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AN ASSESSMENT OF ANTIVIRAL DRUGS FOR THE MANAGEMENT OF INFECTIOUS DISEASES IN HUMANS

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INTRODUCTION

It has long been held that antiviral agents of necessity would be too toxic for practical application, since the need to affect viral replication at the intracellular level would also risk damage to normal cell function. Recent results have shown that this problem can be avoided; relatively non-toxic compounds have become available, virus-specific agents are under clinical study and others are under development. The field is in an exciting and productive period.

The need for and importance of these agents cannot be overemphasized. Viral diseases remain among the greatest cause of human morbidity and economic loss. The average person has from two to six viral infections per year. As our ability to prolong life through transplants and treatment of cancer increases, viral diseases become an even greater problem, since many of these patients, being immunosuppressed, will acquire viral infections of life-threatening importance. Although considerable progress has been made and several agents are approved for clinical use, we are only on the treshold of this important field. Much more careful work needs to be done.

The purpose of this review is to discuss the clinically applicable antiviral agents. The emphasis is on those agents that are generally accepted and approved by appropriate government agencies. To be of value to the widest audience, the review is divided by disease state. Only those diseases for which antivirals are available or under study are discussed.

INFLUENZA

Influenza will be treated separately because it is one of the most serious of the respiratory diseases – the etiological agent is one of the more complex viruses to deal with – and because there is an effective antiviral. Influenza continues to defy control in spite

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of the availability of effective vaccines. Immunization is a problem because of the ability of the virus to change its antigenic structure; a second problem is difficulty in clinical recognition of influenza, resulting in a tendency of the patient and some clinicians to attribute any severe respiratory infection to 'the flu', giving the impression that the control measure used was ineffective There are three types of influenza viruses: A, B and C. A is the most common and the most frequent cause of influenza epidemics; C rarely causes epidemics or serious infection; B is intermediate between the two. The antigenic components that lend themselves to 'drift' and 'shift' are the surface antigens, hemagglutinin and neuraminidase. These antigens seem to be continually changing in type A, to a much lesser extent in B, and not at all in C.

Influenza is characterized by abrupt onset of fever, chills, headache, myalgia and sometimes prostration; generalized aches and pains, most pronounced in the back and retro-orbital area, are common. Symptoms of respiratory illness such as sore throat, coryza, unproductive cough (which can be severe and protracted) are frequent. Usually, the disease is self-limited with recovery in 2–7 days. Persistence of fever, cough and other respiratory symptoms for longer than 5 days may indicate a secondary bacterial infection of the respiratory tract.

Although sporadic cases do occur, recognition is commonly by epidemiologic characteristics. Outbreaks usually occur abruptly, spreading rapidly through specific communities (usually in the winter months) to infect 20–50% of susceptible individuals. Epidemics peak within three weeks and subside in another three to four weeks.

The currently recommended vaccine should be administered each year, particularly to those designated as high risk. The World Health Organization and local authorities make recommendations each year on proper usage of the vaccine. Consideration should be given to the use of the antiviral agent, amantadine hydrochloride (Symmetrel) in instances where vaccine has not been given, when a new pandemic strain appears or as a supplement to the vaccine.

Amantadine hydrochloride (Symmetrel)

Amantadine has been shown to be effective in the prevention and treatment of influenza type A but not types B or C. This drug was approved in 1966 for the prevention of Asian (H2N2) influenza in the U.S. Since that time it has been used to various degrees in different parts of the world. The greatest amount of use appears to be in the U.S.S.R. For various reasons, including concerns about side effects, it was not used widely in the U.S. When H3N2 appeared in 1968, amantadine was no longer recommended in the U.S., since it was originally approved only for H2N2. In 1976, after a thorough review of the available data concerning the use of amantadine in influenza and its use in patients with Parkinson's disease, the F.D.A. approved it for prophylaxis and therapy of all influenza A infections. Since there was still a reluctance on the part of some clinicians to use this drug, new clinical studies were done when H1N1 reappeared [30]. It was again demonstrated that it is greater than 70% effective in the prevention of influenza A. In October

1979, the N.I.H. held a Consensus Development Conference to review all the data and make a recommendation (J. Am. Med. Assoc., 1979, 242, 2383). The Conference concluded that under the appropriate epidemiologic and clinical conditions, amantadine should be used in the prevention and treatment of influenza caused specifically by strains of influenza A virus.

Indications

Amantadine should be considered especially for high-risk patients, for close household or hospital ward contacts of index cases, and for patients with severe influenza A virus illness. It does not appear to suppress the antibody response and, therefore, can be used chemoprophylactically in conjunction with vaccine. The drug is contraindicated in patients with known hypersensitivity to it. Since the drug has not been adequately tested in pregnant women, its use in this population should be undertaken only after weighing the possible risks to the fetus against the benefit to the patient. Since it is secreted in the milk, the drug should not be administered to nursing mothers. Patients with a history of epilepsy or other 'seizures' should be observed closely for possible increased seizure activity. Patients with compromised renal function should receive altered dosage schedules, since the drug is not metabolized and is excreted almost entirely by the kidney.

Side effects

Central nervous system symptoms (insomnia, lightheadedness, nervousness, difficulty in concentration, or drowsiness) have been observed in up to 7% of individuals receiving amantadine (200 mg daily) in excess over control subjects receiving placebo. If these side effects appear, they do so within a few hours after initiation of the drug and are transient. If they do not appear within the first 48 h, they are not likely to occur; therefore, patients should be cautioned or observed accordingly. Other side effects may occur at a lower frequency and are of a less serious nature.

Dosage and administration

Prophylaxis should begin in high-risk individuals and those at high risk of exposure as soon as influenza A is identified in the community and should continue throughout the period of risk, usually 5–6 weeks. Amantadine is supplied in 100 mg capsules and tablets; the recommended adult dosage is two 100 mg capsules or tablets as a single daily dose in the morning or it may be split into one capsule or tablet twice a day. In children less than nine years of age the total dose should be calculated on the basis of 2–4 mg per pound of body weight per day, not to exceed 150 mg/day. The drug is also available as a syrup. The dosage may need careful adjustment in patients with renal impairment. Since amantadine is not metabolized and is mainly excreted in the urine, it may accumulate when renal function is inadequate. Care should also be exercised with patients with liver disease or with psychoses or severe psychoneurosis not controlled by chemotherapeutic agents.

