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Antiviral Agents

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Potent effective antiviral drugs recently have been licensed for several viral diseases, ushering in a new era in the treatment of viral diseases. At the same time, we have seen widespread adoption of rapid diagnostic tests to identify specific viral etiologies. These developments bring us to a point where the diagnosis and effective treatment of many viral diseases are commonplace.

Several antiviral agents and their targets will be examined in this review. Acyclovir is effective against herpes simplex virus and varicella zoster virus; ribavirin, recently introduced, is effective against respiratory syncytial virus; amantadine is effective against the influenza type A viruses. Anticytomegalovirus agents, antihuman immunodeficiency virus agents, and immunomodulators such as the interferons are under investigation. Older agents such as adenosine arabinoside and idoxuridine are being replaced by newer, more effective agents.

It has taken us a long time to reach this point because rendering a virus inactive is a more formidable feat than killing a bacteria. Bacteria reproduce outside of human cells and have several unique features that distinguish them from human cells. Viruses, in contrast, reproduce within human cells and have fewer unique features that selectively can be inhibited.[36] In recent years, several unique features in the process of a viral infection have been identified as target points for interference or inhibition. These unique steps in the process and the interfering compounds are the subject of this review.

ACYCLOVIR

Acyclovir (Zovirax) currently is the most effective agent against several herpesviruses. It is a synthetic acyclic purine (guanosine) nucleoside ana-

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logue without the cyclic sugar moiety of natural nucleosides. Naturally occurring nucleosides are composed of five carbon sugars attached to a base with a single ring (thymidine or deoxycytidine) or a double ring (deoxyguanosine or deoxyadenosine). A nucleoside analogue differs from a natural one by changes in the sugar or base moiety (Fig. 1). Phosphates attach to the nucleoside to form nucleotides. The nucleoside analogue interrupts the replication of a growing nucleic acid chain by interfering with phosphorylation, enzyme binding, and other mechanisms.

Acyclovir (ACV) has antiviral activities against certain members of the herpesvirus family; that is, herpes simplex types 1 and 2, varicella zoster virus, and Epstein-Barr virus, but not against cytomegalovirus.

Mechanism of Action. ACV inhibits the viral DNA polymerase by utilizing the infected cell's virus-specific thymidine kinase. When the drug enters the infected cell, viral thymidine kinase phosphorylates ACV to its monophosphate derivative. The drug is further phosphorylated by host cell enzymes to a triphosphate derivative that then inhibits the viral DNA polymerase.[23]

The triphosphate compound selectively inhibits viral DNA polymerase by competing with host guanosine triphosphate as a substrate for this enzyme. DNA chain elongation and replication thereby are inhibited (Fig. 2).

The triphosphate compound is a more potent inhibitor of viral DNA polymerase than cellular DNA polymerase. This makes phosphorylated ACV a highly specific agent for herpes infected cells. ACV binds 200 times more avidly to viral thymidine kinase than to cellular thymidine kinase. In addition, ACV is phosphorylated more rapidly by viral thymidine kinase than by cellular thymidine kinase. The amount of the ACV triphosphate compound generated in infected cells is 40 to 100 times more than in normal cells.

A second mechanism of action of ACV has been recognized to explain the drug's activity against Epstein-Barr virus (EBV). EBV does not have a viral specific thymidine kinase, so ACV is not phosphorylated avidly or rapidly in EBV infected cells. Instead, the drug appears to have a direct action on the EBV viral DNA polymerase.[41]

Pharmacokinetics. Acyclovir is excreted by the kidney and the half-life and total body clearance of ACV are dependent on renal function. In patients with normal renal function, the half-life is 2.9 hours; in neonates, it is slightly longer at 3.8 hours; and in anuric patients it increases to 18 hours.[50]

After infusion of a 5 mg per kg per 8 hours, peak plasma concentrations average 9.4 μg per ml, with a trough level of 0.7 μg per ml. After 10 mg per kg per 8 hours, the peak is 20.7 μg per ml, with a trough of 2.3.

The bioavailability of oral ACV is 15 to 30 per cent. After an oral dose of 200 mg, peak plasma levels of 0.3 to 0.9 μg per ml occur between 1.5 and 4 hours later. Steady-state plasma levels are reached by the second day of dosing.

Cerebrospinal fluid concentrations are approximately one half of plasma values. Salivary concentrations average 13 per cent of plasma levels after an oral dose, whereas vaginal secretion concentrations range from 15 to 17 per cent of plasma values.

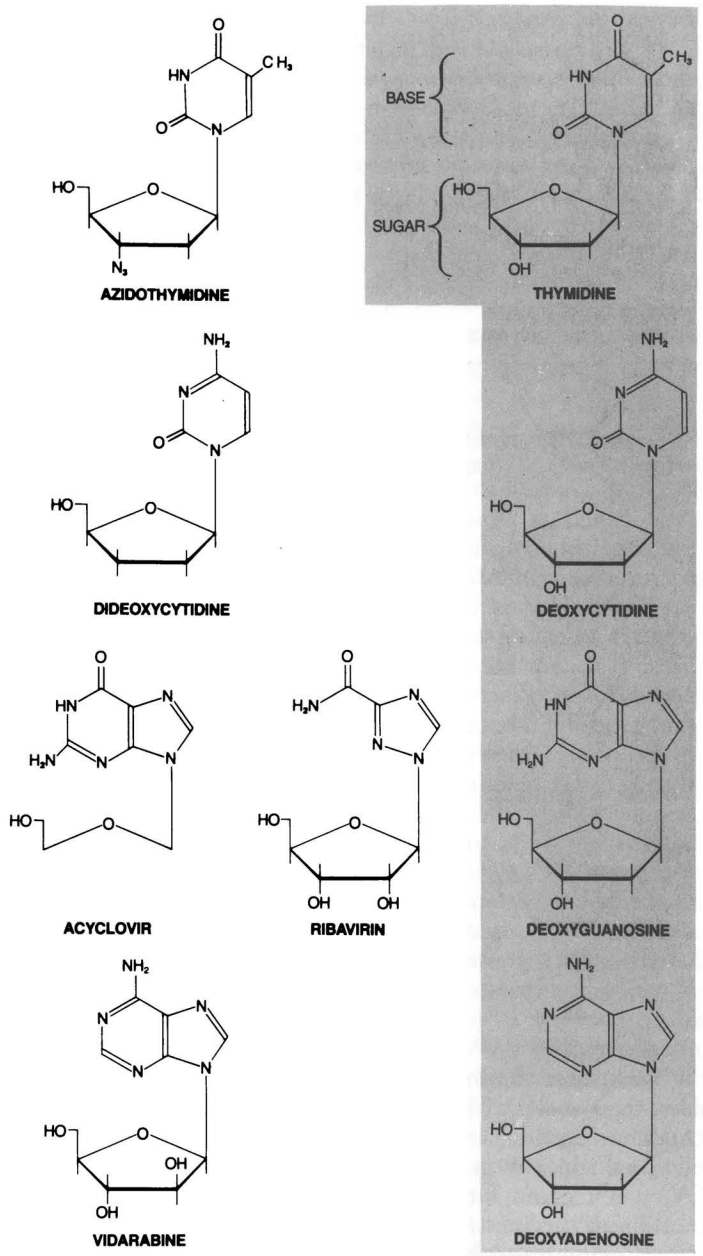

Figure 1. Five nucleoside analogues used as antiviral agents are shown on the left and can be contrasted to the four nucleosides used to make the DNA chain. (*From* Hirsch MS, Kaplan JC: Antiviral therapy. Sci Am 256:76, 1987; with permission.)

