Use of Ribavirin in the Treatment of Respiratory Syncytial Virus Infection

Committee on Infectious Diseases

Ribavirin is an antiviral drug that was approved by the Food and Drug Administration in 1986 for aerosol treatment of serious respiratory syncytial virus (RSV) infections in hospitalized children. Ribavirin has a broad spectrum of antiviral activity in vitro, where it inhibits replication of RSV, influenza, parainfluenza, adenovirus, measles, Lassa fever, and Hantaan viruses. Proof of efficacy for human infection has been obtained in double-blind placebo-controlled studies of RSV, Lassa fever, and Korean hemorrhagic fever. Presently, only anecdotal reports support the efficacy of this drug for treatment of measles or parainfluenza. Ribavirin treatment for RSV infections has been controversial because of the aerosol route of administration, concern for potential toxicity for exposed persons, cost, and the unpredictable and highly variable course of illness in the absence of specific therapy. These issues necessitate ongoing review of ribavirin therapy and the following updated recommendations by the American Academy of Pediatrics.

BACKGROUND

RSV Disease

Respiratory syncytial virus is the most important cause of lower respiratory tract disease in infants and young children. Disease usually appears in yearly outbreaks in the winter or spring, and essentially all children become infected during their first 3 years of life. The number of infected infants who require hospitalization has been estimated to range from 1 to 50 per 1000 in different locations. Currently, the mortality rate in hospitalized infants who previously were healthy is low (less than 1%). In infants with underlying diseases, however, the mortality can be much higher. Conditions that increase the risk of severe or fatal RSV infection are cysanotic or complicated congenital heart disease (including pulmonary hypertension); underlying pulmonary disease, especially bronchopulmonary dysplasia; prematurity; and immunodeficiency disease or therapy causing immunosuppression at any age.

Most previously healthy infants infected with RSV do not require hospitalization, and many who are hospitalized improve within a few days with supportive care and are discharged after a stay ranging from 3 to 5 days. Long-term sequelae of RSV infection are difficult to assess. Evidence recently has accumulated suggesting that some infected children develop long-term abnormalities in pulmonary function. Although these abnormalities may be subclinical in most children, some subjects have recurrent wheezing. Whether treatment of the initial respiratory syncytial virus infection can alter the rate or severity of such sequelae is unknown.

Ribavirin

Aerosolized ribavirin is the first specific drug available for treatment of RSV infections. It is a synthetic nucleoside analogue (1-b-D-ribafuranosyl-1,2,4-triazole-3-carboxamide) resembling guanosine and inosine; it appears to interfere with the expression of messenger RNA and to inhibit viral protein synthesis. It is not significantly incorporated into host cell RNA or DNA.

Clinical Studies

Ribavirin is administered as aerosolized particles small enough (median aerosol diameter, 1 to 2 μm) to reach the lower respiratory tract. It is delivered via an oxygen hood, tent, or mask for 12 to 20 hours each day for a mean of 4 days. In controlled studies involving both healthy infants and those with underlying disease, clinical improvement was greater in ribavirin recipients than in placebo recipients. Ribavirin had a beneficial effect on some signs, such as retraction and rales, but not on others, such as fever and wheezing. However, these latter signs were present in only a minority of patients. Improvement in arterial blood oxygenation following ribavirin therapy has been substantial. In one study, the treated group had a mean arterial oxygen pressure (Pao2) of 49.4 mm Hg at the start of therapy and 62.4 mm Hg at the end, a mean increase of 13 mm Hg, which was significantly greater than the comparable values for the placebo group (at the start and end of therapy 52 mm Hg and 56 mm Hg, respectively). The effect of therapy on persistence of virus in secretions differed in various studies.

No appreciable toxicity has been observed in any of the controlled trials or in other follow-up studies. Although reversible bronchospasm has been observed occasionally (less than 0.1%), hyperactivity of the airways has not been demonstrated in studies of pulmonary function during administration of ribavirin aerosol. The effect of ribavirin aerosol on pulmonary function was examined in adult volunteers infected with RSV in a controlled, double-blind study. Serial pulmonary function tests, which included carbachol challenge, showed no alterations in volunteers during ribavirin therapy or when tested 1

The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.

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month later. The long-term effects of ribavirin on pulmonary function and on the sequelae of RSV infection require further investigation.

