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Antiviral Agents Against Respiratory Viruses

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Introduction

Respiratory virus infections are important causes of mortality and morbidity. They also have social and economic impact, contributing to lost days from work for patients and families. Advances have been made in the development of antiviral agents to treat these infections. These advances and future prospects will be reviewed.

Respiratory Viruses

Several viruses are known to cause respiratory tract infections, including influenza A, B, and C; parainfluenza 1, 2, and 3; respiratory syncytial virus (RSV); adenovirus; rhinoviruses; and coronaviruses. Currently, antiviral agents are available for only two of these virus groups: influenza and RSV.

Influenza

Amantadine and Rimantadine

Spectrum

Amantadine (1-adamantanamine hydrochloride) and rimantadine (α-methyl-1-adamantane methylamine hydrochloride) are related, symmetric, tricyclic amines. Both inhibit replication of influenza A viruses only, at concentrations less than 1 μg/ml. They are active against several strains of influenza A virus, including H1N1, H2N2, and H3N2 subtypes. Rimantadine is 4 to 10 times more active than amantadine in vitro. At higher concentrations, which are not achievable clinically because of toxicity, rimantadine has in vitro activity against other enveloped viruses, such as influenza B, parainfluenza, rubella, and dengue.

Mechanism of action

At low concentrations, these drugs act by blocking the ion channel formed by the M2 protein spanning the viral membrane. This affects viral uncoating or disassembly of the virion during endocytosis (1). As hydrogen ions enter endocytotic vesicles, the pH falls. The hydrogen ions pass through the M2 channel into the interstices of the viral particle and promote the dissociation of the M1 protein from the ribonucleoprotein complexes so that the ribonucleoprotein can enter the cell nucleus and initiate replication. Amantadine and rimantadine enter the ion channel and block penetration by hydrogen ions, thereby preventing the dissociation of M1 from the ribonucleoprotein. Amantadine and rimantadine are also concentrated in the lysosomal fraction of mammalian cells, increasing lysosomal pH. This pH increase may inhibit virus-induced membrane fusion events and partly explain the broader antiviral spectrum observed at higher concentrations (2,3).

Resistance

Resistant viruses can be readily selected by in vitro virus passage in the presence of amantadine or rimantadine (4). Resistant strains can also arise following treatment with either drug. From 25 to 35% of treated patients will shed resistant virus by the fifth day of therapy (5). Single nucleotide mutations leading to amino acid changes in the M2 protein have been shown to confer resistance to amantadine or rimantadine. The most common mutation site observed clinically is amino acid 31 (6). Amantadine and rimantadine share cross-susceptibility and cross-resistance.

Avian models have shown that resistant influenza strains are genetically stable and have the same virulence and fitness as wild-type isolates (7). In humans, transmission of resistant virus, associated with failure of drug prophylaxis, has been documented in household contacts of rimantadine-treated index cases and in nursing home residents receiving amantadine (8,9). Infections caused by a resistant strain do not lead to prolonged illness or a rebound of illness and are similar to infections caused by a susceptible strain (8). However, it is prudent to avoid use

In This Issue

During the last decade significant changes have occurred in the rapid diagnosis and treatment of respiratory viral infections. It is now possible to detect the most common respiratory viruses, such as influenza and respiratory syncytial virus (RSV) within hours of specimen collection. Some rapid tests can be performed point-of-care, and certain methods even allow differentiation of influenza A from influenza B when both are endemic in the community. This article reviews the older and newer antiviral agents that can be used to treat influenza and RSV and how their use relates to specific viral diagnosis.