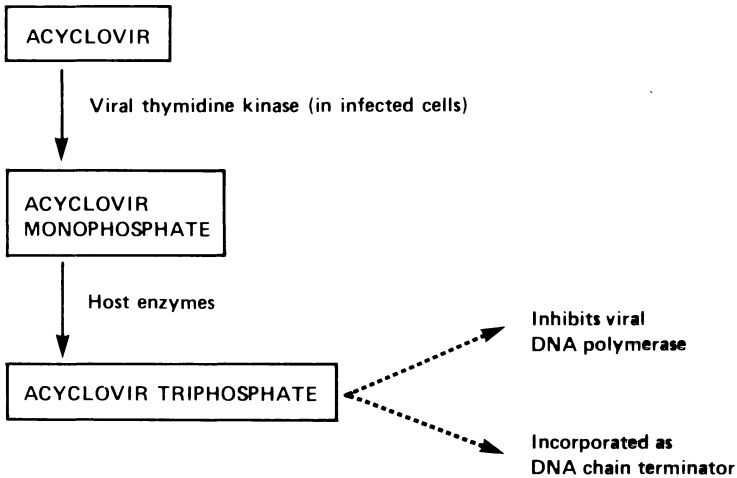

Figure 2. Mechanism of action of acyclovir. (*From* Chou S, Merigan TC: Antiviral chemotherapy. *In* Field's Virology Textbook. Edition 1. New York, Raven Press, 1985; with permission.)

Percutaneous absorption of ACV is poor.[27]

Renal excretion of ACV is by glomerular filtration and renal tubular secretion. The kidney excretes mostly unmetabolized acyclovir. Less than 15 per cent is excreted as 9-carboxymethoxy-methylguanine or as other metabolites. Tubular secretion accounts for 60 to 90 per cent of an administered dose.

A dosage reduction is recommended for patients with a creatinine clearance less than 50 ml per minute per 1.73 m^2. ACV is easily hemodialyzed; during a routine 6-hour dialysis, 60 per cent of the drug is removed.[44]

ACV may reduce the renal clearance of other drugs secreted by the kidney; methotrexate is one such example.

Toxicity and Side Effects. There are no contraindications to the use of acyclovir except for patients known or suspected to have hypersensitivity reaction to it. When used orally for a short course, the most common adverse reactions are nausea, vomiting, and headaches, For longer courses the most common adverse reactions are headaches, nausea, vomiting, and diarrhea.

Topically applied ACV may cause transient burning when applied to genital lesions, most commonly at time of the first episode and more often in females than males. The polyethylene glycol base of topical ACV is known to cause erythema when applied vaginally and should not be used for intravaginal application.

ACV, when given intravenously, usually is well tolerated, although local irritation at the infusion site has been noted. Uncommon side effects include rash, diaphoresis, hematuria, hypertension, headaches, and nausea. Encephalopathic changes have been noted in 1 per cent of patients. These changes include lethargy, dullness, tremors, confusion, hallucinations, delirium, seizures, or coma. Risk factors for these neurologic symptoms include use of high doses intravenously (that is 500 mg per m^2 per 8 hours)

and simultaneous administration of methotrexate or interferon. They are seen in 4 per cent of bone marrow transplant patients. Resolutions of these symptoms occur with discontinuation of the drug; they return when the patient is put back on the drug.

Renal dysfunction has been noted in patients treated with intravenous ACV. The impairment of renal function is caused by crystal formation in the renal tubules. Crystal formation occurs when plasma concentrations are high immediately following a bolus injection. Slow infusion of ACV over 1 hour and good hydration seems to prevent crystalluria. In addition to dehydration, high-dose rapid infusion and renal insufficiency also are risk factors for developing crystalluria. Particular care should be taken when ACV is given to a patient on aminoglycosides, cyclosporine, or other nephrotoxic agents.

ACV also has been associated with abnormal hepatic function and bone marrow depression in immunocompromised patients. The drug is not teratogenic nor mutagenic and can be used in pregnancy without fear of injury to the fetus and, in fact, treatment of severe herpes infections may prevent placental transmission of the infection.[46]

There have been reports of drug resistance of herpes simplex virus in patients treated with ACV,[55] but lack of clinical response because of resistance has yet to be reported.

Indications. Acyclovir has been used topically, orally, and intravenously for a variety of types of herpetic infections. Genital herpes simplex infections initially were treated with topical ACV and the duration of viral shedding was significantly reduced. Topical ACV was not effective in reducing time to crusting, time of healing, development of new lesions, or constitutional symptoms, such as pain, however.[62] In addition, mild transient burning or pain was associated with topical application. It recently has been shown that the poor clinical response is due to the failure of topical acyclovir in a polyethylene glycol base to penetrate the skin.[27]

Treatment with oral ACV has replaced topical acyclovir as the treatment of choice for genital herpes infections. Use of oral ACV shortens the mean duration of viral shedding, time of crusting, time of healing, duration of local pain, and constitutional symptoms.[56] ACV can be given intravenously for severe primary genital herpes simplex infections; it substantially decreases symptoms, duration of lesions, and complications.[18]

Treatment with oral ACV has been successful for recurrent genital herpes. When ACV therapy was instituted within 48 hours of the appearance of a lesion, the duration of viral shedding was shortened and healing was faster. In situations where patients started therapy as soon as possible after the appearance of new lesions, there were similar changes in the time to crusting, healing, and duration of viral shedding. In addition, fewer new lesions formed.[63]

Oral ACV also suppresses recurrent herpes simplex virus-2 infections; recurrent lesions appear but are significantly fewer in number than in untreated cases. The therapy is well tolerated with long-term use. After 4 months of suppressive therapy, resistant strains have not been found, but long-term suppressive therapy with ACV may result in the development of drug resistance.[48, 76] Most resistant isolates so far have come from immu-

nocompromised patients who received multiple courses of therapy for active infection.[30] These resistant strains typically are deficient in thymidine kinase.

The length of therapy for suppression has not been adequately defined, nor have long-term side effects or toxicities been studied when ACV is used as suppressive therapy over several years. Current recommendations are to treat these patients for up to 12 months to suppress their recurrent genital herpes infections.[30] Chronic suppressive therapy is most cost effective in patients with six or more recurrences per year. Therapy also is indicated for patients who experience serious complications with recurrences, such as erythema multiforme, aseptic meningitis, and eczema herpeticum.

Chronic suppressive therapy should be stopped after 6 to 9 months to determine whether the frequency of recurrences has changed. If the rate has decreased significantly, chronic prophylaxis may be stopped. Clinical trials currently are in progress to evaluate the efficacy and safety of suppressive therapy for 12 or more months. Recurrences in ACV-treated patients were less frequent and shorter in duration than those in the placebo group.[76] Similar results have been shown in other smaller trials. Once the drug is discontinued, however, recurrences return to the pretreatment frequency and some patients have reported unusually severe symptoms with the first posttreatment recurrence. Resistant strains of herpes are not responsible for breakthrough recurrences.[48, 55]

ACV has been used in immunocompromised patients to treat as well as to suppress mucocutaneous herpes simplex infections.[71, 74, 75] Oral ACV is as effective as intravenous ACV in treating these infections. Suppressive therapy has been used successfully for as long as 6 months, but reoccurrences developed after cessation of therapy. Safety beyond 6 months of use of the drug is unknown and is being investigated.

