50 Antiviral Drugs

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DRUG LIST

VIRAL INFECTION AND DISEASE

Viruses are obligate intracellular parasites that use many of the host cell's biochemical mechanisms and products to sustain their viability. A mature virus (virion) can exist outside a host cell and still retain its infective properties. However, *to reproduce, the virus must enter the host cell, take over the host cell's mechanisms for nucleic acid and protein synthesis, and direct the host cell to make new viral particles.*

Classification of Viruses

Viruses are composed of one or more strands of a nucleic acid (core) enclosed by a protein coat (capsid). Many viruses possess an outer envelope of protein or lipoprotein. Viral cores can contain either DNA or RNA; thus, viruses may be classified as DNA viruses or RNA viruses. Further classification is usually based on morphology, cellular site of viral multiplication, or other characteristics.

Examples of DNA viruses and the diseases that they produce include adenoviruses (colds, conjunctivitis); hepadnaviruses (hepatitis B); herpesviruses (cytomegalovirus, chickenpox, shingles); papillomaviruses (warts); and poxviruses (smallpox). Pathogenic RNA viruses include arborviruses (tick-borne encephalitis, yellow fever); arenaviruses (Lassa fever, meningitis); orthomyxoviruses (influenza); paramyxoviruses (measles, mumps); picornaviruses (polio, meningitis, colds); rhabdoviruses (rabies); rubella virus (German measles); and retroviruses (AIDS).

Viral Replication

Although the specific details of replication vary among types of viruses, the overall process can be described as consisting of five phases: (1) attachment and penetration, (2) uncoating, (3) synthesis of viral components, (4) assembly of virus particles, and (5) release of the virus. An overview of the viral replication cycle is shown in Figure 50.1.

Infection begins when specific receptor sites on the virus recognize corresponding surface proteins on the host cell. The virus penetrates the host membrane by a mechanism resembling endocytosis and is encapsulated

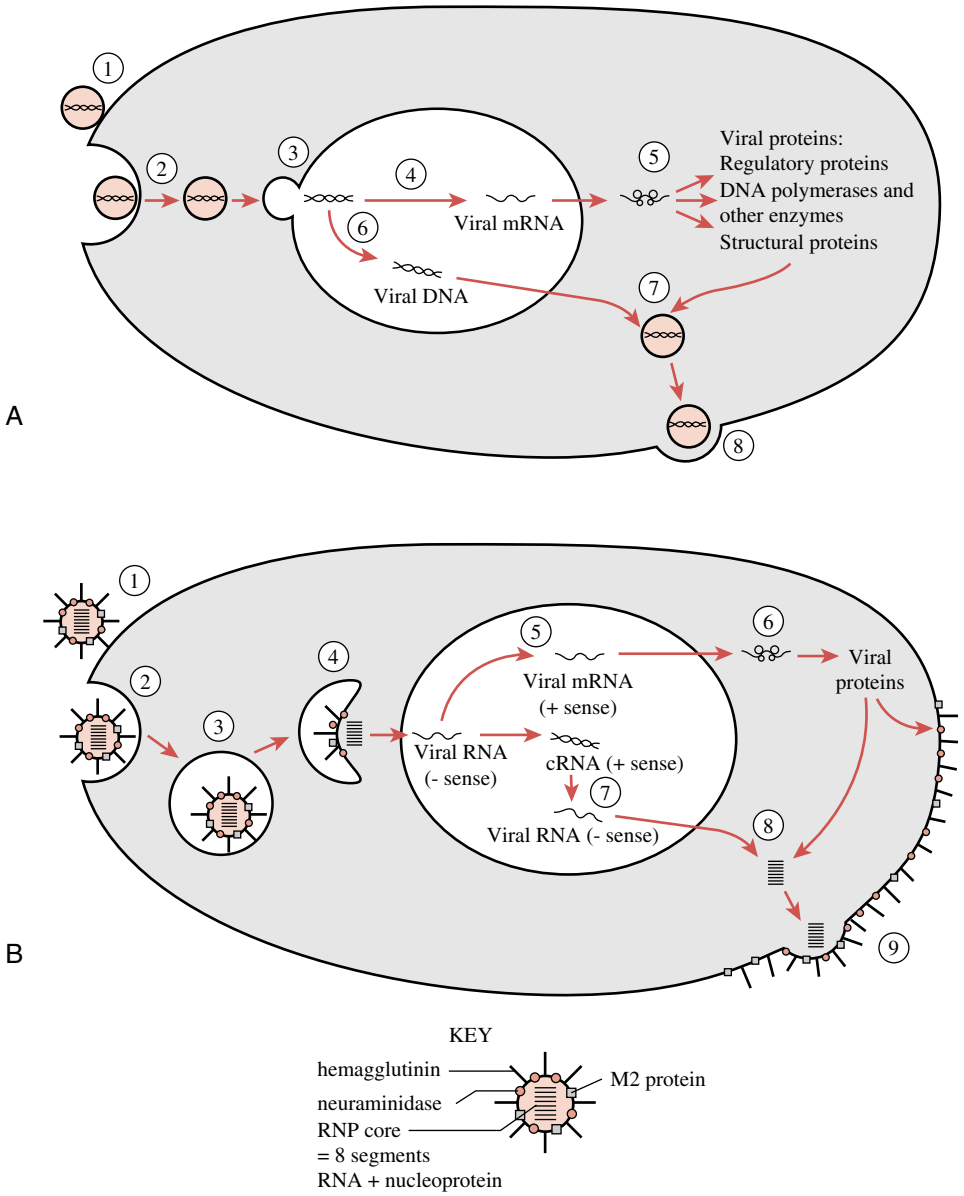

FIGURE 50.1

Replicative cycles of representative DNA and RNA viruses. **A.** Replicative cycle of a herpesvirus, an example of a DNA virus. *1.* Attachment. *2.* Membrane fusion. *3.* Release of viral DNA through nuclear pores. *4.* Transcription of viral mRNA. *5.* Synthesis of viral proteins by host cell's ribosomes. *6.* Replication of viral DNA by viral polymerases. *7.* Assembly of virus particles. *8.* Budding and release of progeny virus. **B.** Replicative cycle of an influenza virus, an example of an RNA virus. *1.* Attachment. *2.* Endocytosis. *3.* Influx of H^+ through M2 protein. *4.* Fusion of the viral envelope with the endosomes membrane, dissociation of the RNP complex, and entry of viral RNA into the nucleus. *5.* Synthesis of viral mRNA by viral RNA polymerase. *6.* Translation of viral mRNA by host cell's ribosomes. *7.* Replication of viral RNA, using viral RNA polymerase, via cRNA replicative form. *8.* Assembly of virus particles. and *9.* Budding and release of progeny virus.

by the host cell's cytoplasm, forming a vacuole. Next, the protein coat dissociates and releases the viral genome, usually into the host cell's nucleus.

Following the release of its genome, the virus synthesizes nucleic acids and proteins in sequence. In DNA viruses, the first genes to be transcribed are the immediate–early genes. These genes code for regulatory proteins that in turn initiate the transcription of the early genes responsible for viral genome replication. After the viral DNA is replicated, the late genes are transcribed and translated, producing proteins required for the assembly of the new virions. RNA viruses have several major strategies for genome replication and protein expression. Certain RNA viruses contain enzymes that synthesize messenger RNA (mRNA) using their RNA as a template; others use their own RNA as mRNA. The retroviruses use viral reverse transcriptase enzymes to produce DNA using viral RNA as a template. The newly synthesized DNA integrates into the host genome and is transcribed into mRNA and genomic RNA for progeny virions.

Following their production, the viral components are assembled to form a mature virus particle. The viral genome is encapsulated by viral protein; in some cases (e.g. adenovirus, poliovirus), it is not encapsulated. In certain viruses, such as the poxviruses, multiple membranes surround the capsid. Release of the virus from the host cell may be rapid and produce cell lysis and death. A slower process resembling budding may allow the host cell to survive.

Overview of Antiviral Therapy

Three basic approaches are used to control viral diseases: vaccination, antiviral chemotherapy, and stimulation of host resistance mechanisms. Vaccination has been used successfully to prevent measles, rubella, mumps, poliomyelitis, yellow fever, smallpox, chickenpox, and hepatitis B. Unfortunately, the usefulness of vaccines appears to be limited when many stereotypes are involved (e.g., rhinoviruses, HIV). Furthermore, vaccines have little or no use once the infection has been established because they cannot prevent the spread of active infections within the host. Passive immunization with human immune globulin, equine antiserum, or antiserum from vaccinated humans can be used to assist the body's own defense mechanisms. Intramuscular preparations of immune globulin may be used to prevent infection following viral exposure and as replacement therapy in individuals with antibody deficiencies. Peak plasma concentrations of intramuscular immune globulins occur in about 2 days. In contrast, intravenously administered immune globulin provides immediate passive immunity.

