for resistance are performed when failure of antiviral therapy is suspected (see later). In other clinical settings in which antiviral resistance may be relatively common, such as in HIV-1 infection, genotypic assays of virus isolates may be used to select or monitor an antiviral regimen.

QUANTITATION OF VIRUS (VIRUS LOAD)

Quantitation of virus in body fluids, most commonly in plasma but also in cerebrospinal fluid, is a measure of the extent and possible severity of a viral infection. Highly sensitive, specific, and precise assays for virus load are now commercially available and approved by the US Food and Drug Administration (FDA) and by Conformité Européenne (CE) marking in the European Union. The majority of these assays use nucleic acid amplification tests that report results in copies of nucleic acid per milliliter (see Chapter 16). Virus load measurements are used most frequently to monitor the effect of antiviral therapy, but they also may be used to establish or confirm the diagnosis and to provide assessment of the extent and possible severity of the viral infection. Their most extensive use is in patients with HIV-1 infection, in which plasma virus loads are used to monitor the effectiveness of antiretroviral therapy (see Chapter 128). The goal of antiretroviral therapy is to reduce viral load in plasma to below the level of detection of the assay, generally less than 20 to 80 copies of HIV RNA/mL in commercially available assays. Virus load assays are then periodically performed to ensure that the effect of antiretroviral therapy is maintained, and rises in virus load are investigated for cause, including assays for development of resistance. Virus loads are also used to assess the effect of antiviral therapy for hepatitis B and C infections and are the basis for definition of a sustained viral response to a particular antiviral regimen. Virus loads are also used to follow immunosuppressed patients with potential or established viral infections, including CMV, BK virus, and adenovirus. These may be used to assess whether the particular viral infection needs antiviral therapy or whether preemptive therapy might be desirable, as well as to monitor the effects of antiviral therapy, once instituted.

RESISTANCE TO ANTIVIRAL AGENTS

As is the case with antibacterial antibiotics, resistance to antiviral agents is also increasingly recognized as an important problem in antiviral therapy. The possibility of drug resistance is usually recognized because of a lack of clinical or virologic response to treatment. However, clinical failures of antiviral therapy may also involve drug-sensitive viruses in immunocompromised patients who are unable to mount effective host responses. Factors favoring the emergence of resistant variants include high viral replicative load, as in infections with prolonged and rapid viral turnover; high intrinsic viral mutation rates, which are generally greater in RNA than in DNA viruses; degree of selective drug pressure, which is higher with prolonged or repeated courses of drug therapy, particularly with suboptimal doses; and an antiviral target that can mutate without adversely affecting viral fitness. As a consequence, most drug-resistant viruses (including herpes simplex virus, varicella-zoster virus, CMV, and HIV-1) are recovered from immunocompromised patients, although resistant influenza A virus and hepatitis B and C viruses can be seen in immunocompetent individuals.

The consequences of the emergence of resistance may vary according to the specific virus and to the antiviral drug that is involved. If a resistant virus has similar replicative ability ("viral fitness") to the parent sensitive virus, then a failure of antiviral therapy may ensue and may be associated with prolonged or severe disease in immunocompromised hosts. If resistant variants are at some biologic disadvantage ("less fit") with respect to transmissibility, ability to establish chronic or latent infection, or ability to persist in the absence of selective drug pressure, emergence of resistance may have less overall impact or may be associated with an indolent clinical course.

Although the prevalence of resistant virus is generally related to increasing clinical use of drugs, the emergence and global spread of oseltamivir-resistant influenza A/H1N1 viruses in 2008, before the influenza A/H1N1 pandemic of 2009, did not appear to be related to concurrent oseltamivir use, nor did the subsequent emergence of resistance to the adamantanes. This highlights the limited understanding of factors associated with emergence of resistant strains. The laboratory selection of a drug-resistant strain of virus implies that the drug has a specific antiviral mechanism. The development of resistance results from mutations in the viral genome, and the presence of selective drug pressure leads to the emergence of a resistant virus population. Resistant subpopulations often exist naturally in clinical isolates, but resistant mutations can also arise during drug exposure. Single-nucleotide mutations leading to critical amino-acid substitutions in a target protein are often sufficient to cause antiviral resistance, as has been noted in HIV, hepatitis B and C, and influenza A virus infections.

COMBINATIONS OF ANTIVIRAL AGENTS

Combinations of antiviral agents with different mechanisms of action are used as a means to prevent or reduce the likelihood of development of drug resistance. Viral isolates from treated and even untreated patients may be genetically heterogeneous with respect to mixtures of sensitive and resistant viruses. They may also include viruses with different resistance mutations that affect similar mechanisms of action. In such cases, combinations of antiviral agents may provide broader activity than single agents alone. Combination antiviral therapy is now the standard of care in HIV and hepatitis C virus infections and is likely to become increasingly used in other viral infections.[18]

Combinations of antiviral agents have the potential advantage to increase antiviral activity by additive effects at the same site or at different tissue or cellular sites. This rationale has supported the use of combination therapy for particularly severe cases of viral infection, but evidence of clinical benefit is not available, other than for the infections noted earlier.

The use of combinations of antivirals also offers the opportunity to reduce individual drug dosage and perhaps reduce toxicity. However, combinations of antiviral agents may also result in increased toxicity, as is seen with combinations of interferon and ribavirin.

PHARMACODYNAMICS

Human pharmacokinetic studies that define absorption, stability in body fluids, tissue distribution, and metabolic fate of antiviral drugs are essential for selection of proper dosages and regimens of administration of antiviral agents. Data from such studies that describe relationships between antiviral drug concentrations in blood or other body fluids and clinical effects or toxicities, are not nearly as extensive as those compiled for antibacterial agents. However, such data for various antiviral agents are now becoming increasingly available.

The most extensive studies of pharmacodynamics of antiviral agents have been conducted with antiretroviral drugs. These have associated peak plasma concentration (C_{max}), trough plasma concentration (C_{min}), as well as area under the concentration-time curve (AUC) with virologic responses to antiretroviral agents (see Chapter 19). The AUC has been correlated with virologic effects for protease inhibitors,[32,33] including atazanavir, darunavir, nelfinavir, and lopinavir, as well as for the inhibitor of CCR5 binding by maraviroc.[34] Relationships of C_{min} with virologic responses have been noted for the NNRTIs nevirapine[35] and efavirenz.[36] Defining concentration-effect relationships between nucleoside analogue reverse-transcriptase inhibitors has been difficult because those drugs require intracellular phosphorylation, which may be impacted by different intracellular phosphorylation activities in different cell types and under different metabolic conditions.

Pharmacodynamic relationships have also been established for antiviral treatment of certain herpesvirus infections. Foscarnet, a pyrophosphate analogue that inhibits viral DNA polymerases of CMV and other herpesviruses, has a correlation of AUC with treatment effects and with development of toxicity.[37] In hepatitis C virus infection, virologic suppression by boceprevir and telaprevir is closely related to C_{min} concentrations.[38,39]

Topical application of an antiviral agent to the cornea, skin, mucous membranes, or respiratory tract is intended to provide high concentrations at the site of infection and to avoid the possible toxicity of systemic administration. However, topically applied drugs must be able to penetrate such barriers as stratified epithelium or local secretions to reach the site of active viral replication.

Progress in the development of antiviral drugs has been extraordinary during recent years. It has been accompanied by advances in understanding of the appropriate clinical use of such drugs for antiviral therapy and prophylaxis. Despite this success, antivirals are not yet available for the vast majority of viral infections. Thus this promises to be an area of continued major research activity, building on what has been learned from the considerable accomplishments thus far.

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45 Antiviral Drugs for Influenza and Other Respiratory Virus Infections

Fred Y. Aoki

SHORT VIEW SUMMARY

INFLUENZA A AND B

Neuraminidase Inhibitor Drugs

- Oseltamivir
  - Most influenza A and B viruses are inhibited in vitro at concentrations achievable with standard doses in patients.
  - Drug of choice for prevention and treatment of patients of all ages with influenza A or B.
  - Administered orally and well absorbed even in critically ill patients.
  - Effective in prevention and treatment of uncomplicated influenza in otherwise healthy adults.
  - Therapeutic efficacy is optimal when therapy is initiated as soon as possible after symptom onset.
  - Efficacy for treatment of those with avian influenza uncertain.
  - Observational studies during the 2009 swine flu pandemic indicate it is beneficial up to 5 days after symptom onset in patients with serious illness, including pregnant women.
  - Side effects are modest and primarily gastrointestinal.
  - Substantial data exist on its safety for the pregnant woman and her fetus based on use during the 2009 swine flu pandemic.
  - Failure due to selection of resistant mutants is not uncommon during prolonged treatment of immunocompromised patients.
- Peramivir
  - Intravenously administered neuraminidase inhibitor.
  - Shares cross-resistance of influenza A viruses resistant to oseltamivir.
  - Efficacious as a single-dose intravenous (IV) treatment for uncomplicated influenza in adult patients with symptomatic disease of no more than 2 days' duration.
  - Well tolerated.
- Zanamivir
  - Orally inhaled powder similar to oseltamivir in effectiveness. Active against oseltamivir-resistant strains.
  - May lead to bronchospasm in individuals with asthma or chronic obstructive pulmonary disease.
  - Efficacy of an experimental IV formulation of zanamavir based on case reports and a controlled trial comparing it with oral oseltamivir in hospitalized patients remains uncertain.

Endonuclease Inhibitor Drug

- Baloxavir
  - Inhibits cap-dependent endonuclease of influenza RNA-dependent RNA polymerase.
  - Active against multiple influenza A subtypes and influenza B, including oseltamivir-resistant strains.
  - A single dose of baloxavir was as efficacious as 5 days of oseltamivir, with greater effect in virus shedding.
  - Posttreatment viruses with reduced baloxavir susceptibility developed in 10% of baloxavir recipients and in no placebo recipients.
  - Place in influenza therapeutics is evolving.
  - Licensed in Japan in February 2017.

INFLUENZA A

Investigational Agents

- Laninamivir
  - Orally inhaled neuraminidase inhibitor with prolonged presence and effect in the respiratory tract.
  - Therapeutic efficacy remains uncertain.
  - A single dose inhaled once daily for 1 to 3 days prevents infection in household contacts of index cases when initiated within 48 hours of onset in the index case.
- Favipiravir
  - Inhibits a wide spectrum of RNA viruses in vitro and in vivo in animals.
  - Polymerase inhibitor.
  - Orally administered.
  - Clinical trials are underway, including in patients with influenza and Ebola virus infection.

Adamantanes

- Amantadine and rimantadine
  - Widespread resistance is present in currently circulating influenza A viruses, so the adamantanes should not be used unless sensitivity of isolates is demonstrated.
  - Orally administered and effective against uncomplicated influenza A.
  - Effectiveness in serious illness is not established.
  - Toxicity with amantadine is primarily central nervous system symptomatology, and with rimantadine is gastrointestinal intolerance.

RESPIRATORY SYNCYTIAL VIRUS AGENTS

- Ribavirin
  - A guanosine analogue with activity against a broad variety of viruses, including respiratory syncytial virus (RSV) and influenza.
  - Approved for aerosol administration to children hospitalized with RSV pneumonia or bronchiolitis.
  - Has been administered orally and intravenously to treat respiratory RSV and other virus infections in immunosuppressed patients.
  - Teratogenic, so aerosolized ribavirin should not be used near potentially pregnant staff.
- RSV604
  - An investigational agent that inhibits RSV through interaction with the nucleocapsid protein.
  - Well absorbed orally, and phase II studies are underway.

PARAINFLUENZA VIRUSES AGENT

- DAS181 (Fludase)
  - An investigational compound with activity against parainfluenza and influenza viruses.
  - An orally inhaled sialidase, it reduces virus binding to epithelial cells.
  - Has been used to treat parainfluenza 3 infections in immunosuppressed patients.
  - Development of adverse respiratory side effects may limit treatment to fewer than 7 to 10 days.
  - Development of antibodies may preclude repeated treatment courses.

TABLE 45.1 Antiviral Agents of Established Therapeutic Effectiveness for Respiratory Virus Infection

VIRAL INFECTION	DRUG	ROUTE	USUAL ADULT DOSAGE
Influenza Viruses			
Influenza A and B viruses	Oseltamivir	PO	75 mg bid for 5 d[a]
	Peramivir	IV	300 or 600 mg once
	Zanamivir	Inhalation	10 mg bid by inhaler for 5 d[b]
	Laninamivir octanoate	Inhalation	40 mg once[c]
Influenza A virus	Amantadine	PO	100 mg bid for 5 d for treatment[d]
	Rimantadine	PO	100 mg bid for 5 d for treatment[e]
Respiratory Syncytial Virus			
	Ribavirin	Aerosol	Aerosol treatment 18 h/d for 3–7 d[f]

Note: Please consult text and manufacturer's product prescribing information for dosage adjustments in renal or hepatic insufficiency and in other circumstances.
[a]Pediatric dosages: For infants 2 wk to <1 yr of age, dose is 3 mg/kg twice daily. For children ≥1 yr of age, doses are weight adjusted: 30 mg bid for <15 kg, 45 mg bid for 16–23 kg, 60 mg bid for 24–40 kg, and 75 mg bid for >40 kg. Prophylactic dosage is given once daily (one-half of total daily treatment dosage). Not US Food and Drug Administration (FDA) approved currently for prophylaxis in children <1 yr old or treatment in children <2 wk old.
[b]FDA approved at same dosage for treatment of children ≥7 yr. Prophylactic dose is 10 mg inhaled once daily for adults and children ≥5 yr old.
[c]Adult dose and for children ≥10 yr old. Pediatric dose: 20 mg once for children <10 yr of age.
[d]Maximum recommended dosage for older adults (≥65 yr old) is 100 mg/d. Recommended pediatric dosage is 5 mg/kg/d up to a maximum of 150 mg/d in divided doses. For prophylaxis, the same daily dosage should be given for period of risk.
[e]Pediatric dosage is 5 mg/kg up to a maximum of 150 mg/d in divided doses. Not approved by FDA for treatment in children <13 yr old. For prophylaxis, same daily dosage should be given for period of risk.
[f]Reservoir concentration of 20 mg/mL. Special aerosol-generating device (available from manufacturer) and expert respiratory therapy monitoring for administration are required. Higher reservoir concentration (60 mg/mL) given for 2 h tid is an alternative.

This chapter reviews antiviral agents against influenza viruses and certain other respiratory viruses, such as parainfluenza virus and respiratory syncytial virus (RSV) (Table 45.1). The antivirals are presented in alphabetical order in the text of the chapter and include licensed (approved) as well as investigational agents. Agents that have been investigated in rhinovirus infections but have been utilized primarily in non–respiratory tract infections, such as interferons and pleconaril, are discussed in Chapter 48.

AMANTADINE AND RIMANTADINE

Spectrum

Amantadine (1-adamantanamine hydrochloride; Symmetrel) and rimantadine (α-methyl-1-adamantane methylamine hydrochloride; Flumadine) are symmetrical tricyclic amines (Fig. 45.1) that specifically inhibit the replication of influenza A viruses at low concentrations (<1 μg/mL). Influenza B and C viruses are resistant.[1] In the past, epidemic human and avian strains of influenza viruses have generally been susceptible to amantadine.[2] However, since 2008–2009, influenza A(H1N1) and A(H3N2) isolates, the highly pathogenic avian H5N1 isolate, and the influenza A(H1N1)pdm09 isolate have become resistant to amantadine and rimantadine (discussed further under "Resistance").[3] By plaque assay, inhibitory concentrations of the drugs range from 0.1 to 0.4 μg/mL or less for sensitive human influenza A viruses. Rimantadine is 4 to 10 times more active than amantadine in some assay systems. Both drugs inhibit virus containing the M protein from the 1918 pandemic strain.[4]

Higher concentrations (10–50 μg/mL) inhibit other enveloped viruses in vitro, including parainfluenza, influenza B, rubella, dengue, several arenaviruses (Junin, Lassa, Pinchindé), rabies, and African swine fever virus, but these concentrations are not achievable clinically and can be cytotoxic in vitro.[5] Rimantadine has pH-dependent trypanocidal activity at concentrations of approximately 1 μg/mL[6]; amantadine at the same concentration in combination with doxycycline inhibits *Coxiella burnetii*.[7] Amantadine may transiently inhibit hepatitis C virus (HCV) replication in humans.[8]

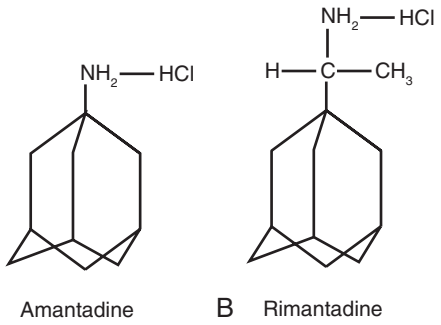

FIG. 45.1 Chemical structures of amantadine hydrochloride (A) and rimantadine hydrochloride (B).

These agents have prophylactic and therapeutic activity in experimental influenza A virus infection of animals after oral or parenteral dosing. Combinations of M2 protein inhibitors and neuraminidase inhibitors (NAIs) and ribavirin show enhanced antiviral and therapeutic effects in vitro or in animal models of influenza.[9–12]

Mechanism of Action

Amantadine and rimantadine share two concentration-dependent mechanisms of antiinfluenza action. Low concentrations inhibit the ion channel function of the M2 protein of influenza A viruses, which affects two different stages in virus replication.[13–15] The primary effect involves inhibition of viral uncoating or disassembly of the virion during endocytosis. For subtype H5 and H7 viruses, a late effect on hemagglutinin maturation and viral assembly is presumably mediated through altered pH regulation of the *trans*-Golgi network. Amantadine and rimantadine block proton permeation and prevent M2-mediated changes in pH. This action probably accounts for inhibition of the acid-mediated dissociation of the matrix protein from the ribonucleoprotein complex within endosomes early in replication and potentiation of acidic pH–induced alterations in the hemagglutinin during its transport late in infection.

Amantadine and rimantadine are also concentrated in the lysosomal fraction of mammalian cells. Drug-mediated increases in lysosomal pH may inhibit virus-induced membrane fusion events and account for the broader antiviral spectrum at higher concentrations. In contrast, the selective anti–influenza A virus effects are quickly lost after removal of the drug from the surrounding medium, which suggests that drug must be present in extracellular fluid early in the replicative cycle.

Amantadine inhibits the ion channel activity of expressed HCV p7 protein at low concentrations,[16] an effect that might account for its reported anti-HCV effects in vivo. Neither amantadine nor rimantadine inhibit HCV enzyme functions or internal ribosome entry in biochemical assays.[17]

Resistance

Amantadine-resistant virus is readily selected by virus passage in the presence of drug. Resistance with more than 100-fold increases in inhibitory concentrations has been associated with single amino acid substitutions at critical sites (positions 26, 27, 30, 31, and 34) in the transmembrane region of the M2 protein.[13] Analysis of 32,251 global M2 protein sequences from 1902 to 2013 for mutations known to mediate adamantane resistance revealed that 45% of influenza A virus H1 through H17 subtypes circulating globally are resistant. The vast majority of resistant viruses possess the S31N M2 protein mutation and about 1% possess the V27A mutation. H1, H3, H5, H7, H9, and H17 subtype influenza A viruses exhibit high-level adamantane resistance. Resistance mutants in H2, H4, H6, H10, and H11 subtypes were rare.

TABLE 45.2 Clinical Pharmacokinetic Characteristics of Amantadine and Rimantadine in Healthy Adults

	AMANTADINE		RIMANTADINE	
CHARACTERISTIC	**Young**	**Elderly**	**Young**	**Elderly**
Relative oral bioavailability (%)	62–93	53–100	75–93	NA
V_d (L/kg) at 200 mg/d	6.1 ± 2.1	3.6 ± 1.1	18.4 ± 9.6	11.5 ± 2.9
Plasma protein binding (%)	67	NA	40	NA
Clearance (mL/min/kg)				
Plasma or total	5 ± 2.1	2 ± 0.9	6.1 ± 1.9	4.7 ± 2
Renal	6.4 ± 3.7	2 ± 1.1	1.2 ± 0.4	NA
Nonrenal	0	0	6.4 ± 1.4	NA
Urinary excretion of unchanged drug (%)	62–93	53–100	8.3–43	NA
Plasma half-life (h)	14.8 ± 6.2	26.1 ± 9.7	29.1 ± 9.7	36.5 ± 14.5
Therapeutic range (ng/mL)				
C_{max}				
200 mg/d	475 ± 110	—	416 ± 108	447 ± 108
100 mg/d	—	362 ± 158	—	—
C_{trough}				
200 mg/d	302 ± 80	—	300 ± 75	310 ± 87
100 mg/d	—	301 ± 75	—	—

NA, Not available; *V_d,* volume of distribution.
Modified from Hayden FG, Aoki FY. Amantadine, rimantadine, and related agents. In: Yu VL, Edwards D, McKinnon S, et al., eds. Antimicrobial Therapy and Vaccines. *2nd ed. Pittsburgh, PA: E Sun Technologies; 2002:714.*

No adamantane-resistant mutants were identified in H8 or H12 through H16 subtypes.[18]

Amantadine and rimantadine share cross-resistance. In avian models, resistant viruses are virulent, genetically stable, and able to compete with wild-type virus so that transmission of drug-resistant virus may occur after cessation of drug use.

Before 2003, a small percentage of untreated patients (<1%) had infection with resistant influenza A virus.[19] However, approximately 30% of drug-treated ambulatory children and adults and 80% of hospitalized children or immunocompromised patients shed resistant virus.[20–22] Immunocompetent individuals shedding resistant virus resolve their illness promptly,[23] whereas immunocompromised hosts may experience prolonged illness associated with persistent virus shedding.[21] Transmission of M2 inhibitor–resistant virus, associated with failure of drug prophylaxis, occurs in household contacts of treated index cases[24] and in nursing home residents.[25] Resistant variants can cause typical influenza illness. It is prudent to avoid contact between treated patients and susceptible high-risk contacts, and to avoid use of treatment (specifically of young children) and postexposure prophylaxis in the same household.

Globally, up to 2003, epidemic influenza A H1N1 and H3N2 strains were M2 inhibitor sensitive. Since 2003, the prevalence of amantadine resistance has increased progressively, although rates vary by virus type and geography.[26,27,28] Among H3N2 isolates, amantadine resistance increased from 12% worldwide in 2003[26] to 91% by 2005 and greater than 95% in 2008–2009.[27] In the United States prior to March 2009, nearly all of the A(H1N1) isolates tested were sensitive to the adamantanes, but subsequently virtually all A(H1N1) isolates have been resistant, including the A(H1N1)pdm09 virus.[29] Among nonpandemic A(H1N1) isolates, the prevalence of amantadine resistance was 4% in 2004–2005 worldwide and 16% in isolates from 2005–2006, with rates ranging from 2% in South Korea to 72% in China.[27,30,31] The reason for the emergence and global spread of amantadine-resistant strains is unclear. Widespread inappropriate use of amantadine[32] and acquisition of undefined advantageous mutations combined with lack of fitness impairment may have been contributing factors. Ribavirin and the NAIs zanamivir and oseltamivir carboxylate inhibit M2 inhibitor–resistant strains.

Adamantane derivatives have been developed that inhibit amantadine-resistant and amantadine-sensitive influenza virus in vitro[33,34] and in vivo in animals with induced influenza.[33]

The triple combination of amantadine, oseltamivir, and ribavirin impedes the selection of drug-resistant influenza A virus in vitro at clinically achievable concentrations[35] compared to double combinations and the agents used singly in vitro.[36] The same combination of drugs was also synergistic in vitro in inhibiting the growth of both amantadine- and oseltamivir-resistant influenza A virus strains at concentrations that had no activity as single agents.[36] The clinical efficacy of this triple combination has been studied (see "Clinical Studies" later).[37]

Pharmacokinetics

The clinical pharmacokinetic characteristics of amantadine and rimantadine are shown in Table 45.2.

Amantadine

Amantadine is well absorbed after oral administration of capsule, tablet, or syrup forms.[5] Steady-state peak plasma concentrations average 0.5 to 0.8 μg/mL with a 100-mg twice-daily regimen in healthy young adults. Older adults require only one-half of the weight-adjusted dosage needed for young adults to achieve equivalent trough plasma levels of 0.3 μg/mL. Plasma protein binding of amantadine is about 67%, and amantadine's volume of distribution is large (4–5 L/kg). Nasal secretion and salivary levels of amantadine approximate those found in the serum. Cerebrospinal fluid (CSF) levels are 52% to 96% of those in plasma, and amantadine is excreted in breast milk.

Amantadine is eliminated largely unchanged in the urine by glomerular filtration and probably by tubular secretion by a bicarbonate-dependent organic cation transporter.[38] The plasma elimination half-life ($t_{½elim}$) is about 12 to 18 hours, ranges widely, and correlates with creatinine clearance (CrCl). Because of age-related declines in renal function, $t_{½elim}$ increases twofold in older adults and even more in patients with impaired renal function. Dosage reductions are required in renal insufficiency (see "Toxicity" later). Amantadine is inefficiently cleared in patients receiving hemodialysis or continuous ambulatory peritoneal dialysis, and additional doses are not required. Monitoring of plasma concentrations in such patients is desirable, but impractical.

Amantadine pharmacokinetics remained unaffected by concurrent administration of oseltamivir and ribavirin in healthy adult volunteers or stable immunocompromised patients.[39]

Rimantadine

Rimantadine is well but slowly absorbed, with the time to peak plasma concentration averaging 2 to 6 hours. Absorption does not seem to be decreased by food. With multiple doses of 100 mg twice daily, the steady-state peak and trough plasma concentrations in healthy adults are approximately 0.4 to 0.5 μg/mL and 0.2 to 0.4 μg/mL, respectively. In infants receiving dosages of 3 mg/kg each day, peak serum levels

range from 0.1 to 0.6 µg/mL. No important age-related changes in pharmacokinetics have been found in healthy older adults or in children. However, steady-state plasma concentrations in older nursing home residents receiving 100 mg twice daily average more than twofold higher (mean 1.2 µg/mL) than concentrations observed in healthy adults, which indicates the need for lower dosages in these patients. Plasma protein binding is about 40%. Rimantadine has a very large volume of distribution (about 12 L/kg), and concentrations in nasal mucus average 50% higher than those in plasma.

In contrast to amantadine, rimantadine undergoes extensive metabolism by hydroxylation, conjugation, and glucuronidation before renal excretion.[5] The plasma $t_{½elim}$ of rimantadine averages 24 to 36 hours. No clinically important changes in pharmacokinetics are found in patients with chronic liver disease without significant hepatocellular dysfunction. In hemodialysis patients with severe renal failure, the clearance of rimantadine is decreased by 40%, and the $t_{½elim}$ is about 55% longer. Reducing dosages by one-half (e.g., to 100 mg/day) is recommended for marked hepatic or renal insufficiency (CrCl <10 mL/min). Hemodialysis removes only a small amount of rimantadine, so supplemental doses are not required.

Interactions

The risks of central nervous system (CNS) adverse effects with amantadine and possibly with rimantadine are increased by concomitant ingestion of antihistamines, antidepressants, anticholinergic drugs, and other drugs affecting CNS function. Concurrent use of trimethoprim-sulfamethoxazole or triamterene-hydrochlorothiazide has been associated with CNS toxicity resulting from decreased renal clearance of amantadine. Cimetidine is associated with 15% to 20% increases, and aspirin or acetaminophen is associated with 10% decreases, in plasma rimantadine concentrations, but such changes are unlikely to be significant. Neither adverse clinical nor adverse pharmacokinetic effects are observed when amantadine and oseltamivir are coadministered.[40]

Concurrent administration of recommended doses of amantadine, oseltamivir, and ribavirin for 10 days was well tolerated.[39]

TABLE 45.3 Amantadine Dosage Regimens for Treatment in Patients With Normal and Reduced Renal Function

CONDITION	SUGGESTED DOSAGE
No Renal Insufficiency	
Children 1–9 yr	5 mg/kg/d in 2 divided doses, ≤150 mg/d
Ages 10–64 yr	100 mg q2d
Ages ≥65 yr	100 mg qd[a]
Creatinine Clearance (mL/min/1.73 m²)[b]	
≥75	100 mg (1.4 mg/kg) twice daily
74–35	100 mg qd
34–25	100 mg q2d
24–15	100 mg q3d
<15	100 mg q7d
Older Adults and Creatinine Clearance (mL/min/1.73 m²)[c]	
≥80	100 mg qd
60–79	100 mg and 50 mg on alternate days
40–59	100 mg q2d
30–39	100 mg twice/wk
20–29	50 mg three times/wk
10–19	100 mg and 50 mg on alternate wk

[a]Use weight-adjusted dosing for smaller patients (<50 kg). Dosages of 1.4 mg/kg/d have been suggested.[5]
[b]Based on adult dosage of 200 mg/d. Proportionate reductions should be made for older adults receiving lower dosages and for children.
[c]This dosing schedule for older adults with renal insufficiency is taken from the Canadian guidelines and has been found to be reasonably well tolerated.[49]
Modified from Wu MJ, Ing TS, Soung LS, et al. Amantadine hydrochloride pharmacokinetics in patients with impaired renal function. Clin Nephrol. *1982;17:19–23.*

Toxicity

Amantadine or rimantadine given in treatment courses of 5 days is generally well tolerated in young healthy adults.[41] Longer periods of administration, such as 6 weeks for seasonal prophylaxis in young adults,[41] or administration to fragile, elderly nursing home residents such as octogenarians for 10 days for outbreak control, are associated with a significant frequency of adverse reactions and drug withdrawals.[42]

A case-control study demonstrated that in children less than 12 months of age, amantadine and rimantadine were well tolerated, as was oseltamivir.[43] No evidence of adverse maternal or neonatal outcomes was observed after influenza antepartum treatment with adamantanes.[44]

The most common side effects related to amantadine ingestion are minor, dose-related gastrointestinal and CNS complaints, including nervousness, lightheadedness, difficulty concentrating, confusion, insomnia, and loss of appetite or nausea.[45] Complaints typically develop within the first week of administration, often resolve despite continued ingestion, and are reversible on drug discontinuation. Central nervous system side effects occur in approximately 5% to 33% of amantadine recipients at dosages of 200 mg/day, but are significantly less frequent with rimantadine. When amantadine is used for influenza prophylaxis in ambulatory adults, dosages of 200 mg/day are associated with excess withdrawals in 6% to 11% of recipients because of drug side effects. Dosages of 100 mg/day are better tolerated and may be protective against influenza illness. Amantadine dosage reductions are required in older adults (100 mg/day), but 20% to 40% of nursing home residents experience significant adverse effects on this lower dosage despite some adjustment for renal insufficiency.[46–48] Consequently, further dosage reductions based on CrCl are warranted in this population[49] (Table 45.3).

In the setting of renal insufficiency or high dosages, serious neurotoxic reactions, including delirium, hostility, hallucinations, tremor, myoclonus, seizures, or coma; cardiac arrhythmias; and death can occur in association with elevated amantadine plasma concentrations (1–5 µg/mL).[50] Neurotoxic reactions may be transiently reversed by physostigmine administration, and lidocaine has been used to treat ventricular arrhythmias. Long-term amantadine ingestion has been associated with livedo reticularis, livedo racemose,[51] peripheral edema, orthostatic hypotension, and, rarely, congestive heart failure, vision loss, corneal edema,[52] or urinary retention. Peripheral edema and livedo reticularis may improve if treatment is switched from amantadine to rimantadine.[53] Patients with preexisting seizure disorders have an increased frequency of major motor seizures during amantadine use, and dosage reductions are advised. Psychiatric side effects in patients with Parkinson disease and psychotic exacerbations in patients with schizophrenia may occur with addition of amantadine. Rash and leukopenia have been described rarely.

Rimantadine administration is associated with dose-related side effects similar to those observed with amantadine, although the risk for CNS side effects is lower with rimantadine at dosages of 200 or 300 mg/day in ambulatory adults.[5] During prophylaxis, excess withdrawal rates are usually less than 5%. In older nursing home residents, dosages of 200 mg/day are associated with higher side effect rates, whereas dosages of 100 mg/day seem to be better tolerated.[46,54] Rimantadine may uncommonly cause exacerbations of seizures in patients not receiving anticonvulsants, and was associated with an unexplained excess mortality in one nursing home study.[54]

The clinical observations of dry mouth, pupillary dilation, toxic psychosis, and urinary retention in acute amantadine overdose suggest that anticholinergic activity is present in humans. Amantadine shows activity on the adrenergic nervous system by affecting accumulation, release, and reuptake of catecholamines in the CNS and in the peripheral nervous system. Malignant ventricular arrhythmia after amantadine overdose has been described in humans.