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Table 1. Antiviral drugs approved for prevention or treatment of influenza infections

Drug	Trade name	Influenza type	Cost (US$)[a]	Approved age (yr)	Route	Dose (for 5 d)	Half-life (h)
Amantadine	Symetrel Generic	A	9.83 1.72	≥1	PO	100 mg bid	15 adults 30 elderly
Rimantadine	Flumadine	A	18.87	≥1[b] ≥18[c]	PO	200 mg/d	30
Zanamivir	Relenza	A and B	44.49	≥7	Aerosol	10 mg bid	NA
Oseltamivir	Tamiflu	A and B	53.00	≥18	PO	75 mg bid	6-10

[a] Costs for a 5 day treatment
[b] For prophylaxis
[c] For treatment

of both treatment and postexposure prophylaxis in the same household and to avoid contact between susceptible high-risk individuals and treated patients. Naturally occurring polymorphisms that confer resistance to amantadine or rimantadine have been detected in some H1N1 isolates collected between 1933 and 1945, before the introduction of amantadine, underscoring the potential for emergence of viral resistance (3).

Pharmacokinetics

Amantadine

Dosage: Amantadine is available as tablets, capsules, or syrup formulations. It is absorbed rapidly and almost completely2 h after oral administration. The average steady-state peak concentrations range from 0.5 to 0.8 μg/ml, following the recommended dose of 100 mg twice daily (Table 1). Concentrations achieved in nasal secretions and saliva are similar to those in serum. Cerebrospinal fluid (CSF) levels are one-half of those in plasma. Plasma protein binding of amantadine is about 67%.

Metabolism: Amantadine is excreted unmetabolized in the urine through glomerular filtration and possibly through tubular secretion. The dose of amantadine should be reduced in renal insufficiency. Amantadine is not cleared by hemodialysis, therefore supplemental doses are not required (10). The plasma half-life is approximately 12 to 18 h in subjects with normal renal function but may be as along as 30 h in subjects with renal insufficiency. In particular, because of age-related decrease in renal function, the half-life is increased up to twofold in the elderly, and they require only half of the dose needed for young adults to achieve trough plasma levels of 0.3 μg/ml (11).

Rimantadine

Dosage: Rimantadine is available as tablet or syrup formulations. It is nearly completely absorbed after oral administration, but the time to the peak plasma concentration is about twice that of amantadine (2 to 6 h). The average steady-state peak concentrations are 0.4 to 0.5 μg/ml in healthy young adults; however, levels are increased in elderly subjects indicating the need to lower the doses in such patients. Concentrations in nasal mucus average 50% higher than those in plasma. Rimantadine plasma protein binding is about 40% (12).

Metabolism: Rimantadine undergoes extensive metabolism by hydroxylation, conjugation, and glucuronidation, and three hydroxylated metabolites have been described. It is excreted in the urine. Its plasma half-life averages 24 to 36 h. Subjects with severe hepatic dysfunction and renal insufficiency with creatinine clearance of <10 ml/min require a dose reduction. No supplemental dose is required for hemodialysis.

Drug interactions

Antihistamines or anticholinergic drugs increase the effects of amantadine on the central nervous system (CNS). CNS toxicity has also been associated with concurrent use of trimethoprim-sulfamethoxazole or triamterene-hydrochlorothiazide, due to decreased renal clearance (13). Patients receiving drugs likely to affect CNS function, such as antihistamines, antidepressants, and benzodiazepines, should be monitored closely. Cimetidine induces a 15 to 20% increase and aspirin or acetaminophen a 10% decrease in rimantadine concentration (14); these small changes are of unclear significance.

Toxicity

Adverse effects observed with the use of amantadine or rimantadine are usually mild in young, healthy adults. They include dose-related gastrointestinal and CNS side effects, such as nervousness, lightheadedness, difficulty concentrating, insomnia, and loss of appetite or nausea (15-17). These CNS side effects occur more frequently with the use of amantadine (5 to 33%) than rimantadine (2%) and are presumably due to amantadine's activity on the adrenergic nervous system, which affects accumulation, release, and re-uptake of catecholamines (18-20). During prophylaxis, drug discontinuation rates are usually less than 5% for rimantadine and range from 6 to 11% for amantadine (19). In elderly subjects or patients with renal failure, serious neurotoxic reactions have been reported with the use of amantadine, including tremor,

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hallucinations, seizures, and coma. An increased rate of seizure activity has been observed in patients with a history of epilepsy (21). At high plasma levels, cardiac arrhythmias and death can occur (22). Amantadine has anticholinergic effects that can cause dry mouth and mydriasis, and this drug is contraindicated in patients with untreated angle-closure glaucoma (15).