The chemotherapy of viral infections may involve interference with any or all of the steps in the viral replication cycle. *Because viral replication and host cell processes are so intimately linked, the main problem in the chemotherapy of viruses is finding a drug that is selectively toxic to the virus.* Stimulation of host resistance is the least used of the antiviral intervention strategies.

This chapter focuses on agents used to combat nonretroviral infections. Detailed information on drugs used to treat HIV is found in Chapter 51.

ANTIHERPESVIRUS AGENTS

The following drugs are used primarily in the treatment of herpesviruses. Among these are herpes simplex virus–1 (HSV-1), which typically causes herpes labialis (cold sores) or herpes esophagitis; herpes simplex virus–2 (HSV-2), which is responsible for most cases of genital herpes; varicella zoster virus (VZV), which produces chickenpox and shingles; Epstein-Barr virus (EBV), which is the major cause of infectious mononucleosis; and cytomegalovirus (CMV), which can produce pneumonia, gastroenteritis, retinitis, encephalitis, and mononucleosis in immunocompromised individuals.

Acyclovir and Valacyclovir

Acyclovir (*Zovirax*) is a guanine nucleoside analogue most effective against HSV-1 and HSV-2, but it has some activity against VCV, CMV, and EBV. Valacyclovir (*Valtrex*) is the L-valine ester prodrug of acyclovir. Acyclovir is converted to its active metabolite via three phosphorylation steps. First, viral *thymidine kinase* converts acyclovir to acyclovir monophosphate. Next, host cell enzymes convert the monophosphate to the diphosphate and then to the active compound, acyclovir triphosphate. *Because viral thymidine kinase has a much greater affinity for acyclovir triphosphate than does mammalian thymidine kinase, acyclovir triphosphate accumulates only in virus-infected cells.*

The active metabolite of acyclovir inhibits herpesvirus DNA replication in two ways. Acyclovir triphosphate acts as a competitive inhibitor for the incorporation of deoxyguanosine triphosphate (dGTP) into the viral DNA. In addition, acyclovir that is incorporated into viral DNA acts as a chain terminator because it lacks the 3′-hydroxy group necessary for further chain elongation. Viral DNA polymerase becomes irreversibly bound to an acyclovir-terminated DNA chain and is unavailable for further replicative activity. The effect of acyclovir on host cell DNA synthesis is much smaller than its effect on the viral enzyme. Concentrations of acyclovir significantly beyond the therapeutic range are required to inhibit host cell growth.

In HSV and VZV, the most common mechanism of resistance to acyclovir involves mutations that result in decreased thymidine kinase activity. Therefore, these viral mutants exhibit cross-resistance to other antiviral agents that require thymidine kinase activation, such

as famciclovir, ganciclovir, and valacyclovir. Less commonly, thymidine kinase mutations result in altered substrate specificity. A rare mechanism of acyclovir resistance involves decreased affinity of viral DNA polymerase for the drug.

Absorption, Metabolism, and Excretion

Valacyclovir is rapidly and completely converted to acyclovir by intestinal and hepatic first-pass metabolism. The bioavailability of acyclovir following oral valacyclovir dosing is three to five times that resulting from oral acyclovir administration and is comparable to that of intravenous acyclovir.

Acyclovir absorption is variable and incomplete following oral administration. It is about 20% bound to plasma protein and is widely distributed throughout body tissues. Significant amounts may be found in amniotic fluid, placenta, and breast milk. Acyclovir is both filtered at the glomeruli and actively secreted. Most of the dose is excreted in the urine as unchanged drug; a small portion is excreted as an oxidized inactive metabolite. The plasma half-life of acyclovir is 3 to 4 hours in patients with normal kidney function and up to 20 hours in patients with renal impairment.

Clinical Uses

Oral acyclovir is useful in the treatment of HSV-1 and HSV-2 infections, such as genital herpes, herpes encephalitis, herpes keratitis, herpes labialis, and neonatal herpes. In initial episodes of genital herpes, oral acyclovir has been found to reduce viral shedding, increase the speed of healing of lesions, and decrease the duration of pain and new lesion formation. Acyclovir appears to be less effective in the treatment of recurrent herpes genitalis but may be used for the long-term suppression of recurrent HSV.

Intravenous acyclovir is used in the treatment of herpes simplex encephalitis, neonatal HSV infection, and mucocutaneous HSV infection in immunocompromised individuals. Acyclovir ointment is used in the treatment of initial genital herpes but is not effective for recurrent disease. Ophthalmic acyclovir formulations, although not available in the United States, are effective in the treatment of herpes keratoconjunctivitis.

Acyclovir reduces the extent and duration of VZV lesions in adults and children, although higher doses are required than for the treatment of HSV infection. Although not recommended for the routine treatment of uncomplicated varicella in children, acyclovir may be used for chickenpox treatment and prophylaxis in high-risk individuals. Acyclovir accelerates healing in patients with herpes zoster (shingles), but it does not affect postherpetic neuralgia.

Immunocompromised individuals and patients receiving immunosuppressive drugs or cancer chemotherapy have a high incidence of severe reactivated HSV and VZV infections. In these patients, acyclovir has been shown to be effective for the prophylaxis and therapy of HSV and VZV.

Valacyclovir demonstrates efficacy similar to that of acyclovir but requires less frequent oral dosing. While indicated for the treatment of herpes zoster and the treatment and suppression of HSV, it is not approved for use in immunocompromised individuals or for the therapy of disseminated herpes zoster.

Adverse Effects, Contraindications, and Drug Interactions

The adverse effects of valacyclovir and acyclovir are similar. Toxicity is generally minimal, consisting largely of headache, nausea, and diarrhea. Less frequently observed are skin rash, fatigue, fever, hair loss, and depression. Reversible renal dysfunction (azotemia) and neurotoxicity (tremor, seizure, delirium) are dose-limiting toxicities of intravenous acyclovir. Adequate hydration and slow drug infusion can minimize the risk of renal toxicity.

Aside from drug hypersensitivity, there are no absolute contraindications to the use of acyclovir and valacyclovir. Adjustment of drug dosage is required in patients with renal impairment. A potentially fatal disorder, thrombotic thrombocytopenic purpura–hemolytic uremic syndrome (TTP–HUS), has been reported in immunocompromised individuals. Animal studies have demonstrated no teratogenic or embryotoxic effects of valacyclovir and acyclovir. Although there are no large, controlled studies of the safety of these drugs in pregnant women, a prospective epidemiological registry of acyclovir use during pregnancy showed no increase in the incidence of common birth defects.

The potential for drug interactions, particularly with other drugs that are actively secreted by the proximal tubules, should be considered. Probenecid has been shown to inhibit the renal clearance of acyclovir. Cyclosporine and other nephrotoxic agents may increase the risk of renal toxicity of acyclovir.

Cidofovir

Cidofovir (*Vistide*) is an acyclic phosphonate cytosine analogue with activity against herpesviruses including CMV, HSV-1, HSV-2, EBV, and VZV. It also inhibits adenoviruses, papillomaviruses, polyomaviruses, and poxviruses. Activation of cidofovir requires metabolism to a diphosphate by host cellular enzymes. *Because this activation does not depend upon viral enzymes, similar levels of cidofovir diphosphate are seen in infected and uninfected cells.* Cidofovir diphosphate competes with deoxycytidine triphosphate (dCTP) for access to viral

DNA polymerase and also acts as an alternative substrate. The incorporation of one cidofovir molecule into the growing DNA chain slows replication; sequential incorporation of two molecules halts DNA polymerase activity.

Absorption, Metabolism, and Excretion

Cidofovir has extremely low oral bioavailability and so must be administered intravenously. Although the plasma elimination half-life averages 2.6 hours, the diphosphate form of the drug is retained within host cells and has an intracellular half life of 17 to 65 hours. A phosphocholine metabolite has a half-life of approximately 87 hours and may serve as an intracellular reservoir of the drug. Cidofovir is not significantly metabolized and is excreted unchanged by the kidney. Glomerular filtration and probenecid-sensitive tubular secretion are responsible for cidofovir elimination.

Clinical Uses

Cidofovir is approved for the treatment and prophylaxis of CMV retinitis in AIDS patients. It has also been used in the treatment of acyclovir-resistant (viral thymidine kinase-deficient) HSV infections, polyomavirus-associated progressive multifocal leukoencephalopathy, condylomata acuminata (anogenital warts), and molluscum contagiosum.