If treatment can be initiated within the first 48 h of symptoms, it is recommended as

an effective therapeutic regimen [23, 24]. The same dosage as above is recommended and should be continued for 24–48 hours after disappearance of symptoms. Some physicians treat influenza pneumonia with considerably higher doses (6 mg/kg/day), but the efficacy of such therapy against pneumonia is not established. Studies to evaluate this drug's efficacy against influenza pneumonia and use of aerosolized amantadine are currently underway.

Rimantadine

Rimantadine hydrochloride is a closely related analogue of amantadine that appears to be somewhat more active both in vitro and in vivo than amantadine. It is also better tolerated and may eventually be the drug of choice. Currently amantadine is approved for use in the U.S. and rimantadine is under study; rimantadine is widely used in the U.S.S.R. A recent study [50] compared the therapeutic efficacy of amantadine and rimantadine in naturally occurring influenza. Forty-five university students with proven H1N1 influenza A were randomly treated with either amantadine, rimantadine, or placebo. Both drugs proved to be effective, but amantadine exerted a more rapid effect and was felt to be the drug of choice by these investigators. Studies comparing these two drugs for prophylaxis and therapy, including aerosol administration, are ongoing.

Ribavirin

Ribavirin is a synthetic nucleoside that has exhibited in vitro and in vivo antiviral activity against both type A and B influenza viruses. Clinical studies have yielded conflicting results. Recently, a collaborative study was performed to determine the role of this drug in influenza [41]. The double-blind, placebo-controlled study included 97 young adult males naturally infected with influenza A (H1N1) in the winter of 1978–79 The dosage used was 1000 mg/day administered orally beginning within 24–28 h of symptoms and continued for five days. There were no differences in clinical signs and symptoms, nor in virus shedding, between the drug and placebo groups. Significant increases in bilirubin and reticulocyte counts were observed in the ribavirin group.

Based on this definitive study, there does not appear to be any role for this agent against influenza A infections. However, it should be noted that some investigators maintain that aerosolized ribavirin is much more effective than amantadine and that the two drugs given together by aerosol yield the best results [57].

Interferon

As summarized below, there are conflicting reports on the role of interferon in respiratory viral diseases. There is currently no conclusive evidence showing efficacy in the prevention and treatment of influenza.

Other antiviral agents

Among the other agents that have been used against influenza are: 2-deoxy-D-glucose, D-glucosamine, 2-deoxy-2,3-trifluoroacetylneuraminic acid (FANA), and Isoprinosine. There is no clear evidence that any of these compounds have a role in prophylaxis or therapy of influenza.

OTHER RESPIRATORY VIRUSES

Even in the absence of influenza epidemics, the leading cause of morbidity is acute viral respiratory disease, accounting for up to six illnesses per person per year. Incidence is highest in children under five with gradual decline with increasing age. Although many of these episodes are mild and of short duration, they are costly in terms of loss from work and school. Each episode results in an average of four days of restricted activity. It has been estimated that in the U.S. an average of 1.6 days are lost from work each year for each person due to acute respiratory disease. There are also instances where, depending on underlying conditions, there may be a progression to more life-threatening episodes, such as pneumonia. There are more than 200 serologically distinct viruses that cause respiratory illness, making the vaccine approach to control infeasible. Such agents include parainfluenza, respiratory syncytial, adeno, rhino and certain corona, Coxsackie and ECHO viruses

Considerable money is spent each year on symptomatic remedies; however, there is currently little that can be done to specifically affect these illnesses. Collectively, they are characterized by fever and one or more constitutional reactions, such as chills, headache or general aching, malaise, and anorexia. The incubation period is usually short with abrupt onset, generally with a scratchy sensation in the throat, followed by sneezing, rhinorrhea and malaise; fever is more common in children but unusual in adults. Greater or lesser involvement of the lower respiratory tract varies with both agent and age.

With the exclusion of influenza, there is currently no specific treatment for viral respiratory diseases. Treatment is limited to alleviating symptoms. Bacterial complications are infrequent, prophylactic antibiotics are unwarranted and in some instances may lead to development of antibiotic-resistant strains. Bed rest and supportive measures for the patient's comfort are recommended; aspirin for myalgia, headache and fever; preparations for alleviating nasal congestion and increased intake of liquids may be useful.

Several antiviral agents have been evaluated against these diseases; some of particular interest will be discussed.

Interferon

There have been conflicting reports on the role of interferon in prevention or treatment of respiratory infections. Some maintain that low doses (approximately 2000 units) are sufficient for prophylaxis [43], whereas other studies indicate that high doses

are necessary. Merigan and his associates [28] reported that very large dosages (14 million units) decreased symptoms due to rhinovirus infections when applied topically in repeated doses. Recently, Greenberg and associates at Baylor [13], in an effort to determine whether smaller (and more practical) doses were efficacious, tested 3 million units of interferon applied by aerosol prior to challenge with rhinovirus type 13. No differences were seen between treated and control groups. Part of the reason for the very high and frequent dosing necessary to obtain an effect may be the rapid clearance of interferon when administered topically [12]. There is currently no evidence to indicate that interferon can be used effectively with a reasonable regimen against clinical viral respiratory disease. However, if rapid clearance can be avoided, the possibility exists.

Ascorbic acid

Another controversial compound is vitamin C. It has been postulated that large oral doses are useful for the treatment and prevention of the common cold. These claims have been reviewed by Chalmers [5] and by Dykes and Meier [9]. More recently, a randomized control trial was conducted in 1524 volunteers [49]. Ten grams of ascorbic acid were administered during the first 2.5 days of the symptoms of naturally occurring colds; no beneficial effects were observed. There appears to be no clear-cut evidence for recommending ascorbic acid for the prevention or treatment of the common cold

Isoprinosine (Inosiplex)

Despite numerous reports on the broad spectrum antiviral and immunopotentiating effects of this compound, there is no convincing evidence for its role in treatment of viral diseases. A controlled, double-blind trial was undertaken to demonstrate this drug's therapeutic effect in volunteers challenged with rhinovirus type 21. Drug (4 g/day) or placebo was started at time of, or 48 h after challenge. This study demonstrated a reduction in the frequency of illness and symptom score in the drug-treated volunteers compared to the placebo group [51]. Another study with a daily dose of 6 g given for 2 days prior to challenge with rhinovirus type 9 and for 5 days following challenge [44] showed no evidence of useful antiviral activity. Similar results showing lack of efficacy were obtained by Pachuta et al. [32].

