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. Therapy for viral diseases is further complicated by the fact that the clinical symptoms appear late in the course of the disease, at a time when most of the virus particles have replicated. [Note: This contrasts with bacterial diseases, in which the clinical symptoms are usually coin- cident with bacterial proliferation.] At this late, symptomatic stage of the viral infection, administration of drugs that block viral replication has lim- ited effectiveness. However, some antiviral agents are useful as prophy- lactic agents. Only a few virus groups, including those that cause the viral infections discussed in this chapter, respond to available antiviral drugs. To assist in the review of these drugs, they are grouped according to the affected organisms (Figure 38.1).

**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). [Note: Immunization against influenza A is the preferred approach. However, antiviral agents are used when patients are allergic to the vaccine, when the outbreak is due to an immunologic variant of the virus not covered by vaccines (for example, H1N1), or when outbreaks occur among unvaccinated individuals who are at risk and in closed settings (for example, in nursing homes).]

1. **Neuraminidase inhibitors**

Orthomyxoviruses that cause influenza contain the enzyme neura- minidase, which is essential to the life cycle of the virus. Viral neura- minidase can be selectively inhibited by the sialic acid analogs, oseltamivir [os-el-TAM-i-veer] and zanamivir [za-NA-mi-veer]. These drugs prevent the release of new virions and their spread from cell to cell. Unlike the adamantane analogs discussed below, 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, neura minidase 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 symptom

1. **Mode of action**: Influenza viruses employ a specific neura minidase that is inserted into the host cell membrane for the purpose of releasing newly formed virions. 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 (Figure 38.2).
3. **Adverse effects**: The most common side effects of oseltamivir are gastrointestinal (GI) discomfort and nausea, which can be alleviated by taking the drug with food. Zanamivir is not associated with GI disturbance, because it is administered directly to the airways. Irritation of the respiratory tract does occur, however. Zanamivir should be avoided in individuals with severe reactive asthma or chronic obstructive respiratory disease, because bronchospasm may occur with the risk of fatality. Neither drug has been reported to have clinically significant drug interactions.
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.
5. **Inhibitors of viral uncoating**

The therapeutic spectrum of the adamantane derivatives, amantadine [a-MAN-ta-deen] and rimantadine [ri-MAN-ta-deen], 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 with- in the fi rst 48 hours after exposure to the virus (Figure 38.3). Neither impairs the immune response to influenza A vaccine, and either can be administered as a supplement to vaccination, thus providing protection until antibody response occurs (usually 2 weeks in healthy adults). Treatment is particularly useful in high-risk patients who have not been vaccinated and during epidemics. [Note: Amantadine is also eff ective in the treatment of some cases of Parkinson disease.]

 **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 mem- brane that ultimately forms the endosome (created when the virus is internalized by endocytosis). [Note: The acidic environment of the endosome is required for viral uncoating.] These drugs may also interfere with the release of new virions.

**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 to the same extent. Amantadine is not extensively metabolized. It is excreted into the urine and may accumulate to toxic levels in patients with renal failure. On the other hand, rimantadine is extensively metabolized by the liver, and both the metabolites and the parent drug are eliminated by the kidney (Figure 38.4).

**3. Adverse effects**: The side effects of amantadine are mainly associated with the CNS. 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, cerebral atherosclerosis, renal impairment, or epilepsy. Rimantadine causes fewer CNS reactions, because it does not efficiently cross the blood-brain barrier. Both drugs cause GI intolerance. Amantadine and rimantadine should be used with caution in pregnant and nursing mothers, because they have been found to be embryotoxic and teratogenic in rats.

 **4. Resistance**: Resistance can develop rapidly in up to 50 percent of treated individuals, and resistant strains can be readily transmit- ted to close contacts. Resistance has been shown to result from a change in one amino acid of the M2 matrix protein. Cross-resistance occurs between the two drugs.