Recently, recommendations have been broadened for the prophylactic use of ACV in the immunocompromised host. For patients undergoing bone marrow transplants or induction chemotherapy for hematologic malignancies, routine screening for herpes antibodies should be performed. Seropositive patients should be given ACV beginning the day of conditioning or induction and continued for approximately 6 weeks. Some investigators stop ACV when the absolute granulocyte count is over 500 or when marrow engraftment has been successful.[30] Similar recommendations may be appropriate for cardiac, renal, and liver transplant patients and for patients with acquired immunodeficiency syndrome (AIDS), although the doses will vary depending on the clinical setting.

ACV used intravenously currently is the treatment of choice for herpes simplex encephalitis. The recommended dosage is 10 mg per kg per 8 hours. Compared with vidarabine therapy, intravenous ACV showed lower morbidity and mortality.[82] ACV also is used in the normal host for mucocutaneous herpes infections such as herpetic whitlow.[47]

ACV is effective in controlling certain manifestations of varicella zoster virus in both immunocompromised and immunocompetent hosts. It most commonly is used in immunocompromised patients for herpes zoster with dissemination, but can be used for local zoster to prevent dissemination.

For these patients, acyclovir is administered intravenously at doses of 10 to 12.5 mg per kg per 8 hours.[4]

ACV has been shown to be an effective agent for varicella zoster infection in immunocompetent hosts.[7, 8, 60] For both the localized zoster rash and disseminated disease, ACV prevents progression of dissemination, enhances the rate of clearance and provides faster relief of pain than placebo. Intravenous ACV has been used in an outpatient setting for treating herpes zoster, but a higher frequency of adverse reactions has been seen, possibly due to poorer hydration states. No in vivo resistance has been found in treating varicella zoster with ACV.[14]

A case recently has been reported of herpes zoster-associated encephalitis that responded rapidly to intravenous ACV (30 mg per kg per day). Within 72 hours, there was resolution of the encephalopathy with normalization of the electroencephalogram.[39]

The use of ACV has been extended to herpes virus infections beyond herpes and varicella zoster viruses. Epstein-Barr virus (EBV) infection (severe acute infectious mononucleosis, in particular) has been treated with ACV. The only significant effect of the drug in acute mononucleosis is in inhibiting oropharyngeal shedding of EBV. It does not affect the humoral or cellular immune responses nor does it affect viral latency. Moreover, clinical symptoms such as fever, weight loss, pharyngitis, and sense of well-being are not significantly better when examined individually. But when all clinical findings are combined, there is a significant positive effect seen with ACV treatment compared with placebo treatment.[1] Severe chronic EBV infection associated with fever and interstitial pneumonitis seems to respond to intravenous ACV.[69]

The use of ACV in the treatment of Sézary's syndrome and mycosis fungoides recently has been reported.[64, 68] These diseases are grouped together as cutaneous T-cell lymphomas and there is evidence that they may be caused by a viral infection.

Dosage

1. Genital herpes: First episode: 200 mg five times daily for 7 to 10 days. Recurrent episode: 200 mg five times daily for 5 days. Chronic suppressive therapy: 200 mg five times daily for first three days, then 200 mg two to four times daily for 6 to 9 months.
2. Herpes simplex encephalitis: 10 to 12.5 mg per kg per 8 hours intravenously.
3. Herpes prophylaxis for bone marrow transplant or induction chemotherapy in hematologic malignancy in seropositive patients: 200 mg four times daily orally or 250 mg per m^2 per 8 hours intravenously.
4. Varicella zoster: Immunocompetent: 5 to 10 mg per kg per 8 hours intravenously; oral dose not yet determined.
   Immunocompromised: 10 to 12.5 mg per kg per 8 hour orally.
5. Epstein-Barr virus: Unknown at present.

RIBAVIRIN

Ribavirin (Virazole) is a nucleoside analogue first synthesized in 1972. Unlike ACV, another nucleoside analogue active against only the herpes

viruses, ribavirin has a broad spectrum activity. It is a derivative of 1,2,4-triazole-3-carboxamide and ribofuranosine and closely resembles guanosine and inosine (see Fig. 1).

Mechanism of Action. Ribavirin is virostatic. Its mode of action is poorly understood and several different mechanisms have been postulated: (1) decrease in the intracellular concentration of guanosine triphosphate caused by competitive inhibition of inosine monophosphate dehydrogenase; (2) inhibition of 5′-cap formation of messenger RNA (mRNA); and (3) inhibition of the function of virus coded RNA polymerases necessary to prime and elongate viral RNA.

It does not appear to interfere with the attachment or penetration of virus into cells; it does not induce interferon; it is not incorporated into whole cell RNA or DNA.

Spectrum of Activity. Ribavirin in vitro inhibits both DNA and RNA viruses. It has inhibitory activity against all three major human DNA viral groups: the adenoviruses, herpesviruses, and the poxviruses. The RNA viruses that are inhibited include respiratory viruses such as influenza type A and B, respiratory syncytial virus (RSV), and the parainfluenza viruses. Measles, arenavirus, and bunyavirus also are sensitive to ribavirin. In animal models, the enteroviruses do not appear to be sensitive. Because ribavirin does not cross the blood-brain barrier well, it has not been effective against the viral encephalitides.

Pharmacokinetics. Ribavirin can be administered by aerosol or by mouth. With inhalation of ribavirin, only low concentrations appear in the systemic circulation, while the concentration in respiratory secretions can be 100 times higher than when given orally. Thus areosol administration results in extraordinarily high levels in respiratory secretions with little systemic absorption.[31] Ribavirin accumulates in the blood when administered by aerosol if the length of therapy is greater than 8 hours. Peak levels increase on each subsequent day of treatment. After 8 to 20 hours of administration, the mean peak plasma level is 1 to 3 μg per ml, but the mean peak level in respiratory secretions is over 1000 μg per ml.[16] The minimal inhibitory concentration for RSV is in the range of 4 to 16 μg per ml. The half-life of ribavirin in plasma is about 9 hours and in respiratory secretions, 1 to 2 hours.

The metabolism of ribavirin is incompletely understood. With either oral or intravenous administration, ribavirin accumulates in red blood cells and may persist for weeks after cessation of therapy. After oral administration, the half-life in red blood cells is 40 days compared with 10 to 12 hours in urine. The long half-life in red blood cells is caused by the phosphorylation of ribavirin to ribavirin triphosphate (RTP) in red cells and to the cells' inability to dephosphorylate RTP.[20] Ribavirin appears in the urine after being metabolized to the 1,2,4-triazolecarboxamide form.

Toxicity and Adverse Reactions. There is little toxicity with ribavirin when administered by aerosol; it has been well tolerated with no significant adverse effects reported, although rash and conjunctivitis have occurred. There have been no reports of lung damage with acute use of aerosol. The effect of long-term use on developing lungs has not been adequately studied, however.[32] Ribavirin used in patients on mechanical ventilators can result

in malfunction of the respirator caused by precipitation of the drug on valves and in the tubing. The aerosolized drug therefore is not used for patients on respirators.[29]

After oral or intravenous use, a transient normochromic, normocytic anemia has been reported. The anemia is dose-dependent and is caused by rapid extravascular clearing of red blood cells. At higher doses, suppression of the red blood cell line in the bone marrow can occur. Early studies using oral ribavirin showed elevated bilirubin levels, which may be a reflection of the rapid clearance of the red blood cells.

In monkey and rat studies, ribavirin is mutagenic, teratogenic, embryotoxic, and possibly carcinogenic.

