Antiviral Drugs

I. OVERVIEW

Viruses are obligate intracellular parasites. They lack both a cell wall and a cell membrane, and they do not carry out metabolic processes. Viral reproduction uses much of the host’s metabolic machinery, and few drugs are selective enough to prevent viral replication without injury to the host.

II. TREATMENT OF RESPIRATORY VIRUS INFECTIONS

Viral respiratory tract infections for which treatments exist include those of influenza A and B and respiratory syncytial virus (RSV).

A. Neuraminidase inhibitors

Orthomyxoviruses that cause influenza contain the enzyme neuraminidase, which is essential to the life cycle of the virus. Viral neuraminidase can be selectively inhibited by the sialic acid analogs, oseltamivir and zanamivir. Oseltamivir and zanamivir are effective against both Type A and Type B influenza viruses. They do not interfere with the immune response to influenza A vaccine. Administered prior to exposure, neuraminidase inhibitors prevent infection, and, when administered within the first 24 to 48 hours after the onset of infection, they have a modest effect on the intensity and duration of symptoms.

1. Mode of action: Oseltamivir and zanamivir are transition-state analogs of the sialic acid substrate and serve as inhibitors of the enzyme activity.

2. Pharmacokinetics: Oseltamivir is an orally active prodrug that is rapidly hydrolyzed by the liver to its active form. Zanamivir, on the other hand, is not active orally and is either inhaled or administered intranasally. Both drugs are eliminated unchanged in the urine.

3. Adverse effects: The most common side effects of oseltamivir are gastrointestinal (GI) discomfort and nausea. Zanamivir should be avoided in individuals with severe reactive asthma or chronic obstructive respiratory disease, because bronchospasm may occur with the risk of fatality.
4. Resistance: Mutations of the neuraminidase enzyme have been identified in adults treated with either of the neuraminidase inhibitors. These mutants, however, are often less infective and virulent than the wild type.

B. Inhibitors of viral uncoating

Amantadine and rimantadine, is limited to influenza A infections, for which the drugs have been shown to be equally effective in both treatment and prevention. For example, these drugs are 70 to 90 percent effective in preventing infection if treatment is begun at the time of, or prior to, exposure to the virus. Also, both drugs reduce the duration and severity of systemic symptoms if started within the first 48 hours after exposure to the virus.

1. Mode of action: The primary antiviral mechanism of amantadine and rimantadine is to block the viral membrane matrix protein, M2, which functions as a channel for hydrogen ions. This channel is required for the fusion of the viral membrane with the cell membrane that ultimately forms the endosome (created when the virus is internalized by endocytosis).

2. Pharmacokinetics: Both drugs are well absorbed orally. Amantadine distributes throughout the body and readily penetrates into the central nervous system (CNS), whereas rimantadine does not cross the blood-brain barrier. Rimantadine is extensively metabolized by the liver, and eliminated by the kidney.

3. Adverse effects: Minor neurologic symptoms include insomnia, dizziness, and ataxia. More serious side effects have been reported (for example, hallucinations and seizures). The drug should be employed cautiously in patients with psychiatric problems. Rimantadine causes fewer CNS reactions, because it does not efficiently cross the blood-brain barrier.

4. Resistance: Resistance can develop rapidly in up to 50 percent of treated individuals. Resistance has been shown to result from a change in one amino acid of the M2 matrix protein.

C. Ribavirin

Ribavirin is a synthetic guanosine analog. Ribavirin is used in treating infants and young children with severe RSV infections. [Note: It is not indicated for use in adults with
Ribavirin is also effective in chronic hepatitis C infections when used in combination with interferon-α. Ribavirin may reduce the mortality and viremia of Lassa fever.

1. Mode of action: Ribavirin-triphosphate, which exerts its antiviral action by inhibiting guanosine triphosphate formation, preventing viral messenger RNA (mRNA) capping, and blocking RNA-dependent RNA polymerase.

2. Pharmacokinetics: Ribavirin is effective orally and intravenously. Absorption is increased if the drug is taken with a fatty meal. An aerosol is used in certain respiratory viral conditions such as the treatment of RSV infection.

