# Antiviral Chemotherapy and Chemoprophylaxis

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*Summary.* Antiviral compounds have been developed for use in chemoprophylaxis and chemotherapy of a variety of infections in humans, including those caused by influenza viruses, respiratory syncytial virus, and herpesviruses. The efficacy of several of these compounds has been demonstrated in rigorously controlled trials. Advances in molecular virology have led to the identification of biochemically defined, virus-specific functions that serve as appropriate targets for the future development of antiviral compounds. Clinical investigators and practicing physicians are now confronting questions previously raised with the use of antibacterial antibiotics. These questions concern appropriate routes of administration for antiviral compounds, optimal dosage regimens, risks of long-term prophylaxis, and the emergence of resistant organisms.

Interest in compounds for use in antiviral chemotherapy and chemoprophylaxis has markedly increased in recent years, and developments in the field have progressed to the point that antiviral compounds have now become objects of interest for practicing physicians as well as for laboratory and clinical investigators. Much of this interest has been stimulated by demonstration of the effectiveness of several antiviral compounds in rigorously controlled clinical studies in humans, and their subsequent licensure for use in patients. These studies have established the concept that compounds can be found that are able to distinguish between intimately related host cell functions and virus functions with sufficient discrimination to be effective and yet nontoxic. Advances in molecular virology in recent years have further provided a rational basis for the development of antiviral compounds that will interfere with biochemically defined, virus-specific functions. In turn, availability of effective antiviral chemotherapy has stimulated development of techniques for rapid diagnosis of viral infections, upon which appropriate use of antiviral compounds will ultimately depend.

Much of the recent work in this area has been concentrated on the therapy and prophylaxis of two groups of virus infections, those of the respiratory tract and those caused by the herpesviruses, and in this article I focus on recent advances in the use of antiviral compounds in these infections.

## Viral Respiratory Infections

Viral respiratory tract infections are a major source of morbidity and mortality throughout the world, and they continue to represent the most common disease experience in families in developed countries, including the United States. Despite efforts to develop effective control measures, viral respiratory tract infections remain a major, uncontrolled public health problem. Recently, several studies have shown that antiviral chemoprophylaxis or therapy may be useful in infections caused by two of the major viral respiratory tract pathogens, influenza virus and respiratory syncytial virus.

*Amantadine and rimantadine.* Amantadine and a closely related analog, rimantadine, have been studied since the early 1960's but have undergone a "renaissance" during the last 5 years. Amantadine (1-adamantanamine hydrochloride) has been licensed for the prophylaxis and therapy of influenza A infections in the United States since 1966 but has received relatively little use for that purpose. Rimantadine (α-methyl-1-adamantanamine hydrochloride) is an experimental compound in the United States, but it has been used extensively in the Soviet Union where investigators believe the drug to be more effective and less toxic than amantadine (*1*).

Both amantadine and rimantadine are primary symmetrical amines that have an unusual chemical structure (Fig. 1). In practical terms, the antiviral activity of both compounds is limited to influenza A viruses (*2*), although some activity has been reported against parainfluenza and rubella viruses at higher concentrations of the drugs (*3*).

The precise mechanisms of action of amantadine and rimantadine have not been established. They inhibit influenza A virus at an unspecified step in its replication, probably after it penetrates the cell surface. It has been suggested that these compounds interfere either with uncoating of the virus (*4*), an event that is poorly understood in molecular terms, or with primary transcription of viral RNA (*5*). Both compounds are active against isolates of all of the influenza A virus subtypes that have been tested (*3*). In vitro, rimantadine is generally two to four times more active than amantadine on a weight basis, although there is some variation depending on the test system used. Resistant mutants can be readily generated in the laboratory by repeated passaging of the virus in the presence of amantadine or rimantadine (*6*). In some studies, in vitro resistance has been correlated with the viral gene that codes for the M or matrix protein of influenza virus (*7*), while other studies have suggested that other genes, including those that code for hemagglutinin, neuraminidase, or nucleoprotein, may also influence the sensitivity of influenza A isolates to amantadine (*8*). Resistant virus has only rarely been reported from naturally occurring human influenza, although few investigators have searched for such resistant viruses (*9*).

Studies of naturally occurring and experimentally induced influenza A infections have demonstrated that both amantadine and rimantadine are effective in prophylaxis and therapy. These studies included populations of diverse ages and different epidemiologic settings (*10–15*). The results indicated that prophylaxis with either drug provided 55 to 80 percent protection against influenza-like illness during outbreaks of influenza A; the rates of protection were even higher when influenza A virus-specific attack rates were calculated. A recent study compared prophylaxis of amantadine with rimantadine in a double-blind, placebo controlled, randomized trial in 450 young adults on a college campus (*15*).

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The trial was initiated when a threshold for influenza A activity in the community was exceeded, as determined by a clinical and laboratory surveillance network. During the trial, subjects took tablets of amantadine or rimantadine, at a dose of 200 mg/day, or placebo, for a 6-week-period. As shown in Table 1, influenza-like illness, as well as laboratory documented influenza, occurred significantly less frequently in amantadine or rimantadine recipients than in placebo recipients. Both compounds were generally less effective in the prevention of infection than in the prevention of illness, which is a potentially desirable feature of chemoprophylaxis since subclinical infection may confer immunity. In this trial, as well as in other studies conducted in the United States, amantadine and rimantadine appeared to be equally effective, although studies in the Soviet Union suggest that rimantadine may be somewhat more effective (*1*).

Although amantadine has been generally well tolerated by the populations in which it has been studied, variable rates of side effects have been reported, most commonly in 5 to 10 percent of recipients (*14*). These side effects have been primarily mild symptoms affecting the central nervous system, such as anxiety, jitteriness, insomnia, and difficulty in concentrating. The side effects, although troublesome, clear rapidly with discontinuation of the drug. That such effects may occur, however, has probably contributed to the reluctance to use amantadine for prophylaxis, particularly since the attack rate for influenza may vary considerably from outbreak to outbreak.