Clinical Use. Ribavirin has been used therapeutically around the world for a variety of viral infections, including RSV, influenza type A and B, Lassa fever, Junin virus, and Machupo virus.

Ribavirin now is commercially available in the United States to treat RSV in infants. It is delivered on an almost continuous basis via the aerosol route. It has been demonstrated that ribavirin therapy improves the arterial blood gases and decreases the amount of viral shedding and nasal washings. No toxicity has been observed.[32]

Ribavirin has been an effective agent against influenza when given by the aerosol route. Aerosolized ribavirin begun within 24 hours after the onset of flu-like symptoms decreases viral shedding, fever, and systemic symptoms caused by influenza types A and B.[29, 43, 53, 86] In this setting, ribavirin is given for 12 to 16 hours almost continuously each day for 5 days.

The use of oral ribavirin has yielded mixed results. It has been shown to be effective in the treatment of Lassa fever that results from an infection with an arenavirus. Mortality in Lassa fever has been directly related to two risk factors: high levels of aspartate aminotransferases and viremia. Patient groups with one of these risk factors treated with oral or intravenous ribavirin had mortality reduced from 71 to 31 per cent compared with those groups that were treated with Lassa fever immune plasma.[54]

Ribavirin has been shown to be effective in animal models for infections with the Junin virus, the agent of Argentine hemorrhagic fever, and with Machupo virus, the agent of Bolivian hemorrhagic fever. Ribavirin decreased the viremia and increased survival, although the animals ultimately died from subsequent encephalitis.[42] Finally, in animals, ribavirin has been shown to inhibit growth of the vesicular stomatitis virus.[77]

Dose and Administration. Ribavirin is delivered by oxygen mask as a small particle aerosol. The drug is administered by means of a specific small particle Collison generator that produces an aerosol with a median particle size of about 1.4 mm. The concentration of ribavirin in the reservoir is 20 mg per ml. The dose of ribavirin delivered is estimated to be 0.8 mg per kg per hour of administration.[17]

Aerosol administration in this manner results in high levels in the respiratory secretions with little systemic absorption. For RSV and influenza infections, ribavirin is given continually (12 to 18 hours per day) except during meals. It is given for at least 3 days but no more than 7. The highest concentrations are obtained when administration is via endotracheal tube

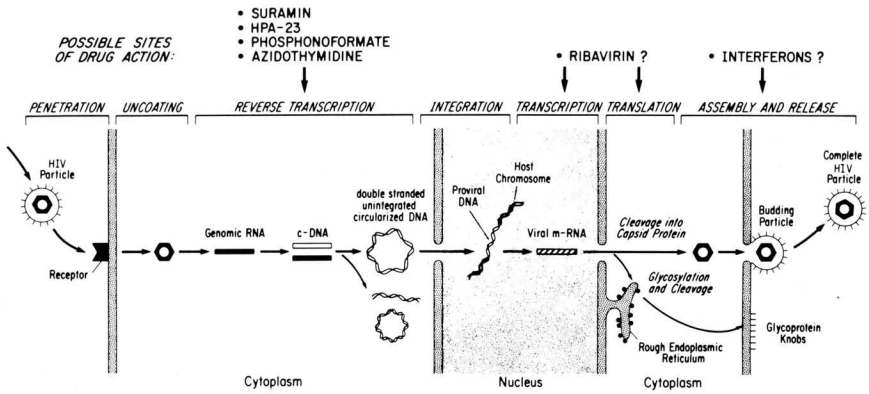

Figure 3. Replication cycle of human immunodeficiency virus and possible sites of drug action. (*From* Vogt M, Hirsch MS: Prospects for the prevention and therapy of infections with the human immunodeficiency virus. Rev Infect Dis 8:991, 1986; with permission.)

rather than by oxygen hood, mask, or tent. The Collison generator is supplied by ICN Pharmaceuticals, the manufacturer of ribavirin (Virazole).

For Lassa fever, ribavirin is given orally as a 2 g loading dose followed by 1 g per day in divided doses every 8 hours for 10 days. Intravenous ribavirin also is used for Lassa fever and is given as a 2 g loading dose, followed by a 1 g dose every 6 hours for 4 days, then every 8 hours for 6 days.

VIDARABINE

Vidarabine (Ara-A, Vira-A, adenine arabinoside, or 9-B-D-arabinocytidine) was one of the first effective antiherpesvirus drugs available for intravenous use in humans. Vidarabine is an analogue of deoxyadenosine (or adenine deoxyriboside) (see Fig. 1). It also is a DNA synthesis inhibitor.

Spectrum. Vidarabine has in vitro activity against herpes simplex viruses types 1 and 2, varicella zoster virus, EBV, vaccinia and variola, rhabdoviruses, and some RNA tumor viruses. Its activity against cytomegalovirus (CMV) is variable, but in vitro it inhibits replication of ACV-resistant herpes strains, ACV-resistant varicella zoster, and idoxuridine-resistant herpes strains.[10, 26, 28]

Mechanism of Action. Cellular enzymes convert adenine arabinoside (vidarabine) to adenine arabinoside triphosphate, which directly inhibits the DNA polymerase of herpes simplex virus. It also may act as a substrate for incorporation into herpes virus DNA (Fig. 3). The triphosphate compound acts as a chain terminator for newly synthesized herpes simplex DNA. The primary metabolite is hypoxanthine arabinoside (Ara-Hx), which has 30 to 50 times less activity than Ara-A.[28] Ara-Hx, however, seems to enhance the activity of Ara-A.[13]

Ara-A also inhibits S-adenosylhomocysteine hydrolase in vitro and in red blood cells from patients treated with Ara-A. S-adenosylhomocysteine hydrolase is an enzyme involved in transmethylation. The effect of Ara-A on this enzyme persists after the cessation of therapy and may explain the toxicity of Ara-A.

Pharmacokinetics. Vidarabine is relatively insoluble in water and is administered intravenously with large volumes of fluid by slow infusion. Following infusion, vidarabine rapidly is metabolized by adenosine deaminase to Ara-Hx. Plasma levels peak at 3 to 6 μg per ml with almost no detectable levels of vidarabine. Ara-Hx crosses the blood-brain barrier and is present in the cerebrospinal fluid at 35 per cent of plasma concentration. Vidarabine is renally cleared, 40 to 53 per cent as Ara-Hx and 1 to 3 per cent as vidarabine. The serum half-life is about 3.5 hours in adults. Vidarabine can be detected in red blood cells 1 to 3 weeks after ending therapy. With renal insufficiency, plasma Ara-Hx concentrations are elevated and may increase the risk of toxicity. A 25 per cent reduction in dosage is recommended for severe renal insufficiency. Vidarabine is removed during hemodialysis.[2]

Toxicity and Adverse Reactions. The major side effects of vidarabine are nausea, vomiting, diarrhea, anorexia, and weight loss. Because of poor solubility, the drug must be administered in 1.5 to 2.5 L of fluid. The daily dosage is 15 mg per kg per day. At conventional doses, no liver, renal, or bone marrow toxicity has been seen. But at a dosage of 20 mg per kg per day, megaloblastic bone marrow changes, with anemia, leukopenia, and thrombocytopenia have been reported. Infusion-related thrombophlebitis, weakness, rash, hypokalemia, and the inappropriate antidiuretic hormone syndrome also have been reported.[66] Neurotoxicities have been described, including pain syndromes of the extremities that can last up to 6 months after cessation of therapy. Intention tremors, grimaces, myoclonus, ataxia, mood and behavior changes, dysgraphia, disorientation, aphasia, depression, mutism, agitation, and hallucinations also have been seen. Coma and seizures are rare. High dosages and pre-existing hepatic or renal failure are predisposing risk factors and the concomitant use of interferon or allopurinol increases the risk of toxicity. Serum concentrations of Ara-Hx were found to be higher in toxic patients.

