Goodman & Gilman's

The Pharmacological Basis of THERAPEUTICS

eleventh edition

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GOODMAN AND GILMAN'S
THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 11/E

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Cover illustration: Imposed on the cover is a schematic rendering of the alpha subunit of the heterotrimeric G protein G_s as determined by x-ray crystallography (Sunahara, R.K., Tesmer, J.J.G., Gilman, A.G., and Sprang, S.R., Science vol 278, p 1943–1947, [1997]). Figure credit to Mark Wall, PhD.

zine reversibly decreases the number and motility of sperm but does not impair female fertility. It also inhibits intestinal folate absorption; therefore, folate usually is given with sulfasalazine.

The newer mesalamine formulations generally are well tolerated, and side effects are relatively infrequent and minor. Headache, dyspepsia, and skin rash are the most common. Diarrhea appears to be particularly common with olsalazine (occurring in 10% to 20% of patients); this may be related to its ability to stimulate chloride and fluid secretion in the small bowel. Nephrotoxicity, although rare, is a more serious concern. Mesalamine has been associated with interstitial nephritis; while its pathogenic role is controversial, renal function should be monitored in all patients receiving these drugs. Both sulfasalazine and its metabolites cross the placenta but have not been shown to harm the fetus. Although they have not been studied as thoroughly, the newer formulations also appear to be safe in pregnancy. The risks to the fetus from the consequences of uncontrolled IBD in pregnant women are believed to outweigh the risks associated with the therapeutic use of these agents (*see* below).

GLUCOCORTICOIDS

The effects of glucocorticoids on the inflammatory response are numerous and well documented (*see* Chapters 52 and 59). Although glucocorticoids are universally recognized as effective in acute exacerbations, their use in either ulcerative colitis or Crohn's disease involves considerable challenges and pitfalls, and they are indicated only for moderate to severe IBD. Because the same issues have an impact on steroid use in both ulcerative colitis and Crohn's disease, they are addressed together.

The response to steroids in individual patients with IBD divides them into three general classes: steroid-responsive, steroid-dependent, and steroid-unresponsive. Steroid-responsive patients improve clinically, generally within 1 to 2 weeks, and remain in remission as the steroids are tapered and then discontinued. Steroid-dependent patients also respond to glucocorticoids but then experience a relapse of symptoms as the steroid dose is tapered. Steroid-unresponsive patients do not improve even with prolonged high-dose steroids. Approximately 40% of patients are steroid-responsive, 30% to 40% have only a partial response or become steroid-dependent, and 15% to 20% of patients do not respond to steroid therapy.

Steroids sometimes are used for prolonged periods to control symptoms in steroid-dependent patients. However, the failure to respond to steroids with prolonged remission (*i.e.,* a disease relapse) should prompt consideration of alternative therapies, including immunosuppressives and *infliximab* (*see* below). Steroids are not effective in maintaining remission in either ulcerative colitis or Crohn's disease (Steinhart *et al.*, 2003); thus their significant side effects (*see* Chapter 59) have led to increased emphasis on limiting the duration and cumulative dose of steroids in IBD.

The approach to steroid therapy in IBD differs somewhat from that in diseases such as asthma or rheumatoid arthritis. Initial doses are between 40 to 60 mg *prednisone* or equivalent per day; higher doses generally are no more effective. The glucocorticoid dose in IBD is tapered over weeks to months. Even with these slow tapers, however, efforts should be made to minimize the duration of steroid therapy.

Glucocorticoids induce remission in the majority of patients with either ulcerative colitis or Crohn's disease (Faubion *et al.*, 2001). Oral prednisone is the preferred agent for moderate to severe disease, and the typical dose is 40 to 60 mg once a day. Most patients improve substantially within 5 days of initiating treatment; others require treatment for several weeks before remission occurs. For more severe cases, glucocorticoids are given intravenously. Generally, *methylprednisolone* or *hydrocortisone* is used for intravenous therapy, although some experts believe that *corticotropin* (ACTH) is more effective in patients who have not previously received any steroids.

Glucocorticoid enemas are useful in patients whose disease is limited to the rectum (proctitis) and left colon. Hydrocortisone is available as a retention enema (100 mg/60 ml), and the usual dose is one 60-ml enema per night for 2 or 3 weeks. When administered optimally, the drug can reach up to or beyond the descending colon. Patients with distal disease usually respond within 3 to 7 days. Absorption, while less than with oral preparations, is still substantial (up to 50% to 75%). Hydrocortisone also can be given once or twice daily as a 10% foam suspension (CORTIFOAM) that delivers 80 mg hydrocortisone per application; this formulation can be useful in patients with very short areas of distal proctitis and difficulty retaining fluid.

Budesonide (ENTOCORT ER) is an enteric-release form of a synthetic steroid that is used for ileocecal Crohn's disease (Greenberg *et al.*, 1994; McKeage and Goa, 2002). It is proposed to deliver adequate steroid therapy to a specific portion of inflamed gut while minimizing systemic side effects owing to extensive first-pass hepatic metabolism to inactive derivatives. Topical therapy (*e.g.,* enemas and suppositories) also is effective in treating colitis limited to the left side of the colon. While the topical potency of budesonide is 200 times higher than that of hydrocortisone, its oral systemic bioavailability is only 10%. In some studies, budesonide was associated with a lower incidence of systemic side effects than prednisone, although data also indicate that systemic steroids are more effective in patients with higher Crohn's Disease Activity Index scores. Budesonide (9 mg/day for 10 to 12 weeks) is effective in the acute management of mild-to-moderate exacerbations of Crohn's disease, but its role in maintaining remission has not been fully delineated (Hofer, 2003).

A significant number of patients with IBD fail to respond adequately to glucocorticoids and are either steroid-resistant or steroid-dependent. The reasons for this failure are poorly understood but may involve complications such as fibrosis or strictures in Crohn's disease, which will not respond to antiinflammatory measures alone; local complications such as abscesses, in which case the use of steroids may lead to uncontrolled sepsis; and intercurrent infections with organisms such as cytomegalovirus and *Clostridium difficile*. Steroid failures also may be related to specific pharmacogenomic factors such as up-regulation of the multidrug

resistance (*mdr*) gene (Farrell *et al.*, 2000) or altered levels of corticosteroid-binding globulin.

IMMUNOSUPPRESSIVE AGENTS

Several drugs developed initially for cancer chemotherapy or as immunosuppressive agents in organ transplants have been adapted for treatment of IBD. While their initial use in IBD was based on their immunosuppressive effects, their specific mechanisms of action are unknown. Increasing clinical experience has defined specific roles for each of these medicines as mainstays in the pharmacotherapy of IBD. However, both real and potential side effects mandate a careful assessment of potential risks and benefits in each patient.

Thiopurine Derivatives

The cytotoxic thiopurine derivatives *mercaptopurine* (6-MP, PURINETHOL) and azathioprine (IMMURAN) (*see* Chapters 51 and 52) are used to treat patients with severe IBD or those who are steroid-resistant or steroid-dependent (Pearson *et al.*, 1995). These thiopurine antimetabolites impair purine biosynthesis and inhibit cell proliferation. Both are prodrugs: Azathioprine is converted to mercaptopurine, which is subsequently metabolized to 6-thioguanine nucleotides that are the presumed active moiety (Figure 38–5). These drugs generally are used interchangeably with appropriate dose adjustments, typically azathioprine (2 to 2.5 mg/kg) or mercaptopurine (1.5 mg/kg). As discussed below, the pathways by which they are metabolized are clinically relevant, and specific assays can be used to assess clinical response and to avoid side effects. Because of concerns about side effects, these drugs were used initially only in Crohn's disease, which lacks a surgical curative option. They now are considered equally effective in Crohn's disease and ulcerative colitis. These drugs effectively maintain remission in both diseases; they also may prevent (or, more typically, delay) recurrence of Crohn's disease after surgical resection. Finally, they are used successfully to treat fistulas in Crohn's disease. The clinical response to azathioprine or mercaptopurine may take weeks to months, such that other drugs with a more rapid onset of action (*e.g.*, mesalamine, glucocorticoids, or infliximab) are preferred in the acute setting.

The decision to initiate immunosuppressive therapy depends on an accurate assessment of the risk/benefit ratio. In general, physicians who treat IBD believe that the long-term risks of azathioprine–mercaptopurine are lower than those of steroids. Thus, these purines are used in steroid-unresponsive or steroid-dependent disease and in patients who have had recurrent flares of disease requiring repeated courses of steroids. Additionally, patients who have not responded adequately to mesalamine but are not acutely ill may benefit by conversion from glucocorticoids to immunosuppressive drugs. Immunosuppressives therefore may be viewed as steroid-sparing agents.

