Lippincott's Illustrated Reviews:

Pharmacology

You will have learned within, those are

Chapter no. **36** to **40**

SL	Chapter No.	Title / Chapter Name
1	Chapter 36	Antiprotozoal Drugs
2	Chapter 37	Anthelmintic Drugs
3	Chapter 38	Antiviral Drugs
4	Chapter 39	Anticancer Drugs
5	Chapter 40	Immunosuppressants

LID—NUB05121027

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Copyright Â©2009 Lippincott Williams & Wilkins

Chapter 36

Antiprotozoal Drugs

I. Overview

Protozoal infections are common among people in underdeveloped tropical and subtropical countries, where sanitary conditions, hygienic practices, and control of the vectors of transmission are inadequate. However, with increased world travel, protozoal diseases, such as malaria, amebiasis, leishmaniasis, trypanosomiasis, trichomoniasis, and giardiasis, are no longer confined to specific geographic locales. Because they are eukaryotes, the unicellular protozoal cells have metabolic processes closer to those of the human host than to prokaryotic bacterial pathogens. Protozoal diseases are thus less easily treated than bacterial infections, and many of the antiprotozoal drugs cause serious toxic effects in the host, particularly on cells showing high metabolic activity, such as neuronal, renal tubular, intestinal, and bone marrow stem cells. Most antiprotozoal agents have not proved to be safe for pregnant patients. Drugs used to treat protozoal infections are summarized in Figure 36.1.

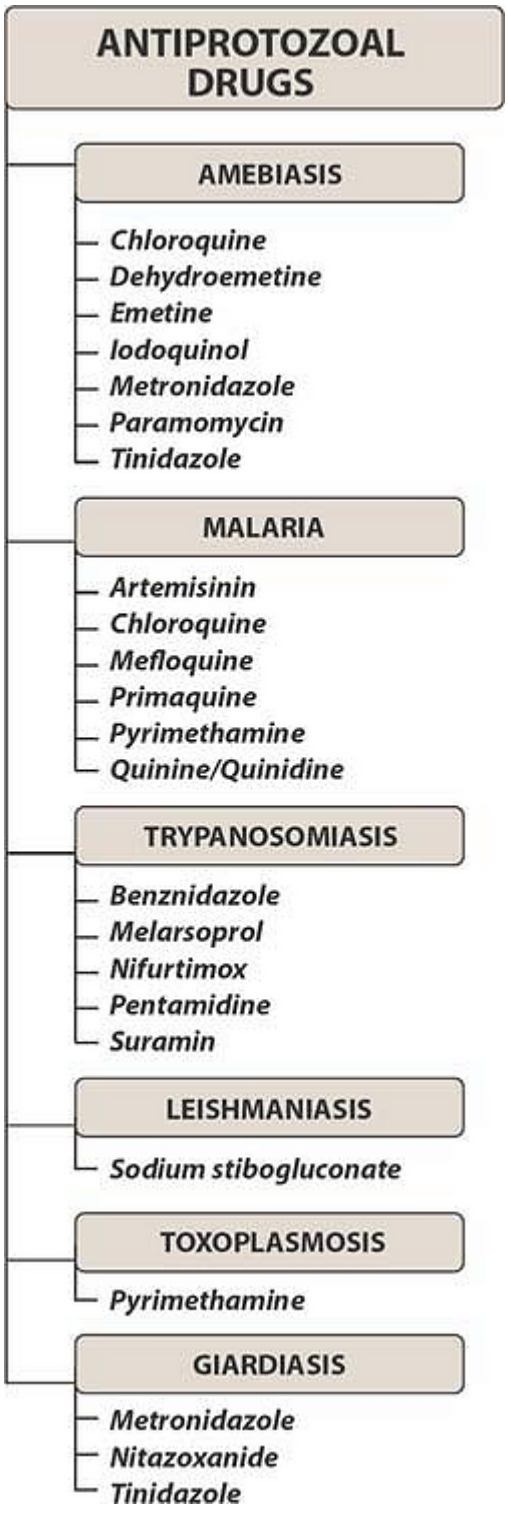


Figure 36.1 Summary of antiprotozoal agents.

II. Chemotherapy For Amebiasis

Amebiasis (also called amebic dysentery) is an infection of the intestinal tract caused by Entamoeba histolytica. The

disease can be acute or chronic, with patients showing varying degrees of illness, from no symptoms to mild diarrhea to fulminating dysentery. The diagnosis is established by isolating E. histolytica from fresh feces. Therapy is aimed not only at the acutely ill patient but also at those who are asymptomatic carriers, because dormant E. histolytica may cause future infections in the carrier and be a potential source of infection for others.

A. Life cycle of Entamoeba histolytica

Entamoeba histolytica exists in two forms: cysts that can survive outside the body, and labile but invasive trophozoites that do not persist outside the body. Cysts, ingested through feces-contaminated food or water, pass into the lumen of the intestine, where the trophozoites are liberated. The trophozoites multiply, and they either invade and ulcerate the mucosa of the large intestine or simply feed on intestinal bacteria. [Note: One strategy for treating luminal amebiasis is to add antibiotics, such as *tetracycline*, to the treatment regimen, resulting in a reduction in intestinal floraâ€"the ameba's major food source.] The trophozoites within the intestine are slowly carried toward the rectum, where they return to the cyst form and are excreted in feces.

Large numbers of trophozoites within the colon wall can also lead to systemic invasion. A summary of the life cycle of E. histolytica is presented in Figure 36.2.

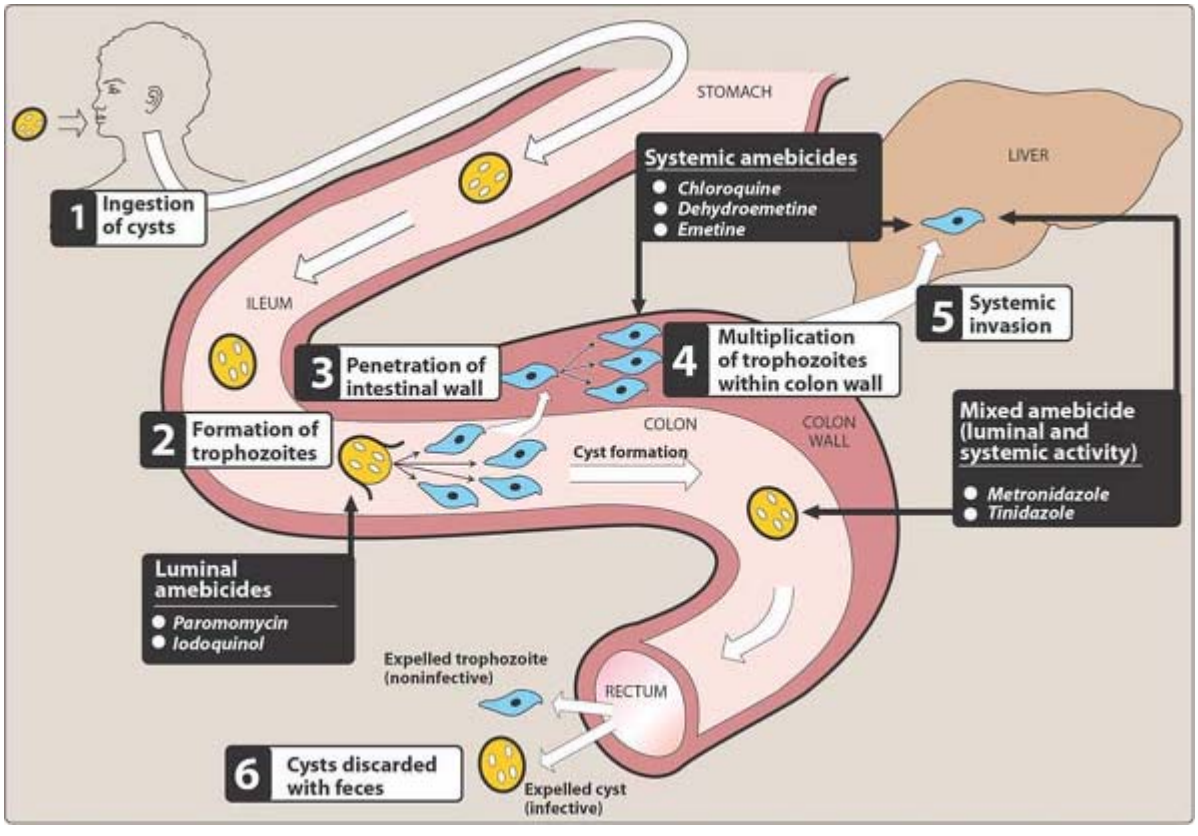


Figure 36.2 Life cycle of Entamoeba histolytica, showing the sites of action of amebicidal drugs.

B. Classification of amebicidal drugs

Therapeutic agents are classified as luminal, systemic, or mixed (luminal and systemic) amebicides according to the site where the drug is effective (see Figure 36.2). For example, luminal amebicides act on the parasite in the lumen of the bowel, whereas systemic amebicides are effective against amebas in the intestinal wall and liver. Mixed

amebicides are effective against both the luminal and systemic forms of the disease, although luminal concentrations are too low for single-drug treatment.

C. Mixed amebicides (metronidazole and tinidazole)

1. **Metronidazole:** *Metronidazole* [me-troe-NYE-da-zole], a nitroimidazole, is the mixed amebicide of choice for treating amebic infections; it kills the E. histolytica trophozoites. [Note: *Metronidazole* also finds extensive use in the treatment of infections caused by Giardia lamblia, Trichomonas vaginalis, anaerobic cocci, and anaerobic gram-negative bacilli (for example, Bacteroides species). *Metronidazole* is the drug of choice for the treatment of pseudomembranous colitis

caused by the anaerobic, gram-positive bacillus Clostridium difficile and is also effective in the treatment of brain abscesses caused by these organisms.]

   a. **Mechanism of action:** Some anaerobic protozoal parasites (including amebas) possess ferrodoxin-like, low-redox-potential, electron-transport proteins that participate in metabolic electron removal reactions. The nitro group of *metronidazole* is able to serve as an electron acceptor, forming reduced cytotoxic compounds that bind to proteins and DNA, resulting in cell death.

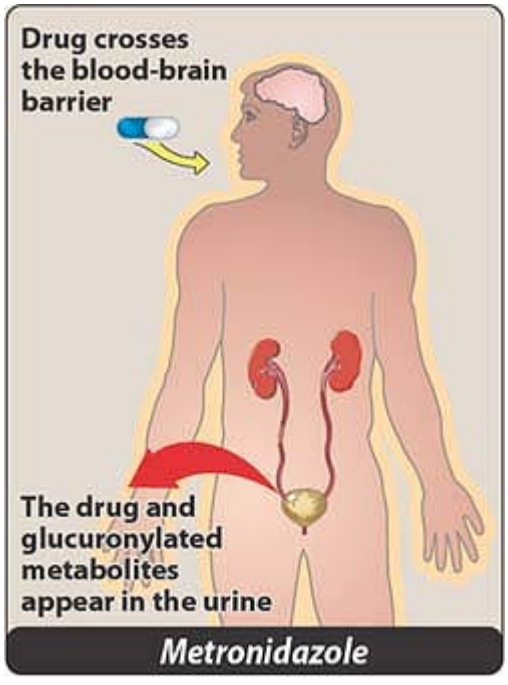


Figure 36.3 Administration and fate of *metronidazole*.

   b. **Pharmacokinetics:** *Metronidazole* is completely and rapidly absorbed after oral administration (Figure 36.3). [Note: For the treatment of amebiasis, it is usually administered with a luminal amebicide, such as *iodoquinol* or *paromomycin*. This combination provides cure rates of greater than 90 percent.] *Metronidazole* distributes well throughout body tissues and fluids. Therapeutic levels can be found in vaginal and seminal fluids, saliva, breast milk, and cerebrospinal fluid (CSF). Metabolism of the drug depends on hepatic oxidation of the *metronidazole* side chain by mixed-function oxidase, followed by glucuronylation. Therefore, concomitant treatment with inducers of this enzymatic system, such as *phenobarbital*, enhances the rate of metabolism. Conversely, those drugs that inhibit this system, such as

cimetidine, prolong the plasma half-life of *metronidazole.* The drug accumulates in patients with severe hepatic disease. The parent drug and its metabolites are excreted in the urine.

c. **Adverse effects:** The most common adverse effects are those associated with the gastrointestinal tract, including nausea, vomiting, epigastric distress, and abdominal cramps (Figure 36.4). An unpleasant, metallic taste is often experienced. Other effects include oral moniliasis (yeast infection of the mouth) and, rarely, neurotoxicologic problems, such as dizziness, vertigo, and numbness or paresthesias in the peripheral nervous system. [Note: The latter are reasons for discontinuing the drug.] If taken with alcohol, a *disulfiram*-like effect occurs (114).

d. **Resistance:** Resistance to *metronidazole* is not a therapeutic problem, although strains of trichomonads resistant to the drug have been reported.

2. **Tinidazole:** *Tinidazole* [tye-NI-da-zole] is a second-generation nitroimidazole that is similar to *metronidazole* in spectrum of activity, absorption, adverse effects and drug interactions. It was approved by the U.S. Food and Drug Administration in 2004 for treatment of amebiasis, amebic liver abcess, giardiasis, and trichomoniasis but was used outside the United States for decades prior to approval. *Tinidazole* is as effective as *metronidazole*, with a shorter course of treatment, yet is more expensive than generic *metronidazole.*

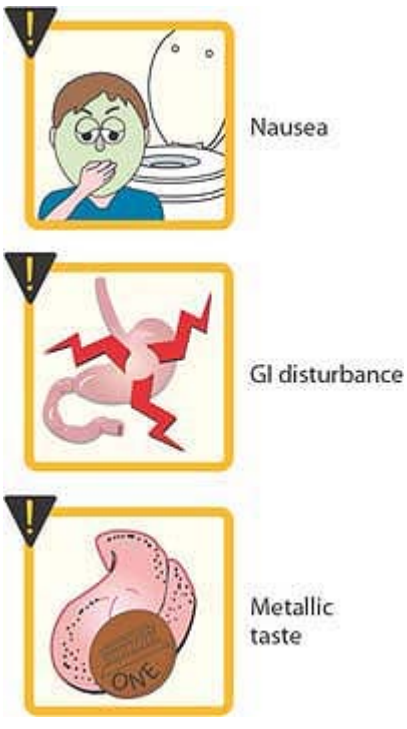


Figure 36.4 Adverse effects of *metronidazole*.

D. Luminal amebicides

After treatment of invasive intestinal or extraintestinal amebic disease is complete, a luminal agent, such as *iodoquinol, diloxanide furoate*, or *paromomycin*, should be administered for treatment of asymptomatic colonization state.