Early studies suggested that rimantadine may be better tolerated than amantadine, and recent trials comparing the two compounds at the recommended dosage of 200 mg/day have supported those observations (*15*). In the study already discussed, amantadine was clearly more toxic than rimantadine, primarily as a result of the side effects (see Table 2). Rimantadine was remarkably well tolerated among the young adults who participated in that study, since the withdrawal rate in rimantadine recipients was not significantly different from that in placebo recipients. The reasons for the differences between the rates of side effects in amantadine and rimantadine recipients remain unclear. Although there are differences in the pharmacokinetics (*16*) and metabolic disposition between the two compounds, the relation of these properties to antiviral efficacy and toxicity are not well understood. Amantadine is well absorbed orally, and is excreted virtually unchanged in the urine, with a half-life of approximately 15 hours. Rimantadine is also well absorbed but is largely metabolized and has a half-life of approximately 30 hours. Since rimantadine at a dose of 200 mg per day has been demonstrated to be efficacious and nontoxic, it is this drug that is particularly attractive for use in prophylaxis.

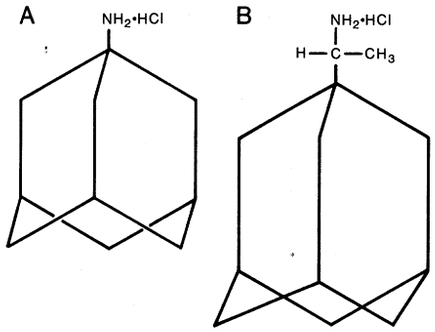



Fig. 1. (A) Amantadine (1-adamantanamine hydrochloride). (B) Rimantadine (α-methyl-1-adamantanamine hydrochloride).

Large-scale studies of prophylaxis with amantadine or rimantadine have been carried out almost entirely in young adults, and it would be of interest to determine whether these compounds are also effective and well tolerated in populations who are at high risk for complications of influenza, such as the elderly. A recently completed study involving 105 elderly subjects in two nursing homes indicated that rimantadine was effective and generally well tolerated (*17*), but additional studies are needed in that population group. Of particular interest was the finding (*17*) that the prophylactic effect of rimantadine occurred primarily among subjects who had received vaccination against influenza A, indicating that protection afforded by the vaccine and rimantadine may be additive, as has been suggested by workers in the Soviet Union and elsewhere (*1*).

In addition to studies of prophylaxis against infection, both amantadine and rimantadine have been studied in the therapy of influenza A, again primarily in young adults with uncomplicated disease (*14, 18–21*). As illustrated in Fig. 2, most of the studies have demonstrated a modest therapeutic effect for amantadine or rimantadine compared to placebo. Drug recipients experienced more rapid resolution of symptoms and fever, generally with a mean reduction of illness of 1 to 2 days. Although these effects are modest, it should be noted that the type of disease that was studied, namely uncomplicated influenza in young adults, is generally short-lived and self-limited, usually lasting 2 to 5 days. Since therapy is ordinarily administered 24 to 72 hours after the onset of illness, a reduction of duration of illness by 1 to 2 days may

Table 1. Influenza-like illness and laboratory-documented influenza among volunteers receiving placebo, rimantadine, or amantadine. [Adapted from (*15*)].

| Treatment group | Number of subjects | Number with influenza-like illness* | | Number with laboratory-documented influenza† | |
|---|---|---|---|---|---|
| | | Total | Percentage | Total | Percentage |
| Placebo | 132 | 54 | 41 | 27 | 21 |
| Rimantadine | 133 | 19 | 14‡ | 4 | 3‡ |
| efficacy rate¶ | | | 65 | | 85 |
| Amantadine | 113 | 10 | 9‡ | 2 | 2‡ |
| efficacy rate¶ | | | 78 | | 91 |

*Defined as a cough or an oral temperature of >37.7°C, or both, and at least two of the following: sore throat, headache, and myalgia. †Defined as influenza-like illness along with virus isolation or a rise in serum antibody to influenza A virus. ‡$P < 0.001$ compared with placebo by $\chi^2$ analysis. ¶Efficacy rate compared to placebo.

Table 2. Withdrawal rates among recipients of placebo, rimantadine, or amantadine. Adapted from (*15*).

| Treatment group | Number of subjects | Withdrawals | | Reasons for withdrawals (percentage of subjects) | | | |
|---|---|---|---|---|---|---|---|
| | | Total | Percentage | CNS side effects* | Non-CNS side effects | Unrelated to side effects | Unknown |
| Placebo | 148 | 16 | 11 | 6 ( 4) | 1 (0.7) | 8 (5) | 1 (0.7) |
| Rimantadine | 147 | 14 | 10 | 9 ( 6) | 1 (0.7) | 4 (3) | 0 (0) |
| Amantadine | 145 | 32 | 22† | 19 (13)‡ | 4 (3) | 3 (2) | 6 (4) |

*Primarily insomnia, jitteriness, and difficulty in concentrating; CNS denotes central nervous system. †$P < 0.01$ compared with placebo and $P < 0.005$ compared with rimantadine by $\chi^2$ analysis. ‡$P < 0.01$ compared with placebo and $P < 0.05$ compared with rimantadine.