Other antiviral agents

Several other compounds have been investigated Rifampin has been shown to have some in vitro activity against adenoviruses [46]. However, achievement at such levels in blood would require dosages that are far above the toxic level for man. 2-Deoxy-D-glucose and D-glucosamine are effective in inhibiting glycosylation of proteins and can inhibit enveloped viruses such as orthomyxoviruses and paramyxoviruses [18]. However, their clinical application is unlikely due to their effect on normal cells. Guanidine and

2-(α-hydroxybenzyl)-benzimidazole have been shown to have an antiviral effect against picornaviruses in vitro and in mice [10,21], but any clinical applicability remains unproven and doubtful.

A compound that shows some promise is 2-amino-1-(isopropyl sulfonyl)-6-benzimidazole phenyl ketone oxime (Zinviroxime). It appears to be a highly specific inhibitor of picornavirus replication in human embryonic nasal organ cultures when added 26 h post infection at doses far below the toxic level [8]. Results obtained in tissue culture and in animals suggest possible efficacy in man; clinical studies in rhinovirus infections remain to be done.

The list of compounds cited here is far from inclusive, and deals only with those compounds receiving the widest testing or offering the best potential. It is clear that for the common cold an antiviral must be free of toxicity and side effects and it must be readily available to the patient for use at first signs of a cold. For the more serious manifestations of viral respiratory disease, some side effects may be acceptable. Although the results to date have not been successful, considerable work is being pursued and should be encouraged.

HERPES VIRUS INFECTIONS

These viruses are among the most common infectious disease agents of man, second only to the respiratory disease agents. This group includes herpes simplex types 1 and 2 (stomatitis and skin eruptions, including 'fever blisters', encephalitis, eye and genital infections), B virus (encephalitis), varicella zoster virus (chickenpox, shingles), cytomegalovirus (disseminated infections, mononucleosis, hepatitis, etc.) and Epstein–Barr virus (Burkitt's lymphoma, infectious mononucleosis). One of the characteristics shared by the members of this group is their tendency to become latent with periodic reactivation. Primary infections may often be subclinical, but usually they are more severe than the recurrent infection. They are a major problem in the immunocompromised patient and the newborn. Fortunately these viruses lend themselves to antiviral intervention. There are several agents with demonstrated clinical efficacy, and others under development appear promising.

Herpes simplex

Infections of the eye

This infection, usually with type 1, affects 1 per 1000 individuals yearly and is the leading cause of corneal blindness Primary infection is an acute keratoconjunctivitis with or without skin involvement. Clinically, the disease begins a few days after exposure and can be readily diagnosed by the typical branching dendritic ulcer on the cornea visualized with fluorescein stain. Following primary infection, the virus may become latent, probably residing in the trigeminal ganglion. It has been demonstrated [4] that there is a recurrence rate of 26% within two years of the initial episode and a 43% recurrence rate

following a second attack. Unlike other herpesvirus recurrent infections, ocular recurrence is generally more severe than the primary lesion. Although there are a number of antiviral agents that are widely approved for treatment of this disease (iododeoxyuridine, adenine arabinoside, and trifluorothymidine), it remains a difficult therapeutic problem. Repeated usage of some antivirals may result in clinical resistance, chemical intolerance and, in some instances, hypersensitivity.

Iododeoxyuridine (Stoxil, idoxene) This compound (IDU) was first demonstrated to be effective for the treatment of viral keratitis in 1962 [20], achieving the distinction of being the first widely used antiviral agent. However, it has become apparent that IDU therapy is not always clinically effective. It has been demonstrated that viral resistance can develop and ocular toxicity of the drug has been observed.

The drug is available as a 0.1% ophthalmic solution in distilled water and as a 0.5% ophthalmic ointment in petrolatum base. It is recommended that one drop of the solution be placed in the infected eye every hour during the day and every 2 h at night. Treatment should be continued until definite improvement is observed, and continued every 2 h during the day and 4 h at night for up to 3–5 days after healing appears to be complete. When the ointment is used, it should be administered 5 times a day every 4 h with the last dose just prior to bedtime. The ointment should be placed in the conjunctival sac of the infected eye; treatment should be continued up to 3–5 days after healing appears to be complete. Some physicians prescribe the drop formulation for daytime use and the ointment for nighttime use.

This drug is contraindicated in patients with known or suspected hypersensitivity to any of its components and should be used with caution in pregnant women. Since there are some resistant strains of herpes simplex virus, treatment should be discontinued if no response is seen after 7–8 days of treatment. Irritation, pruritus, pain, inflammation, or edema may be observed. Allergic reactions have also been reported.

Adenine arabinoside (vidarabine, vira-A). This drug (ara-A) was approved in the U.S for treatment of herpetic ocular disease in January 1977 Much of the data are in a compendium of papers presented at a symposium held in 1974 [35] and recently reviewed by Buchanan and Hess [3]. Ara-A appears to be at least as effective as IDU, and probably more effective It is especially useful in patients who cannot receive IDU because of allergy, toxicity or clinical resistance

The drug is available as a 3% ophthalmic ointment in a petrolatum base. Approximately 0.5 inch of ointment should be placed into the lower conjunctival sac five times daily at 3–4 h intervals. An average of 7–9 days of treatment is required to achieve corneal re-epithelialization. In controlled trials, 3 weeks treatment were required for complete re-epithelialization. If there are no signs of improvement after 7 days, or complete re-epithelialization has not occurred by 21 days, other forms of therapy should be considered.

The drug should not be used in patients who have a history of sensitization to ara-A. Although there are no data indicating toxicity to the fetus or newborn in pregnant or lactating women, the drug should be used with great care in such patients. However, toxicity of this drug with topical application should not be as serious a concern as it would be with systemic use. Adverse reactions have included lacrimation, foreign body sensation, burning, and irritation, as well as other complaints that could be associated with the underlying disease. A more soluble form of this drug, adenine arabinoside monophosphate, is currently under study.

Trifluorothymidine (viroptic, trifluridine). This drug (F_3T) is available worldwide, and was approved in 1980 in the U.S. for treatment of ocular herpes. This is the most soluble of the compounds discussed in this section, a feature that contributes to its bioavailability and effectiveness. It is minimally toxic and appears to be at least as effective if not more so than the other drugs currently approved for use in the treatment of this disease [19]. Controlled studies comparing the three drugs (ara-A, IDU and F_3T) reported the superiority of F_3T [16, 17]. This drug has been effective in the treatment of epithelial keratitis that has not responded clinically to IDU or ara-A.

The drug is available as a 1% ophthalmic solution. One drop should be placed onto the cornea of the infected eye every 2 h while awake for a maximum daily dosage of 9 drops until the corneal ulcer has completely re-epithelialized. It is recommended that the drug be continued for an additional 7 days of one drop every 4 h while awake for a minimum daily dosage of 5 drops. If there are no signs of improvement after 7 days or complete re-epithelialization after 14 days of therapy, other drugs should be considered. Continuous treatment with F_3T for periods exceeding 21 days should be avoided.

