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## Antiviral Chemotherapy and Prophylaxis of Viral Respiratory Disease

Steven J. Sperber, MD,\* and Frederick G. Hayden, MD†

Viral respiratory infections are the most common infectious diseases of humans and are a major cause of morbidity and mortality. In developing countries respiratory viruses remain an important cause of childhood mortality.<sup>1,68</sup> In the United States influenza epidemics have caused at least 10,000 excess deaths during 18 of the last 28 years.<sup>2</sup> The average adult experiences 2 to 5 and the average child 8 to 12 respiratory illnesses per year. These account for about 250 million days of restricted activity and about 30 million days lost from work and school.<sup>29</sup> During influenza epidemics, costs related to excess hospitalizations are estimated to be in the hundreds of millions of dollars.<sup>9</sup> The estimated direct costs related to upper respiratory illnesses treated in the outpatient setting exceeded \$3.5 billion in 1984.<sup>36</sup> Certain viruses, especially influenza<sup>2</sup> and respiratory syncytial virus (RSV),<sup>65</sup> are important nosocomial pathogens that infect both hospital personnel and patients.

The respiratory viruses, which are listed in Table 1, differ from each other in fundamental biochemical characteristics, epidemiologic patterns, and clinical manifestations of infection. These viruses cause a number of overlapping clinical syndromes, including the common cold, pharyngitis, laryngitis, tracheobronchitis, pneumonia, and, in children, croup and bronchiolitis. In addition to multiple etiologies for each syndrome, each type of virus is capable of causing more than one clinical syndrome. Consequently, rapid viral diagnosis is an important aspect of applying specific interventions for prevention and treatment.

Active immunization has not been successful, except against influenza A and B viruses and certain adenovirus serotypes (see Table 1). This is due in part to the vast antigenic diversity of these viruses. The different serotypes of rhinoviruses, which account for about 40 per cent of common

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\*Fellow in Infectious Diseases, Division of Epidemiology and Virology, Department of Internal Medicine, University of Virginia School of Medicine, Charlottesville, Virginia

†Associate Professor of Internal Medicine and Pathology, and Associate Director, Clinical Microbiology Laboratory (Virology), University of Virginia School of Medicine, Charlottesville, Virginia

**Table 1.** *Clinical Applications of Antiviral Agents in Naturally Occurring Respiratory Viral Infections*

VIRUS	EFFECTIVE FOR PROPHYLAXIS	EFFECTIVE FOR TREATMENT	VACCINE AVAILABLE
Influenza A	Amantadine (oral) Rimantadine (oral)†	Amantadine (oral)* Rimantadine (oral)† Ribavirin (aerosol)*†	Inactivated
Influenza B Respiratory syncytial Parainfluenza		Ribavirin (aerosol)*† Ribavirin (aerosol) Ribavirin (aerosol)†	Inactivated
Rhinovirus Adenovirus Coronavirus	IFN- $\alpha$ 2 (intranasal)†		Attenuated

\*Uncomplicated disease only

†Currently not approved for this use

colds, currently number 100. Additionally, antigenic changes in epidemic virus strains, as occurs with influenza A, necessitate annual reformulation and administration of this vaccine. Thus, a need exists for effective antiviral agents. This article reviews antivirals useful in the prevention and treatment of respiratory viral infections. In addition to discussing those of proven clinical value (see Table 1), it concludes by briefly considering agents and approaches of investigational interest.

## AMANTADINE

Amantadine (1-adamantanamine) hydrochloride, the first antiviral agent licensed for treatment of respiratory virus infections in the United States, specifically inhibits the replication of influenza A viruses. This symmetric tricyclic amine (Fig. 1A), given orally, has therapeutic<sup>165, 177</sup> and prophylactic<sup>8, 39, 50, 129, 131</sup> efficacy in human influenza A virus infections.

### Mechanism of Action

The exact mechanism of action of amantadine has not been defined, but it appears to inhibit an early stage of replication, possibly uncoating of the virus within lysosomes.<sup>107, 141</sup> One proposed mechanism of action relates to raising the pH within lysosomes and possibly interfering with the low pH-mediated events of uncoating.<sup>128</sup> Although amantadine is readily concentrated in the lysosomes of mammalian cells, most of the cell-associated amantadine does not appear to contribute significantly to its antiviral action.<sup>143</sup> Furthermore, a nonspecific effect on lysosomal pH would not explain amantadine's restricted spectrum activity. Genetic studies indicate that susceptibility of human influenza viruses to low concentrations (1  $\mu$ g per ml) of amantadine is conferred by the RNA segment coding for the M (matrix) proteins of the virus, and recent evidence indicates that single amino acid changes in the transmembrane portion of the M2 protein can lead to amantadine resistance.<sup>68</sup>

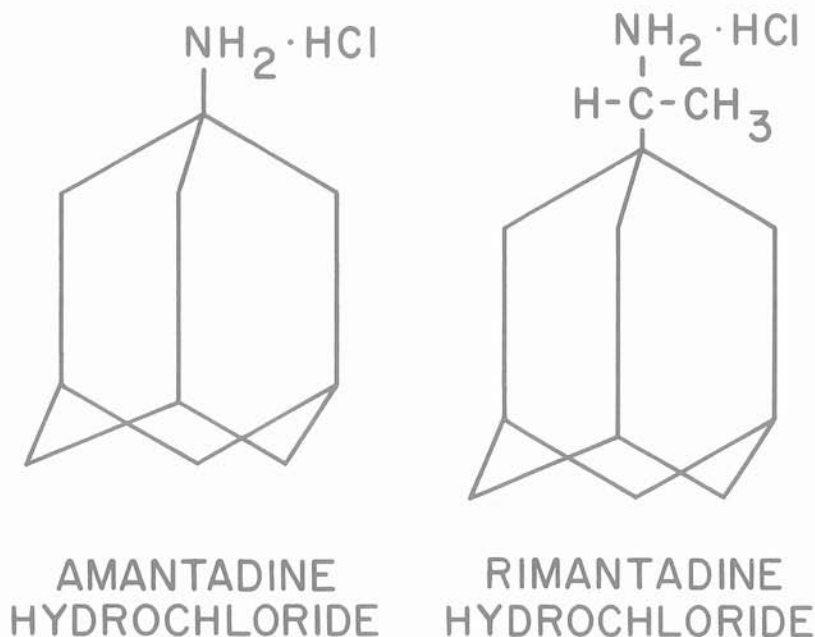


Figure 1. Chemical structures of amantadine hydrochloride and rimantadine hydrochloride.

### Preclinical Studies

Although high concentrations (10  $\mu\text{g}$  per ml or greater) are inhibitory for other viruses, low concentrations (1  $\mu\text{g}$  per ml or less) inhibit only influenza A viruses.<sup>31</sup> By plaque reduction assay, the 50 per cent inhibitory concentration of amantadine ranges from 0.2 to 0.4  $\mu\text{g}$  per ml for most common influenza A isolates.<sup>73</sup> In mice, amantadine given subcutaneously, intraperitoneally, or orally before virus challenge provides dose-dependent protection against death from influenza.<sup>32</sup> Therapeutic activity is observed in mice if treatment is begun as late as 72 hours after infection. Aerosolized amantadine is more efficacious than intraperitoneal administration in mice.<sup>166</sup>

At high concentrations (25 to 50  $\mu\text{g}$  per ml), not achievable in humans with conventional doses, lymphocyte transformation responses to mitogens and specific antigens *in vitro* are inhibited.<sup>116</sup> High doses are teratogenic in certain laboratory animals.