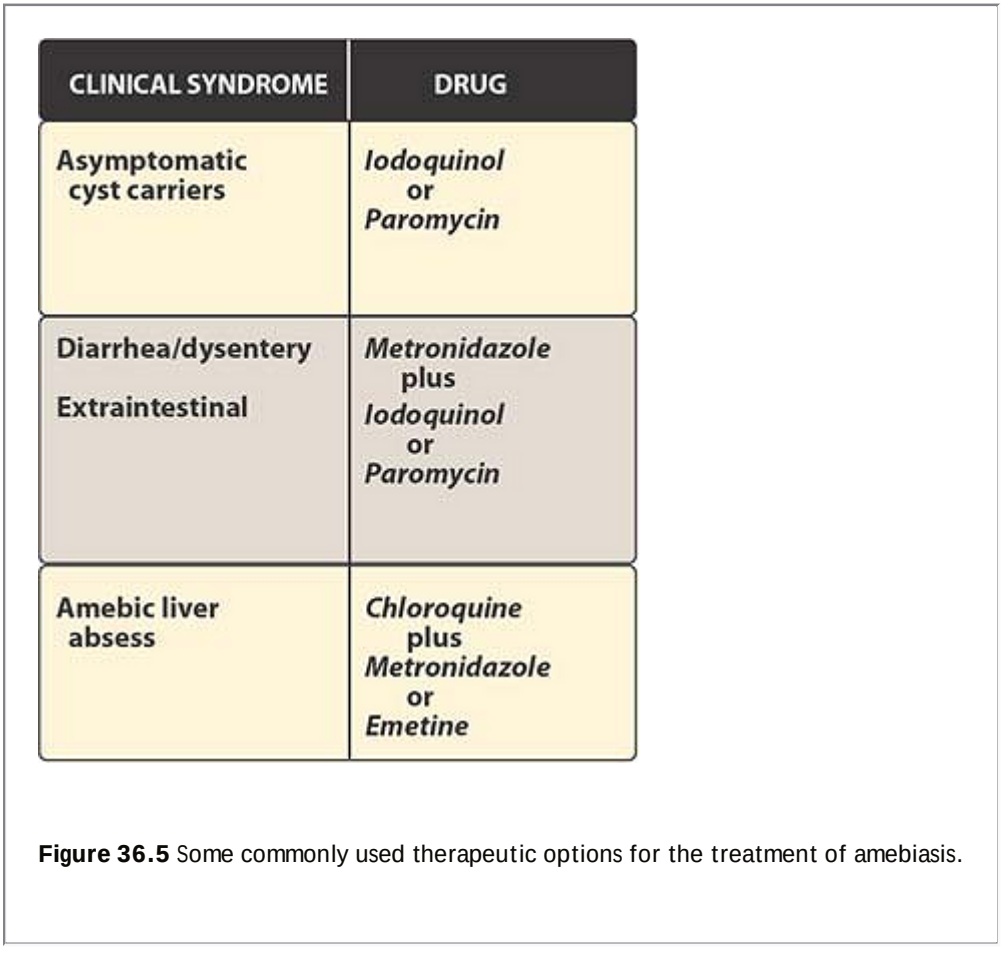
1. **Iodoquinol:** *Iodoquinol* [eye-oh-doe-QUIN-ole], a halogenated 8-hydroxy quinolone, is amebicidal against E.

histolytica, and is effective against the luminal trophozoite and cyst forms. Side effects from *iodoquinol* include rash, diarrhea, and dose-related peripheral neuropathy, including a rare optic neuritis. Long-term use of this drug should be avoided.

2. **Paromomycin:** *Paromomycin* [par-oh-moe-MYE-sin], an aminoglycoside antibiotic, is only effective against the intestinal (luminal) forms of E. histolytica and tapeworm, because it is not significantly absorbed from the gastrointestinal tract. It is an alternative agent for cryptosporidiosis. Although directly amebicidal, *paromomycin* also exerts its antiamebic actions by reducing the population of intestinal flora. Its direct amebicidal action is probably due to the effects it has on cell membranes, causing leakage. Very little of the drug is absorbed on oral ingestion, but that which is absorbed is excreted in the urine. Gastrointestinal distress and diarrhea are the principal adverse effects.

E. Systemic amebicides

These drugs are useful for treating liver abscesses or intestinal wall infections caused by amebas.



CLINICAL SYNDROME	DRUG
Asymptomatic cyst carriers	*Iodoquinol* or *Paromycin*
Diarrhea/dysentery Extraintestinal	*Metronidazole* plus *Iodoquinol* or *Paromycin*
Amebic liver absess	*Chloroquine* plus *Metronidazole* or *Emetine*

Figure 36.5 Some commonly used therapeutic options for the treatment of amebiasis.

1. **Chloroquine:** *Chloroquine* [KLOR-oh-kwin] is used in combination with *metronidazole* and *diloxanide furoate* to treat and prevent amebic liver abscesses. It eliminates trophozoites in liver abscesses, but it is not useful in treating luminal amebiasis. *Chloroquine* is also effective in the treatment of malaria.

2. **Emetine and dehydroemetine:** *Emetine* [EM-e-teen] and *dehydroemetine* [de-hye-dro-EM-e-teen] are alternative agents for the treatment of amebiasis. They inhibit protein synthesis by blocking chain elongation.[1] Intramuscular injection is the preferred route. *Emetine* is concentrated in the liver, where it persists for a month after a single dose. It is slowly metabolized and excreted, and it can accumulate. Its half-life in plasma is 5 days. The use of these ipecac alkaloids is limited by their toxicities (*dehydroemetine* is less toxic than *emetine*), and close clinical observation is necessary when these drugs are administered. They should not be

taken for more than 5 days. *Dehydroemetine* is only available under a compassionate investigational new drug protocol through the Centers of Disease Control and Prevention. Among the untoward effects are pain at the site of injection, transient nausea, cardiotoxicity (for example, arrhythmias or congestive heart failure), neuromuscular weakness, dizziness, and rashes. A summary of the treatment of amebiasis is shown in Figure 36.5.

III. Chemotherapy for Malaria

Malaria is an acute infectious disease caused by four species of the protozoal genus Plasmodium. The parasite is transmitted to humans through the bite of a female Anopheles mosquito, which thrives in humid, swampy areas. Plasmodium falciparum is the most dangerous species, causing an

acute, rapidly fulminating disease that is characterized by persistent high fever, orthostatic hypotension, and massive erythrocytosis (an abnormal elevation in the number of red blood cells accompanied by swollen and reddish condition of the limbs). P. falciparum infection can lead to capillary obstruction and death if treatment is not instituted promptly. Plasmodium vivax causes a milder form of the disease. Plasmodium malariae is common to many tropical regions, but Plasmodium ovale is rarely encountered. Resistance acquired by the mosquito to insecticides, and by the parasite to drugs, has led to new therapeutic challenges, particularly in the treatment of P. falciparum.

A. Life cycle of the malarial parasite

When an infected mosquito bites, it injects Plasmodium sporozoites into the bloodstream (Figure 36.6). The sporozoites migrate through the blood to the liver, where they form cyst-like structures containing thousands of merozoites. [Note: Diagnosis depends on laboratory identification of the parasites in red blood cells of peripheral blood smears.] Upon release, each merozoite invades a red blood cell, becoming a trophozoite and using hemoglobin as a nutrient. The trophozoites multiply and become merozoites. Eventually, the infected cell ruptures, releasing heme and merozoites that can enter other erythrocytes. [Note: Alternatively, released merozoites can become gametocytes,

which are picked up by mosquitoes from the blood they ingest. The cycle thus begins again, with the gametocytes becoming sporozoites in the insect.] The effectiveness of a drug treatment is related to the particular species of infecting plasmodium and the stage of its life cycle that is targeted. A summary of the life cycle of the parasite and the sites of therapeutic interventions are presented in Figure 36.6.

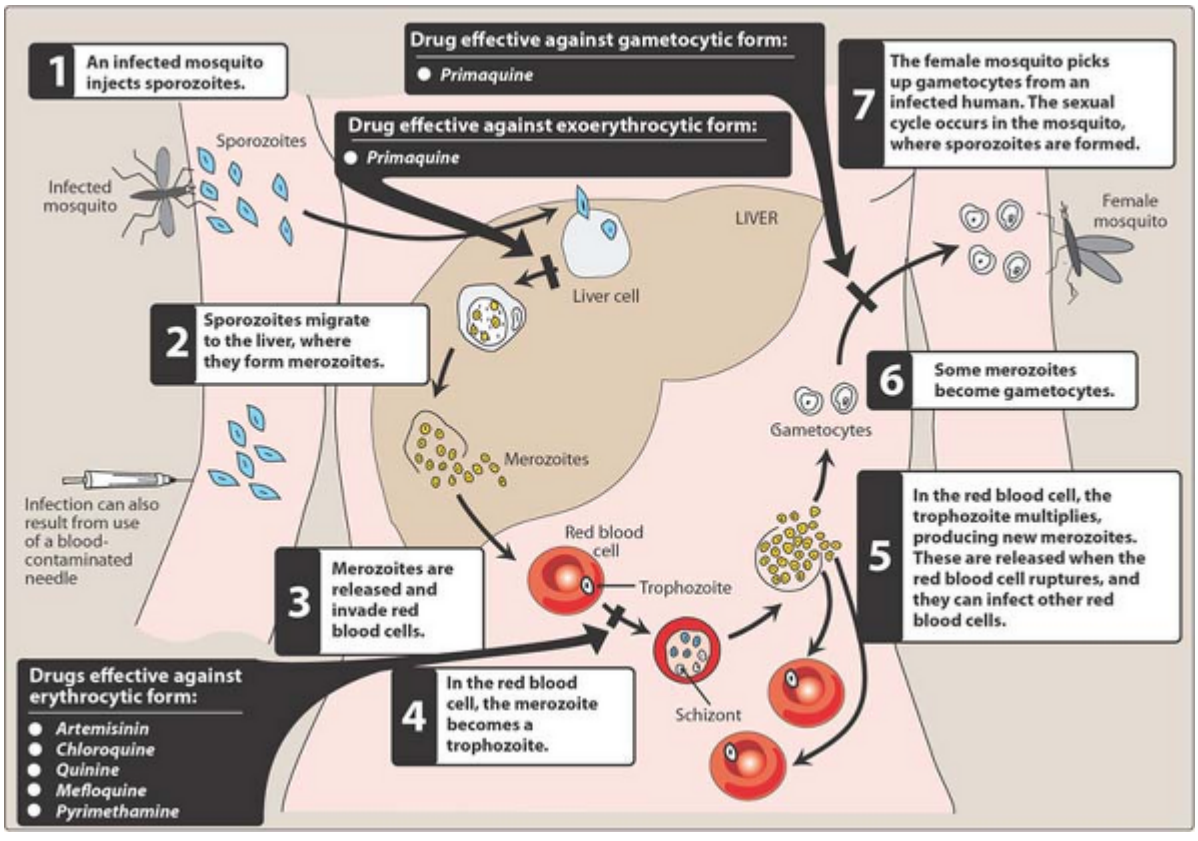


Figure 36.6 Life cycle of the malarial parasite, Plasmodium falciparum, showing the sites of action of antimalarial drugs.

B. Tissue schizonticide: Primaquine

Primaquine [PRIM-a-kwin] is an 8-aminoquinoline that eradicates primary exoerythrocytic forms of P. falciparum and P. vivax and the secondary exoerythrocytic forms of recurring malarias (P. vivax and P. ovale). [Note: *Primaquine* is the only agent that can lead to radical cures of the P. vivax and P. ovale malarias, which may remain in the liver in the exoerythrocytic form after the erythrocytic form of the disease is eliminated.] The sexual (gametocytic) forms of all four plasmodia are destroyed in the plasma or are prevented from maturing later in the mosquito, thus interrupting the transmission of the disease. [Note: *Primaquine* is not effective against the erythrocytic stage of malaria and, therefore, is often used in conjunction with a blood schizonticide, such as *chloroquine, quinine, mefloquine*, or *pyrimethamine*.]

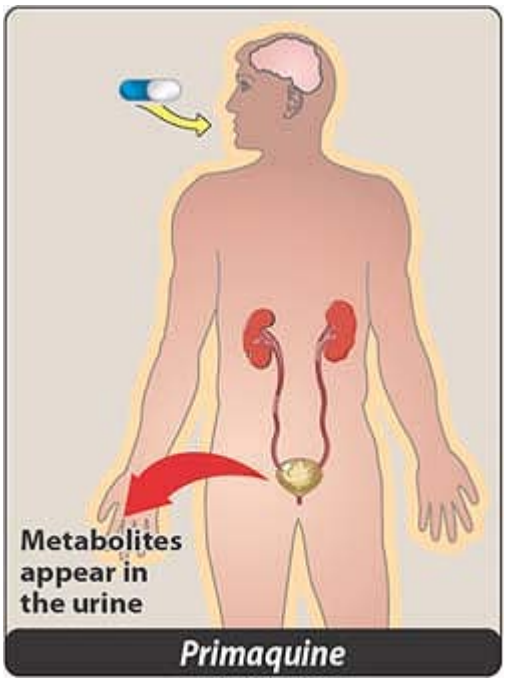


Figure 36.7 Administration and fate of *primaquine*.

1. **Mechanism of action:** This is not completely understood. Metabolites of *primaquine* are believed to act as oxidants that are responsible for the schizonticidal action as well as for the hemolysis and methemoglobinemia encountered as toxicities.
2. **Pharmacokinetics:** *Primaquine* is well absorbed on oral administration and is not concentrated in tissues. It is rapidly oxidized to many compounds, the major one being the deaminated drug. It has not been established which compound possesses the schizontocidal activity. Metabolites appear in the urine (Figure 36.7).
3. **Adverse effects:** *Primaquine* has a low incidence of adverse effects, except for drug-induced hemolytic anemia in patients with genetically low levels of glucose-6-phosphate dehydrogenase[2] (Figure 36.8). Other toxic manifestations observed after large doses of the drug include abdominal discomfort, especially when administered in combination with *chloroquine* (which may affect patient compliance), and occasional methemoglobinemia. Granulocytopenia and agranulocytosis are rarely seen, except in patients with lupus or arthritis (both conditions are aggravated by the drug). *Primaquine* is contraindicated during pregnancy. All Plasmodium species may develop resistance to *primaquine*.

C. Blood schizonticide: Chloroquine

Chloroquine [KLOR-oh-kwin] is a synthetic 4-aminoquinoline that has been the mainstay of antimalarial therapy, and it is the drug of choice in the treatment of erythrocytic P. falciparum malaria, except in resistant strains. *Chloroquine* is less effective against P. vivax malaria. It is highly specific for the asexual form of plasmodia. *Chloroquine* is also effective in the treatment of extraintestinal amebiasis. [Note: The anti-inflammatory

action of *chloroquine* explains its occasional use in rheumatoid arthritis and discoid lupus erythematosus.]

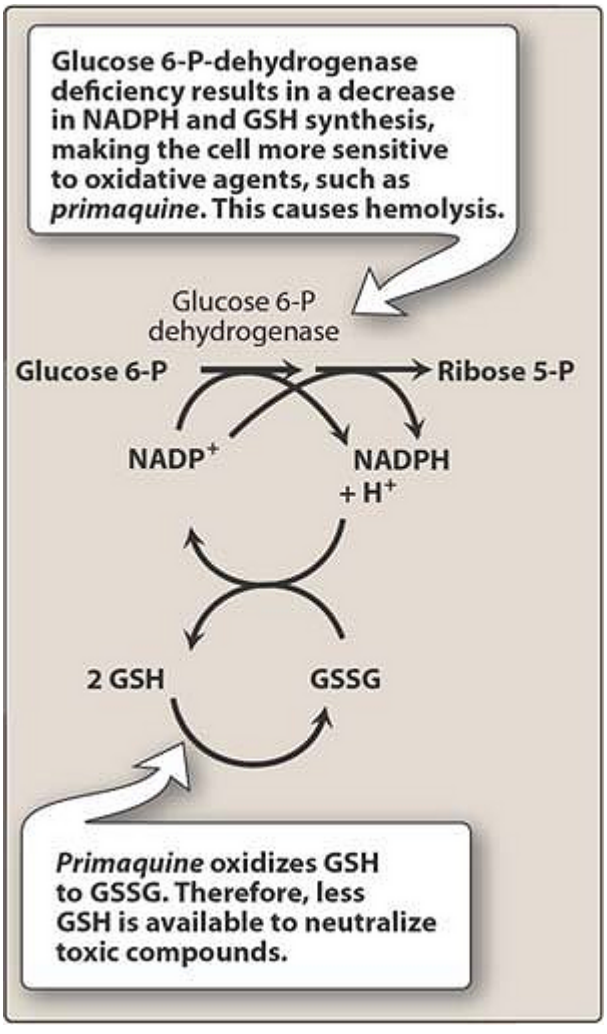


Figure 36.8 Mechanism of *primaquine*-induced hemolytic anemia. GSH = reduced glutathione; GSSG = oxidized glutathione; NADP+ = nicotinamide adenine dinucleotide phosphate; NADPH = reduced nicotinamide adenine dinucleotide phosphate.