 **C. Ribavirin**

Ribavirin [rye-ba-VYE-rin] is a synthetic guanosine analog. It is effective against a broad spectrum of RNA and DNA viruses. For example, ribavirin is used in treating infants and young children with severe RSV infections. [Note: It is not indicated for use in adults with RSV.] 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:** The mode of action of ribavirin has been studied only for the influenza viruses. The drug is first converted to the 5’-phosphate derivatives, the major product being the compound ribavirin-triphosphate, which exerts its antiviral action by inhibiting guanosine triphosphate formation, preventing viral messenger RNA (mRNA) capping, and blocking RNA-dependent RNA polymerase. [Note: Rhinoviruses and enteroviruses, which contain preformed mRNA and do not need to synthesize mRNA in the host cell to initiate an infection, are relatively resistant to the action of ribavirin.]

**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. Studies of drug distribution in primates have shown retention in all tissues, except brain. The drug and its metabolites are eliminated in urine (Figure 38.5).

**3. Adverse effect**s: 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. Therefore, monitoring is essential. Because of teratogenic effects in experimental animals, ribavirin is contraindicated in pregnancy (Figure 38.6).

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 (Figure 38.7) and are the only hepatic viral infections for which therapy is currently avail- able. [Note: Hepatitis A is a commonly encountered infection, but it is not a chronic disease.] Chronic hepatitis B may be treated with peginterferon- α-2a, which is injected subcutaneously once weekly. [Note: Interferon-α- 2b injected intramuscularly or subcutaneously three times weekly is also useful in the treatment of hepatitis B, but peginteferon-α-2a has similar or slightly better efficacy.] Oral therapy includes lamivudine, adefovir, entecavir, tenofovir, or telbivudine. Combination therapy of an interferon plus lamivu- dine is no more effective than monotherapy with lamivudine. Patients with acquired immunodeficiency syndrome (AIDS) who are co-infected with hepatitis B are usually poor responders to interferon therapy. In the treatment of chronic hepatitis C, the preferred treatment is the combination of peginterferon-α-2a or peginterferon-α-2b plus ribavirin, which is more effective than the combination of standard interferons and ribavirin.

1. **Interferon**

Interferon [in-ter-FEER-on] is a family of naturally occurring, inducible glycoproteins that interfere with the ability of viruses to infect cells. Although interferon inhibits the growth of many viruses in vitro, its activity in vivo against viruses has been disappointing. The interferons are synthesized by recombinant DNA technology. At least three types of interferons exist, α, β, and γ (Figure 38.8). 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 hairy- cell leukemia and Kaposi sarcoma. Interferon-β has some effectiveness in the treatment of multiple sclerosis. In so-called “pegylated” formu- lations, bis-monomethoxy polyethylene glycol has been covalently attached to either interferon-α-2a or -α-2b to increase the size of the molecule. 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**: The antiviral mechanism is incompletely under- stood. 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 sub- side with subsequent administrations. The principal dose-limiting toxicities are bone marrow suppression including granulocytopenia; neurotoxicity characterized by somnolence and behavioural 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 [la-MI-vyoo-deen] 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. As with many nucle- otide analogs, the intracellular half-life of the triphosphate is many hours longer than its plasma half-life. Chronic treatment is associated with decreased plasma HBV DNA levels, improved biochemical markers, and reduced hepatic inflammation. Lamivudine is well absorbed orally and is widely distributed. Its plasma half-life is about 9 hours. Seventy percent is excreted unchanged in urine. Dose reductions are necessary when there is moderate renal insufficiency (creatinine clearance less than 50 mL/min). Lamivudine is well tolerated, with rare occurrences of headache and dizziness.

1. **Adefovir**

Adefovir dipivoxil [ah-DEH-for-veer die-pih-VOCKS-ill] 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. Adefovir does not seem to have significant drug interactions. The drug should be used cautiously in patients with existing renal dysfunction.