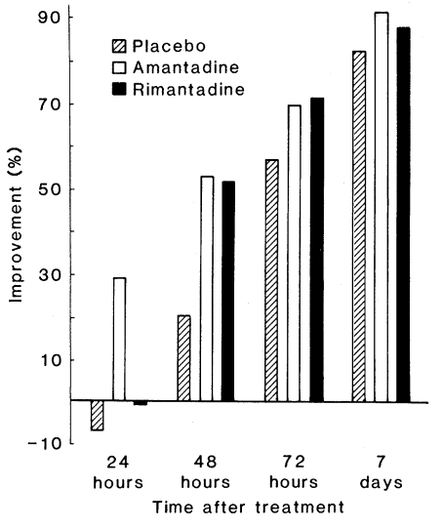



Fig. 2. Percentage improvement in symptom scores in college students with naturally occurring influenza A who were treated with amantadine, rimantadine, or placebo. $P < 0.025$ for amantadine or rimantadine versus placebo. From (*20*).

represent a 50 percent decrease in symptoms or signs of illness after therapy. In two recently completed studies, the efficacy of rimantadine was compared to that of a commonly used symptomatic therapy (acetaminophen) for treatment of influenza A in children. The results showed that rimantadine was either superior (*22*) or at least equal (*23*) to acetaminophen in clinical effectiveness.

All of these studies, whether in young adults or children, have been carried out in cases of uncomplicated influenza. Therefore, a major question that remains is whether amantadine and rimantadine are effective in the therapy of complicated influenza A infections, such as those in which pneumonia is present, particularly in high-risk individuals. Any information now available on this question is anecdotal, and although rimantadine appears to be nontoxic and effective in uncomplicated cases, its efficacy in the treatment of more serious disease has yet to be proved.

*Ribavirin.* As has been the case with antibacterial antibiotics, concern has been raised regarding the delivery of orally or parenterally administered antiviral compounds to the site of infection. Several studies with experimental models have suggested that antiviral compounds delivered by aerosol may be particularly effective in the therapy of respiratory tract viral infections, especially those involving the lower airways. This approach is illustrated by recent studies with ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide), a purine nucleoside analog with activity in vitro against a wide spectrum of RNA and DNA viruses (Fig. 3) (*24–28*). The precise mechanism of action of ribavirin is not clear, and may be different for different groups of viruses. Ribavirin is first phosphorylated to 5′-mono-, di-, and triphosphates by cellular enzymes (*24*). Ribavirin 5′-monophosphate blocks the conversion of inosine 5′-monophosphate to xanthosine 5′-monophosphate, thus inhibiting synthesis of guanosine 5′-monophosphate, which results in inhibition of both DNA and RNA synthesis (*29*). Synthesis of deoxythymidine triphosphate is also inhibited by ribavirin. Recently, it has been noted that ribavirin 5′-triphosphate blocks capping of virus-specific RNA by inhibition of messenger RNA guanylyl transferase activity (*30*), and it has been suggested that this mechanism may be important in the inhibition of influenza virus replication by ribavirin.

Ribavirin administered orally to humans with naturally occurring influenza A virus infection is generally ineffective (*31*). However, ribavirin administered by small-particle aerosol may be effective in the treatment of both influenza A and B infection (*25, 26*). The ribavirin aerosol was produced by means of a generator, and the particles were of sufficiently small size to be deposited in the lower airways (<1.3 μm in diameter). The aerosol may be delivered through a mask, directly into the inhalation tubing of a respirator, or into an oxygen tent in the case of infants. Controlled studies were conducted in which ribavirin aerosol was administered to healthy young adults with influenza A- or B-associated illness of less than 24 hours duration. The results indicated a modest but statistically significant reduction in signs and symptoms of systemic illness and in virus shedding (*25, 26*).

Recently, a ribavirin aerosol was also reported to be beneficial in the therapy of infants with respiratory syncytial virus (RSV) infection, which is a common cause of serious respiratory tract infection (pneumonia, bronchiolitis) in infants and young children, for which there is no other therapy or immunoprophylaxis (*27, 28*). In a controlled study in which ribavirin or placebo was administered to 33 infants by a continuous aerosol for 3 to 6 days, ribavirin-treated infants had a more rapid resolution of illness and of lower respiratory tract signs, and a higher arterial oxygen saturation than placebo-treated infants (Table 3) (*27*). Viral shedding was also decreased in the ribavirin-treated group.

Although orally administered ribavirin has been associated with hematopoietic toxicity, such toxicity has not been observed in subjects treated with ribavirin aerosol, apparently because little drug is absorbed systemically when it is administered by this route. As is the case with rimantadine and amantadine, it is not known whether a ribavirin aerosol would be effective in the therapy of complicated influenza or life-threatening RSV infection. With the currently available technology for small-particle aerosol generation, treatment of viral respiratory tract infections with aerosols is limited to hospitalized patients. However, continued development of technology in this area may result in the availability of small particle aerosols that can be administered on an outpatient basis or even at home.

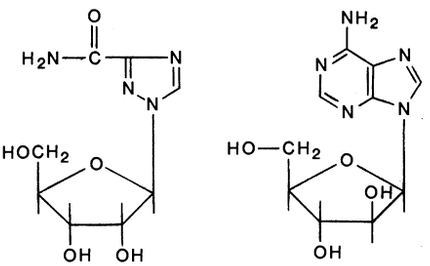



Fig. 3 (left). Ribavirin (1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamide). Fig. 4 (right). Vidarabine (9-β-D-arabinofuranosyl adenine).

## Herpesvirus Infections

Herpesvirus infections result in a broad spectrum of human diseases, ranging from minor annoyances such as cold sores to highly destructive infections of the central nervous system (encephalitis), and serious neonatal infections. It has been long recognized that herpesvirus infections are more severe in certain immunosuppressed patients, particularly those with depressed cellular mediated immunity. Genital herpesvirus infections have increased markedly in recent years, and can result in considerable morbidity in adult hosts as well as in serious infections in the newborn. A major problem in the chemotherapy of herpesvirus infections is the propensity of the virus to cause latent infections. Antiviral compounds have been developed that exert an effect on the acute manifestations of several herpesvirus infections, but these have little or no effect on the establishment or maintenance of latent infection. In contrast to the large amount of information obtained in recent years on the molecular biology of herpesvirus replication, the molecular events involved in the establishment of latency and in reactivation remain poorly understood. This presents an additional impediment to the

development of effective chemotherapy for herpesvirus infections.