3. Adverse effects: Side effects reported for oral or parenteral use of ribavirin have included dose-dependent transient anemia. Elevated bilirubin has been reported. The aerosol may be safer, although respiratory function in infants can deteriorate quickly after initiation of aerosol treatment.

III. TREATMENT OF HEPATIC VIRAL INFECTIONS

The hepatitis viruses thus far identified (A, B, C, D, and E) each have a pathogenesis specifically involving replication in and destruction of hepatocytes. Of this group, hepatitis B and hepatitis C are the most common causes of chronic hepatitis, cirrhosis, and hepatocellular carcinoma. Chronic hepatitis B may be treated with peginterferonα-2a, which is injected subcutaneously once weekly. [Note: Interferon-α2b injected intramuscularly or subcutaneously three times weekly is also useful in the treatment of hepatitis B, but peginterferon-α-2a has similar or slightly better efficacy.] Oral therapy includes lamivudine, adefovir, entecavir, tenofovir, or telbivudine. In the treatment of chronic hepatitis C, the preferred treatment is the combination of peginterferon-α-2a or peginterferon-α-2b plus ribavirin.

A. Interferon

Interferon is a family of naturally occurring, inducible glycoproteins that interfere with the ability of viruses to infect cells. The interferons are synthesized by recombinant DNA technology. At least three types of interferons exist, α, β, and γ. One of the 15 interferon-α glycoproteins, interferon-α-2b, has been approved for treatment of hepatitis B and C, condylomata acuminata, and cancers such as hairycell leukemia and Kaposi sarcoma. Interferon-β has some effectiveness in the treatment of multiple sclerosis. In so-called
“pegylated” formulations. The larger molecular size delays absorption from the injection site, lengthens the duration of action of the drug, and also decreases its clearance.

1. **Mode of action:** It appears to involve the induction of host cell enzymes that inhibit viral RNA translation, ultimately leading to the degradation of viral mRNA and tRNA.

2. **Pharmacokinetics:** Interferon is not active orally, but it may be administered intraleSIONALLY, subcutaneously, or intravenously. Very little active compound is found in the plasma, and its presence is not correlated with clinical responses. Cellular uptake and metabolism by the liver and kidney account for the disappearance of interferon from the plasma. Negligible renal elimination occurs.

3. **Adverse effects:** Adverse effects include flu-like symptoms on injection, such as fever, chills, myalgias, arthralgias, and GI disturbances. Fatigue and mental depression are common. These symptoms subside with subsequent administrations. The principal dose-limiting toxicities are bone marrow suppression including granulocyto­penia; cneurotoxicity characterized by somnolence and behavioral disturbances; severe fatigue and weight loss; autoimmune disorders such as thyroiditis; and, rarely, cardiovascular problems such as congestive heart failure. Acute hypersensitivity reactions and hepatic failure are rare.

4. **Drug interactions:** Interferon interferes with hepatic drug metabolism, and toxic accumulations of theophylline have been reported. Interferon may also potentiate the myelosuppression caused by other bone marrow–depressing agents such as zidovudine.

**B. Lamivudine**

This cytosine analog is an inhibitor of both hepatitis B virus (HBV) DNA polymerase and human immunodeficiency virus (HIV) reverse transcriptase. Lamivudine must be phosphorylated by host cellular enzymes to the triphosphate (active) form. This compound competitively inhibits HBV DNA polymerase at concentrations that have negligible effects on host DNA polymerase. Lamivudine is well absorbed orally and is widely distributed. Its plasma half-life is about 9 hours. Seventy percent is excreted unchanged in urine.

**C. Adefovir**
Adefovir dipivoxil is a nucleotide analog that is phosphorylated to adefovir diphosphate, which is then incorporated into viral DNA. This leads to termination of further DNA synthesis and prevents viral replication. Adefovir is administered once a day and is excreted in urine, with 45 percent as the active compound. Clearance is influenced by renal function. Both decreased viral load and improved liver function have occurred in patients treated with adefovir. As with other agents, discontinuation of adefovir results in severe exacerbation of hepatitis in about 25 percent of patients. The drug should be used cautiously in patients with existing renal dysfunction.

