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IDN
Infectious Diseases Newsletter

Volume 4, Number 10, October 1985

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Elsevier

Ribavirin

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Ribavirin is a seemingly new antiviral agent. It was actually discovered over a decade ago, but only recently has the breadth of its therapeutic potential been explored. In contrast to the other currently available antiviral drugs, ribavirin has activity against a broad spectrum of viruses, including the epidemic respiratory viruses. It is for this use that approval by the Food and Drug Administration is currently being sought.

The structure of ribavirin (1-β-D-ribafuranosyl-1,2,4-triazole-3-carboxamide) is similar to that of guanosine and inosine (Figure 1). It is a synthetic nucleoside that appears to exert its virustatic effect through several different mechanisms. The monophosphate, diphosphate, and triphosphate metabolites of ribavirin are inhibitory to viral replication. Viral associated enzymes appear to be specifically inhibited, and ribavirin becomes incorporated into the viral messenger RNA, resulting in an interference with the synthesis of the viral proteins.

Ribavirin is active against a wide variety of both RNA and DNA viruses (Table 1). In vitro and in animal models, inhibitory activity has been demonstrated for the three major groups of respiratory viruses that are epidemic in the United States: the influenza viruses, respiratory syncytial virus, and the parainfluenza viruses. Other viruses of clinical importance that are inhibited by ribavirin experimentally include measles, the arenaviruses, and the herpesviruses.

Clinical trials in the United States were initially aimed at the prevention and treatment of influenza virus infections by daily peroral administration of ribavirin. In these studies, the efficacy of ribavirin prophylactically and therapeutically was variable. Subsequently Knight and colleagues developed an apparatus to administer ribavirin as a small-particle aerosol. Aerosol administra-

0278-2316/85/$0.00 + 2.20 ISSN 0278-2316 IDINDN 4(10)73-80, 1985

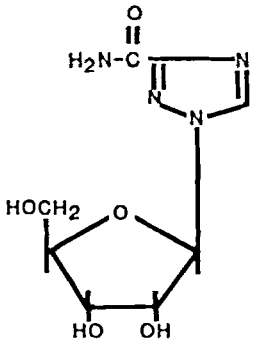

Figure 1. Ribavirin is a synthetic nucleoside that is similar to guanosine and inosine.

tion in a controlled manner for a total of 12 hours per day to college-aged students with acute influenza resulted in a significant amelioration of the signs and symptoms of acute, uncomplicated infections whether caused by influenza A or influenza B viruses. Viral shedding was also diminished in the patients receiving ribavirin, and no toxicity was noted.

The activity of ribavirin against respiratory syncytial virus (RSV) in vitro was of particular interest, because RSV remains the major respiratory pathogen of infants and young children and has thus far defied control by immunization or other means of prophylaxis. When studies using cotton rats appeared to be promising, investigation was undertaken in volunteers infected experimentally with RSV. The experimental disease was mild, but there appeared to be some clinical benefit. More importantly, sequential pulmonary function studies, including carbechol challenge, showed no adverse effects from the aerosol either in the patients treated with ribavirin or in the controls treated with placebo.

Trials evaluating the efficacy of treating infants hospitalized with RSV lower respiratory tract disease were then initiated at the University of Rochester and Baylor University in 1981. At Rochester, ribavirin was administered for 20 hours per day for an average of 5 days to moderately-to-severely ill infants with RSV pneumonia; at Baylor somewhat more mildly ill infants with bronchiolitis received the aerosol for 12 hours each day. In both of these double-blind, controlled studies the rate of improvement in the infants receiving ribavirin was significantly greater. Diminished viral shedding and significant improvement in the arterial oxygen saturation of the treated infants were also noted. The most recent studies at these and several other centers have confirmed the beneficial effect of ribavirin aerosol on the course of RSV lower respiratory tract disease in hospitalized infants, including those with underlying cardiac and pulmonary diseases who are most at risk for severe or fatal illness. In none of these studies has toxicity from the drug been observed.

Ribavirin's greatest clinical éclat may come in other parts of the world where arenaviruses and bunyaviruses circulate. In Sierra Leone, McCormick and colleagues have demonstrated a remarkable reduction in the mortality from Lassa fever with the use of oral and intravenous ribavirin. Also of interest, but of unknown significance, is the recent observation that ribavirin suppressed the replication of the human T-lymphotropic virus type III (HTLV-III).