### Resistance

Amantadine-resistant influenza A viruses have been recovered under laboratory conditions, when virus is passaged in the presence of amantadine.<sup>25, 97</sup> In experimental avian influenza, amantadine- and rimantadine-resistant viruses have been isolated from drug-treated birds.<sup>167</sup> These birds were able to infect and cause illness in contact birds that were receiving amantadine prophylaxis. Although no cases of drug resistant isolates have

been reported in persons receiving amantadine for prophylaxis or therapy, the monitoring of drug susceptibilities of respiratory viruses will assume increasing importance as the use of respiratory antivirals increases. Resistant viruses have reportedly been isolated from non-drug exposed patients.<sup>90</sup>

### Human Pharmacokinetics

Amantadine is well-absorbed after oral administration with time to peak plasma levels averaging 1 to 4 hours.<sup>12</sup> Steady-state levels are obtained within 3 days.<sup>6</sup> Measurement of amantadine concentrations has been achieved by gas liquid chromatography with electron capture or flame ionization detection.<sup>12, 98, 151</sup> After administration of 200 mg daily in divided doses, steady-state peak and trough plasma concentrations in healthy adults average 0.5 to 0.7  $\mu\text{g}$  per ml<sup>81</sup> and 0.3  $\mu\text{g}$  per ml,<sup>6</sup> respectively. During long-term administration of 6 mg per kg per day to children with cystic fibrosis, mean plasma concentrations of 0.6  $\mu\text{g}$  per ml are detected.<sup>175</sup>

Salivary and nasal mucus concentrations are similar to those in the blood.<sup>12, 85, 153</sup> In the mouse lung, 15- to 60-fold greater concentrations are found than in the blood following oral drug administration.<sup>12</sup> In one report the amantadine concentration in autopsy lung tissue from an infant with immunodeficiency was 21.4  $\mu\text{g}$  per ml, 14-fold the serum concentration.<sup>48</sup> Despite the high concentration, viral replication was not eliminated.

Approximately 90 per cent of orally administered amantadine is recovered unmetabolized in the urine.<sup>98, 164</sup> It is excreted by glomerular filtration and probably tubular secretion.<sup>98</sup> The mean plasma half-life is about 12 hours (range: 9 to 31 hours) in healthy young adults,<sup>98</sup> which allows dosing once or twice daily. The plasma half-life increases with renal insufficiency and is over 30 days in anuric patients.<sup>98</sup> Because of age-related decreased renal clearance, higher blood levels are also seen in the elderly<sup>5</sup>; consequently, dose reductions are indicated to reduce the risk of side-effects. Only a small portion of the drug is removed by hemodialysis.<sup>98</sup>

### Toxicity

The occurrence of dose-related side-effects may be responsible in part for the slow acceptance by clinicians of amantadine as an effective anti-influenza agent. Central nervous system adverse effects, including nervousness, lightheadedness, difficulty concentrating, insomnia, and fatigue, are reported by 5 to 33 per cent of those receiving 200 mg per day. Loss of appetite and nausea also occur infrequently.<sup>79</sup> In long-term prophylaxis studies using amantadine 200 mg daily, the excess drop-out rate due to drug side-effects has ranged from 6 to 11 per cent<sup>39, 123, 132</sup> (Table 2). During a 4-week uncontrolled prophylaxis trial involving 78 residents of a mental institution, 46 per cent had clinical manifestations compatible with adverse effects and 19 per cent had increased seizure activity on a relatively high dosage (6.6 mg per kg per day).<sup>8</sup> One third of college students taking 200 mg daily for 5 days in one study complained of difficulty concentrating or lightheadedness, and 14 per cent did not complete a 5-day course of treatment,<sup>165</sup> whereas another study in a similar population found complete compliance despite minor symptoms.<sup>177</sup> Doses of 300 mg per day are associated with high rates of adverse complaints and decreased psychomotor

**Table 2.** *Influenza A Virus-Induced Illness, Laboratory-Documented Influenza A, and Withdrawal Rates Among Volunteers Receiving Placebo, Rimantadine, or Amantadine for Seasonal Prophylaxis\**

TREATMENT GROUP	PER CENT OF SUBJECTS			
	INFLUENZA A ILLNESS†	INFLUENZA A INFECTION‡	WITHDRAWALS	WITHDRAWAL FOR CNS SIDE-EFFECTS
Placebo	21	24	11	4
Rimantadine	3	8	10	6
% reduction§	85	66		
Amantadine	2	6	22¶	13**
% reduction§	91	74		

\*From Dolin R, Reichman RC, Madore HP, et al: A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. *N Engl J Med* 307:580, 1982; with permission

†Defined as influenza-like illness along with virus isolation or a rise in serum antibody to influenza A virus. *Influenza-like illness* is defined as a cough and/or an oral temperature of  $>37.7^{\circ}\text{C}$ , and at least two of the following: sore throat, headache, and myalgia

‡Laboratory evidence of influenza A virus infection (serology, virus isolation)

§Per cent reduction compared to rate in placebo group

|| $p < 0.001$ , compared with placebo

¶ $p < 0.01$ , compared with placebo, and  $p < 0.005$ , compared with rimantadine

\*\* $p < 0.01$ , compared with placebo, and  $p < 0.05$ , compared with rimantadine

performance on tests of sustained attention and problem-solving ability.<sup>79</sup> Neurotoxicity is most common at plasma concentrations above  $1.0 \mu\text{g per ml}$ <sup>81</sup> and with concomitant administration of antihistamines<sup>122</sup> or anticholinergics.<sup>148</sup> Confusion and auditory and visual hallucinations have occurred at toxic levels in patients with renal failure.<sup>101</sup> Serious neurologic reactions may be transiently reversed by physostigmine.<sup>21</sup>

Aerosol administration of amantadine is generally well-tolerated but causes mild local side-effects such as rhinorrhea and nasal irritation in healthy adults.<sup>80</sup> Reversible deterioration in pulmonary function, associated with coughing and wheezing, may occur in patients with pre-existing airway abnormalities.<sup>108</sup>

### Clinical Efficacy

A number of controlled, blinded studies have documented the efficacy of oral amantadine for both prophylaxis and treatment of experimentally induced and natural influenza A infections. Amantadine 200 mg per day is approximately 70 to 90 per cent effective in preventing naturally acquired influenza when taken for the duration of the outbreak in the community, usually 6 to 8 weeks<sup>39</sup> (see Table 2). Some amantadine recipients experience subclinical infection manifested by seroconversion. This is a desirable feature of chemoprophylaxis, because it would protect against reinfection by the same strain. Amantadine prophylaxis appears to be effective in preventing nosocomial infections in hospitals and institutions,<sup>8, 129</sup> among household family contacts,<sup>50</sup> and in boarding schools.<sup>131</sup> Dosages of 100 mg per day, which are well-tolerated, have been effective in teenagers.<sup>131</sup> Protection has been demonstrated against a range of strains including all three subtypes of human influenza A virus.

