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Short communication

Combination antiviral therapy for respiratory virus infections

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Abstract

A limited number of antiviral drug combinations have been shown to have enhanced activity for important human respiratory viruses. Rimantadine or amantadine combined with ribavirin shows increased antiviral effects in vitro and in experimental animal models. This combination warrants testing in human influenza. Immunoglobulin containing neutralizing anti-RSV antibody combined with ribavirin shows enhanced antiviral effects in experimental animal infections and provides clinical benefit in severe RSV infections of transplant patients. Generally, more effective treatments for acute respiratory viral infections will likely involve combinations of both antivirals and agents that modulate host inflammatory responses to infection.

1. Introduction

The development of antiviral drug combinations for treatment of respiratory viral infections has proceeded slowly. This is partly due to the fact that there are paucity of effective monotherapies for specific respiratory viruses and also to concerns about optimal routes of administration, toxicity, and appropriate indications for use. Nevertheless, it has been possible to identify drug combinations which potentiate antiviral activity (Table 1). The reasons for using combinations of antiviral in managing other types of viral infections, e.g. enhancement of antiviral activity, improved tolerance, and prevention of resistance emergence, also pertain for infections due to respiratory viruses. The following sections consider the use of specific antivirals and their combinations for the three representative respiratory viruses principally responsible for the syndromes of influenza, bronchiolitis and pneumonia in young children, and common colds.

2. Influenza virus

In vitro studies have found that combinations of amantadine or rimantadine with ribavirin and/or interferon showed additive or synergistic antiviral activity in vitro against a range of influenza A viruses without increased cytotoxicity (Hayden, 1986). Similarly, combinations of amantadine or rimantadine and ribavirin given either systemically or by small particle aerosol have shown

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Table 1
Combinations of antiviral agents which show increased antiviral activity for representative respiratory viruses

Virus	In vitro	Animal models	Human infections
Rhinovirus	Interferon	—	—
	+ enviroxime	NT	Not increased
	+ capsid-binding agents	NT	NT
	+ soluble ICAM-1	NT	NT
Influenza A virus	Amantadine/rimantadine	Amantadine/rimantadine	
	+ ribavirin	+ ribavirin	NT
	+ interferon	NT	NT
	+ GG167	NT	NT
	+2'-deoxy-2'-fluoroguanosine	NT	NT
	NT	Rimantadine + aprotinin	NT
Respiratory syncytial virus	—	Anti-RSV immunoglobulin + ribavirin	Anti-RSV immunoglobulin + ribavirin[a]

[a]Based on open trial in bone marrow transplant patients with RSV pneumonia (Whimbey et al., 1994).

enhanced antiviral activity and improved survival in murine models of experimental influenza (Hayden, 1986). Aerosol administration has been associated with greater antiviral effect than intraperitoneal (Wilson et al., 1980). Limited in-vitro observations also suggest that interferon increases the antiviral activity of these drugs. Another combination showing enhanced protection in experimental murine influenza is parenterally-administered rimantadine and aprotinin, a polypeptide antiproteinase that inhibits cleavage activation of the virus hemagglutinin (Zhirnov, 1987). Whether the combination of such agents can prevent the development of amantadine/rimantadine-resistant influenza A virus in vitro remains to be determined. Appropriate trials are needed to determine whether the combination of ribavirin with amantadine or ribavirin is clinically useful.

More recently, four anti-influenza agents with different mechanisms of antiviral action, rimantadine, ribavirin, 2'-deoxy-2'-fluoroguanosine (2-FDG) and the neuraminidase inhibitor 4-guanidino-Neu5Ac2en (GG167), were tested against clinical isolates of influenza A H3N2 and H1N1 subtype viruses in cell culture by an ELISA method (Madren et al., 1995). Although differences were seen depending on inoculum, almost all of the dual interactions observed in this system were additive in nature. The results indicated that anti-influenza agents with differing mechanisms of antiviral action interact principally in an additive manner. Whether certain combinations can prevent the development of selection of drug-resistant virus, which emerges with exposure to amantadine, rimantadine, 2-FDG and GG167 alone in vitro, remains to be determined.