The drug is teratogenic, carcinogenic, and mutagenic in certain animals.

Clinical Indications. Vidarabine initially was used for treating herpesvirus infections, especially herpes simplex encephalitis. It also is effective in treating neonatal herpes simplex, varicella zoster, and herpes simplex keratitis. Vidarabine has been shown to reduce mortality from herpes simplex encephalitis in biopsy proven patients.[83, 84] More recent studies, however, have confirmed that ACV is the drug of choice for these diseases.[82] Vidarabine has limited therapeutic usefulness in mucocutaneous herpes simplex infections in the immunocompromised patient[85] and therefore largely has been replaced by ACV for treatment of most of these infections.

Vidarabine also has been used in patients with chronic hepatitis B infections. Hepatitis B virus specific DNA polymerase as well as HBsAg and HBeAg titers were reduced in some treated patients.[6] Greater benefit

occurred when interferon was added to vidarabine therapy for the treatment of chronic hepatitis B.[70]

Dosage. For herpes simplex encephalitis: range, 10 to 20 mg per kg per day; average, 15 mg per kg per day for 10 days.

Vidarabine monophosphate (adenine arabinoside 5′1-monophosphate, Ara-Amp, Vira-amp), a new form of vidarabine, is undergoing clinical testing. Its major advantages are that it can be given intramuscularly and does not require large volumes of fluid when given intravenously because it is more soluble than Ara-A. The intramuscular form may be advantageous for ambulatory therapy of patients with varicella zoster infections.

DHPG (GANCICLOVIR)

DHPG (9-[1,3-dihydroxy-2-propoxymethyl] guanine) is an antiviral purine analogue. It is an acyclic nucleoside structurally related to ACV.

Spectrum. DHPG has activity against all of the herpesviruses, including CMV. It also has some activity against other DNA viruses such as vaccinia and adenovirus, but is inactive against RNA viruses.

Mechanism of Action. The action of DHPG is not dependent on virus specific thymidine kinase. In CMV infected cells, DHPG is phosphorylated to a monophosphate derivative by a cellular deoxyguanosine kinase. It then is further phosphorylated to a triphosphate. It is phosphorylated 10 times more readily in infected cells. DHPG-triphosphate competitively inhibits binding of deoxyguanosine triphosphate to DNA polymerase, thus inhibiting DNA synthesis and terminating DNA elongation.

Pharmacokinetics. The mean plasma half-life of DHPG is 3.6 hours; with poor renal function, it increases to 9 hours. Drug levels in the lung and liver average 99 per cent and 92 per cent of blood levels, respectively. DHPG penetrates into the central nervous system at about 38 per cent of blood levels. In published studies, mean peak plasma levels have exceeded the mean inhibitory doses for CMV.[73] It is excreted 78 per cent unchanged in the urine within 24 hours.

Toxicity and Adverse Effects. Adverse effects often are dose-related and include inhibition of spermatogenesis, bone marrow depression, obstructive nephropathy, and atrophy and necrosis of the gastrointestinal mucosa. Bone marrow effects include leukopenia and thrombocytopenia; eosinophilia has been reported as well. Gastrointestinal reactions have included nausea, anorexia, vomiting, and increased liver enzymes. One reported patient developed edema. Disorientation has also been reported.

Clinical Indications. DHPG is as of this writing not commercially available, but has promise as an anti-CMV agent. There are published reports of its use for CMV infection in transplant patients, AIDS patients, and other immunocompromised patients.[40b] Healing of retinal lesions and resolution of viremia and virus shedding are seen with use of DHPG in treating CMV retinitis.[25] Once the drug is discontinued, however, further deterioration of vision occurs, with new hemorrhages seen on the retina. In AIDS patients, maintenance therapy appears to be necessary to prevent reoccurrence.[3] Reversal of retinitis has been seen with DHPG, but more

often treatment just stabilizes and arrests further progression of retinal damage.[15, 52]

In animal studies, comparison of ACV and DHPG for therapy in CMV pneumonitis showed that DHPG was more effective than ACV in reducing the concentration of live virus in lung tissue and salivary glands. Both drugs reduced the severity of pneumonitis but neither was able to prevent it.[72]

In a study of CMV pneumonitis in transplant patients, DHPG therapy suppressed viral replication with cessation of viremia and viruria; in addition, CMV was eliminated from respiratory secretions. DHPG did not promptly reverse progressive infection despite good in vitro and in vivo antiviral effects, and no improvement in survival occurred. All patients relapsed after the cessation of therapy.[73]

Dosage. Intravenous: 7.5 to 15 mg per kg per day in three divided doses is given over 1 hour per infusion. The dose interval is adjusted according to the serum creatinine. Total dose is reduced in the presence of neutropenia and other side effects. Length of therapy 14 to 30 days. Maintenance regimen: 2.5 mg per kg in two to five divided doses each week. Because DHPG is still an experimental therapy the dosage is not yet standardized. An oral preparation is being investigated.

AMANTADINE

Spectrum. Amantadine (Symmetrel) is a narrow spectrum compound active only against influenza A viruses.[61]

Mechanism of Action. Amantadine appears to inhibit the uncoating of the virus after it enters the cell: in the presence of amantadine, the virus attaches normally to and then penetrates mammalian cells, but uncoating of the virus fails to occur. Amantadine also appears to inhibit initiation of transcription at some point between uncoating of the virus and the initiation of viral specific RNA synthesis.[59]

Pharmacokinetics. Amantadine can be administered orally as a capsule, tablet, or syrup. The appearance of peak plasma levels varies widely, but averages 3 to 4 hours. After a 100 mg dose, peak plasma concentrations average 0.3 to 0.4 μg per ml; plasma half-life is 12 to 17 hours. The half-life increases in the elderly and in the presence of renal insufficiency. Amantadine is excreted unmetabolized in the urine by glomerular filtration and tubular secretion.

Toxicity and Side Effects. Orally administered amantadine is well tolerated without serious renal, hepatic, or hematopoietic toxicities. Amantadine may cause mild transient central nervous system reactions such as insomnia, lightheadedness, and difficulty in concentrating. These neurotoxicities are enhanced by simultaneous use of anticholinergic agents or antihistamines.[57] There may be some gastrointestinal complaints such as anorexia or nausea. These reactions are related to the dose and duration of administration. Reactions have been associated with doses of 300 mg per day but are less likely with doses of 200 mg per day in healthy young adults.

Clinical Indications. Amantadine has been used prophylactically as

well as therapeutically against influenza A. It has been used effectively to prevent infection with the subtypes of influenza A (for example, H3N2 and H1N1 subtypes).

It is recommended as prophylaxis for the elderly or chronically ill who have not received vaccination or as an adjunct to late immunization in high-risk individuals, for immunodeficient persons expected to show a poor antibody response to immunization, for healthy persons caring for high-risk persons, and for those in whom the vaccine is contraindicated.[19]

As therapy for influenza A infections, amantadine reduces the duration of fever and other symptoms by about 50 per cent in patients treated in the first 48 hours of their illness. There also is decreased viral shedding. Antibody response to the infection is not diminished by amantadine.

