The bioavailability of aerosolized VIRAZOLE is unknown and may depend on the mode of aerosol delivery. After aerosol treatment, peak plasma concentrations of ribavirin are 85% to 98% less than the concentration that reduced RSV plaque formation in infant cells. The respiratory tract secretions are likely to contain ribavirin in concentrations manifold higher than those required to reduce plaque formation. However, RSV is an intracellular virus, and it is unknown whether plasma concentrations or respiratory secretion concentrations of ribavirin better reflect intracellular concentrations in the respiratory tract.

In man, rats, and rhesus monkeys, accumulation of ribavirin and/or metabolites in the lungs were noted. Plateauing in red cells in man in about 4 days and gradually declining with an apparent half-life of 40 days (the half-life of erythrocytes). The elimination of ribavirin following inhalation therapy is not well defined.

**Animal Toxicology**

Ribavirin, when administered orally or as an aerosol, produced cardiac lesions in mice, rats, and monkeys, when given at doses of 30, 36 and 48 mg/kg or greater for 4 weeks or more (estimated human equivalent doses of 4.8, 12.3 and 11.1 mg/kg for a 5 kg child, or 2.5, 5.1 and 40 mg/kg for a 60 kg adult, based on body surface area adjustment; see Warnings and Precautions). Aerosolized ribavirin administered to developing fetuses at 60 mg/kg or 10 or 30 days resulted in inflammatory and possibly emphysematous changes in the lungs. Pro liferative changes were seen in the lungs following exposure at 131 mg/kg for 30 days. The extent of these findings to human administration is unknown.

**INDICATIONS AND USAGE**

VIRAZOLE (Ribavirin for Inhalation Solution, USP) is indicated for the treatment of hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus. Treatment early in the course of severe lower respiratory tract infection may be necessary to achieve efficacy.

Only severe lower respiratory tract infections should be treated with VIRAZOLE. The vast majority of infants and children with RSV infection have disease that is mild, self-limited, and does not require hospitalization or antiviral treatment. Many children with mild lower respiratory tract infection will require support of the respiratory system but will not be required for a full course of VIRAZOLE aerosols (3 to 7 days) and should not be treated with the drug. Thus the decision to treat with VIRAZOLE should be based on the severity of the RSV infection. The presence of an underlying condition such as prematurity, immunosuppression or cardiopulmonary disease may increase the severity of clinical manifestations and complications of RSV infection.

Use of aerosolized VIRAZOLE in patients requiring mechanical ventilator assistance should be undertaken only by physicians and support staff familiar with the mechanics of administration and the specific ventilator being used (see WARNINGS and DOSAGE AND ADMINISTRATION).

**Diagnosis**

RSV infection should be documented by a rapid diagnostic method such as demonstration of viral antigen in respiratory tract secretions by immunofluorescence or ELSA before or during the first 24 hours of treatment. Treatment may be initiated while awaiting rapid diagnostic test results. However, treatment should not be continued without documentation of RSV infection. Non-culture antigen detection techniques may have false positive or false negative results. Assessment of the clinical situation, the time of year and other parameters may warrant revulsion of the laboratory diagnosis.

**Description of Studies**

**Non-Mechanically Ventilated Infants**: In two placebo-controlled trials in infants with RSV lower respiratory tract infection, aerosolized VIRAZOLE treatment had a therapeutic effect, as judged by the reduction in severity of clinical manifestations of disease and treatment duration. Day 3’s treatment was most effective when instituted within the first 3 days of clinical illness. Further, ribavirin crystals in respiratory secretions were also significantly reduced with VIRAZOLE in one of these original studies. Additional controlled studies conducted since these initial trials have shown VIRAZOLE in the treatment of RSV infection have supported these data.

**Mechanically-Ventilated Infants**: A randomized, double-blind, placebo-controlled evaluation of aerosolized VIRAZOLE at the recommended dose was conducted in 28 infants requiring mechanical ventilation for respiratory failure caused by documented RSV infection. Mean age was 1.4 months (SD, 1.7 months). Seven patients had underlying diseases predisposing them to pneumonia or disease and 21 were previously normal. Aerosolized VIRAZOLE treatment significantly decreased the duration of mechanical ventilation (4.6 vs. 9.9 days, p=0.01) and duration of required supplemental oxygen (8.7 vs. 13.5 days, p=0.01). Intensive patient management and monitoring techniques were employed in this study. These included endotracheal tube suctioning every 1 to 2 hours; recording of pulse, resonator, and FIO2 every hour; and arterial blood gas monitoring every 2 to 6 hours. To reduce the risk of VIRAZOLE precipitation and ventilator malfunction, humidification, two bacterial filters connected in series in the expiratory limb of the ventilator (with filter changes every 4 hours thereafter) and pressure relief valves to monitor internal ventilator pressures were used in connecting ventilator circuits to the SPAG-2.

Employing these technical difficulties with VIRAZOLE administration were encountered during the study. Adverse events consisted of bacterial pneumonia in one case, staphylococcal pneumonia in one case and two cases of post-intubation stridor. None were felt to be related to VIRAZOLE administration.

**CONTRAINDICATIONS**

VIRAZOLE is contraindicated in individuals who have shown hypersensitivity to the drug or its components, and in women who are or may become pregnant during exposure to the drug. Ribavirin has demonstrated significant teratogenic and/or embryocidal potential in all animal species in which adequate studies have been conducted (rodents and rabbits). Therefore, although clinical studies have not been performed, it should be assumed that VIRAZOLE may cause fetal harm in humans. Studies in which the drug has been administered systemically demonstrate that ribavirin is concentrated in the red blood cells and persists for the life of the erythrocyte.

