2, and two children with predominantly H1N1 infection had H3N2 isolated on at least 1 day during the illness, suggesting a mixed infection. Of the initial positive isolates, 24 were from patients who received rimantadine, and 28 were from patients who received acetaminophen. An equal distribution of influenza A serotypes occurred between each treatment group. The 13 children with negative nasal wash cultures for influenza A and a child with culture proven influenza B infection had the same clinical presentation and course as the remaining 49 children with documented influenza A infection.

The clinical data were analyzed, focusing on those 49 children with confirmed influenza A isolates. A two-tailed t-test assessed differences in symptom scores for each treatment group. Missing variables were not included in analysis. No statistical differences in initial symptom complex, severity or course of illness between the treatment groups were observed (Table I). The illness resolved rapidly with most children returning to school within 48 hours of the onset of symptoms. Since high fever is characteristic of influenza infections, mean temperatures at 4-hour intervals after initiation of drug were analyzed by two-tailed t-test to detect differences between groups (Fig. 1). Both treatment groups presented with very similar mean Fahrenheit (F) temperatures (101.8 F for rimantadine and 101.2 F for acetaminophen). At 4 and 8 hours after presenting to the office, the rimantadine group showed a higher mean temperature by 1.5 F and 0.8 F, respectively. In spite of this apparent difference, no statistical differences in fever were evident between the two groups. In a comparison of the H3N2 and H1N1 infections, respiratory symptoms appeared more persistent in those with H3N2 infection than those with H1N1, however, statistical differences were not demonstrated.

The number of children shedding influenza A virus was significantly less with rimantadine than acetaminophen on days 1 ($p < 0.01$) and 2 ($p < 0.005$) after initiation of therapy (Fig. 2). The two-tailed t-test also demonstrated a significant

TABLE I. A Comparison of Mean Symptom Scores During the Course of Influenza A Infection by Treatment*

Symptom complex	Group	No. subjects	Treatment days 0	1	2	3	4
Respiratory	Rimantadine	(24)	3.4	3.2	2.3	1.8	1.1
	Acetaminophen	(25)	3.6	3.3	2.3	1.7	1.7
Systemic	Rimantadine	(24)	4.4	2.3	1.12	0.47	0.25
	Acetaminophen	(25)	4.3	1.6	0.76	0.05	0.03
Gastro-intestinal	Rimantadine	(24)	0.9	0.9	0.2	0.4	0.1
	Acetaminophen	(25)	0.6	0.2	0.2	0.1	0.08
Drug-related	Rimantadine	(24)	0.04	0.3	0.10	0.2	0.1
	Acetaminophen	(25)	0.2	0.3	0.3	0.1	0.04

*No statistical differences in initial symptom complex, severity, or course of illness between treatment groups.

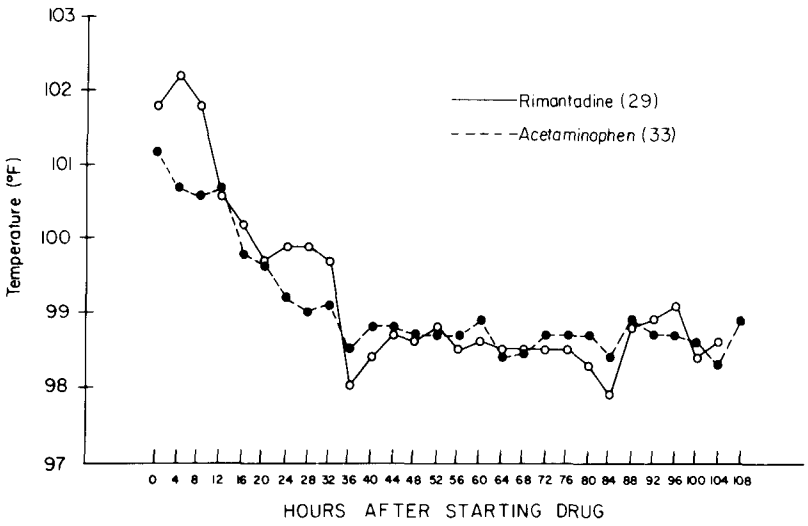

Fig. 1. Mean 4-hour interval temperatures after initiation of therapy.

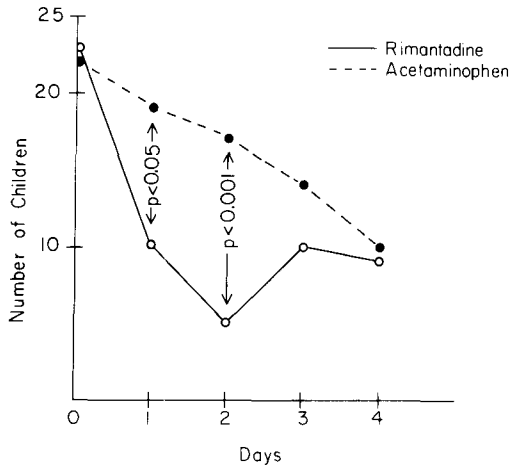

Fig. 2. Influenza A virus shedding after initiation of therapy.

reduction of the geometric mean titer (GMT) of influenza A on days 1 and 2 of those shedding virus who were receiving rimantadine.

With treatment groups combined, there was a significantly greater ($p < .05$) GMT of H3N2 virus shed on all days (Fig. 3) when compared with H1N1. There was constant H3N2 shedding during the 4 days of followup in the three patients receiving acetaminophen. The three H3N2 infected rimantadine-treated patients had a lower GMT on days 1 and 2 with an increase in shedding on day 4 compared to the level seen in the acetaminophen recipients. Compliance was not a factor in the late increase of shedding in the rimantadine treated group because all subjects infected with the H3N2 serotype were compliant in both treatment groups.

