

Oral Ribavirin Treatment of Influenza A and B

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Received 2 March 1987/Accepted 19 May 1987

A loading dose and short-term administration of oral ribavirin significantly improved symptoms and signs of influenza type A or B infection in 25 patients. The antiviral effect was not significant. No adverse clinical effects or significant laboratory values were observed. Oral treatment of patients with influenza A or B infection might be possible with ribavirin.

Ribavirin (1- β -D-ribofuranosyl-1,2,4-triazol-3-carboxamide) inhibits in vitro replication of a broad spectrum of RNA and DNA viruses, including influenza types A and B (10). As treatment for influenza, a small-particle aerosol of ribavirin has been effective in accelerating defervescence, increasing the clearance of virus from respiratory secretions, and producing clinical and radiologic improvement (4). University students given oral ribavirin as treatment for mild influenza A infection showed no benefit from a relatively small dose of 1.0 g per day (11). In this investigation a loading dose and larger maintenance doses of oral ribavirin were given to ambulatory adults with uncomplicated influenza A or B infection in a randomized, prospective, placebo-controlled, double-blind trial.

(This study was presented in part at the 26th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, La. [C. M. Creticos, D. S. Stein, G. G. Jackson, J. Bernstein, T. Sorg, G. Schiff, and F. Hayden, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 91, 1986].)

Thirty-three ambulatory patients (ages, 23 to 64) without high-risk factors and with the required clinical manifestations of influenza were enrolled in this study. The criteria were a fever of at least 100°F (37.8°C; oral); three or more symptoms of influenza (headache, chilliness, malaise, muscle aching, retroorbital pain, coryza, cough, dyspnea, burning respiration, and increased respiratory secretions); and illness of not more than 30 h. A total of 10 patients, 2 with influenza A and 8 with influenza B, were enrolled in the study in Chicago, Ill.; 9 patients with influenza A and 1 with influenza B were enrolled in Dayton, Ohio; and 3 patients and 2 patients with influenza B were enrolled in Charlottesville, Va., and Cincinnati, Ohio, respectively. A physician examined each patient and recorded fever and symptoms. All of the patients were over 18 years of age and gave informed consent for participation in the study. A blood specimen was taken on enrollment in the study for the measurement of cell counts, hemoglobin, hematocrit, serum chemistry values, and the titer of influenza antibodies. Throat gargles, nasal washes, or both were collected and inoculated onto tissue culture monolayers for isolation of influenza viruses. Patients at each site were assigned sequentially to the drug or placebo treatment according to a ran-

domized, blinded code. No patient received antibiotics or another antiviral agent during the study.

Treatment was begun with an initial dose of 1,200 mg of ribavirin or a comparable placebo taken as three capsules; the same dose was repeated 1 and 2 h later. Subsequent maintenance doses of 1,200 mg were given at 12-h intervals for 48 h (8.4 g in 2 days). The oral temperature was recorded by the patient every 4 h during the day (7 a.m. to 11 p.m.). Every 12 h (morning and evening) the patients rated each of 20 respiratory or constitutional symptoms as absent, mild, moderate, or severe. Every other day for 1 week patients were examined by a physician; throat gargles, nasal washes, or both for viral cultures and blood for follow-up laboratory studies were obtained. Clinical and laboratory examinations were repeated after 10 to 14 and 21 to 28 days. The mean daily symptom load was determined as a product of the mean symptom scores times the hourly interval between the data points. The degree hours of fever were determined as the mean degrees of temperature above 99°F (37.2°C) times the hours in the period preceding the temperature readings. Confirmation of influenza was based on isolation of influenza virus or a fourfold or greater increase in the titer of complement-fixing anti-influenza antibody in serum. The categorical data collected were analyzed by the chi-square test; arithmetic means were analyzed by nonpaired *t* tests, and slopes of graphic data were examined by regression analysis and analysis of variance by using the statistical package for the social sciences.

