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Antiviral Agents in Clinical Practice

ANTIVIRAL THERAPY

Respiratory Infections, Genital Herpes, and Herpetic Keratitis

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THIS and remaining two articles of the series concentrate on the clinical application of antiviral agents in man. Guidelines for treatment will be offered at the end of each section.

VIRAL RESPIRATORY INFECTIONS

As a group, viral upper-respiratory-tract infections remain a leading cause of acute morbidity and economic loss throughout the world. Coryza and related symptoms are caused by a multitude of viruses and serotypes, some of which are antigenically unstable and most of which are uncontrollable by vaccination. The common cold and influenza have long been major targets for antiviral chemotherapy. This section summarises data concerning influenza A and B, rhino, corona, and respiratory syncytial virus (RSV) infections against which antivirals have distinct but limited efficacy.

Influenza A: Prophylaxis

Both amantadine and the structurally related compound rimantadine are effective in the prevention of illness caused by H1N1, H2N2, and H3N3 subtypes of influenza A (but not influenza B), both naturally acquired and experimentally induced, in man. Prophylactic efficacy has been reported in chronically sick and elderly people (including those in hospital[1,2]) and in children,[1,3] as well as in healthy adults.[4,5] On the evidence of controlled studies in many thousands of people, amantadine and rimantadine are about 50% effective in the prevention of infection but 70–100% effective in the prevention or amelioration of *illness:* this distinction may be a desirable feature of prophylaxis since subclinical infection could confer immunity against reinfection.

Concern over side-effects has cast doubt on the usefulness of both amantadine and rimantadine. During an outbreak of influenza A with an attack-rate of 5–20%, prevention or amelioration of illness with amantadine is accomplished at the expense of minor central-nervous-system side-effects in about the same numbers. Rimantadine is far better tolerated in this respect;[4,6] even so, treatment with either drug is best restricted to people at high risk of infection or its consequences. When there is influenza A in the locality, possible candidates would be unvaccinated children and adults at high risk because of underlying disease, unvaccinated adults in essential community positions, household contacts of an index case, people unable to receive influenza vaccine because of egg sensitivity, and people living in semi-closed institutions.

In the USSR, intranasal administration of low-titre interferon-alpha was reported in 1969 to prevent influenza A,[7] but the results have yet to be substantiated. Oral inosiplex (isoprinosine, a 1:3 molar complex of inosine with dimethylaminoisopropanol-*p*-acetamidobenzoate), an immunopotentiator, and oral ribavirin have been evaluated in man; both had side-effects and yielded inconsistent results.

Influenza A: Treatment

Oral treatment with amantadine or rimantadine, when started within the first 48 hours of symptoms, cuts the duration of fever and other effects of influenza A by 1–2 days—ie, it shortens illness by roughly one-third.[4,5,8,9] The reduction of influenzal symptoms far outweighs the toxic effects.[8,9] In addition, both agents may reduce the duration and amount of viral shedding, and oral amantadine accelerates resolution of the peripheral airways abnormalities that accompany influenza.[10] To date there have been no controlled studies on the therapeutic effect of amantadine on primary influenza pneumonia; the few people who have been treated with 400–550 mg a day do not seem to have benefited.

Amantadine is not widely prescribed, and the reasons include unfamiliarity with the drug's antiviral effect, delayed medical consultation, and concern that patients with respiratory infections other than influenza A might be treated and placed at unnecessary risk from its toxic effects. During a known influenza outbreak, however, almost all individuals with acute onset of feverishness, cough, headache, myalgia, or anorexia, but without vomiting or diarrhoea, will have influenza and ought to be considered for treatment. More than 48 hours after the onset of symptoms, the prospect of benefit diminishes.