The two assays of rimantadine sensitivity gave comparable results although the hemagglutination yield assay gave lower mean inhibitory concentration of drug. In

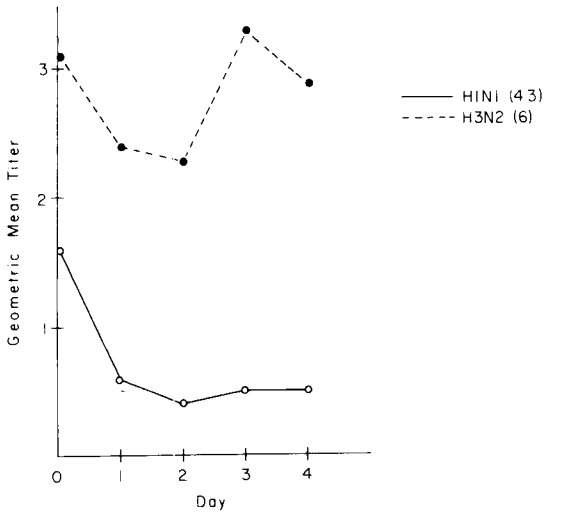

Fig. 3. Geometric mean titer of H1N1 and H3N2 virus shed on indicated day. All differences significant by chi square analysis ($p < 0.05$).

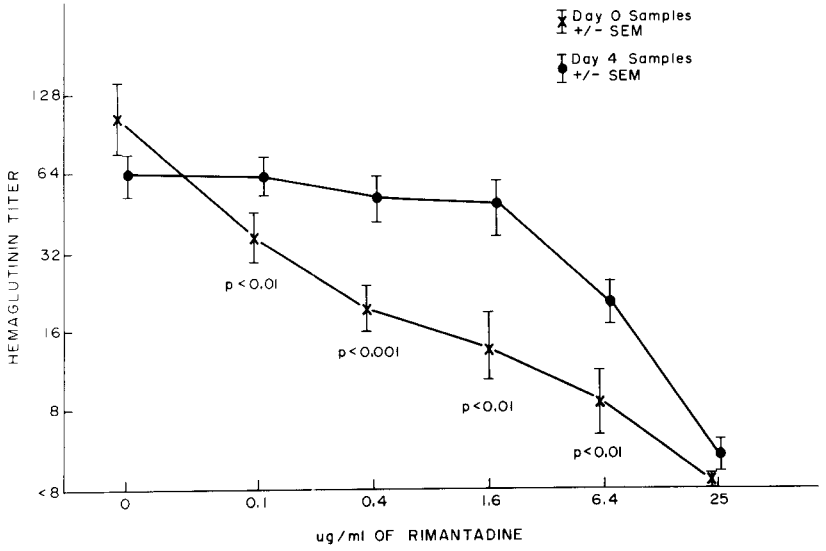

Fig. 4. Rimantadine sensitivity as determined by hemagglutination yield assay on 11 children (seven acetaminophen treated, four rimantadine treated). Significant differences determined by two-tailed t-test.

both assays done on 11 children shedding virus through day 4 there was an increase in rimantadine resistance in the virus shed on day 4 when paired with the initial isolates from the same patients. This in vitro rimantadine resistance was observed in both rimantadine and acetaminophen treated groups (Fig. 4).

DISCUSSION

The accuracy of physician diagnosis of influenza during periods when influenza A virus has been identified in the community was evident by growing the virus in

79% of clinically diagnosed children. The illness caused by the H1N1 serotype was quite mild with rapid resolution in most children in 24 to 48 hours.

A collaboratively designed project, in Rochester, N.Y., demonstrated illness of considerably greater severity with an H3N2 epidemic studied under the same clinical protocol (Hall et al, 1984). Differences in clinical course and in virus shedding need to be explored further among varying influenza strains. In this study, the total number of six H3N2 isolates did not yield a sufficient number to make definitive such comparisons. However, it is suggested by this trial, by comparisons with the Rochester trial, and by previous experience that H3N2 is a more virulent strain than H1N1 in young children (Wright et al, 1980).

The mild course of influenza with rapid resolution made assessment of comparative drug efficacy difficult in the population under study. As demonstrated, the clinical course of illness was the same in each treatment group. Rimantadine and acetaminophen were not statistically different in their effectiveness in controlling the overall course of the illness nor in resolving symptoms that they might be judged specific indications for one or the other drug, i.e. fever and systemic symptoms with acetaminophen or respiratory symptoms with rimantadine. Both drugs were well tolerated without any discernible side effects. Of particular interest is the decline in numbers of children shedding virus and a reduction in geometric mean titers of virus in the rimantadine group, which may potentially limit virus spread. The increase in virus titers after 72 hours of treatment (particularly noticeable in the H3N2 shedding) suggests that either residual virus is becoming resistant to rimantadine or that rimantadine is perhaps altering the host defense mechanism against influenza by decreasing the initial antigenic exposure. An unexplained observation was the tendency of influenza virus shed late in the course of illness to be more resistant to rimantadine than initial isolates in both rimantadine and acetaminophen groups. The numbers of children who shed virus throughout the trial and the difficulties in achieving a fully reproducible assay of rimantadine resistance precluded further analysis of this observation.

CONCLUSION

Rimantadine treatment caused no apparent adverse reactions. However, in normal children experiencing a mild illness from influenza A serotype H1N1 it is no more effective than acetaminophen used for symptomatic treatment. Further studies are needed to clarify the rebound of virus shedding seen in rimantadine treated patients, the efficacy of rimantadine against the more virulent H3N2 strain, and the development of in vitro resistance to rimantadine of virus shed late in the illness.

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