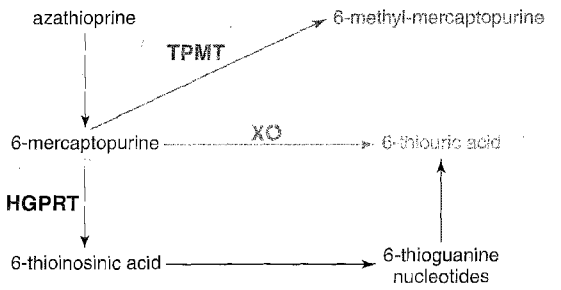


Figure 38–5. *Metabolism of azathioprine and 6-mercaptopurine.* TPMT = thiopurine methyltransferase; XO = xanthine oxidase; HGPRT = hypoxanthine–guanine phosphoribosyl transferase. The activities of these enzymes vary among humans because genetic polymorphisms are expressed differentially, explaining responses and side effects when azathioprine–mercaptopurine therapy is employed. *See* text for details.

Adverse effects of azathioprine–mercaptopurine can be divided into three general categories: idiosyncratic, dose-related, and possible. Although the therapeutic effects of azathioprine–mercaptopurine often are delayed, their side effects occur at any time after initiation of treatment and can affect up to 10% of patients. The most serious idiosyncratic reaction is pancreatitis, which affects approximately 5% of patients treated with these drugs. Fever, rash, and arthralgias are seen occasionally, whereas nausea and vomiting are somewhat more frequent. The major dose-related side effect is bone marrow suppression, and circulating blood counts should be monitored closely when therapy is initiated and at less frequent intervals during maintenance therapy (*e.g.*, every 3 months). Elevations in liver function tests also may be dose-related. Although keeping drug levels in the appropriate range diminishes these adverse effects, they can occur even with therapeutic serum levels of 6-thioguanine nucleotides. The serious side effect of cholestatic hepatitis is relatively rare. Although the increased risk of infection is a significant concern with immunosuppressives, especially if pancytopenia occurs, infections are linked more closely to concomitant glucocorticoid therapy than to the immunosuppressives (Aberra *et al.*, 2003).

There is some concern that the immunosuppressive agents may increase the risk of hematological malignancies. Immunosuppressive regimens given in the setting of cancer chemotherapy or organ transplants have been associated with an increased incidence of malignancy, particularly non-Hodgkin's lymphoma. Definitive conclusions about the causative roles of azathioprine–mercaptopurine in lymphomas are complicated by the possible increased incidence of lymphomas in IBD *per se* and by the relative rarity of these cancers. The increased risk, if any, must be relatively small.

Pharmacogenetics. Favorable responses to azathioprine–mercaptopurine are seen in up to two-thirds of patients.

Table 49–2
Nomenclature of Antiviral Agents

GENERIC NAME	OTHER NAMES	TRADE NAMES (USA)	DOSAGE FORMS AVAILABLE
Antiherpesvirus agents			
Acyclovir	ACV, acycloguanosine	ZOVIRAX	IV, O, T, ophth*
Cidofovir	HPMPC, CDV	VISTIDE	IV
Famciclovir	FCV	FAMVIR	O
Foscarnet	PFA, phosphonoformate	FOSCAVIR	IV, O*
Fomivirsen	ISIS 2922	VITRAVENE	Intravitreal
Ganciclovir	GCV, DHPG	CYTOVENE	IV, O, intravitreal
Idoxuridine	IDUR	HERPES, STOXIL, DENDRID	Ophth
Penciclovir	PCV	DENAVIR	T, IV*
Trifluridine	TFT, trifluorothymidine	VIROPTIC	Ophth
Valacyclovir		VALTREX	O
Valganciclovir		VALCYTE	O
Anti-influenza agents			
Amantadine		SYMMETREL	O
Oseltamivir	GS4104	TAMIFLU	O
Rimantadine		FLUMADINE	O
Zanamivir	GC167	RELENZA	Inhaled
Antihepatitis agents			
Adefovir dipivoxil	Bis-pom-PMEA	HEPSERA	O
Interferon-alfa		INTRON A, ROFERON A, INFERGEN, ALFERON N, WELLFERON*	Injected
Lamivudine	3TC	EPIVIR	O
Pegylated interferon alfa		PEGASYS, PEG-INTRON	SC
Other antiviral agents			
Ribavirin		VIRAZOLE, REBETOL, COPEGUS	O, inhaled, IV
Imiquimod		ALDARA	Topical

*Not currently approved for use in USA. ABBREVIATIONS: IV, intravenous; O, oral; T, topical; ophth, ophthalmic.

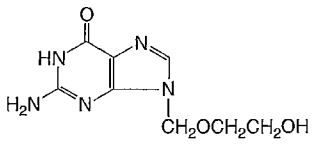
ANTIHERPESVIRUS AGENTS

Infection with herpes simplex virus type 1 (HSV-1) typically causes diseases of the mouth, face, skin, esophagus, or brain. Herpes simplex virus type 2 (HSV-2) usually causes infections of the genitals, rectum, skin, hands, or meninges. Both cause serious infections in neonates. HSV infection may be a primary one in a naive host, a nonprimary initial one in a host previously infected by other viruses, or the consequence of activation of a latent infection.

The first systemically administered antiherpesvirus agent, *vidarabine,* was approved by the Food and Drug Administration (FDA) in 1977. However, its toxicities restricted its use to life-threatening infections of HSV and varicella-zoster virus (VZV). The discovery and development of *acyclovir,* approved in 1982, provided the first effective treatment for less severe HSV and VZV infections in ambulatory patients. Intravenous acyclovir is superior to vidarabine in terms of efficacy and toxicity in HSV encephalitis and in VZV infections of immunocompromised patients. Acyclovir is the prototype of a group of antiviral agents that are phosphorylated intracellularly by a viral kinase and subsequently by host cell enzymes to become inhibitors of viral DNA synthesis. Other agents employing this strategy include *penciclovir* and *ganciclovir.*

Acyclovir and Valacyclovir

Chemistry and Antiviral Activity. Acyclovir (9-[(2-hydroxy-ethoxy)methyl]-9H-guanine) is an acyclic guanine nucleoside analog that lacks a 3′-hydroxyl on the side chain. *Valacyclovir* is the L-valyl ester prodrug of acyclovir.



ACYCLOVIR

Acyclovir's clinically useful antiviral spectrum is limited to herpesviruses. *In vitro,* acyclovir is most active against HSV-1 (0.02 to 0.9 μg/ml), approximately half as active against HSV-2 (0.03 to 2.2 μg/ml), a tenth as potent against VZV (0.8 to 4.0 μg/ml) and Epstein-Barr virus (EBV), and least active against cytomegalovirus (CMV) (generally greater than 20 μg/ml) and human herpesvirus (HHV-6) (Wagstaff *et al.*, 1994). Uninfected mammalian cell growth generally is unaffected by high acyclovir concentrations (>50 μg/ml).

Mechanisms of Action and Resistance. Acyclovir inhibits viral DNA synthesis *via* a mechanism outlined in Figure 49–2 (Elion, 1986). Its selectivity of action depends on interaction with two distinct viral proteins: HSV thymidine kinase and DNA polymerase. Cellular uptake and initial phosphorylation are facilitated by HSV thymidine kinase. The affinity of acyclovir for HSV thymidine kinase is about 200 times greater than for the mammalian enzyme. Cellular enzymes convert the monophosphate to acyclovir triphosphate, which is present in forty- to one hundredfold higher concentrations in HSV-infected than in uninfected cells and competes for endogenous deoxyguanosine triphosphate (dGTP). The immunosuppressive agent *mycophenolate mofetil* (*see* Chapter 52) potentiates the antiherpes activity of acyclovir and related agents by depleting intracellular dGTP pools. Acyclovir triphosphate competitively inhibits viral DNA polymerases and, to a much smaller extent, cellular DNA polymerases. Acyclovir triphosphate also is incorporated into viral DNA, where it acts as a chain terminator because of the lack of a 3′-hydroxyl group. By a mechanism termed *suicide inactivation,* the terminated DNA template containing acyclovir binds the viral DNA polymerase and leads to its irreversible inactivation.

Acyclovir resistance in HSV has been linked to one of three mechanisms: absence or partial production of viral thymidine kinase, altered thymidine kinase substrate specificity (*e.g.*, phosphorylation of thymidine but not acyclovir), or altered viral DNA polymerase. Alterations in viral enzymes are caused by point mutations and base insertions or deletions in the corresponding genes. Resistant variants are present in native virus populations, and heterogeneous mixtures of viruses occur in isolates from treated patients. The most common resistance mechanism in clinical HSV isolates is absent or deficient viral thymidine kinase activity; viral DNA polymerase mutants are rare. Phenotypic resistance typically is defined by *in vitro* inhibitory concentrations of greater than 2 to 3 μg/ml, which predict failure of therapy in immunocompromised patients.

Acyclovir resistance in VZV isolates is caused by mutations in VZV thymidine kinase and less often by mutations in viral DNA polymerase.