Amantadine, rimantadine, and ribavirin have been given by aerosol in the hope of providing high concentrations of drug throughout the airways with a minimum of toxicity. When compared with placebo, an amantadine aerosol of 1 g/dl given for 20 minutes three times a day for 4 days accelerated recovery from naturally acquired influenza A virus infection.[11] It does, however, cause mild local side-effects, is inconvenient to administer, and seems no more effective than orally administered drug. Similar results were obtained with rimantadine aerosol in experimental influenza A infection.[12]

Ribavirin has a broader spectrum of antiviral activity (including influenza B and RSV) than either amantadine or rimantadine but the results of oral treatment are inconsistent. When given by aerosol within the first 24 h of symptoms from H1N1 influenza (about 1·15 g of drug in 23 h over 3 days) ribavirin accelerated the resolution of fever and illness and reduced virus shedding,[13] but the improvements were at best modest and certainly insufficient to justify treatment in otherwise healthy subjects.

Influenza B: Treatment

In influenza B ribavirin small-particle aerosol yields results similar to those in influenza A. To date, benefit has been seen only in patients with symptoms of less than 24 hours' duration who received 39 h of treatment in a total of 60 h.[14]

Respiratory Syncytial Virus: Treatment

The therapeutic efficacy of ribavirin by aerosol has been further evaluated in adults infected with RSV experimentally and infants infected naturally. In the adult volunteers, ribavirin or placebo was started 2 days after intranasal inoculation with RSV and given for a total of 12 h each day for 3 days.[15] Ribavirin had no effect on minor upper-respiratory-tract symptoms (rhinitis, sore throat, sneezing, and lymphadenopathy), but did reduce systemic complaints, cough, and fever. The drug was then evaluated in a double-blind controlled trial in children aged 1 week to 2 years who were in hospital with RSV pneumonia.[16] Treatment was initiated a mean of 4½ days after onset of symptoms; drug or placebo was administered almost continuously over 3–6 days into an infant oxygen hood, oxygen tent, or inhalation tubing of a respirator at an estimated dosage of 0·82 mg/kg body-weight per hour. By the end of treatment, infants receiving

ribavirin had significantly greater improvement of cough, rales, intercostal muscle retraction, lethargy, arterial oxygen saturation, and viral shedding, whereas temperature, nasal congestion, rhinorrhoea, and wheezing were unaffected. In another study, daily 12-hour treatments over 5 days were associated with a more rapid resolution of bronchiolitis, and there was a trend towards a more rapid improvement of rhinitis with nasal discharge and obstruction.[17] In no study were toxicity or side-effects noted.

Ribavirin remains investigational, but there is a good case for its use in certain infants with RSV infection during the first few months of life—for example, those admitted to hospital and those with congenital heart disease or severe combined immunodeficiency disease.

Rhinovirus: Prophylaxis

In 1973, Merigan et al[18] showed that $1 \cdot 4 \times 10^7$U of partly purified interferon-alpha given as frequent nasal sprays over 4 days could reduce the symptoms and virus shedding resulting from experimental infection with rhinovirus type 4 on the second day. Several groups have confirmed its efficacy in preventing or ameliorating illness, but its influence on the infection rate has varied. Since subclinical infection could confer immunity against reinfection a high infection rate is by no means disappointing. The main drawback is that, in the quantities necessary for a beneficial effect, intranasal interferon may cause local complications, and long-term use is inappropriate for prophylaxis of such a minor illness. Instead, it could be given for short periods to close contacts of an index case; indeed, preliminary data indicate that this approach may be both safe and effective.[19]

The prophylactic effect of interferon-beta has been little studied to date. In one experiment 0·25 ml of 10^5–$10^{6 \cdot 8}$ U/ml was given into each nostril 3 times daily for 4 days, with rhinovirus challenge on the second day, but there was no reduction of symptoms or viral shedding.[20] The scarcity of interferon in the past prompted several clinical trials of interferon inducers. Trials with topically applied polyinosinic/polycytidilic acid, a synthetic double-stranded RNA, pointed to some reduction in symptoms in volunteers infected with rhinovirus,[21] but this agent is probably too toxic for use in such acute self-limited conditions. An investigational agent, a propanediamine called CP-20,961, seems non-toxic and consistently reduced symptoms of rhinovirus infection when administered as a nasal spray three or four times daily from day 1 before virus challenge. However, in a double-blind placebo-controlled study it was ineffective in the prevention of "colds" when given once daily for 30 days.[22] The alternative approach of using specific antivirals has not so far yielded encouraging results. Enviroxime, a potent inhibitor of rhinovirus replication in vitro, has been evaluated clinically both in the United States and Britain. Although prophylactic administration of the drug has been associated with a reduction of certain symptoms, clinical scores of treatment and placebo groups have not differed significantly nor has the drug prevented infection.