The most frequent adverse reactions observed have been mild transient burning or stinging and palpebral edema in 3–5% of those studied. The drug should not be used in those who develop hypersensitivity to it. Although it is unlikely that this drug would present problems to pregnant or lactating women, it should not be prescribed unless the potential benefits outweigh the risks.

Other treatment. If there is no corneal ulceration, one of the above drugs should be applied as directed. If there is corneal ulceration, therapy should consist of simple debridement with a sterile cotton-tip applicator after proparacaine drops, followed by F_3T, ara-A or IDU as directed. Topical antibiotics should be used if the cornea is ulcerated [34].

Other drugs also available in Europe for ocular herpes, include 5-ethyl-2′-deoxyuridine (Aedurid) available as a preparation for subconjunctival injection, as drops, or as a 0.3% gel. Tromantadine HCl (Viru-Merz) is available as an ointment, and iododeoxycytidine (Cebe-Viran) is available as a solution or ointment.

Need for improved drugs. Although favorable results have been achieved in the treatment of the acute episode, there has been no success in the prevention of recurrences. Further-

more, there clearly is a need for drugs that are more virus specific, therefore less toxic and hopefully faster acting.

Studies have been done to evaluate the prevention of recurrences by prophylactic application of interferon eye drops. As yet an effective regimen has not been established, nor has interferon been shown to be clinically relevant in acute episodes. The combination of interferon with either a thermomechanical debridement of the diseased corneal epithelium or with F_3T eye drops has proved to be more effective than any single therapy tested. The concentration of interferon used for eye drops was 3×10^7 units/ml [47].

Acyclovir and E-5-(2-bromovinyl)-2′-deoxyuridine are two relatively new antiviral agents that are very specific for herpesviruses and appear very promising for infections by this agent in rabbits. Definitive clinical studies remain to be done.

In addition to herpes simplex, other viral infections of the eye include varicella zoster, cytomegalovirus, adenovirus and poxviruses. Unfortunately, there is no current specific antiviral treatment for these diseases. There are isolated reports on positive results but none widely accepted. The prognosis for effective antivirals to treat these localized infections is good; however, what is needed are drugs which will eliminate the deep-seated viral reservoirs.

Encephalitis (HSE)

This is a rare complication of herpes simplex infection, yet it is one of the more common sporadic infections of the human central nervous system. Since herpes simplex is one of several agents causing encephalitis, the exact incidence is not known, its frequency may range from 3 to 50 cases/million/year. Very little is known about pathogenesis; the virus is probably spread via the neural routes to the brain during primary or recurrent infections. The disease has an acute to subacute onset, with headache, fever, behavior changes, and lethargy, usually with no antecedent history of infection. In severe cases the symptoms proceed to convulsions, confusion, +/- meningismus, motor paralysis, ataxia and other focal signs within hours or days. The mortality rate of this disease is 70%, with severe residual effects in a large percentage of the survivors. The clinical presentation may suggest HSE; however, the diagnosis can only be confirmed by direct examination of brain tissue [55]. HSV encephalitis should be suspected in patients with a history of acute febrile encephalopathy associated with disordered mentation, altered level of consciousness and focal cerebral signs. Brain biopsy is required in order to confirm the etiological diagnosis by means of viral isolation in cell culture and/or fluorescent antibody techniques. Electron microscopy can provide presumptive diagnosis.

Adenine arabinoside (vidarabine, vira-A). It was demonstrated in a placebo-controlled study [55] that parenteral administration of this drug reduced the mortality from 70% to 28% with a concomitant reduction in moderately debilitating neurologic sequelae in the treated patients. However, patients who were already in coma did not benefit from therapy. Based on these statistically significant results, the placebo-controlled study was terminated and the drug approved for treatment of herpes encephalitis Several questions

regarding the initial study were raised, primarily related to the small number of cases. These small numbers also were insufficient to evaluate morbidity in survivors. The study was continued, treating all biopsy-proven cases of herpes encephalitis and following the patients' progress. 57% (75/132) of clinical encephalitis patients were positive for herpes simplex virus. The mortality rate compared well with the original study, 33% one month after onset and a total of 39% up to 12 months following treatment. A survey of other studies of brain biopsy-proven encephalitis showed a mortality rate of 72% (28/39) in patients treated with placebo, cytosine arabinoside or idoxuridine. Morbidity of survivors (in the Whitley studies) one year after treatment was as follows: normal 53% (30/56), moderately debilitated 29% (16/56) and severely damaged 18% (10/56). Those who did best were young patients less than 30 years of age and with the highest level of consciousness. Older patients and those in coma did poorly [56].

Studies are currently under way to evaluate adenine arabinoside monophosphate, a more soluble derivative of ara-A that can be administered without large volumes of fluid, and acyclovir in comparison to ara-A.

Ara-A is available for intravenous administration only. Each milliliter of suspension contains 200 mg of the monohydrate equivalent to 187.4 mg of ara-A. Following i.v. administration, it is rapidly deaminated to arabinosylhypoxanthine, the principal metabolite, which is promptly distributed into the tissues. Ara-A does not alter the course of disease or serious neurological sequelae in comatose patients; early diagnosis of herpes encephalitis is essential.

Dosage and administration. The contents of the vial containing the drug should be diluted in appropriate intravenous solution prior to administration. It should be given via slow-drip infusion at a dosage of 15 mg/kg/day for 10 days. Rapid or bolus injection must be avoided. Treatment should be initiated in suspected cases at time of biopsy, but should be discontinued if the biopsy material is negative. Care must be taken to avoid fluid overload or cerebral edema. Special care must be taken with patients with kidney or liver dysfunction. It should be emphasized that, due to the poor solubility of ara-A in aqueous medium ($\sim$ 0.5 mg/ml), the intravenous infusion would require approximately 2 l fluid/day for an adult infusion ($\sim$ 79 kg).

Contraindications. Ara-A should not be administered to those with a hypersensitivity to the drug. It should not be given intramuscularly or subcutaneously, and use in pregnant women should be limited to life-threatening illnesses. Patients on ara-A treatment should not be allowed to breast-feed their infants.

Side effects. The principal adverse reactions involve the gastrointestinal tract and are anorexia, nausea, vomiting and diarrhea. These reactions are usually mild and seldom require termination of drug. CNS disturbances have been reported at therapeutic dosages; these include tremor, dizziness, hallucination, confusion, psychosis and ataxia. Hematological changes include a decrease in hemoglobin or hematocrit, white cell count and platelet count. SGOT elevations may also be observed.