Absorption, Distribution, and Elimination. The oral bioavailability of acyclovir ranges from 10% to 30% and decreases with increasing dose (Wagstaff *et al.*, 1994). Peak plasma concentrations average 0.4 to 0.8 μg/ml after 200-mg doses and 1.6 μg/ml after 800-mg doses. Following intravenous dosing, peak and trough plasma concentrations average 9.8 and 0.7 μg/ml after 5 mg/kg every 8 hours and 20.7 and 2.3 μg/ml after 10 mg/kg every 8 hours, respectively.

Valacyclovir is converted rapidly and virtually completely to acyclovir after oral administration in healthy adults. This conversion is thought to result from first-pass intestinal and hepatic metabolism through enzymatic hydrolysis. Unlike acyclovir, valacyclovir is a substrate for intestinal and renal peptide transporters. The relative oral bioavailability of acyclovir increases three- to fivefold to approximately 70% following valacyclovir administration (Steingrimsdottir *et al.*, 2000). Peak acyclovir concentrations average 5 to 6 μg/ml following single 1000-mg doses of oral valacyclovir and occur approximately 2 hours after dosing. Peak plasma concentrations of valacyclovir are only 4% of acyclovir levels. Less than 1% of an administered dose of valacyclovir is recovered in the urine, and most is eliminated as acyclovir.

Acyclovir distributes widely in body fluids, including vesicular fluid, aqueous humor, and cerebrospinal fluid. Compared with plasma, salivary concentrations are low, and vaginal secretion concentrations vary widely. Acyclovir is concentrated in breast milk, amniotic fluid, and placenta. Newborn plasma levels are similar to maternal ones. Percutaneous absorption of acyclovir after topical administration is low.

The mean plasma $t_{\frac{1}{2}}$ of elimination of acyclovir is about 2.5 hours, with a range of 1.5 to 6 hours in adults with normal renal function. The elimination $t_{\frac{1}{2}}$ of acyclovir is about 4 hours in neonates and increases to 20 hours in anuric patients (Wagstaff *et al.*, 1994). Renal excretion of unmetabolized acyclovir by glomerular filtration and tubular secretion is the principal route of elimination. Less than 15% is excreted as 9-carboxymethoxymethylguanine or minor metabolites. The pharmacokinetics of oral acyclovir and valacyclovir appear to be similar in pregnant and nonpregnant women (Kimberlin *et al.*, 1998).

Untoward Effects. Acyclovir generally is well tolerated. Topical acyclovir in a polyethylene glycol base may cause mucosal irritation and transient burning when applied to genital lesions.

Oral acyclovir has been associated infrequently with nausea, diarrhea, rash, or headache and very rarely with renal insufficiency

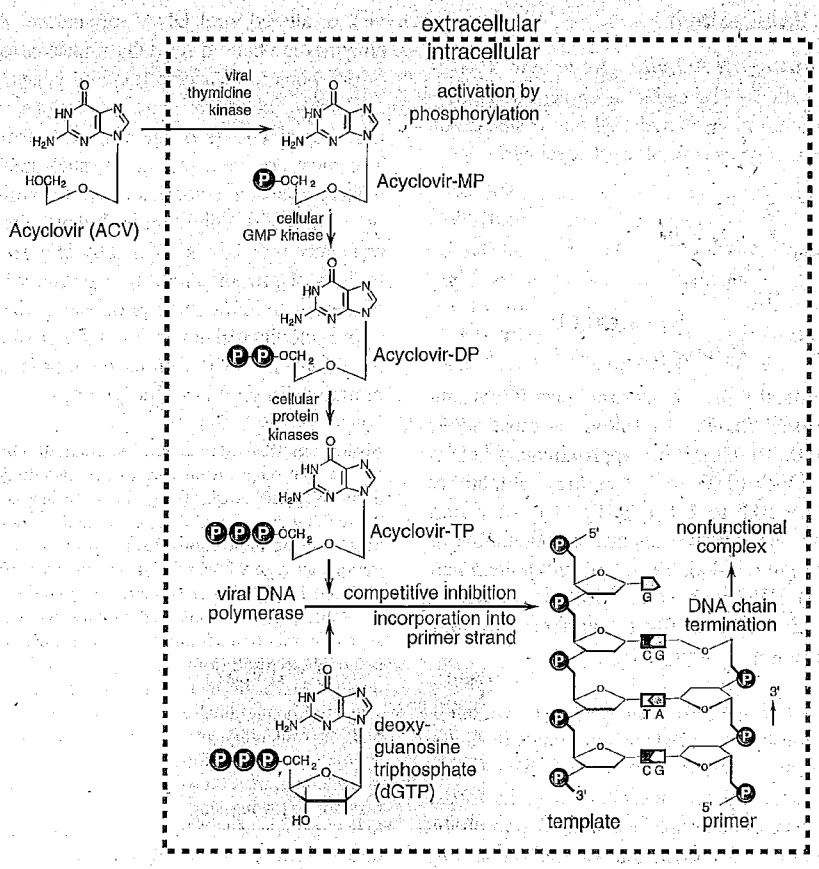


Figure 49–2. ***Conversion of acyclovir to acyclovir triphosphate leading to DNA chain termination.*** Acyclovir is converted to the monophosphate (MP) derivative by a herpesvirus thymidine kinase. Acyclovir-MP is then phosphorylated to acyclovir-DP and acyclovir-TP by cellular enzymes. Uninfected cells convert very little or no drug to the phosphorylated derivatives. Thus, acyclovir is selectively activated in cells infected with herpesviruses that code for appropriate thymidine kinases. Incorporation of acyclovir-MP from acyclovir-TP into the primer strand during viral DNA replication leads to chain termination and formation of an inactive complex with the viral DNA polymerase. (Adapted from Elion, 1986, with permission.)

or neurotoxicity. Valacyclovir also may be associated with headache, nausea, diarrhea, nephrotoxicity, and central nervous system (CNS) symptoms. High doses of valacyclovir have been associated with confusion and hallucinations, nephrotoxicity, and uncommonly, severe thrombocytopenic syndromes, sometimes fatal, in immunocompromised patients (Feinberg *et al.*, 1998). Acyclovir has been associated with neutropenia in neonates. Chronic acyclovir suppression of genital herpes has been used safely for up to 10 years. No excess frequency of congenital abnormalities has been recognized in infants born to women exposed to acyclovir during pregnancy (Ratanajamit *et al.*, 2003).

The principal dose-limiting toxicities of intravenous acyclovir are renal insufficiency and CNS side effects. Preexisting renal insufficiency, high doses, and high acyclovir plasma levels (>25 μg/ml) are risk factors for both. Reversible renal dysfunction occurs in approximately 5% of patients, probably related to high urine levels causing crystalline nephropathy. Manifestations include nausea, emesis, flank pain, and increasing azotemia. Rapid infusion, dehydration, and inadequate urine flow increase the risk. Infusions should be given at a constant rate over at least an hour. Nephrotoxicity usually resolves with drug cessation and volume expansion. Neurotoxicity occurs in 1% to 4% of patients and may be manifested by altered sensorium, tremor, myoclonus, delirium, seizures, or extrapyramidal signs. Phlebitis following extravasation, rash, diaphoresis, nausea, hypotension, and interstitial nephritis also have been described. Hemodialysis may be useful in severe cases.

Severe somnolence and lethargy may occur with combinations of *zidovudine* and acyclovir. Concomitant *cyclosporine* and probably other nephrotoxic agents enhance the risk of nephrotoxicity. *Probenecid* decreases the acyclovir renal clearance and prolongs the plasma $t_{\frac{1}{2}}$ of elimination. Acyclovir may decrease the renal clear-

ance of other drugs eliminated by active renal secretion, such as *methotrexate.*

Therapeutic Uses. In immunocompetent persons, the clinical benefits of acyclovir and valacyclovir are greater in initial HSV infections than in recurrent ones, which typically are milder in severity (Whitley and Gnann, 1992). These drugs are particularly useful in immunocompromised patients because these individuals experience both more frequent and more severe HSV and VZV infections. Since VZV is less susceptible than HSV to acyclovir, higher doses must be used for treating varicella or zoster infections than for HSV infections. Oral valacyclovir is as effective as oral acyclovir in HSV infections and more effective for treating herpes zoster.

Herpes Simplex Virus Infections. In initial genital HSV infections, oral acyclovir (200 mg five times daily or 400 mg three times daily for 7 to 10 days) and valacyclovir (1000 mg twice daily for 7 to 10 days) are associated with significant reductions in virus shedding, symptoms, and time to healing (Kimberlin and Rouse, 2004). Intravenous acyclovir (5 mg/kg every 8 hours) has similar effects in patients hospitalized with severe primary genital HSV infections. Topical acyclovir is much less effective than systemic administration. None of these regimens reproducibly reduces the risk of recurrent genital lesions. Patient-initiated acyclovir (200 mg five times daily or 400 mg three times daily for 5 days or 800 mg three times daily for 2 days) or valacyclovir (500 mg twice daily for 3 or 5 days) shortens the manifestations of recurrent genital HSV episodes by 1 to 2 days. Frequently recurring genital herpes can be suppressed effectively with chronic oral acyclovir (400 mg twice daily or 200 mg three times daily) or with valacyclovir (500 mg or, for very frequent recurrences, 1000 mg once daily). During use, the rate of clinical recurrences decreases by about 90%, and subclinical shedding is markedly reduced, although not eliminated. Valacyclovir suppression of genital herpes reduces the risk of transmitting infection to a susceptible partner by about 50% over an 8-month period (Corey *et al.*, 2004). Chronic suppression may be useful in those with disabling recurrences of herpetic whitlow or HSV-related erythema multiforme.