*Vidarabine*. Most antiviral compounds that have been studied for therapy of herpesvirus infections have been purine and pyrimidine nucleoside analogs that inhibit virus DNA synthesis. The first of these to be licensed in the United States for therapy of systemic herpesvirus infection was ara-A or vidarabine (9-β-D-arabinofuranosyladenine) (Fig. 4). Vidarabine is a purine nucleoside analog that has activity against all members of the herpesvirus group in humans, including herpes simplex type 1 (HSV-1), herpes simplex type 2 (HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) (*32*). The compound inhibits viral DNA synthesis by its 5′-triphosphorylated metabolite (*33*). It has been suggested that vidarabine's antiviral activity is exerted through one or more of the following mechanisms: inhibition of virus-specific DNA polymerase, inhibition of virus-specific ribonucleotide reductase, or through direct incorporation into herpesvirus DNA. There are conflicting data on the relative importance of each of these mechanisms, as well as on the selectivity of vidarabine for inhibition of viral compared to analogous cellular enzymes. Nonetheless, vidarabine inhibits viral nucleic acid synthesis at concentrations clearly below those required to inhibit host-cell DNA synthesis.

The recent detection of HSV mutants with altered DNA polymerases that are resistant to vidarabine suggests that an important aspect of the activity of vidarabine involves viral DNA polymerase function. In vivo, vidarabine is rapidly deaminated by adenosine deaminase to its hypoxanthine derivative, ara-Hx. This latter compound is 10 to 50 times less active than ara-A but may account for most of the antiviral effect in vivo. Recently, a carbocyclic analog of vidarabine, cyclaradine (*34*), was developed that is active against HSV but is resistant to adenosine deaminase, and this compound is currently being evaluated in animal models.

A problem with the use of vidarabine is its relatively poor solubility in aqueous solutions, so that the manufacturers of the compound recommend that amounts of no more than 450 mg be dissolved in 1 liter of fluid. Since vidarabine can only be administered intravenously, generally over a 12-hour infusion period, therapy with vidarabine involves administration of significant amounts of fluid which may represent a hazard for patients, particularly those with herpes simplex encephalitis (HSE).

The first demonstration of the effectiveness of intravenously administered vidarabine was in the treatment of herpes zoster (shingles) in immunosuppressed patients in a large-scale, placebo controlled trial (*35*). Vidarabine, given intravenously at 10 mg per kilogram of body weight per day for 5 days, demonstrated beneficial effects on the cutaneous manifestations of herpes zoster, including a reduction in the rates of new lesion formation and duration of virus shedding. These effects were confirmed by the same group in another large-scale study, which also showed that vidarabine reduces cutaneous and visceral dissemination of herpes zoster (*36*). Postherpetic neuralgia, the refractory and often disabling long-term pain that can follow acute episodes of herpes zoster, was significantly shortened in the vidarabine-treated group. Beneficial effects have also been observed in the treatment of varicella (chicken pox) in immunosuppressed patients with vidarabine (*37*). At the doses used in these studies, significant clinical toxicity was not observed, and the compound has recently been approved by the Food and Drug Administration for treatment of varicella-zoster infections in immunosuppressed patients.

An important by-product of the above carefully controlled studies was an improved understanding of the natural history of varicella-zoster infections. While varicella may be a life-threatening infection in immunosuppressed patients, it is now clear that herpes zoster is a problem largely of morbidity rather than mortality. Morbidity consists primarily of cutaneous or visceral dissemination and of postherpetic neuralgia. However, the majority of immunosuppressed patients with herpes zoster do not have either dissemination or severe sequelae and, therefore, do not require hospitalization. Efforts are currently directed toward identification of patients who are at high risk for serious sequelae, or toward development of regimens of antiviral chemotherapy that can be used on an outpatient basis.

Vidarabine has also been demonstrated to be effective in the therapy of HSE, a frequently serious, highly destructive infection of the brain which affects all ages and which occurs in apparently normal hosts. In a placebo controlled study, vidarabine reduced mortality from 70 percent in the placebo group to 28 percent in the vidarabine-treated group at the end of 1 month and to 40 percent in vidarabine recipients at 6 months (*38*). A larger, open study in which 75 patients were treated with vi-

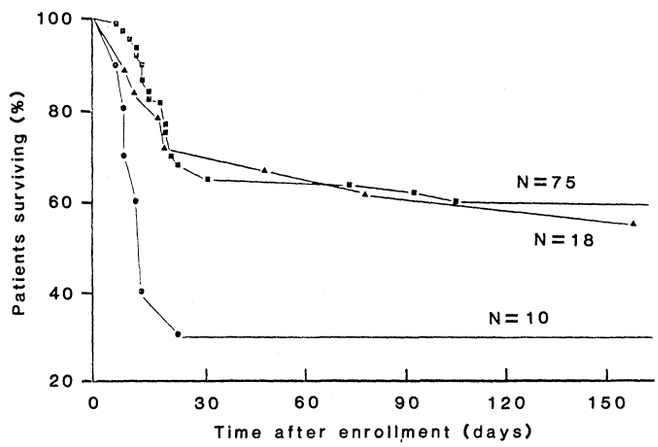



Fig. 5. Survival of patients with biopsy-proved herpes simplex encephalitis treated with vidarabine (triangles or squares) or placebo (circles). From (*39*).