Neonatal infections

Although relatively uncommon, this disease has a high mortality rate. A majority of these patients acquire the infection at or immediately preceding delivery, infected genitalia are the primary source of transmission. Infant to infant spread or transmission by hospital personnel has been reported, though rare. Incidence has been reported between 1 and 3–30 thousand live births. Skin vesicles may be observed at birth or as late as one month of life; however, clinical manifestations usually occur at between one and two weeks of life. Infection may be either disseminated with multiple organ involvement, often including the brain, or can be localized to the central nervous system (CNS), skin, eye and/or mouth without evidence of visceral involvement. The mortality rate of disseminated and localized CNS disease, which accounts for over 75% of all neonatal herpes, is 82% and 40% respectively [31].

Adenine arabinoside (vidarabine, vira-A). A collaborative study has recently been completed evaluating this drug in infected newborns. The mortality observed in this study was somewhat greater than previously reported, although quite similar. Overall mortality in babies with CNS and disseminated disease was reduced from 75% to 38% with drug therapy In babies with localized CNS disease, the prognosis was best; mortality was reduced from 50% to 10% with drug therapy. The outcome with disseminated disease was a reduction of from 86% to 57%. Mortality was uncommonly associated with localized skin, eye or mouth infections, severe sequelae occurred in 38% of placebo recipients but in none of those on drug therapy. These latter patients did have minor chorioretinitis which did not impair development. The drug was administered intravenously at a dose of 15 mg/kg/day over a 12 h period for 10 days, similar to the encephalitis study.

Morbidity was not significantly improved by drug therapy in patients with disseminated herpetic infection. However, the effect was more striking in newborns with localized CNS disease; 3/6 placebo patients survived, but only one was developing normally at one year. Only 1/10 treated newborns died, and 5/9 survivors were normal at one year. Very little toxicity of the drug was observed; side effects seen in older patients are difficult to assess in sick newborns. Objective laboratory measurements were similar in treated and placebo groups [54].

These studies have recently been published and will be reviewed by proper authorities before any recommendation can be made on clinical usage. It is expected that a favorable decision will be made; however, improvement in the mode of therapy and the development of more effective antivirals is essential.

Local infections (genitalis and labialis)

These infections are marked by latency and repeated, recurrent, localized infections. Primary infection with herpes simplex virus type I is usually acquired in childhood and infection persists with periodic lesions of herpes labialis throughout life. Herpes simplex virus type II, the cause of herpes genitalis, is acquired through sexual contact, and is increasing in prevalence. Both are annoying and can be debilitating diseases. Herpes

genitalis is usually considered more serious, since it could be a major problem for childbearing women as well as causing severe social problems. Several studies have been conducted to evaluate the use of antivirals in these infections. None of the drugs tested to date, including adenine arabinoside, adenine arabinoside monophosphate, 2-deoxy-D-glucose and iododeoxyuridine, have proven efficacious. Acyclovir and phosphonoformate are currently under study in both clinical syndromes, and may prove of some benefit. Studies with trisodium phosphonoformate (Foscarnet) have been done in Europe, primarily Sweden, in over 200 patients with herpes labialis. The drug in ointment form is applied at the first indication of a lesion; the results are currently being evaluated. Also under study is the use of exogenous interferon in the treatment of acute primary genital herpes and its role in the prevention of recurrences.

Herpes zoster

Herpes zoster (shingles)

Herpes zoster is a local manifestation of recurrent, recrudescent or reactivation infection of varicella-zoster virus. It is characterized by neuralgia and a vesicular skin rash that is unilateral and dermatomal in distribution. Vesicles similar to those of chickenpox are restricted to skin areas supplied by sensory nerves of a single or associated group of dorsal root ganglia. It occurs mainly in older adults, although it may be a serious problem in patients treated with immunosuppressive drugs. With the advent of transplants and improved treatment of malignant neoplasms, there is an increased incidence of zoster.

Several drugs have been and are being studied for efficacy in this disease, notably exogenous interferon, adenine arabinoside, adenine arabinoside monophosphate and acyclovir. E-5-(2-bromovinyl)-2′-deoxyuridine also holds promise [7].

Merigan et al. [27] demonstrated that high doses of interferon, 5.1×10^5 units/kg/day, significantly affected the progression of lesions in the primary dermatome, the incidence and extent of cutaneous dissemination, and the incidence of postherpetic neuralgia and visceral complications. Clinical studies with adenine arabinoside have been completed, and the results are currently being evaluated.

Other studies of interest

Pazin et al. [36] have examined the prophylactic potential of exogenous interferon in patients with a 60% chance of serious herpes recurrence following microsurgery for trigeminal neuralgia. Thirty-seven patients were followed in a double-blind placebo-controlled trial. Nineteen patients received interferon at a dose of 7×10^4 units/kg/day starting on the day prior to surgery and continuing for 4 days after surgery; 18 others were in a placebo group. The frequency of reactivation following surgery was 83% (15/18) in the placebo group as compared to 47% (9/19) in the interferon group. There was also a highly significant reduction in the frequency and duration of virus shedding.

The role of interferon in preventing viral infections in organ transplant patients is

under study. Preliminary results [6] indicate that interferon could alter cytomegalovirus (CMV) infections in patients who were seropositive prior to transplant. The treatment group received 3×10^6 units twice a week for a total of 15 doses. Interferon did help diminish the occurrence of CMV viremia when the patient was not simultaneously receiving antithymocyte globulin. Further studies are underway to determine the optimal dosage schedules of interferon for both primary CMV infections and reactivated CMV disease in renal transplant patients. These same investigators have observed a reduction in Epstein–Barr virus excretion in patients treated with interferon. A similar study by Weimar et al. [52] using fibroblast (β) interferon failed to show an effect when only serology and clinical illness were monitored. This latter study did not include regular attempts at virus isolation.

In a controlled study patients with localized herpes zoster and cancer, Feldman et al. [11] were not able to show any therapeutic effect of isoprinosine.