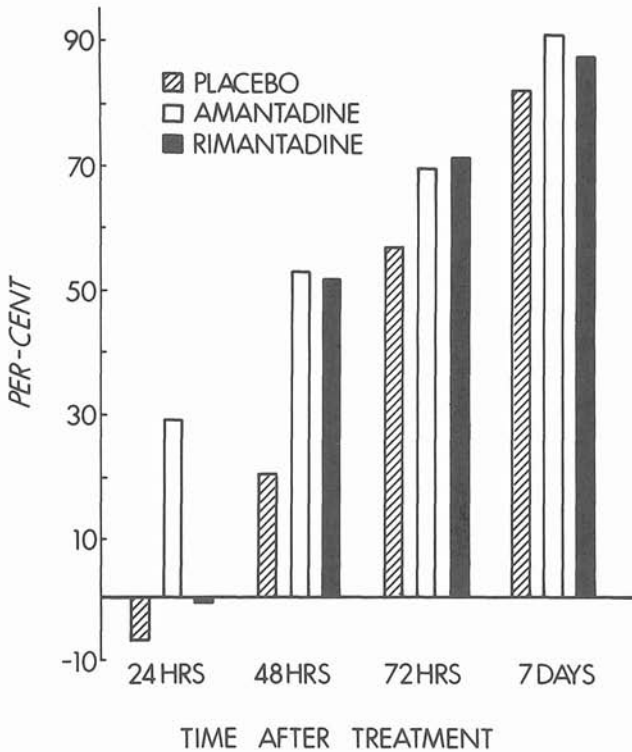


Figure 2. Per cent improvement in total symptoms and signs during treatment of influenza A with amantadine hydrochloride and rimantadine hydrochloride. At 48 hours each drug group differs significantly from placebo ( $p < 0.025$ ). (From Van Voris LP, Betts RF, Hayden FG, et al: Successful treatment of naturally occurring influenza A/USSR/77 H1N1. JAMA 245:1128, 1981; with permission. Copyright 1981, American Medical Association.)

Amantadine is an effective agent for the treatment of uncomplicated influenza A infections.<sup>165, 177</sup> When begun within 48 hours of onset of symptoms, a dosage of 200 mg per day is effective in decreasing the height and duration of fever, viral shedding, and the time to subjective improvement (Fig. 2). One study in college students found that amantadine treatment reduced the number of missed classes compared to placebo.<sup>165</sup> Another study in college students compared amantadine to aspirin for the treatment of influenza and found more rapid defervescence among the aspirin recipients, but amantadine recipients had significantly more rapid symptom improvement.<sup>177</sup> Certain abnormalities in peripheral airway function also improve more rapidly in amantadine recipients.<sup>113, 114</sup> Higher doses of amantadine (up to 500 mg per day) have been used under uncontrolled conditions to treat influenza pneumonia,<sup>30, 109</sup> but the efficacy of amantadine in treating severe influenza or its complications has not been established. Intermittent aerosolized amantadine had limited therapeutic effects in uncomplicated influenza infections.<sup>80</sup> The use of aerosolized amantadine, which can achieve high levels in respiratory secretions, has not been evaluated in influenza pneumonia.

Table 3. *Clinical Uses of Oral Amantadine and Rimantadine*


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<i>Prevention</i>
Seasonal prophylaxis in high-risk patients:
Vaccine ineffective
Vaccine toxicity or allergy
Supplemental protection
Short-term prophylaxis after immunization
Control of institutional outbreaks
Postexposure prophylaxis—family contacts (?)*
<i>Therapy</i>
Uncomplicated illness (<48 hours)
Prevention of complications in high-risk patients (?)*
Treatment of viral pneumonia (?)*

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\*(?) = efficacy not established

Oral amantadine is currently the only anti-influenza agent approved in the United States for both prevention and treatment of influenza A illness. The clinical uses of amantadine are summarized in Table 3, and a detailed discussion of prophylaxis strategies has been published by the Centers for Disease Control.<sup>2</sup> The usual adult dose of amantadine for both prophylaxis and treatment is 200 mg per day orally as either single or twice daily administration. Splitting the dose may decrease the incidence of side-effects.<sup>2</sup> The duration of administration for treatment is usually 5 to 7 days. For prevention, the duration of use depends on the specific prophylaxis strategy (for example, 2 weeks in conjunction with immunization, or 4 to 8 weeks for seasonal prophylaxis). Amantadine dosage must be decreased in the elderly (100 mg once daily) and those with renal insufficiency (creatinine clearance less than 80 ml per minute).<sup>2, 5, 98</sup> Nonelderly persons with an active seizure disorder appear to be at increased risk of seizure activity and should also be given reduced dosages (for example, 100 mg per day).<sup>2</sup>

## RIMANTADINE

Rimantadine (alpha-methyl-1-adamantane-methylamine) hydrochloride (see Fig. 1B), a derivative of amantadine, also has specific anti-influenza A activity. Similar to amantadine, rimantadine is believed to block a late step in the intracellular uncoating of the influenza A virus.<sup>16</sup>

### Preclinical Studies

Rimantadine appears to have greater intrinsic antiviral activity than amantadine.<sup>160</sup> Rimantadine concentrations required to cause 50 per cent inhibition of influenza A virus plaque formation range from 0.1 to 0.4 µg per ml.<sup>73</sup> Compared to amantadine, rimantadine produces significantly longer protection against influenza virus-induced cytopathic effects in ferret tracheal ciliated epithelium, and exhibits comparable protective effect at four- to eightfold lower concentrations.<sup>18</sup> At high concentrations (16 or 32 µg per ml) rimantadine is more toxic for uninfected epithelium than is amantadine.<sup>18</sup>



In mice, subcutaneous rimantadine has greater therapeutic efficacy against influenza than does equimolar doses of amantadine.<sup>160</sup> Prophylactic intraperitoneal rimantadine, beginning 24 hours prior to virus inoculation, results in lower pulmonary virus titers, less severe lung lesions, diminished antibody response, and decreased capability to transmit infection to contact animals, compared with amantadine or placebo.<sup>147</sup>

### Resistance

Passage of influenza A virus in the presence of rimantadine leads to the development of resistance.<sup>17</sup> One study found that *in vitro* passage of an H2N2 virus in the presence of amantadine resulted in resistance to amantadine but only slight resistance to rimantadine, whereas passage in the presence of rimantadine resulted in marked resistance to amantadine with only slight resistance to rimantadine.<sup>160</sup> Rimantadine-resistant viruses have been isolated from birds treated with this drug.<sup>167</sup> Recently, rimantadine treatment of children was associated with prolonged viral shedding and recovery of resistant isolates.<sup>66A, 158A</sup>

### Human Pharmacokinetics

Despite their structural similarity (see Fig. 1), significant differences exist between amantadine and rimantadine kinetics in man. Rimantadine has a longer plasma half-life, lower plasma concentrations, and different metabolism than amantadine. Rimantadine has good oral bioavailability but relatively slow absorption with time to peak plasma levels of 3 to 6 hours.<sup>85</sup> At steady-state in young adults given dosages of 100 mg twice daily, peak plasma concentrations are approximately 0.4  $\mu\text{g}$  per ml.<sup>81</sup> In an elderly population receiving 100 mg twice daily for 3 months, peak steady-state plasma levels average 1.2  $\mu\text{g}$  per ml.<sup>130</sup>

In healthy adults the plasma half-life averages 24 to 36 hours.<sup>85, 164</sup> Rimantadine undergoes extensive metabolism with subsequent renal elimination of metabolites. Less than 10 per cent of the parent drug is excreted unchanged in the urine. The elimination half-life is increased about 50 per cent in dialysis patients, but hemodialysis does not remove significant amounts of rimantadine. Rimantadine concentrations are determined by gas chromatography using methods similar to those for amantadine but with modified initial derivatization steps.<sup>81</sup>