Oral acyclovir is effective in primary herpetic gingivostomatitis (600 mg/m^2 four times daily for 10 days in children) but provides only modest clinical benefit in recurrent orolabial herpes. Short-term, high-dose valacyclovir (2 g twice over one day) shortens the duration of recurrent orolabial herpes by about one day (Anonymous, 2002). Topical acyclovir cream is modestly effective in recurrent labial (Spruance *et al.*, 2002) and genital herpes simplex virus infections. Preexposure acyclovir prophylaxis (400 mg twice daily for one week) reduces the overall risk of recurrence by 73% in those with sun-induced recurrences of HSV infections. Acyclovir during the last month of pregnancy reduces the likelihood of viral shedding and frequency of cesarean section in women with primary or recurrent genital herpes (Sheffield *et al.*, 2003).

In immunocompromised patients with mucocutaneous HSV infection, intravenous acyclovir (250 mg/m^2 every 8 hours for 7 days) shortens healing time, duration of pain, and the period of virus shedding. Oral acyclovir (800 mg five times per day) and valacyclovir (1000 mg twice daily) for 5 to 10 days are also effective. Recurrences are common after cessation of therapy and may require long-term suppression. In those with very localized labial or facial HSV infections, topical acyclovir may provide some benefit. Intravenous acyclovir may be beneficial in viscerally disseminating HSV in immunocompromised patients and in patients with HSV-infected burn wounds.

Systemic acyclovir prophylaxis is highly effective in preventing mucocutaneous HSV infections in seropositive patients undergoing immunosuppression. Intravenous acyclovir (250 mg/m^2 every 8 to 12 hours) begun prior to transplantation and continuing for several weeks prevents HSV disease in bone marrow transplant recipients. For patients who can tolerate oral medications, oral acyclovir (400 mg five times daily) is effective, and long-term oral acyclovir (200 to 400 mg three times daily for 6 months) also reduces the risk of VZV infection (Steer *et al.*, 2000). In HSV encephalitis, acyclovir (10 mg/kg every 8 hours for a minimum of 10 days) reduces mortality by over 50% and improves overall neurologic outcome compared with vidarabine. Higher doses (15 to 20 mg/kg every 8 hours) and prolonged treatment (up to 21 days) are recommended by many experts. Intravenous acyclovir (20 mg/kg every 8 hours for 21 days) is more effective than lower doses in viscerally invasive neonatal HSV infections (Kimberlin *et al.*, 2001). In neonates and immunosuppressed patients and, rarely, in previously healthy persons, relapses of encephalitis following acyclovir may occur. The value of continuing long-term suppression with valacyclovir after completing intravenous acyclovir is under study.

An ophthalmic formulation of acyclovir (not available in the United States) is at least as effective as topical vidarabine or *trifluridine* in herpetic keratoconjunctivitis.

Infection owing to resistant HSV is rare in immunocompetent persons; however, in immunocompromised hosts, acyclovir-resistant HSV isolates can cause extensive mucocutaneous disease and, rarely, meningoencephalitis, pneumonitis, or visceral disease. Resistant HSV can be recovered from 6% to 17% of immunocompromised patients receiving acyclovir treatment (Bacon *et al.*, 2003). Recurrences after cessation of acyclovir usually are due to sensitive virus but may be due to acyclovir-resistant virus in AIDS patients. In patients with progressive disease, intravenous *foscarnet* therapy is effective, but vidarabine is not (Chilukuri and Rosen, 2003).

Varicella-Zoster Virus Infections. If begun within 24 hours of rash onset, oral acyclovir has therapeutic effects in varicella of children and adults. In children weighing up to 40 kg, acyclovir (20 mg/kg, up to 800 mg per dose, four times daily for 5 days) reduces fever and new lesion formation by about one day. Routine use in uncomplicated pediatric varicella is not recommended but should be considered in those at risk of moderate-to-severe illness (persons over 12 years old, secondary household cases, those with chronic cutaneous or pulmonary disorders, or those receiving *corticosteroids* or long-term *salicylates*) (Committee on Infectious Diseases American Academy of Pediatrics, 2003). In adults treated within 24 hours, oral acyclovir (800 mg five times daily for 7 days) reduces the time to crusting of lesions by approximately 2 days, the maximum number of lesions by one-half, and the duration of fever (Wallace *et al.*, 1992). Intravenous acyclovir appears to be effective in varicella pneumonia or encephalitis of previously healthy adults. Oral acyclovir (10 mg/kg four times daily) given between 7 and 14 days after exposure may reduce the risk of varicella.

In older adults with localized herpes zoster, oral acyclovir (800 mg five times daily for 7 days) reduces pain and healing times if treatment can be initiated within 72 hours of rash onset. A reduction in ocular complications, particularly keratitis and anterior uveitis, occurs with treatment of zoster ophthalmicus. Prolonged acyclovir

and concurrent *prednisone* for 21 days speed zoster healing and improve quality-of-life measures compared with each therapy alone. Valacyclovir (1000 mg three times daily for 7 days) provides more prompt relief of zoster-associated pain than acyclovir in older adults (≥50 years) with zoster (Beutner *et al.*, 1995).

In immunocompromised patients with herpes zoster, intravenous acyclovir (500 mg/m^2 every 8 hours for 7 days) reduces viral shedding, healing time, and the risks of cutaneous dissemination and visceral complications, as well as the length of hospitalization, in disseminating zoster. In immunosuppressed children with varicella, intravenous acyclovir decreases healing time and the risk of visceral complications.

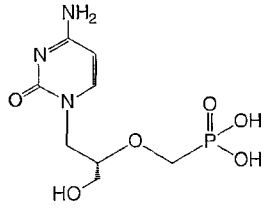
Acyclovir-resistant VZV isolates uncommonly have been recovered from HIV-infected children and adults who may manifest chronic hyperkeratotic or verrucous lesions and sometimes meningoradiculitis. Intravenous foscarnet also appears to be effective for acyclovir-resistant VZV infections.

Other Viruses. Acyclovir is ineffective therapeutically in established cytomegalovirus (CMV) infections but has been used for CMV prophylaxis in immunocompromised patients. High-dose intravenous acyclovir (500 mg/m^2 every 8 hours for one month) in CMV-seropositive bone marrow transplant recipients is associated with about 50% lower risk of CMV disease and, when combined with prolonged oral acyclovir (800 mg four times daily through 6 months), improves survival (Prentice *et al.*, 1994). Following engraftment, valacyclovir (2000 mg four times daily to day 100) appears as effective as intravenous ganciclovir prophylaxis in such patients (Winston *et al.*, 2003). High-dose oral acyclovir or valacyclovir (2000 mg four times daily) suppression for 3 months may reduce the risk of CMV disease and its sequelae in certain solid-organ transplant recipients (Lowance *et al.*, 1999), but oral *valganciclovir* is the preferred agent for mismatched graft recipients (Pereyra and Rubin, 2004). Compared with acyclovir, high-dose valacyclovir reduces CMV disease in advanced HIV infection but is associated with greater toxicity and possibly shorter survival (Feinberg *et al.*, 1998).

In infectious mononucleosis, acyclovir is associated with transient antiviral effects but no clinical benefits. EBV-related oral hairy leukoplakia may improve with acyclovir. Oral acyclovir in conjunction with systemic corticosteroids appears beneficial in treating Bell's palsy, but valacyclovir is ineffective in acute vestibular neuritis.

Cidofovir

Chemistry and Antiviral Activity. Cidofovir (1-[(*S*)-3-hydroxy-2-(phosphonomethoxy)-propyl]cytosine dihydrate) is a cytidine nucleotide analog with inhibitory activity against human herpes, papilloma, polyoma, pox, and adenoviruses (Hitchcock *et al.*, 1996).



CIDOFOVIR

In vitro inhibitory concentrations range from greater than 0.2 to 0.7 μg/ml for CMV, 0.4 to 33 μg/ml for HSV, and 0.02 to 17 μg/ml for adenoviruses. Because cidofovir is a phosphonate that is phosphorylated by cellular but not virus enzymes, it inhibits acyclovir-resistant thymidine kinase (TK)–deficient or TK-altered HSV or VZV strains, ganciclovir-resistant CMV strains with UL97 mutations but not those with DNA polymerase mutations, and some foscarnet-resistant CMV strains. Cidofovir synergistically inhibits CMV replication in combination with ganciclovir or foscarnet. Ether lipid esters of cidofovir are orally active in animal models of poxvirus and CMV infections (Kern *et al.*, 2004).