Currently, Food and Drug Administration approval is being sought for the use of ribavirin administered as an aerosol in the treatment of RSV infection. The equipment required to generate small-particle aerosols restricts ribavirin treatment to hospitalized patients. The greatest benefit of such therapy may be for those infants at high risk for severe or complicated RSV disease—those infants in the first few months of life with congenital heart disease, bronchopulmonary dysplasia, and immune deficiency diseases. Also, ribavirin may be of particular value in controlling the often overwhelming infections with respiratory viruses that occur in infants with severe combined immunodeficiency disease. Because of the apparent lack of toxicity of aerosolized ribavirin, and the relative ease of administering it to infants in an oxygen tent or hood, treatment of less severely ill infants hospitalized with RSV infection should be considered. The indication for ribavirin treatment may be most compelling for RSV-infected infants on ventilators; however, it is with these infants that the greatest technical expertise is required.

Other doses and different routes of administration of ribavirin have not been well explored for the treatment of respiratory viral infections. However, aerosol administration

Table 1. Viruses Inhibited by Ribavirin Either In Vitro or In Vivo

RNA viruses	*DNA viruses*
Influenza A and B viruses	Herpes simplex viruses 1, 2
Parainfluenza viruses	Some adenoviruses
Respiratory syncytial virus	Varicella-zoster
Mumps	Cytomegalovirus
Coronaviruses	Vaccinia
Some picornaviruses	Papovaviruses (Shope fibroma)
Some arenaviruses	
Some bunyaviruses	
Some togaviruses	
Measles	
Reoviruses 1, 2, 3	
Vesicular stomatitis virus	
Retroviruses (Friend leukemia virus)	

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produces extraordinarily high concentrations of ribavirin in the respiratory secretions, with relatively low concentrations in the serum; some accumulation will occur with prolonged administration.

The extent of application of ribavirin is difficult to predict at this time. Nevertheless, ribavirin and, probably, congeners thereof have several important traits—low toxicity, broad activity, and apparently little capacity for engendering resistance.

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Ratio of Bacterial Mass to Colony-Forming Units: A New Criterion for the Study of Susceptibility to Antimicrobics

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Quantitation of the susceptibility of bacteria to antimicrobics in either a clinical or a research laboratory often involves enumeration of viable bacteria as counts of colony-forming units (CFUs). In the absence of an inhibitor of growth, one bacterium trapped on the surface of drug-free agar medium will give rise to one CFU. A quantitative estimate of antibacterial activity is derived by comparing the number of CFUs of bacteria remaining after exposure to varying concentrations of an antimicrobic with the number of CFUs present in the unexposed control population. This estimate is accurate only if a one-to-one relationship of a single bacterium to a single CFU is strictly maintained. Surprisingly, this fundamental requirement for quantitative susceptibility testing is neither generally nor widely acknowledged.

Soon after the discovery of antibacterial antimicrobics it was observed that in the presence of such drugs, the morphology of bacteria may be altered. Gram-negative bacilli elongate and become filamentous when exposed to β-lactam antimicrobics and many non-β-lactam antibiotics. The elongated bacilli are elongated cells that contain a number of genomes within a common cytoplasm; the number of genomes represents the number of replications that occurred while under exposure to the antimicrobic (Figure 1). When such a filament is removed from the drug-containing medium and is placed in drug-free medium, it will separate into individual bacilli, corresponding in number to the number of viable genomes contained in that filament. In the CFU agar system, regardless of the number of viable genomes contained in one filament, one filament will give rise to one CFU. Therefore, the utilization of the CFU system as the single criterion for determining the activity of an antimicrobic will result in an erroneous interpretation because the number of viable genomes contained in the filament will not be detected. Filaments can form in vivo after the administration of an antimicrobic. When the concentration of the drug drops below that required for the maintenance of a filamentous morphology, the filament will yield viable bacilli corresponding in number to the number of viable genomes contained in that filament. Antimicrobics that are active against gram-positive cocci have a similar effect. For example, exposure of *Staphylococcus aureus* to subinhibitory concentrations of β-lactam antimicrobics causes the development of a cluster of cells held together by thick cross walls. Such a cluster may contain as many as 16 cells (genomes), but will yield on subculture to drug-free agar only one CFU. As with filaments, clusters, in the absence of the drug, separate into the constitutive staphylococci.

The morphological effects of antimicrobics might also cause problems of interpretation in studies that utilize CFUs as a means of de-

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