HEPATITIS

Hepatitis may be caused by a wide range of viruses. The most important are hepatitis A (HAV), hepatitis B (HBV) and non-A, non-B hepatitis. Significant advances have been made in the study and control of these important worldwide agents, particularly HBV, in spite of the inability to cultivate any of these viruses until recently. HAV has now been grown in vitro and candidate vaccines should soon be available for hepatitis A [37]. Studies on the efficacy of HBV vaccines in homosexuals have been successful [48] and studies in hemodialysis patients are nearing completion; the antigen was obtained by plasmaphoresing carriers of the HBV surface antigen. The prospects for a safe and effective HBV vaccine were recently reviewed by McAuliffe et al [25]. Chronic infection with HBV is a serious sequela of acute infection in about 15% of patients, although it may develop insidiously without symptoms. The carrier may be infectious to contacts and may develop liver failure and/or cirrhosis. There are also some indications that HBV is associated with hepatoma. It is estimated that there are approximately 176 million HBV carriers worldwide. The great majority of carriers are in the Far East and Africa where the carrier rate may be as high as 5–20% of the population. The carrier rate in the U.S. and Western Europe is lower but still impressive at 0.2–0.5%. Because of the seriousness and the wide distribution of chronic active hepatitis B, therapeutic measures have been investigated. Although there is currently no accepted treatment, progress has been made.

Most patients with chronic hepatitis B are asymptomatic, but some may present with non-specific malaise, anorexia, fatigue and intolerance to fatty foods or alcohol. Jaundice is variable but not always present. Dane particles, HBV DNA polymerase, and HBV surface antigen are readily found in the serum; e antigen may also be detected. Liver biopsy demonstrates both surface and core antigen in the hepatocytes.

Merigan and his associates at Stanford [15] have sought an effective antiviral treatment for the eradication of HBV carriage and reversal of liver damage. To date, they have

treated 38 chronic hepatitis B patients in an uncontrolled study and found that premenopausal women appear to be the best candidates for antiviral treatment. However, the majority of hepatitis B carriers are men; thus, studies at Stanford are focused on developing regimens that will be effective in men as well as women. Currently, they report that the best results are obtained using pulses of combined therapy with ara-A (5–10 mg/kg/day) and interferon (7.5×10^4 units leucocyte interferon/kg/day) followed by a maintenance course with interferon lasting several months. On this regimen, 8 of 16 patients in an open study have shown a reduction of Dane particles, a fall in hepatitis e antigen below the level of detection, a partial reduction of surface antigen, and the disappearance of core antigen from the liver biopsy. Although eradication of all signs of carriage are desirable, the type 2 response described by Merigan wherein there is a permanent eradication of Dane particles and e antigen with only a partial reduction of surface antigen is sufficient to eradicate the infectivity of the sera of these patients for chimpanzees [39]. Recently, Weimar and associates [53], studying the effect of interferon alone, noted only a transient drop in DNA polymerase. One difference between these studies and those of Merigan et al. [29] was that the total dosage at Stanford was considerably higher (400–900 million units per patient) and given for longer periods (10–14 day courses of doses varying from 5 to 20 million units daily, separated by 2 week intervals, maximum of 4 such courses). In the Stanford studies, it was reported that 4/16 patients showed a permanent fall in HBV-associated DNA polymerase activity in serum to undetectable levels and permanent loss of serum hepatitis B e antigen (HBeAg). In two of these patients, serum hepatitis B surface antigen (HBsAg) also became undetectable and one developed antibody to hepatitis B surface antigen.

Recent studies in England (H. Thomas, personal communication) and France (C. Trepo, personal communication) indicate that results with ara-A and particularly with ara-AMP are quite encouraging in the treatment of chronic active hepatitis B. It is imperative that proper placebo controlled studies be performed to properly determine the efficacy of these drugs, both individually and in combination. Although the early promise of interferon does not seem to be holding up, there is still hope for the successful treatment of these carriers based on studies with other antivirals. The definitive studies remain to be done.

There is currently no adequate antiviral therapy for acute hepatitis (A or B). Contrary to earlier reports, Lam et al. [22] concluded that isoprinosine was ineffective in the treatment of classical acute viral hepatitis. They performed a prospective double-blind controlled study in 81 patients and were not able to demonstrate a therapeutic benefit.

SUBACUTE SCLEROSING PANENCEPHALITIS

SSPE is a progressive inflammatory brain disease of children and young adults which produces intellectual deterioration, convulsive seizures, and motor abnormalities. It often ends fatally. The pathogenesis of SPPE remains to be defined. Measles virus has been implicated as the etiological agent. It has been observed in brain tissue by electron micros-

copy, fluorescent antibody techniques and by propagation of the virus from biopsy material. It has been suggested that measles viral infection may occur early in life when passive maternal antibody is present and the host immune response is immature. This may result in the establishment of a chronic infection and selection of cell-associated neurotropic strains that eventually produce SSPE 5–9 years later.

Isoprinosine (Inosiplex, methisoprinol, immunoviral, viruxan). A derivative of the purine inosine, this drug has been reported to have both antiviral and immune-potentiating effects; however, its role in the therapy of viral diseases remains unclear. It is currently available (not in the U.S.) for a variety of viral diseases, including SSPE. A review of the literature does not indicate any clear-cut double-blind, controlled studies to substantiate a beneficial role in this disease. Open studies are available wherein claims of efficacy are made, but, as pointed out by Alter [1], the beneficial results seen may have been spontaneous. Only a properly controlled trial can prove efficacy. An equal number of studies have been done where no efficacy could be demonstrated; notable among these is a study by Haddad and Risk [14]. They administered isoprinosine to 18 patients with SSPE. No great improvement occurred in any patient soon after treatment. They concluded that there were no significant differences in clinical improvement between treated patients and controls.

ANTIVIRALS UNDER DEVELOPMENT

A number of promising antiviral compounds are currently undergoing clinical evaluation. As stated above, *Adenine arabinoside monophosphate* is more soluble than adenine arabinoside and appears to be equally effective. If it proves clinically efficacious, one of the problems with ara-A (large fluid load) can be circumvented. *Acyclovir* [9-(2-hydroxyethoxymethyl)guanine] is another promising anti-herpes drug. It has low toxicity and appears to be highly specific; it is phosphorylated to a monophosphate by herpesvirus-specified thymidine kinase, whereas this does not occur in uninfected cells. Trials in herpes encephalitis, neonatal herpes, herpes labialis and herpes genitalis are currently underway. Although high hopes are held for this drug, the definitive clinical studies remain to be done. *Phosphonoacetic acid* (PAA) caused a considerable stir of interest when it was shown to be an effective anti-herpes drug. However, interest lagged when it was shown to be retained by the bone in treated animals Studies continue in an effort to find an analog that has antiviral efficacy but less toxic potential. *Phosphonoformic acid* (PFA, Foscarnet) is such an analog. It inhibits the DNA polymerase of herpes viruses and, thereby, viral replication. It does not affect cellular DNA synthesis or cell proliferation unless higher concentrations are used. In vivo studies show promises for this compound, but problems with bone retention still need further study. Unlike PAA, phosphonoformate does not have toxicity when applied to skin. The good therapeutic activity and lack of dermal toxicity make it a promising compound for topical use. Clinical studies with an ointment for topical application are underway in Sweden for herpes labialis.