In mechanically ventilated infants, most of whom were previously healthy, ribavirin treatment was safe and was associated with a reduced need for mechanical ventilation and supplemental oxygen, shorter duration of hospitalization, and cost-effectiveness.7

One potential problem is deposition of the drug in the ventilator delivery system, which appears to be dependent on temperature, humidity, and electrostatic forces. This deposition can lead to malfunction or obstruction of the expiratory valve, resulting in inadvertently high positive end-expiratory pressures. The use of one-way valves in the inspiratory lines, a breathing circuit filter in the expiratory line, and frequent monitoring and filter replacement by trained staff have been effective in preventing these problems.

Experience with antiviral agents used to treat other viruses has raised the additional concern of development of resistance to ribavirin by RSV. To date, no change in susceptibility of any viral isolate to ribavirin has been observed, even with prolonged administration.

Safety for Health Care Personnel

Although mucous membrane irritation has been reported following exposure to ribavirin (especially in the eyes of contact lens wearers), it occurs in a small percentage of exposed personnel and is reversible.8 Reproductive and teratogenic toxicities were observed in pregnant rodents administered oral ribavirin. These effects were not reproduced in baboons and have not been reported in humans. Studies have indicated that although absorption of ribavirin can occur in health care personnel from environmental exposure, no deleterious effects have been reported. Concern about the safety of ribavirin has led some hospitals to apply strict precautions for use of ribavirin to minimize exposure of health care workers.

A review of animal and human data on ribavirin safety is summarized and interpreted as follows9:

1. In hamsters after a single oral dose of 2.5 mg/kg, and in rats after a daily oral dose of 10 mg/kg for 60 days or longer, fetal malformations have been noted. In rabbits, the species most sensitive to the effects of ribavirin, skeletal malformations were observed after daily oral administration of 0.1 to 0.3 mg/kg for 12 days. In contrast, seven pregnant baboons were treated orally with 60 to 120 mg/kg of ribavirin for 4 consecutive days, during the time of fetal organogenesis. The offspring of six of these baboons showed no evidence of teratogenicity. The seventh animal aborted at day 45 (60-mg dose) but no traces of implantation were recovered, implying fetal death and resorption prior to organogenesis and prior to ribavirin therapy.9,10

2. Extrapolation from these animal experiments involving oral administration of ribavirin to circumstances of human exposure to ribavirin aerosol is difficult, especially in view of species differences in teratogenicity and the high doses administered.

3. During treatment with aerosolized ribavirin, dissemination of the drug in the environment of the patient can occur, with the potential for inhalation by those caring for treated children. However, while 60% to 70% of the inhaled drug may be deposited in the airways, absorption from the respiratory tract into the circulation is minimal. In infants receiving aerosolized ribavirin, the mean peak plasma concentration was less than 1 μmol/L at a time when the peak concentrations in endotracheal secretions were greater than 1700 μmol/L.11

Studies of health care personnel also have demonstrated minimal absorption. In one study of 19 non-pregnant nurses who were caring for infants receiving ribavirin by aerosol treatment via an oxygen tent, hood, or ventilator, nurses were exposed for a mean of 8 hours per day during a 3-day period (a total of 20 to 35 hours).12 Total air exchanges occurred 5.4 to 24 times per hour in the patients' rooms. Blood samples for analysis of ribavirin were obtained 1 day before exposure, 1 hour after the final exposure, and 3 to 5 days later; urine was collected before and 3 to 5 days after exposure. Ribavirin was not detected in any sample of plasma, erythrocytes, or urine. The lower limit of sensitivity of the radioimmunoassay used to measure ribavirin in the study was 0.02 μg/mL. In a similar study of health care personnel caring for infants treated with ribavirin, 90 samples of serum, urine, and erythrocytes were assayed for ribavirin.13 Ribavirin was detected in a concentration of 0.44 μg/mL in only one erythrocyte sample. (The minimum level of detection of the test used was 0.02 μg/mL.) The concurrent serum and urine samples were negative. No symptoms were reported by any health care workers in this study.

These findings and the lack of validated reports of adverse effects in human fetuses after 7 years of clinical use of the drug in the United States suggest that the teratogenic risk of ribavirin exposure in humans is extremely low. The National Institute for Occupational Safety and Health (NIOSH) recently conducted a study at a Florida Hospital, where the technique they employed consistently found small concentrations of ribavirin in the postshift urine of nurses. No clinical findings were reported in association with these observations.14 NIOSH recommends review of work policies and institution of engineering controls in order to reduce environmental concentration of ribavirin in the patient's room.