Amantadine and rimantadine lack mutagenicity in vitro; carcinogenicity studies have not been reported for either. Amantadine is teratogenic and embryotoxic in rats, and rimantadine may cause teratogenic effects in rabbits and maternal toxicity and embryotoxicity at high dosages in

rodents. Both drugs are classified as pregnancy category C. Birth defects have been reported after amantadine exposure during pregnancy.[55] The safety of neither amantadine nor rimantadine has been established in pregnancy. Because of excretion in breast milk, use is not recommended in nursing mothers.

Clinical Studies

Influenza A

Amantadine and rimantadine have been efficacious for the prevention and treatment of influenza A virus infections in young healthy adults.[5,45,56] A systematic review of published studies in children and the elderly concluded that available data only demonstrate amantadine prophylactic efficacy and a modest therapeutic effect in children.[57] In the elderly, no data were available to support a conclusion of prophylactic or therapeutic efficacy of either adamantane. The emergence of widespread and nearly complete amantadine resistance among influenza A(H3N2) isolates,[27] as well as the amantadine resistance of the pandemic A(H1N1)pdm09 strain, precludes the empirical use of adamantanes for management of untyped influenza A outbreaks. Amantadine and rimantadine, both at a dosage of 200 mg/day in adults, are about 70% to 90% protective against clinical illness caused by various susceptible influenza A subtypes, including susceptible pandemic strains.[58] Prophylaxis is effective in preventing nosocomial influenza and possibly in curtailing nosocomial outbreaks caused by such strains. Protection seems to be additive to that provided by vaccine.[59]

Rimantadine was less effective than zanamivir in reducing cases of influenza A illness in adults in a long-term care facility.[60] The difference in protective efficacy was largely due to the emergence of rimantadine-resistant viruses that caused rimantadine prophylactic failure; no zanamivir-resistant viruses were isolated. Rimantadine administration to school-age children (5 mg/kg/day) decreased the risk for influenza A illness in recipients and possibly in their family contacts. Postexposure prophylaxis with these drugs provided inconsistent protection to family contacts, however, in part depending on whether ill index children were treated.[20] A dosage of 100 mg/day seems to protect against influenza A illness and is well tolerated in adults.[61]

Amantadine and rimantadine are also effective therapies for uncomplicated adamantane-susceptible influenza A illness in healthy adults,[5,23] but it is uncertain whether treatment reduces the risk for complications in high-risk patients or is useful in patients with established pulmonary complications. Early treatment in ambulatory adults (200 mg/day for 5 days) reduces the duration of fever and systemic complaints by 1 to 2 days, decreases virus shedding, and shortens time to resumption of usual activities.[23] In illness caused by H3N2-subtype influenza viruses, certain abnormalities of peripheral airways function, but not of airway hyperreactivity, resolve more quickly in amantadine-treated patients. Amantadine or rimantadine treatment in adults with leukemia or stem cell transplantation may reduce the risk for pneumonia,[62] but more recent data suggest that in stem cell transplant recipients, early NAI therapy may be preferred to adamantanes because it may prevent progression to pneumonia and decrease viral shedding, thereby possibly preventing both influenza-related death in index patients and nosocomial transmission to others.[63] In children, rimantadine treatment is associated with lower symptom burden, fever, and viral titers during the first 2 days of treatment compared with acetaminophen administration, but rimantadine-treated children have more prolonged shedding of virus. Treatment generally does not seem to affect immune responses to infection but may blunt secretory antibody levels.[64]

In a randomized controlled trial of 633 individuals,[37] 316 received the combination of amantadine (100 mg), oseltamivir (75 mg), and ribavirin (600 mg), and 317 received oseltamivir (75 mg) each twice daily for 5 days. Of evaluated patients, 80 of 200 (40%) in the combination group and 97 of 194 (50%) in the monotherapy group had influenza detectable by polymerase chain reaction (PCR) ($P = .046$) at day 3, but there were no differences in secondary clinical end points such as median duration of symptoms (4.5 days in the combination group and 4.0 days in the monotherapy group; $P = .21$).

Intermittent aerosol administration of amantadine or rimantadine seems to be therapeutically useful in uncomplicated influenza. No injectable formulation of either drug is available in the United States.

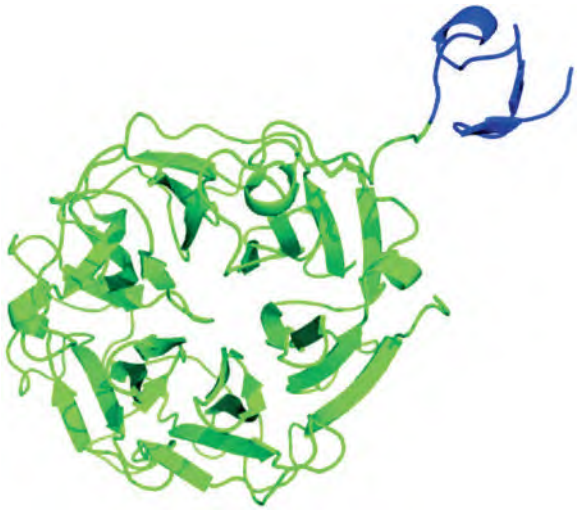

FIG. 45.2 Molecular model of DAS181. The catalytic domain of the *Actinomyces viscosus* sialidase is colored in green and the protruding amphiregulin anchoring domain on the C terminus in blue. *(From Malakhov MP, Aschenbrenner LM, Smee DF, et al. Sialidase fusion protein as a novel broad-spectrum inhibitor of influenza virus infection.* Antimicrob Agents Chemother. *2006;50:1470.)*

Other Viruses

Amantadine has been used in multiple trials for treatment of chronic hepatitis C with inconsistent evidence for increases in sustained viral response (SVR). In treatment-naïve patients, the addition of amantadine (200 mg daily in single or divided doses) to interferon (IFN)[65,66] or to IFN plus ribavirin[67] may modestly increase biochemical responses and the likelihood of SVR. In re-treatment of IFN nonresponders, the combination of IFN plus amantadine is ineffective,[68] but the addition of amantadine to the combination of IFN plus ribavirin may be associated with SVR in 10% to 25%.[69] Amantadine plus combined pegylated IFN (PEG IFN) and ribavirin may increase SVR modestly in treatment-experienced patients compared with PEG IFN plus ribavirin.[70] Reports of possible activity in *Bornavirus* infections and associated neuropsychiatric symptoms require confirmation.

DAS181 (FLUDASE)

DAS181 is an orally inhaled investigational antiviral agent with activity against influenza A and B viruses and parainfluenza viruses types 1, 2, and 3.[71–75] It has a novel mechanism of action in that it is a sialidase from *Actinomyces viscosus* (Fig. 45.2), linked to a respiratory epithelium-anchoring domain.[76] It cleaves the terminal sialic acid residues on the surface of human respiratory cells, thus reducing the binding of respiratory viruses, which use those as receptors. Desialylation is rapid and results in an antiviral effect, which lasts for at least 2 days.[77] The 50% effective concentration against influenza A and B viruses ranged from 0.04 to 0.9 nM.[71] DAS181 is active against influenza viruses that are resistant to NAIs.[78] Low-level resistance to DAS181 can be induced, but resistant variants appear to be reduced in fitness.[79]

In volunteers, adverse respiratory events developed after 7 days of therapy. Rapidly declining serum levels of drug appeared thereafter, consistent with the induction of DAS181 antibodies, which were detected in 15 of 18 subjects in day 30 serum samples. These effects could preclude use of this medication for longer than 7 days or for repeated courses.[80] In a phase II placebo-controlled trial in 177 subjects with influenza A and B virus infections, DAS181 was administered either as a single 10-mg dose or as a daily 10-mg dose for 3 days.[81] Compared to placebo recipients, DAS181 recipients had a statistically significant decrease in virus load determined by PCR between days 1 and 3 and days 1 and 5. However, there were no differences in resolution of clinical illness among the groups. Treatment for up to 3 days was well tolerated, although transient elevations in alkaline phosphatase were seen.[81]

DAS181 has also been utilized to treat parainfluenza virus type 3 infections in lung transplantation and stem cell transplantation

patients.[82,83] These case reports described clinical improvement, increased pulmonary function, and decreased virus loads. Additional clinical studies of DAS181 are being planned.

FAVIPIRAVIR (T-705)

Favipiravir (5-fluoro-2-hydroxypyrazine-3-carboxamide; T-705) is a potent broad spectrum inhibitor of influenza and other RNA viruses[84] (Fig. 45.3). In 2014 in Japan, a tablet formulation was approved as Avigan, an antiinfluenza drug with a mechanism of action different from those of marketed M2 inhibitors (adamantanes) and NAI drugs. It was approved for release at the request of the Minister of Health, Labor and Welfare of Japan for patients infected with novel or reemerging influenza viruses.

Favipiravir is a prodrug that is converted to the antiviral molecule T-705-4-ribofuranosyl-5-triphosphate (T-705) intracellularly.[85] T-705 inhibits RNA virus replication by selectively inhibiting RNA-dependent RNA polymerase and causing RNA chain termination after incorporation into the nascent RNA strand. T-705 inhibits influenza A/PR/8/34 (H1N1),[86] A(H1N1)pdm09,[87] A(H3N2),[87] A(H5N1),[88] A(H7N9),[87] and B viruses[87] both sensitive and resistant to oseltamivir. T-705 plus oseltamivir synergistically inhibit H1N1, H3N2 and H5N1 in vivo,[89,90] and prolong the treatment window for H5N1 infection in mice and in vitro.[91] Combinations of favipiravir and peramivir are more effective for treating pandemic influenza A/California/04/2009 (H1N1) virus infections in mice than suboptimal doses of each compound alone.[92] In 57 pairs of different influenza viruses isolated from patients pre– and post–T-705 administration, no instances of reduced susceptibility to T-705 or neuraminidase inhibition were observed.[87]

Few data on T-705 pharmacokinetics have been published. In hamsters, induced arenavirus hemorrhagic fever infection reduced T-705 plasma concentrations,[93] presaging what was observed in 66 T-705–treated patients with Ebola virus infection.[94] T-705 inhibits acetaminophen metabolism, but the effect is unlikely to be of clinical importance.[95] It does not prolong the QT interval after a single dose of 2400 mg.[96]

The use of T-705 for treatment of Ebola virus infection is discussed in Chapter 164.

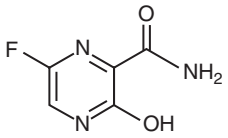

FIG. 45.3 **Chemical structure of favipiravir (T-705, Avigan).**

LANINAMIVIR OCTANOATE

Laninamivir octanoate (Inavir) is an investigational drug except for its approval in Japan. It is the prodrug of laninamivir, an inhibitor of influenza A and B neuraminidases.[97] Laninamivir is derived from zanamivir by replacement of its 7-OH group by a methoxy group.[98] Laninamivir is (2R,3R,4S)-3-acetamido-2-[(1R,2R-2,3-dihydroxy-1-metoxypropyl]-4-guanidino-3,4-dihydro-2H-pyran-6-carboxylic acid (Fig. 45.4D). Laninamivir octanoate consists of an octanoic acid ester side chain attached at the C_3 position of laninamivir. Laninamivir octanoate and polymeric zanamivir conjugates share the pharmacokinetic characteristic of persisting for a prolonged period in the respiratory tract after administration intranasally or intratracheally in animals or by oral inhalation in humans. These observations have presaged therapeutic effects of a single dose in animals with experimentally induced influenza and in patients with naturally acquired infection.

Spectrum

Laninamivir octanoate exhibits 1/30th to 1/50th of the influenza virus neuraminidase inhibitory activity of laninamivir in vitro.[99] However, its hydrolysis product is a potent inhibitor of neuraminidases of N1 to N9 influenza A viruses plus influenza B virus and their replication in cell culture at nanomolar concentrations.[100] These include seasonal and pandemic influenza A(H1N1), highly pathogenic avian influenza (HPAI) H5N1 viruses, and clinical isolates of oseltamivir-resistant A(H1N1), A(H3N2), A(H5N1), and A(H1N1)pdm09. Median inhibitory concentrations in cell culture vary over a wide range and in general appear to be intermediate between those of oseltamivir carboxylate (lower) and zanamivir (higher), but the clinical importance of these differences is not yet known.

In preclinical studies, laninamivir octanoate reduced fever in ferrets, mortality in mice, and virus concentrations in lung in ferrets and mice and in brain in mice after induced influenza with a variety of viruses: A/PR/8/34, HPAI H5N1, A(H1N1)pdm09, and B/Malaysia/2506/2004 as well as oseltamivir-resistant A(H1N1) and HPAI H5N1 clinical isolates possessing the H274Y mutation, as reviewed by Yamashita.[100] In these studies, laninamivir octanoate was administered as a single intranasal dose following intranasal inoculation of virus and was as, or more, efficacious than multiple doses of oral oseltamivir or intranasal zanamivir. The results of these studies in animals with experimental influenza have been replicated in part in therapeutic trials of a single laninamivir octanoate dose in the clinic (see "Clinical Studies" later).

Single doses of laninamivir octanoate are also efficacious prophylactically in mice. One dose prevents mortality and reduces virus concentration in lungs and brain when administered as much as 7 days before virus challenge.[101]

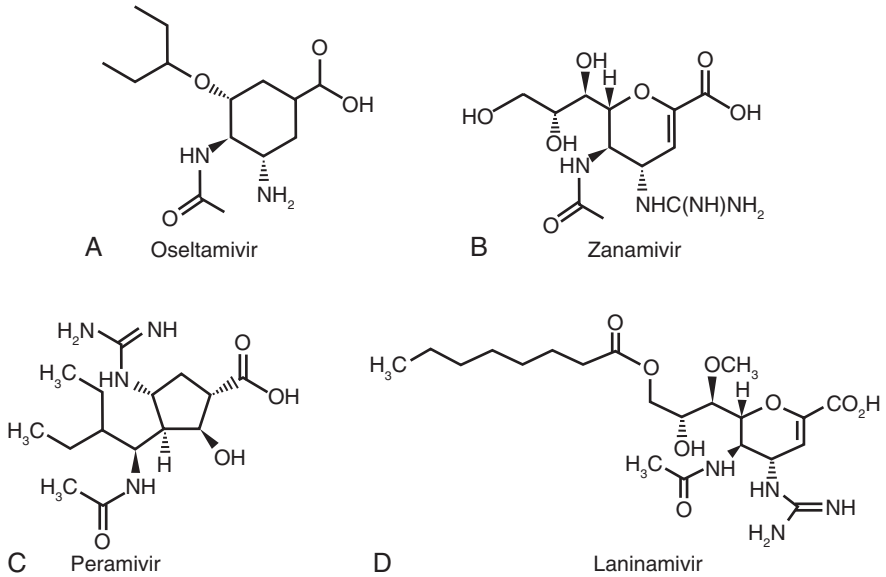

FIG. 45.4 **Chemical structures of oseltamivir carboxylate (A), zanamivir (B), peramivir (C), and laninamivir (D).**

Mechanism of Action

See subsequent discussion of mechanism of action under "Oseltamivir."

The basis for the prolonged persistence of laninamivir in the respiratory tract after intranasal or intratracheal administration of laninamivir octanoate in animals or oral inhalation in humans is not completely understood. In human volunteers, bronchoalveolar lavage samples obtained serially over 24 hours following oral inhalation of a single 40-mg dose of laninamivir octanoate revealed concentrations that exceed influenza virus neuraminidase inhibitory concentrations at all test times.[102] In mice, intranasal administration of ^{14}C-labeled laninamivir octanoate demonstrates prolonged retention of laninamivir in lung tissues. Microautoradiography indicates that laninamivir octanoate is taken into airway epithelial cells, seemingly hydrolyzed to the antiviral molecule laninamivir by intracellular esterases, and then released slowly extracellularly, perhaps as a result of its hydrophobic poor membrane permeability.[103] The cellular and molecular processes underlying these observations are not yet determined.

Resistance

Laninamivir resistance has been demonstrated infrequently. In the four winter seasons from 2010 to 2014 in Japan, where laninamivir has been marketed since 2010, no laninamivir resistance was observed in influenza A(H1N1)pdm09, influenza A(H3N2), and influenza B viruses.[104]

Pharmacokinetics

Epithelial lining fluid (ELF) concentrations of laninamivir octanoate and laninamivir calculated from analysis of bronchoalveolar lavage washings after a single oral inhalation of 40 mg laninamivir octanoate were 102.4 and 8.6 μg/mL, respectively, at 4 hours in healthy adult volunteers.[97] The disappearance half-times in bronchoalveolar lavage were 41 and 141 to 241 hours, respectively. The plasma $t_{½elim}$ values were 2.6 and 45.7 hours, respectively. Laninamivir concentrations in ELF exceeded the median inhibitory concentrations for influenza neuraminidases at all time points for 240 hours after dose inhalation. In other healthy adult volunteers, the pharmacokinetics of laninamivir octanoate and laninamivir were evaluated after oral inhalation of single doses from 5 to 120 mg.[105] Laninamivir octanoate appeared rapidly in plasma with a peak serum concentration (C_{max}) at 0.5 to 1.0 hour compared to 4.0 hours for laninamivir. Plasma $t_{½elim}$ values were 1.8 and 71.6 to 80.8 hours, respectively. The plasma area under the concentration-time curve (AUC) of laninamivir octanoate was linearly related to dose while that of laninamivir increased disproportionately. The mean cumulative excretion in urine over 144 hours was 2.3% to 3.6% and 10.7% to 14.6%, respectively.

After intravenous administration of ^{14}C-laninamivir in rats, almost 90% of the radioactivity was recovered in urine.[106] In human volunteers, the clearance of both laninamivir octanoate and laninamivir is linearly related toCrCl.[107] In subjects with none, mild, moderate, or severe renal impairment given a single orally inhaled dose of 20 mg laninamivir octanoate, the renal clearances of laninamivir octanoate and laninamivir are directly related to CrCl, whereas $t_{½elim}$ values are not. Geometric mean laninamivir octanoate clearance values declined from 26.0 mL/min in normal control subjects to 6.5 mL/min in patients with severe renal impairment. However, $t_{½elim}$ values were 2.3 to 3.5 hours and not different among the four groups. Laninamivir renal clearance declined from 65.0 to 12.7 mL/min across the four groups, while $t_{½elim}$ was not different among the groups, ranging from 53.2 to 57.0 hours. The likely explanation is that the elimination of both laninamivir octanoate and laninamivir reflects slow release of these compounds from tissues into plasma, rather than renal elimination, a pharmacokinetic concept called "flip-flop."[108] These pharmacokinetic data indicate that reduction of laninamivir octanoate doses may be appropriate for patients with renal impairment for pharmacokinetic reasons, but the lack of clear dose-related toxicity (see under "Toxicity") and the minimal absorption of orally inhaled drugs suggest that no dose adjustment will be needed.

Toxicity

Like orally inhaled zanamivir, orally inhaled laninamivir octanoate powder is well tolerated. In a double-blind study in healthy adult volunteers, single doses from 5 to 120 mg or multiple doses of 20 or 40 mg twice daily for 5 days were as well tolerated as placebo.[107]

In clinical trials, patients with influenza were randomized to single laninamivir octanoate doses of 20 or 40 mg in adults or children 10 years old or older, 20 mg in children less than 10 years old, or inhaled zanamivir as the control NAI treatment. Inhaled laninamivir octanoate once was as well tolerated as inhaled zanamivir 20 mg twice daily for 5 days.[109] In a double-blind trial in children 9 years of age or under with influenza, a single dose of inhaled laninamivir octanoate of 20 or 40 mg was as well tolerated as oral oseltamivir at 2 mg/kg body weight twice daily for 5 days.[110] In a phase III double-blind trial in adults 20 years of age or older with influenza, a single dose of inhaled laninamivir octanoate of 20 or 40 mg was as well tolerated as oral oseltamivir at 75 mg twice daily for 5 days.[111] Notwithstanding the lack of data from large, randomized, double-blind, placebo-controlled trials to establish the tolerability of laninamivir octanoate across the range of persons in healthy and high-risk groups, these published data on laninamivir octanoate tolerance plus those from studies of orally inhaled zanamivir collectively suggest that orally inhaled laninamivir octanoate will likely prove to be well tolerated and safe in the clinic.

Postmarketing studies of laninamivir octanoate in Japan concluded that the safety profile of laninamivir octanoate for abnormal behavior/delirium and syncope is similar to that of other NAIs.[112] In Japan, it is recommended in the product labeling that teenage patients inhaling laninamivir octanoate should remain under constant parental supervision for at least 2 days to monitor for behavioral changes to prevent associated self-injury. To avoid syncope, patients should inhale laninamivir octanoate in a relaxed sitting position. In another postmarketing survey for laninamivir octanoate tolerance, 50 of 3542 patients (1.4%) reported an adverse event.[113] Commonly reported adverse events included psychiatric disorders (abnormal behavior), gastrointestinal symptoms, and nervous system disorders such as dizziness, with frequencies of 0.48%, 0.45%, and 0.17%, respectively. These usually appeared on the day of laninamivir octanoate treatment and resolved in 3 days. These adverse reactions and their frequencies were considered comparable to those previously observed during clinical trials, and thus were thought to confirm no noticeable problem with safety.

A single orally inhaled dose of laninamivir octanoate appeared to be safe for pregnant women and did not increase the risk of miscarriage, preterm birth, or congenital malformation.[114]

Clinical Studies

No data from placebo-controlled trials have been published on the efficacy of orally inhaled laninamivir octanoate for influenza treatment, although other studies have demonstrated its efficacy for postexposure prophylaxis. Three randomized, controlled trials on the therapeutic efficacy and tolerance of laninamivir octanoate and one observational study comparing it to other NAIs have been reported. In these trials, laninamivir octanoate has been administered as an orally inhaled powder with a proprietary device that has two containers of 10 mg dry laninamivir octanoate powder. The manufacturer's instructions recommend two inhalations from each 10-mg chamber. For children, 4 inhalations are necessary, while 8 inhalations from two devices are required for adults. Occasionally, young children do not inhale the medication completely due to technical difficulty with the device.[109]

Of 112 pediatric patients with influenza of less than 48 hours' duration, evaluations were completed on 44 who were randomized to treatment with a single inhaled dose of laninamivir octanoate, 20 or 40 mg according to age, and 41 who were randomized to inhaled zanamivir 10 mg twice daily for 5 days.[109] Median times to fever resolution were 36 hours in the laninamivir octanoate groups and 37 hours in the zanamivir-treated group. This relatively small study suggested that a single dose of inhaled laninamivir octanoate was as efficacious as the recommended 5-day treatment with zanamivir. In another study, 184 children 9 years or younger with influenza of less than 36 hours' duration were randomized to a single oral inhalation of 40 ($n = 61$) or 20 mg ($n = 61$) laninamivir octanoate, or oseltamivir 2 mg/kg ($n = 62$) ingested twice daily for 5 days.[110] Of the 184 children, 112 (62%) were infected with influenza A(H1N1) virus, of which all but 4 cases possessed the H274Y mutation, mediating oseltamivir resistance. Thus oseltamivir therapy was likely

not to have been different from placebo. The median times to alleviation of influenza illness in children were significantly less (49.6 and 44.3 hours) in the laninamivir 40- and 20-mg groups, respectively, than in the oseltamivir-treated group (110.5 hours). Treatment effects on virus concentration and persistence in upper airway secretions were inconsistent, although on day 3, 10%, 0%, and 25% of subjects in the three groups, respectively, were still excreting virus. There were no clinical therapeutic or virologic differences among children infected with influenza A(H3N2) or B viruses, but the numbers of cases with these strains were small.

In a randomized, double-blind noninferiority trial, 1003 young healthy adults with febrile influenza for no more than 36 hours were randomized to receive either 40 mg or 20 mg laninamivir octanoate by oral inhalation once or oseltamivir 75 mg twice daily orally for 5 days.[111] The primary end point was time to influenza illness alleviation. Unfortunately, as in the pediatric study of Sugaya and Ohashi,[110] 66% of the subjects were infected with oseltamivir-resistant influenza A(H1N1) virus. The median times to resolution of illness in patients infected with this virus were 74.0, 85.8, and 77.8 hours, respectively, which were not different. Virus was detected by culture significantly less often at day 3 in the groups treated with laninamivir octanoate 40 mg (28%) and 20 mg (32%) than in the oseltamivir-treated group, which might be considered analogous to a placebo-treated cohort. Among cases infected with oseltamivir-susceptible influenza A(H3N2) virus, median times to illness alleviation were not different between the groups treated with laninamivir octanoate 40 mg (73.5 hours) and oseltamivir (67.5 hours) but were significantly longer in the group treated with laninamivir octanoate 20 mg (91.2 hours). There were no differences among the groups in H3N2 virus concentration in upper airway secretions or persistence. The 95% confidence intervals of the pooled analysis of all data were less than the prescribed noninferiority margin. It was concluded that a single inhalation of laninamivir octanoate is effective for treatment of seasonal influenza, including that caused by oseltamivir-resistant virus in adults.

In an observational study, 211 children with febrile influenza of less than 48 hours due to influenza A(H3N2) infection and 45 with A(H1N1) pdm09 infection were treated according to the recommendations of clinicians and the preference of patients or their guardians.[115] Of the 256 children, 119 were treated with oseltamivir in weight-appropriate doses, 124 with zanamivir, 4 with one dose of intravenous peramivir, and 9 with a single dose of orally inhaled laninamivir octanoate of 40 mg for those 10 years or older or 20 mg for those less than 10 years. The primary end point was duration of fever from the first dose of NAI. There were no differences in the duration of fever among the oseltamivir, zanamivir, or laninamivir octanoate groups. The median time to resolution of fever in the peramivir group (17.0 hours) was significantly less than in the other three groups.

The prophylactic efficacy of laninamivir for postexposure prophylaxis in household contacts of index cases who developed laboratory-confirmed influenza has been studied in three randomized, placebo-controlled trials. In the first trial, laninamivir 20 or 40 mg or placebo inhaled once on days 1 and 8 did not reduce the incidence of laboratory-proved influenza in contacts (3.6% [7 of 197 cases] and 3.7% [7 of 188 cases] in the two laninamivir treatment groups, respectively, compared to 6.6% [17 of 183 cases] in the placebo group).[116] Laninamivir 20 mg once daily for 2 days or 3 days reduced the incidence of influenza significantly to 3.9% (19 of 487 cases) and 3.7% (18 of 486 cases) compared to 16.9% (81 of 478 cases) in the placebo-treated group.[116] In another study, laninamivir 40 mg inhaled orally once and 20 mg inhaled once daily for 2 days both reduced the incidence of influenza significantly compared to placebo (4.5% [12 of 267 cases], 4.5% [13 of 269 cases], and 12.1% [32 of 265 cases] in the three groups, respectively).[117] In a third study, laninamivir 20 mg inhaled orally once by household contacts less than 10 years of age reduced the incidence of influenza significantly compared to placebo (11% [18 of 171 cases] compared to 19% [33 of 170 cases] in the two groups, respectively).[118]

In summary, a single inhaled dose of laninamivir octanoate is as efficacious as oral oseltamivir or inhaled zanamivir, both for 5 days, for treatment in children with influenza of less than 48 hours' duration, but this conclusion is not strongly supported by data from controlled trials. Efficacy in other populations, especially those with high-risk conditions, remains to be evaluated, as does the impact on complications of influenza. Laninamivir octanoate 20 or 40 mg inhaled orally is efficacious for postexposure prophylaxis in the household setting. The optimal dose is unclear: 20 mg/day for 2 or 3 consecutive days are also efficacious.

OSELTAMIVIR

Spectrum

Oseltamivir phosphate (Tamiflu) is the ethyl ester prodrug of oseltamivir carboxylate, a sialic acid analogue (Fig. 45.4A) that is a potent, specific inhibitor of the neuraminidases of influenza A and B viruses.[119,120] The metabolite, oseltamivir carboxylate, is approximately 50-fold more potent than the phosphate prodrug.[121] Oseltamivir carboxylate competitively and reversibly interacts with the active enzyme site to inhibit neuraminidase activity at low nanomolar concentrations.[122] Inhibitory concentrations for NAIs in cell culture have a broad range (≥1000-fold), depending on the assay method, and may not correlate with in vivo activity.[123,124] Oseltamivir carboxylate is active against viruses containing all nine influenza A neuraminidase subtypes recognized in nature, including more recent pathogenic avian viruses (H5N1, H7N7, H9N2), reassortant virus-containing neuraminidase from the 1918 pandemic strain, M2 inhibitor–resistant strains,[4,125] and the recently circulating (2009) pandemic A(H1N1) viruses (swine-origin influenza virus).[29] Resistance to oseltamivir has been recently reported in an H7N9 isolate.[126,127]

Influenza B viruses are 10-fold to 20-fold less susceptible to oseltamivir carboxylate than influenza A viruses, and influenza B virus illness responds less well clinically and virologically to oseltamivir than does influenza A illness.[128,129,130] The carboxylate is not cytotoxic and inhibits neuraminidases from mammalian sources or other pathogens only at 10^6-fold higher concentrations. Oral oseltamivir is active in murine and ferret models of influenza.[120,123] A prophylactic regimen given orally twice daily for 10 days completely protected ferrets against morbidity and mortality caused by H5N1 infection and did not interfere with development of protective immunity against subsequent H5N1 infection.[131] Neuraminidase inhibitors combined with M2 inhibitors or ribavirin show enhanced antiviral activity in vitro and in animal models of influenza A virus infection,[132] including H5N1 virus.[133,134] Amantadine combined with oseltamivir prevented the emergence of amantadine resistance in cell culture.[135]

Mechanism of Action

The NAI drugs oseltamivir, zanamivir, peramivir, and laninamivir share a common mechanism of action. Influenza neuraminidase cleaves terminal sialic acid residues on glycoconjugates and destroys the receptors recognized by viral hemagglutinin on cells, on newly released virions, and on respiratory tract mucins. This action is essential for release of virus from infected cells and for spread within the respiratory tract.[136] Inhibition of neuraminidase action causes newly formed virions to adhere to the cell surface and to form viral aggregates. Inhibitors thus limit spread of virus within the respiratory tract, and may prevent virus penetration of respiratory secretions to initiate replication.