Mechanisms of Action and Resistance. Cidofovir inhibits viral DNA synthesis by slowing and eventually terminating chain elongation. Cidofovir is metabolized to its active diphosphate form by cellular enzymes; the levels of phosphorylated metabolites are similar in infected and uninfected cells. The diphosphate acts as both a competitive inhibitor with respect to dCTP and as an alternative substrate for viral DNA polymerase. The diphosphate has a prolonged intracellular half-life and competitively inhibits CMV and HSV DNA polymerases at concentrations one-eighth to one six-hundredth of those required to inhibit human DNA polymerases (Hitchcock *et al.*, 1996). A phosphocholine metabolite has a prolonged intracellular half-life (~87 hours) and may serve as an intracellular reservoir of drug. The prolonged intracellular half-life of cidofovir diphosphate allows infrequent dosing regimens, and single doses are effective in experimental HSV, varicella, and poxvirus infections.

Cidofovir resistance in CMV is due to mutations in viral DNA polymerase. Low-level resistance to cidofovir develops in up to about 30% of retinitis patients by 3 months of therapy. Highly ganciclovir-resistant CMV isolates that possess DNA polymerase and UL97 kinase mutations are resistant to cidofovir, and prior ganciclovir therapy may select for cidofovir resistance. Some foscarnet-resistant CMV isolates show cross-resistance to cidofovir, and triple-drug-resistant variants with DNA polymerase mutations occur.

Absorption, Distribution, and Elimination. Cidofovir is dianionic at physiological pH and has very low oral bioavailability (Cundy, 1999). The plasma levels after intravenous dosing decline in a biphasic pattern with a terminal half-life that averages about 2.6 hours. The volume of distribution approximates total-body water. Penetration into the CNS or eye has not been well characterized, but cerebrospinal fluid (CSF) levels are low. Extemporaneously compounded topical cidofovir gel may result in low plasma concentrations (<0.5 μg/ml) in patients with large mucocutaneous lesions.

Cidofovir is cleared by the kidney *via* glomerular filtration and tubular secretion. Over 90% of the dose is recovered unchanged in the urine without significant metabolism in human beings. The probenecid-sensitive organic anion transporter 1 mediates uptake of cidofovir into proximal renal tubular epithelial cells (Ho *et al.*, 2000). High-dose probenecid (2 g 3 hours before and 1 g 2 and 8 hours after each infusion) blocks tubular transport of cidofovir and reduces renal clearance and associated nephrotoxicity. At cidofovir doses of 5 mg/kg, peak plasma concentrations increase from 11.5 to 19.6 μg/ml with probenecid, and renal clearance is reduced to the level of glomerular filtration. Elimination relates linearly to creatinine clearance, and the half-life increases to 32.5 hours in patients on chronic ambulatory peritoneal dialysis (CAPD). Both CAPD and hemodialysis remove over 50% of the administered dose (Cundy, 1999).

Untoward Effects. Nephrotoxicity is the principal dose-limiting side effect of intravenous cidofovir. Proximal tubular dysfunction includes proteinuria, azotemia, glycosuria, metabolic acidosis, and uncommonly, Fanconi's syndrome. Concomitant oral probenecid (*see* above) and saline prehydration reduce the risk of renal toxicity. On maintenance doses of 5 mg/kg every 2 weeks, up to 50% of patients develop proteinuria, 10% to 15% show an elevated serum creatinine concentration, and 15% to 20% develop neutropenia. Anterior uveitis that is responsive to topical corticosteroids and cycloplegia occurs commonly and ocular hypotony occurs infrequently with intravenous cidofovir. Concurrent probenecid administration is associated with gastrointestinal upset, constitutional symptoms, and hypersensitivity reactions, including fever, rash, and uncommonly, anaphylactoid manifestations. Administration with food and pretreatment with *antiemetics, antihistamines,* and/or *acetaminophen* may improve tolerance.

Probenecid but not cidofovir alters zidovudine pharmacokinetics such that zidovudine doses should be reduced when probenecid is present, as should the doses of drugs similarly affected by probenecid [*e.g., β-lactam antibiotics, nonsteroidal antiinflammatory drugs* (NSAIDs), acyclovir, *lorazepam, furosemide,* methotrexate, *theophylline,* and *rifampin*]. Concurrent nephrotoxic agents are contraindicated, and an interval of at least 7 days before beginning cidofovir treatment is recommended after prior exposure to an *aminoglycoside,* intravenous *pentamidine, amphotericin B,* foscarnet, NSAID, or contrast dye. Cidofovir and oral ganciclovir are poorly tolerated in combination at full doses.

Topical application of cidofovir is associated with dose-related application-site reactions (*e.g.,* burning, pain, and pruritus) in up to one-third of patients and occasionally ulceration. Intravitreal cidofovir may cause vitreitis, hypotony, and visual loss and is contraindicated.

Preclinical studies indicate that cidofovir has mutagenic, gonadotoxic, embryotoxic, and teratogenic effects. Because cidofovir is carcinogenic in rats, it is considered a potential human carcinogen. It may cause infertility and is classified as pregnancy category C.

Therapeutic Uses. Intravenous cidofovir is approved for the treatment of CMV retinitis in HIV-infected patients. Intravenous cidofovir (5 mg/kg once a week for 2 weeks followed by dosing every 2 weeks) increases the time to progression of CMV retinitis in previously untreated patients and in those failing or intolerant of ganciclovir and foscarnet therapy. CMV viremia may persist during cidofovir administration. Maintenance doses of 5 mg/kg are more effective but less well tolerated than 3 mg/kg doses. Intravenous cidofovir has been used for treating acyclovir-resistant mucocutaneous HSV infection, adenovirus disease in transplant recipients (Ljungman *et al.*, 2003), and progressive multifocal leukoencephalopathy or extensive molluscum contagiosum in HIV patients. Reduced doses (0.25 to 1 mg/kg every 2 to 3 weeks) without probenecid may be beneficial in BK virus nephropathy in renal transplant patients (Vats *et al.*, 2003).

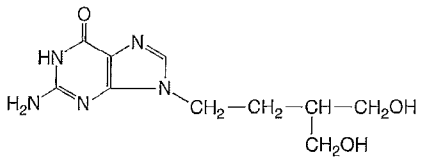
Extemporaneously compounded topical cidofovir gel eliminates virus shedding and lesions in some HIV-infected patients with acyclovir-resistant mucocutaneous HSV infections and has been used in treating anogenital warts and molluscum contagiosum in immunocompromised patients and cervical intraepithelial neoplasia in women. Intralesional cidofovir induces remissions in adults and children with respiratory papillomatosis.

Docosanol

Docosanol is a long-chain saturated alcohol that has been approved by the FDA as a 10% over-the-counter cream for the treatment of recurrent orolabial herpes. Docosanol inhibits the *in vitro* replication of many lipid-enveloped viruses, including HSV, at millimolar concentrations. It does not inactivate HSV directly but appears to block fusion between the cellular and viral envelope membranes and inhibit viral entry into the cell. Topical treatment beginning within 12 hours of prodromal symptoms or lesion onset reduces healing time by about one day and appears to be well tolerated (Anonymous, 2000). Treatment initiation at papular or later stages provides no benefit.

Famciclovir and Penciclovir

Chemistry and Antiviral Activity. Famciclovir is the diacetyl ester prodrug of 6-deoxy penciclovir and lacks intrinsic antiviral activity. *Penciclovir* (9-[4-hydroxy-3-hydroxymethylbut-1-yl] guanine) is an acyclic guanine nucleoside analog. The side chain differs structurally in that the oxygen has been replaced by a carbon, and an additional hydroxymethyl group is present. The structure of penciclovir is



PENCICLOVIR

Penciclovir is similar to acyclovir in its spectrum of activity and potency against HSV and VZV (Safrin *et al.*, 1997). The inhibitory concentrations of penciclovir

depend on cell type but are usually within twofold of those of acyclovir for HSV and VZV. It also is inhibitory for HBV.

Mechanisms of Action and Resistance. Penciclovir is an inhibitor of viral DNA synthesis. In HSV- or VZV-infected cells, penciclovir is phosphorylated initially by viral thymidine kinase. Penciclovir triphosphate serves as a competitive inhibitor of viral DNA polymerase (Safrin *et al.*, 1997) (Figure 49–2). Although penciclovir triphosphate is approximately one one-hundredth times as potent as acyclovir triphosphate in inhibiting viral DNA polymerase, it is present in much higher concentrations and for more prolonged periods in infected cells than acyclovir triphosphate. The prolonged intracellular $t_{\frac{1}{2}}$ of penciclovir triphosphate, 7 to 20 hours, is associated with prolonged antiviral effects. Because penciclovir has a 3′-hydroxyl group, it is not an obligate chain terminator but does inhibit DNA elongation.