RECOMMENDATIONS

Experience in more than 100 000 patients indicates that aerosolized ribavirin treatment for RSV infection is both safe and effective. As with other antiviral therapy, the maximum benefit will be derived by early treatment of high-risk patients. The route of administration, cost, and need for hospitalization support a strategy of selective use of ribavirin as follows:

1. Patients at High Risk for Complications Due to Other Conditions. Ribavirin treatment is recom-
mended for the following patients hospitalized with RSV lower respiratory tract disease:

a. Infants at high risk for severe or complicated RSV infection, including those with complicated congenital heart disease (including pulmonary hypertension); those with bronchopulmonary dysplasia, cystic fibrosis, and other chronic lung conditions; premature infants; children with immunodeficiency (especially those with acquired immunodeficiency syndrome or severe combined immunodeficiency disease); recent transplant recipients; and patients undergoing chemotherapy for malignancy.

b. Infants who are severely ill. Because severity of illness is often difficult to judge clinically in infants with RSV infection, determination of blood gas concentrations is often necessary. Values for $\text{PaO}_2$ of less than 65 mm Hg (ie, oximetry reading less than 90%) and increasing concentration of carbon dioxide arterial pressure ($\text{PaCO}_2$) are useful indicators of severity.

c. All patients mechanically ventilated for RSV infection.

2. Treatment for Hospitalized Infants. Ribavirin treatment should also be considered for hospital-ized infants who may be at increased risk of progressing from a mild to a more complicated course by virtue of young age (less than 6 weeks) or underlying condition, such as multiple congenital anomalies or certain neurologic or metabolic diseases (eg, severe cerebral palsy, myasthenia).

3. Diagnosis of RSV Infection. Rapid diagnostic techniques to identify RSV antigen in respiratory secre-tions should be performed when the child is admitted to the hospital. Tissue culture isolation requires 3 to 5 days. If rapid tests are not available, patients in the recommended categories who have bronchiolitis or pneumonia clinically compatible with RSV infection and who are admitted during the RSV season (generally November to April) should be considered for ribavirin therapy. If the etiology of the infant's pulmonary disease is subsequently found to be an agent other than RSV, ribavirin therapy can be discontinued. If no agent is identified initially as the cause of the lower respiratory tract disease, but the most likely clinical diagnosis remains RSV infection and the infant is severely ill, continuation of treatment is reasonable. Further diagnostic efforts to ascertain the causative agent should be undertaken, recognizing that false-negative rapid diagnostic test results have been noted in 5% to 20% of cases.

4. Administration. Ribavirin is nebulized by a small-particle aerosol generator into an oxygen hood, tent, or mask from a solution containing 20 mg of ribavirin per milliliter of water. The generator is supplied with the drug by the manufacturer. The aerosol is administered for 12 to 20 hours per day, usually for 3 to 5 days depending on the patient’s clinical course; a longer duration of therapy may be useful in immunodeficient patients. A recent study noted good patient tolerance and favorable ribavirin pharmacokinetics when a regimen of 60 mg/mL for 2 hours three times daily was used; however, the efficacy of this dosage has not been proven.\textsuperscript{11} Maximal therapeutic responses usually are noted after 2 to 4 days of treatment.

5. Isolation of Patients. Treatment with ribavirin does not eliminate the need for contact isolation of patients with RSV.\textsuperscript{15}

6. Precautions for Health Care Personnel and Visitors. Health care personnel and visitors should be informed about the potential but unknown risks of environmental exposure to ribavirin. In-service education for hospital personnel is most effective just prior to the RSV season. While evidence of human teratogenicity is lacking, in view of the embryopathic effects in nonprimate animals, pregnant women should be advised not to care directly for patients who are receiving ribavirin.\textsuperscript{16} Several methods have been employed to lower environmental exposure. For example, aerosol administration should be stopped temporarily when the hood or tent is open. Also, the drug should be administered in well-ventilated rooms (at least six air changes per hour).

No additional precautions to protect patients, visitors, or hospital workers in the room are required. Masks designed to block absorption of 1- to 2-µg particulate droplets may reduce inhalation of ribavi-rin, but clinical studies are lacking. Standard surgical masks do not block particles of this size. Gloves and gowns are not essential since dermal absorption of ribavirin appears to be negligible. However, gloves and gowns may lower the risk of nosocomial spread of RSV. Scavenger devices to lower the escape of aerosolized ribavirin into a room also can be used.\textsuperscript{17} Additional research and clinical experience are needed to establish more specific guidelines regarding occupational exposure.
REFERENCES

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