Resistance

Resistant variants selected by in vitro passage with oseltamivir carboxylate or zanamivir have point mutations in the viral hemagglutinin or neuraminidase genes.[124,137] Hemagglutinin variants generally have mutations in or near the receptor binding site that make them less dependent on neuraminidase action for release from cells in vitro, and that confer cross-resistance among NAIs. Most of these variants retain full susceptibility in vivo.[124] Neuraminidase variants contain single amino acid substitutions in the framework or catalytic residues of the active enzyme site that alter drug binding and cause approximately 30-fold to more than 1000-fold reduced susceptibility in enzyme inhibition assays.[122] Influenza A variants selected by oseltamivir carboxylate are subtype specific, most commonly Arg292Lys in N2 and H275Y in N1, without cross-resistance to zanamivir. The altered neuraminidases have reduced activity or stability in vitro, and early studies of these variants usually demonstrated decreased infectivity and transmissibility in animals.[138] However, neuraminidase mutations in an A(H7N9)

strain led to enhanced replicative fitness and virulence.[139] Permissive additional neuraminidase mutations improved replication of oseltamivir-resistant A(H1N1) viruses with an H275Y neuraminidase change in vitro.[140]

Globally, prior to the first approval of an NAI drug in 1999, no oseltamivir-resistant strains were detected among clinical isolates.[141] Oseltamivir therapy has been associated with recovery of viruses with reduced susceptibility in about 1% of immunocompetent adult and 18% of pediatric recipients.[142,143] Generally, emergence of resistant variants has not been associated with clinical worsening, although prolonged recovery of resistant variants, sometimes in combination with M2 inhibitor resistance, has been observed in highly immunocompromised hosts.[144] Transmission of oseltamivir-resistant virus has been documented.[145,146] However, in 2007–2008, oseltamivir-resistant seasonal H1N1 virus appeared widely in immunocompetent individuals in Norway in the absence of antiviral pressure.[147] This mutant virus became the transmissible, pathogenic prevalent global H1N1 virus strain. Similarly, during and since the 2009 A(H1N1)pdm09 pandemic, there has been no linkage between prevalent use of oseltamivir in immunocompetent patients and the appearance of oseltamivir-resistant A(H1N1)pdm09 strains, which remain uncommon. Worldwide, from April 2009 to May 2014, the prevalence of influenza A(H1N1)pdm09 isolates with reduced susceptibility to oseltamivir has remained low at less than 3.4%, as reviewed.[148] Among influenza A(H3N2) global isolates to 2014, a very low pooled prevalence of oseltamivir resistance of 0.2% was observed.[148] Among influenza B global isolates from 2008 to 2014, 4 of 17,714 isolates reported in six studies were resistant to oseltamivir.[148] In the 2015–2016 influenza season in Japan, there was no trend toward decreased susceptibility to oseltamivir compared to results from 2010–2011 through to 2015–2016.[148]

On the other hand, oseltamivir-resistant isolates are not uncommonly recovered from immunocompromised patients being treated with the drug.[149] In one study, 17% (4 of 24) of immunocompromised hospitalized patients with influenza A(H1N1)pdm09 infection treated with oseltamivir shed resistant virus with the H275Y neuraminidase mutation.[150] Reports indicated that some of the A(H1N1)pdm09 oseltamivir-resistant strains retained replicative fitness, transmissibility, and pathogenicity comparable to wild-type oseltamivir strains in humans,[146,151] and in murine and ferret models of influenza infection.[152] Clinical illness caused by oseltamivir-resistant H1N1 strains in immunocompetent children responded less well to oseltamivir[153] as evidenced by higher fever at day 4 or 5 of treatment, although some found no evidence of prolonged illness in children infected with drug-resistant virus.[154] Others reported a significantly longer time to achieve nondetectable virus load in patients with oseltamivir-resistant H1N1 compared to oseltamivir-sensitive strains.[155]

Pharmacokinetics

Oral oseltamivir is rapidly absorbed and metabolized by esterases in the gastrointestinal tract, liver, and blood to the active carboxylate. The estimated bioavailability of the carboxylate is approximately 80%,[156] and its time to maximum plasma concentrations averages 2 to 4 hours. Dose proportionality of oseltamivir has been reported over the dose range from 75 to 675 mg. Only low blood levels of the prodrug are detectable. Rarely, possession of a constitutive variant of carboxylesterase 1, the enzyme that normally catalyzes the conversion of oseltamivir phosphate to carboxylate, can markedly impair the hydrolysis of the parent compound, resulting in the potential for a compromised antiviral effect after oseltamivir administration.[157] Ingestion with food delays absorption slightly but does not decrease overall bioavailability. Oseltamivir administered via a nasogastric tube to patients with respiratory failure requiring mechanical ventilation is well absorbed and converted to oseltamivir carboxylate.[158,159] In healthy adults, peak and trough plasma concentrations average 0.35 μg/mL and 0.14 μg/mL, respectively, after 75-mg doses.[160] In infants up to 1 year of age, systemic exposure (AUC_{0-12}) to the carboxylate exhibits decreasing variability while clearance increases.[161] Recommended doses of oseltamivir are 3.0 mg/kg twice daily for infants 0 to 8 months of age and 3.5 mg/kg twice daily for those 9 to 11 months of age. In children older than 1 year, carboxylate exposure increases gradually with increasing age[160] so that weight-based dosing is recommended.[162] In healthy elderly adults, overall drug exposure is about 25% greater than in younger adults, most likely due to differences in renal elimination. Morbid obesity (body mass index ≥40 kg/m^2) does not alter oseltamivir pharmacokinetics to a clinically important degree.[163–165] The effects of pregnancy on the pharmacokinetics of oseltamivir are unclear. One study reported no differences among women in the third trimester of pregnancy and historical controls,[166] whereas two reported 25% to 30% reductions in systemic (AUC_{0-12}) oseltamivir-carboxylate exposure in pregnant women compared to concurrent nonpregnant controls,[167,168] perhaps suggesting a need for 75 mg three times daily of oseltamivir for treatment.[167]

Plasma protein binding of the prodrug (42%) and the carboxylate (<3%) is low.[156] The volume of distribution is moderate (23–26 L). In animals, lower respiratory tract levels are similar to or exceed the levels in blood,[169] and in humans, the carboxylate is detectable in middle ear and maxillary sinus fluid at concentrations similar to those in plasma.[170]

Oseltamivir appears in breast milk.[171] In the ex vivo human placenta model, oseltamivir was extensively metabolized to the carboxylate moiety, but transplacental passage of oseltamivir carboxylate occurred at a low rate, inferring that fetal exposure during maternal treatment with oseltamivir may be minimal.[172] No carboxylate was detected in CSF in one child,[173] whereas C_{max} values in CSF were 2.1% and 3.5% of corresponding plasma concentrations for oseltamivir and oseltamivir carboxylate, respectively, in eight healthy adults after ingestion of 150 mg of oseltamivir.[174] After oral oseltamivir, the plasma $t_{½elim}$ of the carboxylate averages 6 to 10 hours in healthy adults. The prodrug and carboxylate are excreted primarily unchanged through the kidney; the carboxylate is eliminated by glomerular filtration and tubular secretion via a probenecid-sensitive anionic transporter. Clearance varies linearly with CrCl, such that $t_{½elim}$ increases to 22 hours in patients with CrCl less than 30 mL/min, and dosage reductions are needed.[156] Oseltamivir carboxylate is removed with different degrees of efficiency by different renal replacement therapies (peritoneal dialysis, hemodialysis, and continuous renal replacement therapies). Doses of oseltamivir for patients with renal impairment receiving renal replacement therapy have been published.[175] Extracorporeal membrane oxygenation per se does not appear to affect oseltamivir clinical pharmacokinetics,[176] although in another report, extracorporeal membrane oxygenation resulted in diminished clearance and increased volume of distribution.[177]

Uncomplicated influenza illness does not seem to alter the pharmacokinetics of oseltamivir.[156] Cystic fibrosis patients appear to clear oseltamivir carboxylate more rapidly than patients who do not have the disease.[178]

Interactions

Probenecid reduces renal clearance of oseltamivir by about 50%.[179] Few other clinically important drug interactions have been recognized to date. Sotalol appeared to induce a torsades de pointes cardiac arrhythmia during oseltamivir therapy of influenza.[180] Specific studies have found no clinically important interactions with antacids, acetaminophen, aspirin, known inhibitors of selected renal tubular secretion pathways, amoxicillin, cimetidine, cyclosporine, mycophenolate, tacrolimus,[156,181] warfarin,[182] rimantadine,[183] or dexamethasone.[184]

Toxicity

Preclinical studies have found no evidence of mutagenic, teratogenic, or oncogenic effects. High-dose oseltamivir causes renal tubular mineralization in mice and maternal toxicity in rabbits. It is classified as pregnancy category C.

Oseltamivir is generally well tolerated in patients of all ages, including pregnant women and fetuses,[185–187] and no serious end-organ toxicity has been recognized.[123,188–190] Oral administration is associated with nausea, epigastric distress, or emesis in about 10% to 15% of adults receiving 75 to 150 mg twice daily. These gastrointestinal complaints are usually mild to moderate in intensity, resolve despite continued dosing, and are ameliorated by administration with food. Nausea and vomiting (and possibly dizziness) are dose related in adults.[191] Discontinuation rates of 1% to 2% were observed in controlled treatment studies. The mechanism of nausea and/or vomiting is uncertain, but the risk

seems to be lower in older adults. Long-term prophylaxis has not been associated with an increased risk for adverse events,[123,192] although headache may occur in older recipients. Self-injury, delirium, and psychiatric illness have been reported in patients with influenza, primarily pediatric or adolescent, treated with oseltamivir, mostly in Japan.[193] Analyses of neuropsychiatric reactions among patients with influenza treated with oseltamivir in three large US administrative databases did not demonstrate such an association.[194–196] The decline in cases in Japan following a regulatory recommendation to restrict oseltamivir use in children 10 to 19 years of age has been associated with a decline in oseltamivir-related cases but a corresponding rise in cases associated with zanamivir, the inhaled, minimally systemically bioavailable NAI. The latter fact raises further doubts about a causal association between oseltamivir therapy and neuropsychiatric and behavioral adverse reactions in patients with influenza.[197]

Erythematous skin rashes and rare instances of severe eruptions of Stevens-Johnson syndrome, hepatic inflammation, hemorrhagic colitis, anaphylaxis, and thrombocytopenia have been reported, but their relationship to oseltamivir is uncertain. Oseltamivir administered to a patient receiving other serotonergic medication may have contributed to serotonin syndrome–like neurotoxicity.[198] Another case report suggested oseltamivir caused hypothermia and respiratory suppression.[199]

Clinical Studies

Oseltamivir is efficacious for the prevention and treatment of influenza A and B virus infection. In the United States, it is approved for the prevention of influenza in patients 1 year of age and older and the treatment of acute uncomplicated influenza in patients 2 weeks of age and older who have been symptomatic for no more than 2 days.[162]

In early clinical experiments in volunteers with induced influenza, it was demonstrated that oral oseltamivir is highly protective against experimental human influenza, and early treatment is associated with reductions in viral titers, symptoms, nasal cytokines, and middle ear pressure abnormalities.[123] Subsequent controlled trials in patients, largely healthy adults and children with naturally acquired mild to moderately severe seasonal influenza A infection, demonstrated that early oseltamivir treatment of acute influenza reduces the time to illness alleviation by up to 3.5 days, fever duration, and viral titers in the upper respiratory tract.[142,200,201,202–204] Earlier treatment maximizes the speed of resolution of illness.[200,205] Treatment of children reduces the risk for otitis media and decreases overall antibiotic use.[142,200] In healthy and high-risk adults with seasonal influenza, early treatment has been reported to decrease the risk for lower respiratory tract complications leading to antibiotic administration and to hospitalization,[206] but this has been questioned.[207] A meta-analysis of observational studies of high-risk patients with seasonal influenza concluded that oseltamivir treatment may reduce hospitalization, while treatment of hospitalized patients reduces respiratory failure, intensive care unit admission, and mortality.[208,209] In hospitalized adults with more severe illness due to A(H1N1)pdm09, oseltamivir provides similar benefits[210,211] even if treatment is started more than 48 hours after clinical illness has begun.[210,212,213] Experts convened by the European Centre for Disease Prevention and Control in February 2015 came to broadly similar conclusions.[214] In children, meta-analysis of five trials describing results of treatment with oseltamivir concluded that it reduced the duration of influenza illness and reduced the risk of developing otitis media.[201] A review of influenza virus infection in pregnancy concluded that early treatment with oseltamivir is associated with a reduced risk of severe disease.[215] Oseltamivir treatment initiated within 24 hours of illness onset did not reduce transmission to and illness in household contacts in one study,[216] although another study reported a slight reduction.[217]

Treatment with higher doses of oseltamivir (150 to 225 mg twice daily) did not appear to improve clinical[218–220] or virologic[218] outcome compared to the standard dose of 75 mg twice daily.

Combined treatment of influenza-infected patients with oral oseltamivir plus inhaled zanamivir was less effective than oseltamivir monotherapy[221] or zanamivir monotherapy.[222] Two controlled trials comparing oseltamivir plus intravenous peramivir,[223] or inhaled zanamivir, compared to oseltamivir alone[224] were underpowered to rigorously compare combination therapy and monotherapy. Combined therapy with oseltamivir, amantadine, and ribavirin reduced virus shedding at day 3 compared to oseltamivir monotherapy, but this difference was not associated with clinical benefit.[37]

In hospitalized patients with severe influenza, intravenous zanamivir 300 or 600 mg or oseltamivir 75 mg, all twice daily, were not different in efficacy or safety.[225] In an open-label, randomized study, clarithromycin 500 mg, naproxen 200 mg, and oseltamivir 75 mg, all twice daily for 2 days, followed by oseltamivir alone 75 mg twice daily for 3 days, reduced 30- and 90-day mortality more than oseltamivir alone in patients hospitalized with influenza.[226] Azithromycin combined with oseltamivir in hospitalized patients with influenza reduced inflammatory cytokines and C-reactive protein faster than oseltamivir alone, although symptoms did not resolve more rapidly nor were viral negativity rates attained more quickly.[227]

Oseltamivir is less efficacious for the treatment of influenza B than for influenza A virus infection in children[129,228] and adults.[129] An analysis of 284 cumulated cases of influenza A(H5N1) infections in a global registry demonstrated that crude mortality was significantly less in those treated with oseltamivir (40%) than in those not treated (76%) when started up to 6 to 8 days after symptoms onset.[230]

Oseltamivir treatment of hematopoietic stem cell transplant recipients with influenza may prevent the development of pneumonia and virus shedding, thereby preventing both influenza-related death in index patients and nosocomial transmission to others.[231] Of 21 patients with leukemia who developed influenza and were treated with oseltamivir, none died compared to 3 of 8 who were not treated.[232]

Prophylactic administration of once-daily oral oseltamivir (75 mg) is highly effective in reducing the risk for developing febrile illness during influenza season in unimmunized adults (efficacy 84%),[233] immunized nursing home residents (efficacy 92%),[234] and transplant recipients (efficacy 80%).[192] Prevention of influenza may reduce secondary complications in institutionalized older adults.[234] Once-daily oseltamivir for 7 to 10 days is also effective for postexposure prophylaxis in household contacts, including children, when ill index cases do[217,235] or do not[236] receive concurrent treatment. Oseltamivir chemoprophylaxis has been used to control institutional outbreaks of influenza A continuing despite M2 inhibitor use, and an influenza B outbreak.[237]

PERAMIVIR

Spectrum

Peramivir ([1S,2S,3R,4R]-3-[(1S)-1-(acetylamino)-2-ethylbutyl]-4-[(aminoiminomethyl)amino]-2-hydroxycyclopentanecarboxylic acid; Rapiacta) (see Fig. 45.4C) was first approved in 2010 in Japan, China, and South Korea for intravenous treatment of influenza. In 2013 in the United States, it was approved as a single-dose intravenous treatment for uncomplicated influenza in patients 18 years of age or older who have been symptomatic for more than 2 days.

Peramivir is a potent, selective inhibitor of influenza A and B virus neuraminidases, including those of all nine avian neuraminidase subtypes[238] and influenza A(H1N1)pdm09.[239] It is a sialic acid analogue designed to be structurally distinct from oseltamivir and zanamivir such that cross-resistance to it among oseltamivir-resistant and zanamivir-resistant strains is not consistently observed.[240,241] Like oseltamivir and zanamivir, peramivir inhibits influenza neuraminidase in enzyme assays at nanomolar concentrations[242] and requires micromolar concentrations to inhibit influenza replication in cell culture.[243] It is a more potent inhibitor of influenza A and B viruses in vitro than is oseltamivir or zanamivir.[243] The clinical relevance of this difference has not yet been evaluated. In murine and ferret models of influenza infection, peramivir is effective when administered intranasally,[244] orally,[245] and intramuscularly.[246]

Combination treatment of influenza A virus infection with peramivir and ribavirin in cell culture and in mice yields additive or synergistic interactions with no increase in toxicity.[247] The antiviral effect of combinations of peramivir plus rimantadine in vitro is variable, ranging from additive to synergistic.[248] In mice with experimental influenza infections, the combination of peramivir and rimantadine is synergistic.[249] The combination of two NAIs, oseltamivir plus peramivir, is synergistic.[250] At this time, the clinical importance of peramivir combined with another small-molecule inhibitor of influenza remains uncertain.

In a controlled clinical trial, intravenous peramivir at 600 mg daily plus oral oseltamivir did not accelerate symptom resolution more than oral oseltamivir alone.[223] More studies are required to determine whether the benefits of peramivir combined with other influenza virus inhibitors exceed those of monotherapy.

Mechanism of Action

See previous discussion of mechanism of action under "Oseltamivir."

Resistance

Peramivir-resistant influenza virus has been selected in vitro,[240,241,251,252] but not from peramivir-treated mice with experimental influenza infection,[253] healthy volunteers given peramivir for prevention or treatment of experimentally induced influenza A or B infection,[254] or healthy treated patients. A peramivir-resistant virus possessing the H275Y mutation emerged during intravenous therapy of the pandemic 2009 influenza A(H1N1) isolate in an immunocompromised patient.[255] Peramivir-resistant mutants generated in vitro may possess unaltered or diminished virulence and replicative capacity in mice and ferrets.[256] Peramivir resistance associated solely with an alteration in the hemagglutinin gene conferred cross-resistance to oseltamivir and zanamivir, and could cause lethal disease in mice. Infection with the resistant virus in mice was still amenable to peramivir therapy, however.[252]

The prevalence of resistance to peramivir in large collections of influenza virus isolates is low as of reporting to 2015.[257] In a survey of 2015–2016 influenza season outbreaks in Japan, peramivir resistance was low and unchanged from the 2010–2011 season.[258] Notwithstanding, there have been at least two outbreaks caused by peramivir-resistant H275Y neuraminidase mutant influenza A(H1N1)pdm09 isolates.[146,259] Nonetheless, resistance to peramivir arising in patients solely treated with it has not yet been reported.

Naturally occurring oseltamivir-resistant influenza viruses possessing the H275Y mutation have a 100-fold[239] to 661-fold[256] reduced susceptibility to peramivir, less than that of oseltamivir (982-fold), but such mutants are clinically uniformly cross-resistant to both drugs. Thus, although studies in mice[260,261] and high-risk patients[262] suggest that infection due to viruses possessing the H275Y mutation may be successfully treated with higher-dose regimens of injected peramivir, data from a case report[255] and an observational study[262] indicate that intravenous peramivir was not more effective than oseltamivir. In 2009, the World Health Organization recommended that for treatment of infection due to A(H1N1)pdm09 strains possessing the H275Y mutation, intravenous peramivir is likely to be suboptimal and intravenous zanamivir is preferred.[263]

Pharmacokinetics

The absolute oral bioavailability of peramivir is 2%.[264] As a result, clinical development has focused on its efficacy and safety after intramuscular and intravenous injection. Fortunately, its long elimination half-life supports single-dose intravenous treatment regimens. At doses up to 2 mg/kg in adults, plasma $t_{1/2}$ and $AUC_{0-\alpha}$ increase in proportion to dose. At higher doses of greater than 2 mg/kg being used in clinical trials in adults, initial estimate of plasma $t_{1/2}$ in healthy adults was approximately 20 hours,[265] which supports single-dose treatment. More recent studies in healthy adults given up to 800 mg intravenously once a day or 400 mg twice daily for 6 days[266–268] confirmed the dose proportionality of maximum plasma concentration and AUC_{plasma}. Apparent volume of distribution in adults was 0.4 L/kg and systemic clearance 89 mL/h/kg.[268] Approximately 90% of peramivir was excreted unchanged into urine within 12 hours after a dose. Mean plasma elimination $t_{1/2}$ after an intravenous dose of 600 mg ranged from 3.3 hours[268] to 8.8 hours.[269] The corresponding values for children with mean age of 9 years are plasma $t_{1/2}$ 7.7 hours, apparent volume of distribution 0.3 L/kg, and systemic clearance 173 mL/h/kg.[270] The physiologic counterpart of this large apparent volume of distribution is unknown, because no locus of drug sequestration has been identified.

Plasma protein binding is less than 30%. Peramivir concentrations in plasma are 10-fold to 50-fold higher than concurrent levels in nasal wash or pharyngeal gargle solutions.[264] Peramivir is detectable at these sites 24 hours after dosing, at concentrations greater than levels that inhibit neuraminidases of most strains of influenza virus. The clinical relevance of these data is unknown. Influenza infection increased peramivir clearance 18% and reduced volume of distribution 6%.

A 300-mg dose injected intravenously once in young healthy adults with influenza illness of less than 48 hours' duration is efficacious and well tolerated.[271] Infusion of this dose over a median of 38 minutes produced median plasma concentrations of 18,100 ng/mL at the end of the infusion and 14.8 ng/mL 18 to 24 hours later. A 600-mg dose yielded corresponding values of 36,300 and 32.8 ng/mL. The median inhibitory concentration for 50% of isolates (IC_{50}) for the neuraminidase of the patient viruses ranged from 1.15 nmol/L for A(H1N1), 1.36 nmol/L for A(H3N2), and 2.81 nmol/L for influenza B isolates.[262] In pediatric patients 1 month to 15 years of age with A(H1N1)pdm09 influenza infection, an intravenous infusion of 10 mg/kg once daily produced comparable plasma concentrations to those seen in young healthy adults (see earlier): median peramivir plasma concentrations were 33,150 ng/mL at the end of the infusion and 20.7 ng/mL 18 to 24 hours later.[270] The relationship of these plasma concentration data to efficacy is unclear. In mice, plasma AUC of peramivir is the pharmacokinetic characteristic related to efficacy.[272]

Data on peramivir distribution into breast milk in humans are unavailable.[264] In rats, less than 5% of ^{14}C-labeled peramivir administered is recovered in breast milk. Peramivir is eliminated unchanged into urine by glomerular filtration, and probenecid does not affect its excretion. In patients with renal insufficiency, mean $t_{1/2}$ ranges from 24 to 30 hours in subjects with mean CrCl of 21 to 68 mL/min. In individuals with dialysis-dependent renal failure, $t_{1/2}$ averages 79 hours.

In adults with normal renal function, the recommended intravenous dose is 600 mg/day and in children 6 to 17 years of age, 10 mg/kg intravenously once daily. For other age groups and patients with renal impairment, including end-stage renal disease requiring different renal replacement therapies, alternative doses have been suggested.[264,273]

Interactions

Adverse drug-drug interactions have not been reported in subjects given peramivir, but the number of individuals exposed is still modest. No pharmacokinetic interaction of intravenous peramivir and oral oseltamivir or rimantadine was observed in healthy volunteers.[269] Drug-drug interactions in individuals receiving peramivir are unlikely because it neither induces nor inhibits important drug-metabolizing cytochrome P-450 enzymes.

Toxicity

Peramivir is generally nontoxic and well tolerated. Preclinical studies revealed no genotoxicity, reproductive toxicity, or developmental toxicity.[264] In multiple species of animals, the only apparent adverse effect is reversible nephrotoxicity, which is species (rabbit only) and gender (female) specific. The nephrotoxic dose is greater than 200 mg/kg/day intravenously for 9 days.

The largest doses administered to humans, 800 mg orally[254] and 600 mg intravenously,[271] have not been associated with consistent adverse symptoms or laboratory abnormalities compared to placebo.[271] In placebo-controlled clinical trials of peramivir orally up to 800 mg/day for 4 to 5 days,[254] 300 mg/day intramuscularly once,[274] and 600 mg intravenously once,[271] adverse symptoms were not reported more frequently in peramivir recipients than in placebo recipients.

In controlled, blinded trials as well as uncontrolled studies of intravenous peramivir, it has been generally well tolerated and safe. In a randomized, double-blind study comparing a single dose of peramivir of 300 or 600 mg and a matching placebo given intravenously to 300 young healthy adults in an outpatient setting,[271] nausea may have been reported more frequently in drug recipients (3.0%, 6.1%, and 1.0%, respectively, in the three groups). Extensive blood and urine laboratory tests revealed no differences among groups. In a randomized, double-blind, double-dummy trial in young healthy adults with influenza treated with 300 mg and 600 mg peramivir intravenously once or oseltamivir 75 mg orally twice daily for 5 days, the overall incidence of adverse effects was lowest in the 300-mg group: 14.0% compared to 18.1% and 20.0% in the other groups, respectively. Diarrhea (3.8%, 5.5%, and 5.2%), nausea

(0.5%, 1.9%, and 4.4%), and a decreased neutrophil count (2.5%, 3.8%, and 3.6%) all tended to be lowest in the 300-mg peramivir group.[275] In the randomized, unblinded study in 137 hospitalized patients treated for influenza with intravenous peramivir 200 or 400 mg once daily, or oseltamivir 75 mg orally twice daily, all for 5 days, the "incidence of adverse events was low and generally similar among treatment groups."[269]

Assessment of side effects of intravenous peramivir in uncontrolled studies in hospitalized adults with high-risk comorbid conditions[262] also suggested that the drug was generally well tolerated. A single case of dilated cardiomyopathy or myocarditis in a volunteer infected with an influenza B challenge virus and treated with peramivir has been reported.[254] The relationship of the cardiac disorder to the drug is unknown.

Two postmarketing studies confirmed the safety and effectiveness of intravenous peramivir in pediatric patients ($n = 1254$)[276] and patients at high risk of influenza complications ($n = 772$).[277]

Clinical Studies

In a study in serosusceptible volunteers, peramivir prophylaxis with 50 to 800 mg orally daily or placebo, initiated 24 hours before influenza A or B virus challenge and continued for 5 days, tended to prevent illness at doses of 200 mg or greater and to reduce viral shedding and titer in nasal washings in subjects inoculated with influenza A virus.[254] No effect on preventing illness caused by influenza B virus was observed, although the duration of virus shedding tended to be less in individuals receiving 400 mg and 800 mg of peramivir.[254]

In early studies in patients with influenza, oral peramivir therapy with doses of 400 to 800 mg daily for 5 days[254] and single intramuscular doses of 150 mg or 300 mg[264] reduced median times to relief of symptoms, but the differences were not statistically significant from controls. Subsequently, controlled trials with an intravenous formulation demonstrated peramivir therapeutic efficacy and tolerance in patients with influenza due to susceptible virus strains. Peramivir treatment of naturally acquired influenza in young adults with illness of 48 hours' duration or less with 300 mg or 600 mg injected once intravenously versus placebo reduced median time to relief of symptoms significantly from 82 hours in the placebo group to 59 hours and 60 hours in the peramivir 300-mg and 600-mg groups, respectively, in the outpatient setting.[271] Peramivir treatments also significantly reduced the proportion of subjects still excreting virus in nasal and throat secretions at day 3 from 51% in placebo recipients to 26% to 37% in those treated with peramivir 600 or 300 mg, respectively.[271] Intravenous peramivir (300 or 600 mg once) was not different from oral oseltamivir (75 mg orally twice for 5 days) in two randomized, controlled trials in influenza-infected adults.[275,278] In 137 hospitalized patients randomized to 5 days' treatment with intravenous peramivir 200 or 400 g/day compared to historical reports with oral oseltamivir at 75 mg twice daily, the reduction in virus concentration in nasopharyngeal secretion was similar across the three treatments.[269] An additional study utilizing a higher dose of peramivir (300 mg twice daily or 600 mg once daily) in 234 hospitalized patients also showed no differences in virologic or clinical end points among the peramivir-treated regimens or compared to reported patients treated with oseltamivir.[279] A randomized controlled study of intravenous peramivir plus standard of care versus standard of care alone in patients hospitalized with influenza was recently terminated because of futility to show a difference between the peramivir and control groups.[223]

As noted earlier, intravenous peramivir is probably not effective for treatment of patients with oseltamivir resistance due to possession of the H275Y mutation; intravenous zanamivir has been recommended.

RIBAVIRIN

Spectrum

Ribavirin (1-β-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide; Virazole, Rebetol, Copegus) is a guanosine analogue (Fig. 45.5) in which the base and the D-ribose sugar are necessary for antiviral activity. Ribavirin inhibits the in vitro replication of a wide range of RNA and DNA viruses, including myxoviruses, paramyxoviruses, arenaviruses, flaviviruses, bunyaviruses, coronaviruses, togaviruses, reoviruses, herpesviruses, adenoviruses, poxviruses, and retroviruses. By plaque assay, inhibitory concentrations range from 3 to 10 μg/mL for influenza virus, parainfluenza virus, and RSV. High concentrations inhibit group C adenoviruses[280] and pathogenic flaviviruses,[281] including West Nile virus in neural cells. Ribavirin does not inhibit severe acute respiratory syndrome coronavirus in vitro.[282]

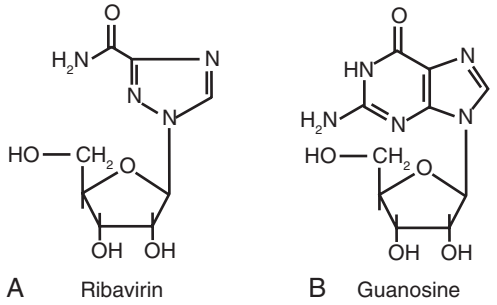

FIG. 45.5 Chemical structure of ribavirin (A) and the nucleoside guanosine (B).

Low concentrations of ribavirin (1–10 μg/mL) reversibly inhibit macromolecular synthesis and the proliferation of rapidly dividing cells.[283] Ribavirin decreases nucleic acid and protein synthesis, inhibits IFN-γ release, and increases apoptosis in human peripheral blood mononuclear cells in vitro,[282,284] but it does not adversely affect polymorphonuclear leukocyte functions.[285] Ribavirin has been postulated to enhance cell-mediated immune responses by increasing type 1 and suppressing type 2 cytokine responses in T cells,[285] and to decrease proinflammatory cytokine elaboration and inflammatory cell numbers. Inhibition of mast cell secretory responses occurs in vitro.

Aerosol administration is more effective than parenteral dosing in animal models of influenza and RSV infection. Parenteral ribavirin has antiviral and therapeutic activity in animal models of infection with Lassa virus, other arenaviruses, and bunyavirus (see Chapters 166 and 167). Combinations of ribavirin with immunoglobulin in RSV infection and with M2 inhibitors or NAIs in influenza A infection or with NAIs in influenza B infection show enhanced antiviral activity.[12] The use of ribavirin in treatment of hepatitis B and C is discussed in Chapter 47.

Mechanism of Action

The antiviral mechanisms of action of ribavirin are complex and most likely vary for different viruses. Ribavirin causes alterations of cellular nucleotide pools, inhibits viral RNA synthesis, and may cause lethal mutagenesis of certain RNA virus genomes.[285–287] Intracellular phosphorylation to the monophosphate, diphosphate, and triphosphate derivatives is mediated by host cell enzymes. In uninfected and RSV-infected cells, the predominant derivative (>80%) is the triphosphate, which is rapidly lost, with an intracellular $t_{½elim}$ of less than 2 hours.

Ribavirin monophosphate competitively inhibits inosine monophosphate dehydrogenase and interferes with the synthesis of guanosine triphosphate (GTP) and with nucleic acid synthesis. Decreased concentrations of competing GTP likely potentiate ribavirin's other antiviral effects. Ribavirin triphosphate inhibits influenza virus RNA polymerase activity and the GTP-dependent 5′-capping of viral messenger RNA. The monophosphate is incorporated inefficiently into viral RNA genomes, and this may lead to lethal mutagenesis and contribute to antiviral activity.[286] HCV RNA polymerase incorporates ribavirin monophosphate into viral RNA, which causes mutations and inhibits viral RNA synthesis.[288] Ribavirin diphosphates and triphosphates also inhibit human immunodeficiency virus (HIV) reverse transcriptase activity.[289]

Ribavirin has immunosuppressive effects in experimental animals, and shows therapeutic activity against transplantable virus-induced tumors and certain autoimmune diseases. Ribavirin increases type 1 cytokine–mediated immune responses in vivo, an effect that may contribute to its therapeutic activities,[285] and seems to augment type 1 cytokine responses ex vivo in peripheral blood mononuclear cells from patients with chronic hepatitis C.[287]

Resistance

Antiviral resistance to ribavirin has been documented only in Sindbis virus and HCV to date. One HCV RNA polymerase variant (F415Y)

selected in genotype 1a–infected, ribavirin-treated patients has been associated with ribavirin resistance in vitro.[290] No ribavirin-resistant RSVs have been detected during aerosol therapy of children.