Clinical studies

Amantadine and rimantadine can be used for prophylaxis or treatment of influenza infection.

Treatment

Several studies have demonstrated that either amantadine or rimantadine, when administered within 48 h of the onset of illness, can reduce the duration (by about a day) and severity (approximately 50% reduction in fever and other symptoms) of uncomplicated influenza A (23-27). In most studies, there was an accompanying reduction in the amount of virus secreted. One comparative study of amantadine and rimantadine showed that the two drugs had similar efficacies (28). The benefit of these drugs in reducing the risk of complications in high-risk patients has not been established. In a study of children with influenza A H3N2 subtype infection, rimantadine treatment was associated with reduction of symptoms on days two and three of the illness but not thereafter. The mean duration of virus shedding was actually prolonged in the rimantadine arm of the study compared with the acetaminophen arm. These findings, as well as the recovery of resistant isolates on day four or later of treatment, led the authors to conclude that rimantadine therapy should be given for 3 rather than 5 days in children (29).

Prophylaxis

Influenza vaccination remains the basis of influenza prophylaxis. The Centers for Disease Control and Prevention have recommended the use of amantadine or rimantadine prophylaxis in certain circumstances (30): (i) persons at high risk for complications of influenza who receive the vaccine after influenza activity has begun in a community, since the development of antibodies can take 2 weeks; (ii) unvaccinated health care workers; (iii) persons expected to mount an inadequate response to the vaccine, such as those with advanced HIV infection; (iv) other persons with a high risk for complications of influenza who cannot receive the vaccine; and, (v) all residents in nursing homes and long-term care facilities, for whom chemoprophylaxis is recommended during an outbreak and should be continued for at least 2 weeks or until 1 week after the end of the outbreak.

These recommendations are based on the results of several studies demonstrating the efficacy of amantadine and rimantadine in preventing symptomatic influenza virus infection. The rate of protection against influenza virus infection has ranged from 0 to 90%, averaging 50%, and both drugs are about 70 to 90% protective against clinical illness (19,20,23,25,27).

Neuraminidase Inhibitors

Zanamivir (4-guanidino-2,4-dideoxy-2,3-dehydro-N-acetylneuraminic) and oseltamivir

Spectrum

Zanamivir (4-guanidino-2,4-dideoxy-2,3-dehydro-N-acetylneuraminic) and oseltamivir (GS4104, the ethyl ester prodrug of GS4071) are related antiviral agents, that are potent and specific inhibitors of the neuraminidases of influenza A and B viruses. These sialic acid analogs competitively and reversibly interact with the active enzyme site to inhibit neuraminidase activity. Zanamivir is approved by the United States Food and Drug Administration (FDA) for treatment of influenza in persons at least 7 years of age who have been symptomatic for less than 2 days. Oseltamivir is approved for treatment in persons at least 18 years of age, and approval for use in those at least 1 year of age is pending (31). It is also approved for prophylaxis in persons at least 13 years of age. A recent study has also shown zanamivir to be efficacious in treating mice infected with various strains of avian influenza viruses responsible for infections in humans in Hong Kong (H5N1, H6N1, and H9N2) (32).

Mechanism of action

Influenza viruses possess two surface glycoproteins with either hemagglutinin (HA) or neuraminidase (NA) activity. These glycoproteins mediate the interaction of influenza A and B with N-acetylneuraminic acid-containing cellular receptors. HA initiates infection by binding to these cellular receptors on respiratory epithelial cell surfaces, whereas NA acts at a later stage to release viruses from infected cells. It does so by cleaving a terminal sialic acid (N-acetylneuraminic acid) residue from an oligosaccharide chain, thereby destroying the HA receptors. NA inhibitors mimic the structure of N-acetyl-neuraminic acid, a receptor determinant recognized by both influenza A and B viruses. They competitively inhibit neuraminidase. This inhibition prevents the progeny virions from self-aggregating and binding to the surface of infected cells, which prevents spread from cell to cell (2,33-35). NA also prevents the entrapment of virus by sialic acid-containing muco-proteins in respiratory secretions; virus binds to the mucus, but elution resulting from the activity of NA allows the virus to circumvent this barrier and penetrate the cells. NA inhibitors prevent this from occurring (3,36).