Table 3. Mean severity score for sign or symptom at start and end of treatment with ribavirin aerosol in infants with respiratory syncytial viral infection (*27*).

| Sign or symptom | Ribavirin group | | Placebo group | | *P* value for change in score* |
|---|---|---|---|---|---|
| | Start | End | Start | End | |
| Temperature (°C) | 37.9 | 37.2 | 37.9 | 37.4 | N.S. |
| Nasal congestion and discharge | 1.8 | 0.6 | 2.2 | 1.0 | N.S. |
| Cough | 2.3 | 0.9 | 1.8 | 1.6 | <0.01 |
| Rales | 2.2 | 0.5 | 1.6 | 1.4 | <0.01 |
| Wheezing | 1.1 | 0.2 | 1.3 | 0.8 | N.S. |
| Retractions | 2.2 | 0.2 | 1.5 | 1.0 | <0.01 |
| Lethargy | 2.3 | 0.2 | 2.0 | 1.2 | <0.01 |

*The *P* value is for the unit change in score from start to end of therapy for the placebo group versus the ribavirin group (Mann-Whitney *U* test and nonpaired *t*-test). N.S. denotes not significant.

darabine demonstrated a mortality rate that was virtually identical to that seen in vidarabine recipients in the previous controlled study (Fig. 5) (*39*). Approximately 50 percent of patients who received vidarabine and who survived had relatively normal central nervous system function at the end of 1 year. Currently, the same collaborative group is comparing vidarabine with acyclovir in the therapy of HSE, and it is anticipated that those studies should be completed in 1985. Of interest is a recently completed study performed in Sweden that indicated that acyclovir may be more effective than vidarabine in the therapy of HSE (*39a*).

The above studies also illustrated the importance of early therapy with vidarabine, since the outcome of treatment was closely correlated with the stage of consciousness of the patients at the time treatment was initiated. However, the diagnosis of HSE on clinical grounds alone is notoriously imprecise, and the only currently available technique with which to establish the diagnosis early in illness is by detection of HSV by brain biopsy (*39*). Because of this problem, considerable effort is under way in the development of noninvasive diagnostic methods that can be used early in illness, such as detection of herpesvirus antigens in the cerebrospinal fluid, or detection of HSV infection in the central nervous system through radionuclide imaging with HSV-specific markers.

Vidarabine has also been studied in the treatment of other HSV infections, including infections in the newborn, which are frequently fatal. In a placebo controlled study, vidarabine at a dose of 15 mg per kilogram per day reduced mortality from 74 percent in placebo recipients to 38 percent in vidarabine recipients (*40*). However, only 29 percent of vidarabine recipients with central nervous system or disseminated disease who survived the infection were normal at 1 year of age. Additional studies in which a higher dose of vidarabine (30 mg per kilogram per day) was used did not improve the clinical outcome (*41*), and in current studies the effects of high doses of vidarabine are being compared with the effects of acyclovir. Recently, vidarabine was also reported to be beneficial in the treatment of HSV mucocutaneous infections in immunosuppressed patients, although the effects observed were limited to patients who had HSV-1 infections and who were older than 40 years of age (*42*).

*Acyclovir.* The most recent antiviral compound to be licensed in the United States is acyclovir [9-(2-hydroxyethoxymethyl) guanine] (Fig. 6) which is a highly potent and specific inhibitor of certain herpesviruses (*43*). The high degree of specificity of acyclovir is related to its mechanism of action, which requires that the compound be first phosphorylated to acyclovir monophosphate. This phosphorylation is efficiently performed by a virus coded thymidine (deoxypyrimidine) kinase which is present in herpesvirus infected cells. In the absence of the virus-induced kinase, phosphorylation of acyclovir is relatively restricted in mammalian cells. Acyclovir monophosphate is subsequently converted to the di- and triphosphates by host cell kinases. Acyclovir triphosphate is a potent inhibitor of HSV-induced DNA polymerase activity but has relatively little effect on host cell DNA polymerase. Acyclovir triphosphate can also serve as a substrate for HSV-induced DNA polymerase, resulting in incorporation of acyclovir into viral DNA with subsequent early chain termination (*44*). However, acyclovir triphosphate is a poor substrate for cellular DNA polymerase. The acyclovir terminated DNA template can also inactivate virus-induced DNA polymerase through noncompetitive binding (*45*).

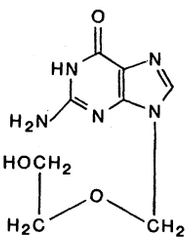



Fig. 6. Acyclovir [9-(2-hydroxyethoxymethyl) guanine].

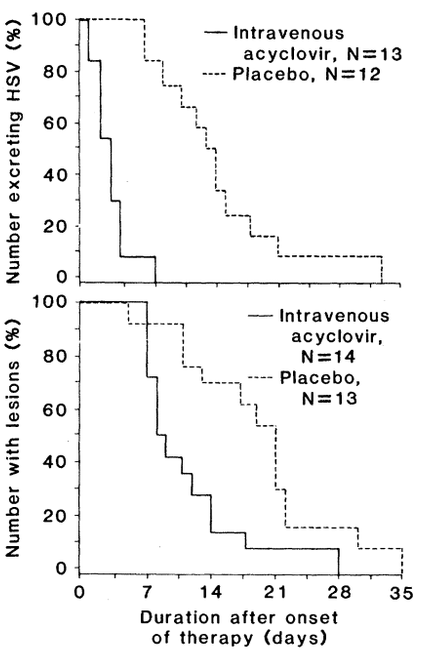



Fig. 7. Comparison of effects of intravenously administered acyclovir and placebo on virus shedding and the presence of lesions in patients with primary genital herpes ($P < 0.001$ for each comparison, Mantel Cox). From (*55*).