Rhinovirus: Treatment

Various compounds, including a propanediamine interferoninducer for the treatment of infection due to rhinovirus and vitamin C for the common cold, have so far yielded disappointing results.

Parainfluenzavirus: Treatment

There is anecdotal evidence that ribavirin by aerosol is useful in life-threatening parainfluenzavirus infection. Gelfand et at[23] treated a 6-month-old infant who had severe combined immunodeficiency and respiratory distress associated with isolation of parainfluenzavirus type 3. At the end of the first 5-day course he was afebrile, the respiratory rate and arterial gases had much improved, and virus was no longer detectable. Within 48 h of drug withdrawal he deteriorated and virus was reisolated, but he responded again to antiviral therapy. Over the next 14 weeks there were repeated exacerbations and in each instance there was improvement with treatment. The boy eventually had a marrow transplant and became well.

TABLE I – GUIDELINES FOR CHEMOPROPHYLAXIS AND CHEMOTHERAPY OF RESPIRATORY INFECTIONS

Pathogen	Prophylaxis/treatment
Influenza A	*Prophylaxis:* amantadine 100 mg orally twice daily; less in children & subjects with renal insufficiency; avoid in women of childbearing potential *Prophylaxis:* rimantadine 50–200 mg orally daily (investigational) *Treatment:* amantadine 100 mg orally twice daily for 5–7 days; or rimantadine 50–200 mg orally daily for 5-7 days
Influenza B	None
RSV	*Investigational treatment:* ribavirin aerosol
Rhinovirus	*Investigational prophylaxis:* topical interferon
Coronavirus	*Investigational prophylaxis:* topical interferon

Coronavirus: Prophylaxis

The prophylactic effect of interferon-alpha has been investigated in volunteers experimentally infected with a strain of coronavirus 229 E.[24] 4×10^6U was administered as an intranasal spray three times daily with coronavirus challenge on the second day of treatment. Compared with placebo, interferon-alpha significantly reduced the number of "colds" and virus shedding was also diminished. As in the studies with rhinovirus, subclinical infections were common in interferon recipients, thus allowing some subjects to acquire natural immunity.

Guidelines

Guidelines are summarised in table I.

GENITAL HERPES

Genital infection with herpes simplex virus, most commonly HSV type 2, is a major cause of genital ulceration worldwide. In Britain, the number of genital herpes simplex infections has increased by up to 23% per annum in recent years and in 1982 14 836 cases were reported from sexually-transmitted-disease clinics. In the United States the numbers may be as high as 300 000 primary cases and 9 million recurrences each year. Primary lesions may persist for several weeks and are very painful. Some complications, such as urinary retention and central-nervous-system manifestations, require admission to hospital. Recurrences tend to be of shorter duration and less severe, though they still cause considerable morbidity; they are also associated with neonatal infection and represent a hazard to new sexual contacts.

Primary Genital Herpes

Topical, oral, and intravenous preparations of acyclovir (ACV) all have a beneficial effect on virus shedding and healing, and generally improve pain and other symptoms.

Topical ACV.—Treatment with 5% ACV cream in a propylene glycol base (applied 5 times daily for up to 10 days) has been evaluated in patients with first episodes of genital herpes of less than 5 days' duration.[25] It reduced the median duration of pain by 1 day, the time to complete healing by 5 days, and virus shedding by 6 days; in women the duration of dysuria was shortened by 5 days. In multicentre trials 5% ACV ointment in a polyethylene glycol base has been compared with placebo, the treatment starting within 6 days of onset of lesions and being applied 4 or 6 times daily for 7 days.[26,27] In patients treated with ACV, the mean duration of viral shedding was reduced by about 3 days; the duration of pain and time to complete healing were also shortened by several days, but here the differences between ACV and placebo groups were not consistently significant. Topical ACV ointment had no effect on systemic sequelae (fever, headache, photophobia, neck stiffness) or dysuria and vaginal discharge.[27]