**WARNINGS**

Sudden deterioration of respiratory function has been associated with initiation of aerosolized VIRAZOLE use in infants. Respiratory function should be monitored carefully during treatment. If initiation of aerosolized VIRAZOLE treatment should be stopped and respiratory function should be assessed with extreme caution, continuous monitoring, and consideration of concomitant administration of bronchodilators.

**Use with Mechanical Ventilators**

Use of aerosolized VIRAZOLE in patients requiring mechanical ventilator assistance should be undertaken only by physicians and support staff familiar with the mechanics of administration and the specific ventilator being used. Strict attention must be paid to procedures that have been shown to minimize the accumulation of drug precipitate, which can result in mechanical ventilator dysfunction and associated increased pulmonary pressures. These procedures include the use of bacteria filters in series in the expiratory limb of the ventilator circuit with frequent changes (every 4 hours), water column pressure release valves to indicate elevated ventilator pressures, frequent monitoring of these devices and verification that ribavirin crystals have not accumulated within the ventilator circuitry, and frequent suctioning and monitoring of the patient (see Description of Studies).

Those administering aerosolized VIRAZOLE in conjunction with mechanical ventilation use should take steps to monitor infants for the development of ribavirin crystals. These steps include use of respirator filters, continuous monitoring of respiratory pressures, and routine monitoring of the patient (see Description of Studies).
and rat, respectively (estimated human equivalent doses of 0.12 and 0.14 mg/kg, based on body surface area adjustment for the adult. Additional side effects not reported in these studies were not employed (see Description of Studies, WARNINGS, and DOSAGE AND ADMINISTRATION).

Pulmonary and Cardiovascular

Pulmonary function significantly deteriorated during aerosolized VIRAZOLE treatment for patients with chronic obstructive lung disease and in four of six asthmatic adults. Dyspnea and chest soreness were also reported in the latter group. Minor abnormalities in pulmonary function were also seen in healthy adult volunteers.

In the original study population of approximately 200 infants who received aerosolized ribavirin, a total of 2 infants died who were treated with VIRAZOLE during or shortly after treatment. The death rate was comparable to that reported in previously published studies of the use of ribavirin in the treatment of RSV infection in infants. N Engl J Med 308:1443-7, 1983.

Although no clinical studies have been performed, VIRAZOLE may cause fetal toxicity. Ribavirin is concentrated in red blood cells and persists for the life of the cell. Thus the terminal half-life for the systemic elimination of ribavirin is essentially that of the half-life of circulating erythrocytes. The minimum interval following exposure to VIRAZOLE before pregnancy may be safely initiated is unknown (see CONTRAINDICATIONS, WARNINGS, and Information for Health Care Personnel).

Lactation

VIRAZOLE has been shown to be toxic to lactating animals and their offspring. It is not known if VIRAZOLE is excreted in human milk.

Information for Health Care Personnel

Health care workers directly providing care to patients receiving aerosolized VIRAZOLE should be aware that ribavirin has been shown to be teratogenic in all animal species in which adequate studies have been performed. Although no reports of teratogenicity in offspring of mothers who were exposed to aerosolized VIRAZOLE have been confirmed, no controlled studies have been conducted in pregnant women. Therefore, exposure to aerosolized ribavirin during treatment settings have shown that the drug can disperse into the immediate bedside area during routine patient care activities. Important factors to consider in the exposure of adults are described below (see Adverse Events in Health Care Workers). Some studies have documented ambient air concentrations of ribavirin. These usually resolve with adequate room ventilation (at least six air exchanges per hour); include administration of VIRAZOLE in negative pressure rooms; should consider avoiding direct care of patients receiving VIRAZOLE; and digitalis toxicity. Bigeminy, bradycardia and tachycardia have been described in patients with underlying congenital heart disease.

Some patients requiring assisted ventilation experienced serious difficulties, due to inadequate ventilation and gas exchange. Placement of ribavirin-exposed infants in the incubator or oxygen tent may be necessary if a hood cannot be employed. The incubator should be inspected visually for particulate matter and discoloration prior to additional administrations. The incubator should be placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

Method of Preparation

VIRAZOLE brand of ribavirin is supplied as 6.5 grams of lyophilized powder per 100 mL vial for aerosol administration. By sterile technique, reconstitute with a minimum of 75 mL of sterile Water for Injection, USP or Inhalation or the original 100 mL sterile Water for Injection, USP or Inhalation or sterile Water for Inhalation (no preservatives added) administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized powder should be stored in a dry place at 25° C (77° F). Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours and when the liquid level is low before adding newly reconstituted solution.

NOW SUPPLIED

VIRAZOLE® (Ribavirin for Inhalation Solution, USP) is supplied in four packs containing 100 mL glass vials with 6 grams of sterile, lyophilized powder (NDC 0187-0007-14) which is to be reconstituted with 300 mL sterile Water for Injection, USP or Inhalation or sterile Water for Inhalation (no preservatives added) and administered only by a small particle aerosol generator (SPAG-2). Vials containing the lyophilized powder should be stored in a dry place at 25° C (77° F) in an unopened container. Reconstituted solutions may be stored, under sterile conditions, at room temperature (20° - 30° C; 68° - 86° F) for 24 hours. Solutions which have been placed in the SPAG-2 unit should be discarded at least every 24 hours.

REFERENCES


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