Dosage. For prophylaxis: 200 mg daily taken orally, started as soon as influenza type A is identified in the community, and continued for 4 to 12 weeks. Amantadine also can be started concomitantly with influenza vaccine administration and continued for 2 weeks until the antibody response has developed.

For therapeutic use: 200 mg per day. Begin within 1 to 2 days of onset of symptoms and continue until 48 hours after the resolution of the illness. Acetaminophen can be given simultaneously to bring down the fever, but salicylate antipyretics should not be used.

In the elderly and in patients with renal failure, the dose should be reduced to 100 mg per day or less, according to the recommendations of the US Public Health Services.[61] In children between 1 and 10 years, the dose is 4.4 to 8.8 mg per day and should not exceed 150 mg daily.[61]

RIMANTADINE

Rimantadine is a structural analogue of amantadine, with the same spectrum of activity, mechanism of action, and clinical indications. Rimantadine currently is an investigational drug. The plasma half-life is approximately 28 hours, about twice that of amantadine. The drug is excreted in the urine as hydroxylated metabolites. The toxicities are similar to amantadine. With rimantadine, however, there is an increased incidence of gastrointestinal complaints but less central nervous system toxicity.[9]

ANTI-HIV AGENTS

AIDS is caused by the human immunodeficiency virus (HIV, formerly HTLV-III/LAV), a retrovirus. HIV requires a reverse transcriptase for viral replication. Several agents that inhibit the reverse transcriptase or other steps in viral replication are undergoing efficacy studies (Fig. 4). Many drugs have anti-HIV activity in vitro. Drugs that affect *attachment* and *penetration* of HIV into a human cell are AL 721, amphotericin B, peptide T, and tunicamycin. *Uncoating* of the virus is affected by immunomodulators such as interferon. *Transcription* of HIV by its reverse transcriptase is inhibited by azidothymidine (AZT), ribavirin, dideoxycytidine, foscarnet,

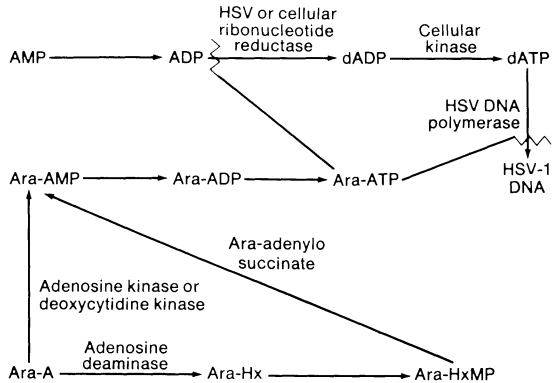

Figure 4. The inhibition of virus replication by Ara-A and Ara-H MP. (*From* Robins RK: Synthetic antiviral agents. Chem Eng News 64:32, 1986; with permission.)

suramin, oligonucleotides, rifamycins (including ansamycin), actinomycin D, daunomycin, and Ara-CTP. *Translation* is inhibited by interferons and antisense oligomers. Viral *assembly* is affected by the interferons and glycosylated inhibitors such as tunicamycin. Inhibition of *budding* of virus from the cell membranes also is being studied. The agents that have been studied most extensively will be reviewed.

Azidothymidine

AZT is a nucleoside analogue of thymidine. It recently was licensed as Retrovir (Zidovudine). Its mechanism of action is to terminate viral DNA synthesis. AZT is incorporated in viral DNA by HIV reverse transcriptase. An azido group (−N) replaces the 3′-hydroxy (−OH) group of thymidine (Fig. 5). The 3′ azido group prevents the formation of the 5′ to 3′ phosphodiester linkage and thereby terminates DNA synthesis. Its action is specific against the reverse transcriptase of HIV[58] and is 100 times more active against the HIV reverse transcriptase than it is against mammalian cell DNA polymerases.

Pharmacokinetics. AZT can be administered orally or intravenously. It is metabolized in the liver by glucuronidation and excreted by the kidneys; the half-life is approximately 1 hour. AZT appears to have good cerebrospinal fluid penetration. Bioavailability in the serum is 60 per cent of an oral dose.

Toxicity and Adverse Reactions. Bone marrow depression is the major adverse reaction. Anemia occurs in 25 per cent of patients taking AZT and appears to be dose-related. Granulocytopenia, thrombocytopenia, or thrombocytosis also occur. Some patients have been treated for more than 1 year without experiencing myelosuppression. Folate or vitamin B_{12} deficiency may enhance the bone narrow suppressant effect of AZT. Headache, agitation, restlessness, and insomnia also occur. Because AZT has not been extensively studied, long-term toxicities are still unknown.

Concomitant administration of other cytotoxic drugs will have additive effects on the bone marrow. Acetaminophen used concomitantly increases the risk of granulocytopenia. Other drugs that interfere with hepatic

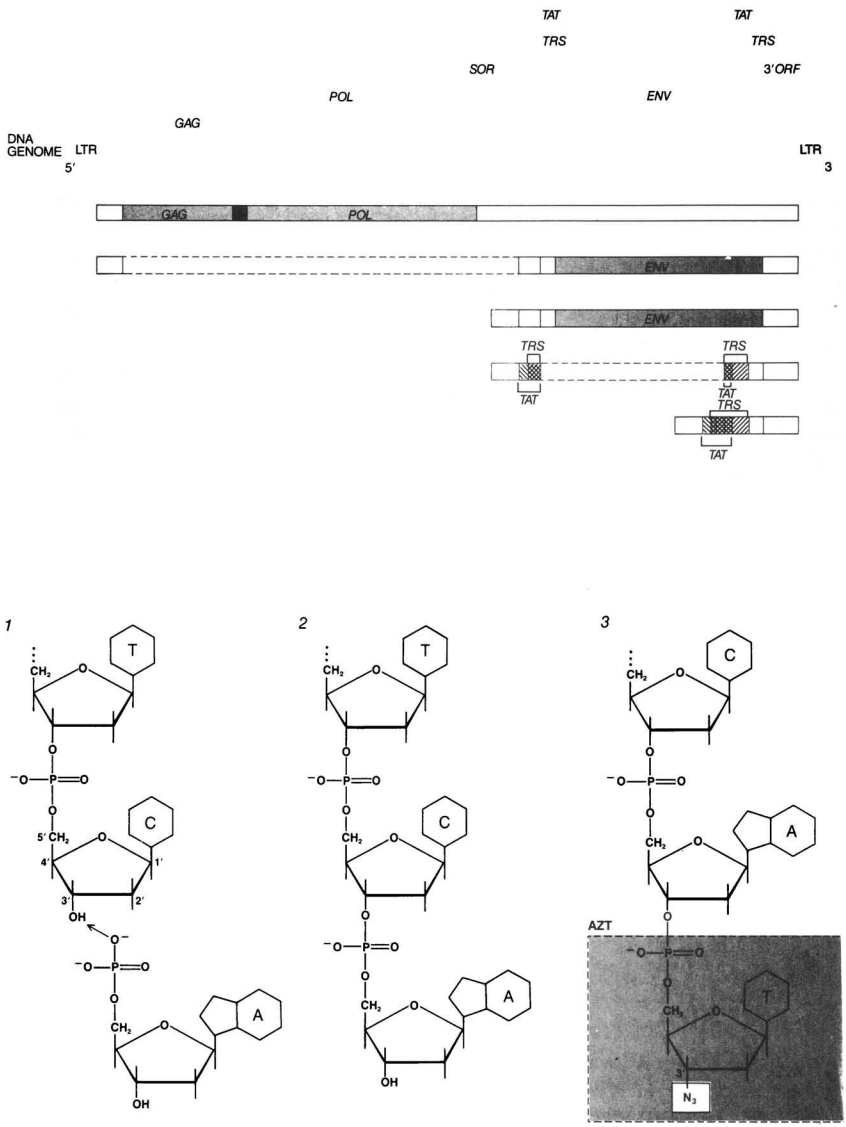

Figure 5. DNA chain termination by azidothymidine (AZT). (*1*) A hydroxyl group is present on the carbon designated 3′. (*2*) The hydroxyl group provides the attachment point for the next nucleotide by taking part in the formation of a linkage called a phosphodiester bond. (*3*) AZT is an analogue of the usual nucleotides. The viral reverse transcriptase will incorporate it into a DNA chain. Because AZT lacks the 3′ hydroxyl group, the chain is terminated, yielding an inactive provirus. (*From* Gallo RC: The AIDS virus. Sci Am 256:54, 1987; with permission.)