Oral ACV.—Treatment with oral ACV (200 mg five times daily for 5 or 10 days) has similarly been investigated in patients with initial episodes of genital herpes of less than 5 or 6 days' duration.[28–30]. Among ACV recipients, the mean duration of viral shedding was reduced by 7–14 days; pain was generally reduced, complete healing was accelerated, and the mean duration of dysuria and tender adenopathy was lessened by 1·3 and 2·3 days respectively.

Intravenous ACV.—Intravenous ACV (5 mg/kg body-weight 8-hourly for 5 days) has also been evaluated in patients with first attacks of genital herpes of less than 6 or 7 days' duration.[31,32] It reduced the median duration of viral shedding by 4–11 days but had no consistent effect on duration of pain; time to complete healing, vaginal discharge, dysuria, sore throat, and other systemic complaints were all significantly reduced by the drug. Since intravenous and oral ACV have about the same efficacy, intravenous therapy can be reserved for hospital patients. Unfortunately, ACV treatment of primary genital herpes does not affect the recurrence rate.

Recurrent Genital Herpes: Treatment

Both topical and oral preparations of ACV have been evaluated in recurrent genital herpes.

Topical ACV.—Topical ACV ointment given four or six times daily for 5 days, but with treatment initiated within 48 h of onset of symptoms, shortens viral shedding at most by 1 day; pain is little affected, if at all; and there is essentially no beneficial effect on healing.[26,27,33] Treatment with ACV cream (applied 5 times daily for 5 days) has been investigated in patients with recurrences of less than 24 hours' duration. It reduced the median duration of pain by 1·5 days and of combined symptoms by 2 days.[25]

Oral ACV.—Oral ACV, 200 mg five times daily for 5 days, has similarly been evaluated in patients with recurrent episodes of less than 48 hours' duration;[29,34,35] in one of the studies,[35] patients began their own treatment a mean of 5 h after the first signs of symptoms of recurrence. Among the ACV recipients, the mean duration of viral shedding was reduced by 1–2 days; the duration of pain was unaffected even in the patient-initiated-therapy group; and the time to complete healing was reduced by 1·1–2 days.

Recurrent General Herpes: Prophylaxis with ACV

Long-term prophylaxis with ACV has been under investigation as a means of preventing frequent debilitating recurrences. Straus et al[36] conducted a trial of oral ACV (200 mg 5 times daily for 5 days then 3 times daily) or placebo in 35 patients (32 evaluable) who took the preparations for 125 days. The drug was well tolerated and there were significantly fewer recurrences in ACV recipients than placebo recipients (incidence of virologically confirmed recurrences 94% versus 12%). Douglas et al[37] recorded the same incidence over 120 days in placebo recipients, compared with 29% in patients receiving 200 mg 5 times a day and 35% in those receiving 200 mg twice a day. In a British trial[38] 200 mg 4 times a day for 12 weeks reduced the recurrence rate to 14% (96% in placebo recipients). Straus et al isolated some drug-resistant viruses from patients receiving ACV; but recurrences in these patients were associated with drug-sensitive viruses. The place of prophylaxis with ACV remains uncertain, especially in view of the scarcity of data on long-term safety and development of resistance. Nevertheless, this agent does seem highly beneficial in patients with frequent recurrences and could be of enormous value in preventing the spread of infection. At present it should be reserved for the severest of cases.