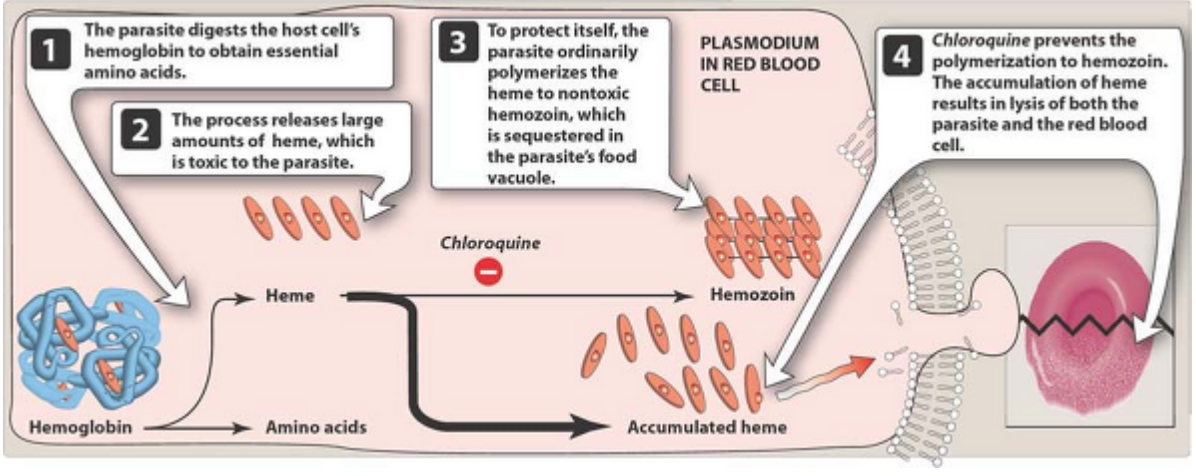


Figure 36.9 Action of *chloroquine* on the formation of hemozoin by Plasmodium species.

1. **Mechanism of action:** Although a detailed explanation of the mechanisms by which *chloroquine* kills plasmodial parasites is still incomplete, the following processes are essential for the drug's lethal action (Figure 36.9). After traversing the erythrocytic and plasmodial membranes, *chloroquine* (a diprotic weak base) is concentrated in the organism's acidic food vacuole, primarily by ion trapping. It is in the food vacuole that the parasite digests the host cell's hemoglobin to obtain essential amino acids. However, this process also releases large amounts of soluble heme (ferriprotoporphyrin IX), which is toxic to the parasite. To protect itself, the parasite ordinarily polymerizes the heme to hemozoin (a pigment), which is sequestered in the parasite's food vacuole. *Chloroquine* specifically binds to heme, preventing its polymerization to hemozoin. The increased pH and the accumulation of heme result in oxidative damage to the membranes, leading to lysis of both the parasite and the red blood cell. The binding to heme and prevention of its polymerization appear to be a crucial step in the drug's antiplasmodial activity, and this may represent a unifying mechanism for such diverse compounds as *chloroquine, quinidine*, and *mefloquine*.

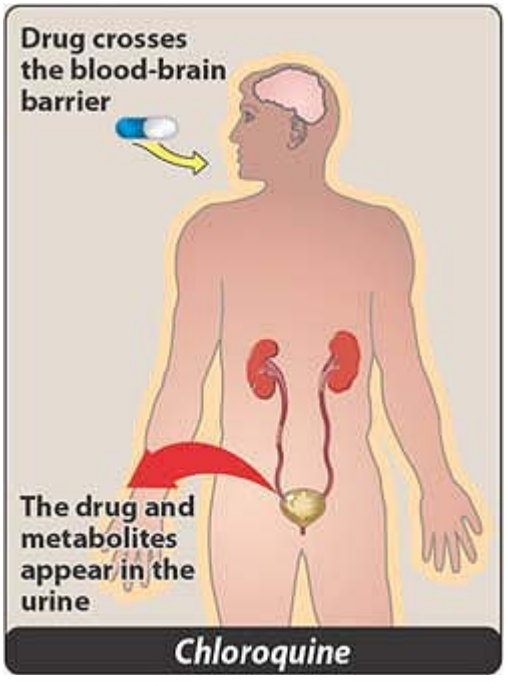


Figure 36.10 Administration and fate of *chloroquine*.

2. **Pharmacokinetics:** *Chloroquine* is rapidly and completely absorbed following oral administration. Usually, 4 days of therapy suffice to cure the disease. The drug concentrates in erythrocytes, liver, spleen, kidney, lung, melanin-containing tissues, and leukocytes. Thus, it has a very large volume of distribution. It persists in erythrocytes (see â€œMechanism of actionâ€ above). The drug also penetrates into the central nervous system (CNS) and traverses the placenta. *Chloroquine* is dealkylated by the hepatic mixed-function oxidase system, but some metabolic products retain antimalarial activity. Both parent drug and metabolites are excreted predominantly in the urine (Figure 36.10). The excretion rate is enhanced as urine is acidified.

3. **Adverse effects:** Side effects are minimal at the low doses used in the chemosuppression of malaria. At higher

doses, many more toxic effects occur, such as gastrointestinal upset, pruritus, headaches, and blurring of vision (Figure 36.11). [Note: An ophthalmologic examination should be routinely performed.] Discoloration of the nail beds and mucous membranes may be seen on chronic administration. *Chloroquine* should be used cautiously in patients with hepatic dysfunction or severe gastrointestinal problems or in patients with neurologic or blood disorders. *Chloroquine* can cause electrocardiographic changes, because it has a *quinidine*-like effect. It may also exacerbate dermatitis produced by *gold* or *phenylbutazone* therapy. [Note: Patients with psoriasis or porphyria should not be treated with *chloroquine*, because an acute attack may be provoked.]

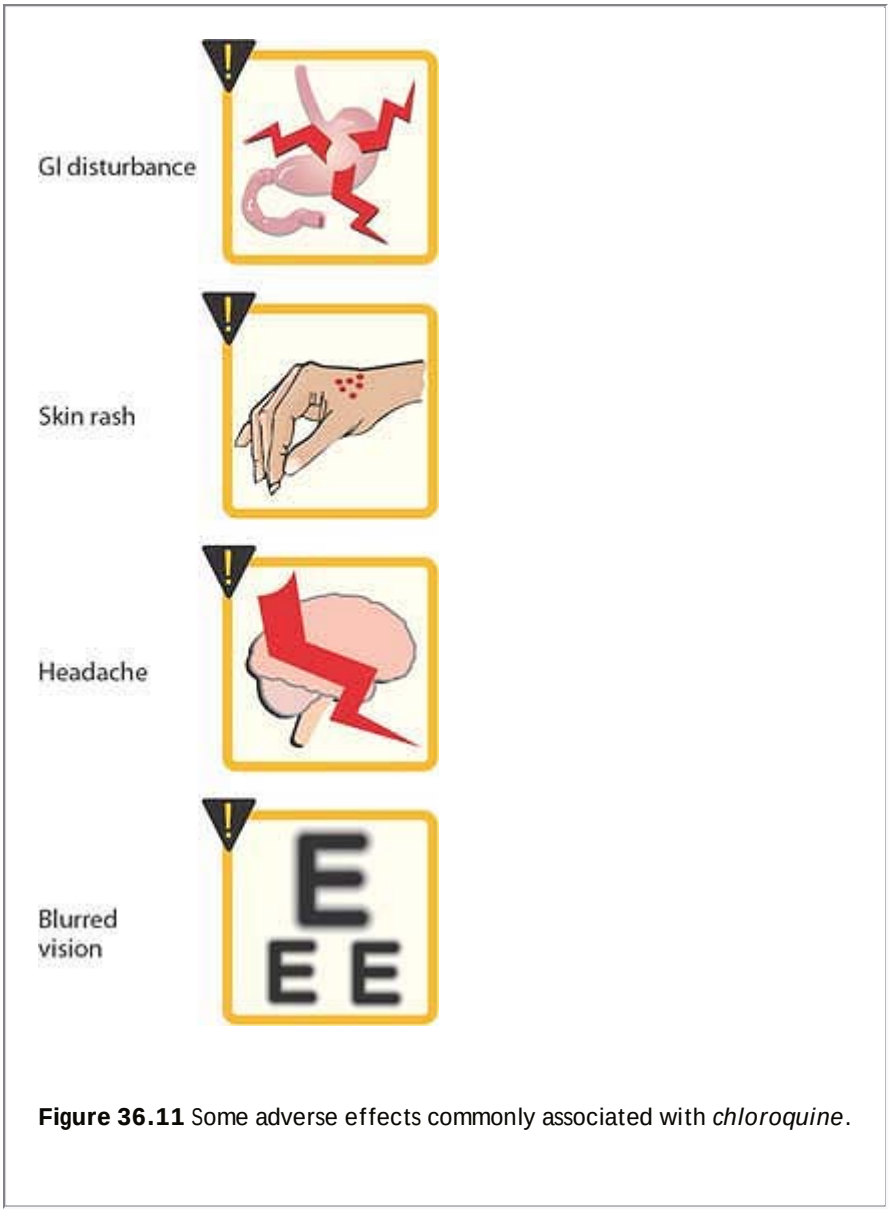


Figure 36.11 Some adverse effects commonly associated with *chloroquine*.

4. **Resistance:** Resistance of plasmodia to available drugs has become a serious medical problem throughout Africa, Asia, and most areas of Central and South America. *Chloroquine*-resistant P. falciparum exhibit multigenic alterations that confer a high level of resistance. [Note: When a *chloroquine*-resistant organism is encountered, therapy usually consists of an orally administered combination of *quinine, pyrimethamine*, and a sulfonamide, such as *sulfadoxine*.]

D. Blood schizonticide: Mefloquine

Mefloquine [MEF-lo-kween] appears to be promising as an effective single agent for suppressing and curing infections caused by multidrug-resistant forms of P. falciparum. Its exact mechanism of action remains to be

determined, but like *quinine*, it can apparently damage the parasite's membrane. Resistant strains have been identified. *Mefloquine* is absorbed well after oral administration and concentrates in the liver and lung. It has a long half-life (17 days) because of its concentration in various tissues and its continuous circulation through the enterohepatic and enterogastric systems. The drug undergoes extensive metabolism. Its major excretory route is the feces. Adverse reactions at high doses range from nausea, vomiting, and dizziness to disorientation, hallucinations, and depression. Electrocardiographic abnormalities and cardiac arrest are possible if *mefloquine* is taken concurrently with *quinine* or *quinidine*.

E. Blood schizonticides: Quinine and quinidine

Quinine [KWYE-nine] and its stereoisomer, *quinidine* [KWIH-ni-deen], interfere with heme polymerization, resulting in death of the erythrocytic form of the plasmodial parasite. These drugs are reserved for severe infestations and for malarial strains that are resistant to other agents, such as *chloroquine*. Taken orally, *quinine* is well distributed throughout the body and can reach the fetus. Alkalinization of the urine decreases its excretion. The major adverse effect of *quinine* is cinchonismâ€”a syndrome causing nausea, vomiting, tinnitus, and vertigo. These effects are reversible and are not considered to be reasons for suspending therapy. However, *quinine* treatment should be suspended if a positive Coombs' test for hemolytic anemia occurs. Drug interactions include potentiation of neuromuscular-blocking agents and elevation of *digoxin* levels if taken concurrently with *quinine*. *Quinine* absorption is retarded when the drug is taken with aluminum-containing antacids. *Quinine* is fetotoxic.

F. Blood schizonticide: Artemisinin

Artemisinin [ar-te-MIS-in-in] is derived from the qinghaosu plant, which has been used in Chinese medicine for more than two millennia in the treatment of fevers and malaria. *Artemisinin* (or one of its derivatives) is available for the treatment of severe, multidrug-resistant P. falciparum malaria. Its antimalarial action involves the production of free radicals within the plasmodium food vacuole, following cleavage of the drug's endoperoxide bridge by heme iron in parasitized erythrocytes. It is also believed to covalently bind to and damage specific malarial proteins. Oral, rectal, and intravenous preparations are available, but the short half-lives preclude their use in chemoprophylaxis. They are metabolized in the liver and are excreted primarily in the bile. Adverse effects include nausea, vomiting, and diarrhea, but overall, *artemisinin* is remarkably safe. Extremely high doses may cause neurotoxicity and prolongation of the QT interval.

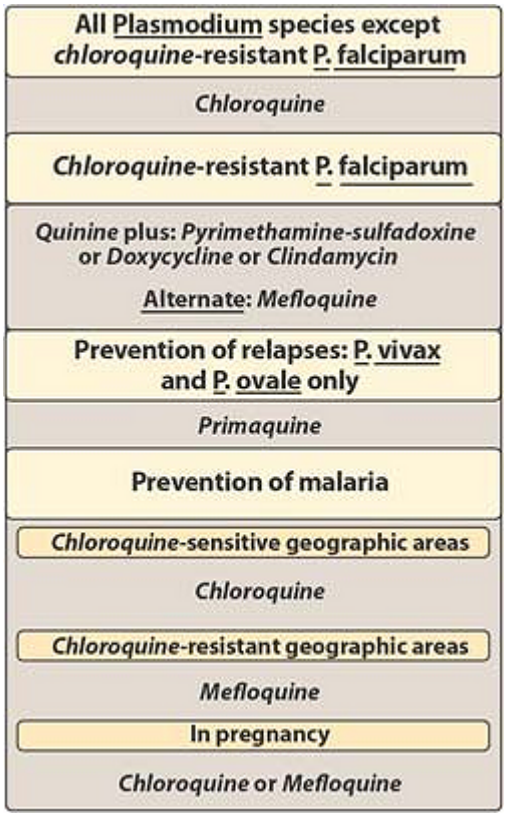


Figure 36.12 Treatment and prevention of malaria.

G. Blood schizonticide and sporontocide: Pyrimethamine

The antifolate agent *pyrimethamine* [peer-i-METH-a-meen] is frequently employed to effect a radical cure as a blood schizonticide. It also acts as a strong sporonticide in the mosquito's gut when the mosquito ingests it with the blood of the human host. *Pyrimethamine* inhibits plasmodial dihydrofolate reductase[3] at much lower concentrations than those needed to inhibit the mammalian enzyme. The inhibition deprives the protozoan of tetrahydrofolateâ€"a cofactor required in the de novo biosynthesis of purines and pyrimidines and in the interconversions of certain amino acids. *Pyrimethamine* alone is effective against P. falciparum. In combination with a sulfonamide, it is also used against P. malariae and Toxoplasma gondii. If megaloblastic anemia occurs with *pyrimethamine* treatment, it may be reversed with *leucovorin*. Figure 36.12 shows some therapeutic options in the treatment of malaria.

IV. Chemotherapy for Trypanosomiasis

Trypanosomiasis refers to two chronic and, eventually, fatal diseases caused by species of Trypanosoma: African sleeping sickness, and American sleeping sickness (Figure 36.13). In African sleeping sickness, the causative organisms, Trypanosoma brucei gambiense and Trypanosoma brucei rhodiense, initially live and grow in the blood. The parasite invades the CNS, causing an inflammation of the brain and spinal cord that produces the characteristic lethargy and, eventually, continuous sleep. Chagas' disease (American sleeping sickness) is caused by Trypanosoma cruzi and occurs in South America.

A. Melarsoprol

Melarsoprol [mel-AR-so-prol] is a derivative of mersalyl oxide, a trivalent arsenical. Its use is limited to the

treatment of trypanosomal infectionsâ€”usually in the late stage with CNS involvementâ€”and it is lethal to these parasites.

1. **Mechanism of action:** The drug reacts with sulfhydryl groups of various substances, including enzymes in both the organism and host.

The parasite's enzymes may be more sensitive than those of the host. There is evidence that mammalian cells may be less permeable to the drug and, thus, are protected from its toxic effects. Trypanosomal resistance may also be due to decreased permeability of the drug.