Influenza A was confirmed in 11 patients, and influenza B was confirmed in 14 patients. Both virologic confirmation and serologic confirmation were obtained in 16 patients, and virologic or serologic evidence alone was obtained in 5 and 4 patients, respectively. A total of 15 patients with documented influenza received ribavirin, and 10 patients received placebo. The demographic characteristics of the two groups were comparable. Among the patients assigned to the ribavirin group, the initial mean symptom score was 29% greater than that of the placebo group. This random difference was of borderline statistical significance ($P = 0.06$). It was not caused by differences in patients from any of the centers and was only partly caused by differences in the severity of influenza A and B. Four patients without confirmed influenza and two patients with respiratory syncytial virus or parainfluenza virus type 2 infections were excluded from the analysis of efficacy but were included for evaluation of the acceptability and side effects of ribavirin. Of the 33

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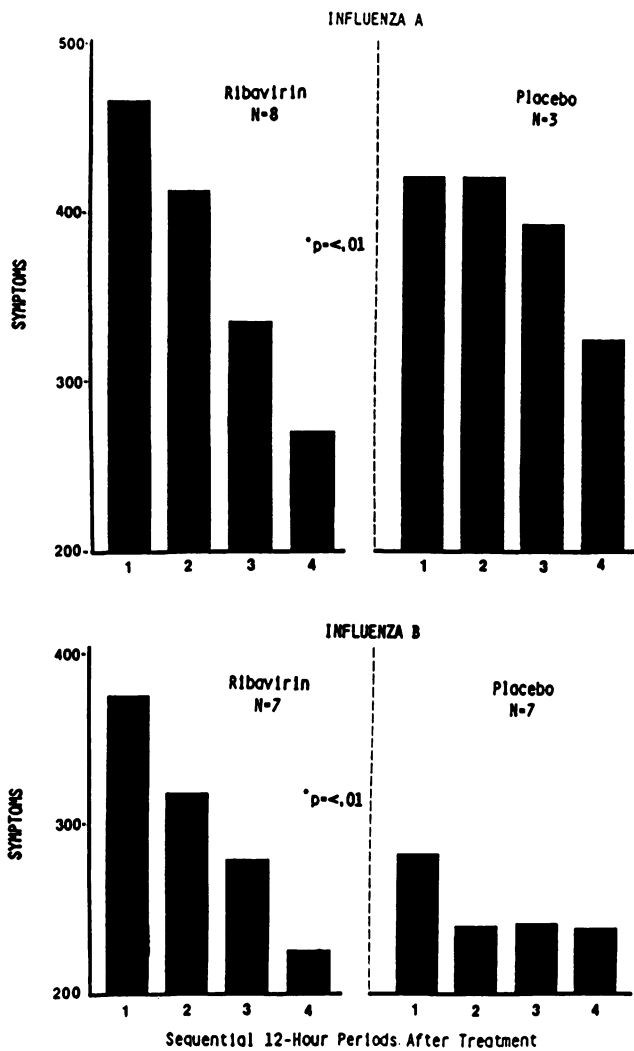


FIG. 1. Effect of treatment on the course of the symptom load in different groups of patients with influenza. The *P* value indicates nonparallelism in regression trend analysis.

patients studied, 2 failed to show up for appointments and were dropped from the study.

The rate of decline of the daily mean total symptom score of individuals with both types of influenza combined was 2.5 times faster in the ribavirin-treated than in the placebo-treated group. The times required for 50% improvement were 48 and 76 h, respectively. These differences were not statistically significant. The calculated group symptom load

TABLE 1. Virus recovery from patients with influenza

Treatment day	Placebo treated		Ribavirin treated	
	No. positive/total	Virus titer ^a	No. positive/total	Virus titer ^a
0	8/10	2.1	10/15	2.9
1-2	5/10	2.5	8/13 ^b	1.6
3-4	3/9 ^b	3.5	4/15	1.4
5-6	1/9	4.0	0/15	

^a Virus titer was mean (log₁₀) tissue culture infective dose (positive specimens only).