Resistant variants owing to thymidine kinase or DNA polymerase mutations can be selected by passage *in vitro,* but the occurrence of resistance during clinical use is currently low (Bacon *et al.*, 2003). Thymidine kinase–deficient, acyclovir-resistant herpes viruses are cross-resistant to penciclovir.

Absorption, Distribution, and Elimination. Oral penciclovir has low (5%) bioavailability. In contrast, famciclovir is well absorbed orally and converted rapidly to penciclovir by deacetylation of the side chain and oxidation of the purine ring during and following absorption from the intestine (Gill and Wood, 1996). The bioavailability of penciclovir is 65% to 77% following oral administration of famciclovir. Food slows absorption but does not reduce overall bioavailability. After single 250- or 500-mg doses of famciclovir, the peak plasma concentration of penciclovir averages 1.6 and 3.3 μg/ml, respectively. A small quantity of the 6-deoxy precursor but no famciclovir is detectable in plasma. After intravenous infusion of penciclovir at 10 mg/kg, peak plasma levels average 12 μg/ml. The volume of distribution is about twice the volume of total-body water. The plasma $t_{\frac{1}{2}}$ of elimination of penciclovir averages about 2 hours, and over 90% is excreted unchanged in the urine, probably by both filtration and active tubular secretion. Following oral famciclovir administration, nonrenal clearance accounts for about 10% of each dose, primarily through fecal excretion, but penciclovir (60% of dose) and its 6-deoxy precursor (<10% of dose) are eliminated primarily in the urine. The plasma half-life averages 9.9 hours in renal insufficiency (Cl_{cr} < 30 ml/min); hemodialysis efficiently removes penciclovir. Lower peak plasma concentrations of penciclovir but no reduction in overall bioavailability occur in compensated chronic hepatic insufficiency (Boike *et al.*, 1994).

Untoward Effects. Oral famciclovir is well tolerated but may be associated with headache, diarrhea, and nausea. Urticaria, rash, and hallucinations or confusional states (predominantly in the elderly) have been reported. Topical penciclovir, which is formulated in 40% propylene glycol and a cetomacrogol base, is associated infrequently with application-site reactions (~1%). The short-term tolerance of famciclovir is comparable with that of acyclovir.

Penciclovir is mutagenic at high concentrations *in vitro.* Although studies in laboratory animals indicate that chronic famciclovir administration is tumorigenic and decreases spermatogenesis and fertility in rodents and dogs, long-term administration (1 year) does not affect spermatogenesis in men. No teratogenic effects have been observed in animals, but safety during pregnancy has not been established.

No clinically important drug interactions have been identified to date with famciclovir or penciclovir (Gill and Wood, 1996).

Therapeutic Uses. Oral famciclovir, topical penciclovir, and intravenous penciclovir are approved for managing HSV and VZV infections in various countries (Sacks and Wilson, 1999). Oral famciclovir (250 mg three times a day for 7 to 10 days) is as effective as acyclovir in treating first-episode genital herpes (Kimberlin and Rouse, 2004). In patients with recurrent genital HSV, patient-initiated famciclovir treatment (125 or 250 mg twice a day for 5 days) reduces healing time and symptoms by about one day. Famciclovir (250 mg twice a day for up to 1 year) is effective for suppression of recurrent genital HSV, but single daily doses are less effective. Higher doses (500 mg twice a day) reduce HSV recurrences in HIV-infected persons. Intravenous penciclovir (5 mg/kg every 8 or 12 hours for 7 days) is comparable with intravenous acyclovir for treating mucocutaneous HSV infections in immunocompromised hosts (Lazarus *et al.*, 1999). In immunocompetent persons with recurrent orolabial HSV, topical 1% penciclovir cream (applied every 2 hours while awake for 4 days) shortens healing time and symptoms by about one day (Raborn *et al.*, 2002).

In immunocompetent adults with herpes zoster of 3 days' duration or less, famciclovir (500 mg three times a day for 10 days) is at least as effective as acyclovir (800 mg five times daily) in reducing healing time and zoster-associated pain, particularly in those 50 years of age and older. Famciclovir is comparable with valacyclovir in treating zoster and reducing associated pain in older adults (Tyring *et al.*, 2000). Famciclovir (500 mg three times a day for 7 to 10 days) also is comparable with high-dose oral acyclovir in treating zoster in immunocompromised patients and in those with ophthalmic zoster (Tyring *et al.*, 2001).

Famciclovir is associated with dose-related reductions in HBV DNA and transaminase levels in patients with chronic HBV hepatitis but is less effective than *lamivudine* (Lai *et al.*, 2002). Famciclovir is also ineffective in treating lamivudine-resistant HBV infections owing to emergence of multiply resistant variants.

Fomivirsen

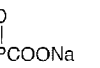
Fomivirsen, a 21-base phosphorothioate oligionucleotide, is the first FDA-approved antisense therapy for viral infections. It is complementary to the messenger RNA sequence for the major immediate-early transcriptional region of CMV and inhibits CMV replication through sequence-specific and nonspecific mechanisms, including inhibition of virus binding to cells. Fomivirsen is active against CMV strains resistant to ganciclovir, foscarnet, and cidofovir. CMV variants with tenfold

reduced susceptibility to fomivirsen have been selected by *in vitro* passage.

Fomivirsen is given by intravitreal injection in the treatment of CMV retinitis for patients intolerant of or unresponsive to other therapies. Following injection, it is cleared slowly from the vitreous ($t_{\frac{1}{2}}$ of approximately 55 hours) through distribution to the retina and probable exonuclease digestion (Geary *et al.*, 2002). Local metabolism by exonucleases accounts for elimination. In HIV-infected patients with refractory, sight-threatening CMV retinitis, fomivirsen injections (330 μg weekly for 3 weeks and then every 2 weeks or on days 1 and 15 followed by monthly) significantly delay time to retinitis progression (Vitravene Study Group, 2002). Ocular side effects include iritis in up to one-quarter of patients, which can be managed with topical corticosteroids; vitritis; cataracts; and increases in intraocular pressure in 15% to 20% of patients. Recent cidofovir use may increase the risk of inflammatory reactions.

Foscarnet

Chemistry and Antiviral Activity. Foscarnet (trisodium phosphonoformate) is an inorganic pyrophosphate analog that is inhibitory for all herpesviruses and HIV (Wagstaff and Bryson, 1994).



FOSCARNET SODIUM

In vitro inhibitory concentrations are generally 100 to 300 μM for CMV and 80 to 200 μM for other herpesviruses, including most ganciclovir-resistant CMV and acyclovir-resistant HSV and VZV strains. Combinations of foscarnet and ganciclovir synergistically inhibit CMV replication *in vitro*. Concentrations of 500 to 1000 μM reversibly inhibit the proliferation and DNA synthesis of uninfected cells.

Mechanisms of Action and Resistance. Foscarnet inhibits viral nucleic acid synthesis by interacting directly with herpesvirus DNA polymerase or HIV reverse transcriptase (Chrisp and Clissold, 1991) (Figure 49–1B). It is taken up slowly by cells and does not undergo significant intracellular metabolism. Foscarnet reversibly blocks the pyrophosphate binding site of the viral polymerase in a noncompetitive manner and inhibits cleavage of pyrophosphate from deoxynucleotide triphosphates. Foscarnet has approximately one hundredfold greater inhibitory effects against herpesvirus DNA polymerases than against cellular DNA polymerase α.

Herpesviruses resistant to foscarnet have point mutations in the viral DNA polymerase and are associated with three- to sevenfold reductions in foscarnet activity *in vitro*.

Absorption, Distribution, and Elimination. Oral bioavailability of foscarnet is low. Following an intravenous infusion of 60 mg/kg every 8 hours, peak and trough plasma concentrations are approximately 450 to 575 and 80 to 150 μM, respectively. Vitreous levels approximate those in plasma, and CSF levels average 66% of those in plasma at steady state.

Over 80% of foscarnet is excreted unchanged in the urine by glomerular filtration and probably tubular secretion. Plasma clearance decreases proportionately with creatinine clearance, and dose adjustments are indicated for small decreases in renal function. Plasma elimination is complex, with initial bimodal half-lives totaling 4 to 8 hours and a prolonged terminal $t_{\frac{1}{2}}$ for elimination averaging 3 to 4 days. Sequestration in bone with gradual release accounts for the fate of an estimated 10% to 20% of a given dose. Foscarnet is cleared efficiently by hemodialysis (~50% of a dose).

Untoward Effects. Foscarnet's major dose-limiting toxicities are nephrotoxicity and symptomatic hypocalcemia. Increases in serum creatinine occur in up to one-half of patients but are reversible after cessation in most patients. High doses, rapid infusion, dehydration, prior renal insufficiency, and concurrent nephrotoxic drugs are risk factors. Acute tubular necrosis, crystalline glomerulopathy, nephrogenic diabetes insipidus, and interstitial nephritis have been described. Saline loading may reduce the risk of nephrotoxicity.