Pharmacokinetics

Oral ribavirin is well absorbed, but bioavailability averages 45% to 65% in adults because of first-pass metabolism.[291–294] Administration with food increases absorption and peak plasma concentrations by 70%.[291] After single oral doses of 600 mg, 1200 mg, or 2400 mg, peak plasma concentrations occur at 1 to 2 hours and average 1.3 μg/mL, 2.5 μg/mL, and 3.2 μg/mL, respectively. Plasma concentrations average approximately 24 μg/mL and 17 μg/mL after intravenous doses of 1000 mg and 500 mg in patients with Lassa fever. During long-term administration, overall exposure and $t_{½elim}$ increase substantially.[291] Steady-state plasma levels of about 1 to 4 μg/mL occur by about 4 weeks with weight-adjusted dosing in chronic hepatitis C, and higher concentrations at 4 weeks correlate with decline in hemoglobin and likelihood of sustained viral responses.[295] Plasma protein binding is negligible, and ribavirin has a large volume of distribution (>2000 L). At steady state, CSF levels are about 70% of those in plasma.[293]

The disposition of ribavirin is complex, involving renal elimination and metabolism. After rapid initial distribution, there is a prolonged terminal $t_{½elim}$ of 37 to 79 hours.[291–293] Ribavirin triphosphate concentrates in erythrocytes with an erythrocyte-to-plasma ratio of 40 : 1 or greater, and erythrocyte levels gradually decline with an apparent $t_{½}$ of 40 days. Renal excretion accounts for approximately 30% to 60% of ribavirin's overall clearance, but the contribution of hepatic metabolism is significant. About 5% to 10% is recovered unchanged in the urine, and a much greater fraction is excreted as triazole carboxamide and carboxylic acid metabolites.[291] Plasma clearance is reduced threefold in patients with advanced renal impairment (CrCl ≤30 mL/min). Dosage adjustments are needed for renal insufficiency, and ribavirin should be used with caution in patients with CrCl less than 50 mL/min. Hemodialysis and hemofiltration remove small amounts of drug. Higher initial blood levels occur in severe hepatic dysfunction.[294]

With aerosol administration, systemic absorption is low (<1% of deposited dose). Peak plasma levels range from 0.5 to 2.2 μg/mL after 8 hours of exposure, and from 0.8 to 3.3 μg/mL after 20 hours in pediatric patients. Respiratory secretion levels often exceed 1000 μg/mL and persist with a $t_{½}$ of 1.4 to 2.5 hours. A special small particle aerosol generator (SPAG-2; Bausch Health) is needed to produce particles of proper aerodynamic size to reach the lower respiratory tract. The delivered dose is twice as high in infants (1.8 mg/kg/h) as in adults.

Toxicity

Ribavirin causes dose-related anemia because of extravascular hemolysis and, at higher dosages, suppression of bone marrow release of erythroid elements.[296] Reversible increases of serum bilirubin (in one-quarter of recipients), serum iron, and uric acid concentrations occur during short-term oral administration. Long-term use of oral ribavirin at dosages greater than 800 mg daily causes hemoglobin reductions of 2 to 4 g/dL in most recipients, usually within 4 weeks. When used in combination with IFN, hemoglobin levels less than 11 g/dL develop in 25% to 30% of patients.[297] Renal impairment increases the risk for hemolysis. Severe anemia requires dosage reduction or cessation, although erythropoietin has been used effectively.[297] Other reported side effects include pruritus, myalgia, rash, nausea, depression, nervousness, and cough or respiratory symptoms.[298] High-dose intravenous ribavirin is associated with headache, hypomagnesemia, and hypocalcemia.[299] Bolus intravenous dosing may cause rigors, so infusion over 10 to 15 minutes is advised.

Aerosolized ribavirin may cause conjunctival irritation, rash, bronchospasm, reversible deterioration in pulmonary function, and, rarely, acute water intoxication. No adverse hematologic effects have been associated with aerosolized ribavirin. The drug may precipitate on contact lenses, so they should not be worn during aerosol exposure. Ribavirin exposure may occur in health care workers working in the environment of aerosol-treated infants.[299,300] Health care worker exposure is higher during delivery by oxygen hood than by ventilator or vacuum-exhausted hood systems.[299] Use of aerosol containment and scavenging systems, turning off the aerosol generator before providing routine care, and use of personal protective equipment have been recommended.[300]

When ribavirin is used in conjunction with mechanical ventilation, in-line filters, modified circuitry, and frequent monitoring are required to prevent plugging of ventilator valves and tubing with precipitates of ribavirin. However, the effects of such modifications on drug delivery to the lower respiratory tract are undefined.

In preclinical studies, ribavirin is mutagenic, gonadotoxic, and teratogenic.[296] Low oral dosages have been teratogenic or embryotoxic in multiple species. Use of ribavirin is relatively contraindicated during pregnancy, and pregnant women should not directly care for patients receiving ribavirin aerosol. Ribavirin is categorized as pregnancy category X, and contraception for men and women is recommended for at least 6 months after discontinuation of treatment or exposure.

Interactions

Antacids slightly decrease the oral bioavailability of ribavirin. During coadministration clinically, ribavirin, amantadine, and oseltamivir do not interact pharmacokinetically.[39] Ribavirin antagonizes the anti–HIV-1 effects of zidovudine, but enhances the activity of purine dideoxynucleosides. Ribavirin use in patients who are coinfected with HIV and HCV and are taking antiretroviral drugs seems to increase the risk for mitochondrial toxicity and lactic acidosis, particularly when ribavirin is combined with didanosine. Ribavirin may inhibit the effect of warfarin.

Clinical Studies

Ribavirin aerosol is approved in the United States for treatment of RSV bronchiolitis and pneumonia in hospitalized children. Oral ribavirin in combination with various IFNs is approved for treatment of chronic hepatitis C. The following describes only clinical studies on the prevention and treatment of respiratory virus infection with ribavirin. Hepatitis C virus treatment is discussed separately (see Chapter 47).

Respiratory Syncytial Virus

Aerosolized ribavirin (18-hour exposure daily for 3 to 6 days) variably shortens the duration of virus shedding, and may improve certain clinical measures in infants hospitalized with RSV illness.[302] However, no consistent reductions in need for ventilatory support or duration of hospitalization have been documented. In infants receiving mechanical ventilation for RSV-related respiratory failure, no significant reductions in duration of ventilatory support, hospitalization, or mortality have been found.[302,303] Intermittent, high-dose therapy (2-hour exposures three times daily for 5 days) is well tolerated, and may be as effective as prolonged exposure.[304]

Use of aerosolized ribavirin is limited by concerns regarding its efficacy, ease of administration, risk of occupational exposure, and cost. The American Academy of Pediatrics states that aerosol treatment for RSV infection "is not recommended for routine use but may be considered for use in selected patients with documented, potentially life-threatening RSV infection."[305] Decreased RSV-specific serum neutralizing antibody titers, and diminished nasopharyngeal secretion RSV-specific immunoglobulin E and immunoglobulin A responses may occur in ribavirin-treated children. No long-term adverse or beneficial effects of ribavirin therapy have been documented in children.[306]

Combinations of aerosolized ribavirin and intravenous immunoglobulin or palivizumab may be beneficial in treating RSV pneumonia in hematopoietic stem cell transplant recipients,[307–310] whereas intravenous ribavirin alone is ineffective.[311] Aerosolized[312,313,314] and oral[315,316] ribavirin therapy appear to prevent progression from upper to lower respiratory tract illness in such patients. A similar benefit of preemptive treatment of RSV upper respiratory tract infection in lung transplant recipients with oral and inhaled ribavirin has been reported.[317,318]

Other Respiratory Viruses

Intravenous and aerosolized forms of ribavirin have been used to treat severe influenza virus infections.[319,320] Aerosolized ribavirin inconsistently reduces viral titers and illness measures in adults with uncomplicated influenza A or B, and has modest efficacy in children hospitalized with influenza.[321] However, oral ribavirin 300 mg three times per day combined

with amantadine 100 mg twice daily and oseltamivir 150 mg twice daily may possibly be effective for treatment of influenza A(H1N1)pdm09 disease, and more so than oseltamivir alone.[322] Oral, intravenous, and aerosolized ribavirin have been used in immunosuppressed patients with severe parainfluenza virus and adenovirus infections with inconsistent clinical benefits.[319,323,324] Intravenous ribavirin has been used to treat adenovirus-associated hemorrhagic cystitis, pneumonia, and invasive infections in immunocompromised patients, and it may be effective even in severe disease.[325,326] Use of intravenous[327,328] and oral[329] ribavirin for treatment of human metapneumovirus pneumonia in immunocompromised patients has been associated with resolution. Aerosolized ribavirin has been used in treating parainfluenza virus infections in solid-organ transplant recipients, but seems ineffective in parainfluenza virus pneumonia in hematopoietic stem cell transplant recipients.[323] Oral ribavirin was effective in accelerating functional graft recovery and reducing late bronchiolitis obliterans in 38 lung transplant recipients[330] and in a bone marrow transplant recipient[331] with parainfluenza respiratory infection. Intravenous ribavirin therapy was associated with successful treatment of paramyxovirus type 3 respiratory infection in cardiac transplant recipients.[332,333] Ribavirin has been used extensively in treating severe acute respiratory syndrome coronavirus infections without proven antiviral effects in vitro[282] or in patients,[334] and has been associated with frequent adverse effects.[299] Intravenous ribavirin seems to be ineffective in treatment of hantavirus cardiopulmonary syndrome,[335] However, it inhibits Andes virus, an important cause of this syndrome in vitro, and is effective in a hamster model of hantavirus cardiopulmonary syndrome caused by this virus (see Chapter 166).[336]

RSV604

RSV604 is an oral benzodiazepine compound ($C_{22}H_{17}FN_4O_2$) under development for treatment of RSV infections (Fig. 45.6).[337,338] It inhibits both RSV types A and B at submicromolar concentrations. Its antiviral activity is expressed through interaction with the RSV nucleocapsid (N) protein, which is highly conserved.[339] The drug is well absorbed orally, and a single dose per day is sufficient to achieve antiviral 90% effective concentration levels. In vitro resistance can be elicited, at an apparent low rate, and resistant virus appears similarly fit to wild-type RSV in terms of replication.[339] Phase II studies of RSV604 are underway in transplant patients with RSV infections.

ZANAMIVIR

Spectrum

Zanamivir (4-guanidino-2,4-dideoxy-2,3-didehydro-*N*-acetylneuraminic acid; Relenza) is a sialic acid analogue (see Fig. 45.4B) that is a potent and specific inhibitor of the neuraminidases of influenza A and B viruses.[340] It inhibits influenza neuraminidase activity at nanomolar concentration, but requires a higher and broader range of inhibitory concentrations in cell culture.[341,342] Compared with oseltamivir carboxylate, zanamivir is more active against influenza B, and data from a comparative trial in children indicate that this difference is clinically important.[343] Zanamivir is less active against neuraminidases of influenza A N2 clinical isolates,[344] but the clinical importance of this difference is uncertain. Zanamivir inhibits certain influenza A neuraminidase variants that are resistant to oseltamivir carboxylate.[122] Combinations of zanamivir plus rimantadine inhibit strains of influenza A(H1N1) and A(H3N2) viruses synergistically, but some concentrations seem antagonistic when assessed by reductions in cell-associated virus yield.[345] Zanamivir is not cytotoxic and is highly selective for influenza neuraminidase, inhibiting neuraminidases from human[346] and other mammalian sources or other pathogens only at 10^6-fold higher concentrations. Millimolar concentrations inhibit parainfluenza virus type 3 in cell culture, most likely by blocking attachment.[347] Topical zanamivir in the respiratory tract is active in murine and ferret models of influenza.[341] Zanamivir has recently been reviewed in detail.[348]

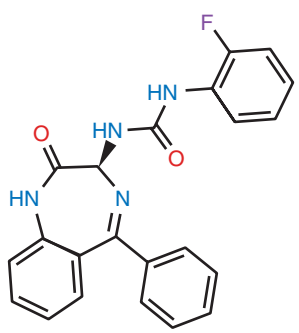

FIG. 45.6 **Chemical structure of RSV604.**

Resistance

Resistance to NAI drugs has developed less frequently than to the adamantane compounds and less frequently to zanamivir than to oseltamivir.

A recent systematic review of the prevalence of NAI resistance among influenza viruses cultured from immunocompetent ambulatory adults enrolled in prophylactic and therapeutic trials of zanamivir found no reports of zanamivir resistance.[349] In surveys of other collections of influenza isolates, a similar absence or dearth of zanamivir resistance was reported: influenza A(H1N1) viruses circulating in the 2008–2009 influenza season in the United States prior to emergence of the 2009 pandemic were resistant to oseltamivir but susceptible to zanamivir.[350] Among 391 nonpandemic A(H1N1) isolates from Australia and Southeast Asia patients from 2006 to 2008, 2.3% were resistant to zanamivir[351] but susceptible to oseltamivir. Zanamivir resistance was not demonstrated among 3359 influenza A(H1N1)pdm09 global isolates[352] nor among 304 oseltamivir-resistant isolates reported by the World Health Organization to August 2010.[353] From 2009 to 2014, the prevalence of zanamivir resistance among global isolates of influenza A(H1N1)pdm09, influenza A(H3N2), and influenza B isolates has been less than 1%.[348] In Japan in the 2015–2016 influenza season, there was no trend toward diminished susceptibility to zanamivir compared to results from 2010–2011 to 2015–2016.[348] Avian influenza A(H5N1) isolates from 2003 to 2005 were susceptible to zanamivir.[354] Of 680 influenza B viruses isolated in China from 2010 and 2011, one with D197N neuraminidase amino acid substitution was resistant to zanamivir.[355]

Several neuraminidase mutations mediate diminished susceptibility to zanamivir: Q136K in an A(H1N1) seasonal virus (300-fold reduction in zanamivir susceptibility),[351] S274N[356] in nonpandemic A(H1N1) virus, and I223R in an A(H1N1)pdm09 isolate (5-fold reduction).[357] The relationship of these virus resistance mutations and prior zanamivir therapy and host immune competence was not consistently apparent. An influenza B virus with an A152L mutation resistant to both zanamivir and oseltamivir was recovered from an immunocompromised child with prolonged virus excretion despite receipt of nebulized zanamivir.[358] The effect of these neuraminidase mutations on infectivity and transmissibility compared to the wild-type parental strains is variable, but only some mutants have been characterized in this regard.[358,359,360]

An observational study in pediatric patients with influenza treated with oseltamivir or zanamivir suggested that the lower prevalence of zanamivir than oseltamivir resistance is more related to the intrinsic properties of the drugs than to differences in the prevalence of use of the drugs.[361]

Pharmacokinetics

The oral bioavailability of zanamivir is low (<5%). The approved formulation is a dry powder containing a lactose carrier delivered by oral inhalation with a proprietary Diskhaler device. The proprietary inhaler device for delivering zanamivir is breath activated and requires a cooperative, trained patient. The use of the Diskhaler device is unreliable in young children, very infirm or elderly patients, or cognitively impaired patients. Although the inhaler has been used effectively in older adults,[362] more than half of hospitalized older adults could not correctly use the device after instruction.[363]

After inhalation of the dry powder using the Diskhaler, approximately 15% is deposited in the lower respiratory tract while the remainder is deposited in the oropharynx.[341,364] Zanamivir concentrations in epithelial lining fluid (ELF) obtained by bronchoalveolar lavage may approximate concentrations in alveoli. Median ELF concentrations of zanamivir 12 hours after oral inhalation of the recommended 10-mg dose by Diskhaler

in healthy volunteers ranged from 0.3 to 0.9 μg/mL.[365] In other uninfected individuals, median zanamivir levels in induced sputum were 1.34 μg/mL, 0.30 μg/mL, and 0.05 μg/mL at 6 hours, 12 hours, and 24 hours after dosing, respectively, with the pulmonary $t_{½elim}$ estimated to be 2.8 hours.[366] Approximately 4% to 17% of an inhaled dose is absorbed systemically, and peak plasma levels are low, averaging 0.04 to 0.05 μg/mL.[341] Because of the low bioavailability of zanamivir inhaled orally, dosage adjustments are not indicated in renal insufficiency.

After intravenous dosing, the plasma $t_{½elim}$ of zanamivir ranges from 1.6 to 2.9 hours,[341,365] with about 90% eliminated unchanged in the urine.[341] Following intravenous administration of 600 mg zanamivir to healthy adults, the median serum C_{max} is 39.4 μg/mL, $AUC_{0–12}$ is 86.6 μg·h/mL, and C_{trough} is 0.6 μg/mL. The pharmacokinetic apparent volume of distribution is independent of dose and averages 14.8 liters.[364] The median ELF concentration 12 hours after dosing is 0.4 μg/mL, very similar to the value after inhalation of 10 mg (see earlier). This is 552 to 1653 times the in vitro IC_{50} for influenza A and B neuraminidases, respectively.[344]

The pharmacokinetics of zanamivir administered intravenously to adults with and without renal impairment were similar to those in previously described studies.[367] Zanamivir renal clearance declines linearly with increasing renal impairment.[368] The suggested dose for adults with normal renal function is 600 mg intravenously given twice daily. Doses for children and for patients with renal impairment who are or are not receiving replacement therapy have been published.[369]

Interactions

No clinically significant drug interactions have been recognized for inhaled zanamivir. Zanamivir at concentrations up to 150 mg/L did not inhibit the metabolism of eight cytochrome P-450 isoenzyme probe substrates by human hepatocyte microsomes in vitro.[370] No clinically relevant pharmacokinetic interaction was demonstrated between oseltamivir 150 mg taken orally twice daily and zanamivir 600 mg administered intravenously every 12 hours in healthy volunteers.[371] Zanamivir does not affect the immune response to injected inactivated influenza vaccine, but similar to all antiviral medications, it has the potential to impair the immunogenicity of live-attenuated influenza virus vaccine administered concurrently. Zanamivir should not be administered from 48 hours before to 2 weeks after intranasal administration of an attenuated influenza vaccine.[372]

Toxicity

Preclinical studies of zanamivir found no evidence of mutagenic, teratogenic, or oncogenic effects. In cell culture, the inhibitory effect of zanamivir on influenza virus replication was not impaired by analgesics, antihistamines, decongestants, or antibacterial drugs.[373] Zanamivir is classified as a pregnancy category C agent.

Orally inhaled zanamivir is generally well tolerated, and the frequencies of complaints are not significantly different from those in placebo recipients among adults and children 5 years old or older.[341,373,374] This includes once-daily oral inhalation for prophylaxis by adults for 16 weeks.[375] Most reported symptoms in treatment studies are likely the result of the underlying illness. Similarly, in high-risk patients receiving zanamivir or placebo, no differences in adverse reactions have been seen in controlled trials.[376] In patients with mild to moderate asthma or chronic obstructive pulmonary disease, orally inhaled zanamivir is associated with fewer bronchitis episodes, similar measurements of forced expiratory volume in 1 second, and more rapid improvement in peak expiratory flow rate than with inhaled placebo.[378] However, postmarketing reports indicate a potential risk for acute bronchospasm, respiratory arrest, or worsening of chronic obstructive pulmonary disease accompanied by pulmonary edema after zanamivir inhalation, particularly in patients with underlying airway disease.[379] Apparent declines in respiratory function have also been rarely reported in patients without recognized airway disease. Consequently, use in patients with underlying airway disease is not generally recommended in the United States, although zanamivir is administered as treatment in at-risk patients in other countries.[380] If used in patients with obstructive airway disease, zanamivir should be administered cautiously under close observation and with availability of fast-acting bronchodilators.

Zanamivir inhaled as an experimental nebulized solution containing 16 mg/mL for 10 minutes four times a day for 5 days for treatment of serious influenza with lower respiratory tract signs in hospitalized patients 10 years or older was well tolerated.[381] However, when the oral formulation containing lactose has been reformulated as a solution and administered into the airway during mechanical ventilation, lactose precipitation in the airway filters has caused obstruction,[382] precluding the reformulation of the powder in the orally inhaled formulation into a solution for nebulization and inhalation.

Zanamivir injected intravenously to healthy volunteers in doses from 50 to 600 mg twice daily for 5 days was also well tolerated.[383] In 130 hospitalized adults with influenza treated with 600 mg zanamivir intravenously twice daily for 5 days or reduced doses in those with renal impairment, no safety signals or clinically significant trends in laboratory values, vital signs, or electrocardiograms were identified that were considered attributable to the drug.[384]

Clinical Studies

Zanamivir has been administered to patients intranasally as a spray, by oral inhalation as a dry powder, by nasal inhalation as an aerosol from a nebulized solution, and by intravenous injection.

Intranasal and intravenous zanamivir are highly protective against experimental human influenza, and early treatment is associated with reductions in viral titers, symptoms, and middle ear pressure abnormalities.[203,341,385] Orally inhaled zanamivir powder is approved in the United States for prevention of influenza in individuals 5 years old and older, and for treatment of influenza in individuals 7 years old and older. Zanamivir (10 mg twice daily for 5 days) inhaled early in the course of illness for treatment of uncomplicated influenza in previously healthy adults and children 5 to 12 years old shortens the times to illness resolution and return to usual activities by 1 to 3 days.[374,386,387] Treatment benefits seem to be greater in patients with severe symptoms at entry, in patients older than 50 years, and in higher-risk patients.[388] Inhaled zanamivir treatment in adults is associated with a 40% reduction in lower respiratory tract events leading to antibiotic use and a 28% overall reduction in antibiotic prescriptions.[389]

Zanamivir inhaled orally is equally efficacious for treatment of influenza A and B infection.[387,390] In individuals with influenza B illness, zanamivir reduces the median duration of fever by 32%, from 53 hours to 36 hours, compared with oseltamivir.[343] In high-risk patients with primarily mild to moderate asthma or other chronic cardiopulmonary conditions, orally inhaled zanamivir treatment reduces illness duration and the incidence of complications leading to antibiotic use.[378,391] It has been used to treat immunocompromised hosts with influenza A and B infections,[392] including a child to whom an aqueous zanamivir solution (16 mg/mL) was administered by aerosol and nebulizer via an endotracheal tube.[393] More recently, in an observational study, orally inhaled zanamivir was more efficacious for treatment of oseltamivir-resistant influenza A(H1N1) than oseltamivir.[394]

Prophylactic administration of once-daily inhaled zanamivir (10 mg) prevents febrile influenza illness during influenza season (84% efficacy),[395] or when used for postexposure prophylaxis in households with or without treatment of the ill index case (82% efficacy).[396,397] In an observational study with limited numbers of patients, orally inhaled zanamivir and oral oseltamivir were not different for prevention of secondary cases during nosocomial outbreaks on pediatric wards.[398] In nursing home residents, 2 weeks of inhaled zanamivir was superior to oral rimantadine in preventing influenza A infection, in part because of a high frequency of rimantadine resistance,[399] and inhaled zanamivir has been used to curtail transmission of amantadine-resistant influenza A in nursing homes.[362]

Orally inhaled zanamivir has been administered in combination with oral oseltamivir. For postexposure prophylaxis in families, such combined zanamivir-oseltamivir administration was not more efficacious than either agent alone.[222] However, a subgroup analysis suggests greater efficacy of the combination treatment among contacts whose prophylaxis was commenced within 24 hours of exposure to the index case compared to oseltamivir or zanamivir alone. For treatment of adults with mainly A(H3N2) influenza, zanamivir-oseltamivir combination treatment was not more efficacious than zanamivir alone and was less efficacious than oseltamivir monotherapy.[221]

Zanamivir has been administered intravenously to treat patients seriously ill with influenza who could not receive, or who had failed, oral oseltamivir therapy. Immunocompetent[400] and immunocompromised[401,402] patients who were infected with oseltamivir-resistant[403] and oseltamivir-susceptible[402,404] A(H1N1) nonpandemic viruses or with oseltamivir-resistant pandemic virus[405] or oseltamivir-sensitive A(H1N1) pdm09 virus[401,406] have been successfully treated with intravenous zanamivir. There is a sense that intravenous zanamivir may be lifesaving.[407] However, an apparent lack of a relationship between intravenous zanamivir treatment-associated reductions in pandemic virus load in upper and lower respiratory tract secretions and mortality have prompted questions about its effectiveness in seriously ill patients.[408] A phase III study comparing intravenous zanamivir at 300 or 600 mg per dose compared to oral oseltamivir 75 mg, all twice daily for 5 days, demonstrated no differences in efficacy or safety in hospitalized patients.[225]

POLYMERIC ZANAMIVIR CONJUGATES

Polymeric zanamivir conjugates are experimental, high-molecular-weight antiinfluenza compounds comprising multiple zanamivir monomers connected at the 7-OH position to backbone or linker molecules of various types and lengths.[409–415] These compounds are second-generation potential inhaled NAIs for influenza chemoprophylaxis and therapy with enhanced potency and prolonged lung retention time compared with zanamivir. In mice, one of these compounds has been associated with prophylactic efficacy for 7 days after a single intranasal administration. Polymeric zanamivir conjugates have recently been reviewed.[348]

Spectrum

Polymeric zanamivir conjugates exhibit broad-spectrum antiinfluenza activity, inhibiting human influenza A N1 and N2 and influenza B viruses and an avian influenza A(H5N1) virus.[409] Inhibitory potency varies according to the length[411] and type of linker molecule,[410] and the number of zanamivir derivatives, whether dimeric,[409] trimeric, or tetrameric.[412] The most potent polymeric zanamivir conjugate is a dimer with a 14-carbon linker, which was 10-fold less potent than zanamivir alone in a neuraminidase enzyme inhibition test (IC_{50} = 7.86 nM vs. 0.76 nM for zanamivir), but is 500,000-fold more potent in inhibiting influenza A/WSN/33 (H1N1) in a cytopathic reduction assay (IC_{50} = 0.0001 nM vs. 56 nM for zanamivir).[409] In mice, this dimeric conjugate is 100 times more potent than zanamivir in preventing influenza virus replication in the lung for 7 days after a single intranasal dose of drug, and 1 day after intranasal virus challenge (drug doses to reduce lung virus titer by 90% were 0.03 mg/kg and 2.92 mg/kg for the dimeric conjugate and zanamivir, respectively). The prophylactic effect is associated with prolonged persistence of dimer conjugate in lung tissue after intranasal administration (see under "Pharmacokinetics"). The specificity of polymeric zanamivir conjugates for influenza A and B neuraminidase is presumed but not yet reported.

A zanamivir polymer can overcome zanamivir resistance. A zanamivir polymer bound to the neuraminidase of zanamivir-resistant avian influenza A viruses possessing a resistance mutation at position 119 bound as much as 2000 times more strongly than did monomeric zanamivir.[416]

Mechanism of Action

The synthesis of polymeric conjugates of zanamivir that retain NAI activity is possible because of the unique position of the molecule when it is docked in the enzymatic pocket, with the 7-OH group pointing out and away from the target site, making it accessible to linkage to different backbone molecules. Electron micrographs show influenza virus clumping in the presence of dimeric zanamivir conjugates. The marked potency of some conjugates is postulated to reflect clumping caused by three types of bivalent binding: binding between two neuraminidase molecules in the tetrameric transmembrane spike protein (intratetramer), binding between sites on different tetramers on the same virion (intravirionic), and head-to-head binding between different neuraminidase sites on separate virions (intervirionic).[409] An additional mechanism for the marked enhancement of potency observed by synthesis of polymer-attached zanamivir is postulated to be the result of interference with intracellular trafficking of endocytosed virus and subsequent virus-endosome fusion.[417]

Resistance

Studies describing attempts to induce resistance in vitro by repeated passage in the presence of drug have not been reported.

Pharmacokinetics

Prolonged retention of polymeric zanamivir compared with monomeric zanamivir in lung tissue accounts for the enhanced antiviral effect of polymeric conjugates. After intratracheal instillation of the same single dose of a polymeric zanamivir conjugate or monomeric zanamivir solution in rats, lung homogenate drug concentrations of the polymeric compound after 48 hours and 168 hours are 35 times and 60 to 113 times greater than zanamivir concentrations, respectively. Generally, lung retention time is directly related to molecular weight because small polar molecules leave the lung by passing through tight junctions between cells. Thus prolonged retention of high-molecular-weight polymeric conjugates compared with monomeric zanamivir is expected. However, the prolonged lung retention time of some smaller conjugates indicates that aqueous insolubility and aggregate formation plus partitioning into cell membrane phospholipids may also play a role in the prolonged retention of zanamivir polymeric conjugates in the lung after inhalation.[409]

Interactions and Toxicity

Toxicity studies have been limited to assessments of in vitro cytotoxicity. For a series of dimeric conjugates, concentrations of 100 to 1000 ng/mL caused no cytotoxicity.[411]

Clinical Studies

No clinical studies have been reported.

BALOXAVIR MARBOXIL

Baloxavir (S-033188/S-033447; Xofluza) is a small-molecule inhibitor of influenza A and B cap-dependent endonuclease, which resides on the N-terminal domain of the PA subunit of the RNA-dependent RNA polymerase of influenza A (Fig. 45.7). Baloxavir interferes with the "cap-snatching" activity of cap-dependent endonuclease that primes viral transcription.[418,419] The N-terminal domain of the PA subunit is highly conserved among subtypes of influenza A, and baloxavir is active in vitro against H1N1, H3N2, H5N1, H7N7, H7N9, and H9N2 strains.[419] It has shown efficacy in the mouse model against influenza A(H5N1) and influenza B infection.[420] The developers of baloxavir have reported activity against oseltamivir-resistant strains of influenza.[421] The drug was stated to have a prolonged half-life, and single-dose oral administration was utilized in clinical trials.

A phase II proof-of-concept, randomized, placebo-controlled trial in influenza found that a single dose of baloxavir at 10 mg, 20 mg, or 40 mg was effective in reduction of time to alleviation of symptoms and resulted in a rapid reduction in viral titer.[420]

A phase III study (CAPSTONE-1) was conducted in 1436 patients 12 to 64 years of age, with onset of influenza-related symptoms within 48 hours, and in whom influenza virus was detected by PCR. Subjects

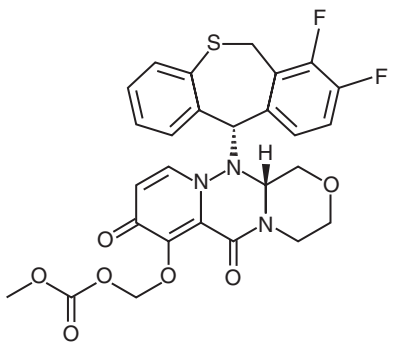

FIG. 45.7 **Chemical structure of baloxavir marboxil.**

received a single dose of 40 or 80 mg of baloxavir according to body weight, 75 mg of oseltamivir twice daily for 5 days, or placebo.[422] Time to alleviation of symptoms was shorter in the baloxavir group (53.7 hours) than in the placebo group (80.2 hours) (P <.0001) but similar to that in the oseltamivir group (53.8 hours). Mean time to cessation of viral shedding was 24 hours in patients who received baloxavir, compared to 72 hours in the oseltamivir group (P <.0001) and 96 hours in the placebo group (P <.0001). Baloxavir administration was generally well tolerated. Polymerase acidic PA 138 T/M protein variants conferring reduced susceptibility to baloxavir developed in 10% of baloxavir recipients and in no placebo recipients.

Baloxavir was licensed in Japan in February 2017 and in the United States in October 2018. Additional studies in immunosuppressed patients and children are planned in the United States.

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46 Antivirals Against Herpesviruses

Fred Y. Aoki

The availability of efficacious and well-tolerated antiviral drugs that collectively inhibit most of the eight human herpesviruses has significantly reduced the morbidity and mortality caused by these viruses in healthy individuals. The availability of these drugs has also contributed to the control of herpesvirus infections resulting from immunosuppression due to diseases such as human immunodeficiency virus (HIV) infection or reticuloendothelial system malignancies such as Hodgkin disease. Moreover and just as important, the availability of these drugs has permitted the increasing and successful use of potent immunosuppressive agents for the management of a wide variety of problems such as transplant rejection, as a substantial proportion of herpesvirus infections are due to reactivation of asymptomatic latent herpesvirus infection. Antiviral drugs that are of established therapeutic effectiveness as evidenced by registration by drug regulatory bodies in various countries are listed in Table 46.1.

ACYCLOVIR AND VALACYCLOVIR

Spectrum

Acyclovir (9-[(2-hydroxyethoxy)methyl]-9H-guanine; acycloguanosine; Zovirax) is a deoxyguanosine analogue that has an acyclic side chain lacking the 3′-hydroxyl group, instead of the cyclic ribose base of natural nucleosides (Fig. 46.1A). Valacyclovir (Valtrex) is the L-valyl ester prodrug of acyclovir. The clinically useful antiviral spectrum of acyclovir is limited to certain herpesviruses. Acyclovir is approximately 10 times more potent against herpes simplex virus type 1 (HSV-1) and HSV-2 than against varicella-zoster virus (VZV), and it is even less active against cytomegalovirus (CMV) (Table 46.2).[1,2] Acyclovir inhibits the replication of Epstein-Barr virus (EBV) in productively infected cells but does not affect latent or persistent infection. Acyclovir has shown antiviral activity in experimental HSV infection when administered topically, parenterally, or orally and in simian varicella when given systemically.[1] Enhanced antiherpesvirus activity occurs when acyclovir is given in combination with interferons (IFNs) and other antiviral agents in vitro and in animal models.[1]

Growth of uninfected mammalian cells is generally unaffected by high acyclovir concentrations. Acyclovir (20 μg/mL) does not reproducibly alter cell-mediated immune responses of human peripheral blood leukocytes or affect human granulocyte progenitor cell growth in vitro.[3]

Mechanism of Action

Acyclovir is the prototype of a group of antiviral agents that are activated by viral thymidine kinase (TK) to become inhibitors of viral DNA polymerase that block viral DNA synthesis.[1,2,4] Acyclovir uptake and intracellular phosphorylation to the monophosphate derivative are catalyzed by HSV TK. Cellular enzymes convert the monophosphate to acyclovir triphosphate, which is present in 40-fold to 100-fold higher concentrations in HSV-infected cells than in uninfected cells. Acyclovir triphosphate competitively inhibits viral DNA polymerase and to a much smaller extent cellular DNA polymerases with respect to deoxyguanosine triphosphate. Acyclovir triphosphate is also incorporated into viral DNA, where it acts as a chain terminator because of the lack of the 3′-hydroxyl group. Formation of a complex between the terminated DNA template containing acyclovir and the enzyme may lead to irreversible inactivation of the DNA polymerase. The DNA polymerases of various herpesviruses differ in their degree of inhibition by acyclovir triphosphate; the polymerases of EBV and CMV seem to be especially insensitive.