D. Entecavir

Entecavir is a guanosine analog approved for the treatment of HBV infections. Following intracellular phosphorylation to the triphosphate, it competes with the natural substrate, deoxyguanosine triphosphate, for viral reverse transcriptase. Entecavir has been shown to be effective against lamivudine-resistant strains of HBV. Liver inflammation and scarring are improved. Entecavir need only be given once a day.

E. Telbivudine

Telbivudine is a thymidine analog that can be used in the treatment of HBV. Unlike lamivudine and adefovir, telbivudine is not active against HIV or other viruses. The drug is phosphorylated intracellularly to the triphosphate. The drug is administered orally, once a day, with or without food. Telbivudine is eliminated by glomerular filtration as the unchanged drug, and no metabolites have been detected. The dose must be adjusted in renal failure.

F. Tenofovir

IV. TREATMENT OF HERPESVIRUS INFECTIONS

A. Acyclovir

Acyclovir (acycloguanosine) is the prototypic antiherpetic therapeutic agent. It has a greater specificity than vidarabine against herpesviruses. Herpes simplex virus (HSV) Types 1 and 2, varicella-zoster virus (VZV), and some Epstein-Barr virus–mediated infections are sensitive to acyclovir. It is the treatment of choice in HSV encephalitis. The most common use of acyclovir is in therapy for genital herpes infections. It is also given prophylactically before bone marrow and after heart transplants.
1. Mode of action: Acyclovir triphosphate competes with deoxyguanosine triphosphate as a substrate for viral DNA polymerase and is itself incorporated into the viral DNA, causing premature DNA-chain termination. The drug is less effective against the host enzyme.

2. Pharmacokinetics: Administration of acyclovir can be by an intravenous (IV), oral, or topical route. The drug distributes well throughout the body, including the cerebrospinal fluid (CSF). Acyclovir is partially metabolized to an inactive product. Excretion into the urine occurs both by glomerular filtration and by tubular secretion. Acyclovir accumulates in patients with renal failure.

3. Adverse effects: Side effects of acyclovir treatment depend on the route of administration. For example, local irritation may occur from topical application; headache, diarrhea, nausea, and vomiting may result after oral administration. Transient renal dysfunction may occur at high doses or in a dehydrated patient receiving the drug IV. High-dose valacyclovir can cause GI problems and thrombotic thrombocytopenic purpura in patients with AIDS.

4. Resistance: Altered or deficient thymidine kinase and DNA polymerases have been found in some resistant viral strains and are most commonly isolated from immunocompromised patients.

B. Cidofovir

Cidofovir is approved for treatment of CMV-induced retinitis in patients with AIDS. Cidofovir is a nucleotide analog of cytosine, the phosphorylation of which is not dependent on viral enzymes. It inhibits viral DNA synthesis. Cidofovir is available for IV, intravitreal (injection into the eye’s vitreous humor between the lens and the retina), and topical administration. Cidofovir produces significant toxicity to the kidney, and it is contraindicated in patients with preexisting renal impairment. Neutropenia, metabolic acidosis, and ocular hypotony also occur. Probenecid must be co-administered with cidofovir to reduce the risk of nephrotoxicity. Since the introduction of HAART (highly active antiretroviral therapy), the prevalence of CMV infections in immunocompromised hosts has markedly declined, and the importance of cidofovir in the treatment of these patients has also diminished.

C. Fomivirsen
Fomivirsen is oligonucleotide directed against CMV mRNA. Its use is limited to those who cannot tolerate or have failed other therapies for CMV retinitis. The drug is administered intravitreally. The common adverse effects include iritis, vitritis, and changes in vision.

D. Foscarnet

E. Ganciclovir

Ganciclovir is an analog of acyclovir that has 8 to 20 times greater activity against CMV, which is the only viral infection for which it is approved. It is currently available for treatment of CMV retinitis in immunocompromised patients and for CMV prophylaxis in transplant patients.

