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CLINICAL APPLICATIONS OF ANTIVIRAL AGENTS FOR CHEMOPHROPHYLAXIS AND THERAPY OF RESPIRATORY VIRAL INFECTIONS

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INTRODUCTION

This paper reviews recent advances that have been made in the clinical use of antiviral agents for respiratory infections by giving an overview of the problems that have hindered development and then by focusing on amantadine HCl, rimantadine HCl, and interferons with particular attention to effective strategies for their use. The clinical use of antiviral agents for respiratory illness has been hampered by the fact that there are multiple causes, including over 200 serologically distinct viruses representing 6 major virus families [1]. So far, virus-specific antiviral agents have been developed only for influenza A viruses (amantadine, rimantadine), and future advances in the field will depend in part on identifying other potent, selective agents. In addition, this large group of viruses cause a relatively small number of overlapping clinical syndromes. Particular syndromes can be caused by a number of different viruses, and conversely, a particular virus can cause a number of different clinical syndromes. The viruses also have different epidemiologic patterns. Together these observations mean that effective prophylaxis against all respiratory viral illnesses would require a broad spectrum agent that could be continuously administered, a possibility which appears remote at the present time. Alternatively, effective intervention depends on the use of narrow spectrum agents in conjunction with rapid, specific viral diagnosis.

One aspect that these viruses share is a common affinity for the human respiratory tract. For the use of antivirals, this means that effective drug concentrations must be achieved at the site of infection, within cells of the respiratory epithelium, and raises the practical problem of gaining adequate delivery of orally or parenterally administered antivirals to the respiratory mucosa. On the other hand, the topical use of antivirals affords the potential of achieving high regional antiviral concentrations while reducing the risks of systemic toxicity or avoiding unfavorable pharmacology associated with systemic use. This approach has been used sucessfully with aerosolized ribavirin [2-6] and with intranasal interferon [7-17], but the nature of the delivery system is a critical variable.

An additional problem is that most respiratory viral infections are self-limited illnesses, which means that potential antiviral agents must have very high therapeutic indicies. In particular, when drugs are used for prophylaxis in normal children or adults, only a fraction of whom will be expected to contract the infection, the antiviral must be free from significant side effects.

STRATEGIES FOR USE

In general, the clinical use of antiviral agents for respiratory viral infections depends on developing strategies that are effective and safe during long-term or repeated drug administration. This includes the emergence of drug resistant viruses [18]. In addition, these strategies must also be economically feasible and accepted by both physicians and the public. Seasonal prophylaxis can be most effectively used against viral infections that occur in epidemics of short duration. This pattern is classically shown by the influenza viruses which cause annual outbreaks, lasting 6-8 weeks in a particular region. While many other viruses, including respiratory syncytial virus, parainfluenza virus types 1 and 2, rhinovirus, and coronavirus have distinctly seasonal patterns, the duration of their periods of activity, the associated attack rates, and the occurrence of overlapping periods of activity are important variables in considering seasonal prophylaxis.

Prophylaxis after exposure to a person with respiratory illness, such as commonly occurs in the family setting, is an effective approach where there are high rates of secondary transmission. Epidemiologic studies have shown this to be the case for rhinovirus colds, as well as for influenza and respiratory syncytial virus infections, where school-aged children are frequently implicated as introducing the virus into the household. Prophylaxis of instutitional populations, such as those in hospitals, nursing homes, boarding schools, or day care centers, is appropriate where there is a documented risk of nosocomial spread, as has been found for influenza A and B viruses, respiratory syncytial virus, and adenovirus.

The therapeutic value of an antiviral agent depends on the frequency of infection and its associated morbidity. Since use is limited to those individuals who are symptomatic, some drug side effects are acceptable, particularly in individuals who are at high risk for serious complications. Important targets for therapy include influenza virus infections in children and adults, and respiratory syncytial virus, parainfluenza virus, and adenovirus infections in children. Others, such as rhinovirus and coronavirus, are such common causes of infection, that they have a high cumulative burden of morbidity and economic losses. They may be associated with important complications, including exacerbations of airways disease in those with chronic lung disease and bacterial infections of the ear and sinuses in previously normal patients. For these reasons, these infections are also appropriate targets for treatment.