TABLE II – GUIDELINES FOR ANTIVIRAL CHEMOPROPHYLAXIS AND THERAPY OF GENITAL HERPES

Category of genital herpes	Recommendation	Comment
Primary		
Severe, with systemic and other symptoms requiring hospital admission	Intravenous ACV 5 mg/kg 8-hourly for 5 days; or oral ACV 200 mg 5 times daily for 5 days	For 70 kg person, intravenous regimen costs £193, oral regimen £25 with comparable efficacy
Not requiring hospital admission	Oral ACV 200 mg 5 times daily for 5 days; or topical 5% ACV cream applied 5 times daily	
Recurrent	No antiviral treatment recommended; for prophylaxis in patients with frequent recurrences 200 mg 3 or 4 times daily could be used cautiously	A year's supply at 4 times daily would cost £1460. Further data on long-term safety needed

Other Treatments

Besides ACV numerous therapies have been evaluated over the years but have mostly proven ineffective or been inadequately assessed. Initial studies with topical surfactants (such as ether and nonoxynol 9) and photodynamic inactivation with proflavine or neutral red suggested an antiviral effect, but placebo controlled studies showed none to be clinically active. Of the controlled investigations of topically applied idoxuridine (IDU), one showed that 0·5% ointment was ineffective;[39] another suggested that 5% or 20% IDU in dimethylsulphoxide (DMSO) shortened viral shedding and aided healing;[40] and another showed no clinical benefit from 30% IDU in DMSO for either primary or recurrent episodes.[41] Topically administered 3% vidarabine cream seems equally ineffective.

Treatment with oral ribavirin (800 mg daily for 10 days) reportedly reduces the severity of pain and new lesion formation, but the results await confirmation.[42] Similarly, topical 2-deoxy-D-glucose, an inhibitor of envelope protein glycosylation, is said to accelerate recovery from initial infections and reduce the frequency and severity of recurrent episodes of genital herpes,[43] though this agent has no therapeutic efficacy in animal models of infection.

Guidelines

Guidelines are summarised in table II.

HERPETIC KERATITIS

Ocular HSV infection, caused usually by HSV-1, is the leading communicable cause of blindness in developed countries. Primary ocular infection is acquired in early life and causes vesicles on the lids and a follicular blepharoconjunctivitis; in many instances the initial infection is subclinical. During recurrences viral replication initially produces small vesicular lesions in the corneal epithelial cells which may rupture and coalesce to form a dendritic or amoeboid ulcer, resulting in disability and pain. The condition may eventually progress to a deep stromal keratitis, necrosis, vascularisation, and scarring. Recurrent ocular herpes tends to be more severe than the primary infection: it arises in 26% of patients within 2 years of the initial episode and in 43% within 2 years of a second attack.[44] Fortunately, there are several drugs with established efficacy in the treatment of ocular herpes.

Idoxuridine

Topically applied IDU has been in use since 1962 for the treatment of herpetic keratitis, the average cure rate being 76%.[45] The cure rates for primary and recurrent cases are identical, and favourable results are commonly achieved during the first 7 days of therapy.[46] Toxic side-effects are not infrequent, however, and the poor ocular penetration makes it less satisfactory for deep infections. IDU is no longer the drug of first choice.

Vidarabine

Vidarabine, another poorly soluble compound, became the second antiviral to be widely used in the treatment of ocular herpes. On the evidence of numerous studies it is more effective than IDU in herpetic keratitis. In one double-blind trial comparing the two, treatment failure was recorded in 18·8% of IDU-treated patients but in only 9·5% of vidarabine-treated patients; the mean time to healing was about 7 days with either drug.[47] Vidarabine coupled with corticosteroid therapy also seems beneficial in stromal disease[48] despite its poor solubility and non-penetration into the healthy human eye.[49] Toxic reactions, similar to those caused by IDU, develop in about 10% of patients. Despite its efficacy, many clinicians now favour acyclovir for initial management of ocular herpes.

Trifluorothymidine

Trifluorothymidine (F3TdR) has been in clinical use for more than a decade and is marketed in some European countries (not in the UK). In the USA it was approved in 1980 for the treatment of ocular herpes. Topically applied F3TdR has proved consistently more effective than IDU, with an average cure rate of 97% for dendritic and geographic corneal lesions.[50] The healing time has also been consistently shorter, by several days, for F3TdR than for IDU.[51] It is also better than vidarabine for the treatment of amoeboid ulcers[52–54] but not dendritic or geographic ulcers, though the trend is towards superiority of F3TdR.[54] F3TdR is effective also in the treatment of keratitis unresponsive to IDU or vidarabine, and is preferable to either agent for large ulcers and complicated disease. Adverse reactions to F3TdR are similar to those to IDU but seem less common. Since there are no reports of cross-toxicity between F3TdR and other ocular antivirals the drug can be used after reactions to other agents.