1. Mode of action: Like acyclovir, ganciclovir is activated through conversion to the nucleoside triphosphate. The nucleotide competitively inhibits viral DNA polymerase and can be incorporated into the DNA, thereby decreasing the rate of chain elongation.

2. Pharmacokinetics: Ganciclovir is administered IV and distributes throughout the body, including the CSF. Excretion into the urine occurs through glomerular filtration and tubular secretion. Valganciclovir, like valacyclovir, valganciclovir has high oral bioavailability, because rapid hydrolysis in the intestine and liver after oral administration leads to high levels of ganciclovir.

3. Adverse effects: Adverse effects include severe, dose-dependent neutropenia. Ganciclovir is carcinogenic as well as embryotoxic and teratogenic in experimental animals.

4. Resistance: Resistant CMV strains have been detected that have lower levels of ganciclovir triphosphate.

F. Penciclovir and famciclovir

Penciclovir is active against HSV-1, HSV-2, and VZV. Penciclovir is only administered topically. It is monophosphorylated by viral thymidine kinase, and cellular enzymes form the nucleoside triphosphate, which inhibits HSV DNA polymerase. Penciclovir triphosphate has an intracellular half-life 20 to 30-fold longer than does acyclovir triphosphate. Famciclovir, is a prodrug that is metabolized to the active penciclovir. The antiviral spectrum is similar to that of ganciclovir, but it is presently approved only for
treatment of acute herpes zoster. The drug is effective orally. Adverse effects include headaches and nausea. Studies in experimental animals have shown an increased incidence of mammary adenocarcinomas and testicular toxicity.

G. Vidarabine (ara-A)

Vidarabine is active against HSV-1, HSV-2, and VZV, its use is limited to treatment of immunocompromised patients with herpetic and vaccinial keratitis and in HSV keratoconjunctivitis. [Note: Vidarabine is only available as an ophthalmic ointment.] Vidarabine, an adenosine analog, is converted in the cell to its 5’-triphosphate analog, which is postulated to inhibit viral DNA synthesis. Some resistant HSV mutants have been detected that have altered polymerase.

H. Trifluridine

Trifluridine is a fluorinated pyrimidine nucleoside analog. It is structurally very similar to thymidine. Trifluridine is active against HSV-1, HSV-2, and vaccinia virus. It is generally considered to be the drug of choice for treatment of HSV keratoconjunctivitis and recurrent epithelial keratitis. Because the triphosphate form of trifluridine can also incorporate to some degree into cellular DNA, the drug is considered to be too toxic for systemic use. Therefore, the use of trifluridine is restricted to topical application as a solution to the eye. A short half-life of approximately 12 minutes necessitates that the drug be applied frequently. Side effects include a transient irritation of the eye and palpebral (eyelid) edema.

V. OVERVIEW OF THE TREATMENT FOR HIV INFECTION

Prior to approval of zidovudine in 1987, treatment of HIV infections focused on decreasing the occurrence of opportunistic infections that caused a high degree of morbidity and mortality in AIDS patients rather than on inhibiting HIV itself. Today, the viral life cycle is understood, and a highly active regimen is employed that uses combinations of drugs to suppress replication of HIV and restore the number of CD4+ cells and immunocompetence to the host. This multidrug regimen is commonly referred to as “highly active antiretroviral therapy,” or HAART. There are five classes of antiretroviral drugs, each of which targets one of four viral processes. These classes of drugs are nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, entry
inhibitors, and the integrase inhibitors. The current recommendation for primary therapy is to administer two NRTIs with either a protease inhibitor, an NNRTI, or an integrase inhibitor. Selection of the appropriate combination is based on 1) avoiding the use of two agents of the same nucleoside analog; 2) avoiding overlapping toxicities and genotypic and phenotypic characteristics of the virus; 3) patient factors, such as disease symptoms and concurrent illnesses; 4) impact of drug interactions; and 5) ease of adherence to a frequently complex administration regimen. The goals of therapy are to maximally and durably suppress viral load replication, to restore and preserve immunologic function, to reduce HIV-related morbidity and mortality, and to improve quality of life.