AMANTADINE AND RIMANTADINE

Prophylaxis

The oldest antiviral compounds useful in respiratory viral infections are amantadine and its analogue rimantadine, which were discovered in the early 1960s. Their clinically effective spectrum is limited to influenza A viruses. Table I shows the results of representative placebo-controlled studies of the prophylaxis of influenza A virus infections and illustrates how an antiviral agent can be used effectively in an epidemic disease such as

influenza. In seasonal prophylaxis in open populations of students, oral amantadine and rimantadine have been associated with protective efficacy ranging up to 90% against illness due to laboratory-confirmed influenza A virus infection [19,20]. These studies have found that the drugs are less effective in preventing infection with influenza A virus than in preventing illness. This may be a desirable feature of prophylaxis, since subclinical infection could provide immunity against subsequent infection.

Several studies have attempted to use amantadine for postexposure prophylaxis in family contacts. Galbraith et al found complete protection against influenzal illness in household contacts of index cases with proven influenza A infection [21], but a follow-up study found little evidence of protection in contacts who were seronegative [26]. Studies of this approach using rimantadine are currently in progress.

TABLE I

PLACEBO-CONTROLLED STUDIES OF AMANTADINE OR RIMANTADINE FOR PROPHYLAXIS OF INFLUENZA A VIRUS INFECTION.

Prophylaxis strategy [ref.]	Drug/dose (mg/day)	Duration (weeks)	% Efficacy in reducing illness	% Efficacy in reducing infection
Seasonal				
Students [19,20]	Amantadine 200	6-7	70-91	39-74
	Rimantadine 200	6	85	66
Postexposure				
Familes [21]	Amantadine 200	10 days	100	63
Institution-based				
Hospital ward [22]	Amantadine 200	4	100	80
Boarding school [23]	Amantadine 100	2	90	N.D.
Nursing home [24,25]	Rimantadine 200	6-7	75 (vaccinees)	55

Several different studies have established the efficacy of institution-based prophylaxis. One trial conducted at the University of Washington found that amantadine was highly effective in preventing illness or infection due to influenza in patients hospitalized on acute medical wards [22]. A recent study found that a lower amantadine dose was highly protective in a large group of teenaged boys housed in an English public boarding school [23]. A study at the University of Rochester found that rimantadine was prophylactically effective in elderly nursing home residents [24,25]. For those who were immunized, a 75% reduction in clinical influenza was found in the rimantadine group compared to placebo. This and other studies have found that an additive effect appears to exist between protection from amantadine or rimantadine and from inactivated influenza vaccine.

Treatment

A number of studies have established that amantadine and rimantadine possess moderate

therapeutic and antiviral activity in uncomplicated influenza in adults [27-30]. Treatment early in the course of disease (≤48 hours) shortens the duration of fever and other symptoms by approximately 50% [27-29] and, in the case of H3N2 subtype infection, reduces the duration of peripheral airway function abnormalities [30]. Studies at the University of Rochester found that amantadine (100 or 200 mg/day for 5 days) was superior to aspirin in providing relief of symptoms [29]. A recent pediatric trial (mean age 4-6 years) from the University of Rochester found that oral rimantadine (3 mg/kg/day up to 150 mg/d for 5 days) was more effective than acetaminophen in relieving the symptoms of influenza A-H3N2 subtype virus infection, although a rebound in virus shedding was observed after stopping therapy [31].

Toxicity

One of the impediments to wider use of amantadine in the United States has been a concern regarding drug side effects. As initially pointed out by Russian investigators [32], rimantadine has significantly lower potential for causing side effects when administered at the same dosage as amantadine. In a study conducted at the University of Vermont, students were given amantadine or rimantadine prophylaxis at a dose of 200 mg per day for a period of 6 weeks [20]. The percent of subjects who developed central nervous system toxicity was significantly higher in the amantadine group (13%) than in either the rimantadine (6%) or placebo (4%) groups. This toxicity was primarily manifested as insomnia, jitteriness, or difficulty concentrating. At the University of Virginia, a short-term study compared the tolerance of these drugs in healthy adults at a dose of 300 mg per day for 5 days [33]. The fraction of amantadine recipients who developed central nervous system toxicity increased to 39%, whereas the rimantadine group (13%) did not differ significantly from placebo (9%). Both drugs were associated with significantly higher rates of GI side effects (amantadine, 20%; rimantadine, 16%), primarily nausea and upset stomach, than placebo (3%).