E-5-(2-bromovinyl)-2′-deoxyuridine (*Bromovinyldeoxyuridine*), also an anti-herpes compound, is yielding exciting results in animals, and early clinical studies show clinical potential. It is relatively non-toxic and seems to be effective against various herpesvirus diseases such as herpes simplex (keratitis) and varicella-zoster (herpes zoster). *Arildone* (4-[6-(2-chloro-4-methoxy)-phenoxyl hexyl]-3,5-heptanedione) and related compounds represent a new class of antiviral drugs that selectively inhibits the replication of some RNA and DNA viruses (herpes virus types 1 and 2, varicella-zoster, poliovirus types II and III, ECHO viruses 9 and 11, rhinoviruses types 2, 14 and 17, equine rhinovirus and respiratory syncytial virus). Although the exact mechanism of action is not known, it is believed to inhibit virus uncoating. Animal studies are currently underway [33].

Rimantadine is available in some countries for treatment of influenza, but its role in prophylaxis and therapy as compared to amantadine is still under study. The clear advantage of rimantadine is its reduced effects on the CNS. *Ribavirin*, an analog of guanosine appears to have a broad antiviral spectrum against RNA and DNA viruses. As indicated above, its early promise against influenza virus did not hold up under the scrutiny of a double-blind controlled study. However, its potential as an aerosolized antiviral against influenza remains to be proven. Studies with this agent were recently reviewed by Smith and Kirkpatrick [42]. The drug appears to have a beneficial effect against arenaviruses. It has been tested against Lassa fever virus, Bolivian hemorrhagic fever (Machupo virus), and Pichinde virus in monkeys. Ribavirin does appear to affect viremia and to enhance survival of treated animals. Clinical studies are planned to evaluate this drug against Lassa fever. *Interferon* remains a promising antiviral with some potential for chronic viral diseases. Its efficacy against herpes viruses and its promise in the treatment of hepatitis, particularly in combination with other antivirals, have been described. However, its potential against other diseases has not been adequately tested. With the advent of DNA recombinant techniques and cloning, it is expected that sufficient quantities of material at a low cost will be available so that proper studies may be done. The most exciting results appear to be in the treatment of juvenile laryngeal papilloma. Interest in *Interferon inducers* (polyinosinic acid · polycytidylic acid · poly-L-lysine, propanediamine, pyrasoloquinoline, pyran copolymer and pyrimidinones) has not lagged; there are those who feel both approaches should be used. There appear to be several types of leucocyte interferon; perhaps each has a specific function. If so, which is the one which should be produced? Perhaps the inducer route will forestall this decision. Inducers appear to be potent immunopotentiators, more so than exogenous interferon. They can also produce higher levels of circulating interferon than can currently be achieved with exogenous interferon. Therefore, in order to most effectively achieve high levels of interferon in the shortest time, it may become feasible to use inducers to obtain rapid high levels of interferon and then maintain desired levels through use of exogenous interferon.

IMMUNE POTENTIATORS

Another approach to the treatment of viral diseases is to stimulate the immune system so as to augment the response of one or more of its components. Interferon, or its inducers, appear to act both directly as an antiviral agent and indirectly as a biological response modifier Other substances which induce an antiviral biological response other than interferon appear to have a more general immunostimulating effect through augmentation of the lymphoproliferative response to infections Two such agents that have been reported to have these properties and that represent different cellular mechanisms of action are levamisole and Isoprinosine.

Levamisole. Levamisole, a phenylimidazo-thiazole, is an effective anti-helmintic agent. It appears to boost the cell-mediated immune response, but only when cell-mediated immunity is depressed. It has also been shown to cause significant increases in serum IgA levels in the elderly. Its action appears to be mediated by alterations in lymphocytic cyclic nucleotide levels following mitogen stimulation. Open studies have been reported on the beneficial role of this agent against herpes and respiratory virus infections, but controlled studies [38] have not demonstrated clinical efficacy. At present, this compound appears to be of very limited value in treatment of viral diseases.

Isoprinosine Isoprinosine, described above, has been used both as an antiviral and an immunopotentiating drug. It was reported to augment both cellular and humoral immune responses. Unlike levamisole, it does not appear to alter cyclic nucleotide levels in lymphocytes nor does it stimulate lymphocytes by itself; it requires a mitogen to augment their proliferation. It has been reported that Isoprinosine increases the phytohemagglutinin response, the mixed lymphocyte culture response and the percentage of active T rosettes. In vivo, it increases the percentage of blood T cells, all indicative of its immunomodulatory effects. At present, the drug effect on T cell function in clinical situation has not been definitely established. Although the drug has been under study for over 10 years, there are a number of conflicting reports, and as yet no clinical study unequivocally demonstrates its efficacy in viral diseases.

CONCLUSION

From the foregoing, two important messages become clear· the pessimism about the prospects for antiviral agents should be dispelled and there should be no question as to the need for carefully controlled, preferably double-blind placebo-controlled, studies prior to general acceptance and use of a drug.

The skepticism concerning antiviral agents and the major problem in the development of these drugs has been the nature of viral replication. Viruses replicate only within the cell, using much of the cell's functions for their purposes. Therefore, it was long felt that any agent which would inhibit viral growth would by necessity be toxic to the

normal cell. Although antivirals free of any side effects have not been developed, it has been well demonstrated that efficacious agents can be found that exhibit minimal toxicity, and the potential for agents with no side effects exists. The efficacy and beneficial effects of topical iododeoxyuridine, adenine arabinoside and trifluorothymidine, and of systemic amantadine and adenine arabinoside have been demonstrated. These drugs are now available and generally accepted. Interferon has been demonstrated to be efficacious in certain viral diseases, but is still not generally available. Other agents, such as Aedurid, Viru-Merz, Cebe-Viran, Isoprinosine and levamisole are available but not generally accepted. Because of the limited success to date, greater emphasis is being placed on antiviral development, and several compounds of promise are being clinically evaluated. These include rimantadine, acyclovir, adenine arabinoside monophosphate, phosphonoformate and bromovinyldeoxyuridine.