Resistance

Because they target a different virus protein, zanamivir and oseltamivir are active against influenza strains resistant to amantadine and rimantadine. In vitro, resistance to NA inhibitors can occur in two steps. The first step consists of a reduction of the virus' dependence on NA activity because of changes in the HA. Mutations in HA at or near the site that binds to sialic acid reduce the affinity of the HA for its receptor. As a result, these variants are less dependent on NA activity for release from cells and subsequent spread to other cells. Variants with these mutations are cross-resistant to other NA inhibitors. The other pathway of resistance development involves the acquisition of mutations in the active site of the NA, which decrease binding of the drugs (Glu119Gly/Ala/Asp); or within the catalytic framework of the NA (Arg292Lys) (37,38). Oseltamivir retains activity against variants with the Glu119 mutation but has less activity than zanamivir against Arg292 variants (37). These mutations may be associated with significantly reduced enzyme activity, and the mutated viruses have decreased infectivity in animal models.

One case of a resistant virus isolated from an immunosuppressed child receiving zanamivir under a compassionate use protocol has been reported

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to date (39). So far, resistant viruses have not been isolated from humans who have received zanamivir in clinical trials. Mutations leading to resistance to oseltamivir have occurred in about 1.5% of treated persons (3). In a study of volunteers experimentally infected with influenza virus (H1N1) and treated with oseltamivir, 2 of 54 (4%) developed resistant virus with substitution at codon His274Tyr of the NA (40).

Pharmacokinetics

Zanamivir has poor oral bioavailability (<5%) and must be administered by inhalation through the mouth or intranasally (41). The inhaler device used for delivery of the drug is breath actuated and requires a cooperative patient. When inhaled at a high flow rate through the mouth, 78% of the dose is deposited in the oropharynx, whereas only 15% reaches the tracheobronchial airways and the lung (42,43). At recommended doses the concentration in secretions should exceed the 90% inhibitory concentration of drug for most strains of influenza virus. Bioavailability ranges from 10 to 20% (44). When administered intravenously, the plasma half-life averages 1.6 h. 90% is excreted unchanged in the urine (45).

Oseltamivir is administered orally. It is converted into its active metabolite, GS4071, by esterases in the gastrointestinal tract or blood. GS4071 has an estimated bioavailability of 80%, and its half-life averages 7 to 9 h. The time to peak plasma concentration is about 3 to 4 h. Administration with food may slightly delay absorption but does not affect peak plasma concentrations. In ferret models, widespread tissue distribution has been demonstrated, whereas in humans, distribution is not well characterized (46). The prodrug and GS4071 are eliminated unchanged in the urine. Guidelines for use in subjects with renal insufficiency are not available, but reductions in the dose are recommended for those with a creatinine clearance of less than 30 ml per min.

Drug interactions

No drug interactions have been observed so far with either zanamivir or oseltamivir.

Toxicity

Zanamivir and oseltamivir are both well tolerated. In initial evaluation of patients with mild-to-moderate asthma, zanamivir did not reduce pulmonary function or increase airway responsiveness to methacholine (47). However, a recent report of respiratory distress in a patient with chronic obstructive pulmonary disease (COPD) following zanamivir inhalation (48), as well as preliminary data from a placebo-controlled trial suggesting reduced airflow in patients with COPD or asthma (49), has led to a warning from the manufacturer to use caution when administering zanamivir in these populations.

Oseltamivir is associated with nausea and vomiting in 10 to 15% of recipients. These side effects are transient and may be ameliorated by ingestion of food (50-53).

Clinical studies

Zanamivir and oseltamivir are effective for treatment and prophylaxis of influenza.