^b Two specimens on day 1-2 and one specimen on day 3-4 were contaminated and could not be assayed.

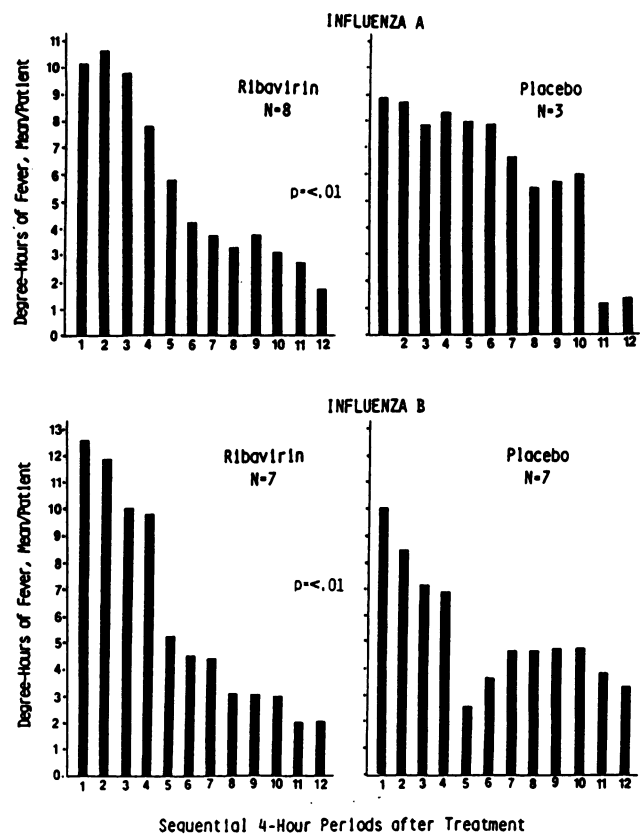


FIG. 2. Effect of treatment on the course of fever in different groups of patients with influenza.

in sequential 12-h periods among ribavirin- and placebo-treated patients infected with influenza A and B is shown in Fig. 1. In each successive observation period, ribavirin recipients with either type A or B influenza had a more rapid and sustained decrease in illness than placebo recipients. Within 48 h patients with influenza A who received ribavirin had a 42% decrease in symptom load compared with 23% for

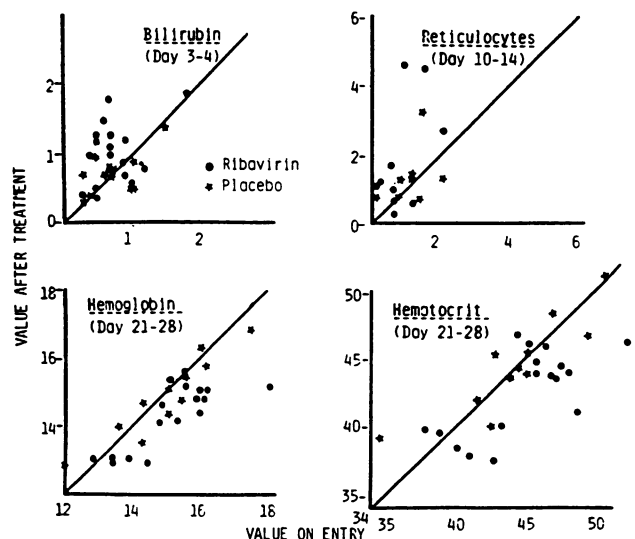


FIG. 3. Paired measurements from individual patients at enrollment and on the posttreatment day of greatest mean change in serum bilirubin, blood reticulocyte count, hemoglobin, and hematocrit.

the patients who received placebo. The patients with influenza B who received ribavirin had a 40% decrease in symptom load compared with 16% for patients who received placebo. By the fourth period (36 to 48 h), the severity of illness for patients with both influenza A and B was less in the groups receiving ribavirin than in the respective groups receiving placebo; this was a reversal of their initial relationships. The differences in the resolution of the symptom load were statistically significant, as determined by regression trend analysis ($P < 0.01$).