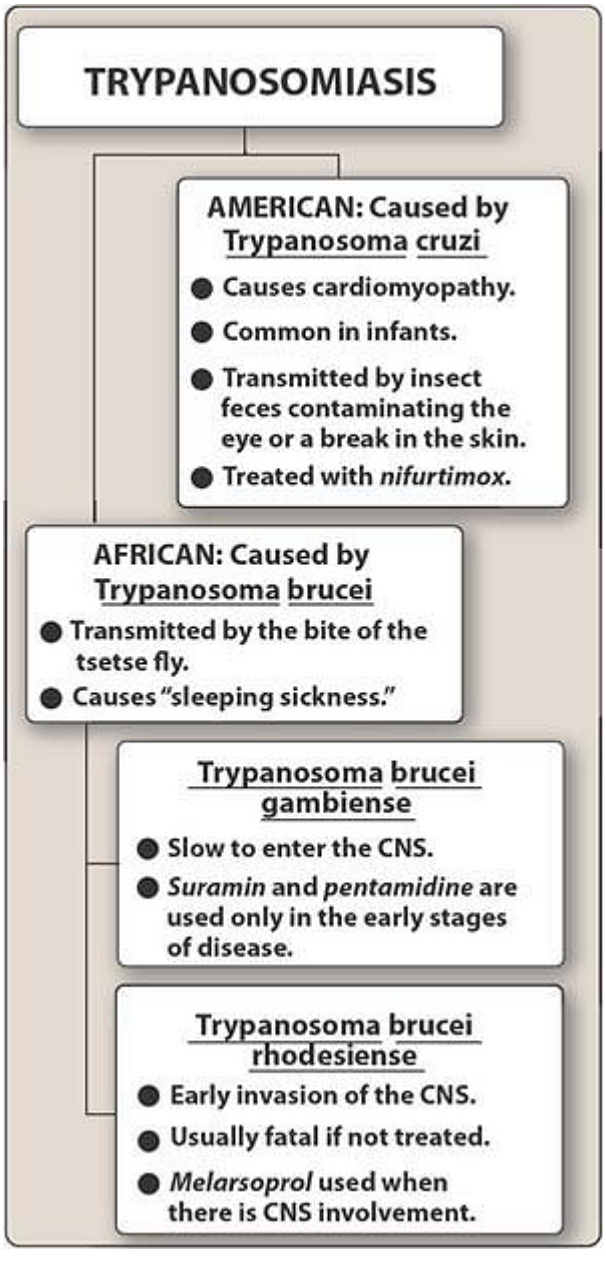


Figure 36.13 Summary of trypanosomiasis.

2. **Pharmacokinetics:** *Melarsoprol* usually is slowly administered intravenously through a fine needle, even though

it is absorbed from the gastrointestinal tract. Because it is very irritating, care should be taken not to infiltrate surrounding tissue. Adequate trypanocidal concentrations appear in the CSF, in contrast to nonpenetration of the CSF by *pentamidine*. *Melarsoprol* is therefore the agent of choice in the treatment of T. brucei rhodesiense, which rapidly invades the CNS, as well as for meningoencephalitis caused by T. brucei gambiense. The host readily oxidizes *melarsoprol* to a relatively nontoxic, pentavalent arsenic compound. The drug has a very short half-life and is rapidly excreted into the urine (Figure 36.14).

3. **Adverse effects:** CNS toxicities are the most serious side effects of *melarsoprol* treatment. Encephalopathy may appear soon after the first course of treatment but usually subsides. It may, however, be fatal. Hypersensitivity reactions may also occur, and fever may follow injection. Gastrointestinal disturbances, such as severe vomiting and abdominal pain, can be minimized if the patient is in the fasting state during drug administration and for several hours thereafter. *Melarsoprol* is contraindicated in patients with influenza. Hemolytic anemia has been seen in patients with glucose 6-phosphate dehydrogenase deficiency.

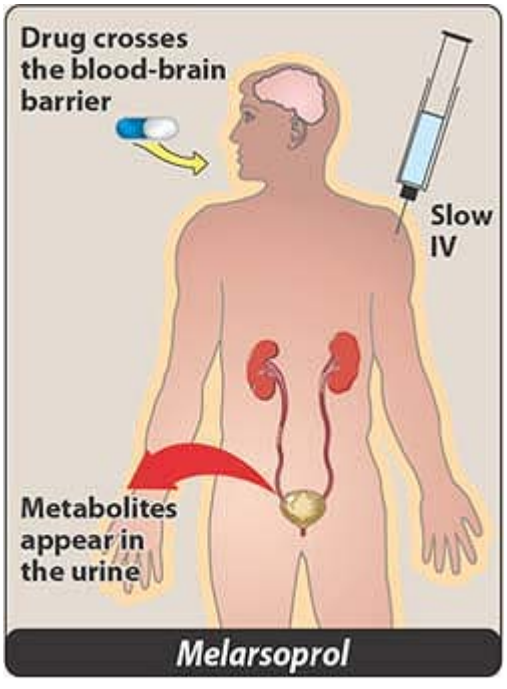


Figure 36.14 Administration and fate of *melarsoprol*.

B. Pentamidine isethionate

Pentamidine [pen-TAM-i-deen] is active against a variety of protozoal infections, including many trypanosomes, such as T. brucei gambiense, for which *pentamidine* is used to treat and prevent the organism's hematologic stage. However, some trypanosomes, including T. cruzi, are resistant. *Pentamidine* is also effective in the treatment of systemic blastomycosis (caused by the fungus Blastomyces dermatitidis) and in treating infections caused by Pneumocystis jiroveci (formerly called Pneumocystis cariniiâ€"a name now used to refer to the organism in animals). [Note: It is now considered to be a fungus, but it is not susceptible to antifungal drugs. *Trimethoprim-sulfamethoxazole* is preferred in the treatment of P. jiroveci infections. However, *pentamidine* is the drug of choice in treating patients with pneumonia caused by P. jiroveci who have failed to respond to *trimethoprim-sulfamethoxazole*. The drug is also used in treating P. jiroveciâ€"infected individuals who are allergic to sulfonamides. Because of the increased incidence of pneumonia caused by this organism in immunocompromised patients, such as those infected with human immunodeficiency virus, *pentamidine* has assumed an important place

in chemotherapy.] *Pentamidine* is also an alternative drug to *stibogluconate* in the treatment of leishmaniasis.

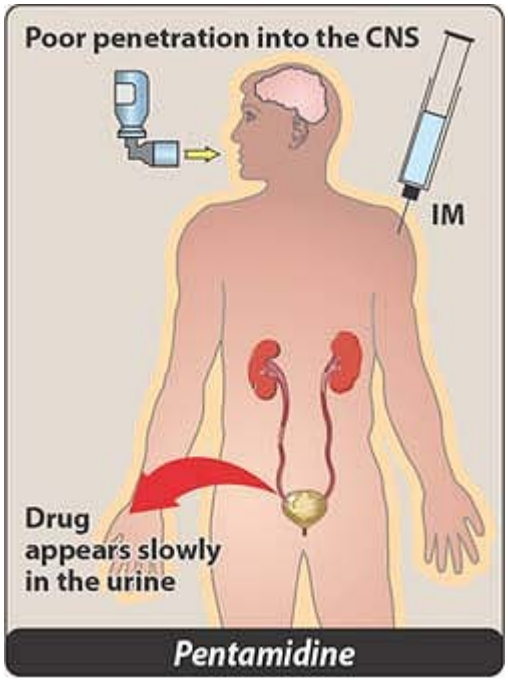


Figure 36.15 Administration and fate of *pentamidine*.

1. **Mechanism of action:** Trypanosoma brucei concentrates *pentamidine* by an energy-dependent, high-affinity uptake system. [Note: Resistance is associated with an inability of the trypanosome to concentrate the drug.] Although its mechanism of action has not been defined, evidence exists that the drug binds to the parasite's DNA and interferes with the synthesis of RNA, DNA, phospholipid, and protein by the parasite.

2. **Pharmacokinetics:** Fresh solutions of *pentamidine* are administered intramuscularly or as an aerosol (Figure 36.15). [Note: The intravenous route is avoided because of severe adverse reactions, such as a sharp fall in blood pressure and tachycardia.] The drug is concentrated and stored in the liver and kidney for a long period of time. Because it does not enter the CSF, it is ineffective against the meningoencephalitic stage of trypanosomiasis. The drug is not metabolized, and it is excreted very slowly into the urine. Its half-life in the plasma is about 5 days.
3. **Adverse effects:** Serious renal dysfunction may occur, which reverses on discontinuation of the drug. Other adverse reactions are hypotension, dizziness, rash, and toxicity to Î² cells of the pancreas.

C. Nifurtimox

Nifurtimox [nye-FER-tim-oks] has found use only in the treatment of acute T. cruzi infections (Chagas' disease), although treatment of the chronic stage of such infections has led to variable results. [Note: *Nifurtimox* is suppressive, not curative.] Being a nitroaromatic compound, *nifurtimox* undergoes reduction and, eventually, generates intracellular oxygen radicals, such as superoxide radicals and hydrogen peroxide[4] (Figure 36.16). These highly reactive radicals are toxic to T. cruzi, which lacks catalase.[5] [Note: Mammalian cells are partially protected from such substances by the presence of enzymes such as catalase, glutathione peroxidase, and superoxide dismutase.] *Nifurtimox* is administered orally, and it is rapidly absorbed and metabolized to unidentified products

that are excreted in the urine. Adverse effects are common following chronic administration, particularly among the elderly. Major toxicities include immediate hypersensitivity reactions such as anaphylaxis, delayed hypersensitivity reactions such as dermatitis and icterus, and gastrointestinal problems that may be severe enough to cause weight loss. Peripheral neuropathy is relatively common, and disturbances in the CNS may also occur. In addition, cell-mediated immune reactions may be suppressed.

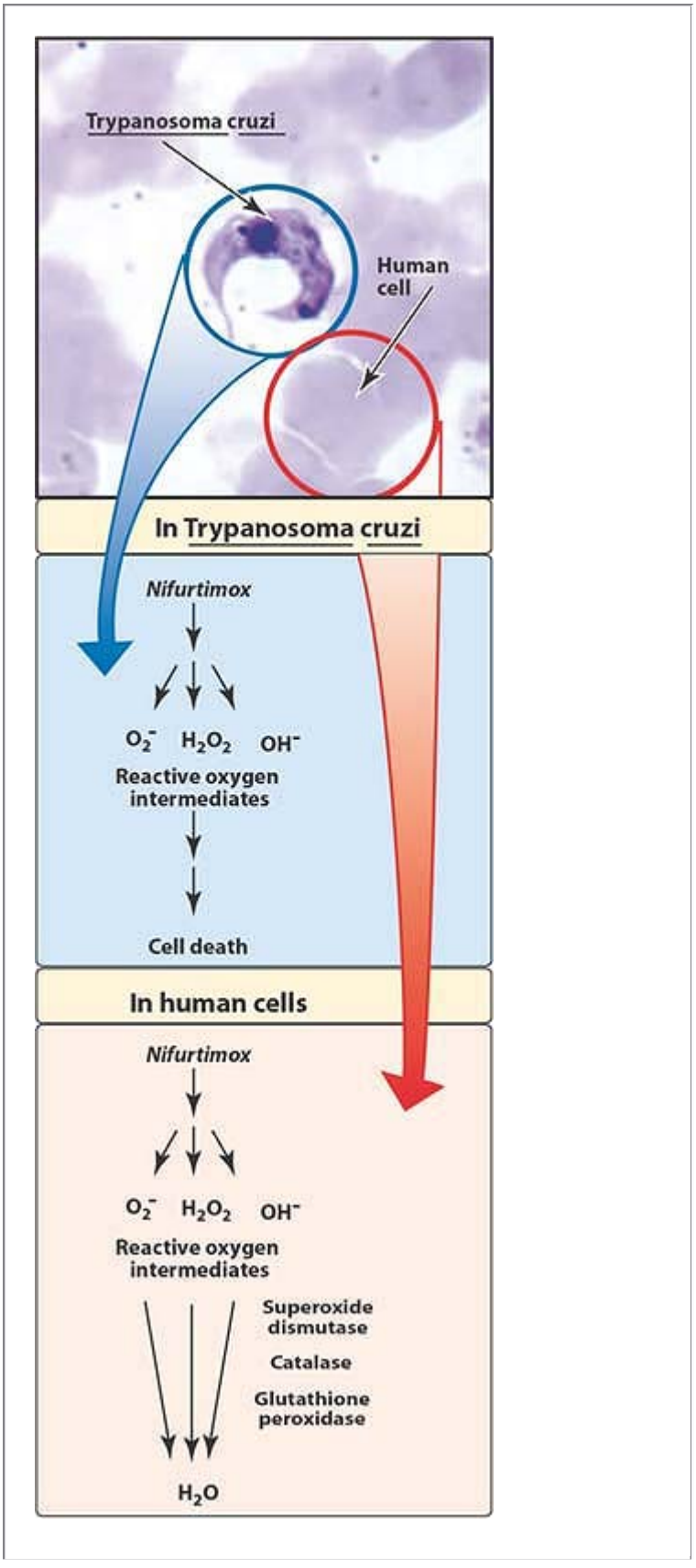


Figure 36.16 Generation of toxic intermediates by *nifurtimox*.

D. Suramin

Suramin [SOO-ra-min] is used primarily in the early treatment and, especially, the prophylaxis of African trypanosomiasis. It is very reactive and inhibits many enzymes, among them those involved in energy metabolism (for example, glycerol phosphate dehydrogenase[6]), which appears to be the mechanism most closely correlated with trypanocidal activity. The drug must be injected intravenously. It binds to plasma proteins and remains in the plasma for a long time, accumulating in the liver and in the proximal tubular cells of the kidney. The severity of the adverse reactions demands that the patient be carefully followed, especially if he or she is debilitated. Although infrequent, adverse reactions include nausea and vomiting (which cause further debilitation of the patient), shock and loss of consciousness, acute urticaria, and neurologic problems, including paresthesia, photophobia, palpebral edema (edema

of the eyelids), and hyperesthesia of the hands and feet. Albuminuria tends to be common, but when cylindruria (the presence of renal casts in the urine) and hematuria occur, treatment should cease.

E. Benznidazole

Benznidazole [benz-NI-da-zole] is a nitroimidazole derivative that inhibits protein synthesis and ribonucleic acid synthesis in the T. cruzi cells. It is an alternative choice for treatment of acute and indeterminate phases of Chagas' disease, but therapy with *benznidazole* does not offer any significant efficacy or toxicity advantages over that with *nifurtimox.* However, *benznidazole* is recommended as prophylaxis for preventing infections caused by T. cruzi among hematopoietic stem cell transplant, recipients because treatment in potential donors is not always effective.

V. Chemotherapy for Leishmaniasis

There are three types of leishmaniasis: cutaneous, mucocutaneous, and visceral. [Note: In the visceral type (liver and spleen), the parasite is in the bloodstream and can cause very serious problems.] Leishmaniasis is transmitted from animals to humans (and between humans) by the bite of infected sandflies. The diagnosis is established by demonstrating the parasite in biopsy material and skin lesions. The treatments of leishmaniasis and trypanosomiasis are difficult, because the effective drugs are limited by their toxicities and failure rates. Pentavalent antimonials, such as *sodium stibogluconate*, are the conventional therapy used in the treatment of leishmaniasis, with *pentamidine* and *amphotericin B* as backup agents. *Allopurinol* has also been reported to be effective (it is converted to a toxic metabolite by the amastigote form[7] of the organism).