Foscarnet is highly ionized at physiological pH, and metabolic abnormalities are very common. These include increases or decreases in Ca^{2+} and phosphate, hypomagnesemia, and hypokalemia. Decreased serum ionized Ca^{2+} may cause paresthesia, arrhythmias, tetany, seizures, and other CNS disturbances. Concomitant intravenous *pentamidine* administration increases the risk of symptomatic hypocalcemia. Parenteral *magnesium sulfate* does not alter foscarnet-induced hypocalcemia or symptoms (Huycke *et al.*, 2000).

CNS side effects include headache in approximately 25% of patients, tremor, irritability, seizures, and hallucinosis. Other reported side effects are generalized rash, fever, nausea or emesis, anemia, leukopenia, abnormal liver function tests, electrocardiographic changes, infusion-related thrombophlebitis, and painful genital ulcerations. Topical foscarnet may cause local irritation and ulceration, and oral foscarnet may cause gastrointestinal disturbance. Preclinical studies indicate that high foscarnet concentrations are mutagenic and may cause tooth and skeletal abnormalities in developing laboratory animals. Safety in pregnancy or childhood is uncertain.

Therapeutic Uses. Intravenous foscarnet is effective for treatment of CMV retinitis, including ganciclovir-resistant infections, other types of CMV infection, and acyclovir-resistant HSV and VZV infections (Wagstaff and Bryson, 1994). Foscarnet is poorly soluble in aqueous solutions and requires large volumes for administration.

In CMV retinitis in AIDS patients, foscarnet (60 mg/kg every 8 hours or 90 mg/kg every 12 hours for 14 to 21 days followed by chronic maintenance at 90 to 120 mg/kg every day in one dose) is

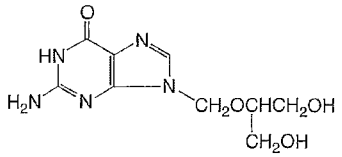
associated with clinical stabilization in about 90% of patients (Wagstaff and Bryson, 1994). A comparative trial of foscarnet with ganciclovir found comparable control of CMV retinitis in AIDS patients but improved overall survival in the foscarnet-treated group (Anonymous, 1992). This improved survival with foscarnet may be related to the drug's intrinsic anti-HIV activity, but patients stop taking foscarnet over three times as often as ganciclovir because of side effects. A combination of foscarnet and ganciclovir is more effective than either drug alone in refractory retinitis; combinations may be useful in treating ganciclovir-resistant CMV infections in solid-organ transplant patients. Foscarnet benefits other CMV syndromes in AIDS or transplant patients but is ineffective as monotherapy in treating CMV pneumonia in bone marrow transplant patients. When used for preemptive therapy of CMV viremia in bone marrow transplant recipients, foscarnet (60 mg/kg every 12 hours for 2 weeks followed by 90 mg/kg daily for 2 weeks) is as effective as intravenous ganciclovir and causes less neutropenia (Reusser *et al.*, 2002). When used for CMV infections, foscarnet may reduce the risk of Kaposi's sarcoma in HIV-infected patients. Intravitreal injections of foscarnet also have been used.

In acyclovir-resistant mucocutaneous HSV infections, lower doses of foscarnet (40 mg/kg every 8 hours for 7 days or longer) are associated with cessation of viral shedding and with complete healing of lesions in about three-quarters of patients. Foscarnet also appears to be effective in acyclovir-resistant VZV infections. Topical foscarnet cream is ineffective in treating recurrent genital HSV in immunocompetent persons but appears to be useful in chronic acyclovir-resistant infections in immunocompromised patients.

Resistant clinical isolates of herpesviruses have emerged during therapeutic use and may be associated with poor clinical response to foscarnet treatment.

Ganciclovir and Valganciclovir

Chemistry and Antiviral Activity. Ganciclovir (9-[1,3-dihydroxy-2-propoxymethyl] guanine) is an acyclic guanine nucleoside analog that is similar in structure to acyclovir except in having an additional hydroxymethyl group on the acyclic side chain. Valganciclovir is the L-valyl ester prodrug of ganciclovir. The structure of ganciclovir is



GANCICLOVIR

This agent has inhibitory activity against all herpesviruses but is especially active against CMV (Noble and Faulds, 1998). Inhibitory concentrations are similar to those of acyclovir for HSV and VZV but 10 to 100 times lower for human CMV strains (0.2 to 2.8 μg/ml).

Inhibitory concentrations for human bone marrow progenitor cells are similar to those inhibitory for CMV replication, a finding predictive of ganciclovir's myelotoxicity during clinical use. Inhibition of human lymphocyte blastogenic responses also occurs at clinically achievable concentrations of 1 to 10 μg/ml.

Mechanisms of Action and Resistance. Ganciclovir inhibits viral DNA synthesis. It is monophosphorylated intracellularly by viral thymidine kinase during HSV infection and by a viral phosphotransferase encoded by the UL97 gene during CMV infection. Ganciclovir diphosphate and ganciclovir triphosphate are formed by cellular enzymes. At least tenfold higher concentrations of ganciclovir triphosphate are present in CMV-infected than in uninfected cells. The triphosphate is a competitive inhibitor of deoxyguanosine triphosphate incorporation into DNA and preferentially inhibits viral rather than host cellular DNA polymerases. Ganciclovir is incorporated into both viral and cellular DNA. Incorporation into viral DNA causes eventual cessation of DNA chain elongation (Figures 49–1B and 49–2).

Intracellular ganciclovir triphosphate concentrations are tenfold higher than those of acyclovir triphosphate and decline much more slowly with an intracellular $t_{\frac{1}{2}}$ of elimination exceeding 24 hours. These differences may account in part for ganciclovir's greater anti-CMV activity and provide the rationale for single daily doses in suppressing human CMV infections.

CMV can become resistant to ganciclovir by one of two mechanisms: reduced intracellular ganciclovir phosphorylation owing to mutations in the viral phosphotransferase encoded by the UL97 gene and mutations in viral DNA polymerase (Gilbert *et al.*, 2002). Resistant CMV clinical isolates have 4 to more than 20 times increases in inhibitory concentrations. Resistance has been associated primarily with impaired phosphorylation but sometimes only with DNA polymerase mutations. Highly resistant variants with dual UL97 and polymerase mutations are cross-resistant to cidofovir and variably to foscarnet. Ganciclovir also is much less active against acyclovir-resistant thymidine kinase–deficient HSV strains.

Absorption, Distribution, and Elimination. The oral bioavailability of ganciclovir averages 6% to 9% following ingestion with food. Peak and trough plasma levels are about 0.5 to 1.2 and 0.2 to 0.5 μg/ml, respectively, after 1000-mg doses every 8 hours. Oral valganciclovir is well absorbed and hydrolyzed rapidly to ganciclovir; the bioavailability of ganciclovir averages 61% following valganciclovir (Curran and Noble, 2001). Food increases the bio-

availability of valganciclovir by about 25%, and peak ganciclovir concentrations average 6.1 μg/ml after 875-mg doses. High oral valganciclovir doses in the fed state provide ganciclovir exposures comparable with intravenous dosing (Brown *et al.*, 1999). Following intravenous administration of 5 mg/kg doses of ganciclovir, peak and trough plasma concentrations average 8 to 11 and 0.6 to 1.2 μg/ml, respectively. Following intravenous dosing, vitreous fluid levels are similar to or higher than those in plasma and average about 1 μg/ml. Vitreous levels decline with a half-life of 23 to 26 hours. Intraocular sustained-release ganciclovir implants provide vitreous levels of about 4.1 μg/ml.

The plasma half-life is about 2 to 4 hours in patients with normal renal function. Over 90% of ganciclovir is eliminated unchanged by renal excretion through glomerular filtration and tubular secretion. Consequently, the plasma $t_{\frac{1}{2}}$ increases almost linearly as creatinine clearance declines and may reach 28 to 40 hours in those with severe renal insufficiency.

Untoward Effects. Myelosuppression is the principal dose-limiting toxicity of ganciclovir. Neutropenia occurs in about 15% to 40% of patients and thrombocytopenia in 5% to 20% (Faulds and Heel, 1990). Neutropenia is observed most commonly during the second week of treatment and usually is reversible within 1 week of drug cessation. Persistent fatal neutropenia has occurred. Oral valganciclovir is associated with headache and gastrointestinal disturbance (*i.e.,* nausea, pain, and diarrhea) in addition to the toxicities associated with intravenous ganciclovir, including neutropenia. Recombinant *granulocyte colony-stimulating factor* (G-CSF, *filgrastim, lenograstim*) may be useful in treating ganciclovir-induced neutropenia (*see* Chapter 53).

CNS side effects occur in 5% to 15% of patients and range in severity from headache to behavioral changes to convulsions and coma. About one-third of patients have had to interrupt or prematurely stop intravenous ganciclovir therapy because of bone marrow or CNS toxicity. Infusion-related phlebitis, azotemia, anemia, rash, fever, liver function test abnormalities, nausea or vomiting, and eosinophilia also have been described.