Following single 200-mg doses, the maximum nasal mucus concentrations of rimantadine and amantadine are similar, and the ratio of nasal mucus to plasma concentration is about twofold higher for rimantadine.<sup>85</sup> These findings suggest that rimantadine may be concentrated in respiratory secretions, a result that could explain rimantadine's comparable efficacy, despite lower plasma concentrations than for amantadine.<sup>81, 85</sup>

### Toxicity

At equivalent dosages of 200 to 300 mg per day, rimantadine is associated with fewer side-effects than is amantadine, and this represents the major clinical advantage of rimantadine. In particular, central nervous system toxicity is uncommon in recipients of rimantadine 200 mg per day<sup>79, 165</sup> and withdrawals due to adverse effects occur less often than with

amantadine<sup>39, 165</sup> (see Table 2). At a dosage of 300 mg per day for 4½ days, 3 per cent of rimantadine recipients considered their work performance impaired, compared with 30 per cent of amantadine recipients.<sup>79</sup> Aerosolized rimantadine has been associated with an unpleasant taste or smell and nasal irritation.<sup>89</sup>

### Clinical Efficacy

The prophylactic and therapeutic efficacy of rimantadine is similar to that of amantadine in naturally occurring influenza A infections. Most studies have been conducted at dosages of 200 to 300 mg per day, although some reports suggest that as little as 50 mg per day is effective for prophylaxis.<sup>178</sup> A dosage of 200 mg per day is approximately 85 per cent effective in preventing laboratory-documented influenza illness (see Table 2).<sup>39</sup> Among children receiving prophylaxis, rimantadine 5 mg per kg per day reduced the influenza A infection rate from 32 to 3 per cent and provided complete protection against influenza A illness.<sup>24</sup> In previously vaccinated nursing home residents, rimantadine was 75 per cent effective in preventing influenza-like illness, compared to placebo.<sup>38</sup>

One study comparing rimantadine and amantadine given 100 mg twice daily for treatment of uncomplicated influenza found slightly more rapid improvement over the first 24 hours of treatment in the amantadine recipients (see Fig. 2). Thereafter, similar functional recovery and reductions in symptoms and viral shedding occurred in both groups, with fewer side-effects in the rimantadine recipients.<sup>165</sup> Another study used a modified loading regimen so that patients received 400 to 500 mg of rimantadine over the first 24 hours and found rapid reductions in viral titers and fever, compared to placebo.<sup>86</sup> In treatment of children with influenza, rimantadine was associated with more rapid symptom improvement and defervescence compared to acetaminophen in one study<sup>66A</sup> but not another.<sup>158A</sup> Aerosolized rimantadine for treatment of experimentally induced influenza infection has effects compared to 150 mg per day of rimantadine orally.<sup>89</sup> Rimantadine is expected to be licensed for oral use in the United States in the near future. Its indications for clinical use are the same as those for amantadine (see Table 3).

## RIBAVIRIN

Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3 carboxamide) is a synthetic nucleoside analog of guanosine (Fig. 3). Its antiviral spectrum includes a variety of DNA and RNA viruses, in particular influenza A and B, parainfluenza, and RSV viruses.<sup>100, 146, 150</sup> Such an agent would have clinical application where serious illness may be caused by any of these viruses and where clinical features are not distinctive enough to allow an etiologic diagnosis. Because of limited effectiveness and concerns regarding hematologic toxicity when ribavirin is given orally, recent studies have focused on aerosol administration.

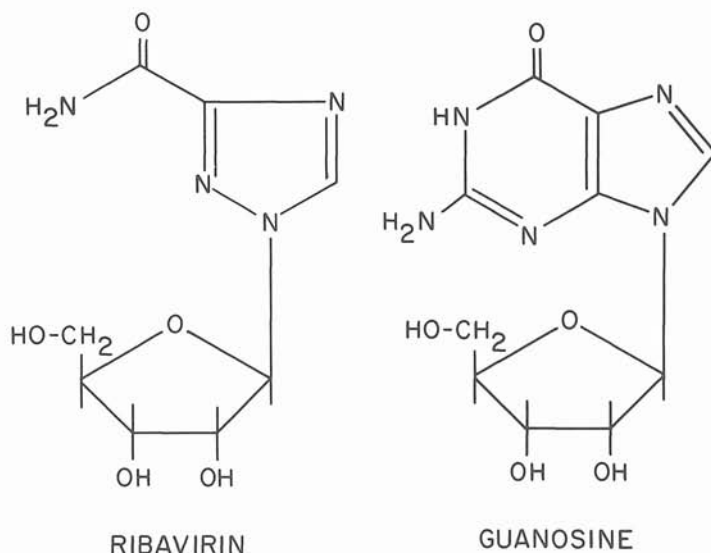


Figure 3. Chemical structures of ribavirin and guanosine.

### Mechanism of Action

Several different mechanisms of antiviral action have been proposed for ribavirin.<sup>57</sup> Ribavirin monophosphate acts as a feedback inhibitor of inosine monophosphate dehydrogenase, an enzyme responsible for the synthesis of guanine nucleotides.<sup>173</sup> Ribavirin triphosphate inhibits steps in the capping and elongation of the messenger RNA of certain viruses.<sup>172</sup> It appears to directly interfere with the influenza virus RNA polymerase complex. In certain test systems ribavirin concentrations of 5 to 25  $\mu\text{g}$  per ml inhibit cellular macromolecular synthesis, cell growth, and lymphocyte proliferative responses.<sup>112, 125, 140, 174</sup> Ribavirin has additional biologic activities including inhibition of humoral antibody responses, and antitumor effects.<sup>139, 152</sup>

### Preclinical Studies

The 50 per cent plaque inhibitory concentrations of ribavirin range from approximately 3 to 9  $\mu\text{g}$  per ml for influenza A and B viruses,<sup>14, 73</sup> 3 to 10  $\mu\text{g}$  per ml for respiratory syncytial viruses (RSV),<sup>99</sup> and from 10 to 12  $\mu\text{g}$  per ml for parainfluenza viruses.<sup>13</sup> By plaque reduction assay in canine kidney (MDCK) cells, influenza A viruses appear to be 10-fold less sensitive to ribavirin than amantadine,<sup>13, 73</sup> but by yield reduction assay in primary rhesus monkey kidney cells, ribavirin appears to be more active than rimantadine.<sup>87</sup>

Aerosolized ribavirin initiated at 6 hours after infection in mice significantly lowers virus titers and prevents pneumonia in experimental influenza infections, whereas similar beneficial effects are not observed with aerosolized amantadine or rimantadine.<sup>166</sup> Relatively brief aerosol exposures (2 hours, twice daily) to high concentrations of ribavirin provides protection

comparable to that observed with longer treatments (11 hours per day) at threefold lower concentrations.<sup>176</sup> Ferrets treated with ribavirin and subsequently infected with influenza virus do not develop a typical febrile reaction or serum or local antibodies, and have 10-fold lower virus titers in nasal washings than untreated animals.<sup>139</sup> Recent studies have shown that intravenous administration of liposome-encapsulated ribavirin is more effective in the treatment of experimental murine influenza than higher doses of free ribavirin given by the same route.<sup>54</sup> High doses are embryotoxic in rabbits and rats, and teratogenic in rats but not baboons.<sup>96</sup>

