

Ribavirin aerosol for acute bronchiolitis

W BARRY, F COCKBURN, R CORNALL, J F PRICE, G SUTHERLAND, AND A VARDAG

Department of Child Health, King's College Hospital, London, and Royal Hospital for Sick Children, Glasgow

SUMMARY A randomised double blind placebo controlled trial of treatment with an aerosolised antiviral agent, ribavirin, was conducted in 26 infants with clinically diagnosed bronchiolitis. Nebulised ribavirin (14 infants) or normal saline aerosol (12 infants) was given for 18 hours a day for at least three days. Respiratory syncytial virus was identified in nasal secretions from 20 cases (10 from both groups). Trends in seven out of eight clinical variables favoured active treatment. Ribavirin aerosol was associated with significantly faster improvement in cough and crepitations and more rapid rate of fall in respiratory and heart rates. In the 20 infants from whose nasal secretions respiratory syncytial virus was identified most variables favoured treatment with ribavirin, with significant reduction in chest recession. No difference was found in the rate of clearance of respiratory syncytial virus. The treatment was well tolerated as judged clinically and from the results of haematological and biochemical studies. The study suggests nebulised ribavirin may have a place in the treatment of some cases of bronchiolitis.

Bronchiolitis is a common cause of respiratory illness in infancy. Occasional fatalities occur, particularly in infants with underlying chest or heart disease or immune disorders. The illness is associated with recurrent wheezing¹ and lung function abnormalities in later childhood.² Respiratory syncytial virus has been implicated in 75% of cases.³ Until recently no treatment other than the administration of oxygen has been shown to influence the course of the illness. Ribavirin, a guanosine analogue, with a broad range of antiviral activity, has been found to reduce viral shedding and systemic symptoms in experimental respiratory syncytial viral infection in young adult volunteers.⁴ Subsequently, nebulised ribavirin has been shown to have a similar beneficial effect in infants with lower respiratory infection due to respiratory syncytial virus.^{5,6} No previous studies of nebulised ribavirin in respiratory syncytial viral infection in infancy have been carried out in the United Kingdom. We therefore performed a double blind placebo controlled trial of treatment with ribavirin in infants with acute bronchiolitis.

Patients and methods

Twenty six infants (19 boys and seven girls) were recruited from among those admitted to the Royal Hospital for Sick Children, Glasgow, and King's

College Hospital, London, during winter epidemics of acute bronchiolitis. The diagnosis of bronchiolitis was made on a history of upper respiratory tract infection followed by cough, breathlessness and wheeze, and clinical signs of chest overinflation, tachypnoea, rhonchi, or crepitations. Infants less than 2 weeks old, cases where it had been less than 41 weeks since mother's last menstrual period, and infants with chronic underlying chest or heart disease, previous bronchiolitis, or immune defect were excluded from the study. Infants with a history of chest symptoms for more than 72 hours were also excluded. Parents gave written informed consent. The study was approved by the ethical committees of the two hospitals.

Infants were allocated to active treatment or placebo by a process of minimisation of the differences in the pretreatment distribution of age, arterialised capillary carbon dioxide tension, respiratory rate and interval since onset of chest symptoms, and in the incidence of a random factor. Ribavirin 20 mg/ml in 0.9% saline or placebo (0.9% saline) was administered as an aerosol for 18 out of 24 hours for at least three days. The aerosol was produced by a Collison's generator. An air or air/oxygen mixture at 26 psi was delivered to the nebuliser and to the condensing chamber. Under these conditions an aerosol of near uniform particle size with mass median diameter of 1.3 microns is

achieved.⁷ The aerosol output from the generator was passed at near atmospheric pressure through 22 mm corrugated plastic tubing to clear plastic baby boxes (in Glasgow) or head boxes (in London). The infants were nursed in these appliances, being taken out for feeding, cleaning, or comforting (until their recovery was complete or near complete). Oxygen was administered as clinically indicated. One infant in the active group and three in the placebo group also received treatment with antibiotics.

The infants were examined before trial entry and in the morning, at midday, and in the early evening each day thereafter. Eight clinical variables (Fig. 1) were recorded. Seven of these were on a three point

scale according to severity, and feeding was recorded as normal, slow, tube fed, or parenteral. Heart and respiratory rates were also measured at each examination.

Before trial entry and each morning thereafter until clinical recovery a sample of nasopharyngeal aspirate was examined for virus particles by immunofluorescent technique and for cytopathic effect on human lung, Hep 2, and baboon kidney cell monolayers. Aerosol treatment was stopped each morning for two hours before these samples were taken.