Resistance

Acyclovir-resistant HSV, often defined by an in vitro inhibitory concentration greater than 2 to 3 μg/mL, can be readily selected by passage in the presence of acyclovir and is present in native virus populations, with an approximate frequency of 1 in 10^3 to 10^4 infectious virions.[4–6] Three basic resistance mechanisms have been identified: absent or low production of viral TK, altered TK substrate specificity (e.g., phosphorylation of thymidine but not of acyclovir), and altered viral DNA polymerase. Changes in these viral enzymes relate to point mutations or base insertions or deletions in the corresponding genes.[7,8] The most common mechanism found in clinical HSV isolates is absent or deficient TK activity.[4,9] Less commonly, resistant isolates have altered TK activity, and DNA polymerase mutants are rare in clinical strains. Heterogeneous mixtures are commonly found. TK-negative variants are cross-resistant to other agents activated by viral TK (e.g., penciclovir, ganciclovir), but TK-altered and DNA polymerase mutants variably retain susceptibility.[4]

The prevalence of acyclovir-resistant HSV isolates in immunocompetent hosts is about 0.1% to 0.7% but increases to approximately 4% to 14% in immunocompromised patients.[4,7,10] During several decades of use, no increase in the prevalence of acyclovir-resistant variants has occurred in immunocompetent individuals.[4,11] Resistant HSV-2 has been found in 0.2% of human immunodeficiency virus (HIV)–negative and 5.3% of HIV-positive individuals with genital herpes[12] and has been recovered from 11% to 17% of individuals with acquired immunodeficiency syndrome (AIDS) or recipients of allograft transplants receiving acyclovir treatment for 2 weeks or longer.[13] Progressive HSV disease associated with recovery of acyclovir-resistant virus and poor response to acyclovir therapy is well recognized in immunocompromised patients. Painful ulcerating perirectal lesions, often indolent and necrotizing, caused by HSV-2 represent the most common pattern in patients with AIDS. Orofacial disease caused by HSV-1 is common in transplant recipients. Risk factors for resistance emergence include degree of immunosuppression, size of lesions, repeated or prolonged use of acyclovir for treatment rather than prophylaxis, and, possibly, the use of topical acyclovir in genital herpes.[11]

TK-negative HSV strains are less neurovirulent than wild-type strains and are unable to reactivate from latency in animal models, although they may cause extensive mucocutaneous disease in immunocompromised hosts.[4,6] TK-deficient, TK-altered, or DNA polymerase mutants have variable decreases in pathogenicity. Acyclovir-resistant HSV recurrent genital or ocular infections have rarely been found in immunocompetent hosts.[4] One case of possible person-to-person spread of resistant HSV has been reported. Recurrences after cessation of acyclovir are usually caused by sensitive virus.[4] In patients with AIDS, persistent shedding of resistant HSV at the site of initial infection and recurrences with acyclovir-resistant variants have been found in the absence of selective drug pressure.[14] Visceral disease is uncommon, but pneumonitis, meningoencephalitis, esophagitis, hepatitis, retinal necrosis, and disseminated infection have occurred with resistant variants, including instances in neonates.[4,12,15]

Depending on the degree of immunosuppression, resistant HSV infections may undergo spontaneous healing during or after cessation of acyclovir therapy. In patients with progressive disease, intravenous foscarnet therapy is effective, but therapy with vidarabine is not.[14] Intravenous cidofovir also seems to be effective. High-dose continuous infusion of acyclovir,[16] topical trifluridine, topical IFN-α2 alone or in

TABLE 46.1 Antiviral Agents of Established Therapeutic Effectiveness for Herpesvirus Infections

VIRAL INFECTION	DRUG	ROUTE	USUAL ADULT DOSAGE
Cytomegalovirus	Ganciclovir	IV	5 mg/kg/12 h in 1-h infusion for 14–21 days[a]
Retinitis	Valganciclovir	PO	900 mg bid for 21 days[a]
	Cidofovir	IV	5 mg/kg once weekly × 2, then every other week
	Fomivirsen	Intravitreal	330 µg every 2 weeks × 2, then every 4 weeks
	Foscarnet	IV	60 mg/kg/8 h in 1- to 2-h infusion for 14–21 days[b]
HSV			
Genital herpes			
First episode	Acyclovir	PO[c]	400 mg tid or 200 mg 5 times/day for 7–10 days
	Famciclovir	PO	250 mg tid for 7–10 days
	Valacyclovir	PO	1 g bid for 7–10 days
Recurrent	Acyclovir	PO	800 mg tid for 2 days or 400 mg tid or 200 mg 5 times/day or 800 mg bid for 5 days
	Famciclovir	PO	125 mg bid for 5 days or 1000 mg repeated once at 12 h for 1 day
	Valacyclovir	PO	500 mg bid for 3 days or 1 g/day for 5 days
Suppression[d]	Acyclovir	PO	400 mg bid or 200 mg tid
	Famciclovir	PO	250 mg bid
	Valacyclovir	PO	500 mg/day or 1 g/day (≥10 episodes/y) or 250 mg bid
Encephalitis	Acyclovir[e]	IV	10–15 mg/kg/8 h in 1-h infusions for 14–21 days
Mucocutaneous disease in immunocompromised hosts	Acyclovir[f]	IV	5 mg/kg/8 h for 7–14 days[g]
		PO	400 mg 5 times/day for 7–14 days
	Valacyclovir[h]	PO	500 mg or 1 g bid for 7–10 days
	Penciclovir[h]	IV	5 mg/kg/8–12 h for 7 days
	Famciclovir	PO	500 mg bid for 7–10 days
Orolabial herpes			
First episode	Acyclovir	PO	Children: 15 mg/kg 5 times/day for 7 days (maximum 200 mg/dose) Adults: drugs and doses recommended for first-episode genital herpes have been used
Recurrent	Penciclovir 1%	Topical	Apply cream every 2 h while awake for 4 days
	Acyclovir 5%	Topical	Apply cream 5 times/day for 4 days
	Acyclovir 5% with hydrocortisone 1% cream	Topical	Apply cream 5 times/day for 5 days
	Docosanol 10%	Topical	Apply cream 5 times/day until healed
	Valacyclovir	PO	2 g repeated once at 12 h
	Famciclovir	PO	1500 mg once or 750 mg repeated once at 12 h
	Acyclovir	PO	400 mg tid/day for 5 days
Neonatal HSV	Acyclovir[i]	IV	10–20 mg/kg/8 h for 14–21 days
Keratitis	Acyclovir	Topical	1 cm of 3% ophthalmic ointment 4 times/day
	Trifluridine[j]	Topical	1 drop of 1% solution topically q2h, ≤9 drops/day
	Vidarabine	Topical	½-inch ribbon of 3% ointment 5 times daily
Varicella-Zoster Virus			
Varicella in normal children	Acyclovir	PO	20 mg/kg (≤800 mg) qid for 5 days
Varicella in immunocompromised hosts	Acyclovir	IV	10 mg/kg/8 h or 500 mg/m^2/8 h for 7–10 days[k]
Herpes zoster in immunocompromised hosts	Acyclovir	IV	10 mg/kg/8 h in 1-h infusion for 7–10 days[k]
Herpes zoster in normal hosts	Acyclovir	PO	800 mg 5 times daily for 7–10 days
	Valacyclovir	PO	1 g tid for 7 days
	Famciclovir	PO	500 mg tid for 7 days
	Brivudin[h]	PO	120 mg daily for 7 days

Consult text and manufacturer's product prescribing information for dosage adjustments in renal or hepatic insufficiency and in other circumstances.
[a]In patients with AIDS or who are otherwise highly immunocompromised, long-term suppression with valganciclovir 900 mg/day is recommended after acute treatment. IV ganciclovir 5 mg/kg given 7 days/wk or 6 mg/kg given 5 days/wk or oral ganciclovir 1 g tid are alternatives for suppression. These dosages are also approved for prevention of cytomegalovirus disease in transplant recipients.
[b]Long-term suppression with daily infusion of 90–120 mg/kg over 2 h is recommended after initial treatment in patients with AIDS.
[c]In patients with severe initial genital herpes and in patients unable to tolerate oral medicines, IV acyclovir 5 mg/kg/8 h for 5–7 days is recommended before a switch to an oral agent.
[d]Famciclovir 500 mg bid and valacyclovir 500 mg bid are effective in reducing recurrences in human immunodeficiency virus–infected patients.
[e]Higher dosages and 21 days of IV therapy are recommended by some authorities. Additional oral valacyclovir treatment afterward provides no additional benefit.[92a]
[f]In acyclovir-resistant HSV or varicella-zoster virus infections, IV foscarnet 40 mg/kg/8 h seems beneficial. Duration of therapy depends on the clinical response. For limited cutaneous infections in immunocompromised patients, 5% acyclovir ointment can be applied to lesions every 3 h up to 6 times daily for 7 days (about ½-inch ribbon per 4 square inches), using a finger cot or glove.
[g]Higher dosages (30 mg/kg/day) are recommended in progressive or visceral infections. Suggested pediatric dosage in children <12 years old is 10 mg/kg/8 h for 7 days per manufacturer.
[h]Not approved by US Food and Drug Administration for this indication. IV penciclovir is unavailable in the United States.
[i]High dosage (20 mg/kg/8 h) seems superior in disseminated and central nervous system disease in neonates.[92]
[j]An ophthalmic ointment of 3% acyclovir is available in some countries. Idoxuridine 0.1% solution, q1h while awake and q2h at night, or 0.5% ointment 5 times/day is a less effective alternative. Treatment of HSV ocular infections should be supervised by an ophthalmologist.
[k]Pediatric dosage of 500 mg/m^2/8 h for 7–10 days for children ≥1 year old, although some experts recommend 10 mg/kg/8 h for these children.[113]
AIDS, Acquired immunodeficiency syndrome; *HSV,* herpes simplex virus; *IV,* intravenously; *PO,* orally.

TABLE 46.2 Representative in vitro Inhibitory Concentrations of Acyclic Nucleosides and Nucleotides for Clinical Isolates of Herpesviruses in Human Cells

	INHIBITORY CONCENTRATION (μg/mL)			
VIRUS	**Acyclovir**	**Penciclovir**	**Ganciclovir**	**Cidofovir**
Herpes simplex virus 1	0.02–1.9	0.2–1.8	0.05–0.6	0.4–3
Herpes simplex virus 2	0.3–2.9	0.3–2.4	0.05–0.6	0.4–3
Varicella-zoster virus	0.8–5.2	0.9–5.1	0.2–2.8	0.25
Cytomegalovirus	2–57	52	0.2–2.8	0.2–0.9
Epstein-Barr virus	1.6	—	1.5	<0.03
Human herpesvirus 6	7–23	—	0.3–7	—
Human herpesvirus 8	15–17	—	0.9–1.4	0.1–0.23

Data from references 6, 8, 14, 159, 162, 250, 252, 373, 418, 420.

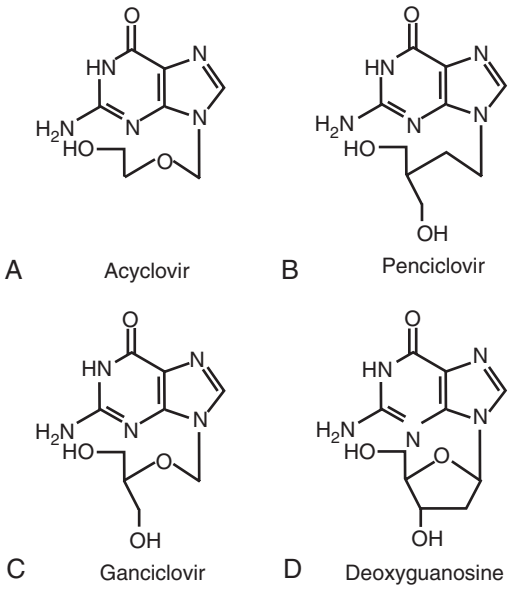


FIG. 46.1 Chemical structures of acyclovir (A), penciclovir (B), and ganciclovir (C) and their natural nucleoside analogue deoxyguanosine (D).

combination with topical trifluridine,[17] topical foscarnet,[18] topical cidofovir gel, and topical imiquimod[19] have been used with variable success.[20]

Acyclovir resistance in VZV isolates, associated with 20-fold to 40-fold increases in inhibitory concentrations, is usually related to mutations in VZV TK with inability to phosphorylate acyclovir or, less often, to mutations in viral DNA polymerase. Although rare, resistant isolates, including the Oka VZV vaccine strain,[21] have been recovered from highly immunocompromised children and adults with chronic disseminated, hyperkeratotic, or verrucous papular lesions that failed to heal with intravenous acyclovir.[22,23] Invasive disease with resistant variants occurs. Long-term suppressive therapy with subtherapeutic dosages of acyclovir seems to be a risk factor. Intravenous foscarnet or cidofovir may be effective for acyclovir-resistant VZV infections.[24,25]

Pharmacokinetics

The bioavailability of oral acyclovir is low (15%–21%) and decreases with increasing dosages.[1] Peak plasma concentrations average 0.4 to 0.8 μg/mL after 200-mg oral doses and increase to about 1.6 μg/mL with 800-mg doses. Bioavailability is lower in transplant recipients in whom doses of 400 mg provide peak levels of 0.7 to 0.9 μg/mL. A liquid suspension has lower oral bioavailability; peak plasma concentrations average 1 μg/mL in children receiving doses of 600 mg/m^2. In neonates and infants younger than 2 years, oral bioavailability averages 12%. Acyclovir kinetics are affected by prematurity and age younger than 1 month, and weight-adjusted dosing is essential.[26] Peak and trough plasma concentrations average 9.8 μg/mL and 0.7 μg/mL, respectively, after intravenous administration of 5 mg/kg every 8 hours and 20.7 μg/mL and 2.3 μg/mL, respectively, after 10 mg/kg every 8 hours. Peak concentrations average 10.3 μg/mL and 20.7 μg/mL after intravenous doses of 250 mg/m^2 and 500 mg/m^2, respectively, in children.

After oral administration, valacyclovir is readily absorbed, most likely via human peptide transporter 1 (hPEPT1), and rapidly converted to acyclovir during first-pass enzymatic hydrolysis in the liver and intestine by an enzyme designated valacyclovir hydrolase.[27,28] The relative bioavailability of acyclovir is three to five times greater after ingestion of valacyclovir, whose absolute bioavailability averages 54% to 70%.[29] Estimated bioavailability is 48% in hospitalized immunocompromised children 5 years old or older.[30] Peak plasma levels of valacyclovir are 0.4 μg/mL or less after 1000-mg doses. Peak plasma acyclovir levels average 5 μg/mL and 8.5 μg/mL after doses of 1000 mg and 2000 mg, respectively, in adults and are estimated to be 7 to 8 μg/mL after doses of 30 mg/kg valacyclovir in children.[29,31,31a] Total acyclovir exposure with administration of valacyclovir is similar to that seen with intravenous acyclovir, although peak plasma concentrations are twofold to fourfold lower.[30] In older adults, peak plasma concentrations increase 15% to 20%, and overall acyclovir exposure increases 30% to 50%,[27] probably because of reduced renal clearance in this population.

Acyclovir is distributed widely in body fluids. Plasma protein binding is less than 20%. Concentrations over time in noninflammatory cerebrospinal fluid (CSF) average 20% of concentrations in serum.[32] Salivary concentrations average 13% of plasma levels, but concentrations in vaginal secretions range from 15% to 170% of those in plasma. Zoster vesicular fluid levels are similar to those in plasma. Aqueous humor levels average 37% of concurrent plasma values. Acyclovir is concentrated in breast milk at approximately threefold higher levels than in maternal serum. Plasma levels in newborns are similar to maternal levels, and amniotic fluid and placental concentrations are several-fold higher.[33] Percutaneous absorption of acyclovir after topical administration seems to be low.

The mean plasma elimination half-life ($T_{½elim}$) of acyclovir is about 2.5 to 3 hours (range, 1.5–6.3 hours) in adults with normal renal function; it is slightly longer (3.8 hours) in neonates and increases to 19.5 hours in anuric patients.[33,34] Renal excretion of unmetabolized acyclovir by glomerular filtration and tubular secretion accounts for 60% to 91% of an administered dose, whereas less than 15% is excreted as 9-carboxymethoxymethylguanine or minor metabolites.[35] Acyclovir and valacyclovir dosage reductions are indicated in patients with a creatinine clearance (CrCl) less than 50 mL/min (Tables 46.3 and 46.4). Hemodialysis removes 33% to 60% of acyclovir during a 6-hour session, whereas peritoneal dialysis removes very little.[36] Dosing is recommended after hemodialysis, but supplementation is not needed during continuous ambulatory peritoneal dialysis. Bioavailability is about 61% after intraperitoneal dosing.[37] Table 46.4 lists dosage adjustments for valacyclovir in patients with impaired renal function.

TABLE 46.3 Acyclovir Dosage Adjustments Suggested for Patients With Impaired Renal Function

CREATININE CLEARANCE (mL/min/1.73 m²)	INTRAVENOUS		ORAL[a]	
	Standard Dosage (%)	Dosing Interval (h)	Dosage (mg)	Dosing Interval (h)
>50	100	8	800	4
>25–50	100	12	800	4
>10–25	100	24	800	8
0–10[b]	50	24	800	12[c]

[a]Oral acyclovir dosage adjustments are needed for severe renal insufficiency. Recommendations are based on the high-dose oral regimen (4000 mg/day). For the low-dose (1000 mg/day) oral regimen, the suggested dosage is 200 mg q12h when creatinine clearance is <10 mL/min/1.73 m².
[b]An alternative in patients with end-stage renal disease is administration of 14% of standard dosage q8h after loading with 37% of the standard dosage. In hemodialysis, use 60%–100% of standard dosage after the hemodialysis run only.
[c]In dialysis-dependent patients, a further dosage reduction to 200 mg/12 h and 400 mg after dialysis is recommended to avoid toxic levels. A dosage of 800 mg orally q24h has been suggested for patients on continuous ambulatory peritoneal dialysis.[36] For adults during continuous renal replacement therapy, give q48h.
Modified from Blum MR, Liao SH, de Miranda P. Overview of acyclovir pharmacokinetic disposition in adults and children. Am J Med. *1982;73:186–192; and Laskin OL, Longstreth JA, Whelton A, et al. Effect of renal failure on the pharmacokinetics of acyclovir.* Am J Med. *1982;73:197–201.*

TABLE 46.4 Dosage Adjustments of Valacyclovir in Patients With Impaired Renal Function

CREATININE CLEARANCE (mL/min/1.73 m²)	HERPES ZOSTER		RECURRENT GENITAL HERPES		RECURRENT OROLABIAL HERPES	
	Dosage	Interval	Dosage	Interval	Dosage	Interval
≥50	1 g	8 h	500 mg	12 h	2 g × 2	12 h
30–49	1 g	12 h	500 mg	12 h	1 g × 2	12 h
10–29	1 g	24 h	500 mg	24 h	500 mg × 2	12 h
<10	500 mg	24 h	500 mg	24 h	500 mg	Once

Based on manufacturer's recommendations. Reductions are also indicated for other dosage regimens (e.g., for genital herpes suppression and initial treatment).

Interactions

Severe somnolence and lethargy may occur with combinations of zidovudine and acyclovir.[38] Concomitant use of cyclosporine and probably of other nephrotoxic agents enhances the risk for nephrotoxicity. Probenecid and cimetidine slow valacyclovir metabolism, decrease renal acyclovir clearance, and increase overall acyclovir exposure by 48% and 27%.[39] By competing for the organic acid secretory pathway, acyclovir may decrease the renal clearance of other drugs eliminated by active renal secretion, such as methotrexate. Thiazide diuretics or the hPEPT1 substrate cephalexin do not substantially alter valacyclovir pharmacokinetics.[27] No pharmacokinetic interaction was observed between tipranavir/ritonavir and single-dose valacyclovir at steady state in healthy volunteers.[28]

Toxicity

Topical acyclovir may cause transient burning when it is applied to genital lesions. The polyethylene glycol base of topical acyclovir may cause mucosal irritation and is not approved for intravaginal use. Acyclovir cream uncommonly causes allergic contact dermatitis.[1]

Intravenous acyclovir is generally well tolerated,[1] although inflammation, phlebitis, and, rarely, vesicular eruption can occur at the injection site after extravasation of the alkaline solution (pH 9–11). Uncommon side effects include rash, diaphoresis, hematuria, hypotension, headache, and nausea. Approximately 1% to 4% of patients receiving intravenous acyclovir have manifested neurotoxicity, characterized by lethargy, confusion, obtundation, tremor, myoclonus, hallucinations, delirium, seizures, extrapyramidal signs, autonomic instability, or coma.[40] Diffuse electroencephalographic abnormalities and increased CSF concentrations of myelin basic protein may occur. Symptoms of neurotoxicity usually develop within 1 to 3 days after starting treatment. Most of these patients have acute renal dysfunction or preexisting renal disease, and neurotoxicity occurs in association with high serum acyclovir concentrations (>25 μg/mL) and detectable CSF levels of 9-carboxymethoxymethylguanine, the main metabolite of acyclovir, which may be the cause of acyclovir neurotoxicity. It has been detected at higher concentrations in the CSF of subjects with neurotoxicity[41] than in asymptomatic normal subjects or subjects with chronic kidney disease.[31] Neurotoxicity occurs more often after valacyclovir. Neurologic side effects usually resolve within several days after drug concentrations decrease. Hemodialysis may be useful in severe cases.

Reversible renal dysfunction has been observed in approximately 5% of patients, including a higher proportion of children, treated with intravenous acyclovir.[1] Acyclovir can cause a crystalline nephropathy and, rarely, interstitial nephritis.[42] Acyclovir solubility decreases to 2.5 mg/mL at 37°C, and crystalluria has been described in adult and pediatric patients. Obstructive nephropathy may manifest as nausea, emesis, flank pain, and increasing azotemia. Co-administration with other nephrotoxic drugs, bolus infusion, dehydration, preexisting renal insufficiency, high doses, and high acyclovir plasma levels are risk factors. Nephrotoxicity usually resolves with drug cessation and volume expansion.

Oral acyclovir has been associated infrequently with nausea, diarrhea, rash, and headache and uncommonly with renal insufficiency or neurotoxicity. Immediate hypersensitivity reactions to acyclovir are rare but may be managed with oral desensitization.[43] Long-term acyclovir suppression for frequently recurring genital or mucocutaneous infections seems well tolerated after long-term use,[44,45] and no adverse effects on sperm production or peripheral blood lymphocyte cytogenetics have been detected.[46] However, oral acyclovir can cause neutropenia in infants.[47] High-dose valacyclovir (8 g/day) is associated with gastrointestinal intolerance, azotemia, and possibly thrombotic microangiopathy in patients with AIDS[48] and with confusion and hallucinations in transplantation patients.[49] Tolerance at lower doses is comparable to that of acyclovir. Localized bullous skin lesions[50] and an acute generalized pustulosis confirmed by patch testing have been reported.[51]

Acyclovir has shown mutagenic activity in some in vitro assays at high concentrations, but no significant immunosuppressive activity, carcinogenicity, or teratogenicity has been noted in animal studies. High doses decrease spermatogenesis and cause testicular atrophy in animals. Acyclovir is classified as pregnancy category B and is present in breast milk. No excess frequency of congenital abnormalities has been recognized in infants born to women exposed to acyclovir during pregnancy, although whether exposure may increase the risk for spontaneous abortion is unresolved.[52,53,54]

Clinical Studies

Acyclovir is the agent of choice for management of many types of HSV and VZV infections because of its efficacy, safety, and ease of administration (see Table 46.1).[1,2] Valacyclovir is comparably effective in most of the conditions in which oral acyclovir is used and offers more convenient dosing regimens.

Herpes Simplex Virus

Acyclovir by various routes is effective in primary genital HSV infections.[55] Topical acyclovir is less effective than oral or intravenous administration, and its use is discouraged. Intravenous acyclovir markedly reduces viral shedding, time to healing, and duration of symptoms in patients with severe primary genital HSV infections. In outpatients, oral acyclovir (200 mg five times daily for 10 days) is associated with significant reductions in virus shedding, symptoms, and time to healing. Higher dosages of oral acyclovir do not increase efficacy,[56] and valacyclovir (1 g twice daily for 10 days) is comparable to acyclovir in efficacy and tolerability for treating first-episode genital herpes.[57] None of these regimens has been associated with consistent reductions in the risk for recurrent genital lesions. Acyclovir therapy decreases the humoral and cellular immune response to HSV after a first episode of genital herpes. Higher oral dosages (400 mg five times daily for 10 days) provide similar benefit in first episodes of HSV proctitis.

In recurrent genital HSV infections, patient-initiated oral acyclovir (200 mg five times daily for 5 days) during the prodrome or at the first sign of lesions is associated with reductions of 1.5 to 2 days in the duration of shedding and time to healing. A 2-day regimen of high-dose acyclovir (800 mg three times daily) is also associated with 2-day reductions in duration of lesions and symptoms.[58] Valacyclovir (500 mg twice daily for 5 days) is comparable to acyclovir and superior to placebo in the treatment of recurrent genital herpes.[59,60] Famciclovir 1000 mg taken twice early in the course of a recurrent episode of genital herpes,[61] a 3-day course of valacyclovir (500 mg twice daily), and a 5-day course of valacyclovir 500 mg twice daily are equally efficacious and well tolerated.[62] Topical acyclovir alone offers minimal clinical benefit in this condition.

In patients with frequently recurring genital herpes, long-term oral acyclovir (400–1000 mg/day in divided doses) reduces the frequency of clinical recurrences by about 90%, protects 65% to 85% of patients from recurrence, and reduces the frequency of subclinical viral shedding and viral DNA detectability.[45,63] Dosages of 400 mg twice daily are effective for longer than 5 years. Once-daily or weekend-only use of acyclovir is inadequate, whereas once-daily valacyclovir (500 mg, or 1000 mg if frequent recurrences) seems to be effective and well tolerated.[64] Valacyclovir suppression (500 mg daily) reduces the risk of transmitting HSV-2 infection to a serosusceptible partner by approximately 50%.[65] Asymptomatic shedding may occur during suppression, and transmission to sexual partners has occurred. After cessation of acyclovir, patients generally return to their previous pattern of recurrent infection. Oral acyclovir and valacyclovir suppression during late pregnancy reduce virus shedding, recurrences, and cesarean delivery rates for HSV after a first episode occurring during pregnancy and in women with recurrent genital herpes.[66,67] Acyclovir 400 mg twice a day from 28 to 36 weeks of gestation tended to reduce premature rupture of membranes from 10% to 4% in placebo recipients and significantly reduced premature delivery from 24% in placebo recipients to 11%.[68]

Long-term suppression may be useful in other patients with disabling recurrences of herpes whitlow or HSV-related erythema multiforme. In patients with recurrent herpes labialis or ocular HSV disease, prolonged oral acyclovir (400 mg twice daily) or valacyclovir (500 mg once daily) reduces the number of recurrences by about half.[69–71] In patients with a history of sun-induced recurrences, short-term prophylaxis (400–800 mg twice daily) inconsistently reduces the risk for recurrence.[72] Short-term prophylaxis during outbreaks in day care centers may be effective in preventing primary infections in children,[73] but the efficacy of postexposure prophylaxis remains to be established.

In recurrent orolabial HSV infections in immunocompetent individuals, topical acyclovir ointment is not beneficial. Topical 5% acyclovir cream is available in many countries outside of the United States, and patient-initiated treatment reduces the duration of an episode by about 0.5 day.[74] A cream consisting of 5% acyclovir and 1% hydrocortisone prevented progression of cold sores to ulcerative lesions and significantly reduced the cumulative lesion area compared with acyclovir cream alone or placebo.[75] High-dose, patient-initiated oral valacyclovir (2 g twice in 1 day) reduces the duration of orolabial herpes episodes and healing time by about 1 day.[76] Oral acyclovir (200–400 mg five times daily for 5 days) provides modest clinical benefit in orolabial HSV but seems to be efficacious in recurrent whitlow.[77] Acyclovir (15 mg/kg five times daily to a maximum of 200 mg/dose for 7 days) is beneficial for treating primary HSV gingivostomatitis in children,[78] and long-term suppression reduces cutaneous recurrences after neonatal infection.