Teratogenicity, embryotoxicity, irreversible reproductive toxicity, and myelotoxicity have been observed in animals at ganciclovir dosages comparable with those used in human beings. Ganciclovir is classified in pregnancy category C.

Zidovudine and probably other cytotoxic agents increase the risk of myelosuppression, as do nephrotoxic agents that impair ganciclovir excretion. Probenecid and possibly acyclovir reduce renal clearance of ganciclovir. *Zalcitabine* increases oral ganciclovir exposure by an average of 22%. Oral ganciclovir increases the absorption and peak plasma concentrations of *didanosine* by approximately twofold and that of zidovudine by about 20%.

Therapeutic Uses. Ganciclovir is effective for treatment and chronic suppression of CMV retinitis in immunocompromised patients and for prevention of CMV disease in transplant patients. In CMV retinitis, initial induction treatment (5 mg/kg intravenously every 12 hours for 10 to 21 days) is associated with improvement or stabilization in about 85% of patients (Faulds and Heel, 1990). Reduced viral excretion is usually evident by 1 week, and funduscopic improvement is seen by 2 weeks. Because of the high risk of relapse, AIDS patients with retinitis require suppressive therapy with high doses of ganciclovir (30 to 35 mg/kg per week). Oral ganciclovir (1000 mg three times daily) is effective for suppression of retinitis after initial intravenous treatment. Oral valganciclovir (900 mg twice daily for 21 days initial treatment) is comparable with intravenous dosing for initial control and sustained suppression (900 mg daily) of CMV retinitis (Martin *et al.*, 2002).

Intravitreal ganciclovir injections have been used in some patients, and an intraocular sustained-release ganciclovir implant (VITRASERT) is more effective than systemic dosing in suppressing retinitis progression.

Ganciclovir therapy (5 mg/kg every 12 hours for 14 to 21 days) may benefit other CMV syndromes in AIDS patients or solid-organ transplant recipients (Infectious Disease Community of Practice *et al.*, 2004). Response rates of 67% or higher have been found in combination with a decrease in immunosuppressive therapy. The duration of therapy depends on demonstrating clearance of viremia; early switch from intravenous ganciclovir to oral valganciclovir is feasible. Recurrent CMV disease occurs commonly after initial treatment. In bone marrow transplant recipients with CMV pneumonia, ganciclovir alone appears ineffective. However, ganciclovir combined with intravenous immunoglobulin or CMV immunoglobulin reduces the mortality of CMV pneumonia by about one-half. Ganciclovir treatment may benefit infants with congential CMV disease (Michaels *et al.*, 2003), and further studies are in progress.

Ganciclovir has been used for both prophylaxis and preemptive therapy of CMV infections in transplant recipients (Pillay, 2000; Pereyra and Rubin, 2004). In bone marrow transplant recipients, preemptive ganciclovir treatment (5 mg/kg every 12 hours for 7 to 14 days followed by 5 mg/kg every day to days 100 to 120 after transplant) starting when CMV is isolated from bronchoalveolar lavage or from other sites is highly effective in preventing CMV pneumonia and appears to reduce mortality in these patients. Initiation of ganciclovir at the time of engraftment also reduces CMV disease rates but does not improve survival in part because of infections owing to ganciclovir-related neutropenia.

Intravenous ganciclovir, oral ganciclovir, and oral valganciclovir reduce the risk of CMV disease in solid-organ transplant recipients (Pereyra and Rubin, 2004; Infectious Disease Community of Practice *et al.*, 2004). Oral ganciclovir (1000 mg three times daily for 3 months) reduces CMV disease risk in liver transplant recipients, including high-risk patients with primary infection or those receiving antilymphocyte antibodies. Oral valganciclovir prophylaxis generally is more effective than high-dose oral acyclovir. Oral valganciclovir (900 mg once daily) provides somewhat greater antiviral effects and similar reductions in CMV disease as oral ganciclovir in mismatched solid-organ transplant recipients (Paya *et al.*, 2004).

In advanced HIV disease, oral ganciclovir (1000 mg three times daily) may reduce the risk of CMV disease and possibly mortality in those not receiving didanosine (Brosgart *et al.*, 1998). The addition of oral high-dose ganciclovir (1500 mg three times daily) to the intraocular ganciclovir implant further delays the time to retinitis progression and reduces the risk of new CMV disease and possibly the risk of Kaposi's sarcoma.

Ganciclovir resistance emerges in a minority of transplant patients, especially mismatched solid-organ recipients (Limaye *et al.*, 2000), and is associated with poorer prognosis. The use of antithymocyte globulin and prolonged ganciclovir exposure are risk factors. Recovery of ganciclovir-resistant CMV isolates has been associated with progressive CMV disease in AIDS and other immunocompromised patients. Over one-quarter of retinitis patients have resistant isolates by 9 months of therapy, and resis-

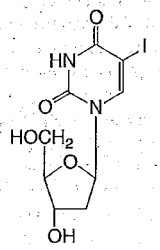
tant CMV has been recovered from CSF, vitreous fluid, and visceral sites.

A ganciclovir ophthalmic gel formulation appears to be effective in treating HSV keratitis (Colin *et al.*, 1997). Oral ganciclovir reduces HBV DNA levels and aminotransferase levels in chronic hepatitis B (Hadziyannis *et al.*, 1999).

Systemic ganciclovir has been studied in conjunction with suicide gene therapy expressing HSV thymidine kinase for treatment of brain tumors and a variety of other malignancies.

Idoxuridine

Idoxuridine (5-iodo-2′-deoxyuridine) is an iodinated thymidine analog that inhibits the *in vitro* replication of various DNA viruses, including herpesviruses and poxviruses (Prusoff, 1988). Its structure is



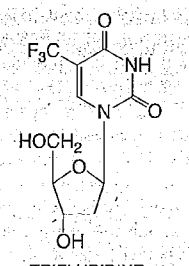
IDOXURIDINE

Inhibitory concentrations of idoxuridine for HSV-1 are 2 to 10 μg/ml, at least tenfold higher than those of acyclovir. Idoxuridine lacks selectivity, in that low concentrations inhibit the growth of uninfected cells. The triphosphate inhibits viral DNA synthesis and is incorporated into both viral and cellular DNA. Such altered DNA is more susceptible to breakage and also leads to faulty transcription. Resistance to idoxuridine develops readily *in vitro* and occurs in viral isolates recovered from idoxuridine-treated patients with HSV keratitis.

In the United States, idoxuridine is approved only for topical treatment of HSV keratitis, although idoxuridine formulated in *dimethylsulfoxide* is available outside the United States for topical treatment of herpes labialis, genitalis, and zoster. In ocular HSV infections, topical idoxuridine is more effective in epithelial infections, especially initial episodes, than in stromal infections. Adverse reactions include pain, pruritus, inflammation, and edema involving the eye or lids; rarely do allergic reactions occur.

Trifluridine

Trifluridine (5-trifluoromethyl-2′-deoxyuridine) is a fluorinated pyrimidine nucleoside that has *in vitro* inhibitory activity against HSV types 1 and 2, CMV, vaccinia, and to a lesser extent, certain adenoviruses. Its structure is



TRIFLURIDINE

Concentrations of trifluridine of 0.2 to 10 μg/ml inhibit replication of herpesviruses, including acyclovir-resistant strains. Trifluridine also inhibits cellular DNA synthesis at relatively low concentrations.

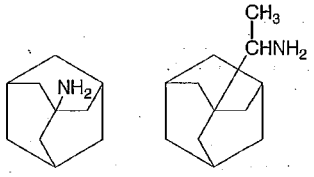
Trifluridine Inhibition of Viral DNA Synthesis. Trifluridine monophosphate irreversibly inhibits thymidylate synthase, and trifluridine triphosphate is a competitive inhibitor of thymidine triphosphate incorporation into DNA; trifluridine is incorporated into viral and cellular DNA. Trifluridine-resistant HSV with altered thymidine kinase substrate specificity can be selected *in vitro*, and resistance in clinical isolates has been described.

Trifluridine currently is approved in the United States for treatment of primary keratoconjunctivitis and recurrent epithelial keratitis owing to HSV types 1 and 2. Topical trifluridine is more active than idoxuridine and comparable with vidarabine in HSV ocular infections. Adverse reactions include discomfort on instillation and palpebral edema. Hypersensitivity reactions, irritation, and superficial punctate or epithelial keratopathy are uncommon. Topical trifluridine also appears to be effective in some patients with acyclovir-resistant HSV cutaneous infections.

ANTI-INFLUENZA AGENTS

Amantadine and Rimantadine

Chemistry and Antiviral Activity. *Amantadine* (1-adamantanamine hydrochloride) and its α-methyl derivative *rimantadine* (α-methyl-1-adamantane methylamine hydrochloride) are uniquely configured tricyclic amines.



AMANTADINE RIMANTADINE