3. Respiratory syncytial virus (RSV)

Parental or aerosol administration of polyclonal or monoclonal antibody containing high titers of anti-RSV neutralizing activity can significantly reduce RSV titers in the respiratory tract of experimentally-infected animals. When such immunoglobulin therapy is combined with aerosolized ribavirin in cotton rats (IVIG intraperitoneally 24 h prior to or 72 h after intranasal RSV challenge; ribavirin aerosol begun 3 days after challenge), significantly greater reductions in lower respiratory tract viral titers were observed with the combination compared to animals treated with either IVIG or aerosolized ribavirin alone (Gruber et al., 1987). Interestingly, no additive antiviral activity between immunoglobulin and ribavirin was observed against RSV in HEp-2 cells in vitro.

This strategy has been recently employed in adult bone marrow transplant recipients with respiratory syncytial virus pneumonia (Whimbey et al., 1994). In this population, aerosolized ribavirin alone has been associated with a 70% mortality

rate. Among twenty patients with pneumonia, four received no specific therapy and all died. Similarly, four individuals receiving late therapy (at the time of intubation for mechanical respiratory support) all died. In contrast, among twelve individuals receiving early therapy (more than 24 h prior to intubation) with aerosolized ribavirin (20mg/ml for 18 h/day) and IVIG (500 mg/kg/qod with high neutralizing antibody titers), 67% survived. These preliminary results suggest that the combination of immunoglobulin and ribavirin improved clinical outcome. This approach warrants study in patients hospitalized with serious RSV infections. An additional strategy would be to administer anti-RSV immunoglobulin to high-risk infants and other patients when RSV is identified in the community, and to treat those with breakthrough illness with ribavirin (Gruber et al., 1987).

4. Rhinovirus

Of the large number of compounds which inhibit rhinovirus replication in vitro, a limited number have shown antiviral activity in experimental and/or natural rhinovirus infections of humans (Arruda and Hayden, 1995). Specifically, intranasal administration of interferon or of the capsid-binding agents R61837 and R77975 (pirodavir) have shown prophylactic activity in experimentally induced rhinovirus infection. Prophylactic intranasal interferon is protective against natural occurring rhinovirus infections. However, none of these agents has provided significant therapeutic benefits in rhinovirus colds when administered after symptom onset. In-vitro studies have demonstrated synergistic antiviral effects in inhibiting rhinovirus replication using various combinations of interferons, capsid-binding agents and enviroxime (Table 1). The most potent combination identified was with interferons and enviroxime, which showed 100-fold greater antiviral activity than each of the agents used alone. However, a single study of this combination found no significant benefit from intranasal enviroxime alone or in combination with interferon (Higgins et al., 1988). Moreover, the poor pharmacokinetic properties of many capsid binding agents, including poor aqueous solubility, low oral bioavailability, and limited distribution to respiratory secretions, has been associated with limited activity in clinical trials. More recently, truncated or soluble forms of the major rhinovirus cellular receptor (intercellular adhesion molecule-1 [ICAM-1]) have been shown to inhibit rhinovirus in vitro and to show enhanced antiviral activity when used in combinations with interferon (Hayden, unpublished observations). This may offer a pharmacologically compatible formulation of antivirals that could be topically administered.

The pathogenesis of symptoms in rhinovirus and other respiratory virus infections relates to more than ongoing viral replication. The hypothesis has been developed that viral infection triggers host inflammatory responses and neurogenic reflexes that lead to the symptoms producing colds (Gwaltney, 1992). Consequently, combination therapeutic approaches to such infections might include both compounds with anti-inflammatory activity and those with antiviral effects. One study using combinations of intranasal interferon-alpha-2b, the topical anticholinergic ipratropium, and oral naproxen beginning 24 h after experimental rhinovirus infection found significant antiviral effects (approximately 1.0 $\log_{10}$ reductions in viral titers) and modulation of symptoms compared to placebo treatment and to historical controls (Gwaltney, 1992). These results support the general concept that effective treatments for acute respiratory viral infections will involve combinations of both antivirals and agents that alter host inflammatory responses (Table 2).

Table 2
Examples of host inflammatory mediators in upper respiratory secretions during respiratory viral infections in humans

Virus/syndrome	Mediator increase
Rhinovirus colds	IL-1, IL-8, kinins, IFN-α
Influenza A virus illness	IFN-α
Respiratory syncytial virus bronchiolitis	Histamine, LTC_4, eosinophil cationic protein

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