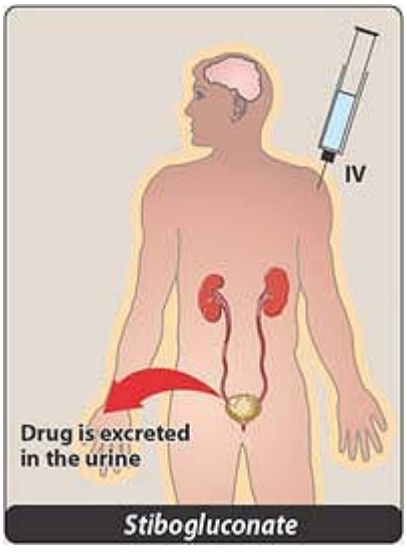


Figure 36.17 Administration and fate of *stibogluconate*.

A. Life cycle of the causative organism: Leishmania species

The sandfly transfers the flagellated promastigote form of the protozoa, which is rapidly phagocytized by macrophages. In the macrophage, the promastigotes rapidly change to nonflagellated amastigotes and multiply, killing the cell. The newly released amastigotes are again phagocytized, and the cycle continues.

B. Sodium stibogluconate

Sodium stibogluconate [stib-o-GLOO-koe-nate] is not effective in vitro. Therefore, it has been proposed that reduction to the trivalent antimonial compound is essential for activity. The exact mechanism of action has not been determined. Evidence for inhibition of glycolysis in the parasite at the phosphofructokinase reaction[8] has been found. Because it is not absorbed on oral administration, *sodium stibogluconate* must be administered parenterally, and it is distributed in the extravascular compartment. Metabolism is minimal, and the drug is excreted in the urine (Figure 36.17). Adverse effects include pain at the injection site, gastrointestinal upsets, and cardiac arrhythmias. Renal and hepatic function should be monitored periodically.

VI. Chemotherapy for Toxoplasmosis

One of the most common infections in humans is caused by the protozoan Toxoplasma gondii, which is transmitted to humans when they consume raw or inadequately cooked, infected meat.[9] An infected pregnant woman can transmit the organism to her fetus. Cats are the only animals that shed oocysts, which can infect other animals as well as humans. The treatment of choice for this condition is the antifolate drug *pyrimethamine*. A combination of *sulfadiazine* and *pyrimethamine* is also efficacious. *Leucovorin* is often administered to protect against folate deficiency. Other inhibitors of folate biosynthesis, such as *trimethoprim* and *sulfamethoxazole*, are without therapeutic efficacy in toxoplasmosis. [Note: At the first appearance of a rash, *pyrimethamine* should be discontinued, because hypersensitivity to this drug can be severe.]

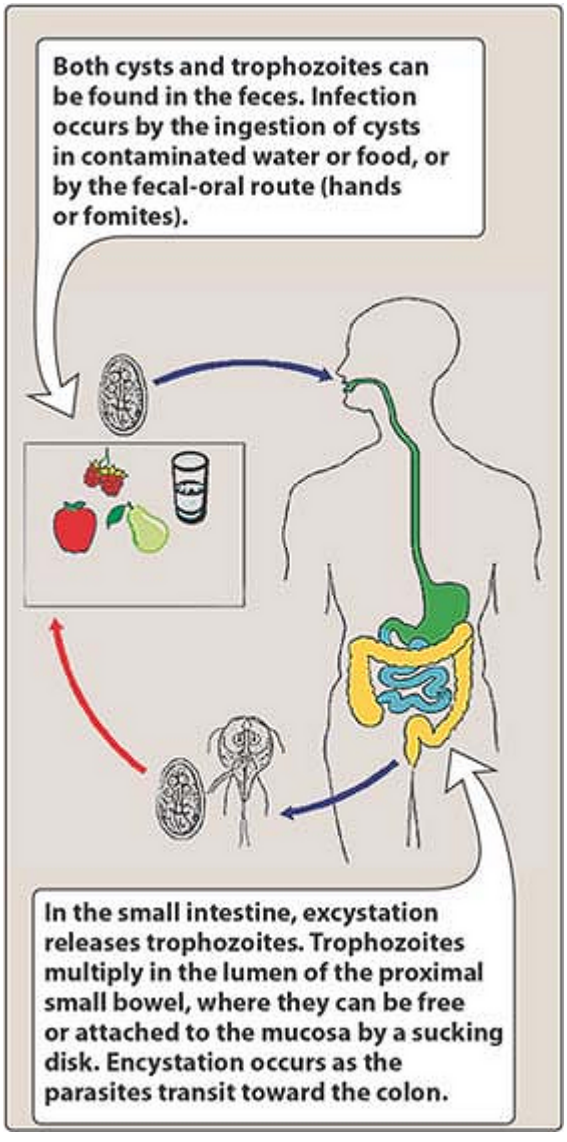


Figure 36.18 Life cycle of Giardia lamblia.

VII. Chemotherapy for Giardiasis

Giardia lamblia is the most commonly diagnosed intestinal parasite in the United States.[10] It has only two life-cycle stages: the binucleate trophozoite with four flagellae, and the drug-resistant, four-nucleate cyst (Figure 36.18). Ingestion, usually from contaminated drinking water, leads to infection. The trophozoites exist in the small intestine and divide by binary fission. Occasionally, cysts are formed that pass out in the stool. Although some infections are asymptomatic, severe diarrhea can occur, which can be very serious in immune-suppressed patients. The treatment of choice is *metronidazole* for 5 days. One alternative agent is *tinidazole*, which is equally effective as *metronidazole* in treatment of giardiasis but with a much shorter course of treatment (2 g given once). *Nitazoxanide* [nye-ta-ZOX-a-nide], a nitrothiazole derivative structurally similar to *aspirin*, was recently approved for treatment of giardiasis. *Nitazoxanide* is also equally efficacious as *metronidazole* and, in comparison, has a 2 day shorter course of therapy.

Study Questions

Choose the ONE best answer.

36.1 A 36-year-old male of Lebanese ancestry is being treated for Plasmodium vivax malaria. He experiences severe fatigue, back pain, and darkened urine. Which one of the following antimalarial drugs is most likely to have caused his symptoms?

A. Pyrimethamine.

B. Artemisinin.

C. Chloroquine.

D. Quinine.

E. Primaquine.

View Answer

36.2 Tinnitus, dizziness, blurred vision, and headache are indicative of toxicity to which one of the following antimalarial drugs?

A. Primaquine.

B. Quinine.

C. Pyrimethamine.

D. Chloroquine.

E. Sulfadoxine.

View Answer

37.3 Which of the following drugs is recommended for the treatment of severe, multidrug-resistant Plasmodium falciparum malaria?

A. Artemisinin.

B. Chloroquine.

C. Quinine.

D. Sodium stibogluconate.

E. Primaquine.

View Answer

37.4 A 22-year-old man, who frequently backpacks, complains of diarrhea and fatigue. Examination of stool specimens shows binucleate organisms with four flagellae. Which one of the following drugs would be effective in treating this patient's infestation?

A. Metronidazole.

B. Quinidine.

C. Pentamidine.

D. Sulfadoxine.

E. Stibogluconate.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Copyright Â©2009 Lippincott Williams & Wilkins

Chapter 37

Anthelmintic Drugs

I. Overview

Three major groups of helminths (worms)â€”the nematodes, trematod, and cestodesâ€”infect humans. As in all antibiotic regimens, the anthelmintic drugs (Figure 37.1) are aimed at metabolic targets that are present in the parasite but are either absent from or have different characteristics than those of the host. Figure 37.2 illustrates the high incidence of helmintic infections.

II. Drugs for the Treatment of Nematodes

Nematodes are elongated roundworms that possess a complete digestive system, including both a mouth and an anus. They cause infections of the intestine as well as the blood and tissues.

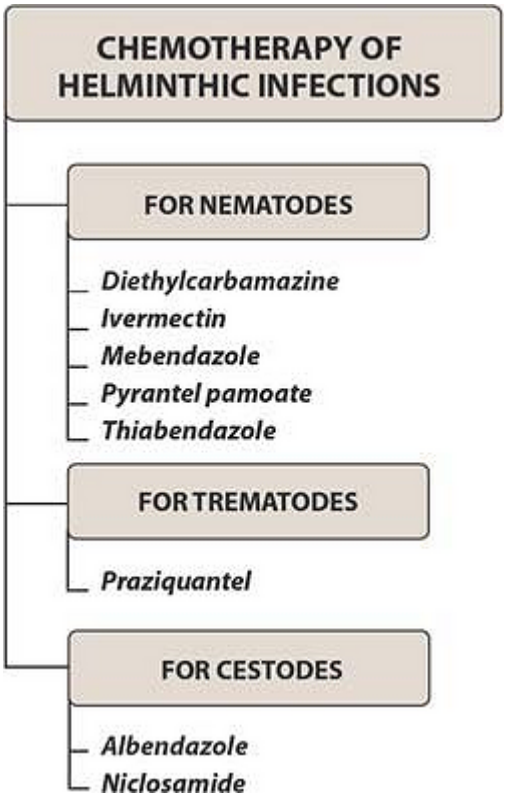


Figure 37.1 Summary of anthelmintic agents.

A. Mebendazole

Mebendazole [me-BEN-da-zole], a synthetic benzimidazole compound, is effective against a wide spectrum of nematodes. It is a drug of choice in the treatment of infections by whipworm (Trichuris trichiura), pinworm (Enterobius vermicularis), hookworms (Necator americanus and Ancylostoma duodenale), and roundworm (Ascariasis lumbricoides). *Mebendazole* acts by binding to and interfering with the assembly of the parasites' microtubules and also by decreasing glucose uptake. Affected parasites are expelled with the feces. *Mebendazole* is nearly insoluble in aqueous solution. Little of an oral dose (that is chewed) is absorbed by the body, unless it is taken with a high-fat meal. It undergoes first-pass metabolism to inactive compounds. *Mebendazole* is relatively free of toxic effects, although patients may complain of abdominal pain and diarrhea. It is, however, contraindicated in pregnant women (Figure 37.3), because it has been shown to be embryotoxic and teratogenic in experimental animals.

B. Pyrantel pamoate

Pyrantel pamoate [pi-RAN-tel PAM-oh-ate], along with *mebendazole*, is effective in the treatment of infections caused by roundworms, pinworms, and hookworms (Figure 37.4). *Pyrantel pamoate* is poorly absorbed orally and exerts its effects in the intestinal tract. It acts as a depolarizing, neuromuscular-blocking agent, causing persistent activation of the parasite's nicotinic receptors. The paralyzed worm is then expelled from the host's intestinal tract. Adverse effects are mild and include nausea, vomiting, and diarrhea.

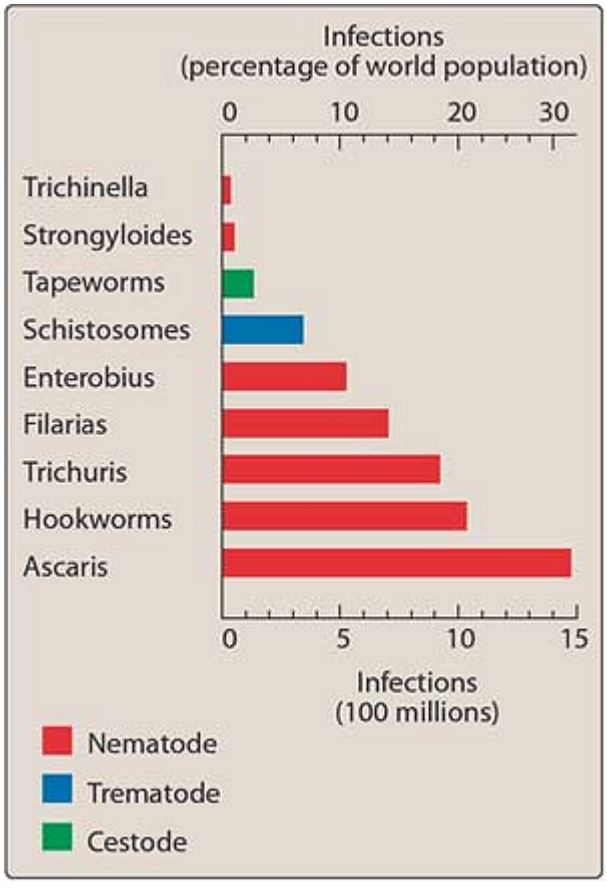


Figure 37.2 Relative incidence of helminth infections worldwide.

C. Thiabendazole

Thiabendazole [thye-a-BEN-da-zole], another synthetic benzimidazole, is effective against strongyloidiasis caused by Strongyloides stercoralis (threadworm), cutaneous larva migrans, and early stages of trichinosis (caused by Trichinella spiralis; see Figure 37.4). *Thiabendazole*, like the other benzimidazoles, affects microtubular aggregation. Although nearly insoluble in water, the drug is readily absorbed on oral administration. It is hydroxylated in the liver and excreted in the urine. The adverse effects most often encountered are dizziness, anorexia, nausea, and vomiting. There have been reports of central nervous system (CNS) symptomatology. Among the cases of erythema multiforme and Stevens-Johnson syndrome reportedly caused by *thiabendazole*, there have been a number of fatalities. Its use is contraindicated during pregnancy.

D. Ivermectin

Ivermectin [eye-ver-MEK-tin] is the drug of choice for the treatment of onchocerciasis (river blindness) caused by Onchocerca volvulus and is a drug of first choice for cutaneous larva migrans and strongyloides. *Ivermectin* targets the parasite's glutamate-gated Cl^- channel receptors. Chloride influx is enhanced, and hyperpolarization occurs, resulting in paralysis of the worm. The drug is given orally. It does not cross the blood-brain barrier and, thus, has no pharmacologic effects in the CNS. However, it is contraindicated in patients with meningitis, because their blood-brain barrier is more permeable and CNS effects might be expected. *Ivermectin* is also contraindicated in pregnancy (see Figure 37.3). The killing of the microfilaria can result in a Mazotti-like reaction (fever, headache, dizziness, somnolence, and hypotension).

E. Diethylcarbamazine

Diethylcarbamazine [dye-eth-il-kar-BAM-a-zeen] is used in the treatment of filariasis because of its ability to immobilize microfilariae and render them susceptible to host defense mechanisms. Combined with *albendazole, diethylcarbamazine* is effective in the treatment of Wucheria bancrofti and Brugia malayi infections. It is rapidly absorbed following oral administration with meals and is excreted primarily in the urine. Urinary alkalosis or renal impairment may require dosage reduction. Adverse effects are primarily caused by host reactions to the killed organisms. The severity of symptoms is related to the parasite load and include fever, malaise, rash, myalgias, arthralgias, and headache. Most patients have leukocytosis. Antihistamines or steroids may be given to ameliorate many of the symptoms. Figure 37.4 summarizes the major infections caused by nematodes and the common therapies for them.



Figure 37.3 *Albendazole, ivermectin*, and *mebendazole* are contraindicated in pregnancy.

III. Drugs for the Treatment of Trematodes

The trematodes (flukes) are leaf-shaped flatworms that are generally characterized by the tissues they infect. For example, they may be categorized as liver, lung, intestinal, or blood flukes (Figure 37.5).

A. Praziquantel

Trematode infections are generally treated with *praziquantel* [pray-zi-KWON-tel]. This drug is an agent of choice for the treatment of all forms of schistosomiasis and other trematode infections and for cestode infections like cysticercosis. Permeability of the cell membrane to calcium is increased, causing contracture and paralysis of the parasite.

P.433

P.434

Praziquantel is rapidly absorbed after oral administration and distributes into the cerebrospinal fluid. High levels occur in the bile. The drug is extensively metabolized oxidatively, resulting in a short half-life. The metabolites are inactive and are excreted through the urine and bile. Common adverse effects include drowsiness, dizziness, malaise, and anorexia, as well as gastrointestinal upsets. The drug is not recommended for pregnant women or nursing mothers. Drug interactions due to increased metabolism have been reported with *dexamethasone, phenytoin*, and *carbamazepine*. *Cimetidine*, which inhibits cytochrome P450 isozymes, causes increased *praziquantel* levels. *Praziquantel* is contraindicated for the treatment of ocular cysticercosis, because destruction of the organism in the eye may damage the organ.