Acyclovir is active against HSV-1 and HSV-2, and against VZV, all of which induce deoxypyrimidine kinases in infected cells. Cytomegalovirus is generally resistant to acyclovir and does not induce a thymidine kinase, although its DNA polymerase is highly sensitive to the action of acyclovir. This observation is consistent with the critical role of the initial phosphorylation step to the antiviral activity of acyclovir. Epstein-Barr virus, which also does not induce its own deoxypyrimidine kinase, is more sensitive than CMV to the action of acyclovir, perhaps by interaction of acyclovir with a highly sensitive EBV DNA polymerase (*46*). Of interest is that a number of acyclovir-resistant mutants have been generated with mutations which involve genes that code for thymidine kinase or for DNA polymerase. Viruses that are unable to induce thymidine kinase ($Tk^-$ mutants), and are thus acyclovir resistant, have been isolated both in the laboratory and from patients, including some who have received acyclovir as well as others who have not (*47*). Mutants whose thymidine kinase has a decreased affinity for acyclovir have also been described, as have viruses whose DNA polymerase is poorly inhibited by acyclovir. HSV $Tk^-$-mutants appear to be less pathogenic in certain animal models, and the presence of such mutants in patients has not been necessarily associated with a poor response to therapy (*48*). However, studies of the frequency of the emergence of acyclovir resistant mutants in various clinical settings, and of the relation of resistant virus to clinical outcome, are in their early stages so that it is difficult to assess the potential significance of this phenomenon. In view of the consequences that the emergence of resistant bacteria has had on the utility of antibacterial antibiotics, the emergence of resistance to antiviral compounds remains an area of concern.

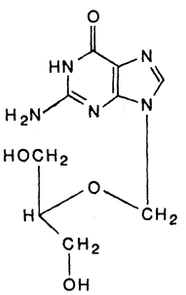
In contrast to vidarabine, acyclovir can be administered intravenously in smaller amounts of fluid, although care must be taken to avoid rapid intravenous injection of the compound which may result in precipitation of acyclovir in the kidneys. A topical form of acyclovir in polyethylene glycol is available, and an oral formulation is currently under consideration for approval by the Food and Drug Administration. Only 20 percent of

an oral dose of acyclovir is absorbed in humans, and analogs of acyclovir that are more efficiently absorbed are currently under development.

Acyclovir has been demonstrated to be effective in the therapy of mucocutaneous HSV infections in several clinical settings. Topical application of acyclovir resulted in a modest beneficial effect in the treatment of primary genital herpes infections (*49*) and of mucocutaneous HSV infections in immunosuppressed patients (*50*), but intravenous administration resulted in a marked beneficial effect (Table 4) (*51, 52*). Administration of acyclovir to patients at high risk for reactivation of HSV infections, but before the development of lesions (that is, prophylaxis), such as those with evidence of prior HSV infection who undergo marrow transplantation or intensive cancer chemotherapy (*53*), has also resulted in the prevention of lesion formation and virus shedding. Of interest was the finding that the beneficial effects occurred only during administration of the drug, and as soon as acyclovir was discontinued virus shedding and lesions recurred, indicating that the drug did not eliminate latent infection.

The most extensive use for acyclovir is likely to be in the therapy of genital herpes infections. In treatment of the primary form of this disease, which is associated with more severe and prolonged manifestations than is the recurrent form of the disease, topical acyclovir exerted a modest beneficial effect, reducing the duration of virus shedding from 7.0 to 4.1 days, and the time to crusting of lesions from 10.5 to 7.1 days (*49*). However, topical acyclovir was relatively ineffective in the therapy of recurrent infections even when it was applied early in the episode (*48, 49, 54*). When administered intravenously, however, acyclovir was markedly effective in primary genital herpes infections, significantly reducing virus shedding, time to healing, new lesion formation, and duration of symptoms (Fig. 7) (*55*). On the basis of these studies, two forms of acyclovir, for topical and for intravenous administration, have been licensed in the United States for the therapy of primary genital herpes infections as well as for therapy of mucocutaneous HSV infections in immunosuppressed patients.

Because intravenous administration of acyclovir requires hospitalization of the patient, investigators have recently examined the effect of orally administered acyclovir on both primary and recurrent genital herpes infections. Three controlled studies have now demonstrated that orally administered acyclovir, at a



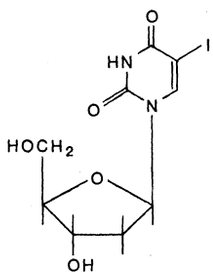


Fig. 8 (left). DHPG [9-(1,3-dihydroxy-2-propoxymethyl) guanine]. Fig. 9 (right). Idoxuridine (5-iodo-2′-deoxyuridine).

dose of 200 mg per day for 5 to 10 days, has a marked therapeutic effect in primary infections comparable to that seen with the intravenously administered preparation (*56, 57*). Therapy with the orally administered form resulted in marked reduction in symptoms and virus shedding and in acceleration in healing of lesions. The largest of these studies did not demonstrate any effect on either the rate or frequency of subsequent recurrences (*57*).