### Resistance

Development of resistance has not been observed during the treatment of human influenza<sup>170</sup> or RSV<sup>62, 64, 119</sup> infections with aerosolized ribavirin. Passage of RSV in the presence of inhibitory concentrations of ribavirin does not select viruses resistant to the drug.<sup>99</sup>

### Human Pharmacokinetics

Limited information is available concerning the pharmacokinetics of ribavirin because of the lack of routine means for measurement. By radioimmunoassay, the plasma half-life averages approximately 9 hours (range: 5.0 to 13.5 hours).<sup>163</sup> Using orally administered 14-C labeled ribavirin, it has been found that 53 per cent of the dose is excreted in the urine.<sup>22</sup> Radioactivity is concentrated in red blood cells with an apparent half-life of 40 days.<sup>22</sup>

The approved use of ribavirin for viral respiratory disease in the United States is currently limited to administration by small-particle aerosol for the treatment of RSV infections. Generators have been designed to produce particles of aerodynamic size averaging 1.5  $\mu\text{m}$  in diameter. Using radiolabeled tracers, inhalation of this aerosol mist by uninfected adults produces uniform distribution of about 70 per cent of the inhaled particles throughout the respiratory tract.<sup>109</sup> Mean peak respiratory secretion levels up to 1900  $\mu\text{g}$  per ml have been measured after 8 hours of exposure in children.<sup>28</sup> Plasma concentrations depend on the duration of exposure and average 0.9  $\mu\text{g}$  per ml and 1.5  $\mu\text{g}$  per ml after 8 hours of exposure daily for 2 and 3 days, respectively.<sup>28</sup> The elimination half-life of ribavirin in respiratory secretions is approximately 2 hours.<sup>28</sup>

### Toxicity

Oral ribavirin administration has been associated with reversible decreases in red blood cell counts, increases in serum bilirubin, and reticulocytosis,<sup>152</sup> which are most likely due to ribavirin accumulation in, and toxicity for, circulating red blood cells. Hematologic toxicity has not been observed with aerosolized treatments.<sup>10, 64, 66, 117, 170</sup> Aerosol administration has been reported to cause bronchospasm in some adults with pre-existing airway disease, but has been well-tolerated when used for treatment of RSV infections in children. One case of transient redness of the eyelids has been described, presumably due to deposition of the drug on the skin.<sup>10</sup> Potential problems with the drug delivery system are discussed in the next section.

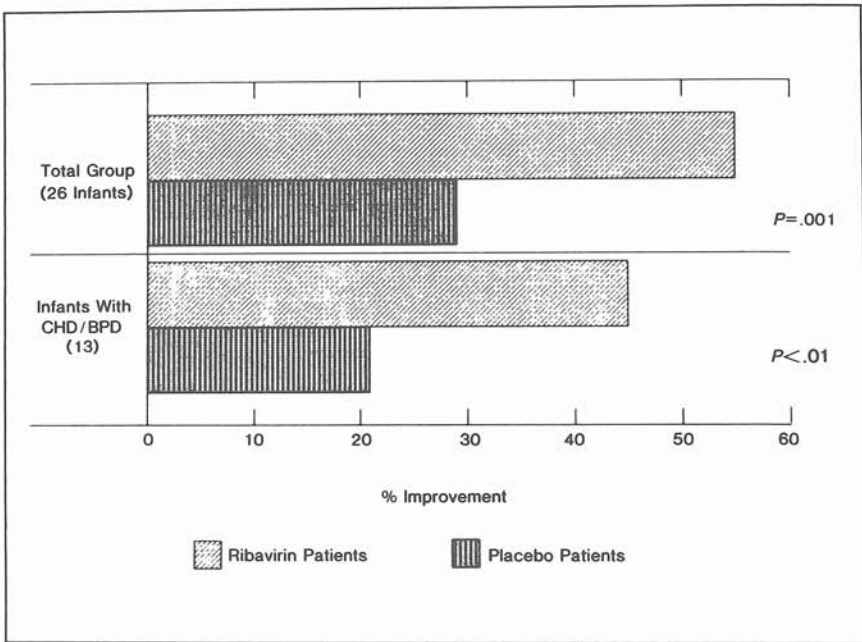


Figure 4. Per cent improvement in illness severity from start to end of therapy in infants with RSV infection who received aerosolized ribavirin or placebo for all infants (top two bars) and for infants with congenital heart disease (CHD) and bronchopulmonary dysplasia (BPD) (bottom two bars). (From Hall CB, McBride JT, Gala CL, et al: Ribavirin treatment of respiratory syncytial viral infection in infants with underlying cardiopulmonary disease. JAMA 254:3047, 1985; with permission. Copyright 1985, American Medical Association.)

### Clinical Efficacy

**Respiratory Syncytial Virus (RSV).** Ribavirin by small particle aerosol is effective in the treatment of experimental<sup>66</sup> and natural<sup>10, 62, 64, 144, 158</sup> RSV infections. In infants with naturally acquired RSV lower respiratory tract disease, ribavirin given by continuous aerosol for 3 to 6 days causes more rapid improvement in illness severity and arterial oxygenation, and after several days of treatment decreases in viral titers in respiratory secretions, compared to placebo.<sup>64</sup> In infants with underlying cardiopulmonary disease and RSV lower respiratory tract infection, ribavirin recipients experience similar clinical benefits (Fig. 4). Decreases in virus titers in respiratory secretions occur by the third day of treatment.<sup>62</sup> Infants with RSV bronchiolitis treated with aerosolized ribavirin for 12 hours daily for 5 days have more rapid recovery from illness but no difference in virus shedding than those receiving placebo.<sup>158</sup> A recent study of infants with bronchiolitis treated with aerosolized ribavirin for 18 hours daily for at least 3 days found more rapid declines in respiratory and heart rates, compared to placebo.<sup>10</sup> In children with RSV infection, RSV-specific IgE and IgA antibody responses develop less frequently in nasopharyngeal secretions after treatment with aerosolized ribavirin, compared to untreated controls.<sup>44</sup> The long-term

benefits or consequences of using ribavirin for treatment of RSV infections have not been determined.

A specific generator unit is required for administration. Aerosol exposure has been given for 12 to 24 hours per day for 3 to 6 days using a reservoir concentration of 20 gm per ml to achieve an hourly dose of approximately 0.82 mg per kg per hour.<sup>64</sup> The usual daily dosage of ribavirin costs about \$250 to the hospital pharmacy, and treatment costs may exceed \$500 per day when respiratory therapy charges are included.