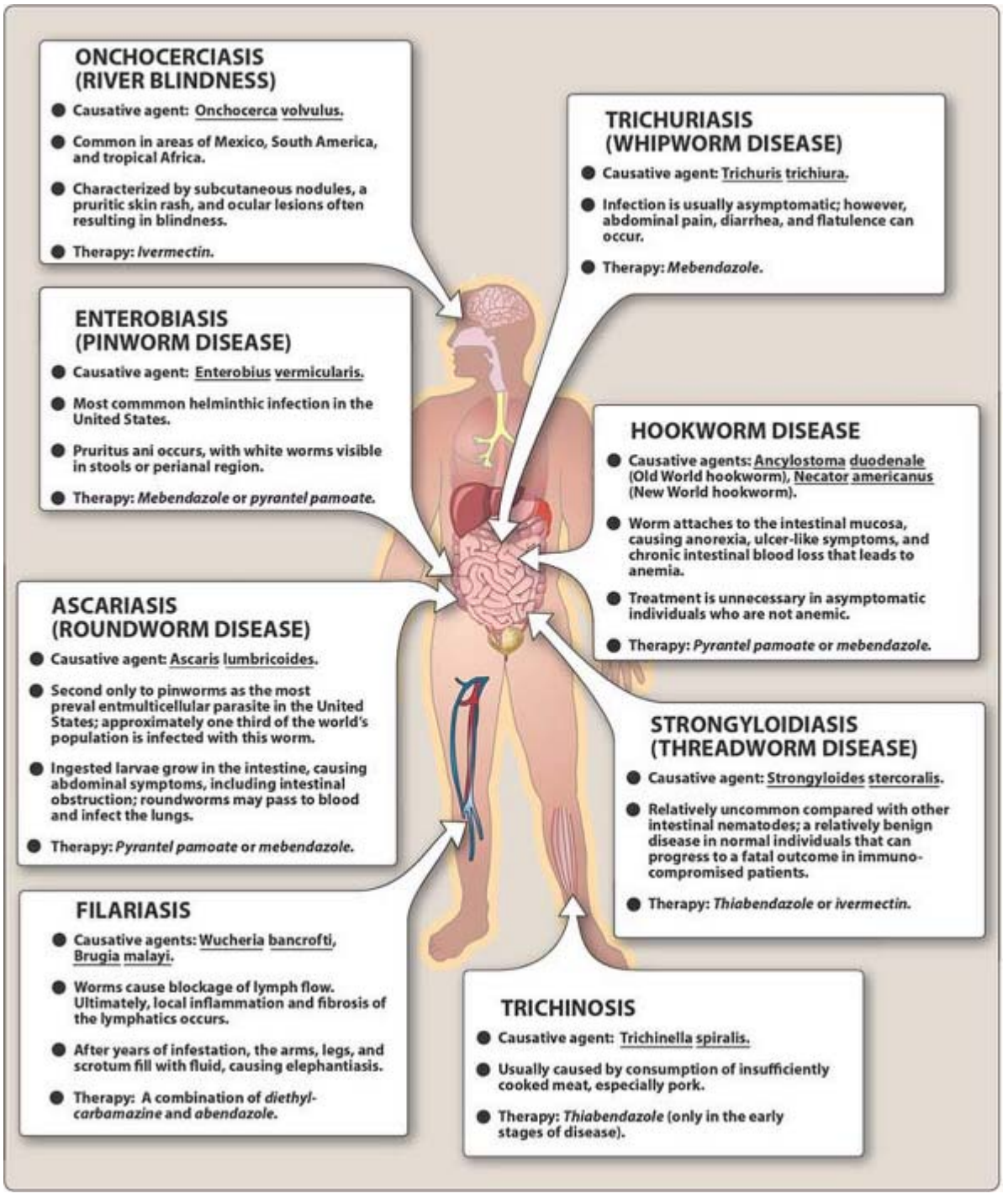


Figure 37.4 Characteristics of and therapy for commonly encountered nematode infections.

IV. Drugs for the Treatment of Cestodes

The cestodes, or â€œtrue tapeworms,â€ typically have a flat, segmented body and attach to the host's intestine (Figure 37.6). Like the trematodes, the tapeworms lack a mouth and a digestive tract throughout their life cycle.

A. Niclosamide

Niclosamide [ni-KLOE-sa-mide] is the drug of choice for most cestode (tapeworm) infections. Its action has been ascribed to inhibition of the

parasite's mitochondrial phosphorylation of adenosine diphospate, which produces usable energy in the form of adenosine triphospate. Anaerobic metabolism may also be inhibited. The drug is lethal for the cestode's scolex and segments of cestodes but not for the ova. A laxative is administered prior to oral administration of *niclosamide*. This is done to purge the bowel of all dead segments and so preclude digestion and liberation of the ova, which may lead to cysticercosis. Alcohol should be avoided within 1 day of *niclosamide*.

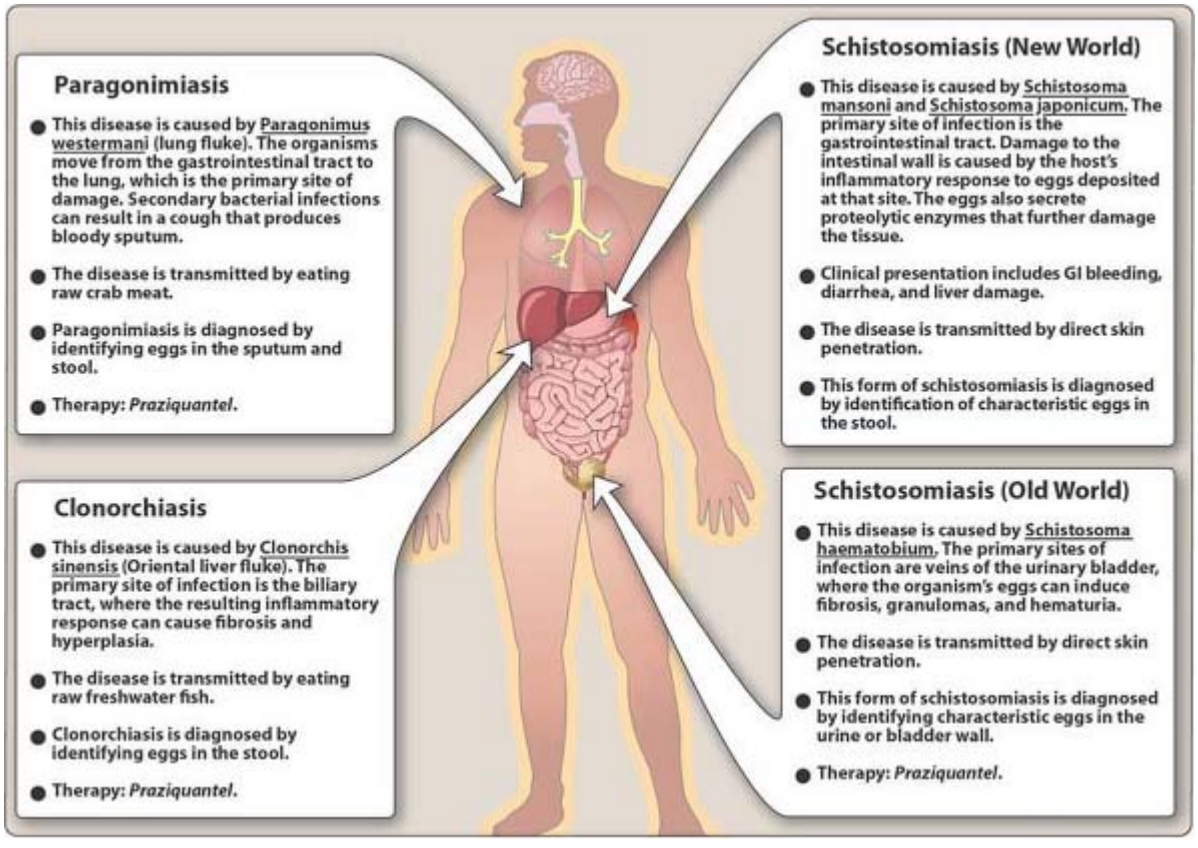


Figure 37.5 Characteristics of and therapy for commonly encountered trematode infections.

B. Albendazole

Albendazole [al-BEN-da-zole] is a benzimidazole that, like the others, inhibits microtubule synthesis and glucose uptake in nematodes. Its primary therapeutic application, however, is in the treatment of cestodal infestations, such as cysticercosis (caused by Taenia solium larvae) and hydatid disease (caused by Echinococcus granulosis). *Albendazole* is erratically absorbed after oral administration, but absorption is enhanced by a high-fat meal. It undergoes extensive first-pass metabolism, including formation of the sulfoxide, which is also active. *Albendazole* and its metabolites are primarily excreted in the urine. When used in short-course

therapy (1â€“3 days) for nematodal infestations, adverse effects are mild and transient and include headache and nausea. Treatment of hydatid disease (3 months) has a risk of hepatotoxicity and, rarely, agranulocytosis or pancytopenia. Medical treatment of neurocysticercosis is associated with inflammatory responses to dying parasites in the CNS, including headache, vomiting, hyperthermia, convulsions, and mental changes. The drug should not be

given during pregnancy (see Figure 37.3) or to children under 2 years of age.

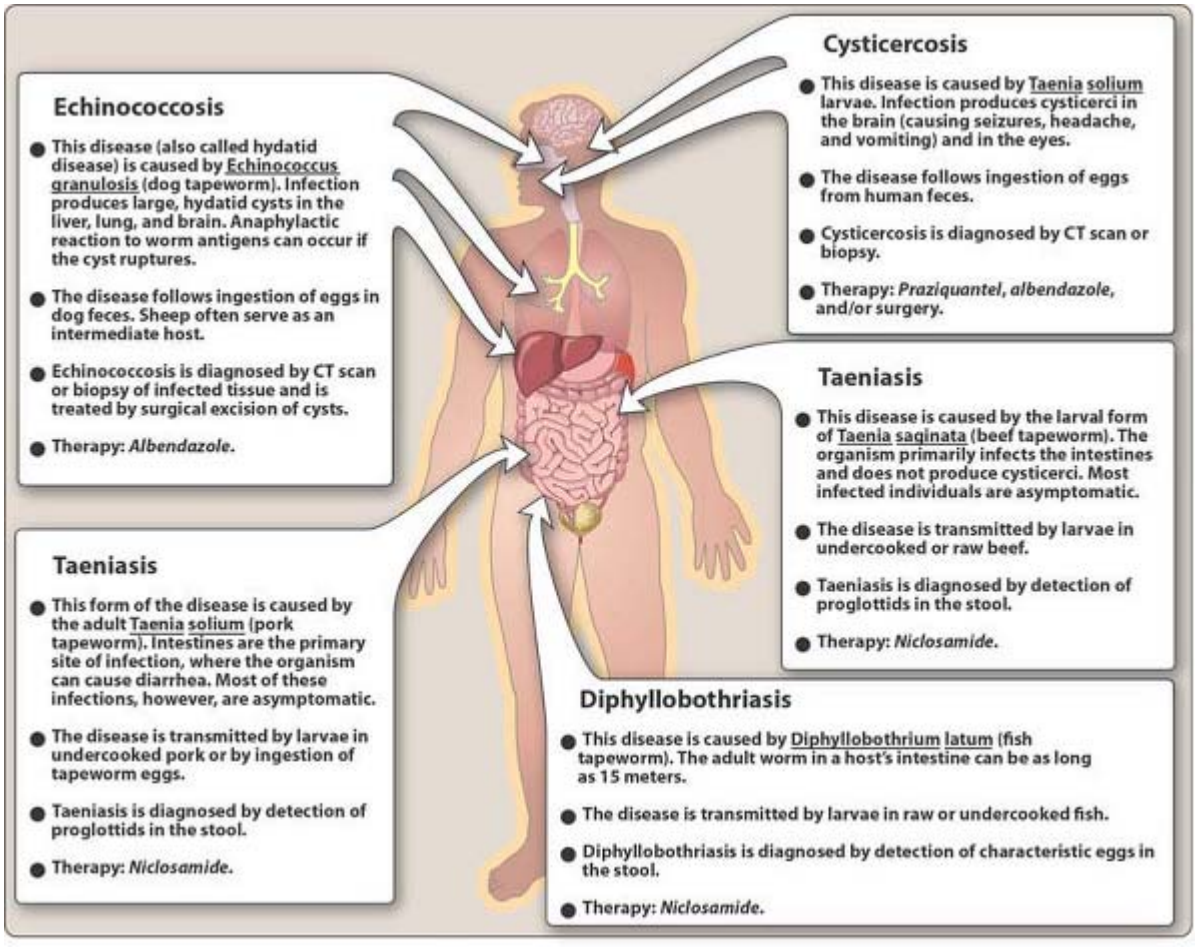


Figure 37.6 Characteristics of and therapy for commonly encountered cestode infections.

Study Questions

Choose the ONE best answer.

37.1 A 48-year-old immigrant from Mexico presents with seizures and other neurologic symptoms. Eggs of Taenia solium are found upon examination of a stool specimen. A magnetic resonance image of the brain shows many cysts, some of which are calcified. Which one of the following drugs would be of benefit to this individual?

A. Ivermectin.

B. Pyrantel pamoate.

C. Albendazole.

D. Diethylcarbamazine.

E. Niclosamide.

View Answer

37.2 A 56-year-old man from South America is found to be parasitized by both schistosomes and Taenia soliumâ€”the pork tapeworm. Which of the following anthelmintic drugs would be effective for both infestations?

A. Albendazole.

B. Ivermectin.

C. Mebendazole.

D. Niclosamide.

E. Praziquantel.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Copyright Â©2009 Lippincott Williams & Wilkins

Chapter 38

Antiviral Drugs

I. Overview

Viruses are obligate intracellular parasites. They lack both a cell wall and a cell membrane, and they do not carry out metabolic processes. Viral reproduction uses much of the host's metabolic machinery, and few drugs are selective enough to prevent viral replication without injury to the host. Therapy for viral diseases is further complicated by the fact that the clinical symptoms appear late in the course of the disease, at a time when most of the virus particles have replicated. [Note: This contrasts with bacterial diseases, in which the clinical symptoms are usually coincident with bacterial proliferation.] At this late, symptomatic stage of the viral infection, administration of drugs that block viral replication has limited effectiveness. However, some antiviral agents are useful as prophylactic agents. Only a few virus groups, including those that cause the viral infections discussed in this chapter, respond to available antiviral drugs. To assist in the review of these drugs, they are grouped according to the organisms that are affected (Figure 38.1).

II. Treatment of Respiratory Virus Infections

Viral respiratory tract infections for which treatments exist include those of influenza A and B and respiratory syncytial virus (RSV). [Note: Immunization against influenza A is the preferred approach. However, antiviral agents are employed when patients are allergic to the vaccine, when the outbreak is due to an immunologic variant of the virus not covered by vaccines, or when outbreaks occur among unvaccinated individuals who are at risk and in closed settings (for example, in nursing homes).]