Adverse Effects, Contraindications, and Drug Interactions

The most immediately serious adverse effect associated with cidofovir therapy is nephrotoxicity. Accumulation of the drug within the proximal tubule epithelial cells can lead to proteinuria, azotemia, glycosuria, elevated serum creatinine, and rarely, Fanconi's syndrome. Probenecid is administered along with cidofovir to block its uptake into the proximal tubule epithelial cells and thereby inhibit its tubular secretion as well as its toxicity. Probenecid carries its own adverse effects, including gastrointestinal upset, hypersensitivity reactions, and a decrease in the elimination of drugs that also undergo active tubular secretion (e.g. nonsteroidal antiinflammatory drugs [NSAIDs], penicillin, acyclovir, zidovudine).

Anterior uveitis and neutropenia are fairly common side effects of cidofovir therapy. Ocular hypotony and metabolic acidosis are rare. Exposure to therapeutic levels of cidofovir causes cancer in rats; therefore, this drug should be considered a potential human carcinogen. Animal studies have also shown cidofovir to produce embryotoxic and teratogenic effects and to impair fertility.

Because of its potential nephrotoxicity, cidofovir should not be used in individuals with renal impairment. Nephrotoxic agents (e.g., aminoglycosides, NSAIDs, amphotericin B, foscarnet) should not be given within 7 days of cidofovir administration.

Docosanol

Docosanol (*Abreva*) is a long-chain saturated alcohol that is clinically effective against HSV. It has in vitro activity against many enveloped viruses, including CMV, influenzavirus, and respiratory syncytial virus.

Docosanol is not directly virucidal; instead, it blocks the entry of the virion into the host cell by inhibiting the fusion of the viral envelope with the host plasma membrane. *Because it does not affect viral replication or protein production, it may be less susceptible to the development of resistance than other antiviral drugs.*

Absorption, Metabolism, and Excretion

Docosanol is topically applied; systemic absorption is minimal.

Clinical Uses

Docosanol cream is approved for the over-the-counter treatment of herpes labialis. It shortens the duration of symptoms of cold sores and fever blisters but does not provide symptomatic relief.

Adverse Effects, Contraindications, and Drug Interactions

Adverse effects of docosanol are minimal. Skin irritation occurs infrequently. Drug interactions are not anticipated.

Famciclovir and Penciclovir

Famciclovir (*Famvir*) is the diacetyl ester prodrug of the acyclic guanosine analogue 6-deoxypenciclovir (*Denavir*). Penciclovir has activity against HSV-1, HSV-2, VZV, and HBV. After oral administration, famciclovir is converted to penciclovir by first-pass metabolism. Penciclovir has a mechanism of action similar to that of acyclovir. It is first monophosphorylated by viral thymidine kinase; then it is converted to a triphosphate by cellular kinases. Penciclovir triphosphate acts as a competitive inhibitor of viral DNA polymerase, but unlike acyclovir, it does not cause chain termination.

Mutations in DNA polymerase or thymidine kinase may result in resistance. *Acyclovir-resistant HSV strains that exhibit thymidine kinase deficiency are also resistant to famciclovir and penciclovir.*

Absorption, Metabolism, and Excretion

Penciclovir is available as a topical cream; its absorption through the skin is undetectable. Famciclovir is well

absorbed following oral administration and is rapidly converted to penciclovir by hepatic first-pass metabolism. The bioavailability of penciclovir following oral famciclovir administration is approximately 77%. Penciclovir is less than 20% bound to plasma proteins.

The plasma elimination half-life for penciclovir is 2 to 3 hours; however, the intracellular half-life of penciclovir triphosphate is 7 to 20 hours in infected cells. Most penciclovir is eliminated unchanged by the kidney via glomerular filtration and active tubular secretion. The plasma half-life is increased in individuals with renal insufficiency.

Clinical Uses

Penciclovir is approved as a topical formulation for the treatment of herpes labialis. In immunocompetent individuals, penciclovir shortens the duration of lesion presence and pain by approximately half a day when it is initiated within an hour of lesion development and applied every 2 hours during waking hours for 4 days.

Famciclovir is indicated for the treatment of acute herpes zoster (shingles); it is at least as effective in reducing pain and healing time. Famciclovir is generally as effective as acyclovir in the treatment of HSV. In immunocompetent patients, famciclovir is approved for the treatment and prophylaxis of recurrent genital herpes. For HIV-infected individuals, famciclovir is approved for the treatment of all recurrent mucocutaneous HSV infections.

Adverse Effects, Contraindications, and Drug Interactions

No significant adverse effects to topical penciclovir have been reported. Oral famciclovir is generally well tolerated. Adverse effects include headache, nausea, and diarrhea. Confusion may occur, particularly in the elderly. Hallucinations and urticaria have been reported. Animal studies have indicated that chronic famciclovir administration may be tumorigenic and impair spermatogenesis. Dosage adjustment is necessary in individuals with renal impairment.

Famciclovir may interact with probenecid or other drugs eliminated by renal tubular secretion. This interaction may result in increased blood levels of penciclovir or other agents.

Fomivirsen

Fomivirsen (*Vitravene*), an anti-CMV agent, is the first antisense oligonucleotide to be approved by the U. S. Food and Drug Administration (FDA) as an antiviral therapy. Fomivirsen is an oligonucleotide complementary to the major immediate early region 2 (IE2) of CMV mRNA. *By binding to IE2 mRNA, fomivirsen prevents its translation to protein and thereby blocks viral replication.* Because this mechanism of action is different from that of other antiviral agents, cross-resistance with other drugs used to treat CMV is unlikely.

Absorption, Metabolism, and Excretion

Fomivirsen is injected directly into the vitreous humor of the eye. Animal studies have shown that this drug accumulates in the retina and iris over 3 to 5 days and is cleared from the vitreous humor within 7 to 10 days. Fomivirsen exhibits minimal systemic absorption and is degraded locally by cellular exonucleases.

Clinical Uses

Fomivirsen is used to treat CMV retinitis in patients with AIDS who have not responded to other treatments or in whom other treatments are contraindicated. It appears to be at least as effective as other treatments and produces fewer side effects. Because CMV retinitis is often associated with CMV infection elsewhere in the body, patients undergoing treatment with fomivirsen should be monitored for extraocular CMV disease.

Adverse Effects, Contraindications, and Drug Interactions

Iritis, which affects up to 25% of patients undergoing fomivirsen therapy, can be managed with topical corticosteroids. Vitreitis and increased intraocular pressure may also result from fomivirsen administration. Fomivirsen is contraindicated in patients who have been treated with cidofovir within the previous 2 to 4 weeks because cidofovir increases the risk of ocular inflammation.

Foscarnet

Foscarnet (*Foscavir*) is an inorganic pyrophosphate analogue that acts in vitro against HSV-1, HSV-2, VZV, CMV, EBV, HBV, and HIV. It acts as a noncompetitive inhibitor of viral DNA polymerase and reverse transcriptase by reversibly binding to the pyrophosphate-binding site of the viral enzyme and *preventing the cleavage of pyrophosphate from deoxynucleoside triphosphates.*

Resistance to foscarnet may result from mutation of viral DNA polymerase. Because this drug does not require phosphorylation for activation, thymidine kinase–deficient mutants should not be resistant to foscarnet.

Absorption, Metabolism, and Excretion

Because of its poor oral bioavailability, foscarnet is administered intravenously. Following intravenous infusion, 14 to 17% of foscarnet is bound to plasma proteins. The concentration of this compound in the vitreous humor is approximately the same as its plasma level. Foscarnet accumulates in bone; this property may account for its bimodal initial half-life of 4 to 8 hours

and prolonged terminal elimination half-life of 45 to 130 hours. Foscarnet is eliminated primarily as unchanged drug via glomerular filtration and active tubular secretion.

Clinical Uses

Foscarnet is indicated for the treatment of CMV retinitis in AIDS patients. Its effectiveness is comparable to that of ganciclovir; these drugs are synergistic when given to counteract refractory retinitis. A decreased incidence of Kaposi's sarcoma has been observed in AIDS patients who have undergone foscarnet therapy.

Foscarnet is approved for the treatment of acyclovir-resistant mucocutaneous HSV infections in immunocompromised individuals. A clinical study indicated that it is more effective than vidarabine. Foscarnet has also been used for the treatment of acyclovir-resistant VZV and nonretinitis forms of CMV infection, although its efficacy is not so well established.

Adverse Effects, Contraindications, and Drug Interactions

The most clinically significant adverse effect of foscarnet is renal impairment. Nephrotoxicity is most likely to occur during the second week of induction therapy but may occur at any time during induction or maintenance therapy. Serum creatinine levels may be elevated in up to 33 to 50% of patients; this effect is usually reversible upon drug discontinuation. Dehydration, previous renal impairment, and concurrent administration of other nephrotoxic drugs increase the risk of renal toxicity. Infusion of fluids along with foscarnet decreases the likelihood of renal impairment to about 12%. Dosage adjustment is required for patients with renal insufficiency.

