Committee on Infectious Diseases

Ribavirin Therapy of Respiratory Syncytial Virus

Ribavirin is an antiviral drug that has recently been approved by the FDA in an aerosolized form for the therapy of respiratory syncytial virus infections in hospitalized children who do not require assisted ventilation. Ribavirin is different from other antiviral drugs both in its spectrum of activity and in its mode of administration.[1,2] The following statement is presented to identify which children should be considered for ribavirin therapy. Questions also have arisen as to the benefits afforded by treatment in comparison to the potential unknown toxicity of the drug and as to whether ribavirin should be administered to infants who require assisted ventilation; the package insert has warned against using the drug in such patients. Whether pregnant women or personnel who care for infants being treated with ribavirin are at risk from exposure to the drug is also of concern. Finally, physicians must be aware that the cost of ribavirin needed for three days of therapy is almost $700.

BACKGROUND

Respiratory Syncytial Virus Disease

Respiratory syncytial virus is the most important cause of lower respiratory tract disease in infants and young children. It usually appears in yearly winter to spring outbreaks and infects essentially all children during their first 3 years of life. The number of infected infants who require hospitalization has been estimated to range in different locations from one in 50 to one in 1,000. Currently, the mortality in hospitalized infants who were previously normal is low, less than 1%.[3] In infants with underlying diseases, however, the mortality may be strikingly higher.[3-5] Conditions that appear to place a child at risk of severe or fatal respiratory syncytial virus infection are pulmonary disease, especially bronchopulmonary dysplasia, prematurity, congenital heart disease, and immunodeficiency disease or therapy causing immunosuppression at any age.[3-5]

Most previously normal infants improve with only supportive care within a few days and are discharged after an average of four to nine days. Possible long-term sequelae are difficult to assess. Evidence has recently accumulated, however, that in some children abnormalities in pulmonary function may develop. These may be relatively asymptomatic or be manifested as recurrent wheezing or lower respiratory tract disease.[6] Whether treatment of the initial respiratory syncytial virus infection can alter the rate or outcome of such sequelae is unknown.

Ribavirin

Ribavirin as an aerosol is the first specific therapy available for respiratory syncytial virus infections. It is a synthetic nucleoside analog (1-β-D-ribafuranosyl-1,2,4-triazole-3-carboxamide) resembling guanosine and inosine; it appears to interfere with the expression of messenger RNA and inhibit viral protein synthesis.[2] It is not significantly incorporated into host cell RNA or DNA.

Teratogenicity has been observed in pregnant rodents given the drug orally for 2 weeks or more but has not been observed in treated pregnant baboons.

Incidental exposure of hospital personnel and visitors to ribavirin aerosol while caring for treated infants is likely to occur. Personnel who have cared for such infants during an entire shift on successive days (at least 25 hours exposure within five successive days) have been examined, and no ribavirin was detected in serum or urine. Even in patients who have received the aerosolized drug directly for five hours, the plasma level is less than 1 μmol/L. Oral administration of ribavirin in doses up to 1 g/d for more than 1 week to adults has resulted in a transient decrease in hematocrit value as great as 20%.[7] However, in adult volunteers receiving riba-

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virin aerosol by mask for 12 h/d for three days, no toxicity or side effects were observed.[8]

Clinical Studies

Trials of ribavirin treatment of infants hospitalized with respiratory syncytial virus lower respiratory tract diseases were begun in 1981 and have involved both normal infants and those with underlying diseases.[9-15] In the controlled studies, ribavirin was associated with a greater clinical improvement than placebo-treated patients.[9-11] Treatment had a beneficial effect on some signs, eg, retraction and rales, but not others, eg, fever and wheezing.[9,10] The improvement in the infants' arterial oxygenation, although statistically significant, is of questionable clinical significance. In one study, the treated group had a mean Pa_{O_2} of 49.4 mm Hg at the start of therapy and 62.4 mm Hg at the end, an increase of 13 mm Hg; the comparable values for the placebo group were 52, 56, and 4 mm Hg.[9] The effect of therapy on persistence of virus in secretions differed in various studies.[9-11]

Ribavirin has been administered as an aerosol with particles small enough (mass median aerosol diameter 1 to 2 μm) to reach the lower respiratory tract and has been delivered via an oxygen hood or tent for an average of three to five days for 12 to 20 hours each day. High levels of ribavirin were obtained in the respiratory secretion by this method with little systemic absorption.[16] No significant toxicity was observed in any of these controlled trials. The effect of the ribavirin aerosol on pulmonary function was examined in adult volunteers infected with respiratory syncytial virus in a controlled, double-blind study.[7] Serial pulmonary function tests, which included carbachol challenge, showed no alterations in volunteers during the ribavirin therapy or when tested 1 month later.[7]

When ribavirin is administered to mechanically ventilated patients, however, technical difficulties could cause adverse effects if proper precautions are not observed. Deposition of the drug in the delivery system occurs, which appears to be dependent on the temperature, humidity, and electrostatic forces. Precipitation of the drug in the respirator tubing and around the expiratory valve of ventilators could, if uncorrected, lead to malfunction or obstruction of the valve, resulting in inadvertently high levels of positive end-expiratory pressure. Use of one-way valves on the inspiratory lines and of a breathing circuit filter in the expiratory line, along with careful monitoring, have been useful in preventing these problems. Additional studies are in progress to facilitate the use of ribavirin in mechanically ventilated patients.