Haemoglobin concentration, mean corpuscular volume, white cell count, reticulocyte count and

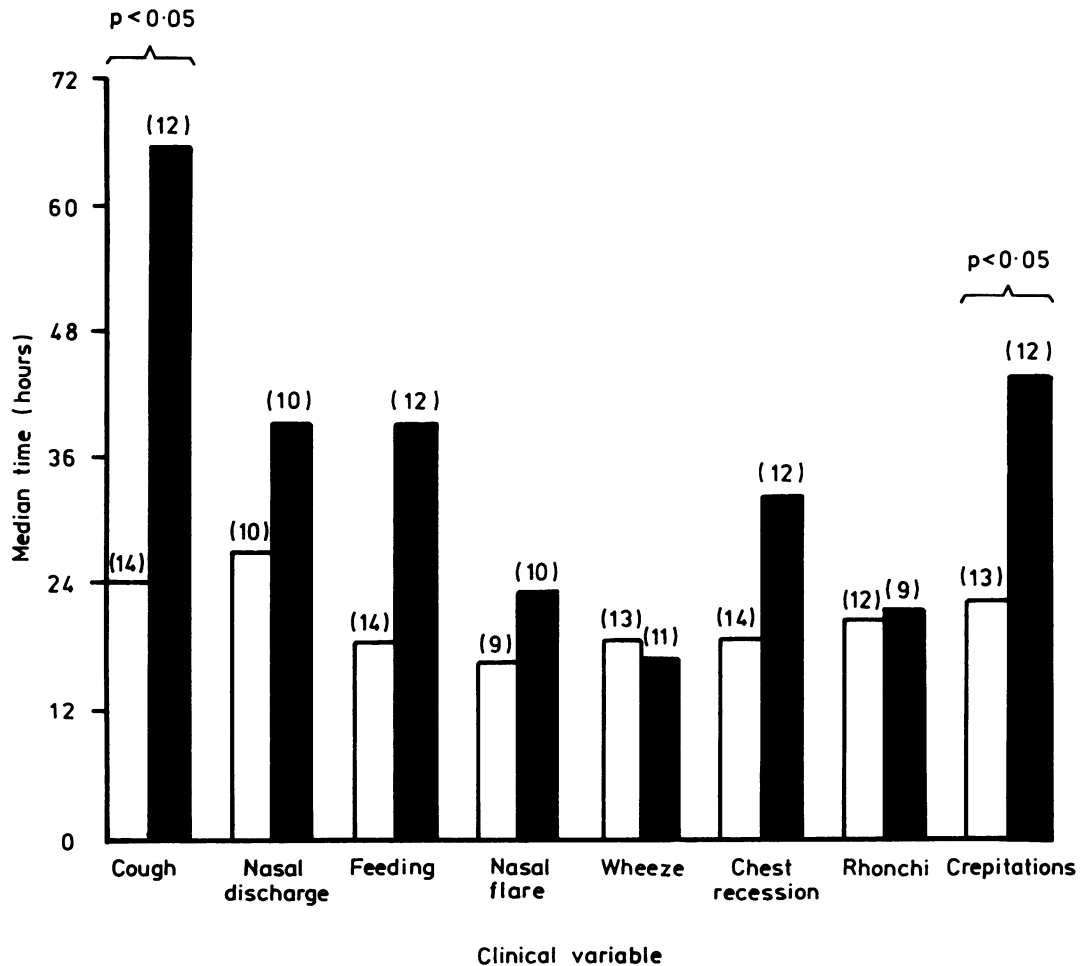


Fig. 1 Median times to sustained improvement in eight clinical variables for all patients (n=26). Open boxes=patients treated with ribavirin (n=14), hatched boxes=patients treated with placebo (n=12). Numbers in parentheses=number of patients involved.

platelets, creatinine, bilirubin, and albumin concentrations, and alanine transaminase and alkaline phosphatase activities were estimated at the start and completion of treatment. Haptoglobin concentrations were measured before and after treatment in some infants.

The time from beginning treatment to sustained improvement in each clinical variable was compared in the ribavirin and placebo groups, using the Wilcoxon rank sum test. The rate of fall in heart and respiratory rates was analysed, using the method of paired comparisons (correlated *t* test), and the time taken to reach a significant fall ($p < 0.05$) was recorded. Differences in rate of fall between the two groups were compared using Student's *t* test. Duration of infectivity after starting treatment was taken as the period up to the first day when virus could no longer be cultured from nasopharyngeal aspirates.

Results

There was no difference in severity of illness or frequency of positive virology at trial entry between the ribavirin and placebo groups, and the duration of treatment was similar (Table).

Median values for times to improvement favoured active treatment in all variables except wheeze. In the case of cough and crepitations these differences attained significance (Fig. 1). When only the data from patients with positive virology were analysed median differences in time to improvement continued to favour active treatment, save for nasal discharge and rhonchi. The difference for chest recession attained significance ($p < 0.05$). Mean respiratory rate fell more rapidly in the active group, where a significant fall had occurred after six hours compared with 24 hours in the placebo group. The drop in respiratory rate from pretreatment values was significantly greater at 24 and 30 hours in the

active group compared with the placebo group ($p < 0.05$) (Fig. 2(a)). Heart rate tended to fall more rapidly in the active group throughout the treatment period, but the drop from entry observations was not significantly greater at any time than in the placebo group. There was a significant fall in heart rate after three hours in the active group compared with 30 hours in the placebo group (Fig. 2(b)).