A large-scale placebo-controlled study of therapy of recurrent genital herpes has been recently completed in which acyclovir was administered orally at a dose of 200 mg five times per day for 5 days (*58*). Two episodes of recurrent infection were treated in each patient. In the first episode treatment was initiated by physicians within 48 hours of the onset of lesions, while in the second episode, treatment was initiated by the patient at home enabling administration of the drug to occur at an earlier stage of illness. In both episodes, acyclovir reduced the duration of virus shedding and accelerated the time to healing and crusting, and in patient-initiated therapy, new lesion formation was also reduced. In general, the effects of acyclovir were more pronounced in the episode in which treatment was initiated by the patient, indicating the importance of early initiation of therapy. The effect of therapy with acyclovir on a single episode of recurrent genital herpes appears to be relatively modest, in that disease manifestations are reduced by a mean of 1 to 2 days. However, it should be noted that each clinical episode of recurrent infection is relatively short-lived, with disease manifestations that last for a mean of 3 to 7 days. Thus, a reduction in duration of illness by 30 percent may result in a significant reduction of morbidity in individuals who have multiple episodes per year. However, large-scale studies of the safety and efficacy of treatment of multiple episodes of recurrent genital herpes with acyclovir have not yet been carried out, although such studies are currently under way.

The favorable experience with acyclovir in these studies, along with the demonstrated importance of early therapy, has stimulated interest in the prophylactic use of orally administered acyclovir over extended periods to prevent recurrences of genital herpes infections. Two recently completed studies in which acyclovir was administered on a long-term basis (for 4 months) have shown promising results in prevention of recurrences (*59–60*) and large studies with more prolonged administration of acyclovir are under way.

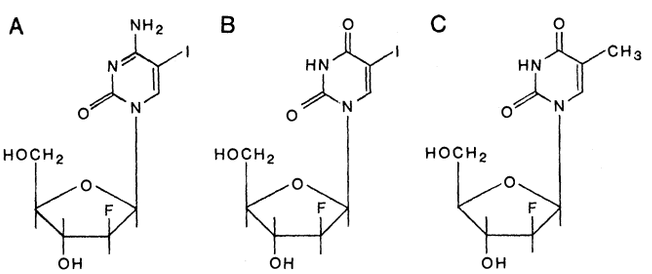


Fig. 10. (A) FIAC (2′-fluoro-2′-deoxy-5-iodo-ara C). (B) FIAU (2′-fluoro-2′-deoxy-5-iodo-ara U). (C) FMAU (2′-fluoro-2′-deoxy-5-methyl-ara U).

Table 4. Effect of intravenously administered acyclovir treatment on mucocutaneous herpes simplex infections in immunosuppressed patients. Data from (*51*).

| Effect | Total number of patients | Patient group | | Relative risk* | *P** |
|---|---|---|---|---|---|
| | | Acyclovir | Placebo | | |
| Virus shedding | 86 | 2.8† | 16.8 | 6.82 | 0.0002 |
| All pain | 82 | 8.9 | 13.1 | 2.00 | 0.01 |
| Scabbing | 87 | 9.3 | 13.5 | 2.21 | 0.004 |
| Healing | 94 | 13.7 | 20.1 | 1.83 | 0.04 |

*Relative risk calculations are derived from proportional hazards regression analysis. The *P* values are two-sided. †Data expressed as median days of virus shedding or lesion pain, or median interval to scabbing (crusting) or complete healing of all lesions.

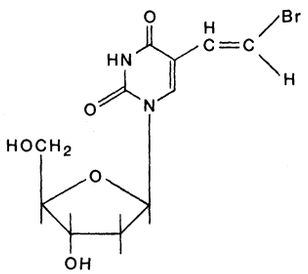


Fig. 11. Bromovinyldeoxyuridine [(E)-5-(2-bromovinyl-2′-deoxyuridine)].

Intravenously administered acyclovir has also been studied in the treatment of varicella-zoster infections in immunosuppressed patients. Placebo-controlled studies have yielded results generally similar to those achieved with vidarabine (*61, 62*), but large-scale studies directly comparing the efficacy of acyclovir with vidarabine in this setting have not been carried out. Treatment of herpes zoster with intravenously administered acyclovir has also been studied in normal (nonimmunosuppressed) patients, and although beneficial effects were observed (*63*) it is unlikely that this represents a practical mode of therapy for most normal patients, since hospitalizaton is required. In addition to efforts now centered on the development of outpatient regimens with which to treat herpes zoster, studies evaluating orally administered acyclovir in that setting are also in progress. Because VZV is less sensitive than HSV to the action of acyclovir, higher doses or preparations with improved oral absorption may be required.

In all of these studies acyclovir has been remarkably well tolerated and free of toxicity, with the exception of occasional renal toxicity after rapid intravenous administration or when patients have been inadequately hydrated. However, the toxicity of the drug when administered on a long-term basis has not been established, nor has the impact of chronically administered acyclovir on the emergence of resistant viruses. These are important questions to be addressed in the future studies.

*DHPG.* A major disappointment with the nucleoside analogs currently available for clinical use is their lack of efficacy against human cytomegalovirus. A recently synthesized analog of acyclovir, DHPG [9 - (1,3 - dihydroxy - 2-propoxy - methyl) guanine] (Fig. 8) has been demonstrated to be highly active in vitro against HSV-1 and HSV-2, and against VZV, and compared to acyclovir has markedly increased activity against CMV and EBV. The mechanism of action of DHPG is believed to be similar to that of acyclovir, but DHPG appears to be a more efficient substrate for the virus-induced deoxypyrimidine kinase, and is therefore also less susceptible to inhibition by endogenously present thymidine (*64*). DHPG 5′-monophosphate is also phosphorylated more efficiently than acyclovir monophosphate by cellular kinases, which apparently results in a more efficient production of DHPG 5′triphosphate in infected cells. DHPG triphosphate, like acyclovir triphosphate, potently inhibits virus-induced DNA polymerase (*64*). Recently, HSV strains that are resistant to acyclovir by virtue of a DNA polymerase mutation (*65*), or by induction of altered viral thymidine kinase (*66*), were found to be sensitive to DHPG. The reasons for the increased activity of DHPG against CMV and EBV compared to acyclovir are unknown, but the activity is unlikely to be mediated through the thymidine kinase system since neither CMV nor EBV induces its own thymidine kinase. DHPG is now undergoing preclinical evaluation, and is soon likely to be available for clinical trials. Cytomegalovirus infections will be a major target for studies with this compound.