glucuronidation, renal excretion, or hepatic blood flow of AZT are probenecid, cimetidine, lorazepam, and indomethacin. They may decrease the metabolic breakdown or excretion of AZT and increase its toxic effects.

Clinical Trials. Nineteen HIV-positive patients with AIDS or AIDS related complex (ARC) initially were treated in trials with AZT. The patients were given 1 to 5 mg per kg intravenously every 4 to 8 hours for 14 days followed by 4 weeks of AZT using 2 to 10 mg per kg per day orally. In fifteen of the 19 patients, T-helper/suppressor cell ratios improved. Delayed hypersensitivity skin reactions developed in six patients who had been anergic prior to therapy. Eight had improvement of their clinical infections.[80] Some had improvement in dementia and other neurological symptoms.

Early in 1986, 281 AIDS and ARC patients participated in a double-blind placebo-controlled study of oral AZT. The study showed a significantly greater mortality in the placebo group. Because AZT appeared to decrease mortality and to improve T-helper/suppressor ratios and the host response to opportunistic infections, the oral drug recently was licensed. The data currently available are not, however, sufficient to definitively comment on the benefit/risks ratio or to determine which group of HIV infected patients will benefit the most from receiving AZT.

Clinical Indications. The drug has been approved for certain HIV infected adult patients who have a history of cytological confirmed *Pneumocystis carinii* pneumonia or an absolute CD4 (T4-helper/inducer) lymphocyte count of less than 200 per mm^3 in the peripheral blood before therapy is begun.

Dosage. Oral: 200 mg (two 100 mg capsules) every 4 hours for 70 kg adult; dose corresponds to 2.9 mg per kg per 4 hours. If anemia or granulocytopenia develops on therapy, the dose should be reduced to 100 mg every 4 hours or discontinued (consult drug package insert for more details).

Intravenous: 1.5 mg per kg every 4 to 8 hours; lower dose if anemia develops.

The required length of therapy is unknown.

Ribavirin

Oral ribavirin has been used in patients with AIDS and AIDS-related complex. In an uncontrolled phase I trial, a daily dose of 600 mg of oral ribavirin was effective in eliminating HIV viremia and in improving the lymphoproliferative response. In the limited number of patients study, the drug was safe and transfusion was required in only 1 of 10 patients.[19b] Additional information on ribavirin was described earlier in this article.

Suramin

Suramin is a hexethal sodium salt derivative of naphthalene trisulfonic acid. It is an antiparasitic agent used against African trypanosomiasis and onchocerciasis.

Mechanism of Action and Pharmacokinetics. Suramin was found to inhibit reverse transcription. It binds to the template or primer binding sites of DNA synthesis and reverse transcriptase activity is reduced.

The drug is highly protein bound. The half-life is about 40 days. Suramin is not absorbed orally; is too painful when administered intramuscularly; so it is administered intravenously. It does not cross the blood-brain barrier. The drug is excreted in the urine.

Toxicity. Rare anaphylactoid reactions have been reported. Because of this, a 200 mg test dose by slow intravenous infusion should be given. Other adverse reactions are common and include fever, skin rash, proteinuria and elevated serum creatinine, increased serum glutamic-oxaloacetic transaminase, neutropenia and thrombocytopenia, adrenal insufficiency, and paresthesias.

Because of the high frequency and severity of side effects, suramin is unlikely to be studied further in the United States.

Clinical Trials. In three separate studies with AIDS and ARC patients, suramin was able to suppress HIV viremia but had no effect on reversing the immunological deficits and did not decrease morbidity.[11, 40, 49]

Dosage. All patients should receive a 200 mg test dose intravenously; then 1 g is given intravenously once a week. The length of therapy is undetermined and further study is unlikely.

HPA-23 (Antimoniotungstate)

HPA-23 is a mineral condensed polyanion active against many RNA and DNA viruses. It competitively inhibits reverse transcriptase. HPA-23 is administered by slow intravenous infusion. It has a short half-life. Its major toxicities are hepatitis and thrombocytopenia. Uncontrolled studies in France have demonstrated a small decrease in the viral titers of HIV but there has been no clear clinical or immunologic improvement.[65] HPA-23 appears to affect the HIV reverse transcriptase but its ability to prevent viral replication is doubtful.[5]

Phosphonoformic Acid

Spectrum and Mechanism of Action. Phosphonoformic acid (foscarnet, PFA) is a pyrophosphate analogue that has been studied as an agent against CMV, hepatitis B, herpes simplex virus, influenza A, and now HIV viruses. Its activity against viral DNA or RNA polymerase is significantly greater than against cellular polymerases.

Pharmacokinetics and Toxicities. Foscarnet is administered intravenously and is given continuously because of its short half-life. There is no metabolic conversion. Most of the drug rapidly is eliminated from soft tissues and excreted in the urine. Some of the drug is retained in the bone matrix, but not in the marrow. It may take months to disperse from the bone, but no bone marrow toxicity has been seen despite this accumulation. Penetration across the blood-brain barrier is controversial.

Clinical Indications. Foscarnet originally was seen as a promising agent for topical therapy against herpes simplex, but it is less effective than ACV and less effective than idoxuridine for herpes keratitis.

It has been used in Europe as an anti-HIV agent for AIDS or ARC patients.[67] Its significant nephrotoxicity, however, has precluded its use in the United States.

AL 721

AL 721 is an experimental lipid compound extracted from egg yolks. It inhibits HIV infectivity. The name indicates that it is an active lipid (AL) with a 7:2:1 ratio (721) of neutral glycerides, phosphatidylcholine, and phosphatidylethanolamine. It extracts cholesterol from the cell membrane and thereby weakens the viral structure that permits attachment of the virus to the human cell. Without viral attachment, entry into the cell is prevented. There are anecdotal reports of reduced levels of viremia and clinical improvement after administration of AL 721 to AIDS patients. No major toxicities or adverse effects have been described, but published reports of the experience with the drug are lacking.

Hybridons

Hybridons are oligonucleotides that are complementary sequences of portions of the HIV nucleic acid. Hybridons affect transcription or translation by competitively inhibiting the viral RNA or mRNA, the so-called "antisense RNA" approach. Clinical experience with this approach is limited.

Poly I-poly C (C12, U) or Ampligen is a mismatched double-strained RNA molecule that appears to have anti-HIV as well as immunomodulatory properties.

Combination Therapy

The use of a combination of two drugs that inhibit the same or different steps in the HIV replication cycle are being studied. Ideally, the effect of the two drugs should be synergistic or at least additive. We need to remember that an antagonistic effect from using two drugs also is possible and should be avoided.