Pharmacokinetics

The reason for rimantadine's lower potential for central nervous system side effects appears to relate to differences in the plasma concentrations and pharmacokinetics of the two drugs [33,34]. Table II lists the combined results of comparative, single-dose pharmacokinetic studies involving elderly (age ≥60 years) and young (age ≤35 years) adults [35]. Amantadine was readily absorbed from the gastrointestinal tract and rapidly achieved high plasma concentrations, whereas rimantadine had slower oral absorption and achieved significantly lower plasma concentrations. The plasma elimination half-life of rimantadine was approximately twice that of amantadine, and urinary excretion of rimantadine was much less than that of amantadine, which is excreted unchanged in the urine. Urinary excretion (0-24 hours) of hydroxylated rimantadine metabolites averaged one-fifth of the dose.

The differences in plasma concentrations between the drugs correlate with differences in the risk of central nervous system side effects [33], but they also raise the question of why rimantadine retains clinical activity despite much lower plasma concentrations than

amantadine. Part of the answer may lie in the in vitro and animal model observations that rimantadine has somewhat greater intrinsic antiviral activity than amantadine. Importantly, the drugs appear to differ in volume of distribution and penetration into respiratory secretions. In the study described above, the maximum measured nasal mucus concentrations during an 8-hour period were similar for amantadine and rimantadine, and the ratio of peak nasal mucus to plasma concentrations was over 2-fold higher for rimantadine (0.71 ± 0.62 vs 1.73 ± 1.04, $p<0.02$), which suggests that rimantadine may be concentrated in respiratory secretions. Since mucus concentrations may more accurately reflect intracellular concentrations in the respiratory mucosa than plasma concentrations, these pharmacokinetic observations may provide part of the explanation for the clinical efficacy of rimantadine at doses which are associated significantly lower plasma concentrations. In summary, the pharmacologic differences between these drugs confirm a clinical advantage for rimantadine with respect to comparable efficacy at doses that have significantly lower potential for side effects.

TABLE II

COMPARATIVE PHARMACOKINETICS OF ORAL AMANTADINE HCL AND RIMANTADINE HCL AFTER SINGLE 200 MG DOSES.

Drug	Cmax (ug/ml)	Tmax (hours)	Tbeta (hours)	Vdss (L)	Urinary excretion (% dose 0-24 hrs)
Amantadine (n=12)	0.66 (0.22)	2.2 (1.6)	16.7 (7.7)	341 (108)	45.7 (15.7)
Rimantadine (n=16)	0.25 (0.06)	4.2 (2.2)	36.5 (15.0)	914 (238)	0.6 (0.8)
p-value	<0.01	0.01	<0.01	0.01	<0.01

Values listed as mean (S.D.). Cmax = maximum plasma concentration, Tmax = time to maximum concentration, Tbeta = elimination half-life, Vdss = steady-state volume of distribution.

INTERFERONS

Because of their broad spectrum in vitro antiviral activity and apparent role in the resolution of viral infections, interferons have long been considered important candidates for the prophylaxis of respiratory virus infections. Work in this area received a tremendous boost when recombinant DNA techniques were successfully applied to the production of interferon, and a wide range of volunteer experiments have been conducted in the past 4 years [7-11].