There was no difference in duration of infectivity. The median duration was 3.5 days (range 1–4 days) in the active group compared with 4 days (range 1–5 days) in the placebo group.

Treatment was well tolerated clinically. One patient in the active group developed redness of the eyelids. Treatment was continued and the redness had resolved by the following day. No differences were found in the results of haematological or biochemical tests between the active and placebo groups. Haptoglobin concentrations measured before and after treatment in five patients in the active group and four in the placebo group remained unchanged.

Table Clinical characteristics at entry to trial and duration of treatment (mean values) and results of initial viral studies

	Treatment group	
	Ribavirin	Placebo
No	14	12
Sex (M:F)	9:5	10:2
Capillary carbon dioxide tension (Kpa)	5.27	5.28
Respiratory rate/min	61	58
Heart rate/min	150	139
Time from onset of respiratory symptoms (hours)	53.6	52.5
Duration of treatment (hours)	67.8	65
Respiratory syncytial virus identified:		
By culture	9	9
By immunofluorescence	9	6
By either method	10	10

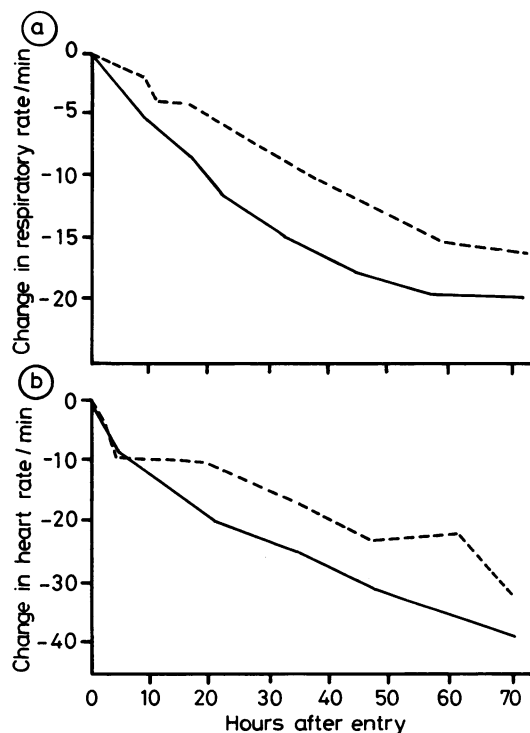


Fig. 2 Rate of change from entry observation of (a) respiratory rate and (b) heart rate in patients receiving ribavirin (—) or placebo (-----).

Discussion

Infants with bronchiolitis who were treated with ribavirin aerosol showed a more rapid rate of improvement than those given saline aerosol. The method of allocation to ribavirin or placebo involved some degree of selection but did include a random factor and ensured that even with fairly small numbers the distribution of severity of disease was similar in the two groups. The difference in rate of recovery was most obvious for lower respiratory tract signs consistently seen in bronchiolitis—namely, cough, tachypnoea, chest recession, and crepitations in the lung fields. In our experience wheezing was a less consistent finding and tended to come and go with consecutive examinations. We found no differences in the rate of resolution of wheeze or of upper respiratory tract signs. These findings are similar to those of Hall *et al*, who investigated the use of nebulised ribavirin in the treatment of respiratory syncytial viral pneumonia in infants, some of whom also had bronchiolitis.⁵ Upper respiratory tract signs are difficult to assess accurately in infants; the Collison generator, however, produces an aerosol of very fine particle size, and it may be that more ribavirin is deposited in the lower than in the upper respiratory tract.

In our study, and that of Hall *et al*,⁵ treatment was administered for a similar duration (18–20 hours each day) to give a predicted ribavirin dose of 15–16 mg/kg/day. In the one other trial of treatment with ribavirin in respiratory syncytial viral bronchiolitis the aerosol was administered for only 12 hours each day, giving a daily dose of roughly 10 mg/kg.⁶ The infants given ribavirin in the latter study improved a little more rapidly than those given placebo, but the differences between the actively treated and placebo groups were less obvious than in the two trials that had a larger daily dose. Hall *et al*⁵ made a quantitative assessment of the amount of respiratory syncytial virus in nasal wash specimens collected daily and found a more rapid rate of clearance of virus in the patients treated with ribavirin. We only assessed duration of infectivity and made no attempt to quantify the amount of virus in nasopharyngeal aspirates. This may explain why we found no differences between the ribavirin and placebo groups.