In Bell's palsy, prednisolone improves the chances of complete recovery. Controlled studies have shown that there is no benefit of acyclovir or valacyclovir alone or in addition to prednisolone for treatment of Bell's palsy, but some consultants still use combined oral steroids and valacyclovir in severe disease.[79,80]

Acyclovir in various regimens and valacyclovir have been used successfully for prevention and treatment of mucocutaneous HSV infections in immunosuppressed patients.[2,81] Intravenous acyclovir (250 mg/m^2 every 8–12 hours or 125 mg/m^2 every 6 hours), begun before transplantation and continuing for several weeks, is highly effective in reducing the incidence of HSV disease in seropositive bone marrow transplant recipients.[82] For patients who can tolerate oral medications, oral acyclovir (400 mg five times daily or 600 mg every 6 hours) or valacyclovir (500 mg twice daily) is effective in marrow transplant recipients, and long-term oral acyclovir (400 mg three times daily for 6 months) reduces the risk for HSV, CMV, and VZV infection.[83,84] Low doses of oral acyclovir (200 mg every 6–8 hours) seem to be effective in renal transplant recipients. Valacyclovir (500 mg twice daily) is effective for suppression of recurrent genital herpes in HIV-infected individuals.[85] Serial HSV DNA plasma load was monitored during successful prevention of recurrent HSV disease with intravenous acyclovir and valacyclovir following hepatic transplantation for treatment of fulminant HSV hepatitis in an immunocompetent host.[86]

In immunocompromised patients with established mucocutaneous HSV infection, intravenous acyclovir (250 mg/m^2 every 8 hours for 7 days) shortens healing time, duration of pain, and virus shedding,[87] although recurrences are common after cessation of therapy. Oral acyclovir (800 mg five times daily) is also effective.[88] Intravenous acyclovir may be beneficial in cases of disseminated HSV in pregnant women and in transplant recipients.[89,90]

In HSV encephalitis, acyclovir reduces mortality to 19% to 28% compared with 50% to 54% with vidarabine.[2] In neonates, in immunosuppressed patients, and, uncommonly, in apparently healthy individuals, early relapse of encephalitis may follow initial acyclovir therapy (see Table 46.1). Neurologic deterioration, interpreted as relapsing HSV encephalitis, seems to be unrelated to direct viral cytolysis.[91] High-dose intravenous acyclovir (60 mg/kg/day for 21 days) seems to be more effective than the lower dosage (10–15 mg/kg/day) approved by the US Food and Drug Administration for neonatal central nervous system (CNS) and disseminated HSV disease.[92] In immunocompetent patients older than 12 years with HSV encephalitis treated with IV acyclovir, subsequent therapy with 3 months valacyclovir 6 g/day did not provide additional benefit.[92a]

Continuous infusion of acyclovir was reported to be effective in a neonate with HSV-2 encephalitis who did not respond to the intermittent recommended acyclovir dose regimen.[93] The efficacy of acyclovir for treating primary or recurring HSV-2 meningitis has not been demonstrated. However, valacyclovir 500 mg twice daily was not effective compared with placebo in preventing recurrent episodes of verified and probable HSV-2 meningitis.[94] Acyclovir seems to be effective for treatment of presumed HSV acute retinal necrosis syndrome.[95] Prolonged oral acyclovir (≥14 weeks) was significantly more effective than a shorter duration (<14 weeks) in preventing involvement of the other eye.[96] Fulminant HSV hepatitis in two pregnant women was successfully treated with intravenous acyclovir.[97]

Epidemiologic studies demonstrate a strong synergistic relationship between the dual contemporary epidemics of genital HSV-2 and HIV-1 infection. HSV-2 increases the risk of HIV-1 acquisition twofold or threefold[98] as well as the risk of transmission. However, prophylactic daily acyclovir does not decrease HIV-1 acquisition rates,[99,100] and

administration of acyclovir does not prevent HIV-1 transmission,[101] even though HIV-1 plasma load[102] as well as genital, rectal, seminal,[103] and, perhaps, cervicovaginal[104] concentrations are reduced. Prevalent HSV acyclovir resistance does not likely explain the incomplete antiviral effect,[105] whereas incomplete adherence may contribute to acyclovir inefficacy.[104]

HSV can cause exophytic, ulcerating, hypertrophic genital lesions in HIV-infected individuals.[106,107] These respond best to intravenous acyclovir.[106] Topical imiquimod may augment the effect of oral acyclovir.[107] Acyclovir 4 g daily was superior to oral erythromycin and no less effective than higher dose of acyclovir for treatment of pityriasis rosacea, which may be due to human herpesviruses, mainly human herpesvirus (HHV)-6 and HHV-7.[108,109]

Varicella-Zoster Virus Infections

High-dose oral acyclovir is effective treatment for herpes zoster in older adults and, if begun within 24 hours after rash onset, for varicella in children,[110] adolescents,[111] and adults.[112] In children, effects of acyclovir include reductions of about 1 day in fever and of 15% to 30% in the severity of other illness measures, so routine use for uncomplicated varicella in otherwise healthy children younger than 13 years is not recommended.[113] In adults with varicella, oral acyclovir (800 mg five times daily for 7 days) initiated within 24 hours after the onset of rash reduces fever and the time to total crusting of lesion by approximately 2 days; it does not affect the course of illness if begun later.[112] Postcontact prophylaxis with oral acyclovir (40 mg/kg daily in divided doses) beginning 9 to 11 days after exposure may reduce the risk for varicella in household contacts.[114]

In immunocompetent older adults with herpes zoster, intravenous acyclovir reduces virus shedding, time to healing of skin lesions, and duration of acute pain. Oral acyclovir (800 mg five times daily for 7–10 days) also reduces acute pain and healing time in older adults if treatment is initiated within 72 hours after rash onset and particularly within 1 or 2 days. In a placebo-controlled study, concomitant administration of steroids and antivirals resulted in improved quality of life.[115] A reduction in ocular complications, particularly keratitis and anterior uveitis, occurs with oral acyclovir (800 mg five times daily for 7 days) or valacyclovir (1 g three times daily for 7 days) treatment of zoster ophthalmicus.[116] No consistent effect of acyclovir on the incidence or severity of postherpetic neuralgia has been found[117]; evidence was insufficient to determine whether valacyclovir prevents postherpetic neuralgia. Compared with acyclovir, oral valacyclovir (1 g three times daily for 7 days) speeds resolution of zoster-associated pain and decreases the frequency of persistent pain.[118] Intravenous acyclovir and steroid treatment was associated with recovery from cervical myelitis occurring 1 month after herpes zoster in an immunocompetent adult.[119]

Intravenous acyclovir is effective for varicella and herpes zoster in immunocompromised patients. It also seems to be effective in varicella pneumonia or encephalitis in previously healthy adults.[120] In immunocompromised patients with herpes zoster, intravenous acyclovir (500 mg/m^2 every 8 hours for 7 days) reduces the risk for cutaneous dissemination and visceral complications. In immunosuppressed children with varicella, intravenous acyclovir reduces the risk for visceral complications and time to full crusting. Early relapse of infection may occur after cessation of therapy, and treatment may be ineffective in visceral disease. Early treatment with oral acyclovir (800 mg five times daily for 7 days) may be effective in immunocompromised children.[121] Valacyclovir 1000 mg three times daily is not different from 2000 mg three times daily, both for 7 days, in efficacy and safety for the treatment of uncomplicated herpes zoster in immunocompromised adults.[121a] Herpes zoster recurrence in patients with multiple myeloma treated with bortezomib-based therapy can be successfully prevented with acyclovir.[122] Valacyclovir 1000 mg twice daily for 4 through 24 months after transplantation is more efficacious than placebo in preventing herpes zoster in bone marrow transplant recipients.[123]

Cytomegalovirus

Acyclovir is therapeutically ineffective in established CMV infections. However, for prophylaxis, high-dose intravenous acyclovir (500 mg/m^2 every 8 hours) beginning 5 days before allogeneic bone marrow transplantation and continuing for 30 days afterward is associated with a delayed risk for CMV infection; when high-dose intravenous acyclovir is followed by oral acyclovir (800 mg four times daily for 6 months), overall survival is improved.[124,125] In seropositive allogeneic bone marrow or stem cell transplant recipients, valacyclovir (2 g four times a day after initial intravenous acyclovir) was more effective than high-dose oral acyclovir (800 mg four times a day)[126] and comparable to intravenous ganciclovir[127] in preventing CMV reactivation.

High-dose oral acyclovir also reduces the risk for CMV disease in renal and liver transplant recipients but seems to be less effective than ganciclovir,[128,129] although in one report valacyclovir and valganciclovir were similarly effective.[129] Acyclovir has not proved effective in liver transplant recipients receiving OKT3 therapy or in lung transplant recipients. High-dose valacyclovir prophylaxis (2 g four times a day for 90 days) reduces the risk for CMV disease and of graft rejection in renal transplant recipients including CMV-seronegative recipients of seropositive grafts[130] and seems to be effective in preventing CMV reactivation after heart transplantation.[131] In an uncontrolled study, in HIV-infected pregnant women, valacyclovir 500 mg twice daily begun at 34 weeks of gestation and continued for 1 year did not reduce acquisition of CMV by infants compared with placebo.[132] In another uncontrolled study, in non–HIV-infected pregnant women with a fetus with ultrasound features of intrauterine CMV infection, valacyclovir 8 g/day increased the proportion of asymptomatic neonates to 82% compared with 43% without treatment.[133] However, the American Society for Fetal-Maternal Medicine advises against any such antenatal therapy at this time.[134]

Other Viruses

Valacyclovir is recommended in managing herpesvirus B (*Cercopithecine herpesvirus* 1) exposures, and high-dose intravenous acyclovir (12.5–15 mg/kg/8 h) or ganciclovir is recommended for treating non-CNS herpesvirus B infections; intravenous ganciclovir (5 mg/kg/12 h) is advised for CNS infection (see Chapter 141).[135] High-dose acyclovir has been reported to provide a modest survival benefit in advanced HIV infection, although this remains controversial.[136] Valacyclovir reduced oropharyngeal shedding of HHV-8 in HIV-1–infected individuals, but not as markedly as did antiretroviral drugs.[137]

In infectious mononucleosis, acyclovir is associated with transient suppression of salivary EBV excretion but no important effects on illness parameters.[138] High-dose acyclovir is ineffective in patients with chronic fatigue syndrome.[139] Some cases of post-transplantation EBV-related polyclonal lymphoproliferation may respond to acyclovir.[140] However, a systematic review and meta-analysis concluded that antiviral prophylaxis (acyclovir, valacyclovir, ganciclovir, and valganciclovir) in solid-organ transplant recipients did not prevent EBV-associated post-transplantation lymphoproliferative disease.[141] Long-term acyclovir or related antivirals possibly reduce the risk for AIDS-related lymphoma.[142] EBV-related oral hairy leukoplakia usually regresses with oral acyclovir or valacyclovir treatment but then recurs.[143] Topical 5% acyclovir with 25% podophyllin resin is effective in resolving lesions of oral hairy leukoplakia with a reduced recurrence rate compared with podophyllin resin alone in HIV-1–seropositive patients.[144] Neither intravenous nor oral acyclovir enhances the response to IFN in patients with chronic hepatitis B. Long-term acyclovir does not reduce neurologic deterioration in multiple sclerosis.[145]

BRIVUDIN

Brivudin ([*E*]-5-[2-bromovinyl]-2′-deoxyuridine) is a halogenated thymidine nucleoside analogue that is licensed for treatment of herpes zoster in several European Union countries, but not the United States (Fig. 46.2).[146] Brivudin potently and selectively inhibits replication of VZV and to a lesser extent HSV-1 in vitro. In vitro inhibitory concentrations of brivudin average 0.0033 µM for clinical VZV isolates and are more than 100-fold lower than those for acyclovir and penciclovir.[147] Brivudin-resistant HSV-1 clones can be readily selected in vitro during replication in the presence of drug.[148,149] Cross-resistance to acyclovir is common.[148,149]

When used for early treatment of nonophthalmic herpes zoster in immunocompetent adults, oral brivudin (125 mg once daily) is not

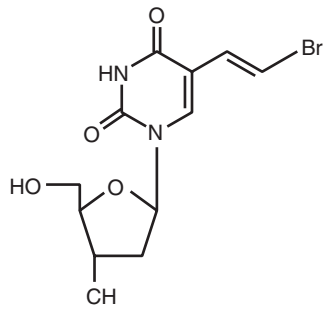
different from famciclovir given at 250 mg three times a day, both given for 7 days.[150] The same brivudin regimen is generally comparable to acyclovir (800 mg five times daily) in effects on acute pain and healing of lesions, although it may accelerate cessation of new lesion formation to a slightly greater extent.[146] In adults 50 years old and older, brivudin treatment seems to reduce modestly the frequency, although not the duration, of postherpetic neuralgia compared with acyclovir.[151] Treatment-related adverse effects are similar to those of acyclovir, with low frequencies of gastrointestinal upset, headache, and dizziness[151]; delirium and hepatitis have been reported during therapy.[152,153] The main metabolite of brivudin is bromovinyluracil, which interferes with the catabolism of fluorinated pyrimidines such as 5-fluorouracil, with the result that potentially serious drug interactions can occur.[154]

CIDOFOVIR

Spectrum

Cidofovir (S)-1-[3-hydroxy-2-(phosphomethoxy) propyl] cytosine dihydrate; HPMPC; Vistide) is an acyclic phosphonate nucleotide analogue of deoxycytidine monophosphate (Fig. 46.3A) with inhibitory activity against human herpesviruses including HSV, CMV, EBV, HHV-6, HHV-7, and HHV-8 and certain other DNA viruses including papillomaviruses, polyomaviruses, poxviruses, and adenoviruses.[155–158] In vitro inhibitory concentrations range from less than 0.2 to 0.7 μg/mL for CMV,[159] 0.4 to 33 μg/mL for HSV,[160] and 0.02 to 17 μg/mL for adenoviruses.[161] Because phosphorylation does not depend on virus-specified enzymes, cidofovir is inhibitory for acyclovir-resistant, TK-deficient, or TK-altered HSV strains and ganciclovir-resistant CMV strains with *UL97* mutations, although not for strains with *UL54* mutations. TK mutants of HSV show 20-fold enhanced susceptibility to cidofovir compared with wild-type HSV because mutant viruses induce smaller elevations in competing deoxycytidine triphosphate pools in infected cells.[162] Cidofovir inhibits parvovirus B19 in vitro.[163]

In vitro, cidofovir shows synergistic inhibition of CMV in combination with ganciclovir or foscarnet.[157] The prolonged intracellular $T_{½}$ of the diphosphate is associated with persistent antiviral activity and enables infrequent dosing regimens. Cidofovir is active in animal models of herpesvirus, papillomavirus, and, given systemically or by aerosol, poxvirus infections.[164–166] Topical cidofovir is active against ocular adenovirus infection in rabbits but is associated with local irritation.[167]



Brivudin

FIG. 46.2 Chemical structure of brivudin.

Mechanism of Action

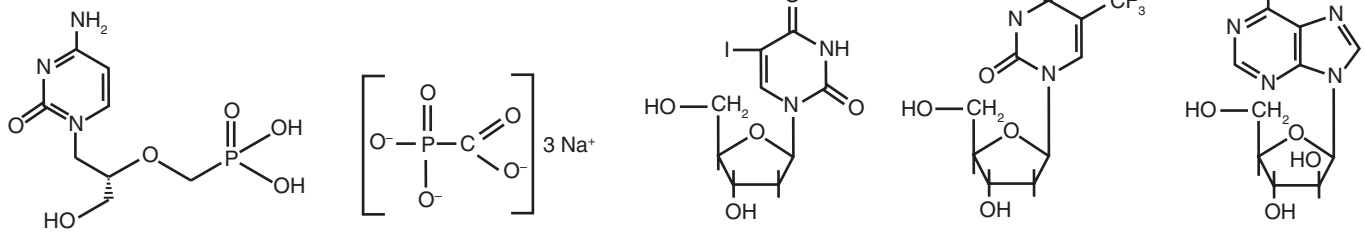
Cidofovir inhibits viral DNA synthesis. Cidofovir is metabolized intracellularly to its active diphosphate form by cellular enzymes, and the levels of phosphorylated metabolites are similar in infected and uninfected cells. The diphosphate acts as a competitive inhibitor with respect to deoxycytidine triphosphate and as an alternative substrate for viral DNA polymerase. Incorporation of cidofovir slows chain elongation and abrogates it if two consecutive cidofovir molecules are introduced. The diphosphate has a prolonged intracellular $T_{½}$, averaging 17 to 65 hours depending on the cell type, and it competitively inhibits CMV and HSV DNA polymerase at concentrations 8-fold to 600-fold lower than concentrations inhibitory for human DNA polymerases.[156,168] An adduct with prolonged intracellular $T_{½}$ (>2 days) may serve as a reservoir of drug.

Resistance

Resistance to cidofovir selected by in vitro passage of CMV, poxviruses, and adenoviruses relates to point mutations in viral DNA polymerase. Highly ganciclovir-resistant clinical isolates of CMV that possess *UL54* mutations show cross-resistance to cidofovir in vitro with 8-fold to 16-fold reductions in inhibitory concentrations.[169] Foscarnet-resistant CMV and HSV isolates may retain susceptibility to cidofovir, but multidrug-resistant CMV variants with DNA polymerase mutations occur.[170] The development of resistance to cidofovir as a result of cidofovir therapy seems to be uncommon and low level (less than eightfold change in susceptibility).[159,171] In patients with CMV retinitis, reduced cidofovir susceptibility has been detected in about 5% of CMV isolates before treatment and in 29% by 3 months of therapy.[172] Poxviruses selected for resistance to cidofovir in vitro (8-fold to 27-fold reduced susceptibility) seem less virulent than wild-type viruses but are resistant to cidofovir in vivo.[173]

Pharmacokinetics

Oral bioavailability of cidofovir is low (<5%). After intravenous infusion, plasma levels are proportional to dose and decline in a biphasic pattern, with a terminal $T_{½elim}$ that averages about 2.6 hours.[174] The maximum plasma concentration averages 19.6 μg/mL after a dose of 5 mg/kg in conjunction with probenecid.[175] Plasma protein binding is low (<7%), and the volume of distribution approximates total body water (0.5 L/kg). CSF penetration is low.[174] Cidofovir is cleared by the kidney via glomerular filtration and active tubular secretion. More than 90% of the dose is recovered unchanged in the urine, and no significant metabolism has been recognized in humans. High-dose probenecid (2 g 2 hours before and 1 g 2 hours and 8 hours after each infusion) reduces renal clearance by blocking tubular secretion of cidofovir and increases blood levels. Clearance correlates with CrCl, and $T_{½elim}$ increases to 32.5 hours in patients receiving continuous ambulatory peritoneal dialysis. About 50% of a dose is removed by hemodialysis, but cidofovir is not significantly cleared by continuous ambulatory peritoneal dialysis.[175a] After application of cidofovir gel, systemic absorption is low (peak plasma concentrations <0.5 μg/mL) and is related to lesion size.[160]



A Cidofovir B Foscarnet C Idoxuridine D Trifluorothymidine E Vidarabine

FIG. 46.3 Chemical structures of cidofovir (A), foscarnet (B), idoxuridine (C), trifluorothymidine (D), and vidarabine (E).

Interactions

Concomitant therapy with other nephrotoxic agents is contraindicated during cidofovir therapy, and an interval of at least 7 days is recommended after aminoglycoside, intravenous pentamidine, amphotericin B, foscarnet, nonsteroidal anti-inflammatory drug, or contrast dye exposure.

Toxicity

Dose-related nephrotoxicity is the principal side effect of intravenous cidofovir.[157] It is characterized by proximal tubular dysfunction including proteinuria, azotemia, glycosuria, metabolic acidosis, and, uncommonly, Fanconi syndrome. Nephrotoxicity occurs as a result of a cidofovir-avid renal organic anion transport protein that causes drug accumulation in the renal cortex. Nephrotoxicity occurs because of apoptosis induced by cidofovir in renal tubular epithelial cells.[176] Concomitant oral probenecid and vigorous saline prehydration reduce the risk for renal toxicity, whereas prior foscarnet therapy and concurrent use of other nephrotoxic agents increase the risk. On maintenance dosing (5 mg/kg every other week), approximately 12% to 39% of patients develop proteinuria, and 15% to 24% have elevated serum creatinine. Severe nephrotoxicity requiring dialysis sometimes occurs. Initiation of cidofovir is relatively contraindicated in patients with CrCl less than 55 mL/min or with significant proteinuria (2+). Dosage reductions (3 mg/kg) are indicated for minor increases in serum creatinine (0.3–0.4 mg/dL), and cessation of administration is indicated for greater creatinine increases or development of proteinuria of 3+ or higher.

Neutropenia develops in approximately 24% of patients, and regular monitoring of neutrophil counts is necessary. Fever, nausea, emesis, diarrhea, headache, rash, asthenia, iritis, uveitis, and ocular hypotony may occur during combined therapy with cidofovir and probenecid.[157,177] Maintenance is withdrawn in approximately 25% to 35% of patients with AIDS because of intolerance.

Mucosal application is associated with dose-related application site reactions (burning, pain, pruritus) in one-third of patients and occasionally with ulceration.[160] Although no evidence of systemic toxicity was reported, topical cidofovir treatment of two severely immunocompromised patients with refractory multidrug-resistant HSV infection resulted in irreversible acute kidney injury.[178] Intravitreal cidofovir may cause iritis, vitreitis, reduced intraocular pressure, and visual loss.[179] Anterior uveitis has been reported after intravenous cidofovir administration.[180] Conjunctival application causes local irritation; persistent epiphora related to lacrimal canalicular blockade has developed in some patients.

Intravesical cidofovir (2.5–5 mg/kg in 50–100 mL normal saline) was administered via a transurethral catheter to treat BK or adenovirus hemorrhagic cystitis.[181,182] In one study, pain was reduced by cidofovir treatment in 8 of 9 patients, but in another study, due to the development of significant lower abdominal pain, only two of six patients could tolerate the 2-hour dwell time.[181] Compared with the reported area under the curve for the first 24 hours after time zero (AUC0–24) for an equivalent intravenous dose, intravesicular cidofovir resulted in 1% to 74% of the corresponding systemic exposure. One patient developed a >50% increase in serum creatinine, suggesting the need for more studies on the renal safety of intravesicular cidofovir.

Preclinical studies indicate that cidofovir has mutagenic, gonadotoxic, embryotoxic, and teratogenic effects. Because cidofovir causes carcinomas in rats, this agent is considered a potential human carcinogen. Intralesional cidofovir in patients with recurrent respiratory papillomatosis does not seem to increase the frequency of laryngeal dysplasia.[183,184] In a case report, progressive laryngeal dysplasia developed during intralesional cidofovir therapy of recurrent laryngeal papillomatosis over 27 months.[185] Safety during pregnancy is uncertain, and cidofovir is classified as pregnancy category C.

Clinical Studies

Intravenous cidofovir is approved for the treatment of CMV retinitis in patients with AIDS. Intravenous cidofovir (5 mg/kg once a week for 2 weeks, followed by every-other-week dosing) significantly increases the time to progression of CMV retinitis in previously untreated patients and in patients failing or intolerant of ganciclovir and foscarnet therapy.[157,186,187] Maintenance dosages of 5 mg/kg every other week are more effective but less well tolerated than 3 mg/kg dosages.[188] Clearance of viruria, but not viremia, has been shown.[189] Intravenous cidofovir seems comparable to a combined regimen of oral ganciclovir plus implant in preventing retinitis progression and mortality.[190] When used as preemptive therapy for post-transplant CMV infection or treatment of established disease including CMV pneumonia, cidofovir has been associated with responses in 50% or more of allogeneic stem cell recipients.[191,192]

Intravenous cidofovir has been used as preemptive therapy for post-transplant CMV infections as an alternative to prophylaxis with ganciclovir or valganciclovir for prevention of CMV disease.[193] Intravenous cidofovir has been used to treat acyclovir-resistant or foscarnet-resistant mucocutaneous HSV infection[155,194,195] and ganciclovir-resistant CMV disease including encephalitis in a stem cell transplant recipient.[196,197] Early treatment has been advocated as being possibly efficacious in controlling severe adenovirus pneumonia in nonimmunocompromised patients[198] and invasive adenoviral infections of transplant recipients,[199–201,202–204] although altered dosage schedules (e.g., 1 mg/kg thrice weekly) may be needed to reduce nephrotoxicity.[205] Low intravenous dosages (0.25–1 mg/kg every 1–3 weeks, with or without probenecid) have been used in treating refractory BK virus–associated nephropathy in renal transplantation recipients[206,207] and BK virus–associated[208] and adenovirus-associated[209] hemorrhagic cystitis in stem cell transplant recipients. Cidofovir has been instilled in the bladder for treatment of BK-hemorrhagic cystitis.[182] The addition of intravenous cidofovir to antiretroviral therapy (ART) has inconsistent effects on neurologic outcomes and survival in HIV-associated progressive multifocal leukoencephalopathy,[210,211] but a review of 33 cases suggests that cidofovir does not increase survival independent of the beneficial effect of ART.[212] Primary HHV-8 disease and Kaposi sarcoma in a liver transplant recipient was successfully treated with combination therapy including glucocorticoids, doxorubicin, and intravenous cidofovir.[213] However, cidofovir did not reduce HHV-8 viral load in peripheral blood mononuclear cells or prevent progression in Kaposi sarcoma in another report.[214] Intracavitary cidofovir was associated with resolution of pleural and peritoneal HHV-8–associated lymphoma in HIV-negative patients.[215–217]

Topical cidofovir gel formulated in polyethylene glycol reduces pain, virus shedding, and lesion healing time in HIV-infected patients and stem cell transplant recipients with acyclovir-resistant mucocutaneous HSV infections.[160,218] Cidofovir 3% oral rinses controlled acyclovir-resistant and foscarnet-resistant HSV-1 orolingual infection in an immunocompromised host.[219] Intralesional cidofovir and aerosolized cidofovir induce remissions in respiratory papillomatosis.[220–222] However, in a randomized, double-blind, placebo-controlled trial, intralesional cidofovir was not more efficacious than placebo.[223] Intralesional cidofovir suppresses recurrent EBV-associated nasopharyngeal carcinoma.[224] Topical cidofovir has been used for the treatment of recurrent anogenital herpes including exophytic pseudotumorous lesions, anogenital warts, refractory condyloma, orf poxvirus lesions,[155,225–228] recurrent HPV-related nasal squamous papillomatosis,[229] high-grade vulvar[230] and anal[231] intraepithelial neoplasia, and trichodysplasia spinulosa due to polyomavirus.[232] Intravenous cidofovir has resulted in resolution of anogenital[233] and generalized[234] warts. Topical and intravenous preparations have been used in recalcitrant molluscum contagiosum in immunosuppressed patients.[155,235] Intravitreal cidofovir injection may be effective for treatment of CMV retinitis[179] but is relatively contraindicated because of toxicity. A 1% ophthalmic solution reduced the risk for corneal opacities in adenoviral keratoconjunctivitis but was associated with severe, dose-dependent local toxicity.[236]

CMX-001 (Brincidofovir)

Alkoxyalkyl ester prodrugs of cidofovir exhibit enhanced cellular uptake and are more potent poxvirus inhibitors than the parent molecule, are well absorbed orally, and are not renally concentrated.[237] In cells, the esters are cleaved to release cidofovir. Two ether lipid esters, hexadecyloxypropyl-cidofovir and octadecyloxyethyl-cidofovir, administered orally, are highly active in experimental poxvirus, CMV, and adenovirus infections in animals.[238–240] Hexadecyloxypropyl-cidofovir (CMX-001 or brincidofovir) has undergone phase I and phase II testing. The renal toxicity of cidofovir is related to its accumulation in renal tubular epithelial cells by organic anion transporter 1 (OAT1). As CMX-001 is not a substrate for OAT1, it has not been associated with nephrotoxicity.[241]

A phase II study of CMX-001 for the prevention of CMV infection in stem cell transplant recipients showed a reduction in new or progressive CMV infections in patients who received 100 mg twice a week. Diarrhea was dose limiting at a dose of 200 mg twice a week.[216] Neither myelosuppression nor nephrotoxicity was observed. In an uncontrolled trial, CMX-001 prevented HSV and VZV infections in human stem cell transplant (HSCT) recipients.[242]

Retrospective case studies suggested that CMX-001 therapy was effective for treating adenovirus viremia in HSCT recipients.[243–245] Brincidofovir was associated with successful treatment of one patient with cancer and acyclovir-resistant HSV and two patients with ganciclovir-resistant (*UL97* gene mutation) CMV infection. One patient with ganciclovir-resistant CMV disease due to a *UL54* mutation did not respond.[246]

DOCOSANOL

Docosanol (*n*-docosanol or behenyl alcohol; Abreva) is a saturated 22-carbon aliphatic alcohol that inhibits a broad range of lipid-enveloped viruses including HSV-1 and HSV-2 at millimolar concentrations in vitro.[247] Docosanol is not directly virucidal, and its principal anti-HSV mechanism of action in vitro apparently relates to interference with viral fusion to host cell membranes early in replication, although other inhibitory effects may be possible.[247] A nonantiviral mechanism of action resulting from anti-inflammatory effects has been described. In a guinea pig model of cutaneous HSV, topical docosanol did not show antiviral or therapeutic benefits and was less active than topical penciclovir and acyclovir.[248] No emergence of resistance has been described to date.

Docosanol 10% cream is available over the counter for treatment of recurrent herpes labialis in immunocompetent individuals. Early treatment (five applications daily until healing up to maximum of 10 days) shortens the time to complete healing by about 0.7 day and time to resolution of symptoms by 0.5 day.[249] Application site reactions occur in about 2%, and its use is generally well tolerated. Whether combined treatment with docosanol and topical nucleosides might provide greater therapeutic effects remains to be determined.

FAMCICLOVIR AND PENCICLOVIR

Spectrum

Penciclovir (9-[4-hydroxy-3-hydroxymethylbut-1-yl] guanine; Denavir) is an acyclic guanosine analogue (see Fig. 46.1B) similar to acyclovir in its spectrum of activity and potency against herpesviruses (see Table 46.2).[250] Famciclovir (Famvir) is a prodrug, the diacetyl ester of 6-deoxy penciclovir, and lacks intrinsic antiviral activity. Because of its dependence on viral TK for initial phosphorylation, penciclovir is inactive against TK-deficient strains of HSV or VZV, but it may be active against some TK-altered or polymerase mutants that are resistant to acyclovir and against some foscarnet-resistant HSV isolates.[251,252] Penciclovir is also inhibitory for hepatitis B virus (HBV) and shows enhanced inhibition in combination with lamivudine or adefovir in vitro.[253,254] Topical, parenteral, and oral penciclovir and oral famciclovir are active in experimental HSV infections.[255] In a guinea pig model of primary cutaneous HSV-1 infection, penciclovir 1% cream was more efficacious than acyclovir 5% cream.[256]

Mechanism of Action

Penciclovir is an inhibitor of viral DNA synthesis. In infected cells, penciclovir is preferentially phosphorylated to its active form, penciclovir triphosphate, which serves as a competitive inhibitor of viral DNA polymerase.[257] In contrast to acyclovir, it is not an obligate chain terminator. Although penciclovir triphosphate is approximately 100-fold less potent in inhibiting viral DNA polymerase than acyclovir triphosphate, it is present in much higher concentrations and for more prolonged periods in infected cells. The prolonged intracellular $T_{½}$ of penciclovir triphosphate, which ranges from 7 to 20 hours, is associated with a sustained antiviral effect in cell culture and in animal models.[258] This effect may allow for infrequent dosing during clinical use. Although not preferentially phosphorylated in HBV-infected cells, penciclovir triphosphate is also a potent inhibitor of HBV DNA polymerase reverse transcriptase.[259]

Resistance

Penciclovir-resistant variants of HSV selected by in vitro passage have mutations in viral TK or DNA polymerase. Acyclovir-resistant, TK-negative mutants are resistant to penciclovir, but some variants with altered TK substrate specificity or with DNA polymerase mutations are susceptible.[4,260] Resistant HSV is detected in about 0.3% of patients with orolabial herpes, and emergence during clinical use has been very low in immunocompetent hosts.[5,261] As seen with acyclovir, higher rates have been observed in immunocompromised patients.[9] Resistance of HBV to penciclovir is associated with point mutations in viral DNA polymerase, particularly L528M.[262] Lamivudine resistance is associated with this mutation and predicts poor virologic response to famciclovir.[263]

Pharmacokinetics[264]

Famciclovir is a prodrug that is well absorbed orally and is rapidly converted to penciclovir by deacetylation and oxidation of the purine. This occurs during and after absorption through the intestinal wall and in the liver.[265] Although penciclovir itself is poorly absorbed, its bioavailability averages 77% after oral administration of famciclovir. Little or no famciclovir is detectable in blood or urine. Penciclovir is less than 20% bound to plasma proteins. The volume of distribution is approximately double that of body water. After single 250-mg and 500-mg doses of oral famciclovir, the peak plasma concentration of penciclovir averages 1.6 to 1.9 μg/mL and 2.7 to 4.0 μg/mL, respectively. Food reduces peak plasma concentrations but does not significantly alter overall bioavailability. After intravenous infusion of penciclovir (10 mg/kg), peak plasma levels average 12 μg/mL.

The plasma $T_{½elim}$ of penciclovir averages 2 to 3 hours, and approximately 70% is recovered unchanged in the urine. About 5% is excreted as the 6-deoxy precursor. Rapid renal clearance of penciclovir suggests elimination by filtration and active tubular secretion. Nonrenal clearance accounts for about 30% of the dose, primarily by fecal excretion of penciclovir and its 6-deoxy precursor. The plasma elimination rate is reduced approximately 4-fold, and penciclovir exposure is increased 10-fold in patients with severe renal failure (CrCl <30 mL/min).[266] Dosage reductions are indicated in moderate or advanced renal failure (Table 46.5). In patients with compensated liver disease, peak plasma levels are reduced by approximately 40%, but overall penciclovir exposure is unchanged, and dosage adjustments are unnecessary.[267] The pharmacokinetics of a single 1500-mg dose of famciclovir in adolescents with herpes labialis are similar to those in adults.[268] The pharmacokinetics of famciclovir in infants[269] and children 1 to 12 years old[270] have been used to develop dosage regimens that yield pharmacokinetic parameters comparable to those observed with 500-mg doses in adults. Older adults have approximately 40% higher penciclovir exposure because of lower renal clearance.

Interactions

No clinically important drug interactions have been identified to date. Famciclovir does not interact pharmacokinetically with cimetidine, theophylline, allopurinol, digoxin, or zidovudine to a clinically significant extent.[271]

TABLE 46.5 Dosage Adjustment of Famciclovir for Renal Insufficiency

STANDARD DOSAGE[a]	CREATININE CLEARANCE (mL/min)[b]	ADJUSTED DOSAGE
500 mg q8h or q12h	40–59	500 mg q12h
	20–39	500 mg q24h
	<20	250 mg q24h
250 mg q12h	≥40	250 mg q12h
	20–39	125 mg q12h
	<20	125 mg q24h
125 mg q12h	≥40	125 mg q12h
	20–39	125 mg q12h
	<20	125 mg q24h

[a]Dosage is based on manufacturer's recommendations.
[b]For hemodialysis patients, give the adjusted dosage for creatinine clearance <20 mL/min after dialysis.

