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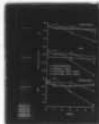
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Effect of Ribavirin given in Small-Particle Aerosols
on Selected Clinical and Hematological Responses^{1,2}

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Short Title: TOXICITY OF RIBAVIRIN

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ABSTRACT

Effect of Ribavirin given in Small-Particle Aerosols on Selected Clinical and Hematological Responses. BERENDT, R. F. and STEPHEN, E. L. (1979). Toxicol Appl. Pharmacol. The effect of 40 mg/kg/day of ribavirin given for 4 days by aerosol to squirrel monkeys was compared to 40 and 400 mg/kg orally and to additional monkeys given water by the aerosol or oral route. Suppression of erythrocyte and hemoglobin levels occurred with the high oral dose, and all groups of ribavirin-treated monkeys had some dyspnea and lethargy. In view of these transient effects short courses of ribavirin may be administered safely.

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Recently aerosols of ribavirin (1- β -D-ribofuranosyl-1,2,4-triazole-3-carboxamide)³ have been reported as effective for the therapy of experimental influenza infection in mice and squirrel monkeys (Stephen et al., 1976; Walker et al., 1976; Berendt et al., 1977; Stephen et al., 1977). Although the manufacturer has reported little toxicity following oral administration (Sidwell et al., 1977), data on toxicity following aerosol administration are lacking.

This study was undertaken to determine whether squirrel monkeys would exhibit adverse reactions during relatively short-term administration of aerosols containing ribavirin.

METHODS

The squirrel monkeys (Saimiri sciureus) used were juvenile males weighing 550 g ($\pm$ 100 g). The apparatus for exposure of monkeys to aerosols has been described by Young et al. (1977), except that the cages described were replaced by a plexiglas chamber (32 x 25 x 40 cm) capable of exposing 4 monkeys to aerosols simultaneously. The exposure chamber was fitted with perches, trays for food and water, and collection of waste, thus permitting continuous aerosol exposures. Aerosol samples were collected with all-glass impingers containing distilled water and were assayed for ribavirin content spectrophotometrically as described by Stephen et al. (1976). Inhaled doses were calculated as described by Berendt et al. (1978).

Daily clinical studies included determination of rectal temperature, respiratory rate, appetite, weight, activity, coughing, sneezing, and presence of labored breathing (dyspnea). Twice weekly, total and differential leukocyte and erythrocyte counts, hemoglobin, hematocrit, and direct and total bilirubin were determined. Serum lactic dehydrogenase (LDH), glutamic-oxaloacetic transaminase (GOT) and glutamic-pyruvic transaminase (GPT) activities were also evaluated twice weekly.

RESULTS AND DISCUSSION

In the first experiment, 8 monkeys were given an estimated dosage of 40 mg of ribavirin/kg/day for 4 days and four were employed as water-controls. To achieve the required dosage of ribavirin 4 monkeys were exposed to aerosols continuously for 22 hr/day. The remaining 2 hr were reserved for maintenance of equipment and clinical evaluation of all monkeys. After the fourth day monkeys were moved to holding cages for 5 additional days. Four monkeys were then exposed to aerosols of distilled water for 22 hr/day for 4 days and observed for 5 additional days. Finally, 4 more monkeys were exposed to ribavirin in the same manner as the first group. No significant changes were seen in any of the parameters measured.

Since no significant changes were seen in the first experiment an additional group of 6 monkeys (2 groups of 3 each) given 40 mg/kg of ribavirin per day by exposing them to aerosols for 150 min/day for 4 days. The dose was adjusted by greatly increasing the concentration of ribavirin in the disseminator and shortening the time of exposure. For the purpose of comparison, 6 monkeys were given 40 mg/kg/day for 4 days by stomach tube, and 6 additional monkeys were given an oral dose of 400 mg/kg/day. The latter dose was used as a positive control to ascertain the sensitivity of our clinical criteria to evaluate adverse reactions. Monkeys given ribavirin were lethargic when compared to monkeys given aerosols of water, regardless of dose or route of administration (Fig. 1). While 20% of the monkeys in the ribavirin aerosol and the 40 mg/kg oral groups were dyspneic (Fig. 1), all monkeys in the group given an oral dose of 400 mg/kg were. None of the monkeys responded adversely to aerosols of water.

Dyspnea and lethargy disappeared by day 6. Hematocrit, erythrocyte count and hemoglobin concentrations were lower compared to control values in the 400 mg/kg oral dose group (Fig. 2). This observation is consistent with that of Sidwell et al. (1977) for monkeys given 200 mg/kg/day. Erythrocyte-associated parameters continued to fall after treatment was terminated on day 4, but returned to normal by day 13 (not shown). Both groups of monkeys given oral ribavirin showed mild anorexia on the second and third days and transient weight loss (maximum of 5%). No other changes were noted. Since only transient reactions were observed in monkeys following aerosol treatment with 40 mg/kg/day, it is concluded that short courses of aerosolized ribavirin may be administered safely. The dose is five times greater than the minimal effective dose previously reported (Berendt et al.) in experimentally induced influenza virus infection of squirrel monkeys.

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FOOTNOTES

¹In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as promulgated by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council. The facilities are fully accredited by the American Association for Accreditation of Laboratory Animal Care.

²The views of the authors do not purport to reflect the positions of the Department of the Army or the Department of Defense.

³Virazole^R, ICN Pharmaceuticals, Irvine, California.

FIGURE LEGENDS

- Fig 1. Effect of ribavirin on the appearance of lethargy (top) and dyspnea (bottom) in squirrel monkeys. Doses: aerosol drug - 40 mg/kg/day for 4 days, low dose - oral drug 40 mg/kg, high-dose oral - 400 mg/kg. The ordinate shows the percent of monkeys in each group in which a positive response was noted.
- Fig 2. Effect of ribavirin on hematocrit, erythrocyte (RBC) and hemoglobin levels. Doses: aerosol drug - 40 mg/kg/day for 4 days, low-dose oral - 40 mg/kg, high-dose oral - 400 mg/kg/day.