*Halogenated pyrimidine nucleoside analogs.* There is considerable interest in the antiviral effect of a number of halogenated pyrimidine nucleoside analogs. Historically, the first antiviral compound demonstrated to be clinically effective and therefore licensed for treatment in the United States was 5-iodo-2′-deoxyuridine (IUDR) (*67*) (Fig. 9). The compound has been studied for a number of mucocutaneous HSV infections, but its use in this country is restricted to the topical treatment of herpes simplex keratitis. Although it had been used previously to treat herpes simplex encephalitis, a collaborative study conducted in the United States indicated that the drug was ineffective and toxic in that setting, and it is no longer used systemically.

Studies have recently been conducted with 2′-fluoro-2′-deoxy-5-iodo-ara C (FIAC), 2′-fluoro-2′-deoxy-5-iodo-ara U (FIAU), and 2′-fluoro-2′-deoxy-5-methyl-ara U (FMAU), which are potent inhibitors of herpesvirus replication in vitro (Fig. 10) (*68, 69*). These compounds are all efficient substrates for herpesvirus-induced deoxypyrimidine kinase, and FIAC triphosphate is a potent inhibitor of herpesvirus-induced DNA polymerase. FIAC is apparently deaminated to FIAU in vivo and has been reported to be effective when administered intravenously to immunosuppressed patients

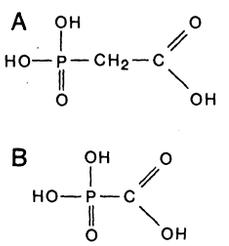


Fig. 12. (A) Phosphonoacetic acid. (B) Phosphonoformic acid.

with VZV infections (*70*). These compounds also have activity against human CMV isolates and may therefore be of particular interest for use in those infections. Another substituted pyrimidine nucleoside analog, 5-trifluoromethyl-2′-deoxyuridine has also been demonstrated to be a potent inhibitor of HSV in vitro and in animal systems (*71*). Its current use in humans is restricted to the topical treatment of herpetic keratitis for which it has been licensed in the United States.

A number of 5-halogenovinyl pyrimidine nucleoside analogs have also been investigated for antiviral activity. The most extensively studied of these is (E)-5-(2-bromovinyl-2′-deoxyuridine) (BVDU) which exhibits marked activity in vitro against HSV-1 and VZV (Fig. 11) but is considerably less active against HSV-2 (*72*). This differential activity is related to the fact that BVDU has a much higher affinity for the thymidine-thymidylate kinase induced by HSV-1 or by VZV than for the HSV-2–induced kinase. BVDU triphosphate is a potent inhibitor of HSV-induced DNA polymerase, and BVDU can also be incorporated into DNA in virus-infected cells. Particular interest exists in BVDU as a chemotherapeutic agent for varicella-zoster infections, and studies to evaluate this compound in humans are currently under way.

*Phosphonoformate.* An entirely different class of antiviral compounds is illustrated by phosphonoacetic acid (PAA) (*73*) and phosphonoformic acid or foscarnet (PFA) (*74*) (Fig. 12), which are potent inhibitors of the replication of herpesviruses and have been studied extensively in vitro. PAA exerts its action through noncompetitive inhibition of herpesvirus-induced DNA polymerase, interacting directly with the enzyme at the pyrophosphate binding site. PAA probably exerts some inhibition of host cell DNA polymerase but at considerably higher levels than of virus DNA polymerase. PAA and PFA are effective against herpesvirus infection in animal models (*73,*

74), and topically administered PFA has been reported to be effective in the therapy of genital herpes infections in humans (75). Skin irritation has been noted in previous studies with PAA, but a 3 percent PFA cream apparently does not result in dermal irritation. Neither PAA nor PFA is metabolized, and both are known to accumulate in bone, although no specific toxic effects have been attributed to such accumulation. Additional clinical trials with PFA are currently under way.

## Other Antiviral Agents

I have discussed here only certain "chemical" antiviral compounds and have not attempted to review recent advances in the use of such naturally occurring substances as interferon. Interferon has now been used in clinical trials involving VZV, CMV, HSV, chronic hepatitis B virus, papilloma virus, rhinovirus, and influenza A virus infections. The availability of greatly increased quantities of interferon, particularly as a result of recombinant DNA technology, has contributed to a marked expansion of studies of this substance, and much new information on the use of interferon in antiviral therapy and prophylaxis should emerge in the next several years.

## Conclusions

Significant advances have been made in the development of effective antiviral chemotherapy and chemoprophylaxis for a number of viral infections. The advent of these antiviral compounds represents an important addition to the therapies available for the treatment of infectious diseases. As with other advances, however, nearly as many questions are raised by the use of antiviral compounds as are answered. Many of these questions are all too familiar to those who use antibacterial antibiotics. They include questions regarding the appropriate routes of administration, optimal dosage regimens, the risks of long-term prophylaxis, and the emergence of resistant organisms. Investigators are also beginning to address the possibility of combination chemotherapy with two or more antiviral compounds and to study the use of immunoprophylaxis in combination with antiviral compounds. The optimal use of antiviral compounds is likely to require the development of individualized regimens for different populations of patients in whom risk factors for illness are variably represented. To physicians who care for patients with infectious diseases, as well as to investigators in the field, questions addressing the best manner in which to use antiviral compounds are welcome ones.

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76. We thank R. C. Reichman, R. F. Betts, and C. B. Hall for advice and W. Shannon for useful information. This work was supported, in part, by a contract (NOI AI 02653) from the Development and Applications Branch of the National Institute of Allergy and Infectious Diseases, Bethesda, Md.