The long-term effects of ribavirin on pulmonary function and on the sequelae of respiratory syncytial virus infection are currently being examined. Thus far, when the limited number of infants enrolled in the original controlled studies were examined 2 to 4 years later for pulmonary function, the infants who received ribavirin did at least as well as those who received placebo.

Experience with other new antiviral agents has raised the additional concern of the development of resistance to ribavirin by respiratory syncytial virus. With limited experience, no change in sensitivity of any viral isolate to ribavirin has been observed,[9] even with prolonged administration.[15]

COST-BENEFIT ANALYSIS

It is uncertain whether the use of this expensive drug will reduce the cost of hospitalization of children with respiratory syncytial virus infection. Cost of the drugs, not including administration, is almost $700 for three days.[17]

RECOMMENDATIONS

Candidates

Based on the data currently available, the committee recommends that of the infants hospitalized with lower respiratory tract disease caused by respiratory syncytial virus, those in the following categories should be considered for treatment with ribavirin aerosol.

1. Infants at high risk for severe or complicated respiratory syncytial virus infection. This includes infants with congenital heart disease, bronchopulmonary dysplasia and other chronic lung conditions, and certain premature infants. In addition, children with immunodeficiency, especially those with severe combined immunodeficiency disease, recent transplant recipients, and those undergoing chemotherapy for malignancy should also be considered to be at high risk for complicated respiratory syncytial virus infection.

2. Infants hospitalized with respiratory syncytial virus lower respiratory tract disease who are severely ill. Because severity of illness is often difficult to judge clinically in infants with respiratory syncytial virus infection, determination of blood gas values is often necessary. Infants with Pa_{O_2} levels of less than 65 mm Hg and those with increasing Pa_{CO_2} levels should be considered as candidates for ribavirin therapy. Oximetry may be used as a noninvasive means of determining the arterial oxygen saturation.

3. Infants who might be considered for treatment are those hospitalized with lower respiratory tract disease that is not initially severe, but who may be at some increased risk of progressing to a more

complicated course by virtue of young age (<6 weeks) or in whom prolonged illness might be particularly detrimental to an underlying condition, such as those with multiple congenital anomalies or neurologic or metabolic diseases.

Diagnosis of Respiratory Syncytial Virus

Institutions planning to use ribavirin should be encouraged to avail themselves of the rapid diagnostic techniques to identify respiratory syncytial virus antigen in the respiratory secretions. These tests should be performed when the child is admitted to the hospital. Traditional tissue culture isolation may be useful in providing epidemiologic information about the presence of respiratory syncytial virus in the community. It many not yield results rapidly enough to be useful in making decisions about use of ribavirin. If rapid tests are not available, candidates in the three categories with bronchiolitis or pneumonia clinically compatible with respiratory syncytial virus infection who are admitted during the respiratory syncytial virus season (which is generally December to April) might still be considered for ribavirin therapy. If the etiology of the infant's pulmonary disease is subsequently shown to be an agent other than respiratory syncytial virus, one may wish to discontinue therapy. It should be noted, however, that ribavirin may be effective in influenza virus infections.[18,19] If no agent is initially identified as the cause of the lower respiratory tract disease, but the most likely clinical diagnosis remains respiratory syncytial virus infection and the infant is severely ill, it is reasonable to continue the treatment while continuing to ascertain the causative agent. Although diagnosis by viral isolation may sometimes require more than seven days, treatment ordinarily should not be continued beyond the usual course of three to seven days without a confirmed diagnosis. In ventilated infants, it is particularly important to confirm the diagnosis of respiratory syncytial virus infection.

Administration of Drug

Ribavirin is nebulized into an oxyhood, tent, or mask from a solution containing 20 mg of ribavirin per milliliter of water by a small-particle aerosol generator supplied with the drug by the manufacturer. The aerosol is administered for 12 to 18 hours/d for three to seven days. In the controlled studies, most children had improved by the third to fifth day of treatment.

Infants Requiring Mechanical Ventilation

The package insert for ribavirin carries a warning that ribavirin should not be used in patients requiring simultaneous assisted ventilation because of the precipitation of ribavirin within the ventilator apparatus which may cause an increased positive end-expiratory pressure. Infants who require mechanical ventilation because of severe respiratory syncytial virus infection, however, are those who may be most likely to benefit from ribavirin treatment. The technical aspects of delivering ribavirin aerosol via a ventilator requires special expertise. If such infants are treated, it should be done in facilities whose personnel have specific training and experience in the administration of ribavirin to ventilated infants. The technical precautions, as mentioned above, must be followed; as with any infant requiring mechanical ventilation, constant monitoring is mandatory.

Isolation of Patients

It is essential that proper isolation procedures for patients with respiratory syncytial virus infection be observed. It is of particular importance in intensive care units to prevent spread of virus to other critically ill patients. Careful handwashing, proper disposition of secretions and contaminated equipment, and contact isolation are required. Nosocomial spread of respiratory syncytial virus virus has been well documented[20] and has resulted in fatalities in children with underlying pulmonary and cardiac disease.[21] Treatment with ribavirin does not eliminate the need for careful isolation of these patients.

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Ribavirin Therapy of Respiratory Syncytial Virus
Pediatrics 1987;79;475

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