Foscarnet is also associated with adverse effects on a variety of other organ systems. It may induce changes in serum electrolytes, including hypocalcemia, hypophosphatemia, hyperphosphatemia, hypomagnesemia, and hypokalemia. Neurological and cardiovascular signs such as paresthesia, tetany, arrhythmias, and seizures may result from these mineral imbalances. Anemia and granulocytopenia occur fairly commonly but seldom require discontinuation of therapy. Headache, vomiting, and diarrhea also occur with regularity. Genital ulceration has been reported and is likely due to high levels of ionized drug in the urine. While studies in rats indicate a lack of carcinogenicity, cell culture studies suggest a mutagenic effect. The safety of foscarnet during childhood, pregnancy, and lactation has not been established.

Foscarnet should not be used in combination with drugs that cause renal toxicity (e.g., acyclovir, aminoglycosides, amphotericin B, NSAIDs). Abnormal renal function has been noted when foscarnet is used with ritonavir or ritonavir and saquinavir. Pentamidine may increase the risk of nephrotoxicity, hypocalcemia, and hypomagnesemia. Caution should be used when foscarnet is given in combination with agents that can cause mineral imbalances.

Ganciclovir and Valganciclovir

Ganciclovir (*Cytovene*) is an acyclic analogue of 2′deoxyguanosine with inhibitory activity toward all herpesviruses, especially CMV. Valganciclovir (*Valcyte*) is the L-valyl ester prodrug of ganciclovir. Activation of ganciclovir first requires conversion to ganciclovir monophosphate by viral enzymes: protein kinase pUL97 in CMV or thymidine kinase in HSV. Host cell enzymes then perform two additional phosphorylations. The resultant ganciclovir triphosphate competes with dGTP for access to viral DNA polymerase. Its incorporation into the growing DNA strand causes chain termination in a manner similar to that of acyclovir. *Ganciclovir triphosphate is up to 100-fold more concentrated in CMV-infected cells than in normal cells and is preferentially incorporated into DNA by viral polymerase.* However, mammalian bone marrow cells are sensitive to growth inhibition by ganciclovir.

Resistance to ganciclovir has been found in individuals exposed to the drug for long periods and in people who have never been treated with this agent. The principal mechanism of resistance is mutation of the protein kinase gene. Mutations in the DNA polymerase have been seen more rarely.

Absorption, Metabolism, and Excretion

Ganciclovir can be given orally or intravenously; however, its oral absorption is poor (6–9%). Valganciclovir is well absorbed from the gastrointestinal tract and is rapidly metabolized to ganciclovir. The bioavailability of ganciclovir following valganciclovir administration is approximately 60%. Following intravenous administration, ganciclovir is found in the vitreous humor at concentrations approximately equal to plasma levels. Ganciclovir is not metabolized appreciably and is eliminated by glomerular filtration and active tubular secretion. Its rate of elimination is inversely proportional to creatinine clearance. The terminal half-life of ganciclovir is approximately 3.5 hours following intravenous administration and 4.8 hours following oral administration. The half-life of ganciclovir following oral valganciclovir administration is about 4 hours. The intracellular half-life of ganciclovir triphosphate is over 24 hours.

Clinical Uses

Intravenous ganciclovir is indicated for the treatment of CMV retinitis in immunocompromised individuals, including those with AIDS, and for the prevention of CMV infection in organ transplant recipients. Oral ganciclovir is less effective than the intravenous preparation but carries a lower risk of adverse effects. It is

approved for the prevention of CMV disease in immunocompromised individuals and transplant patients. It is also indicated as a maintenance therapy for treatment of CMV retinitis in AIDS and other immunocompromised conditions. Ganciclovir is also available as an intravitreal implant (*Vitrasert*) for the treatment of CMV retinitis in AIDS patients.

Oral valganciclovir is comparable to intravenous ganciclovir for the treatment and suppression of CMV retinitis in AIDS patients.

Adverse Effects, Contraindications, and Drug Interactions

Myelosuppression is the most common serious adverse effect of ganciclovir treatment; therefore, patients' blood counts should be closely monitored. Neutropenia and anemia have been reported in 25 to 30% of patients, and thrombocytopenia has been seen in 5 to 10%. Elevated serum creatinine may occur following ganciclovir treatment, and dosage adjustment is required for patients with renal impairment. In animal studies, ganciclovir causes decreased sperm production, teratogenesis, and tumor formation.

Ganciclovir interacts with a number of medications, some of which are used to treat HIV or transplant patients. Ganciclovir may cause severe neutropenia when used in combination with zidovudine. Ganciclovir increases serum levels of didanosine, whereas probenecid decreases ganciclovir elimination. Nephrotoxicity may result if other nephrotoxic agents (e.g., amphotericin B, cyclosporine, NSAIDs) are administered in conjunction with ganciclovir.

Idoxuridine

Idoxuridine (*Herplex*) is a water-soluble iodinated derivative of deoxyuridine that inhibits several DNA viruses including HSV, VZV, vaccinia, and polyoma virus. The triphosphorylated metabolite of idoxuridine inhibits both viral and cellular DNA synthesis and is also incorporated into DNA. Such modified DNA is susceptible to strand breakage and causes aberrant viral protein synthesis. *Because of its significant host cytotoxicity, idoxuridine cannot be used to treat systemic viral infections.* The development of resistance to this drug is common.

Absorption, Metabolism, and Excretion

Idoxuridine is marketed strictly for topical ophthalmic use, and systemic exposure is insignificant. However, after oral dosing, the drug is rapidly metabolized and excreted. It tends not to accumulate in body tissues.

Clinical Uses

The only FDA-approved use of idoxuridine is in the treatment of herpes simplex infections of the eyelid, conjunctiva, and cornea. It is most effective against surface infections because it has little ability to penetrate the tissues of the eye. intravenous idoxuridine was designated an orphan drug for the treatment of soft tissue sarcoma.

Adverse Effects, Contraindications, and Drug Interactions

Idoxuridine may cause local irritation, mild edema, itching, and photophobia. Corneal clouding and small punctate defects in the corneal epithelium have been reported. Allergic reactions are rare.

Trifluridine

Trifluridine (*Viroptic*) is a fluorinated pyrimidine nucleoside that has in vitro activity against HSV-1 and HSV-2, vaccinia, and to a lesser extent, some adenoviruses. Activation of trifluridine requires its conversion to the 5′monophosphate form by cellular enzymes. Trifluridine monophosphate inhibits the conversion of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP) by thymidylate synthetase. In addition, it competes with deoxythymidine triphosphate (dTTP) for incorporation by both viral and cellular DNA polymerases. Trifluridine-resistant mutants have been found to have alterations in thymidylate synthetase specificity.

Absorption, Metabolism, and Excretion

No detectable trifluridine is found in the blood following topical instillation of trifluridine into the eyes. Its half-life is approximately 12 minutes.

Clinical Uses

Trifluridine is administered as a topical ophthalmic solution for the treatment of primary keratoconjunctivitis and recurrent keratitis due to HSV-1 or HSV-2. It is not effective in the prophylaxis of these infections; however, it is effective in treating patients who were unresponsive or intolerant to topical idoxuridine or vidarabine.

Adverse Effects, Contraindications, and Drug Interactions

The most frequent adverse reactions to trifluridine administration are transient burning or stinging and palpebral edema. Other adverse reactions include superficial punctate keratopathy, epithelial keratopathy, hypersensitivity, stromal edema, irritation, keratitis sicca, hyperemia, and increased intraocular pressure.

Trifluridine is mutagenic in vitro and carcinogenic and teratogenic when administered subcutaneously to animals. Topical trifluridine was not teratogenic in animal studies. Because it is applied topically in humans, the likelihood of systemic effects is low.

Vidarabine

Vidarabine (adenine arabinoside, *Vira-A*) is an adenine nucleoside analogue containing arabinose in place of ribose. It is obtained from cultures of *Streptomyces antibioticus* and has activity against HSV-1, HSV-2, VZV, CMV, HBV, poxviruses, hepadnaviruses, rhabdoviruses, and certain RNA tumor viruses.

Vidarabine's specific mechanism of action is not fully understood. Cellular enzymes convert this drug to a triphosphate that inhibits DNA polymerase activity. Vidarabine triphosphate competes with deoxyadenosine triphosphate (dATP) for access to DNA polymerase and also acts as a chain terminator. Although vidarabine is incorporated into host DNA to some extent, viral DNA polymerase is much more susceptible to inhibition by vidarabine. Vidarabine also inhibits ribonucleoside reductase and other enzymes. Resistance occurs as a result of DNA polymerase mutation.

Absorption, Metabolism, and Excretion

Vidarabine is administered only as a topical ophthalmic ointment. It has relatively limited solubility and is not significantly absorbed after application to the eye. Within the tissues, it is rapidly deaminated to its principal metabolite, arabinosyl hypoxanthine, which retains some degree of antiviral activity.