Volunteer studies

These studies have generally used similar designs in which volunteers were given intranasal interferon in spray or drop form before and for several days after being exposed to a

rhinovirus by nasal challenge. Studies conducted at several centers have conclusively shown that (1) recombinant alpha2 interferons, specifically leukocyte A interferon (rIFN-αA) and interferon-alpha2 (rIFN-α2), provide protection against experimental rhinovirus colds involving a range of rhinovirus serotypes [8,9,12]. (2) In studies at the Common Cold Unit, protection has also been observed with human leukocyte-derived interferon, lymphoblastoid interferon, and recently with recombinant IFN-β [7,11]. (3) Protection depends on the interferon dose and duration of use prior to virus challenge. High doses (22-44x10^6 IU per day) will prevent both infection and illness [8,12], whereas lower doses in the range of 10x10^6 IU per day prevent illness with a high degree of efficacy but allow subclinical infection to take place [9]. Recent studies at the University of Rochester found that even relatively low doses of rIFN-α2 (approximately 2x10^6 IU per day) were protective against infection and illness when begun 1 week prior to virus challenge [36]. (4) Studies at the University of Virginia demonstrated that single daily doses of intranasal rIFN-α2 were also protective [8]. (5) Protection has also been observed against coronavirus infection [37], but only partial protection has been found against experimental influenza A virus infection [7,38].

Field studies

The encouraging results observed in volunteer studies led to field trials designed to determine whether intranasal interferon could protect against natural respiratory virus infections. The first of these double-blind, placebo-controlled studies was conducted in Charlottesville in September 1982 and was timed to coincide with the annual fall peak in rhinovirus activity [14]. Recombinant IFN-α2 was administered by intranasal spray at a dose of 10x10^6 IU once daily. During the 3-week spray period, 13 rhinoviruses and 1 enterovirus were recovered from placebo subjects with upper respiratory illness, an attack rate of about 9%, whereas none of the interferon group had documented rhinovirus colds. Importantly, no rebound in rhinovirus infection was observed during the 4 weeks after stopping spray use. However, the number of respiratory illnesses (defined as the occurrence of 2 respiratory symptoms on 1 day or, alternatively, the occurrence of ≥ 1 symptoms on ≥ 2 consecutive days) was significantly higher in the interferon (94 illnesses) than placebo group (64 illnesses). Further analysis showed that these illnesses occurred principally during the second and third weeks of interferon administration and were largely due to complaints of nasal obstruction, which is now recognized to be a manifestation of the local side effects of interferon.

In a effort to identify dose regimens which would be acceptable for seasonal prophylaxis in healthy adults, investigators at the University of Michigan and University of Adelaide have conducted similar studies at lower interferon doses. These studies found that rIFN-α2 1x10^6 IU twice daily for 4 weeks provided approximately 75-87% protection against natural rhinovirus infections [15,16]. However, these studies have not found protection against coronavirus, influenza A, or parainfluenza virus infections. More importantly, the field studies using long-term administration have not been able to clearly show a beneficial

effect in regard to prevention of respiratory symptoms. This is due in part to the observation that up to one-half of interferon-exposed adults will develop nasal side effects after several weeks of exposure [16,17].

Toxicity

The most commonly encountered complaints are nasal stuffiness, blood-tinged nasal mucus, and nasal dryness. The occurrence of these complaints is related to both the dose and duration of exposure [9,14-17]. On examination, symptomatic individuals have had signs of mucosal friability, including punctate bleeding sites and, less often, ulcerations. In addition, up to 10% of interferon recipients receiving approximately $10x10^6$ IU per day developed transient leukopenia after 3 weeks of use [14], a finding which indicates that high intranasal doses may be associated with systemic effects.

Several placebo-controlled studies have been conducted to determine the histology of the nasal mucosa before and after interferon exposure. In the first tolerance study, healthy adults were given rIFN-α2 at a dose of $8.5x10^6$ IU per day for 28 days [39]. Fifty-eight percent of interferon recipients but none of those in the placebo group had a moderate or severe degree of subepithelial inflammatory cell infiltration, which consisted primarily of lymphocytes. When affected interferon recipients were rebiopsied 8 weeks after completing exposure, the biopies had returned to normal, indicating that the histopathologic changes were reversible [39]. In a follow-up study, immunohistochemical techniques were used to determine the nature of the inflammatory infiltrate [40]. These studies were conducted with rIFN-αA at a dosage of $9x10^6$ units per day and found that approximately one-half of interferon recipients developed increased numbers of subepithelial T-lymphocytes as early as the fourth day of exposure, prior to any symptoms of nasal irritation. While the clinical significance of these observations remains to be determined, the histologic changes may be secondary to the immunologic activity of recombinant alpha2 interferons and linked to the clinical intolerance observed.