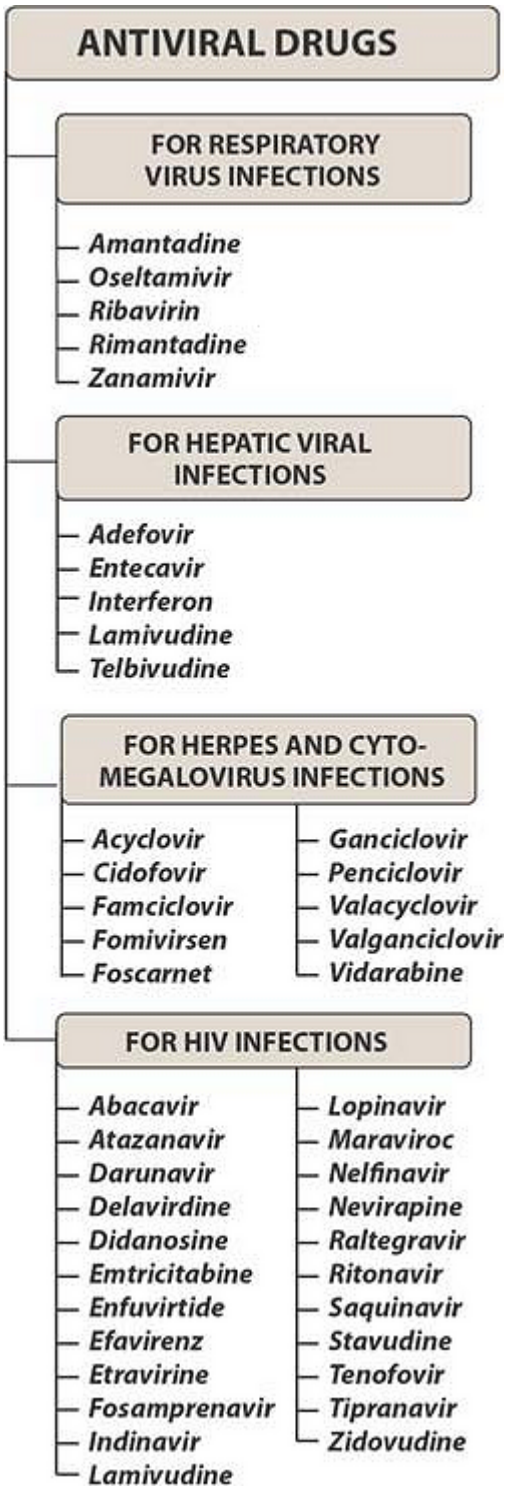


Figure 38.1 Summary of antiviral drugs. HIV = human immunodeficiency virus.

A. Neuraminidase inhibitors

Orthomyxoviruses that cause influenza contain the enzyme neuraminidase, which is essential to the life cycle of the virus. Viral neuraminidase can be selectively inhibited by the sialic acid analogs, *oseltamivir* [os-el-TAM-i-veer] and

zanamivir [za-NA-mi-veer]. These drugs prevent the release of new virions and their spread from cell to cell. Unlike the *adamantine* analogs discussed below, *oseltamivir* and *zanamivir* are effective against both Type A and Type B influenza viruses. They do not interfere with the immune response to influenza A vaccine. Administered prior to exposure, neuraminidase inhibitors prevent infection, and when administered within the first 24 to 48 hours after the onset of infection, they have a modest effect on the intensity and duration of symptoms.

1. **Mode of action:** Influenza viruses employ a specific neuraminidase that is inserted into the host cell membrane for the purpose of releasing newly formed virions. *Oseltamivir* and *zanamivir* are transition-state analogs of the sialic acid substrate and serve as inhibitors of the enzyme activity. Virions accumulate at the internal infected cell surface.
2. **Pharmacokinetics:** *Oseltamivir* is an orally active prodrug that is rapidly hydrolyzed by the liver to its active form. *Zanamivir*, on the other hand, is not active orally and is either inhaled or administered intranasally. Both drugs are eliminated unchanged in the urine (Figure 38.2).
3. **Adverse effects:** The most common side effects of *oseltamivir* are gastrointestinal discomfort and nausea, which can be alleviated by taking the drug with food. *Zanamivir* is not associated with gastrointestinal disturbance, because it is administered directly to the airways. Irritation of the respiratory tract does occur, however. *Zanamivir* should be avoided in individuals with severe reactive asthma or chronic obstructive respiratory disease, because bronchospasm may occur with the risk of fatality. Neither drug has been reported to have clinically significant drug interactions.
4. **Resistance:** Mutations of the neuraminidase have been identified in adults treated with either of the neuraminidase inhibitors. These mutants, however, are often less infective and virulent than the wild type.

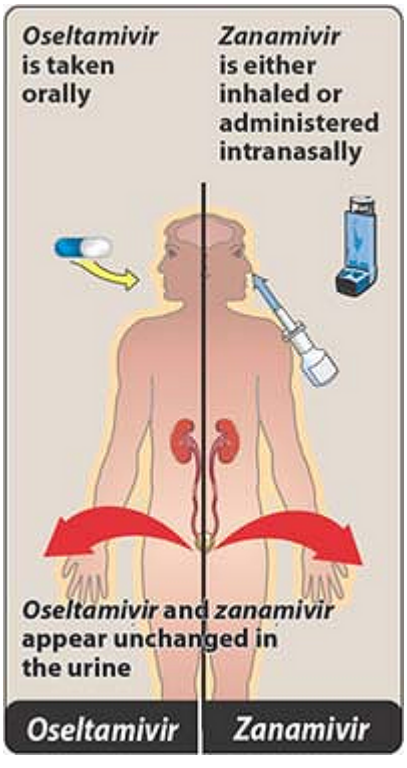


Figure 38.2 Administration and metabolism of *oseltamivir* and *zanamivir*.

B. Inhibitors of viral uncoating

The therapeutic spectrum of the *adamantine* derivatives, *amantadine* [a-MAN-ta-deen] and *rimantadine* [ri-MAN-ta-deen], is limited to influenza A infections, for which the drugs have been shown to be equally effective in both treatment and prevention. For example, these drugs are 70 to 90 percent effective in preventing infection if treatment is begun at the time ofâ€"or prior toâ€"exposure to the virus. Also, both drugs reduce the duration and severity of systemic symptoms if started within the first 48 hours after exposure to the virus (Figure 38.3). Neither impairs the immune response to influenza A vaccine, and either can be administered as a supplement to vaccination, thus providing protection until antibody response occurs (usually 2 weeks in healthy adults). Treatment is particularly useful in high-risk patients who have not been vaccinated and during epidemics. [Note: *Amantadine* is also effective in the treatment of some cases of Parkinson's disease (see p. 101).]

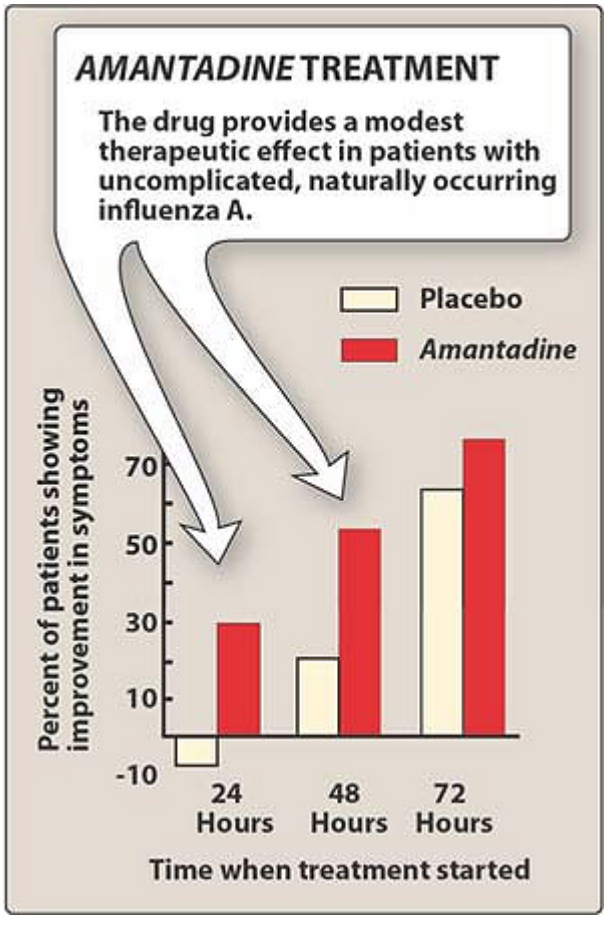


Figure 38.3 Improvement in symptoms of individuals with naturally occurring influenza infections treated with *amantadine*.

1. **Mode of action:** The primary antiviral mechanism of *amantadine* and *rimantadine* is to block the viral membrane matrix protein, M2, which functions as a channel for hydrogen ion. This channel is required for the fusion of the viral membrane with the cell membrane that ultimately forms the endosome (created when the virus is internalized by endocytosis). [Note: The acidic environment of the endosome is required for viral uncoating.] These drugs may also interfere with the release of new virions.
2. **Pharmacokinetics:** Both drugs are well absorbed orally. *Amantadine* distributes throughout the body and

readily penetrates into the central nervous system (CNS), whereas *rimantadine* does not cross the blood-brain barrier to the same extent. *Amantadine* is not extensively metabolized. It is excreted into the urine and may accumulate

to toxic levels in patients with renal failure. On the other hand, *rimantadine* is extensively metabolized by the liver, and both the metabolites and the parent drug are eliminated by the kidney (Figure 38.4).

3. **Adverse effects:** The side effects of *amantadine* are mainly associated with the CNS. Minor neurologic symptoms include insomnia, dizziness, and ataxia. More serious side effects have been reported (for example, hallucinations and seizures). The drug should be employed cautiously in patients with psychiatric problems, cerebral atherosclerosis, renal impairment, or epilepsy. *Rimantadine* causes fewer CNS reactions, because it does not efficiently cross the blood-brain barrier. Both drugs cause gastrointestinal intolerance. *Amantadine* and *rimantadine* should be used with caution in pregnant and nursing mothers, because they have been found to be embryotoxic and teratogenic in rats.

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

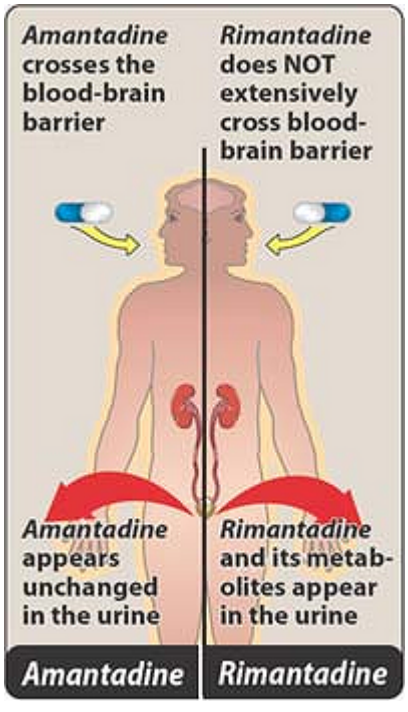


Figure 38.4 Administration and metabolism of *amantadine* and *rimantadine*.

C. Ribavirin

Ribavirin [rye-ba-VYE-rin] is a synthetic guanosine analog. It is effective against a broad spectrum of RNA and DNA viruses. For example, *ribavirin* is used in treating infants and young children with severe RSV infections. [Note: It is not indicated for use in adults.] *Ribavirin* is also effective in chronic hepatitis C infections when used in combination with *interferon-Î±-2b*. *Ribavirin* may reduce the mortality and viremia of Lassa fever.

1. **Mode of action:** The mode of action of *ribavirin* has been studied only for the influenza viruses. The drug is

first converted to the 5'-phosphate derivatives, the major product being the compound ribavirin-triphosphate, which exerts its antiviral action by inhibiting guanosine triphosphate formation, preventing viral mRNA capping,[1] and blocking RNA-dependent RNA polymerase. [Note: Rhinoviruses and enteroviruses, which contain preformed mRNA and do not need to synthesize mRNA in the host cell to initiate an infection, are relatively resistant to the action of *ribavirin*.]

2. **Pharmacokinetics:** *Ribavirin* is effective orally and intravenously. Absorption is increased if the drug is taken with a fatty meal. An aerosol is used in certain respiratory viral conditions, such as the treatment of RSV infection. Studies of drug distribution in primates have shown retention in all tissues, except brain. The drug and its metabolites are eliminated in the urine (Figure 38.5).

3. **Adverse effects:** Side effects reported for oral or parenteral use of *ribavirin* have included dose-dependent transient anemia. Elevated bilirubin has been reported. The aerosol may be safer, although respiratory function in infants can deteriorate quickly after initiation of aerosol treatment. Therefore, monitoring is essential. Because of teratogenic effects in experimental animals, *ribavirin* is contraindicated in pregnancy (Figure 38.6).

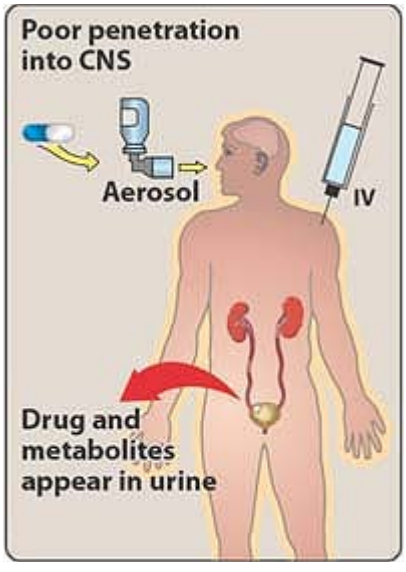


Figure 38.5 Administration and metabolism of *ribavirin*.

III. Treatment of Hepatic Viral Infections

The hepatitis viruses thus far identifiedâ€"A, B, C, D, and Eâ€"each have a pathogenesis specifically involving replication in and destruction of hepatocytes. Of this group, hepatitis B and hepatitis C are the most common causes of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (Figure 38.7) and are the only hepatic viral infections for which therapy is currently available. [Note: Hepatitis A is a commonly encountered infection, but it is not a chronic disease.] Chronic hepatitis B is usually treated with *peginterferon-Î±-2a,* which is injected subcutaneously once weekly. [Note: *Interferon-Î±-2b* injected intramuscularly or subcutaneously three times weekly is also useful in the treatment of hepatitis B, but *peginterefron-Î±-2a* has similar or slightly better efficacy.] Oral therapy includes *lamivudine, adefovir, enetecavir,* or *telbivudine.* Combination therapy of an *interferon* plus *lamivudine* is no more effective than monotherapy with *lamivudine*. Patients with acquired immunodeficiency syndrome (AIDS) who are coinfected with hepatitis B are usually poor responders to *interferon* therapy. In the treatment of chronic hepatitis C, the preferred treatment is the combination of *peginterferon-Î±-2a* or *peginterferon-Î±-2b* plus *ribavirin*, which is more effective than the combination of standard interferons and ribavirin.



Figure 38.6 Ribavirin causes *teratogenic* effects.

A. Interferon

Interferon [in-ter-FEER-on] is a family of naturally occurring, inducible glycoproteins that interfere with the ability of viruses to infect cells. Although *interferon* inhibits the growth of many viruses in vitro, its activity in vivo against viruses has been disappointing. The interferons are synthesized by recombinant DNA technology. At least three types of *interferon* exist, Î±, Î², and Î³ (Figure 38.8). One of the 15 *interferon*-Î± *glycoproteins*â€"*interferon*-Î±-*2b*â€"has been approved for treatment of hepatitis B and C, condylomata acuminata, and cancers such as hairy-cell leukemia and Kaposi's sarcoma. *Interferon*-*Î²* has some effectiveness in the treatment of multiple sclerosis. In so-called â€œpegylatedâ€ formulations, bis-monomethoxy polyethylene glycol has been covalently attached to either *interferon*-Î±-2a or -Î±-2b to increase the size of the molecule. The larger molecular size delays absorption from the injection site, lengthening the duration of action of the drug, and also decreases its clearance.