A consensus regarding which infants should receive this newly available therapy has not been reached. During a winter RSV epidemic, therapy might be appropriate for an illness consistent with RSV in an infant in one of the high-risk groups (congenital heart disease and pulmonary hypertension, bronchopulmonary dysplasia, severe combined immunodeficiency syndrome, or cystic fibrosis). Another potential indication for therapy is the group of presumed RSV-infected infants who manifest progressive deterioration likely to result in intubation.<sup>118</sup> Candidates include those with PaO<sub>2</sub> levels lower than 65 mm Hg or with rising PaCO<sub>2</sub> levels.<sup>4A</sup> In such cases, ribavirin could be started while awaiting results of rapid viral diagnostic tests. More controversial is its early use in RSV-infected infants who are not seriously compromised, or in infants already on ventilators, which may become clogged by the drug.<sup>118, 169</sup> Use of in-line filters may ameliorate this problem. Precipitation has also been reported with delivery of the drug in an infant receiving oxygen through a hood.<sup>93</sup> For these reasons, frequent routine checking of the tubing and equipment is essential.<sup>63</sup> Another concern, currently under study, is contamination of the environment and possible exposure of hospital personnel to ribavirin. Recent studies have not found ribavirin in the urine or sera of such personnel.<sup>4A</sup>

**Influenza.** Prophylactic oral administration of ribavirin 1000 mg per day reduces illness severity and virus titers in experimental influenza A infections,<sup>115</sup> but the same dose beginning within 24 hours after the onset of symptoms has no clinical benefit or inhibitory effects on viral shedding in natural influenza A infections.<sup>152</sup> Prophylactic oral ribavirin 600 mg per day has marginal effectiveness against experimental influenza B<sup>159</sup> and no activity against influenza A infection.<sup>26</sup>

Aerosolized ribavirin provides some therapeutic benefit in young adults with uncomplicated influenza A or B virus infection if started within 24 hours of symptom onset.<sup>58, 110, 117, 170</sup> Given to college students for up to 18 hours the first day and then 12 hours daily over the next 2 to 3 days, aerosolized ribavirin is associated with significant reductions in the height and duration of fever, systemic symptoms, and virus shedding, compared to placebo aerosol (average dose of ribavirin 2.4 gm over 42 hours).<sup>58</sup> Studies comparing the therapeutic activities of aerosolized ribavirin and oral amantadine or rimantadine have not been done. The use of aerosol therapy, which requires hospitalization and special equipment, for the treatment of uncomplicated influenza infections appears to be limited. A few patients with influenza pneumonia due to influenza types A and B have been treated with aerosolized ribavirin,<sup>109, 110</sup> but controlled trials are needed in high-risk groups.

**Other Respiratory Viruses.** Aerosolized ribavirin may be beneficial in

children with severe combined immunodeficiency syndromes complicated by RSV and parainfluenza type 3 infections.<sup>56, 119</sup> Two children with adenovirus pneumonia have also been treated with continuous aerosolized ribavirin for 3 days with apparent clinical benefit.<sup>15</sup>

## INTERFERONS

Interferons are regulatory proteins that can affect a variety of host cell functions including cell growth, immune response, and inhibition of virus replication. In particular, these proteins are capable of inducing a broad spectrum of antiviral activity, including all of the respiratory viruses. Once named for their principal cellular source, human interferons are currently classified by specific molecular types.<sup>105</sup> Alpha interferons (formerly leukocyte) include over 12 species. Beta interferon (formerly fibroblast) has at least one species, which appears to share the same cellular receptor as alpha interferons. Gamma, or immune, interferon is a lymphokine derived from stimulated lymphocytes. The molecular weights of alpha and beta interferons are approximately 17,000 daltons.

Because of the unavailability of sufficient quantities of pure interferon, initial research emphasized the use of chemical interferon inducers. These experiments were generally unsuccessful owing to problems of inadequate *in vivo* induction of interferon and, in some instances, poor tolerance. With advances in genetic engineering techniques during the past decade, however, it has become possible to produce large amounts of purified interferons. Recent studies have shown that intranasal administration of recombinant interferon-alpha 2b is effective in preventing experimental and natural rhinovirus colds.<sup>70</sup>

### Mechanism of Action

The exact mechanisms by which interferons induce an antiviral state in host cells are not fully understood.<sup>105</sup> Interferons induce the formation of several antiviral proteins in target cells that inhibit the translation of viral messenger RNA. Interferon exposure activates the enzyme 2,5-oligoadenylate synthetase to produce oligoadenylates, which in turn activate an endonuclease capable of degrading viral mRNA. In addition, interferons activate a protein kinase that catalyzes the phosphorylation of a subunit of the initiation factor eIF<sub>2</sub>, thereby inhibiting the initiation of viral protein synthesis. For certain viruses inhibition of maturation and assembly appears to occur. Detailed studies in mice have determined that a particular gene and its product, the Mx protein, confer selective resistance to influenza virus infection after interferon exposure.<sup>155A</sup>

### Preclinical Studies

Interferons have the broadest antiviral spectrum of current agents. Different assay techniques have been used to assess *in vitro* activity.<sup>83</sup> Important variables in these assays include the virus strain, cell type,<sup>19</sup> timing of interferon addition to cell culture and duration of exposure, size of the virus inoculum, and the duration of culture.<sup>87</sup>



Alpha and beta interferons have similar inhibitory effects against rhinovirus in human fibroblast cells (0.5 to 5.0 units) but have less activity in HeLa cells.<sup>19</sup> Alpha interferons inhibit various strains of influenza A virus at low concentrations (0.1 to 1.0 units per ml) in human embryonic kidney cells.<sup>142</sup> Higher concentrations (2000 to 10,000 units per ml) inhibit replication of influenza A and B viruses in primary rhesus monkey kidney cells.<sup>87</sup> Alpha interferon at concentrations of 3 to 100 units per ml causes a dose-dependent inhibition of parainfluenza virus type 1 in human embryonic kidney cells.<sup>126</sup> At concentrations of 30 to 500 units beta interferon has activity against many adenovirus types.<sup>52, 53</sup> Because the antiviral activity of interferons is usually species-specific, human interferons have not been studied extensively in animal models. Using a human interferon hybrid that is active in mouse cells, aerosolized interferon was found to have limited efficacy in experimental murine influenza.<sup>156</sup>

Interferon concentrations can be determined biologically by measuring inhibition of viral replication (by plaque or yield reduction techniques), virus specific metabolism (protein production or RNA synthesis), or virus-induced cytopathic effects. Additionally, immunoassays are now available for measuring the concentrations of specific interferons in specimens.<sup>83</sup>

### Resistance

Because interferons act principally on host cells, it would be expected that viral resistance would not develop with their use. Resistance has not been recognized in interferon treatment of nonrespiratory viruses.<sup>7</sup>

### Human Pharmacokinetics

Most studies of interferon for preventing respiratory infections have used intranasal delivery with the hope of achieving local antiviral effects while avoiding systemic toxicity. The initial half-life of intranasal interferon is about 20 minutes,<sup>133</sup> but its antiviral effects persist at least 18 hours.<sup>59</sup> The concentration dependency of antiviral effects and rapid nasal clearance may explain the necessity for high dosages to achieve protection in clinical trials. Interventions to maintain higher local concentrations—such as the use of oral antihistamines to decrease clearance, or saturated cotton pledgets—reduce the amount of interferon necessary to achieve an antiviral effect,<sup>59</sup> but are probably of limited clinical value. Furthermore, it has been shown that beta interferon may be directly inactivated by nasal secretions.<sup>67</sup> Variable concentrations (10 to 10,000 units per ml) are found in nasal washings after intranasal application of alpha interferons, but the relationship between such levels and clinical efficacy has not been established.