Clinical Uses

The principal use of vidarabine is in the treatment of HSV keratoconjunctivitis. It is also used to treat superficial keratitis in patients unresponsive or hypersensitive to topical idoxuridine.

Adverse Effects, Contraindications, and Drug Interactions

The most commonly observed side effects associated with vidarabine are lacrimation, burning, irritation, pain, and photophobia. Vidarabine has oncogenic and mutagenic potential; however, the risk of systemic effects is low because of its limited absorption. It should not be used in conjunction with ophthalmic corticosteroids, since these drugs increase the spread of HSV infection and may produce side effects such as increased intraocular pressure, glaucoma, and cataracts.

ANTIINFLUENZA AGENTS

Influenza is responsible for several thousand deaths each year. Individuals over the age of 65, residents of long-term care facilities, and patients with long-term health problems (i.e., diabetes, HIV or AIDS, heart disease, kidney disease, lung disease, cancer) are at highest risk for severe influenza and complications. Yearly vaccination can prevent influenza infection and minimize the severity of symptoms in those who do contract this disease. However, infection can occur in immunized persons, because influenza viruses mutate rapidly and may not be covered by a particular year's vaccine. The following drugs are used in the treatment of influenza strains A and B and in some cases other viral infections.

Amantadine and Rimantadine

Amantadine (*Symmetrel*) is a synthetic tricyclic amine, and rimantadine (*Flumadine*) is its α-methyl derivative. Both drugs inhibit the replication of the three antigenic subtypes of influenza A (H1N1, H2N2 and H3N2) and have negligible activity against influenza B.

Their mechanism of action involves inhibition of the viral M2 protein, an integral membrane protein that acts as a H^+ channel. Blockade of the M2 protein prevents the acid-mediated dissociation of the ribonucleoprotein complex that occurs early in replication. In certain strains, the pH changes that result from M2 inhibition alter the conformation of hemagglutinin, hence inhibit viral assembly.

Viral resistance develops rapidly in approximately 30% of individuals treated with amantadine or rimantadine. Resistant viruses are associated with the failure of drug prophylaxis in close contacts of infected individuals who have been treated with these antiviral agents. Mutation in the transmembrane domain of the M2 protein is the most frequent cause of resistance to amantadine and rimantadine.

Absorption, Metabolism, and Excretion

Amantadine is rapidly and completely absorbed from the gastrointestinal tract, and peak blood levels are achieved in 2 to 5 hours. The serum half-life of amantadine averages 17 hours in young adults and 29 hours in the elderly. Most of the drug (90%) is eliminated unchanged by glomerular filtration and tubular secretion.

Rimantadine is well absorbed following oral administration, with peak blood levels achieved in 5 to 7 hours. Its elimination half-life averages 25 hours in young adults and 32 hours in the elderly. Less than 25% of the dose is excreted in the urine as unchanged drug; the remainder is eliminated as hydroxylated or conjugated metabolites.

Clinical Uses

Amantadine and rimantadine are used for the treatment of diseases caused by influenza A strains. When these agents are administered within 48 hours of the onset of symptoms, they reduce the duration of fever and systemic complaints by 1 to 2 days and may decrease the duration of viral shedding. Evidence is insufficient to suggest that treatment with these drugs will prevent

the development of influenza A virus pneumonitis or other complications in high-risk patients.

The Centers for Disease Control's (CDC) Immunization Practices Advisory Committee recommends annual vaccination as the method of choice in the prevention of influenza infection. However, when vaccination is contraindicated or early vaccination is not possible, amantadine and rimantadine are effective prophylactic agents that have been shown to protect approximately 70 to 90% of patients from influenza A infection. *Since these drugs do not prevent the host immune response to influenza A, they may be used to prevent infection during the 2- to 4-week period required to develop immunity following vaccination.* An additional use of amantadine, unrelated to its antiviral activity, is in the therapy of Parkinson's disease (see Chapter 31).

Adverse Effects, Contraindications, and Drug Interactions

The most frequently reported side effects of amantadine and rimantadine are nausea, anorexia, dizziness, and insomnia. These effects are dose-related and are more common with amantadine than rimantadine. Depression, impaired coordination, confusion, anxiety, light-headedness, urinary retention, and dry mouth are also more frequent with amantadine. High doses of amantadine may produce cardiac arrhythmias, delirium, hallucinations, and suicidal ideation; long-term treatment may cause peripheral edema, orthostatic hypotension, and rarely, congestive heart failure. Abrupt withdrawal of amantadine may produce a neuroleptic malignant syndrome. Both drugs can produce seizures or worsen preexisting seizure disorders. Animal studies have shown that amantadine is teratogenic and rimantadine may be embryotoxic.

Neither drug should be given during pregnancy and lactation. Individuals with congestive heart failure, edema, orthostatic hypotension, seizure disorders, or uncontrolled psychosis should be closely monitored during therapy with amantadine. The dosage of rimantadine must be decreased in cases of renal or hepatic impairment, whereas amantadine requires dosage adjustment only when renal impairment is present. The elderly are more susceptible to the central nervous system (CNS) and gastrointestinal effects of these drugs; rimantadine is generally better tolerated in this population. Individuals over age 65 require half the dose of either drug given to younger adults.

Several drug interactions involving amantadine and rimantadine are clinically significant. Anticholinergic drugs can potentiate the toxicity of amantadine. Thiazide–triamterene, trimethoprim–sulfamethoxazole, quinine, and quinidine increase plasma amantadine levels. Cimetidine decreases rimantadine clearance, and aspirin and acetaminophen decrease rimantadine plasma levels.

Oseltamivir

Oseltamivir phosphate (*Tamiflu*) is the ethyl ester prodrug of oseltamivir carboxylate, an analogue of neuraminic (sialic) acid that is a reversible competitive antagonist of influenza A and B neuraminidase. Neuraminidase, like hemagglutinin, is a viral surface glycoprotein that interacts with host cell receptors containing terminal neuraminic acid residues. The binding of hemagglutinin to its cellular receptors initiates viral penetration and promotes the fusion of the viral envelope to the plasma membrane. Neuraminidase then destroys these hemagglutinin receptors by breaking the bond between the terminal neuraminic acid residue and its adjacent oligosaccharide. The cleavage of hemagglutinin receptors is required for the release of progeny virus from the host cell. It also facilitates the spread of infection by allowing viral particles to penetrate the neuraminic acid–rich respiratory mucus and by preventing the clumping of virus that results from the binding of hemagglutinins to neuraminic acid residues on neighboring viral particles. *Inhibition of neuraminidase activity prevents the release of progeny virus and inhibits viral spread.* The active site of neuraminidase is highly conserved in influenza A and B viruses; thus, oseltamivir and other neuraminidase inhibitors (e.g., zanamivir) are effective against a variety of influenza strains.

Influenza virus resistant to oseltamivir has not been found in naturally acquired isolates but has been isolated from influenza patients who have undergone treatment with this drug. These resistant strains contain mutations in the active site of neuraminidase and are generally less virulent and infective than nonresistant virus. In vitro passage of influenza virus in the presence of oseltamivir carboxylate can produce mutations in hemagglutinin that decrease the overall dependence of viral replication on neuraminidase; however, the clinical relevance of this resistance mechanism is unknown.

Absorption, Metabolism, and Excretion

Orally administered oseltamivir phosphate is rapidly absorbed and converted by hepatic esterases to oseltamivir carboxylate. Approximately 80% of an oral dose reaches the systemic circulation as oseltamivir carboxylate, with peak plasma concentrations achieved within 2.5 to 5 hours. The plasma elimination half-life of oseltamivir carboxylate is 7 to 9 hours. Elimination of the parent drug and its active metabolite occurs primarily by active tubular secretion and glomerular filtration.

Clinical Uses

Oseltamivir is approved for the treatment of uncomplicated acute influenza in patients aged 1 year and older. It decreases the duration of illness by 1 to 1.5 days when treatment is initiated within 48 hours of the onset of

symptoms. Oseltamivir is also indicated for the prophylaxis of influenza in individuals aged 13 and older. It reduces infection rates to approximately 10 to 25% of that found in untreated populations; however, it is not intended to substitute for the early vaccination recommended by the CDC. Oseltamivir can be used as postexposure prophylaxis in household contacts of infected patients, with infection rates of treated patients around 10% of placebo control levels.

Adverse Effects, Contraindications, and Drug Interactions

The most frequently reported adverse effects of oseltamivir are nausea and vomiting. These events are usually mild to moderate, occur during the first 1 to 2 days of treatment, and can be lessened by taking the drug with food. Bronchitis, insomnia, and vertigo may also occur.