Treatment

Both drugs have been approved for treatment of influenza in persons who have been symptomatic for less than 2 days. Several studies of zanamivir and oseltamivir have demonstrated a clinical benefit, illustrated by a 1- to 1.5-day decrease in the duration of symptoms associated with a reduction in virus shedding in respiratory secretions (51,53-57). The ability of these drugs to decrease the frequency of pneumonia associated with influenza remains to be determined, although some studies indicated a decreased frequency of complications such as sinusitis, purulent bronchitis, and otitis media (3).

Prophylaxis

Only oseltamivir is FDA approved for prophylaxis of influenza, although three recent clinical trials have shown efficacy of zanamivir in preventing new cases of influenza in families or close contacts of infected individuals. In contrast to what had been reported with rimantadine prophylaxis, there was no emergence of resistant viruses in family contacts who received prophylaxis (58-60). In different clinical trials, oseltamivir was evaluated as prophylaxis when given before exposure, after exposure to infected family members, and after exposure in nursing home settings. It was effective in preventing influenza in contacts and preventing outbreaks within households. The benefit was sustained even in a vaccinated nursing home population (61-63).

Other neuraminidase inhibitors in development

RWJ-270201 is the most potent compound of a novel series of cyclopentane derivatives discovered through structure-based drug design. It is still in preclinical development. In vitro studies have shown comparable or slightly higher anti-influenza activity than that of zanamivir and oseltamivir. In a murine influenza model, protection was observed when the drug was administered before or within 48 h of viral challenge. It is active against both influenza A and B (64,65).

Respiratory Syncytial Virus

Respiratory syncytial virus is the single most important cause of lower respiratory tract infection during infancy and early childhood and causes significant morbidity in immunocompromised adults, especially bone marrow transplant recipients. So far, the only agent approved by the FDA for the treatment of RSV lower respiratory tract infection is ribavirin, which can be used alone or in association with specific RSV immune globulin.

Ribavirin

Spectrum

Ribavirin (1-β-D-ribofuranosyl-1,2,4-thiazole-3-carboxamide) is a guanosine analog. It is active in vitro and in vivo against a wide range of RNA and DNA viruses, including myxo-, paramyxo-, arena-, bunya-, adeno-, pox-, retro-, herpes-, and viruses (66-68). In RSV infection, its aerosol administration is more effective than parenteral dosing, and enhanced activity is observed when ribavirin is combined with immunoglobulin (69,70). Parenteral ribavirin has antiviral and therapeutic activity against hepatitis C virus, Lassa virus, other arenavirus, and bunyavirus infections (68).

Mechanism of action

Ribavirin is phosphorylated intracellularly into mono-, di-, and triphosphate derivatives by host-cell enzymes. Ribavirin monophosphate competitively inhibits inosine-5'-phosphate dehydrogenase and interferes with the synthesis of guanosine triphosphate and, therefore, with nucleic acid synthesis. Ribavirin triphosphate may inhibit influenza virus RNA polymerase activity and competitively inhibit the guanosine

triphosphate-dependent 5'- capping of viral messenger RNA (2). Ribavirin diphosphates and triphosphates have also been shown to inhibit HIV reverse transcriptase activity (71). In vitro, combinations of ribavirin and zidovudine show antagonistic interactions. However, ribavirin enhances the activity of purine dideoxynucleosides (72,73).

Resistance

There is no evidence that RSV develops resistance to ribavirin either in vitro or in clinical use. The only reported virus to have developed resistance to ribavirin is Sindbis virus.

Pharmacokinetics

The pharmacokinetics of ribavirin are complex. Bioavailability ranges from 33 to 45% after oral administration. The peak plasma concentrations after oral dosing occur 1 to 2 h after administration. When the drug is administered intravenously, peak plasma levels are 10 times higher than following oral intake. At steady state, CSF levels are 70% of those in plasma. Its elimination occurs in two phases: α-phase with a half-life of 2 h and a terminal phase with a half-life of 18 to 36 h. Its triphosphate concentrates in erythrocytes, and these are eliminated with a half-life of approximately 40 days. Hepatic metabolism is an important route of elimination. After oral administration, 4% is recovered unchanged in the urine, and 39% is excreted as the metabolite 1,2,4-triazole-3-carboxamide (74-76).