### Toxicity

In contrast to the multiple adverse effects of parenteral interferon, the only observed systemic toxicity of intranasal interferon has been transient leukopenia at high doses—that is, 10 million units (MU) per day or greater—and in subjects with mucosal abnormalities.<sup>47, 74</sup>

Nasal intolerance has been the major limiting factor in the intranasal use of both recombinant and natural alpha interferons. The occurrence of symptoms (nasal dryness, obstruction, discomfort, blood-tinged mucus) and



signs (mucosal friability, bleeding sites, erosions, ulcerations on nasal examination) depends on the dose and duration of use. Symptoms of nasal irritation have been reported after both short-term use of high-dose (22.5 MU per day for 4 days)<sup>149</sup> and long-term use of low-dose (2 MU per day for 2 to 4 weeks)<sup>41</sup> alpha interferons. Histologic studies have documented moderate or severe subepithelial chronic inflammation.<sup>84, 88</sup> These reversible changes occur within 4 days of initiating treatment and appear to be related to the immunologic effects of interferons. Recent long-term studies with recombinant beta interferon indicate that it is better tolerated than alpha interferons at comparable dosages.<sup>82</sup>

One potential problem with the use of intranasal interferons is the development of anti-interferon antibodies. Limited attempts thus far have failed to detect such antibodies in nasal secretions,<sup>84</sup> but additional studies are needed, because such therapies would be expected to be used repetitively or on a prolonged basis. The development of circulating anti-interferon antibodies after intranasal administration has been observed very infrequently.<sup>155</sup>

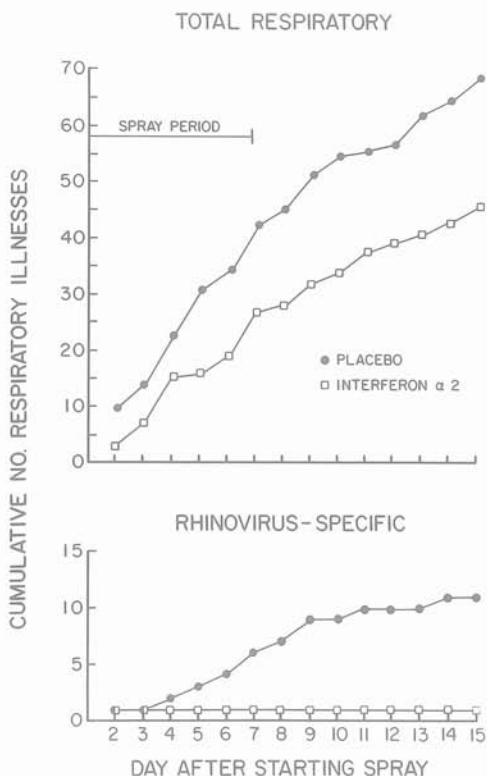
### Clinical Efficacy

**Rhinovirus.** Intranasal administration of natural or recombinant alpha interferons is effective in preventing experimentally induced rhinovirus colds.<sup>71</sup> The level of protection is dependent on both the interferon dosage and the duration of administration prior to virus challenge. Short-term administration of high doses (22.5 to 46.0 MU per day) protects against both illness (defined by occurrence of colds and measurement of mucus production) and infection (determined by virus isolation and/or seroconversion).<sup>74, 149</sup> Lower dosages (10 MU per day) allow infection to take place but protect against illness.<sup>145</sup> A dosage that permits subclinical infection to occur would be desirable, because this could allow the development of natural immunity to subsequent infection.

The efficacy of alpha interferons to prevent natural rhinovirus colds has been evaluated in seasonal prophylaxis studies in which interferon has been given over a period of several weeks. Ten MU daily provides high levels of protection against rhinovirus infections but is associated with unacceptable degrees of nasal irritation.<sup>11, 47</sup> Lower daily doses (2 to 3 MU per day)<sup>41</sup> cause significant reductions (75 to 88 per cent) in rhinovirus infections compared to placebo but nasal side-effects still occur in 20 to 40 per cent of recipients.

Another approach is the short-term use of interferon after exposure to a close contact with upper respiratory illness. Recent studies using 5 MU per day for 7 days for postexposure prophylaxis in family members found nearly 40 per cent reduction in total respiratory illness and 90 per cent reduction in rhinovirus-specific illness (Fig. 5).<sup>72</sup> Another study found a 41 per cent reduction in definite respiratory illnesses overall, and an 86 per cent illness reduction in those exposed to rhinovirus.<sup>42</sup> However, the beneficial effect of this prophylactic strategy appears to be limited to rhinovirus infections, because influenza and parainfluenza virus infections are not prevented at these dosages (see subsequent discussion). Interferon is generally well-tolerated when used in this manner.

Figure 5. Total number of respiratory and rhinovirus-specific illnesses during daily contact prophylaxis with intranasal alpha<sub>2</sub>-interferon and placebo for 7 days (treatment period indicated by horizontal bar). Total respiratory and rhinovirus-specific illnesses are decreased by 39 per cent ( $p=0.02$ ) and 88 per cent ( $p=0.003$ ), respectively, in interferon sprayers compared to placebo sprayers. (From Hayden FG, Albrecht JK, Kaiser DL, et al: Prevention of natural colds by contact prophylaxis with intranasal alpha<sub>2</sub>-interferon. *N Engl J Med* 314:71, 1986; with permission.)



The use of interferons for the treatment of rhinovirus infections has been less successful. In experimental colds, alpha interferon (27 MU per day) beginning 28 hours after rhinovirus challenge does not prevent rhinovirus infection or illness, although viral shedding is reduced.<sup>75</sup> Recent studies in naturally occurring colds have confirmed the lack of beneficial therapeutic effects at doses up to 20 MU per day.<sup>70</sup>

Beta interferons have been studied less extensively in rhinoviral infections. Recombinant interferon beta-serine (6 MU per day) is effective in preventing rhinovirus colds.<sup>94</sup> Further studies with this interferon are in progress.

**Other Respiratory Viruses.** Limited evidence suggests that interferons may be effective against infections caused by coronavirus, which is responsible for 10 to 15 per cent of common colds. Alpha interferon 12 MU per day significantly protects against experimental coronavirus infection and illness but has little effect in volunteers lacking antibody to the challenge virus.<sup>95</sup> Lower dosages (2 MU per day) protect against illness but allow subclinical infection to occur.<sup>161</sup> However, no effect on naturally occurring coronavirus illness has been observed at low dosages in seasonal and family-based prophylaxis studies.<sup>41, 42</sup>

In experimental influenza virus infections, alpha interferon 10 MU per day reduces the frequency and severity of illness and number of days of

viral shedding,<sup>37</sup> whereas other studies using lower doses have found less clinical benefit.<sup>135</sup> In seasonal prophylaxis studies, no apparent reduction of infections due to influenza or parainfluenza viruses<sup>41, 78, 124</sup> have been observed with alpha interferons.

Therefore, at the present time, the major utility for interferons in respiratory viral disease appears to be through use of short-term dosing strategies for the prevention of rhinovirus colds. Further studies are needed to determine optimal dosing schedules, methods of administration, and effectiveness in groups at increased risk for the complications of respiratory viral infections.

## ANTIVIRAL AGENTS AND APPROACHES OF INVESTIGATIONAL INTEREST

A need exists for additional antiviral agents with expanded spectrum, diminished toxicity, and increased ease of use. Several new agents, some of which are the result of exciting advances in molecular biology, are at varying stages of investigation and may have clinical usefulness. Other agents are of historic interest.

### Virucidal Agents

Virucidal agents are those capable of causing contact inactivation of viral infectivity. An important practical application is their use in interrupting transmission of infection. Under experimental conditions, paper handkerchiefs impregnated with virucidal agents such as citric acid and malic acid are more effective in blocking transmission of rhinovirus than are regular paper handkerchiefs.<sup>35, 91</sup> The application of virucidal substances, such as iodine, to the fingertips<sup>61, 92</sup> or disinfection of contaminated fomites prior to fingertip contact also reduces the risk of rhinovirus transmission under experimental conditions.<sup>60</sup> These approaches are of considerable potential value but have not yet been proven to be effective under natural conditions.