The degree hours of fever in sequential 4-h periods among patients with influenza A and B treated with ribavirin or placebo are shown in Fig. 2. Influenza B caused more fever but fewer symptoms than influenza A. Defervescence among ribavirin-treated patients with influenza A began 12 h after treatment; fever declined sharply on the first day of treatment (59%) and rebounded minimally on the second day (periods 7 to 12). Among the placebo recipients with influenza A, defervescence on the first day of treatment was slight (11%), and fever was relatively sustained on the second day. Among patients with influenza B, defervescence on the first day was similar for patients treated with either ribavirin or placebo. Fever recurred on the second day of placebo treatment but was not observed among ribavirin-treated patients. Regression trend analysis showed the difference in fever to be statistically significant ($P < 0.01$). The time required for the mean temperature to fall below 99°F (37.2°C) was 44 h in the group treated with ribavirin and was not reached in the group treated with placebo in 48 h, when regular temperature recordings were omitted.

The frequency of recovery of influenza viruses from respiratory secretions and the infectious titer are given in Table 1. With one exception, all 24 patients tested were free of virus by days 5 to 6. There was no difference in the rate of elimination of virus-positive status between the placebo and treated groups for patients with either influenza A or B. An antiviral effect might be reflected by the infectious titer.

The larger doses and modified regimen compared with those used in earlier studies of oral ribavirin (5, 8, 11) suggest clinical and laboratory benefits not previously observed. More rapid improvement offset the initially more severe illness among the ribavirin recipients and produced a milder illness within 36 h. Defervescence measured a different response than symptoms and also was faster and more complete following ribavirin than placebo administration. The trial was intended to test the value of the intensive short-term regimen. The doses were well accepted. Limited pharmacologic data showed incomplete and variable absorption (data not shown), with levels in serum being below the usual *in vitro* inhibitory concentration for influenza A or B. Better pharmacokinetic studies will require more applicable methods for the accurate and reproducible measurement of drug levels to evaluate their relation to clinical benefit.

Erythrocytes accumulate and harbor ribavirin, causing a dose duration-related increase in extravascular hemolysis (9). Hemolysis has not been clinically apparent after oral or aerosol administration and has been modest in patients given large intravenous doses (4, 6). Paired data from hematologic tests for individual patients on entry into the study and on the day of greatest mean change are plotted in Fig. 3, and the mean values at sequential periods were calculated (data not shown). There were no statistically significant differences, nor were there statistically significant differences between the two groups in tests for liver or renal function (data not shown). The sample size provided only a low statistical power for excluding the probability of toxicity.

The apparent beneficial effect of ribavirin against both influenza types A and B extends antiviral chemotherapy of influenza beyond that available with amantadine (3, 12, 13). The different site and mechanism of action with equal activity against amantadine-susceptible and -resistant strains could allow ribavirin to have a role in overcoming amantadine resistance (1, 2, 7) and could have a potential additive or synergistic effect. Confirmation of the observed benefits and demonstration of other benefits will require observations in a larger and more ill group of patients.

We gratefully recognize the essential help of many colleagues who participated directly and indirectly by referring patients, performing tests, and developing the data. Mary Rubenis (Chicago), Cheryl Stokes and Charlene Sorensen (Dayton), and J. R. Sherwood (Cincinnati) performed the diagnostic virology and serologic tests. Vijai Moses (Chicago) assisted in statistical analysis. Karl Johnson and Humberto Fernandez, Viratek Corp., Costa Mesa, Calif., were active participants in the design of the studies, randomized the medication, and performed unblinded administrative assistance in the conduct of the investigation.

Funds to support the research were furnished by Viratek Corp.

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