1. **Entecavir**

Entecavir [en-TECK-ah-veer] is a guanosine analog approved for the treatment of HBV infections. Following intracellular phosphorylation to the triphosphate, it competes with the natural substrate, deoxyguanos- ine 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. Entecavir undergoes both glomerular filtration and tubular secretion. Very little, if any, drug is metabolized. Renal function must be assessed periodically, and drugs that have renal toxicity should be avoided. Patients should be monitored closely for several months after discontinuation of therapy because of the possibility of severe hepatitis.

1. **Telbivudine**

Telbivudine [tel-BIV-yoo-dine] 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 intra- cellularly to the triphosphate, which can either compete with endogenous thymidine triphosphate for incorporation into DNA or else be incorporated into viral DNA, where it serves to terminate further elongation of the DNA chain. 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. The combination of telbivudine with lamivudine has been no more effective than telbivudine alone. F. Tenofovir (See HIV section.)

IV. TREATMENT OF HERPESVIRUS INFECTIONS

Herpes viruses are associated with a broad spectrum of diseases, for exam- ple, cold sores, viral encephalitis, and genital infections (the latter being a hazard to the new born during parturition). The drugs that are effective against these viruses exert their actions during the acute phase of viral infections and are without effect during the latent phase. Except for foscarnet and fomivirsen, all are purine or pyrimidine analogs that inhibit viral DNA synthesis.

1. **Acyclovir**

Acyclovir [ay-SYE-kloe-ver] (acycloguanosine) is the prototypic anti- herpetic therapeutic agent. It has a greater specifi city than vidarabine against herpesviruses. Herpes simplex virus (HSV) Types 1 and 2, varicel- la-zoster virus (VZV), and some Epstein-Barr virus–mediated infections are sensitive to acyclovir. It is the treatment of choice in HSV encephalitis and is more efficacious than vidarabine at increasing the rate of survival. The most common use of acyclovir is in therapy for genital her- pes infections. It is also given prophylactically to seropositive patients before bone marrow and after heart transplants to protect such indi- viduals during posttransplant immunosuppressive treatments.

 **1. Mode of action**: Acyclovir, a guanosine analog that lacks a true sugar moiety, is monophosphorylated in the cell by the herpes virus–encoded enzyme, thymidine kinase (Figure 38.9). Therefore, virus-infected cells are most susceptible. The monophosphate ana- log is converted to the di- and triphosphate forms by the host cells. Acyclovir triphosphate competes with deoxyguanosine triphosphate as a substrate for viral DNA polymerase and is itself incorpo- rated into the viral DNA, causing premature DNA-chain termination (see Figure 38.9). Irreversible binding of the acyclovir-containing template primer to viral DNA polymerase inactivates the enzyme. The drug is less effective against the host enzyme.

**2. Pharmacokinetics**: Administration of acyclovir can be by an intra- venous (IV), oral, or topical route. [Note: The efficacy of topical applications is doubtful.] 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 fi ltration and by tubular secretion (Figure 38.10). Acyclovir accumulates in patients with renal failure. The valyl ester, valacyclovir [val-a-SYE-kloe-veer], has greater oral bioavailability than acyclovir. This ester is rapidly hydrolyzed to acyclovir and achieves levels of the latter comparable to those from IV acyclovir administration.

**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. Cross-resistance to the other agents in this family occurs. [Note: Cytomegalovirus (CMV) is resistant, because it lacks a specific viral thymidine kinase.]

 **B. Cidofovir**

Cidofovir [si-DOE-foe-veer] is approved for treatment of CMV-induced retinitis in patients with AIDS. Cidofovir is a nucleotide analogue of cytosine, the phosphorylation of which is not dependent on viral enzymes. It inhibits viral DNA synthesis. Slow elimination of the active intracellular metabolite permits prolonged dosage intervals and eliminates the permanent venous access used for ganciclovir therapy. 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 (Figure 38.11), and it is con- traindicated in patients with preexisting renal impairment and in those who are taking concurrent nephrotoxic drugs, including nonsteroidal anti-inflammatory drugs. Neutropenia, metabolic acidosis, and ocular hypotony also occur. Probenecid must be co-administered with cidofovir to reduce the risk of nephrotoxicity, but probenecid itself causes rash, headache, fever, and nausea. Since the introduction of HAART (highly active antiretroviral therapy), the prevalence of CMV infections in im- munocompromised hosts has markedly declined, and the importance of cidofovir in the treatment of these patients has also diminished.