### Ascorbic Acid

Vitamin C (ascorbic acid) has been espoused for the treatment and prevention of the common cold. *In vitro* data as to its specific antiviral effect are lacking, and data from recent controlled clinical trials indicate negligible efficacy.<sup>20, 45, 138, 162</sup> Some earlier studies were confounded by inadequate blinding and potential bias in reporting of symptoms.<sup>23, 106</sup>

### Zinc

Zinc chloride (0.1 mM) has been shown to significantly inhibit rhinovirus plaque formation in HeLa cells for eight of nine serotypes.<sup>111</sup> However, zinc gluconate and other zinc salts at this concentration result in only minimal reductions in virus yield and modest delay in virus cytopathic effect in cell culture, whereas slightly higher concentrations are cytotoxic.<sup>55</sup> One clinical study reported that zinc gluconate lozenges, 23 mg dissolved in the mouth up to eight times daily after the onset of cold symptoms,

resulted in a significant reduction in the symptoms of natural colds.<sup>43</sup> However, the lozenges were distinguishable from placebo and virologic analysis was not performed. A recent study with zinc gluconate lozenges, 23 mg taken eight times daily, has failed to show clinical or antiviral effects in experimental rhinovirus infection.<sup>46</sup> Another placebo-controlled trial using zinc acetate lozenges, 10 mg dissolved in the mouth six to eight times daily, found no beneficial effect on symptoms of natural colds.<sup>40</sup>

### Flavones and Chalcones

A flavone, isolated from a Chinese medicinal herb, selectively inhibits rhinovirus and coxsackievirus replication but is poorly absorbed from the gastrointestinal tract.<sup>104</sup> Ro 09-0410, a chalcone derivative of this compound, specifically inhibits 50 per cent of rhinovirus types tested at a concentration of 0.03  $\mu\text{g}$  per ml.<sup>102</sup> Inhibition appears to be mediated through binding to the virus capsid.<sup>127</sup> A phosphate ester, Ro 09-0415, is well-absorbed from the gastrointestinal tract and converted to the active chalcone, which achieves sufficient levels of the chalcone in the respiratory tract of rodents,<sup>103</sup> but clinical trials have not shown prophylactic activity in man.<sup>134</sup> Despite demonstrable blood levels, the parent and active compounds were undetectable in nasal wash specimens. These results illustrate the importance of achieving adequate antiviral concentrations at the site of infection in the respiratory tract.

### Enviroxime

In cell and organ culture, enviroxime, 2-amino-1-(isopropyl sulfonyl)-6-benzimidazole phenyl ketone oxime, is a potent inhibitor of rhinovirus replication.<sup>34</sup> It appears to inhibit translation of viral mRNA. When given by intranasal spray at concentrations many times higher than those inhibitory for rhinovirus *in vitro*, enviroxime provides inconsistent protection against experimentally induced rhinovirus infection<sup>33</sup> and is associated with nasal irritation.<sup>76</sup> Combined oral and intranasal administration leads to decreased cold symptoms and virus titers but is associated with gastrointestinal side-effects.<sup>136</sup> Intranasal enviroxime has modest therapeutic activity in experimental rhinovirus colds<sup>137</sup> and is ineffective in the treatment of natural colds.<sup>121</sup> A modified derivative, enviradene, is undergoing further investigation.<sup>157</sup>

### New Cyclo-nonane

A new cyclo-nonane hydrochloride, ICI 130,685, structurally similar to amantadine, has better prophylactic activity against influenza than amantadine in animal studies. Dosages of 100 and 200 mg per day are 72 and 91 per cent effective, respectively, in preventing illness following experimental influenza virus challenge in man.<sup>4</sup> Treatment of experimental infection with 200 mg per day results in significant decreases in virus shedding and clinical symptoms on certain postchallenge days. Drug concentrations in nasal secretions appear to be several times higher than those present in the blood. Neurologic and gastrointestinal side-effects are observed at the higher dosage, but no direct comparisons have been made

with other adamantanes. Prophylactic and therapeutic efficacy in natural influenza infections has not yet been evaluated.

### New Antiuncoating Agent

A potent new antipicornaviral agent 5-(7-[4-(4,5, dihydro-2-oxazol)phenoxy]heptyl) 3-methyl-isoxazole, WIN 51711, inhibits the majority of rhinovirus serotypes tested at concentrations of less than 1  $\mu\text{g}$  per ml. This drug is not directly virucidal but binds to the virus capsid and appears to have its major effects on the uncoating step of viral replication.<sup>49, 154</sup> This antiviral agent is effective orally and parenterally for treatment of enteroviral infection in rodents.<sup>120</sup> Studies in experimentally induced enterovirus infection of man are in progress.

### Receptor Blockade

Nearly 90 per cent of human rhinovirus serotypes share a single type of cellular receptor,<sup>1</sup> and recent efforts have been directed at the development of agents to block the attachment of virus to the host cell receptor. Murine monoclonal antibodies directed against the cellular receptor site are potent *in vitro* inhibitors of rhinovirus replication.<sup>27</sup> Intranasal administration of this murine monoclonal antibody provides partial protection against experimental rhinovirus infections in man.<sup>77</sup> The use of agents capable of blocking attachment of virus to the host cell could prove effective in the prophylaxis and possible treatment of rhinovirus and other viral infections.

### Combination Chemotherapy

The use of combinations of antivirals with different modes of action might allow for broader spectrum of activity, synergistic or enhanced antiviral effects, prevention of drug resistance, and/or diminished toxicity. For rhinoviruses, synergistic antiviral activity has been demonstrated *in vitro* when various types of interferons are combined with each other or with chemical antirhinoviral agents.<sup>3</sup> Additive or synergistic effects have been shown with ribavirin and amantadine or rimantadine against influenza A *in vitro*<sup>51, 87</sup> and in mice,<sup>51, 69, 171</sup> interferon alpha-2 and rimantadine against influenza A *in vitro*,<sup>87</sup> and interferon alpha-2 and ribavirin against influenza A and B *in vitro*.<sup>87</sup> Combination chemotherapy warrants further evaluation in man.

## SUMMARY

Respiratory viruses continue to be major causes of morbidity and mortality. Currently available chemotherapy is limited to oral amantadine for uncomplicated influenza A and aerosolized ribavirin for respiratory syncytial virus (RSV) infections. Amantadine is also efficacious for chemoprophylaxis of influenza A virus infections. Rimantadine has similar clinical efficacy and is better tolerated than amantadine. Aerosolized ribavirin may be useful in the treatment of serious respiratory illness caused by viruses other than RSV. Intranasal application of interferon is effective in inter-

rupting the spread of rhinovirus colds in families, but chronic use is limited by nasal toxicity. Several newer agents and approaches for chemoprophylaxis and therapy are at different stages of clinical investigation. Combinations of antiviral agents may offer the best therapeutic advantage but have not been adequately tested in man. As additional drugs become available and uses expand for the currently available agents, rapid viral diagnosis will assume an increasingly important role in their optimal use.

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Frederick G. Hayden, M.D.  
Department of Internal Medicine  
University of Virginia School of Medicine  
Box 473  
Charlottesville, Virginia 22908