Synergism has been shown between recombinant interferon alpha-A and AZT or foscarnet and between ribavirin and foscarnet.

Antagonism has been shown to occur in vitro between AZT and ribavirin. Ribavirin normally increases the formation of deoxythymidine triphosphate, which in turn inhibits host cell thymidine kinase (TK). This inhibition of thymidine kinase will prevent phosphorylation of AZT.[81]

2′,3′-Dideoxycytidine (DDC) (see Fig. 1), a newer HIV reverse transcriptase inhibitor, as well as other nucleoside analogues with similar metabolic pathways, also should be studied for antagonism when used in combination therapy. DDC appears to have the same clinical benefits as AZT with less toxicity.

Immunomodulators

In treating HIV infection, it is necessary to reverse the immunologic effects of the virus as well as kill it. Several agents are being studied as immunomodulators. They would be used as adjunct therapy to antiviral drugs. Some of the immunomodulator agents being studied include interleukin-2, interferon, isoprinosine, diethyldiothiocarbamate, thymic humoral factors, leukocyte derived immunomodulators (for example, IMREG1, IMREG2, and transfer factor), endogenous human cytokines (GM-CSF:

granulocyte-macrophage colony stimulating factor), naltrexon, and cyclosporin A.[24]

Interferons

Interferons are host derived polypeptide molecules with a broad spectrum of antiviral activity as well as several nonantiviral effects. They are released by cells in response to infection or other stimuli. They are species-specific. They induce a temporary antiviral state in uninfected cells and modulate host immune responses.

There are three classes of interferons: Alpha-interferon (IFN-α), formerly known as leukocyte interferon; beta-interferon (IFN-β), formerly known as fibroblast interferon; and gamma-interferon (IFN-γ), formerly known as immune interferon because it is produced by T lymphocytes. IFN-α and IFN-β are structurally related and are produced in response to viral infections or polyribonucleotide administration. IFN-γ is structurally different and is produced in response to a specific antigenic stimulus.[24]

Mechanism of Action. Interferons act by reversibly binding to a ganglioside and to a second specific cell surface receptor. Then through a series of intermediate metabolic steps, cytoplasmic enzymes (endonuclease, 2-5 oligoadenylate synthetase, and protein kinase) are activated. Finally, these enzymes inhibit transcription, translation, assembly, and release of virus.[80] Cells that do not possess interferon receptors are resistant to the drug. An antiviral state takes several hours to develop and may persist for days. Interferons have immunomodulating functions, including T-cell mediated cytotoxicity, natural killer cell activity, macrophage functions, and effects on antibody synthesis.[33]

Interferons do not kill viruses. They prevent viral reproduction by interfering with nucleic acid or protein synthesis. The advantage of these agents is that they are not virus-specific. They can be used effectively before the infecting virus is identified by culture or serology.

Pharmacokinetics. Interferons can be administered intravenously, intramuscularly, and intranasally. The half-life of IFN-α administered intravenously is 2 to 3 hours; intramuscularly, 3 to 8 hours; and intranasal, 20 minutes. IFN-α does not penetrate well into the cerebrospinal fluid. It is not removed by hemodialysis. Little is excreted in the urine and its metabolism is unknown.

Unlike IFN-α, IFN-β must be given intravenously to obtain therapeutic levels.

Toxicity and Adverse Reactions. Side effects after IFN-α injection occur 2 to 4 hours after administration. They include fever, headache, malaise, chills, and lymphopenia. Because they are reversible with cessation of therapy, many have thought that the flu-like symptoms associated with common respiratory infections are caused by the release of interferon from infected cells. Other toxicities include gastrointestinal disturbances, weight loss, local pain, fatigue, alopecia, paresthesias, confusion, and bone marrow suppression. The hematologic effects are dose-dependent and reversible. Tolerance can develop after several days.

Intranasal use generally is well tolerated. After 5 days of use, nasal congestion, sore throat, hoarseness, nasal burning, increased nasal secre-

tions, mucosal friability, bleeding, crusts, and erosions develop. After 1 month of IFN-α intranasal use, submucosal inflammatory cell infiltrates occur, but resolve on cessation of therapy.

No toxic effects have been seen when IFN-α or IFN-β are applied topically to the eye or vagina. Fever, fatigue, and cerebrospinal fluid pleocytosis have been seen with intrathecal use.

Clinical Indications. The antiviral use of interferons has been studied for treatment of "the common cold" (that is, rhinoviruses), urogenital warts, herpes simplex viruses, CMV, varicella zoster virus, hepatitis B, and papilloma, as well as for AIDS and other HIV-related infections.[79, 80]

In our study, intranasal IFN-α use decreased rhinovirus-induced nasal symptoms by 33 per cent and resulted in 41 per cent fewer episodes of respiratory illness. In another study, treated subjects exposed to rhinovirus had 76 per cent fewer symptomatic days and 86 per cent fewer illnesses than the placebo group.[22] In a further study, interferon helped control the spread of colds among family members.[34] Prophylactic use of interferon intranasally has been shown to shorten and reduce the severity of cold symptoms when challenged with a coronavirus.[78]

IFN-α given prophylactically by the subcutaneous route can suppress recurrent genital herpes simplex virus infections. There are a decreased number of recurrences, shorter duration of lesions, and milder symptoms. The beneficial effect of IFN-α depends on continued administration. Once the prodrome begins, IFN-α has no effect on the clinical course of recurrent herpes.[45]

IFN-α inhibits HIV replication in vitro.[37] Interferon is effective against anogenital warts caused by papilloma virus,[12] but infection with HIV seems to reduce the therapeutic response of anogenital warts to the drug.[21] There are abnormal levels or types of IFN in AIDS patients. In AIDS patients there is IFN inhibitory activity not seen in ARC or normal patients.[38] Patients with ARC have high titers of IFN in their serum compared with AIDS patients. High levels of IFN may defend against viral agents in ARC patients. It may be that AIDS patients have interferon inactivators. High interferon levels are needed for good therapeutic results in patients with Kaposi's sarcoma.

VIRUCIDAL TISSUE PAPER

Tissue paper handkerchiefs impregnated with virucidal compounds are being tested. Paper is treated with citric acid, malic acid, and sodium lauryl sulfate. These chemical compounds are virucidal for rhinoviruses. Because hand-to-hand transmission is a common way that rhinoviruses spread, the use of virucidal pleural tissues may be able to reduce significantly the transmission of these viruses that are the most common cause of the common cold.[37]

OTHER EXPERIMENTAL ANTIVIRAL AGENTS

Several other nucleoside analogues are being investigated, such as FIAC (2′fluoro-S-iodo-1-β-D-arabinofuranosylcytosine), tiazofuror, envirox-

ime, 3- deazaguanine, 3- deazaadenosine and non-nucleoside agents such as arildone, rifampin, and zinc.

Among the more intriguing new agents being studied are the WIN compounds. WIN 51711 and WIN 52084 are being tested against the picornaviruses, especially the rhinoviruses. The WIN compounds inhibit uncoating of the virus after it penetrates the host cell membrane.[35] A canyon or groove in the surface of rhinoviruses appears to be the binding site for these drugs, and these canyon sites are inaccessible to host antibodies. The theoretical advantage of the WIN compounds is clear: A single drug potentially could inhibit most rhinoviruses. Immunization against rhinoviruses is not a practical alternative at this time because there are too many viral strains and reinfection often occurs in the presence of antibody.

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