**C.Fomivirsen**

Fomivirsen [foe-MI-veer-sen] is an antisense oligonucleotide directed against CMV mRNA. Its use is limited to those who cannot tolerate or have failed other therapies for CMV retinitis. A 2 to 4-week hiatus after discontinuing cidofovir is desirable to reduce toxicity. The drug is administered intravitreally. The common adverse effects include iritis, vitritis, and changes in vision.

**D. Foscarnet**

 Unlike most of the antiviral agents, foscarnet [fos-KAR-net] is not a purine or pyrimidine analog. Instead, it is a phosphonoformate (a pyrophos- phate derivative) and does not require activation by viral (or human) kinases. Foscarnet has broad in vitro antiviral activity. It is approved for CMV retinitis in immunocompromised hosts and for acyclovir-resistant HSV and herpes zoster infections. Foscarnet works by reversibly inhibiting viral DNA and RNA polymerases, thereby interfering with viral DNA and RNA synthesis. Mutation of the polymerase structure is responsible for resistant viruses. [Note: Cross-resistance between foscarnet and ganciclovir or acyclovir is uncommon.] Foscarnet is poorly absorbed orally and must be injected IV. It must also be given frequently to avoid relapse when plasma levels fall. It is dispersed throughout the body, and greater than 10 percent enters the bone matrix, from which it slow- ly leaves. The parent drug is eliminated by glomerular filtration and tubular secretion into the urine (Figure 38.12). Adverse effects include nephrotoxicity, anemia, nausea, and fever. Due to chelation with diva- lent cations, hypocalcemia and hypomagnesemia are also seen. In addition, hypokalemia, hypo- and hyperphosphatemia, seizures, and arrhythmias have been reported.

**E.Ganciclovir**

Ganciclovir [gan-SYE-kloe-veer] 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 con- version to the nucleoside triphosphate by viral and cellular enzymes, with the actual pathway depending on the virus. CMV is deficient in thymidine kinase and, therefore, forms the triphosphate by another route. 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 fi ltration and tubular secretion (Figure 38.13). Like acyclovir, ganciclovir accumulates in patients with renal failure. Valganciclovir [val-gan-SYE-kloe-veer] is the valyl ester of ganciclovir. Like valacyclovir, valganciclovir has high oral bioavail- ability, 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. [Note: Combined treatment with zidovudine, azathioprine, or mycophenolate mofetil can result in additive 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 [pen-SYE-kloe-veer] is an acyclic guanosine nucleoside derivative that is active against HSV-1, HSV-2, and VZV. Penciclovir is only administered topically (Figure 38.14). It is monophosphorylated by viral thymidine kinase, and cellular enzymes form the nucleoside triphosphate, which inhibits HSV DNA polymerase. Penciclovir triphos- phate has an intracellular half-life 20 to 30-fold longer than does acy- clovir triphosphate. Penciclovir is negligibly absorbed upon topical application and is well tolerated. Both pain and healing are shortened by approximately half a day in duration compared to placebo-treated subjects. Famciclovir [fam-SYE-kloe-veer], another acyclic analog of 2’-deoxyguanosine, is a prodrug that is metabolized to the active pen- ciclovir. 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 (see Figure 38.14). 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 [vye-DARE-a-been] (arabinofuranosyl adenine, ara-A, ade- nine arabinoside) is one of the most effective of the nucleoside ana- logs. However, it has been supplanted clinically by acyclovir, which is more efficacious and safe. Although 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 keratocon- junctivitis. [Note: Vidarabine is only available as an ophthalmic oint- ment.] Vidarabine, an adenosine analog, is converted in the cell to its 5’-triphosphate analog (ara-ATP), which is postulated to inhibit viral DNA synthesis. Some resistant HSV mutants have been detected that have altered polymerase.