With aerosol delivery, plasma levels increase with the duration of exposure. The half-life of ribavirin in respiratory secretions ranges from 1.4 to 2.5 h (77). Proper delivery necessitates the use of a specialized aerosol generator to reduce the size of the particles in order to reach the lower respiratory tract. Age, as well as several other factors, influence dosage (78).

Toxicity

Ribavirin administered systemically causes anemia by two mechanisms: extravascular hemolysis and bone marrow suppression of the erythroid lineage. Severe anemia may require dose reduction or cessation (79). During short-term oral administration, reversible increases in serum bilirubin, iron, and uric acid concentrations occur frequently. Other side effects include pruritus, rash, nausea, depression, cough, and respiratory symptoms and, when given by bolus intravenous infusion, rigors (80,81). When administered by aerosol, mild conjunctival irritation, rash, bronchospasm, and rarely water intoxication have been observed (82). Aerosolized ribavirin is not associated with hematologic toxicity.

There have been concerns about potential toxicity for health care workers exposed during administration of aerosolized ribavirin. Recommendations have been made to decrease the level of exposure, including the use of aerosol containment systems except during mechanical ventilation, turning off the aerosol generator before providing routine care, and use of protective equipment (83-85). Ribavirin is teratogenic, embryotoxic, mutagenic, tumor promoting, and gonadotoxic. Therefore, pregnant women should not directly care for patients receiving ribavirin aerosols (79).

Clinical Studies

Treatment of RSV bronchiolitis in infancy

A meta-analysis of 11 randomized trials of ribavirin for the treatment of lower respiratory tract infection in infancy has been published (86). In six controlled, randomized studies, ribavirin reduced the severity of RSV illness as demonstrated by a decrease in viral shedding, improvement in oxygen saturation, and improvement in clinical scores. However, ribavirin did not lead to improvement in clinically important outcomes, such as shortened duration of hospitalization (87-92). Studies looking at long-term outcome following ribavirin therapy for RSV infection have shown conflicting results. In several controlled studies, children treated with ribavirin for RSV lower respiratory tract infection had improved clinical and pulmonary evaluations on follow-up compared to controls (93-97). However, in a recent retrospective study of children with or without treatment with ribavirin, no differences in wheezing or other pulmonary function measures were seen at 6 to 8 years of follow-up (98). Diminished levels of RSV-specific IgE and IgA antibodies, which have been associated with more severe clinical illness, have been demonstrated in the secretions of infants treated with ribavirin (99). The growing concern about the efficacy of ribavirin and the high cost associated with its use have led the American Academy of Pediatrics to change the wording of their recommendation from "should be used" to "may be considered" for selected infants and young children at high risk for serious RSV disease, such as those with underlying cardiac, pulmonary, and immunosuppressive conditions (100).

Treatment of RSV infection in immunocompromised patients

Several uncontrolled studies of ribavirin administered by intravenous, oral, or aerosolized routes in various immunocompromised groups with RSV pneumonia have been conducted. Intravenous or aerosolized ribavirin alone appeared to be ineffective in bone marrow transplant subjects (101,102,104). However, combinations of high-titered RSV immunoglobulin plus aresolized ribavirin appeared to be beneficial in bone marrow transplant recipients with RSV pneumonia, reducing the mortality rate to 50% (105). Early initiation of therapy (at least 1 day prior to the onset of respiratory failure) is important, since mortality rates are 100% in patients treated after the onset of respiratory failure (106). There are insufficient data to evaluate the efficacy of ribavirin for the treatment of RSV infections in the elderly (107).

Treatment of other viral respiratory infections with ribavirin

Although use of intravenous and aerosolized ribavirin has been attempted in severe influenza virus as well as parainfluenza and adenovirus infections, results have been inconsistent, and ribavirin is not approved for these indications (108-113).

In Development

New therapies in development to combat RSV infections include sulfated polysaccharide compounds, miscellaneous organic compounds, a variety of proteins (some with known enzymatic activities), and nucleosides other than ribavirin, including antisense oligodeoxyribonucleotides (114).

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