Toxicity

Oral famciclovir is well tolerated but may be associated with headache, nausea, fatigue, and diarrhea.[272] The frequencies of such complaints are generally comparable to frequencies seen with placebo or acyclovir. However, at high doses (1000 mg twice in 1 day) used to treat recurrent genital herpes, headache occurs more commonly (14%) in famciclovir recipients than placebo (5%) recipients.[273] Case reports suggest famciclovir may cause cutaneous vasculitis.[274,275] Urticaria, rash, and, predominantly in older adults, hallucinations or confusional states have been reported. Neutropenia and elevated transaminase values occur in less than 5% of patients. The safety and efficacy of famciclovir are not established in children younger than 18 years. Topical penciclovir, which is formulated in 40% propylene glycol and a cetomacrogol base, is associated with application site reactions at low rates (approximately 1%), comparable to the vehicle.

Famciclovir reduces spermatogenesis and fertility in rodents and dogs, but long-term administration (1 year) does not affect spermatogenesis in men.[276] No teratogenic effects have been observed in animals. Safety of administration in pregnant patients has not been established (pregnancy category B).[53] Very high penciclovir concentrations are mutagenic, and long-term administration of high-dose famciclovir is associated with mammary tumors in female rats but not in mice. The clinical significance of these observations is uncertain. Penciclovir is excreted in the breast milk of animals.

Clinical Studies

Topical penciclovir and oral famciclovir are approved for clinical use in the United States, and intravenous penciclovir has been approved in some countries. In immunocompetent individuals with recurrent orolabial HSV, patient-initiated topical 1% penciclovir cream (applied every 2 hours while awake for 4 days) shortens healing time and symptoms by nearly 1 day.[277]

Oral famciclovir initiated within 1 hour of prodrome in a single dose of 1500 mg or as two doses of 750 mg 12 hours apart shortens cold sore outbreaks by 2 days compared with placebo.[278] A systematic review and meta-analysis concluded that penciclovir and famciclovir do not increase the percentage of aborted herpes labialis episodes as do acyclovir and valacyclovir.[279] Oral famciclovir (250 mg three times daily for 5–10 days) is as effective as acyclovir in treating first episodes of genital herpes.[280] In non–HIV-infected patients with recurrent genital HSV, patient-initiated famciclovir treatment of 125 mg twice daily for 5 days reduces healing time and symptoms and is comparable to acyclovir treatment.[281,282] Famciclovir, 125 mg twice daily for 5 days, is comparable to famciclovir, 500 mg once followed by 250 mg twice daily for 2 days.[283] A single-day treatment with famciclovir, 1000 mg given twice 12 hours apart, reduces median healing times by 1.8 days and increases the percentage of patients whose lesions do not progress beyond the papule stage by 45%—from 13% in placebo recipients to 23% in famciclovir-treated subjects.[273] This famciclovir single-day regimen is not inferior to valacyclovir, 500 mg twice daily for 3 days.[284] Larger doses of 250 mg or 500 mg of famciclovir twice daily do not increase the beneficial effects.[282,285] Suppressive therapy (250 mg twice daily) for 1 year is effective in non–HIV-infected individuals with frequent recurrences, but single daily doses are not as effective.[261] Famciclovir reduces recurrences of genital herpes and asymptomatic genital HSV shedding in individuals with recurring lesions[261,286–289] but does not reduce shedding in asymptomatic seropositive individuals.[287] Famciclovir, 250 mg twice daily, seems to be less effective than valacyclovir, 500 mg daily.[290] Famciclovir suppressive therapy is not different from episodic treatment in terms of quality of life or patient satisfaction with treatment.[291]

In HIV-infected patients, famciclovir suppression (500 mg twice daily) reduces lesional HSV recurrences and asymptomatic viral shedding.[292] Famciclovir (500 mg twice daily for 7 days) is comparable to acyclovir (400 mg five times daily) in the treatment of mucocutaneous HSV infections in HIV-infected patients.[293] Intravenous penciclovir (5 mg/kg every 8 or 12 hours for 7 days) is comparable to intravenous acyclovir in efficacy and tolerance for treatment of HSV infections in non–HIV-infected, immunocompromised hosts.[294]

In immunocompetent adults with herpes zoster of 3 days' duration or less, famciclovir (500 mg three times daily for 7 days) is at least as effective as acyclovir (800 mg five times daily) and is superior to placebo in reducing acute manifestations, particularly in patients older than 50 years.[295–298] The efficacy of famciclovir in preventing postherpetic neuralgia is unclear.[117] Famciclovir and valacyclovir provide comparable therapeutic effects in treating zoster in immunocompetent adults 50 years old or older.[299] Famciclovir is comparable to high-dose oral acyclovir in the treatment of ophthalmic herpes zoster in immunocompetent adults[300] and, given for 10 days, in the treatment of nonophthalmic, localized zoster in immunocompromised patients.[301]

Famciclovir is associated with dose-related reductions in HBV DNA and transaminase levels in patients with chronic hepatitis B[302] but is less effective than lamivudine, with less than 10% of patients experiencing a greater than 100-fold decrease in HBV DNA levels after 12 weeks.[303] Combination therapy with famciclovir and lamivudine may be more efficacious in suppressing HBV replication than either agent alone.[304] Famciclovir induces HBV resistance and is usually ineffective in treating lamivudine-resistant infections.[305] It is ineffective in chronic hepatitis D.[306] It has been used to treat recurrent HBV infection after liver transplantation, with reductions in HBV DNA levels for longer than 18 months in some patients.[307]

Studies of famciclovir combined with prednisone or prednisolone for treatment of idiopathic Bell palsy have shown that it is more effective than the glucocorticoid alone.[308,309] (Controlled studies have not shown a benefit for acyclovir or valacyclovir alone or in combination with steroids compared with steroids alone in treatment of Bell palsy—see earlier.[79,80]) Facial nerve palsy associated with ipsilateral acoustic neuroma resection is not prevented by perioperative famciclovir,[310] and Meniere disease is not ameliorated by famciclovir.[311] Pityriasis rosea may be linked to reactivation of HHV-6 and HHV-7, but famciclovir treatment, 250 mg thrice daily for 7 days, was no more effective in hastening resolution than treatment of historical control subjects with topical corticosteroid.[312] Famciclovir produced resolution of oral hairy leukoplakia for at least 1 year in one HIV-infected patient not receiving ART.[313] Topical penciclovir 1% in 25% podophyllin resin was less effective than acyclovir 5% in 25% podophyllin resin or podophyllin resin alone for treatment of oral hairy leukoplakia in HIV-1–seropositive individuals.[314] Famciclovir reduced oropharyngeal shedding of HHV-8 in HIV-infected individuals but not as markedly as antiretroviral drugs did.[315]

FOMIVIRSEN

Fomivirsen (ISIS 2922; Vitravene) is a 21-nucleotide phosphorothioate oligonucleotide that inhibits human CMV replication through an antisense mechanism.[316] Fomivirsen is complementary to a sequence in the messenger RNA transcripts of the major immediate-early region 2 of CMV, which encodes proteins responsible for regulation of viral gene expression. Other mechanisms of antiviral action may include nonantisense, sequence-dependent inhibition of virus replication and sequence-independent inhibition of virus absorption to the cell.[317] With persistent in vitro passage, it has been possible to isolate CMV clones with 10-fold less susceptibility to inhibition of replication.[318] Fomivirsen, because of its novel mechanism of antiviral action, retains activity against CMV strains that are resistant to ganciclovir, foscarnet, or cidofovir.

Fomivirsen is administered by intravitreal injection. In human eyes, concentrations at 1 hour after injection of 165-μg and 330-μg doses average 5.5 μmol/L and 11.6 μmol/L, respectively.[319] Clearance is first order with a $T_{½elim}$ of approximately 55 hours. The major route of elimination from the eye is metabolism by exonucleases; systemic exposure is not detectable. Similar to other phosphorothioate oligonucleotides, fomivirsen binds readily to proteins.

Fomivirsen is indicated for the intravitreal treatment of CMV retinitis in HIV-infected patients who are intolerant of, have not responded to, or have contraindications to other treatments.[316] Intravitreous injection is associated with delays in time to progression in patients with peripheral retinitis (dosages of 165 μg weekly for 3 weeks, followed by every 2 weeks).[320] In patients with retinitis that reactivated or was persistent despite alternative agents, a comparison of two regimens (330 μg weekly for 3 weeks followed by every 2 weeks vs. 330 μg on days 1 and 15 followed by every 4 weeks) found that the less intense regimen was better tolerated, more convenient, and apparently effective.[321] Dose-dependent inflammation including iritis, uveitis, and vitritis is the most common

adverse ocular effect but usually responds to topical corticosteroids. Increased intraocular pressure is common and needs close monitoring. Retinal pigment epitheliopathy and detachments have been described. Fomivirsen is not recommended for use in patients who have received cidofovir within 2 to 4 weeks because of the increased risk for ocular inflammation.

FOSCARNET

Spectrum

Foscarnet (trisodium phosphonoformate; Foscavir), an inorganic pyrophosphate analogue (see Fig. 46.3B), inhibits herpesviruses and HIV.[322] In vitro inhibitory concentrations vary widely among clinical isolates but are generally 100 to 300 µmol/L for CMV and 80 to 200 µmol/L for HSV, VZV, EBV, and HHV-8.[323] Foscarnet inhibits most ganciclovir-resistant CMV and acyclovir-resistant HSV and VZV strains. Combinations of foscarnet with ganciclovir, acyclovir, or artesunate synergistically inhibit CMV infection in vitro.[324,325] Foscarnet acts synergistically with zidovudine in inhibiting HIV replication.

Concentrations of 500 to 1000 µmol/L reversibly inhibit the proliferation or cellular DNA synthesis of uninfected cells. Foscarnet is active in animal models of herpesvirus and hepadnavirus infection.[322]

Mechanism of Action

In contrast to nucleosides, foscarnet does not undergo significant intracellular metabolism. It directly inhibits herpesvirus DNA polymerase or HIV reverse transcriptase. Foscarnet reversibly blocks the pyrophosphate binding site of the viral polymerase in a noncompetitive manner with respect to deoxynucleotide triphosphates and inhibits cleavage of pyrophosphate from deoxynucleotide triphosphates.[322,326] Concentrations that inhibit cell-free viral polymerases are many times lower than the concentrations required for inhibition of viral replication in cell culture,[322] and cellular uptake is slow. Selectivity of foscarnet relates to its 100-fold greater inhibitory effects against herpesvirus DNA polymerases or HIV reverse transcriptase compared with cellular DNA polymerase-α.[326]

Resistance

Resistance to foscarnet is caused by point mutations in DNA polymerase of HSV and CMV (the *UL54* gene product) or in reverse transcriptase of HIV, which confer 3-fold to more than 10-fold increases in inhibitory concentrations in clinical isolates.[7,327,328] Foscarnet-selected CMV mutations generally are not cross-resistant to ganciclovir or cidofovir, but simultaneous resistance to all three drugs has occurred.[327] Foscarnet-resistant CMV variants, defined by 50% inhibitory concentrations greater than 400 µmol/L in plaque reduction or greater than 600 µmol/L in DNA hybridization assays, develop in 37% of foscarnet recipients by 12 months of therapy and are associated with progressive retinitis.[329] Foscarnet-resistant HSV mucocutaneous and CNS infections have developed during therapy, including dually acyclovir-resistant and foscarnet-resistant variants.[330,331] Some foscarnet-resistant CMV infections respond to ganciclovir or cidofovir, whereas resistant HSV strains usually remain susceptible to cidofovir. The experimental antiviral agent maribavir was effective for treatment of CMV infection resistant or refractory to prior therapy with ganciclovir or foscarnet in hematopoietic stem cell or solid-organ transplant recipients,[332,333] whereas brincidofovir, the oral prodrug of cidofovir, was not.[334] Foscarnet resistance in HIV can phenotypically reverse zidovudine resistance.[335,336]

Pharmacokinetics

Oral bioavailability is low, averaging 7% to 9%. After an infusion of 60 mg/kg every 8 hours, peak and trough plasma concentrations have a broad range but average approximately 450 to 575 µmol/L and 80 to 150 µmol/L, respectively. Peak concentrations range from 490 to 2600 µmol/L after dosages of 90 mg/kg/day. Plasma protein binding is about 15%, and the volume of distribution is 0.4 to 0.7 L/kg. CSF concentrations vary widely but average 66% of plasma values at steady state.[337] Vitreous concentrations average 1.4 times higher than concurrent plasma concentrations.[338]

Foscarnet is eliminated renally with more than 80% of the dose excreted unchanged by glomerular filtration and tubular secretion. Plasma clearance is highly correlated with CrCl, so that dosage adjustments are indicated for small decreases in renal function (Table 46.6). Initial plasma $T_{½elim}$ averages 2 to 3 hours in individuals with normal renal function but increases to a mean of 25 hours in individuals with CrCl less than 25 mL/min.[339] Plasma elimination is complex, with a prolonged terminal $T_{½elim}$ averaging 88 hours, which is attributed to bone deposition that is estimated to account for 15% to 20% of a dose. A hemodialysis run removes about 38% of a dose[339]; dosing after dialysis is recommended. Peritoneal dialysis clears foscarnet to a limited extent.[340]

Interactions

Administration of foscarnet with amphotericin B or other nephrotoxic agents (e.g., aminoglycosides, intravenous pentamidine, intravenous acyclovir, cyclosporine) may cause enhanced renal toxicity,[322] and administration with calcineurin inhibitors may cause neurotoxicity. Probenecid does not affect renal excretion. The risk for symptomatic hypocalcemia is increased by concomitant intravenous pentamidine. Ganciclovir does not alter foscarnet pharmacokinetics. Foscarnet and zidovudine do not affect the clearance of each other, but the risk for anemia is higher with the combination.

Toxicity

Foscarnet has a narrow therapeutic index. Nephrotoxicity with azotemia, proteinuria, and sometimes acute tubular necrosis is the major dose-limiting side effect.[322,341] Approximately one-third of patients develop significant renal impairment (serum creatinine ≥2 mg/dL). Increases in serum creatinine usually occur during the second week of therapy and are reversible within 2 to 4 weeks after cessation in most patients. High dosages, rapid or continuous infusion, dehydration, and concurrent use of nephrotoxic drugs are risk factors. Extra saline hydration before and during infusion seems to reduce the risk for nephrotoxicity.[342,343] Crystalluria, crystalline glomerulopathy, renal tubular acidosis, nephrogenic diabetes insipidus, and interstitial nephritis have also been described.

TABLE 46.6 Foscarnet Dosage Reduction in Renal Insufficiency

CREATININE CLEARANCE (mL/min/kg)	INDUCTION DOSAGES		MAINTENANCE DOSAGES	
	60 mg/kg/8 h	90 mg/kg/12 h	90 mg/kg/day	120 mg/kg/day
>1.4	60 q8h	90 q12h	90 q24h	120 q24h
>1–1.4	45 q8h	70 q12h	70 q24h	90 q24h
>0.8–1	50 q12h	50 q12h	50 q24h	65 q24h
>0.6–0.8	40 q12h	80 q24h	80 q48h	105 q48h
>0.5–0.6	60 q24h	60 q24h	60 q48h	80 q48h
≥0.4–0.5	50 q24h	50 q24h	50 q48h	65 q48h
<0.4	Not recommended	Not recommended	Not recommended	Not recommended

Dosages expressed in mg/kg. Recommendations taken from Aweeka FT, Jacobson MA, Martin-Munley S, et al. Effect of renal disease and hemodialysis on foscarnet pharmacokinetics and dosing recommendations. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1999;20:350–357.

Foscarnet is a potent chelator of divalent cations, and metabolic abnormalities are common, including hypocalcemia (15%–35%), hypomagnesemia (15%–44%), hypokalemia (10%–16%), hypercalcemia, hypophosphatemia, and hyperphosphatemia.[343] Decreased serum ionized calcium may cause paresthesias, arrhythmias, tetany, seizures, and other CNS disturbances.[344] Intravenous magnesium sulfate does not prevent ionized hypocalcemia. Intravenous foscarnet should be administered at a fixed rate (maximum 1 mg/kg/min) by infusion pump to minimize the possibility of acute metabolic abnormalities.[344] Close monitoring with electrolyte supplementation and foscarnet dosage adjustments are often required during induction therapy.

CNS side effects include acute dystonia[345] and headache in about one-fourth of patients, seizures in 10%, tremor, irritability, and hallucinosis. Other reported side effects are fever, generalized rash, diarrhea in 30%, nausea or emesis in up to one-half, abnormal liver function tests, anxiety, fatigue, and painful genital ulcerations.[343] In 59 allogeneic hematopoietic stem cell transplant recipients treated with intravenous foscarnet for 14 days for CMV disease, the incidences of hemorrhagic cystitis and genital ulcers were 37% and 29%, respectively, despite routine pretreatment hyperhydration and postvoiding genital cleaning.[346] In 30% of patients, treatment had to be stopped due to adverse effects. Genital ulcerations are probably caused by high urinary foscarnet concentrations, appear on average after 8 days of treatment, and usually resolve 15 days after therapy is stopped.[346] Although anemia may develop in 20% to 50% of patients with AIDS, granulocytopenia is uncommon. Heart block and electrocardiogram changes occur in 5% or fewer of patients. Oral foscarnet causes dose-related gastrointestinal disturbances.

Preclinical studies indicate that high concentrations are mutagenic and that foscarnet causes fetal skeletal anomalies in rodents and rabbits. It may cause tooth and skeletal developmental abnormalities in growing animals. Safety in pregnancy (pregnancy category C) or in children is uncertain. Foscarnet is excreted in the breast milk of animals.

Clinical Studies

Intravenous foscarnet is approved for treatment of CMV retinitis in patients with AIDS and acyclovir-resistant mucocutaneous HSV infections. With the usual foscarnet regimen (60 mg/kg every 8 hours for 14–21 days, followed by long-term maintenance at 90–120 mg/kg/day), about 90% of patients with retinitis experience clinical stabilization, and a smaller portion of patients cease CMV excretion.[322,347,348] An induction regimen of 100 mg/kg twice daily also is effective but is associated with a higher risk for penile ulceration. Maintenance dosages of 120 mg/kg/day seem to be more effective than 90 mg/kg/day in prolonging survival and controlling retinitis.[349] Comparing foscarnet with ganciclovir, one study found that foscarnet provided comparable control of CMV retinitis in patients with AIDS but improved survival, although patients had to be switched from foscarnet more than three times as often because of side effects.[350] In patients with persistently active or relapsed retinitis, combined foscarnet (90 mg/kg/day) and ganciclovir (5 mg/kg/day) delay progression significantly longer than higher dosages of either single agent.[351] Intravitreal foscarnet has been used.[351a]

Foscarnet was useful in treating CMV encephalitis in a stem cell transplant recipient[352] and patients with ganciclovir-resistant CMV retinitis and other CMV syndromes[347] including gastrointestinal and pulmonary infections in patients with AIDS,[353] but was not useful in treating CMV pneumonia in bone marrow transplant recipients. In allogeneic stem cell transplant recipients with CMV infections, preemptive foscarnet therapy is as effective as intravenous ganciclovir[342,354] and valganciclovir[354] and is associated with less neutropenia.[342] Foscarnet was effective and safe in eradicating viremia in 27 patients among 209 renal allograft recipients who developed ganciclovir-resistant CMV disease following preemptive ganciclovir therapy.[355] Combinations of foscarnet and ganciclovir have been used to treat allogeneic transplant recipients with high CMV loads[356] and solid-organ transplant recipients with ganciclovir resistance.[357] In allogeneic bone marrow, liver, or renal transplant recipients with CMV DNA positivity in blood according to polymerase chain reaction, half-standard doses of foscarnet (90 mg/kg) and ganciclovir (5 mg/kg) given intravenously once daily for 14 days are not more efficacious in eliminating CMV DNA positivity in blood than a standard dose of ganciclovir (5 mg/kg intravenously twice daily for 14 days).[358]

HSV exophytic genital pseudotumors in HIV-1–infected patients respond to foscarnet.[228] In acyclovir-resistant mucocutaneous HSV infections, lower dosages (40 mg/kg every 8 hours) are associated with complete healing in about 75% of patients.[14] Other dosage regimens (e.g., 90 mg/kg every 12 hours) seem to be effective. Acute HSV and VZV retinal necrosis have been successfully treated with intravenous foscarnet.[359] The outcome appears better in patients with HSV compared with VZV infection and with supplemental intravitreal foscarnet injection.[360] Foscarnet is also effective in patients with acyclovir-resistant VZV acute retinal necrosis[361] as well as other VZV infections in patients with AIDS[24] and transplant recipients.[25] An immunocompetent adult with severe encephalomyelitis with integrated HHV-6 recovered after combined foscarnet and ganciclovir therapy.[362] HHV-6 encephalitis[363] and erythrocyte aplasia[364] in transplant recipients responded to foscarnet therapy, but prophylactic foscarnet for 10 days after allogeneic stem cell transplantation did not prevent HHV-6 encephalitis.[365] Foscarnet may reduce the risk for Kaposi sarcoma in HIV-infected patients with CMV disease.[366,367] Severe glandular fever caused by EBV has been treated with intravenous foscarnet and immunoglobulin combined with prednisolone.[368] Foscarnet controlled EBV infection in a lung transplant recipient in whom reduced immunosuppression controlled post-transplantation lymphoproliferative disease.[369] Intravenous foscarnet reduces serum transaminase and viral markers in previously untreated patients with active chronic hepatitis B infection and individuals with lamivudine-resistant HBV infection and severe chronic HBV liver disease.[370] In patients with AIDS, foscarnet administration significantly reduces p24 antigen and HIV RNA levels without clear increases in $CD4^+$ counts.[371] Foscarnet was effective for treatment of HIV-2 disease that did not respond to other antiretroviral drugs.[372] In recurrent orolabial or genital herpes infections of immunocompetent hosts, topically applied foscarnet is not associated with reproducible clinical benefits.

GANCICLOVIR AND VALGANCICLOVIR

Spectrum

Ganciclovir (9-[1,3-dihydroxy-2-propoxymethyl] guanine; Cytovene) is a deoxyguanosine analogue that differs from acyclovir in that it has an additional hydroxymethyl group on the acyclic side chain (see Fig. 46.1C). Valganciclovir (Valcyte) is the L-valyl ester of ganciclovir and is rapidly converted to ganciclovir after oral administration. Ganciclovir has inhibitory activity against herpesviruses (see Table 46.2), but its distinguishing characteristic is potent inhibition of CMV replication.[373] Inhibitory concentrations are 10-fold to more than 50-fold lower than acyclovir for human CMV strains. Combinations of ganciclovir and foscarnet synergistically inhibit CMV replication in vitro.[324] Ganciclovir is about twofold more active than acyclovir for herpes B virus (*Cercopithecine herpesvirus* 1) with an inhibitory concentration of 9 μg/mL.[135] Ganciclovir inhibits some adenoviruses in vitro, and inhibition of HBV occurs in vivo.[374] Systemic ganciclovir is effective at relatively low dosages in animal models of CMV and HSV infections.

Although high concentrations are needed to inhibit the growth of uninfected cells, inhibitory concentrations for human bone marrow progenitor cells are similar to concentrations that inhibit CMV replication. Inhibition of human lymphocyte proliferative responses to mitogen and antigen occurs at concentrations of 1 to 10 μg/mL, so immune responses requiring active DNA synthesis may be depressed at therapeutic ganciclovir concentrations.[3] Cells transfected by viral TK are killed on exposure to ganciclovir in vitro,[375] in animal models in vivo,[376] and in patients with malignancies such as prostate carcinoma[377] and glioblastoma multiforme.[378]

Mechanism of Action

Ganciclovir inhibits viral DNA synthesis.[373,379] Intracellular ganciclovir is phosphorylated to the monophosphate derivative by virus-induced TK during HSV infection and by a viral protein kinase homologue encoded by the *UL97* gene during CMV infection.[380,381] Ganciclovir diphosphate and ganciclovir triphosphate are formed through the

action of cellular enzymes. At least 10-fold higher concentrations of ganciclovir triphosphate are present in CMV-infected than in uninfected cells. Intracellular ganciclovir triphosphate concentrations are also more than 10-fold higher than the concentrations of acyclovir triphosphate in CMV-infected cells, and the intracellular $T_{½}$ of ganciclovir triphosphate is prolonged (16.5 to >24 hours). These differences may account in part for the greater anti-CMV activity of ganciclovir and explain how single daily doses may be effective in suppressing human CMV infections.

Ganciclovir triphosphate is a competitive inhibitor of deoxyguanosine triphosphate incorporation into DNA and preferentially inhibits viral more than host cellular DNA polymerases. Incorporation of ganciclovir triphosphate into viral DNA causes a slowing and subsequent cessation of viral DNA chain elongation. In contrast to acyclovir, ganciclovir is not an obligate chain terminator, and continued viral DNA synthesis results in intranuclear accumulation of short, noninfectious viral DNA fragments.[382] Ganciclovir is incorporated into host cell and viral DNA.

Resistance

Resistance in CMV isolates, often defined by inhibitory concentrations greater than 1.5 to 3 µg/mL in vitro, has been related to two mechanisms: (1) reduced intracellular ganciclovir phosphorylation caused by point mutations or deletions in the phosphotransferase encoded by the *UL97* gene and (2) point mutations in viral DNA polymerase (*UL54* gene).[383,384] Most resistant clinical isolates with 4-fold to 20-fold increases in inhibitory concentrations have single or sometimes multiple *UL97* mutations and usually remain susceptible to foscarnet and cidofovir.[169] Highly resistant CMV strains (inhibitory concentrations >10 µg/mL) typically harbor *UL97* and *UL54* mutations and are cross-resistant to cidofovir but are usually susceptible to foscarnet.[169,170,385]

Ganciclovir resistance is rare in ganciclovir-naïve patients but has been recognized clinically by progressive disease[386] and persistent CMV viremia in patients receiving therapy.[347] Risk factors include prolonged ganciclovir exposure, primary infection, combined immunodeficiency, perhaps subtherapeutic doses,[387,388] and higher immunosuppression including use of antilymphocyte globulin. In patients with AIDS receiving ganciclovir for retinitis, resistant CMV is detectable in about 7% by 3 months and in 28% by 9 months.[389] During the ART era, a 15% frequency of *UL97* mutations has been found by 18 months in valganciclovir recipients.[390] Emergence of resistance, sometimes within several weeks, also occurs with ganciclovir use in children with primary combined immunodeficiency.[391] Ganciclovir-resistant CMV disease developed in 7% of mismatched solid-organ transplant recipients receiving ganciclovir prophylaxis.[392] Valganciclovir prophylaxis may be associated with less risk of ganciclovir-resistant CMV mutants, but the frequency of resistant virus has ranged from 0%[393] to 14%.[394] Mismatched lung transplant recipients are at particular risk for resistance emergence.[395] The transmissibility of ganciclovir-resistant CMV strains is undefined, but patients with such strains may have invasive disease including retinitis, enteritis, polyradiculopathy, or pneumonia.[7,396] Foscarnet or cidofovir therapy may benefit patients with ganciclovir-resistant CMV infections.[347] Successful treatment has been described with leflunomide, which has been postulated to have anti-CMV activity.[397,398] Ganciclovir is more than 40 times less active against acyclovir-resistant, TK-deficient HSV strains than against wild-type strains.

Pharmacokinetics

The oral bioavailability of ganciclovir is about 5% under fasting conditions.[373] Food increases bioavailability to 6% to 9%, so dosing with meals is recommended.[399–401] Peak and trough plasma levels average about 0.9 to 1.2 µg/mL and 0.2 to 0.5 µg/mL, respectively, on an oral regimen of 1000 mg every 8 hours. Valganciclovir is a monovalyl ester prodrug that is well absorbed, most likely by intestinal peptide transporter 1, and rapidly hydrolyzed to the parent molecule by intestinal and hepatic esterases. After administration of oral valganciclovir tablets (900 mg) with food, ganciclovir bioavailability is approximately 60%, prodrug blood levels are low (1%–2% of ganciclovir), ganciclovir peak plasma concentrations average 5.9 to 6.7 µg/mL, and overall ganciclovir exposure is comparable to intravenous dosing of ganciclovir at 5 mg/kg.[402,403] Similarly, in a patient with a small bowel transplant and other patients with stable graft-versus-host disease of the gastrointestinal tract, absolute bioavailability of ganciclovir from valganciclovir is 65%[404] to 75%,[405] and ganciclovir systemic exposure with a 900-mg dose of valganciclovir is not inferior to that of 5 mg/kg of ganciclovir given intravenously.[406] A valganciclovir solution is bioequivalent to the tablet formulation.[407] Valganciclovir has essentially supplanted oral ganciclovir and is commonly used in place of intravenous ganciclovir.

After intravenous administration of doses of 5 mg/kg, peak and trough plasma concentrations average 8 to 11 µg/mL and 0.6 to 1.2 µg/mL, respectively.[373,408] Subcutaneous and intramuscular administration are too irritating for clinical use. Plasma protein binding is only 1% to 2%. After intravenous dosing, aqueous, vitreous, and subretinal fluid levels are similar to those in serum.[338,409] CSF levels are 24% to 70%, and brain tissue levels are 38% of those in plasma.[403] The plasma $T_{½elim}$ averages 2 to 4 hours in patients with normal renal function but increases almost linearly as CrCl declines, increasing to 28 to 40 hours in patients with severe renal insufficiency. Most ganciclovir is eliminated unmetabolized by renal excretion (>90% of dose) by glomerular filtration and tubular secretion. Dosage reductions of ganciclovir (Table 46.7) and valganciclovir (Table 46.8) are necessary in patients with CrCl less than 60 to 70 mL/min. Ganciclovir dosing regimens for patients on continuous venovenous hemodiafiltration are suggested.[410]

A single hemodialysis session reduces the plasma levels of ganciclovir by approximately 50% to 60%, and dosing after dialysis is recommended.[411] In adults on continuous renal replacement therapy, 450 mg every 48 hours produces plasma concentrations comparable to concentrations observed in patients with normal renal function receiving 900 mg daily.[412] In neonates, valganciclovir, 15 mg/kg twice daily, yields plasma concentrations similar to intravenous ganciclovir, 5 mg/kg twice daily.[413] The intravitreal ganciclovir implant is designed to release the drug at a rate of approximately 1 µg/h over 5 to 8 months.[414]

Interactions

Concurrent oral ganciclovir doubles the overall exposure to didanosine, increases zidovudine exposure by a much smaller extent, and may

TABLE 46.7 Ganciclovir Dosage Adjustments in Renal Insufficiency

CREATININE CLEARANCE (mL/min)	IV GANCICLOVIR INDUCTION DOSE (mg/kg)	DOSING INTERVAL (h)	IV GANCICLOVIR MAINTENANCE DOSE (mg/kg)	DOSING INTERVAL (h)
≥70	5	12	5	24
50–69	2.5	12	2.5	24
25–49	2.5	24	1.25	24
10–24	1.25	24	0.625	24
<10	1.25	3 times/wk after hemodialysis	0.625	3 times/wk after hemodialysis

[a]Dosing suggestions are based on manufacturer's recommendations.
IV, Intravenous.

TABLE 46.8 Dosage Adjustments for Valganciclovir in Renal Insufficiency

CREATININE CLEARANCE (mL/min)	INDUCTION DOSAGE	MAINTENANCE DOSAGE
≥60	900 mg bid	900 mg qd
40–59	450 mg bid	450 mg qd
25–39	450 mg qd	450 mg q2d
10–24	450 mg q2d	450 mg 2 times/wk
<10[b]	Not recommended	Not recommended
Hemodialysis[b]	Not recommended	Not recommended

[a]Dosage suggestions are based on manufacturer's recommendations.
[b]Dose <450-mg tablet is needed. Use intravenous ganciclovir.

increase the risk for didanosine concentration–related toxicities.[415] Ganciclovir exposure is reduced about 20% when it is ingested 2 hours after, but not simultaneously with, didanosine. Ganciclovir antagonizes the anti-HIV activity of didanosine and zidovudine in vitro,[416] and zidovudine antagonizes the anti-CMV effects of ganciclovir.[417,418] The clinical significance of these observations is unknown, but didanosine-valganciclovir coadministration resulted in complete suppression of HIV in plasma, a paradoxical $CD4^+$ decline, and didanosine toxicity.[419]

Zidovudine and probably other cytotoxic agents increase the risk for ganciclovir-induced myelosuppression, as do nephrotoxic or other agents (probenecid, trimethoprim-sulfamethoxazole) that impair ganciclovir excretion. In animals, zidovudine (but not amphotericin B, ketoconazole, dapsone, or trimethoprim-sulfamethoxazole) antagonizes the anti-CMV effects of ganciclovir.[417,420] Renal dysfunction may occur in patients given concurrent ganciclovir and either amphotericin B or cyclosporine, and ganciclovir may increase cyclosporine levels.