Oseltamivir may not be indicated for use in certain individuals. Its efficacy in patients with chronic cardiac or respiratory disease has not been established. In clinical trials, no difference in the incidence of complications was seen between treatment and control groups. The efficacy of oseltamivir has not been demonstrated in immunocompromised patients, patients who begin treatment after 40 hours of symptoms, or patients given repeated prophylactic courses of therapy. Dosage adjustment is recommended for individuals with renal insufficiency; the drug's safety in patients with hepatic insufficiency is unknown.

No formal drug interaction studies of oseltamivir have been performed. Oseltamivir and its carboxylate metabolite do not interact with the cytochrome P450 system. Although probenecid decreases the elimination of oseltamivir, dosage adjustment is not required during coadministration of these drugs because of oseltamivir's margin of safety. Oseltamivir does not interfere with antibody production in response to the influenza vaccine.

Zanamivir

Zanamivir (*Relenza*) is a neuraminidase inhibitor with activity against influenza A and B strains. Like oseltamivir, zanamivir is a reversible competitive antagonist of viral neuraminidase. It inhibits the release of progeny virus, causes viral aggregation at the cell surface, and impairs viral movement through respiratory secretions. Resistant variants with hemagglutinin and/or neuraminidase mutations have been produced in vivo; however, clinical resistance to zanamivir is quite rare at present.

Absorption, Metabolism, and Excretion

Zanamivir has a bioavailability of less than 5% when absorbed through the gastrointestinal tract. It is administered using a breath-actuated inhaler device (*Diskhaler*) that delivers the drug as an aerosol in a lactose carrier. The lactose particles are large, and about 78% deposit in the oropharynx. Following oral inhalation, zanamivir has a bioavailability of 12 to 17%, with peak plasma concentrations being reached within 1.5 hours. It is rapidly eliminated by the kidneys without significant metabolism and has a plasma elimination half-life of 2.5 to 5 hours.

Clinical Uses

Zanamivir is indicated for treatment of uncomplicated acute influenza A and B virus in patients aged 7 and older. Treatment should be initiated no later than 2 days after the onset of symptoms. Zanamivir shortens the duration of illness by 1 to 1.5 days. It is also an effective prophylaxis against influenza; however, the FDA has not approved this indication at the time of publication.

Adverse Effects, Contraindications, and Drug Interactions

Zanamivir is generally well tolerated. Bronchospasm and impaired lung function have been reported in some patients taking this medication, but many of these individuals had serious underlying pulmonary disease. Zanamivir should be discontinued if an individual develops bronchospasm or breathing difficulties; treatment and hospitalization may be required. Allergic reactions, including angioedema, have been rarely reported. The efficacy of zanamivir depends upon the proper use of the inhaler device.

Zanamivir is contraindicated in individuals with severe or decompensated chronic obstructive lung disease or asthma because it has not been shown to be effective in these individuals and can cause serious adverse pulmonary reactions. Individuals with mild to moderate asthma may have a decline in lung function when taking zanamivir. The safety and efficacy of this medication have not been determined in individuals with severe renal insufficiency. No clinically significant drug interactions have been reported. Zanamivir does not decrease the effectiveness of the influenza vaccine.

OTHER ANTIVIRAL AGENTS

The drugs described next are used in the treatment in a variety of viral conditions, including HBV, hepatitis C virus (HCV), respiratory syncytial virus (RSV), human papilloma virus (HPV), and VZV. Some are also used in the therapy of HIV infection; detailed information on the treatment of this disease is found in Chapter 51.

Immune Globulin

Immune globulin (γ-globulin, immunoglobulin [Ig] G) is a fraction obtained from the plasma of normal individuals and is rich in antibodies found in whole blood.

It consists primarily of IgG and contains trace amounts of IgA and IgM. *γ-Globulin provides the patient with passive immunity and does not require time for the development of an antibody response.* It is believed to inhibit viral penetration of host cells, opsonize viral particles, activate complement, and stimulate cell-mediated immunity.

Absorption, Metabolism, and Excretion

γ-Globulin is administered parenterally. Intramuscular or intravenous injections are given during the early infectious stage to alleviate the progression of certain viral disorders. Protection lasts for 2 to 3 weeks after a single injection, although for prolonged infections, injections can be repeated every 2 to 3 weeks.

Clinical Uses

Human immune globulin preparations specifically for the treatment and/or prevention of CMV (*CytoGam*), HBV (*BayHep B*), rabies (*BayRab*), RSV (*RespiGam*), and VZV (*VZIG*) are obtained from individuals with high titers of antibodies against these viruses. A pooled heterogeneous human immune globulin solution (*BayGam, Gamimmune,* others) can be used to lessen the likelihood of measles, varicella, or rubella infection in individuals exposed to these viruses. Immune globulin also can be used as an adjunctive form of therapy with other therapeutic approaches.

Adverse Effects, Contraindications, and Drug Interactions

Hypersensitivity reactions (e.g., anaphylaxis, angioedema) associated with γ-globulin are rare but occur most commonly in individuals with agammaglobulinemia, severe hypogammaglobulinemia, or IgA deficiency. The likelihood of anaphylactoid reaction increases following repeated dosing and for certain preparations, intravenous administration. Immune globulins can also cause urticaria, angioedema, fever, and injection site reactions. Preparations that are administered intravenously (e.g., RSV immune globulin) can produce infusion-related side effects such as flushing, dizziness, blood pressure changes, palpitations, abdominal cramps, and dyspnea; slowing the infusion rate may reduce the severity of these effects. High doses of immune globulins have been associated with rare cases of aseptic meningitis syndrome. A possibility of infection by blood-borne pathogens exists with immune globulin and other human blood products. Although preparations are screened for contamination and viral inactivation processes are used, the risk of transmission of new or undetected pathogens cannot be eliminated.

Treatment with immune globulin can interfere with the response to live virus vaccines (e.g., measles, mumps, rubella). Vaccinations should be deferred until several months after the administration of γ-globulin because the antibodies contained in this preparation may interfere with the development of the host immune response. Individuals who were vaccinated shortly before receiving immune globulin may require revaccination at a later time.

Interferons

The enhanced production of the cytokines called *interferons* is one of the body's earliest responses to a viral infection. These endogenous proteins exert potent antiviral, immunoregulatory, and antiproliferative effects and are classified according to the cell type from which they were initially derived. Interferon-α (type I, leukocyte) and interferon β-β (type I, fibroblast) are synthesized by most types of cells in response to viral infection, certain cytokines, and double-stranded RNA. Interferon-γ (type II, immune) is produced by natural killer (NK) cells and T lymphocytes in response to antigens, mitogens, and certain cytokines. Interferon-α and interferon-β exert the most potent antiviral effects; interferon-γ is antiviral and strongly immunomodulatory.

Although interferons do not directly interact with viral particles, they exert a complex range of effects on virus-infected cells that result in the inhibition of viral penetration, uncoating, mRNA synthesis, translation, and/or virion assembly and release. Interferons bind to cell surface receptors and initiate the JAK-STAT signal transduction pathway. This leads to the induction of numerous proteins, including 2′-5′-oligoadenylate synthetase (2′-5′OAS) and interferon-induced protein kinase. 2′-5′OAS initiates the activation of a cellular ribonuclease that cleaves single-stranded RNAs, and interferon-induced protein kinase phosphorylates and inactivates an elongation factor (eIF-2) involved in translation. Interferons also induce the production of inflammatory cytokines and biological oxidants that further enhance the host immune response. Viral families differ with respect to the step or steps at which interferons exert their effects. Certain viruses are resistant to interferons because they produce proteins that counteract interferon's effects.

Absorption, Metabolism, and Excretion

Natural interferons produced by human leukocytes, recombinant interferons produced in bacteria, and recombinant interferons conjugated to monomethoxy polyethylene glycol (PEG; pegylated interferons) are available in the United States. The various preparations may be administered subcutaneously, intramuscularly, intravenously, or intralesionally (e.g., into genital warts). Natural or recombinant interferons typically achieve peak plasma levels within 4 to 8 hours of subcutaneous

or intramuscular injection and are undetectable in the bloodstream within 16 to 36 hours. Maximal plasma concentrations of pegylated interferons are reached 15 to 44 hours after subcutaneous or intramuscular injection and are sustained for much longer than nonpegylated preparations (48 to 72 hours). Intralesional injection of interferons results in negligible systemic absorption. Interferons are eliminated from the bloodstream by a combination of cellular uptake and catabolism in the kidney and liver. Minimal amounts of intact protein are excreted in the urine or feces.