The Collison generator is rather cumbersome and heavy to transport; the manufacturers are currently modifying it to make it simpler and more portable. There were no major problems with administration of the aerosol, either through a head box or a body box.

In one of the previous trials of ribavirin nebulised water was used as placebo.⁵ We used nebulised

normal saline as nebulised water has been found to increase bronchial reactivity.⁸ We monitored plasma sodium concentrations throughout the treatment, and no patients developed hypernatraemia. As in previous studies of ribavirin we have found the aerosol to be well tolerated. The transient redness of the eyelids in one patient was possibly caused, however, by the continuous deposition of drug on his skin. Reports of depression of the red cell count and transient mild rises of bilirubin concentrations have been associated with the use of oral ribavirin.^{9–12} These were not noted in either our study or in the previous reports of the use of nebulised ribavirin.

Treatment with ribavirin aerosol for 18–20 hours each day for at least three days is inconvenient and is likely to prove expensive. It does not seem justified to recommend its routine use in the treatment of bronchiolitis in otherwise healthy infants on the basis of a modest increase in rate of recovery during the acute illness. Recurrent chest symptoms¹³ and persistent abnormalities of lung function are common after acute bronchiolitis,¹⁴ but no studies have been performed yet to discover whether treatment with ribavirin during the acute illness influences the long term outcome. On the other hand, ribavirin may well have a place in the treatment of respiratory syncytial viral bronchiolitis in infants who are likely to be severely affected, such as those with immunodeficiency, congenital heart disease, and bronchopulmonary dysplasia.

We acknowledge the support of T I L Medical for providing equipment and financial help and thank the Virology Departments at the Royal Hospital for Sick Children, Glasgow, and King's College Hospital, London, for their help.

References

- 1 Stokes GM, Milner AD, Hodges IG, Groggins RC. Lung function abnormalities after acute bronchiolitis. *J Pediatr* 1981;**98**:871–4.
- 2 McIntosh K, Ellis EF, Hoffman LS, Lybass TG, Eller JJ, Fulginiti VA. The association of viral and bacterial respiratory infections with exacerbations of wheezing in young asthmatic children. *J Pediatr* 1973;**82**:578–90.
- 3 Gardner PS. Respiratory syncytial virus infections. *Postgrad Med J* 1973;**49**:788–791.
- 4 Hall CB, Walsh EE, Hruska JF, Betts RF, Hall WJ. Ribavirin treatment of experimental respiratory syncytial viral infection. *JAMA* 1983;**249**:2666–70.
- 5 Hall CB, McBride JT, Walsh EE, *et al*. Aerosolized ribavirin treatment of infants with respiratory syncytial viral infection. *N Engl J Med* 1983;**308**:1443–7.
- 6 Taber LH, Knight V, Gilbert BE, *et al*. Ribavirin aerosol treatment of bronchiolitis associated with respiratory syncytial virus infection in infants. *Pediatrics* 1983;**72**:613–8.
- 7 Knight V, McClung HW, Wilson SZ, *et al*. Ribavirin small particle aerosol treatment of influenza. *Lancet* 1981;ii:945–9.
- 8 Schoeffel RE, Anderson SD, Altounyan RE. Bronchial hyper-reactivity in response to inhalation of ultrasonically nebulised

- solutions of distilled water and saline. *Br Med J* 1981;**283**: 1285-7.
- ⁹ Togo Y, McCracken EA. Double-blind clinical assessment of ribavirin (virazole) in the prevention of induced infection with type B influenza virus. *J Infect Dis* 1976;**133**(suppl A):109-13.
- ¹⁰ Magnussen CR, Douglas RG Jr, Betts RF, Roth FK, Meagher MP. Double-blind evaluation of oral ribavirin (virazole) in experimental influenza A virus infections in volunteers. *Antimicrob Agents Chemother* 1977;**12**:498-502.
- ¹¹ Smith CB, Charette RP, Fox JP, Cooney MK, Hall CE. Double-blind evaluation of ribavirin in naturally occurring influenza. In: Smith RA, Kirkpatrick W, eds. *Ribavirin: a broad spectrum antiviral agent*. New York: Academic Press, 1980: 147-64.
- ¹² Sidwell RW, Robins RK, Hillyard IW. Ribavirin: an antiviral agent. *Pharmacol Ther* 1979;**6**:123-46.
- ¹³ Pullan CR, Hey EN. Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory syncytial virus in infancy. *Br Med J* 1982;**284**:1665-9.
- ¹⁴ Henry RL, Hodges IG, Milner AD, Stokes GM. Respiratory problems 2 years after acute bronchiolitis in infancy. *Arch Dis Child* 1983;**58**:713-6.

Correspondence to Dr J F Price, Department of Child Health, King's College Hospital, Denmark Hill, London SE5.

Received 20 March 1986