Toxicity

Myelosuppression is the principal dose-limiting toxicity of ganciclovir and its prodrug. The most common adverse events are neutropenia in 24% to 40% and thrombocytopenia in 15% to 20% of patients with AIDS receiving intravenous ganciclovir or oral valganciclovir.[373] The risk for these toxicities is lower in transplant recipients. Neutropenia occurs in approximately one-fourth of patients receiving oral ganciclovir. Neutropenia is most commonly observed during the second week of treatment and is reversible in most patients within 1 week after drug cessation. Recombinant granulocyte-macrophage colony-stimulating factor may be useful in treating ganciclovir-induced neutropenia.[421]

CNS side effects, ranging in severity from headache, to behavioral changes with confusion or psychosis, to convulsions and coma, have been described in 5% to 15% of patients. Acute neurotoxicity with confusion and hallucinations was associated with serum and CSF concentrations of 3.9 μg/mL and 2.6 μg/mL, respectively, 48 hours after the last valganciclovir dose.[422] One-third of patients receiving intravenous ganciclovir interrupt or prematurely stop therapy because of bone marrow or CNS toxicity, and catheter-related complications are common. Approximately 25% of valganciclovir recipients discontinue maintenance therapy within 10 months for toxicity or other reasons.[423] Increased rates of azotemia occur in transplant recipients receiving intravenous ganciclovir prophylaxis.[424] Oral valganciclovir and ganciclovir are associated with diarrhea and possibly with mild nephrotoxicity.[425]

Anemia, rash, fever, liver function test abnormalities, nausea or vomiting, and eosinophilia have also been reported, as have two cases of lactic acidosis.[426] Phlebitis at the infusion site may be caused by the alkaline pH of the solution. In the event of massive overdosage, hemodialysis and hydration may be effective in reducing plasma ganciclovir levels. Placement of the intravitreal insert and intravitreal injections may be associated with visual changes, hemorrhage, infection, and retinal detachment.[427,428]

Ganciclovir is mutagenic, carcinogenic, and immunosuppressive, and it causes irreversible reproductive toxicity in animals and possibly humans.[373] Teratogenicity, embryotoxicity, testicular atrophy, and bone marrow hypocellularity have been observed in animals at ganciclovir exposures comparable to those in humans. Ganciclovir may be teratogenic in humans (classified pregnancy category C), and mothers should avoid breastfeeding while receiving ganciclovir or valganciclovir. Topical 0.15% ganciclovir ophthalmic gel is well tolerated.[429]

Clinical Studies

Ganciclovir and valganciclovir are currently approved for treatment and long-term suppression of CMV retinitis in immunocompromised patients and prevention of CMV disease in transplant recipients. Because of toxicities, administration is usually limited to patients at risk for or having life-threatening or sight-threatening CMV infections. With initial or induction intravenous dosages of 2.5 mg/kg every 8 hours or 5 mg/kg every 12 hours for 10 to 21 days, about 85% of patients with CMV retinitis experience improvement or stabilization of disease, and funduscopic improvement is usually evident by 10 to 14 days.[373,430] Ganciclovir is comparable to foscarnet in initial control of retinitis.[350] Oral valganciclovir (900 mg twice daily for 3 weeks) is as effective as intravenous ganciclovir for initial treatment of non–sight-threatening disease.[402] Almost all patients with AIDS who respond to initial treatment relapse within weeks without suppressive therapy.[430] High dosages of intravenous ganciclovir (30–35 mg/kg/wk) and oral valganciclovir (900 mg daily)[402] are effective for long-term suppression. Oral ganciclovir suppression (1 g three times daily) seems to be comparably effective to intravenous dosing.[431]

Retinal detachments are common during long-term follow-up. Combined ganciclovir and foscarnet are superior to monotherapy and may be effective when single-agent therapy fails.[351] Intraocular sustained-release ganciclovir implants[414,432] and repeated intravitreal injections are effective in controlling retinitis but do not prevent CMV disease in the other eye or in other sites.

Clinical improvement and virologic responses are also seen in CMV pneumonia and gastrointestinal infections in patients with AIDS and in solid-organ transplant recipients.[379,430] Valganciclovir is as effective as intravenous ganciclovir for viremic CMV disease in solid-organ transplant recipients.[433] Half doses (once daily) each of intravenous ganciclovir combined with foscarnet were not as effective as twice-daily ganciclovir alone for the same indication.[434] CNS syndromes respond less predictably and may progress despite therapy.[435] In biopsy-proven CMV colitis in patients with AIDS, ganciclovir (5 mg/kg every 12 hours for 14 days) is associated with significant antiviral effects, stabilization of weight loss, and lower incidence of extracolonic CMV disease, but no differences in symptoms compared with placebo.[436] In bone marrow transplant recipients, virologic responses (but no reduction in mortality) occur in patients with CMV pneumonia treated with ganciclovir alone or in combination with corticosteroids. In contrast, ganciclovir combined with intravenous immunoglobulin or CMV immunoglobulin reduces the mortality rate among bone marrow transplant recipients with CMV pneumonia (from 80%–90% to 30%–50%). Prolonged ganciclovir and valganciclovir treatment may reduce the risk for hearing loss in symptomatic infants with congenital CMV disease.[437,438]

Intravenous ganciclovir prophylaxis seems to be effective and reasonably well tolerated in preventing CMV disease in bone marrow[439,440] and solid-organ transplant recipients.[424] Preemptive ganciclovir treatment (5 mg/kg every 12 hours for 7–14 days, followed by 5 mg/kg/day for 5–7 days/wk until days 100–120 after transplantation) when CMV is isolated from bronchoalveolar lavage fluid[439] or from other body sites[440] is highly effective in preventing CMV pneumonia and seems to reduce mortality in bone marrow transplant recipients. In seropositive bone marrow transplant recipients, initiation of ganciclovir at the time of engraftment also markedly reduces CMV shedding and disease rates but does not improve survival, in part because of neutropenia-related infections.[441,442]

Short-term ganciclovir administration after transplantation reduces the risk for CMV disease in seropositive allograft recipients undergoing heart, lung, or liver transplantation.[424,443] More prolonged administration provides more sustained protection, but breakthrough CMV infection, toxicity, and resistance can limit its utility.[444] In lung transplant recipients, ganciclovir prophylaxis was associated with less bronchiolitis obliterans, improved survival, and prevention of HSV infection.[444–446] Indefinite

prophylaxis is now recommended in lung transplant recipients.[447] In renal transplant recipients, 24 weeks of prophylaxis was more effective than 12 weeks of prophylaxis in reducing symptomatic CMV disease.[448] Preemptive intravenous ganciclovir during antilymphocyte antibody treatment for 2 weeks reduced the risk for CMV disease in renal transplant recipients.[449] Ganciclovir results in clearance of EBV from oropharyngeal secretions, although a rapid rebound in excretion occurs after cessation of therapy.[450] Valganciclovir was not more effective in preventing blood levels of CMV DNA-emia by PCR compared with valacyclovir in renal transplant recipients.[451]

Oral ganciclovir (1 g three times daily to day 98) prophylaxis markedly reduces the risk for invasive CMV disease in liver transplant recipients including the high-risk group comprising seronegative recipients of organs from seropositive donors.[452] Ganciclovir prophylaxis (1 g three times daily orally for 12 weeks) is also effective in renal transplant recipients.[453] Compared with oral ganciclovir (1 g three times daily), valganciclovir (900 mg once daily) has been associated with a lower rate of CMV viremia on prophylaxis but comparable rates of CMV viremia and disease at 12 months in high-risk mismatched solid-organ transplant recipients in one study,[454] although other investigators have not observed a difference.[455] The optimal duration of prophylaxis remains to be established, and studies of lower doses are underway. Preemptive therapy with oral ganciclovir (1 g three times daily for 8 weeks) when CMV DNA is detectable protects against CMV disease in liver transplant recipients.[456]

Oral ganciclovir (1 g every 8 hours) prophylaxis seems to decrease the incidence of CMV disease in HIV-infected patients with CD4 T-cell counts less than 100 cells/mm,[457] although not when administered with didanosine.[458–460] However, oral ganciclovir is no longer marketed in the United States. In a randomized, placebo-controlled trial, valganciclovir did not reduce CMV end-organ disease in patients with AIDS at high risk (CD4 count <100 cells/mm^3 and CMV viremia),[459] so valganciclovir primary prophylaxis is not recommended for HIV-positive patients who are or are not receiving ART.[460]

In newborn infants with congenital CMV infection, ganciclovir therapy increases "the improvement rate and the rate of CMV infection indexes becoming negative" and decreases the incidence of hearing disturbance with few side effects.[461] In infants with congenital CMV involving the CNS, 6 weeks of intravenous ganciclovir results in fewer developmental delays.[462] In neonates with asymptomatic congenital CMV infection, intravenous ganciclovir for 21 days in the newborn period reduces subsequent hearing loss.[463]

EBV infections have been prevented and treated with ganciclovir and valganciclovir. Primary infection is prevented in high-risk pediatric renal transplant patients receiving a kidney from an EBV-seropositive donor.[464] Preemptive therapy may prevent post-transplantation lymphoproliferative disease in pediatric liver transplant patients.[465] Post-transplantation lymphoproliferative disease of the CNS has been successfully treated with combination therapy including ganciclovir.[466] Severe hepatitis complicating primary EBV infection responded to valganciclovir plus glucocorticoids,[467] as did EBV multicentric Castleman disease.[468]

Intravenous ganciclovir (5 mg/kg every 12 hours) is recommended for initial treatment of herpes B virus infections, particularly for patients with CNS involvement.[135] Intravenous ganciclovir reduces biochemical abnormalities and hepatitis B virus DNA levels by 90% in post-transplantation HBV infection.[374] Additional viral infections treated with intravenous ganciclovir and valganciclovir include varicella acute retinal necrosis,[469] HHV-6 meningoencephalitis or meningoradiculitis,[470–472] HHV-8 Castleman disease,[473,474] and EBV CNS infection and lymphoma.[475,476] Topical 0.15% ganciclovir ophthalmic gel is comparable to acyclovir ointment in treating HSV keratitis[477] but is not different from artificial tears for treatment of adenoviral conjunctivitis.[478]

IDOXURIDINE

Idoxuridine (5-iodo-2′-deoxyuridine, IDU; Herplex) is an iodinated thymidine analogue (see Fig. 46.3C) that inhibits replication of various DNA viruses in vitro, particularly herpesviruses and poxviruses.[479] Plaque production by most clinical isolates of HSV type 1 is inhibited by concentrations of 2 to 10 μg/mL. The median inhibitory concentration for two laboratory vaccinia strains was 0.2 to 0.3 μg/mL.[480] Idoxuridine and cidofovir were reported to synergistically inhibit the growth of a vaccinia virus at concentrations that were not cytotoxic. The antiviral mechanism of action of idoxuridine is not completely defined, but the phosphorylated derivatives interfere with various enzyme systems. The triphosphate inhibits viral DNA synthesis and is incorporated into viral and cellular DNA. Resistance to idoxuridine readily develops under laboratory conditions[481] and occurs in viral isolates recovered from idoxuridine-treated patients with HSV keratitis.

In human patients, extremely low plasma concentrations of idoxuridine (0.1–0.4 ppm) are detected in about half of patients treated topically with 40% idoxuridine in the penetration-enhancing agent dimethyl sulfoxide (DMSO). Idoxuridine is teratogenic, mutagenic, tumor-promoting, and immunosuppressive in preclinical testing. DMSO is teratogenic and can cause adverse ocular effects in laboratory animals.

In the United States, idoxuridine is approved only for topical treatment of HSV keratitis, whereas idoxuridine in DMSO is available in Europe for treatment of herpes labialis, herpes genitalis, and herpes zoster. In ocular HSV infections, topical idoxuridine is more effective in epithelial infections, especially initial episodes, than in stromal infections.[482] In a systematic review of antiviral drugs and other treatments for HSV epithelial keratitis, it was concluded that "trifluridine and acyclovir are more effective than idoxuridine or vidarabine and are similar in effectiveness."[483] Adverse reactions include pain, pruritus, inflammation, or edema involving the eye or lids and, rarely, allergic reactions.

Topical idoxuridine alone in solution is ineffective in mucocutaneous herpesvirus infections. In a small pilot study, optimizing the dispersion of idoxuridine 1% in a 5% liposome in gel formulation increased idoxuridine penetration and retention in vitro compared with a non-optimized formulation and increased healing of HSV skin lesions in patients by 1.6-fold to 2-fold. Itching, burning, and other side effects were much less common with the optimized liposomal gel.[484] Frequent topical application of 5% to 40% idoxuridine dissolved in DMSO seems to hasten healing and shorten pain duration in localized herpes zoster. Topical 30% idoxuridine in DMSO may shorten the duration of viral shedding in recurrent or primary genital HSV infections, but it does not reduce the duration of symptoms or healing time. Topical 15% idoxuridine in DMSO reduces the duration of pain and healing time in recurrent herpes labialis.[485] Mild local burning and aftertaste are common after topical application of DMSO; headache, dizziness, sedation, nausea, and localized and generalized dermatitis have also been reported.

LETERMOVIR (AIC246)

Letermovir inhibits only CMV among human herpesviruses (Fig. 46.4). It was licensed in the United States in 2017 for prevention of CMV infection in adult CMV-seropositive recipients of an allogeneic stem cell transplant. It is a 3,4-dihydro-quinozoline, which inhibits CMV replication by binding to and inhibiting the viral terminase enzyme complex (UL51, UL56, or both).[486] It does not require phosphorylation as ganciclovir does or act by inhibiting viral DNA polymerase similar to ganciclovir, cidofovir, or foscarnet. It is therefore active against most CMV isolates that are resistant to the currently available anti-CMV

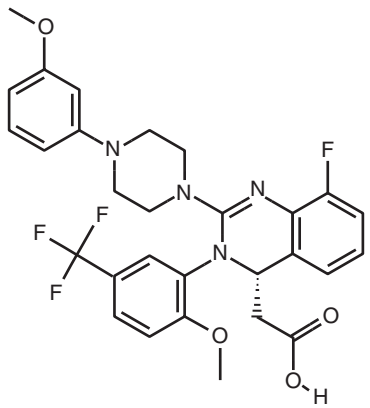


FIG. 46.4 Chemical structure of letermovir.

agents. Letermovir has highly potent anti-CMV activity, with an ID_{50} of 5 μM in tissue culture and a selective lack of cellular toxicity.[487] Drug-resistant virus can be selected by a one-step selection process due to a specific point mutation in the terminase complex.[486]

Letermovir is administered orally or by intravenous injection. It was well tolerated in phase I trials. A phase II study of letermovir was undertaken in stem cell transplant patients as prophylaxis against CMV disease. Once-daily doses of 120 mg or 240 mg or placebo were administered for 84 days. Failure of prophylaxis was significantly less in recipients of either dose of letermovir than in the placebo group. A modest excess of vomiting and edema in the letermovir group was observed.[488] In a phase III study, 495 adults were given 480 mg/day letermovir or placebo a median of 9 days after HSCT and continued for approximately 100 days after transplantation.[489] CMV infection was reduced from 61% (103 of 170) in placebo recipients to 38% (122 of 325) in letermovir recipients. All-cause mortality was also less in letermovir recipients (21% vs. 26%). Peripheral edema and vomiting tended to be less common in letermovir recipients. One patient receiving letermovir developed breakthrough CMV infection; his isolate had a *UL56* gene mutation mediating letermovir resistance. Such CMV mutants remain susceptible to ganciclovir.[490] The use of letermovir to treat CMV infection has been reported only in a small trial with a low dose, 80 mg/day, for preemptive treatment of CMV infection in renal transplant recipients.[491] Letermovir and ganciclovir as a control were similarly effective in controlling CMV DNA in blood. In one case report, letermovir treatment cured a lung transplant recipient with multidrug-resistant CMV disease unresponsive to other treatments.[492]

Letermovir pharmacokinetics are complex.[493] The major route of letermovir clearance is via biliary excretion (93% based on studies in rats) of primarily unchanged (71%) drug by organic anion transporting polypeptide 1B1 (OATP1B1) and OATP1B3 transporters. No letermovir is metabolized by human cytochrome P-450 (CYP) isoenzymes.[494] In healthy adults, AUC and C_{max} increase in proportion to dose over the range from 30 to 120 mg/day for 8 days.[494,495] Plasma $T_{½elim}$ (median 13.8 hours) is independent of dose over this range, as is the apparent volume of distribution at steady state (median 241 ± 221 L for the 3 doses). Systemic exposure was equivalent at doses of 480 mg/day administered orally or intravenously but appeared to increase disproportionately (nonlinearly) to 4.6-fold greater with a dose of 720 mg orally twice daily compared with 480 mg once daily.[496]

Renal impairment increases exposure to letermovir.[495] Moderate hepatic impairment increases exposure to letermovir less than twofold, whereas severe hepatic impairment increases letermovir exposure approximately fourfold compared with results in healthy subjects.[494] Concomitant letermovir increases tacrolimus and cyclosporine exposure. Cyclosporine alters letermovir exposure, whereas tacrolimus does not.[497]

TRIFLURIDINE

Trifluridine (trifluorothymidine, 5-trifluoromethyl-2′-deoxyuridine; Viroptic) is a fluorinated pyrimidine nucleoside (see Fig. 46.3D) that has in vitro inhibitory activity against HSV-1, HSV-2, CMV, vaccinia, and, to lesser extent, certain adenoviruses. Concentrations of 0.2 to 10 μg/mL inhibit replication of herpesviruses, including acyclovir-resistant HSV strains.[17] The antiviral mechanism of action involves inhibition of viral DNA synthesis. Trifluridine monophosphate irreversibly inhibits thymidylate synthetase, and the triphosphate competitively inhibits DNA polymerases with respect to thymidine triphosphate. Trifluridine is incorporated into viral and, to a lesser extent, cellular DNA, and it inhibits cellular DNA synthesis at low concentrations. It also exhibits mutagenic, teratogenic, and antineoplastic activities in experimental systems. Trifluridine-resistant HSV with altered TK substrate specificity can be selected on laboratory passage.[481] The clinical significance of this observation is uncertain.

Clinical use of trifluridine is limited to topical therapy for HSV infections, and it is approved in the United States for treatment of primary keratoconjunctivitis and recurrent epithelial keratitis caused by HSV-1 and HSV-2 (see Table 46.1).[482] A recent systematic review concluded that topical trifluridine and acyclovir are more effective than idoxuridine or vidarabine and are similar in effectiveness.[483] Topical trifluridine is effective in some patients who have not responded clinically to idoxuridine or vidarabine. Adverse reactions include discomfort on instillation; palpebral edema; and, uncommonly, hypersensitivity reactions, irritation, and superficial punctate or epithelial keratopathy.

Topical trifluridine also seems to benefit some patients with acyclovir-resistant HSV cutaneous infections.[483a] Combinations of trifluridine and IFN-α synergistically inhibit HSV replication in vitro and have been used to treat ocular and drug-resistant mucocutaneous HSV infections.[17]

VIDARABINE

Vidarabine (9-β-D-ribofuranosyladenine; ara-A, adenine arabinoside; Vira-A) is an analogue of adenosine (see Fig. 46.3E) that has in vitro antiviral activity against herpesviruses, poxviruses, rhabdoviruses, and some RNA tumor viruses. Plaque formation by most HSV and VZV strains is completely inhibited by 3 μg/mL or less of vidarabine, and it is inhibitory for idoxuridine-resistant and acyclovir-resistant strains.

Vidarabine is phosphorylated by cellular enzymes to the triphosphate, which competitively inhibits the activity of viral and, to a lesser extent, cellular DNA polymerases. Vidarabine triphosphate is incorporated into cellular and viral DNA. Vidarabine triphosphate inhibits other host cell enzyme systems including ribonucleoside reductase, RNA polyadenylation, and *S*-adenosylhomocysteine hydrolase. Resistant variants resulting from mutations in viral DNA polymerase can be selected under laboratory conditions, but drug resistance is not a recognized clinical problem.

Little systemic absorption occurs after ophthalmic application. Absorbed vidarabine is rapidly converted to its hypoxanthine metabolite (araHx), which has 30-fold to 50-fold less antiviral activity. The kidneys excrete vidarabine and araHx.

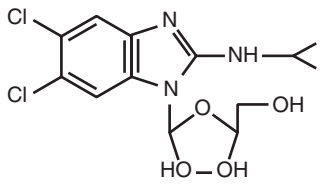
Vidarabine has been shown to be mutagenic, teratogenic, and oncogenic in preclinical testing. Hypersensitivity reactions including pruritus, erythema, ocular pain, and foreign body sensation may occur after ocular application. Other reported effects include photophobia, keratitis after exposure to ultraviolet light, and increased lacrimation.

Vidarabine has activity in certain life-threatening herpesvirus infections, including herpes simplex encephalitis and neonatal HSV[498] and adenovirus infection[499] in immunocompromised individuals and chronic EBV,[500] but not smallpox. Its use was discontinued in the United States in 1992. An ophthalmic ointment of vidarabine is less effective than trifluridine or acyclovir in HSV keratoconjunctivitis (see Table 46.1).[483] It is effective in patients who cannot receive idoxuridine because of allergy, toxicity, or drug resistance.

MARIBAVIR

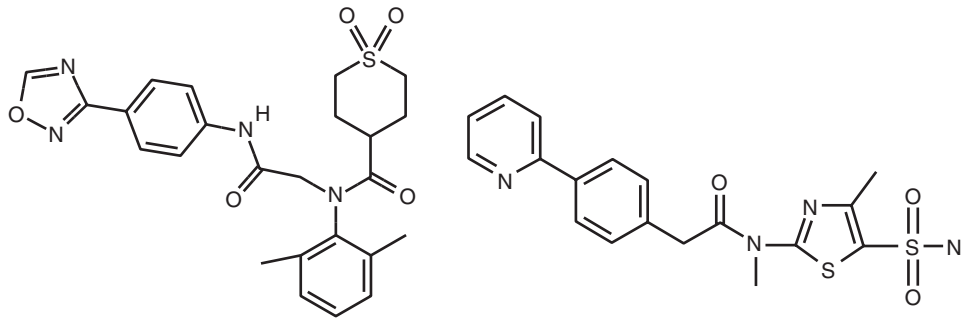
Maribavir {L-ribofuranosyl benzimidazole (5,6-dichloro-2-isopropylamino-1-[β-L-ribofuranosyl]-1H-benzimadazole)} inhibits CMV and EBV but not other human herpesviruses in vitro (Fig. 46.5).[501,502] It inhibits replication of clinical isolates of CMV at concentrations of less than 1 μM to approximately 15 μM in cell culture, including most variants resistant to ganciclovir, cidofovir, or foscarnet.[501,503]

Maribavir has a novel mechanism of anti-CMV action that does not require intracellular phosphorylation. It is a highly specific inhibitor of the protein kinase product of the *UL97* gene.[504] Inhibition of *UL97* function reduces the phosphorylation of several viral proteins, including UL44, which is essential for CMV DNA replication.[505] Maribavir thereby inhibits viral DNA synthesis and blocks nuclear egress of virions. As predicted from its inhibitory effect on *UL97* kinase, which phosphorylates ganciclovir to its active metabolite,[506] maribavir antagonizes the anti-CMV



Maribavir

FIG. 46.5 Chemical structure of maribavir.



A B

FIG. 46.6 **Chemical structures of amenamevir (A) and pritelivir (B).**

effect of ganciclovir,[506] although others report an additive or indeterminate effect.[507,508] As expected, maribavir does not affect the anti-CMV effect of foscarnet or cidofovir, which are drugs that do not require *UL97*-mediated phosphorylation.[506] Maribavir-resistant CMV strains selected during propagation with drug in vitro possess *UL97* kinase mutations that confer moderate to high-level resistance and *UL27* mutations that confer low-level resistance.[509,510] Maribavir-resistant strains are sensitive to ganciclovir,[505] whereas CMV strains resistant to ganciclovir, foscarnet, and cidofovir are sensitive to maribavir, consistent with their different mechanisms of action.[511]

Oral maribavir is rapidly absorbed and shows dose-proportional kinetics.[503] A high-fat meal decreases absorption by 30%.[512] Maribavir is highly bound to plasma proteins (>97%). The plasma $T_{½elim}$ is about 3 to 6 hours, and 30% to 40% of the dose is cleared in the urine as an *N*-alkylated metabolite and less than 2% as the parent molecule.[512] Maribavir pharmacokinetics are not significantly affected by mild (CrCl 50–80 mL/min) to severe (CrCl <30 mL/min) renal impairment.[513] Maribavir does not accumulate during twice-daily dosing for 10 days.[514] A dose of 400 mg twice daily for 10 days does not alter CYP1A2, CYP2C9, CYP3A, *N*-acetyl-transferase-2, and xanthine oxidase drug-metabolizing activity, although this regimen may inhibit CYP2C19 and CYP2D6 activities.[514] However, clinically important pharmacokinetic interactions have been demonstrated during co-administration of maribavir and tacrolimus (increasing tacrolimus exposure), presumably due to inhibition of CYP3A4 or P-glycoprotein, or both,[515] and rifampin (reducing maribavir), presumably due to induction of CYP3A4 or P-glycoprotein, or both.[516] Voriconazole did not interact pharmacokinetically with maribavir.[517]

In a randomized, placebo-controlled trial, maribavir 100–400 mg twice daily reduced the incidence of CMV DNA-emia in plasma compared with placebo,[518a] but did not prevent CMV disease, although 100 mg twice daily was not different from placebo in another study.[518] Similarly, maribavir was safe but not efficacious compared with ganciclovir in preventing CMV disease in adult liver transplant recipients.[519]

At higher doses than those used in the phase III studies, maribavir may be effective for treatment of refractory or resistant CMV infection in transplant recipients,[520] but resistance to it may appear rapidly and preclude a therapeutic effect.[521] In HIV-infected adults, maribavir (330–2400 mg daily in divided doses for 28 days) is associated with approximately 3 $\log_{10}$ or greater reductions in semen CMV titers.[522] Dose-related taste disturbance and diarrhea occur, and other possible adverse effects include rash, pruritus, headache, nausea, and fever.[522]

HELICASE-PRIMASE INHIBITORS (AMENAMEVIR, PRITELIVIR)

Helicase-primase inhibitors are antiviral agents with a novel mechanism of action against HSV-1 and HSV-2. They inhibit the viral heterotrimeric complex consisting of helicase, primase, and cofactor subunits that is essential for viral DNA replication. Both UL5 and UL52 together with the accessory protein UL8 form the enzyme complex that is the molecular target of these inhibitors.[523] They are not nucleoside analogues and do not require phosphorylation by a TK to inhibit HSV replication. Therefore they are active against TK-deficient HSV, which is the major mechanism of resistance to acyclovir and penciclovir.

Amenamevir (ASP2151)

Amenamevir (ASP2151) is an oxadiazolephenyl derivative (Fig. 46.6A) with potent activity against HSV-1 (median effective concentration [EC_{50}] 0.036 μM), HSV-2 (EC_{50} 0.028 μM), and VZV (EC_{50} 0.047 μM).[524] Amenamevir also inhibits nucleoside-resistant HSV strains. Amenamevir was investigated in a dose-finding placebo-controlled study in 437 patients with recurrent genital herpes.[525] Amenamevir was administered orally at one of four doses: 100 mg, 200 mg, or 400 mg daily for three doses or 1200 mg as a single dose. Another group of subjects received valacyclovir at 500 mg twice daily for 3 days. The duration of the recurrent episodes were 1 or 2 days shorter in both amenamevir-treated groups compared with placebo. The single 1200-mg dose amenamevir-treated group had a comparable efficacy rate to 3 days of valacyclovir. HSV isolates resistant to amenamevir were not detected before or after dosing.[526] In a controlled randomized trial in 751 patients with herpes zoster of fewer than 3 days' duration, amenamivir 200 mg or 400 mg orally once daily was not inferior to valacyclovir 1000 mg three times daily, all in 7 days.[527] Amenamevir 200 mg and 400 mg for 7 days was as well tolerated as valacyclovir in immunocompetent adults.

Clinical pharmacokinetics studies of amenamevir demonstrate dose-proportional AUC, C_{max}, and C_{min} over the dose range from 5 to 2400 mg.[528] Severe renal impairment increases AUC 78%, but the clinical importance of reducing doses in such patients is unclear.[529] Moderate hepatic impairment does not appear to produce sufficient pharmacokinetic changes to necessitate dose reductions.

Pritelivir (AIC316)

Pritelivir (AIC316) is a thiazolylamide (Fig. 46.6B) inhibitor of helicase-primase functions of HSV. It has potent antiviral activity with EC_{50} values of 0.026 μM against HSV-1 and 0.029 μM against HSV-2.[530] It is active against TK and DNA polymerase HSV mutants, which are resistant to nucleoside analogues.

The drug is administered orally and has a long half-life (up to 80 hours). Therefore it can be administered once weekly and appears to be well tolerated. Its effect on suppression of genital HSV-2 DNA shedding was studied in 156 individuals.[531] Otherwise healthy adults with genital HSV-2 infection were randomly assigned to one of four doses of pritelivir, 5 mg, 25 mg, or 75 mg daily or 400 mg weekly, or placebo for 28 days. Pritelivir reduced the rates of genital HSV DNA shedding and days with lesions in a dose-dependent manner.[531] No evidence of pritelivir resistance among HSV-2 isolates was observed.[532] In a subsequent study, pritelivir was compared with valacyclovir, 500 mg twice daily. Pritelivir, 100 mg/day for 28 days, reduced the relative risk of shedding of HSV-2 DNA in genital swabs by 58% and days with genital lesions by 60%.[533] However, this study was terminated before completion based on findings in monkeys in a 39-week toxicity study. The findings included dry and crusted skin lesions, alopecia, and anemia the mechanisms of which were not understood. Of note, no trial participants experienced such effects. One trial on the efficacy and safety of pritelivir for treatment

of acyclovir-resistant mucocutaneous HSV in immunocompromised adults is currently recruiting subjects.[534]

Tenofovir

Tenofovir is a nucleotide analogue that inhibits HSV DNA polymerase,[535,536] HBV DNA polymerase, and HIV reverse transcriptase. It is phosphorylated by cellular enzymes to form tenofovir diphosphate, which competitively inhibits HSV DNA polymerase and acts as a chain terminator. In vitro, tenofovir inhibits HSV-2 replication at a concentration of 125 to 176 μg/mL compared with 0.05 to 0.12 μg/mL for acyclovir. Cytotoxic concentrations are >200 μg/mL for tenofovir and >50 μg/mL for acyclovir.[536]

Tenofovir was approved for treatment of HIV infection in 2001 (see Chapter 128) and for treatment of HBV infection in 2006 (see Chapter 47). It is available as the orally administered prodrug tenofovir disoproxil fumarate, the acyclic nucleotide analogue of adenosine monophosphate.

Tenofovir formulated as a 1% topical gel was studied as an antiherpes drug in a double-blind, randomized, placebo-controlled trial in 422 HSV-2–negative women as part of the CAPRISA 004 study.[537] It was applied intravaginally pericoitally 12 hours before sex with a second dose applied within 12 hours after sex. Efficacy was addressed solely by prevention of HSV-2 seroconversion. Subjects receiving tenofovir demonstrated a 51% reduction in cases of HSV-2 infection ($P = .003$). No significant protective effect was observed in HIV-1–infected women, but the sample was small and compliance with use of tenofovir gel was low. In another study of tenofovir for prophylaxis of HSV-2 infection, daily oral tenofovir–based preexposure prophylaxis alone or in combination with emtricitabine reduced the risk of HSV-2 seroconversion significantly by 27% compared with placebo in the entire study population and by 30% in subjects whose partner was HSV-2–positive.[537] The same regimen was evaluated in a cohort comprising HSV-2–seronegative transgender women and men who have sex with men.[538] In contrast to the aforementioned result in heterosexual HIV-uninfected men and women, daily tenofovir-emtricitabine combination did not reduce the seroincidence of HSV-2 infections. Among the plausible explanations posited for the differences in efficacy in the three studies are differences in tenovir concentrations in the vagina achieved with topical and oral tenofovir and in the rectal-anal tissues with the oral formulation.[538]

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