Clinical Uses

Interferon-α-2a (*Roferon-A*) is approved for the treatment of chronic hepatitis C, hairy cell leukemia, AIDS-related Kaposi's sarcoma, and chronic phase Philadelphia chromosome–positive chronic myelogenous leukemia. Interferon-α-2b (*Intron A*) is indicated for hairy cell leukemia, malignant melanoma, follicular lymphoma, condylomata acuminata, AIDS-related Kaposi's sarcoma, and chronic hepatitis B and C. A combination of interferon-α-2b and ribavirin (*Rebetron*) is used for the treatment of chronic hepatitis C. Interferon-α-n3 (*Alferon N*) is a solution of purified natural human interferon-αproteins approved for the treatment of condylomata acuminata by intralesional injection. Interferon alfacon-1 (*Infergen*) is a recombinant interferon constructed from the sequences of several naturally occurring interferon-αsubtypes. This recombinant protein contains the most frequently observed amino acid in each position of the sequence and exhibits in vitro specific activity at least 5 times higher than that of interferon α-2a or -2b. Interferon alfacon-1 and peg interferon-α-2b (*PEG-Intron*) are approved for the treatment of chronic hepatitis C.

Interferon β-1a (*Avonex*) and interferon β-1b (*Betaseron*) are used in the treatment of multiple sclerosis. Interferon γ-1b (*Actimmune*) is used to prevent and diminish the severity of infections associated with chronic granulomatous disease and for delaying the progression of severe, malignant osteopetrosis.

Adverse Effects, Contraindications, and Drug Interactions

Flulike symptoms, including fever, chills, weakness, fatigue, myalgia, and arthralgia, are the most common side effects of interferon therapy. These symptoms occur in more than 50% of patients given injections of interferons either intravenously, intramuscularly, or subcutaneously. Intralesional injection may produce milder flulike symptoms with somewhat less frequency. Tolerance to these symptoms generally develops with repeated dosing.

Interferons are associated with a diverse range of common adverse effects. CNS complaints such as headache, dizziness, impaired memory and concentration, agitation, insomnia, and anxiety occur with regularity. Depression is a common side effect of interferon-α and interferon-β. Suicidal behavior, although rare, can arise in depressed patients; therefore, these individuals should be closely monitored. Myelosuppression occurs frequently and may be dose limiting; potentially fatal aplastic anemia is rare. Gastrointestinal symptoms such as nausea, vomiting, diarrhea, and anorexia are common; however, ulcerative colitis, pancreatitis, hyperglycemia, and diabetes mellitus are rare. Elevation of hepatic enzymes can occur but rarely necessitate discontinuation of treatment. Injection site reaction is common, as is alopecia, for certain interferon preparations. Interferons can decrease fertility and may cause miscarriage at high doses.

Infrequent reactions to interferon therapy include proteinuria, renal toxicity, autoimmune disease, thyroid disease, ophthalmic toxicity, pulmonary dysfunction (pulmonary infiltrates, pneumonitis, and pneumonia), and cardiovascular effects (tachycardia, arrhythmia, hypotension, cardiomyopathy, and myocardial infarction). Rarely, the body may develop antibodies against interferons that inhibit their effectiveness.

Interferons are contraindicated in individuals with autoimmune hepatitis or other autoimmune disease, uncontrolled thyroid disease, severe cardiac disease, severe renal or hepatic impairment, seizure disorders, and CNS dysfunction. Immunosuppressed transplant recipients should not receive interferons. Interferons should be used with caution in persons who have myelosuppression or who are taking myelosuppressive drugs. Preparations containing benzyl alcohol are associated with neurotoxicity, organ failure, and death in neonates and infants and therefore are contraindicated in this population. Interferons should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Interferons reduce the activity of hepatic cytochrome P450 enzymes and decrease the clearance of drugs such as theophylline. Their effects may be additive with other drugs that have neurotoxic, hematotoxic or cardiotoxic activity.

Ribavirin

Ribavirin is a synthetic guanosine analogue that possesses broad antiviral inhibitory activity against many viruses, including influenza A and B, parainfluenza, RSV, HCV, HIV-1, and various herpesviruses, arenaviruses, and paramyxoviruses. Its exact mechanism of action has not been fully elucidated; however, it appears to inhibit the synthesis of viral mRNA through an effect on nucleotide pools. Following absorption, host cell enzymes convert ribavirin to its monophosphate, diphosphate, and triphosphate forms. Ribavirin monophosphate

inhibits the guanosine triphosphate (GTP) synthesis pathway and subsequently inhibits many GTP-dependent processes. Ribavirin triphosphate inhibits the 5′capping of viral mRNA with GTP and specifically inhibits influenza virus RNA polymerase. Ribavirin may also act by increasing the mutation rate of RNA viruses, leading to the production of nonviable progeny virions. Ribavirin resistance has not been documented in clinical isolates.

Absorption, Metabolism, and Excretion

Ribavirin can be administered as an aerosol using a small-particle aerosol generator. When administered by this route, the drug has only minimal systemic absorption, with drug concentrations in respiratory tract secretions approximately 100 times as high as those found in plasma. Oral absorption is rapid, and first-pass metabolism is extensive; ribavirin's oral bioavailability is 64% and can be increased by administration with a high-fat meal. Steady-state levels are reached after 4 weeks.

Ribavirin is reversibly phosphorylated by all nucleated cells. It is also metabolized in the liver to a triazole carboxylic acid metabolite that is eliminated in the urine along with the parent compound. The plasma half-life of ribavirin is 9.5 hours when it is administered by aerosol (2.5 hours/day for 3 days), whereas its half-life is around 12.5 days at steady state. The drug accumulates in erythrocytes, with a half-life of 40 days.

Clinical Uses

Ribavirin aerosol (*Virazole*) is indicated in the treatment of high-risk infants and young children with severe bronchiolitis or pneumonia due to RSV infection. Treatment is most effective if begun within 3 days of the onset of symptoms.

Although ribavirin monotherapy is ineffective against HCV, oral ribavirin in combination with interferon-α (*Rebatron*) is approved for this indication and is effective in patients resistant to interferon therapy alone. Intravenous ribavirin may be useful in the therapy of Hantaan virus infection, Crimean or Congo virus hemorrhagic fever, Lassa fever, and severe adenovirus infection.

Adverse Effects, Contraindications, and Drug Interactions

Most adverse effects associated with aerosol ribavirin are local. Pulmonary function may decline if aerosol ribavirin is used in adults with chronic obstructive lung disease or asthma. Deterioration of pulmonary and cardiovascular function has also been seen in severely ill infants given this preparation. Rash, conjunctivitis, and rare cases of anemia have been reported. Health care workers exposed to aerosol ribavirin during its administration have reported adverse effects including headache, conjunctivitis, rash, and rarely, bronchospasm.

Oral and intravenous ribavirin are associated with additional adverse effects. When given via these routes, ribavirin can produce hemolytic anemia that is reversible following dosage reduction or cessation of therapy. When given in combination with interferon-α, ribavirin increases the incidence of many of its side effects, such as fatigue, nausea, insomnia, depression, and anemia, and may cause fatal or nonfatal pancreatitis. Ribavirin is mutagenic, teratogenic, and embryotoxic in animals at doses below the therapeutic level in humans. *It is contraindicated in pregnant women and in the male partners of pregnant women.* Women of childbearing potential and male partners of these women must use two effective forms of contraception during ribavirin treatment and for 6 months post therapy. Pregnant women should not directly care for patients receiving ribavirin.

Ribavirin is contraindicated in patients with sickle cell anemia and other hemoglobinopathies because of its propensity to cause anemia. Similarly, persons with coronary disease should not use ribavirin, because anemia may cause deterioration of cardiac function. Oral ribavirin should not be given to individuals with severe renal impairment; no dosage adjustment is necessary for the inhaled formulation. However, patients with hepatic impairment may require dosage adjustment.

Little information on the drug interactions of ribavirin is available. In vitro, ribavirin inhibits the phosphorylation reactions that are required for activation of zidovudine and stavudine.

Lamivudine

Lamivudine is a synthetic cytidine analogue used in the treatment of HIV (see Chapter 51) and HBV. Its activation requires phosphorylation by cellular enzymes. Lamivudine triphosphate competitively inhibits HBV DNA polymerase and HIV reverse transcriptase and causes chain termination. It inhibits the activity of mammalian DNA polymerases with a much lower potency.

HIV-1 frequently acquires mutations in reverse transcriptase that result in resistance to lamivudine within 12 weeks of treatment. Mutations in the DNA polymerase of HBV are associated with decreased lamivudine efficacy and have been documented in patients treated with this agent for 6 months or more.

Absorption, Metabolism, and Excretion

Lamivudine is rapidly absorbed from the gastrointestinal tract and has an oral bioavailability of approximately 85 to 90%. Lamivudine is mainly excreted unchanged by the kidney and has an elimination half-life of 5 to 7 hours.

Clinical Uses

Lamivudine is indicated for the treatment of HIV when used in combination with other antiretroviral agents. A lower dose than that used to treat HIV is approved for the treatment of HBV. Although lamivudine initially improves histological and biochemical measures of hepatic function and reduces HBV DNA to below the limits of detection, withdrawal of the drug usually results in disease recurrence. Resistance appears in up to one-third of patients after 1 year of treatment.