The value of a true double-blind, placebo-controlled study in evaluating the efficacy of antiviral drugs cannot be overemphasized. As a result of open studies and historic controls, it was postulated that cytosine arabinoside was effective against herpes zoster and that iododeoxyuridine was effective against herpes encephalitis. It was not until well-controlled studies were done [2, 45] that it was demonstrated that these drugs given systemically were both ineffective and excessively toxic. It is only through such studies that efficacy can be demonstrated in the shortest period of time and toxic manifestations of the drug clearly defined. Although predictive, animal studies cannot accurately measure efficacy or drug toxicity in man. Phase one, open studies are of value in deciding whether a drug is worthy of further study but cannot be the definitive study on efficacy. It is the randomized double-blind placebo or otherwise controlled trial that increases the likelihood of obtaining scientifically precise and reliable information in the shortest time. As has been pointed out in several discussions [1, 26, 40], use of historic controls can be misleading, standards in the treatment of patients differ between hospitals and change with time; unintentional bias in the selection of patients for inclusion in the study cannot be avoided. As was pointed out quite well by Alter [1] in his critique of an Isoprinosine–SSPE study claiming efficacy, the disease can vary greatly among patients. There may be spontaneous remissions and plateaus. Further, it is imperative that no harm be done, and it can only be determined in careful studies that a drug is indeed free of side effects. Great restraint must be demonstrated by investigators and editors in avoiding the publication of encouraging case reports that may lend to the indiscriminate use of drugs which may ultimately prove to be toxic and/or lack efficacy.

It does not require a very elaborate crystal ball to predict that the next few years will yield many useful new antiviral agents which will be clinically important. Our knowledge of the molecular biology of the viruses will enable us to intelligently develop new agents as opposed to the practice of relying on serendipity. However, before such agents can be generally accepted, it is again emphasized that carefully performed double-blind, placebo-controlled studies must be done

TABLE 1

Summary of clinical results[a]

Clinical manifestation	Virus	Agent/dose schedule	Clinical results
Influenza	Influenza A or B	Interferon	No demonstrated efficacy
	Influenza A or B	Ribavirin	No demonstrated efficacy
	Influenza A	Amantadine, Symmetrel® 2 × 100 mg for adults, 2–4 mg/lb body wt in children under 9, not to exceed 150 mg/day	Proven effective in prophylaxis and in therapy if given early
	Influenza A	Rimantadine	Appears to be effective
Other respiratory diseases	Rhinoviurs	Interferon	Effective but no practical regimen demonstrated
	Common cold	Vitamin C	No demonstrated efficacy
Keratitis	Herpes simplex	Iododeoxyuridine (IDU) (Stoxil®, idoxuridine) 0 1% ophthalmic solution, drops every hour; 0 5% opthhalmic ointment 5×/day	Proven therapeutic efficacy; approved by authorities
		Adenine arabinoside (Vidarabine, Vira-A®) 3% ophthalmic ointment 5×/day	Proven therapeutic efficacy; approved by authorities
		Trifluorothymidine (Viroptic®, trifluoridine) 1% ophthalmic solution one drop every 2 h	Proven therapeutic efficacy, approved by authorities
		Bromovinyldeoxyuridine, acyclovir	Under study
Encephalitis	Herpes simplex	Adenine arabinoside (Vidarabine, Vira-A®) slow drip infusion 15 mg/kg/day for 10 days	Proven therapeutic efficacy; approved by authorities
		Adenine arabinoside monophosphate	Under study
Neonatal herpes simplex	Herpes simplex	Adenine arabinoside (Vidarabine, Vira-A®) slow drip infusion 15 mg/kg/day for 10 days	Proven efficacy, not yet approved by authorities
		Adenine arabinoside monophosphate	Under study

TABLE 1 (cont.)

Clinical manifestation	Virus	Agent/dose schedule	Clinical results
Genital herpes and Herpes labialis	Herpes simplex	Topical treatment with adenine arabinoside, adenine arabinoside monophosphate; 2-deoxy-D-glucose; iododeoxyuridine	No efficacy
		Acyclovir, phosphonoformate, bromovinyldeoxyuridine, interferon	Under study; no conclusive evidence available
Shingles	Herpes zoster	Adenine arabinoside	Appears effective
		Adenine arabinoside monophosphate, bromovinyldeoxyuridine, acyclovir	Under study; no conclusive evidence available
		Interferon	Some efficacy reported, but not yet approved by authorities
Chronic active hepatitis B	Hepatitis B	Interferon	Some efficacy reported, still under study
		Adenine arabinoside, adenine arabinoside monophosphate	Under study
Subacute sclerosing panencephalitis (SSPE)	Measles (?)	Isoprinosine® (Inosiplex®)	No clear efficacy demonstrated

[a] Listing selected antivirals approved for use or which are otherwise available

TABLE 2

Status of selected antiviral agents

Agent	Status
Acyclovir	Specific for herpes viruses, currently under clinical study
Adenine arabinoside	Topical efficacy against herpes keratitis and systemic efficacy against herpes encephalitis proven and approved for use by government authorities. Efficacy against neonatal herpes recently proven; efficacy against shingles under study

TABLE 2 (cont.)

Agent	Status
Adenine arabinoside monophosphate	Currently under study against various herpes infections and chronic active hepatitis B
Aedurid	Available in Europe (F R G) for topical treatment of ocular herpes infections Clinical efficacy not established
Amantadine	Proven efficacious for prophylaxis and early therapy of influenza A; approved for use by government authorities
Arildone	Broad spectrum antiviral currently under study
Ascorbic acid	Advocated by some for prevention of respiratory disease, no definite efficacy demonstrated
Cebe-Viran	Available in Europe (France) for topical treatment of ocular herpes infections Clinical efficacy not established
2-Deoxy-D-glucose	Inhibits some enveloped viruses in vitro, including herpes viruses; clinical efficacy not established
L-5-(2-bromovinyl)-2'-deoxyuridine	Specific for herpes viruses, currently under clinical study
Iododeoxyuridine	Effective as topical treatment for herpes keratitis; approved for use by government authorities
Interferon	Broad spectrum antiviral appears clinically effective in some situations, currently under study; generally available at low dosages in U S S R. for use against influenza
Isoprinosine	Immunopotentiator, being tested against a variety of viral diseases, no definitive efficacy demonstrated
Levamisole	Immunopotentiator, no clinical efficacy demonstrated
Phosphonoformate	Currently under clinical study for topical treatment of herpes labialis and genital herpes
Ribavirin	Oral administration not effective against influenza, aerosolized drug under study Efficacy against Lassa fever and other arenaviruses being investigated
Rimantadine	Currently under study against influenza A, generally available in U S.S R
Trifluorothymidine	Effective as topical treatment for herpes keratitis, approved for use by government authorities
Viru-Merz	Available in Europe for topical treatment of herpes infections. Clinical efficacy not established

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