TABLE III—GUIDELINES FOR ANTIVIRAL THERAPY OF HERPETIC KERATITIS

Agent	Instructions
First choice:	
3% ACV ointment	1 cm strip inside lower conjunctival sac 5 times daily; continue for at least 3 days after healing complete
1% F3TdR solution	1 drop 2-hourly during daytime to maximum of 9 drops; on re-epithelialisation continue for additional 7 days at 1 drop 4-hourly (minimum 5 drops daily)
Other possible regimens:	
3% vidarabine ointment	1 cm strip inside lower conjunctival sac 5 times daily; and, upon re-epithelialisation, 2–3 times daily for further 7 days
0·1% IDU solution	1 drop hourly during daytime and 2-hourly at night until improvement is seen; then 2-hourly during day and 4-hourly at night, continued for 3–5 days after healing complete
0·5% IDU ointment	1 cm strip applied 5 times daily; continue for 3–5 days after healing complete

Since there is no cross-resistance between these antivirals, an alternative agent can be confidently substituted if there is no clinical improvement within 7 days. In these circumstances, however, other possible causes for delayed healing should be excluded—for example, insufficient drug application, or an underlying stromal reaction.

Acyclovir

Topical ACV has been thoroughly evaluated in clinical trials[45,55–58] and has shown itself at least as effective as IDU, vidarabine, and F3TdR in the treatment of herpes keratitis, and possibly superior. 97% of patients with dendritic and geographic corneal lesions were healed by ACV. The rate of healing in ACV recipients seems distinctly faster than that with other antivirals—average healing time about 4 days.

Investigational Agents

Uncontrolled trials with an 0·1% ophthalmic preparation of bromovinyldeoxyuridine have yielded promising results in herpes simplex keratitis. Maugdal et al[59] tried this agent in 37 patients many of whom had been unresponsive to IDU or vidarabine. All patients responded favourably, with an average healing time of 7·8 days for dendritic ulcers and 10·8 days for geographic lesions. No signs of toxicity or hypersensitivity were noted in any patient.

Topical application of interferon-alpha has been extensively investigated in dendritic keratitis, mostly with disappointing results. Exogenous interferon alone is not sufficiently effective; it must be used in conjunction with either debridement or another antiviral.[60] Sundmacher et al[61] report that coadministration of F3TdR and interferon (3×10^7 U/ml) gave significantly faster healing than F3TdR alone, so there is scope for improvement in the treatment of HSV keratitis.

Guidelines

Guidelines are summarised in table III.

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Occasional Survey

GALLBLADDER DISEASE AND CHOLECYSTECTOMY RATE ARE INDEPENDENTLY VARIABLE

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Summary In Britain, gallstones can be expected to develop in 1 in 3 women and 1 in 5 men. Gallbladder disease in Dundee was more frequent in 1974–83 than in 1953–73. During 1961–81 the number of cholecystectomies trebled in Dundee and doubled in Scotland as a whole, but this could not be explained by changes in the prevalence of gallbladder disease. Between 1974 and 1983 in Dundee, 48 patients died of gallstone disease. 22 out of 54 (41%) patients with common bileduct stones at necropsy and 26 out of 1034 (2·5%) with gallbladder stones only at necropsy died from an associated cause. A further 26 died from gallbladder surgery without bileduct surgery. Gallbladder disease was not associated with death from myocardial infarction, and there was no relationship between gallstones and gallbladder cholesterolosis. 22 patients were found to have secondary carcinoma of the gallbladder and 17 were found to have primary carcinoma of the gallbladder at necropsy.

INTRODUCTION

GALLBLADDER disease is usually an incidental finding at necropsy.[1] Examination of necropsy data standardised for

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