Adverse Effects, Contraindications, and Drug Interactions

The most common adverse effects of lamivudine seen at doses used to treat HBV are mild; they include headache, malaise, fatigue, fever, insomnia, diarrhea, and upper respiratory infections. Elevated alanine aminotransferase (ALT), serum lipase, and creatine kinase may also occur. The safety and efficacy of lamivudine in patients with decompensated liver disease have not been established. Dosage adjustment is required in individuals with renal impairment. Coadministration of trimethoprim–sulfamethoxazole decreases the renal clearance of lamivudine.

Palivizumab

Palivizumab (*Synagis*) is a humanized monoclonal antibody directed against the highly conserved A antigenic site of the F protein on the surface of RSV. It contains 95% human and 5% murine antibody sequences and tends to have little immunogenicity in humans. Palivizumab is composed of the human framework region of the IgG-1 κ-chain joined to the antigen-binding regions of a mouse monoclonal antibody. *Palivizumab neutralizes RSV and inhibits its ability to fuse with host cell membranes.* Resistant strains of RSV have been derived in vitro but have not been found in clinical isolates to date.

Absorption, Metabolism, and Excretion

Palivizumab is administered prophylactically as a monthly intramuscular injection prior to and during RSV season (November to April in the northern hemisphere). The half-life of palivizumab is approximately 20 days.

Clinical Uses

Palivizumab is used to prevent serious lower respiratory tract infection due to RSV. It is used only in high-risk children who are younger than 24 months of age and have bronchopulmonary dysplasia or chronic lung disease that required treatment in the previous 6 months. It is also indicated for premature infants (less than 32 weeks' gestation) until the age of 6 to 12 months. Palivizumab can reduce the incidence of RSV-related hospitalization by approximately half. The safety and efficacy of palivizumab in the treatment of RSV disease have not been established.

Adverse Effects, Contraindications, and Drug Interactions

Serious adverse reactions caused by palivizumab are rare. Mild erythema and pain may occur at the injection site. Although no anaphylactoid reactions have been reported to date, the possibility of this reaction exists because palivizumab is a protein.

Study Questions

1. Which drug, compared with the rest, would be expected to produce a significantly higher concentration of active metabolite in cells infected with its target virus?
(A) Cidofovir
(B) Foscarnet
(C) Oseltamivir
(D) Penciclovir
(E) Lamivudine

2. Which of the following drugs should not be given in combination with zidovudine because of an increased risk of myelosuppression?
(A) Ganciclovir
(B) Fomivirsen
(C) Rimantadine
(D) Famciclovir
(E) Zanamivir

3. Caitlyn Doe is a 24-year-old woman in her third month of pregnancy. She has had severe pain, swelling, and redness in both eyes for several days and has been unable to see well enough to go to work. Ms. Doe's physician diagnosed herpes simplex keratoconjunctivitis; the infection has spread deep into the surrounding tissues. Which drug is indicated for HSV keratoconjunctivitis but is least likely to harm the fetus?
(A) Cidofovir
(B) Docosanol
(C) Fomivirsen
(D) Acyclovir
(E) Ribavirin

4. Mitchell Jones, a 35-year-old man, began treatment for hepatitis C with interferon-α-2b and ribavirin (*Rebetron*) 4 weeks ago. On returning to his doctor

	Current Values (cells/μL)	Values Before Treatment (cells/μL)	Normal Values (cells/μL)
Erythrocytes	3.3×10^6	5×10^6	$4.3–5.7 \times 10^6$
Platelets	210×10^3	350×10^3	$150–450 \times 10^3$
Myelocytes	0	0	0
Neutrophils, bands	370	350	150–400
Neutrophils, segmented	4800	4200	3000–5800
Lymphocytes	2750	2800	1500–3000
Monocytes	562	480	285–500
Eosinophils	125	100	50–250
Basophils	28	20	15–50
Hemoglobin	9.5 g/dL	16 g/dL	13.5–17.5 g/dL

for routine monitoring of his blood count and liver function, he complained of general fatigue and exertion when walking. His hemoglobin, CBC, differential, and platelet counts are shown in the accompanying table. Which is the most likely explanation of any abnormality?

(A) Ribavirin decreases erythrocyte counts.
(B) Interferon-α-2b decreases erythrocyte counts.
(C) Interferon-α-2b elevates lymphocyte counts.
(D) A and B are true.
(E) A, B, and C are true.

5. Oseltamivir's mechanism of action is generally believed to be

(A) Inhibition of a viral enzyme that aids the spread of virus through respiratory mucus and is required for the release of progeny virus
(B) Competitive inhibition of viral DNA polymerase, which leads to early chain termination of the progeny of viral DNA
(C) Stimulation of the tyrosine kinase activity of the JAK-STAT signal transduction pathway, resulting in enhanced proliferation of immune cells
(D) Inhibition of the synthesis of GTP, which is required for viral genomic replication and is a cofactor for cellular enzymes required for viral replication
(E) Inhibition of the viral protease required for protein processing prior to assembly of progeny virions

ANSWERS

1. D. The conversion of penciclovir to its active form requires initial monophosphorylation by viral thymidine kinases, then conversion to its active triphosphate form by cellular enzymes. Thus, the concentration of penciclovir triphosphate is particularly high in cells infected with its target viruses (e.g., HSV, VZV, HBV). Foscarnet is a pyrophosphate analogue that does not require activation. Oseltamivir is a neuraminidase inhibitor that is converted by hepatic esterases to its active form, oseltamivir carboxylate. Lamivudine is converted to its active triphosphate form by host cellular enzymes.

2. A. Ganciclovir commonly causes myelosuppression and may produce severe neutropenia when given in combination with zidovudine. Fomivirsen is most commonly associated with iritis and other ocular information; rimantadine with nausea, vomiting, anorexia, and dizziness; famciclovir with headache, nausea, diarrhea, and CNS effects; and zanamivir with bronchospasm.

3. D. Acyclovir is in pregnancy category B: animal studies have shown no evidence of harm to the fetus, but no large, controlled studies of human outcomes have been performed. Cidofovir may be used to treat HSV that is resistant to acyclovir; however, it is embryotoxic and teratogenic, and Ms. Doe should avoid it. Docosanol is used for cold sores and is not indicated for ophthalmic use. Fomivirsen is effective against CMV retinitis, not HSV keratitis. Ribavirin is indicated for RSV infection and is also mutagenic, teratogenic, and embryotoxic.

4. D. Interferons and ribavirin are both likely to cause anemia; the combination of these two agents increases this possibility. Interferons do not stimulate lymphocyte proliferation.

5. A. Oseltamivir inhibits neuraminidase, an enzyme that cleaves neuraminic acid from oligosaccharides. Neuraminidase activity aids the movement of viral particles through neuraminic acid–rich respiratory secretions and is required for the release of progeny virions. Inhibition of viral DNA polymerase is the mechanism of action of nucleoside analogue antiviral drugs. Interferons do stimulate the JAK-STAT signaling pathway but do not stimulate proliferation of immune cells. Ribavirin inhibits GTP synthesis, and the antiretroviral protease inhibitors (e.g., ritonavir) inhibit HIV protease.

SUPPLEMENTAL READING

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CASE Study Picking Up More Than Knowledge in College

Jim Smith had severe herpes labialis while he was in college. At that time, the doctor at the student health service prescribed penciclovir cream to decrease the severity and duration of his many cold sores. After 2 weeks of treatment, Mr. Smith's cold sores had mostly healed. However, he developed itching, redness, and blistering around the mouth in the areas where he had applied penciclovir. The drug was discontinued, Mr. Smith was given antihistamines, and the rash healed within a week. Now, at age 28, Mr. Smith has recently changed jobs and moved to a new city following the breakup of a long-term relationship. He has been under great stress at work and has been getting little sleep. He visited his physician because painful eruptions developed on his chest the previous day. His doctor diagnosed acute herpes zoster (shingles) and prescribed oral famciclovir 500 mg every 8 hours for 7 days. Later that day, after beginning his course of treatment, Mr. Smith went to the emergency department complaining of wheezing and an itchy rash over much of his body. His symptoms were consistent with those of a mild anaphylactoid reaction. What happened?

ANSWER: Famciclovir is a prodrug that is rapidly converted to penciclovir, with a bioavailability of 77%. Maximal plasma concentrations of penciclovir are reached within 45 to 60 minutes of famciclovir administration. Mr. Smith developed an allergy to topical penciclovir when he was treated with this drug during college. This prior contact sensitization to penciclovir allowed him to develop an anaphylactoid reaction following the conversion of oral famciclovir to penciclovir by hepatic first-pass metabolism.