Treatment

The occurrence of local intolerance during long-term or seasonal prophylaxis has led to the exploration of alternative strategies for using intranasal interferon. One alternative is treatment of an established infection, and several studies have been conducted in experimentally induced rhinovirus infection to assess therapeutic activity. In one trial at the University of Virginia, rIFN-α2 was given by nasal drops at a dose of $9x10^6$ IU 3 times per day for 5 days beginning 28 hours after infection [41]. The proportion of virus positive days was reduced by over 50% in the interferon group compared to placebo, and the median duration of virus shedding was reduced nearly 3.5 days in the interferon group. Studies of quantitative virus shedding found that interferon markedly reduced virus titers in nasal secretions by the third day of administration compared to placebo. Nasal symptom scores peaked on the second and third days after infection in the placebo group but were significantly lower in interferon recipients. There were also clear trends toward reduced quantities of nasal mucus production on these days. Overall, each of these measures of

illness severity averaged about 50% lower in the interferon group compared to placebo. In summary, interferon administration during the late incubation period of rhinovirus infection significantly modified, but did not prevent rhinovirus colds. Further studies are needed to determine if interferon treatment will reduce symptoms, transmissibility of infection, or the risk of complications in natural colds.

Postexposure prophylaxis

Another logical strategy for preventing common colds is postexposure prophylaxis of family contacts. Investigators at several institutions have recently completed long-term double-blind, placebo-controlled studies to determine the usefulness of intranasal interferon in preventing illness in the household contacts of family members with respiratory illness [42,43]. Whereas low doses of rIFN-αA (0.3 or 1.5 x 10^6 IU/day for 5 days) did not appear to prevent transmission of colds [43], higher doses of rIFN-α2 (5 x 10^6 IU/day for 7 days) significantly reduced respiratory illness occurrence in family contacts [42]. Interferon was also well tolerated when used in this manner, and evidence of cumulative toxicity was not found.

SUMMARY

Table III summarizes clinical applications of antiviral agents in respiratory viral infections.

TABLE III
CLINICAL APPLICATIONS OF ANTIVIRAL AGENTS IN RESPIRATORY VIRAL INFECTION

	Effective for	
Virus	Prophylaxis	Treatment
Influenza A	Amantadine (oral)	Amantadine (oral)*
	Rimantadine (oral)	Rimantadine (oral)*
		Ribavirin (aerosol)*
Influenza B		Ribavirin (aerosol)*
Resp. syncytial		Ribavirin (aerosol)
Rhinovirus	IFN-α2 (intranasal)	

*Efficacy has been established only in uncomplicated disease.

For influenza A virus infections, both oral amantadine and rimantadine are effective when used for seasonal prophylaxis and for prophylaxis in institutional populations. Both of these drugs, as well as aerosolized ribavirin, have antiviral and therapeutic effects in uncomplicated influenza. It remains to be determined whether any of these modalities or possibly their combined use [44] will be useful in treating severe influenza in hospitalized patients or whether they can prevent the development of complications in high risk patients. Unfortunately, there is no parenteral formulation of amantadine or rimantadine

for use in critically ill patients.

Aerosolized ribavirin has also been shown to have modest therapeutic effects in influenza B virus infection. However, a major need exists for an antiviral which is active against influenza B virus and which can be used on an outpatient basis. Controlled clinical trials have shown that aerosolized ribavirin therapy improves arterial oxygenation and modifies the severity of respiratory syncytial virus bronchiolitis and pneumonia [3,5]. Its role in treating life-threatening disease or in modifying the long-term sequelae of RSV infections are unknown at the present time. Again, a specific antiviral agent is needed for outpatient use in preventing or treating RSV infections.

Finally, after over a decade of work since the original observation that intranasal interferon could prevent experimental rhinovirus infection [11], recent studies have established that intranasal rIFN-α2 is effective in the postexposure prophylaxis of rhinovirus colds in families [42]. This strategy needs to be studied with regard to the prevention of infection and its complications in high risk patients and it remains to be determined whether intranasal interferon will have therapeutic activity in established colds.

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