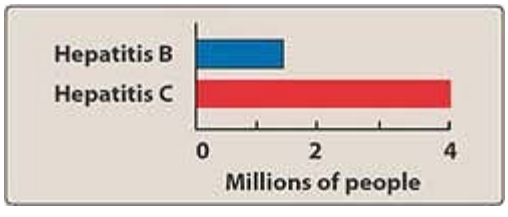
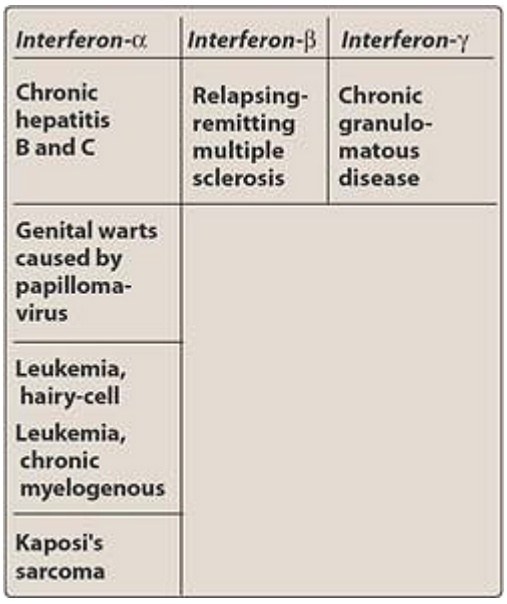


Figure 38.7 The prevalence of chronic hepatitis B and C in the United States.



Interferon-α	*Interferon-β*	*Interferon-γ*
Chronic hepatitis B and C	Relapsing-remitting multiple sclerosis	Chronic granulo-matous disease
Genital warts caused by papilloma-virus		
Leukemia, hairy-cell		
Leukemia, chronic myelogenous		
Kaposi's sarcoma		

Figure 38.8 Some approved indications for *interferon*.

1. **Mode of action:** The antiviral mechanism is incompletely understood. It appears to involve the induction of host cell enzymes that inhibit viral RNA translation, ultimately leading to the degradation of viral mRNA and tRNA.
2. **Pharmacokinetics:** *Interferon* is not active orally, but it may be administered intralesionally, subcutaneously, or intravenously. Very little active compound is found in the plasma, and its presence is not correlated with clinical responses. Cellular uptake and metabolism by the liver and kidney account for the disappearance of *interferon* from the plasma. Negligible renal elimination occurs.
3. **Adverse effects:** Adverse effects include flu-like symptoms on injection, such as fever, chills, myalgias, arthralgias, and gastrointestinal disturbances. Fatigue and mental depression are common. These symptoms subside with subsequent administrations. The principal dose-limiting toxicities are bone marrow suppression including granulocytopenia, neurotoxicity characterized by somnolence and behavioral disturbances, severe fatigue and weight loss, autoimmune

disorders such as thyroiditis, and rarely, cardiovascular problems such as congestive heart failure. Acute hypersensitivity reactions and hepatic failure are rare.

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

B. Lamivudine

This cytosine analog is an inhibitor of both hepatitis B virus (HBV) DNA polymerase and human immunodeficiency virus (HIV) reverse transcriptase. *Lamivudine* [la-MI-vyoo-deen] must be phosphorylated by host cellular enzymes to the triphosphate (active) form. This compound competitively inhibits HBV DNA polymerase at concentrations that have negligible effects on host DNA polymerase. As with many nucleotide analogs, the intracellular half-life of the triphosphate is many hours longer than its plasma half-life, which permits infrequent dosing. Chronic treatment is associated with decreased plasma HBV DNA levels, improved biochemical markers, and reduced hepatic inflammation. *Lamivudine* is well absorbed orally and is widely distributed. Its plasma half-life is about 9 hours.

Seventy percent is excreted unchanged in the urine. Dose reductions are necessary when there is moderate renal insufficiency (creatinine clearance less than 50 mL/min). *Lamivudine* is well tolerated, with rare occurrences of headache and dizziness.

C. Adefovir

Adefovir dipivoxil [ah-DEH-for-veer-die-pih-VOCKS-ill] is a nucleotide analog that is phosphorylated to adefovir diphosphate, which is then incorporated into viral DNA. This leads to termination of further DNA synthesis and prevents viral replication. *Adefovir* is administered once a day and is excreted in the urine, with 45 percent as the active compound. Clearance is influenced by renal function. Both decreased viral load and improved liver function have occurred in patients treated with *adefovir*. As with other agents, discontinuation of *adefovir* results in severe exacerbation of hepatitis in about 25 percent of patients. *Adefovir* does not seem to have significant drug interactions. The drug should be used cautiously in patients with existing renal dysfunction.

D. Entecavir

Entecavir [en-TECK-ah-veer] is a guanosine analog approved for the treatment of HBV infections. Following intracellular phosphorylation to the triphosphate, it competes with the natural substrate, deoxyguanosine triphosphate, for viral reverse transcriptase. *Entecavir* has been shown to be effective against *lamivudine*-resistant strains of HBV. Liver inflammation and scarring are improved. *Entecavir* need only be given once a day. *Entecavir* undergoes both glomerular filtration and tubular secretion. Very little, if any, drug is metabolized. Renal function must be assessed periodically, and drugs that have renal toxicity should be avoided. Patients should be monitored closely for several months after discontinuation of therapy because of the possibility of severe hepatitis.

E. Telbivudine

Telbivudine [tel-BIV-yoo-dine] is a thymidine analog that can be used in the treatment of HBV. Unlike *lamivudine* and *adefovir, telbivudine* is not effective against HIV or other viruses. The drug is phosphorylated intracellularly

to the triphosphate, which can either compete with endogenous thymidine triphosphate for incorporation into DNA or else be incorporated into viral DNA, where it serves to terminate further elongation of the DNA chain. The drug is administered orally, once a day, with or without food. *Telbivudine* is eliminated by glomerular filtration as the unchanged drug, and no metabolites have been detected. The dose must be adjusted in renal failure. Combination of *telbivudine* with *lamivudine* has been no more effective than *telbivudine* alone.

IV. Treatment of Herpesvirus Infections

Herpesviruses are associated with a broad spectrum of diseasesâ€"for example, cold sores, viral encephalitis, and genital infections (the latter being a hazard to the newborn during parturition). The drugs that are effective against these viruses exert their actions during the acute phase of viral infections and are without effect during the latent phase. Except for *foscarnet* and *fomivirsen*, all are purine or pyrimidine analogs that inhibit viral DNA synthesis.

A. Acyclovir

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

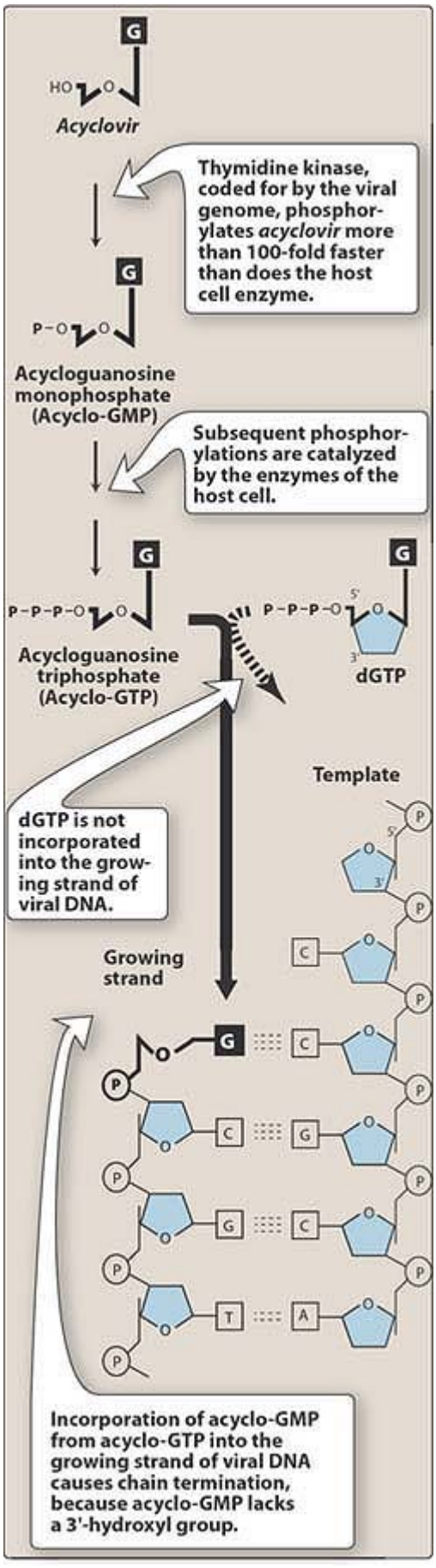

G
HO
O
Acyclovir
Thymidine kinase, coded for by the viral genome, phosphorylates *acyclovir* more than 100-fold faster than does the host cell enzyme.
G
P–O
O
Acycloguanosine monophosphate (Acyclo-GMP)
Subsequent phosphorylations are catalyzed by the enzymes of the host cell.
G
P–P–P–O
O
Acycloguanosine triphosphate (Acyclo-GTP)
G
P–P–P–O
5'
O
3'
dGTP
Template
dGTP is not incorporated into the growing strand of viral DNA.
Growing strand
P
5'
O
3'
C
G
T
A
Incorporation of acyclo-GMP from acyclo-GTP into the growing strand of viral DNA causes chain termination, because acyclo-GMP lacks a 3'-hydroxyl group.

Figure 38.9 Incorporation of *acyclovir* into replicating viral DNA, causing chain termination. dGTP = deoxyguanosine triphosphate

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

2. **Pharmacokinetics:** Administration of *acyclovir* can be by an intravenous, oral, or topical route. [Note: The efficacy of topical applications is doubtful.] The drug distributes well throughout the body, including the cerebrospinal fluid (CSF). *Acyclovir* is partially metabolized to an inactive product. Excretion into the urine occurs both by glomerular filtration and by tubular secretion (Figure 38.10). *Acyclovir* accumulates in patients with renal failure. The valyl ester, *valacyclovir* [val-a-SYE-kloe-veer], has greater oral bioavailability than *acyclovir*. This ester is rapidly hydrolyzed to *acyclovir* and achieves levels of the latter comparable to those from intravenous *acyclovir* administration.

3. **Adverse effects:** Side effects of *acyclovir* treatment depend on the route of administration. For example, local irritation may occur from topical application; headache, diarrhea, nausea, and vomiting may result after oral administration. Transient renal dysfunction may

occur at high doses or in a dehydrated patient receiving the drug intravenously. High-dose *valacyclovir* can cause gastrointestinal problems and thrombotic thrombocytopenia purpura in patients with AIDS.

4. **Resistance:** Altered or deficient thymidine kinase and DNA polymerases have been found in some resistant viral strains and are most commonly isolated from immunocompromised patients. Cross-resistance to the other cyclovirs occurs. [Note: Cytomegalovirus (CMV) is resistant, because it lacks a specific viral thymidine kinase.]

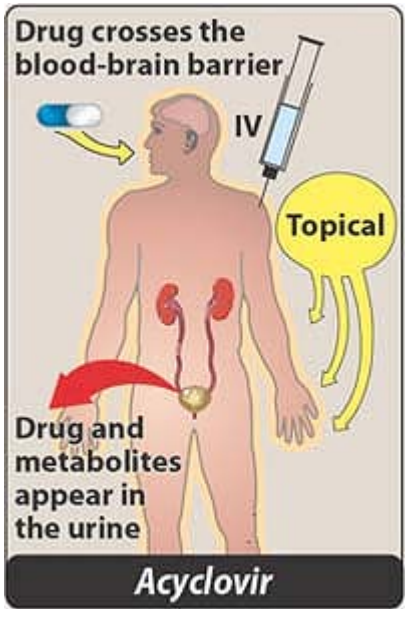


Figure 38.10 Administration and metabolism of *acyclovir*.

B. Cidofovir

Cidofovir [si-DOE-foe-veer] is approved for treatment of CMV-induced retinitis in patients with AIDS. *Cidofovir* is a nucleotide analog of cytosine, the phosphorylation of which is not dependent on viral enzymes. It inhibits viral DNA synthesis. Slow elimination of the active intracellular metabolite permits prolonged dosage intervals and eliminates the permanent venous access used for *ganciclovir* therapy. *Cidofovir* is available for intravenous, intravitreal (injection into the eye's vitreous humor between the lens and the retina), and topical administration. *Cidofovir* produces significant toxicity to the kidney (Figure 38.11), and it is contraindicated in patients with preexisting renal impairment or in those who are taking concurrent nephrotoxic drugs, including nonsteroidal anti-inflammatory drugs. Neutropenia, metabolic acidosis, and ocular hypotony also occur. *Probenecid* must be coadministered with *cidofovir* to reduce the risk of nephrotoxicity, but *probenecid* itself causes rash, headache, fever, and nausea. Since the introduction of HAART (highly active antiretroviral therapy), the prevalence of CMV infections in immunocompromised hosts has markedly declined, and the importance of *cidofovir* in the treatment of these patients has also diminished.

C. Fomivirsen

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

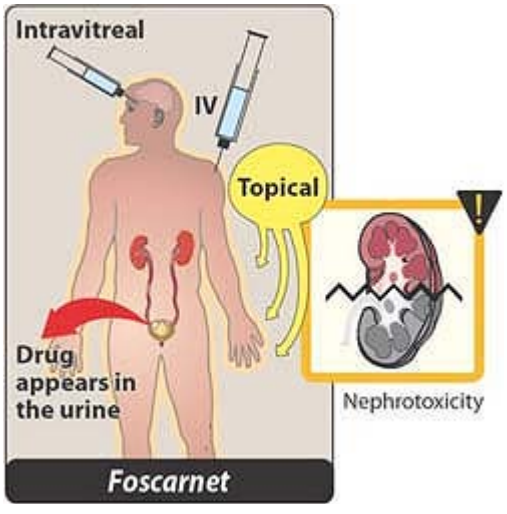


Figure 38.11 Administration, metabolism, and toxicity of *cidofovir*.

D. Foscarnet

Unlike most of the antiviral agents, *foscarnet* [fos-KAR-net] is not a purine or pyrimidine analog. Instead, it is phosphonoformateâ€"a pyrophosphate derivativeâ€"and does not require activation by viral (or human) kinases. *Foscarnet* has broad in vitro antiviral activity. It is approved for CMV retinitis in immunocompromised hosts and for

acyclovir-resistant HSV and herpes zoster infections. *Foscarnet* works by reversibly inhibiting viral DNA and RNA polymerases, thereby interfering with viral DNA and RNA synthesis. Mutation of the polymerase structure is responsible for resistant viruses. [Note: Cross-resistance between *foscarnet* and *ganciclovir* or *acyclovir* is uncommon.] *Foscarnet* is poorly absorbed orally and must be injected intravenously. It must also be given frequently to avoid relapse when plasma levels fall. It is dispersed throughout the body, and greater than 10 percent enters the bone matrix, from which it slowly leaves. The parent drug is eliminated by glomerular filtration and tubular secretion into the urine (Figure 38.12). Adverse effects include nephrotoxicity, anemia, nausea, and fever. Due to chelation with divalent

cations, hypocalcemia and hypomagnesemia are also seen. In addition, hypokalemia, hypo- and hyperphosphatemia, seizures, and arrhythmias have been reported.

E. Ganciclovir

Ganciclovir [gan-SYE-kloe-veer] is an analog of *acyclovir* that has 8- to 20-times greater activity against CMVâ€"the only viral infection for which it is approved. It is currently available for treatment of CMV retinitis in immunocompromised patients and for CMV prophylaxis in transplant patients.

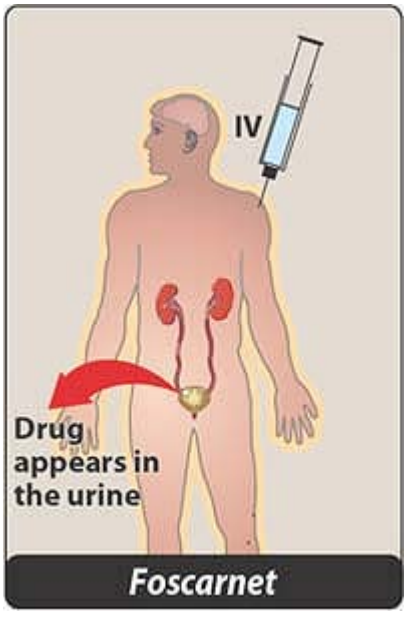


Figure 38.12 Administration and metabolism of *foscarnet*.

1. **Mode of action:** Like *acyclovir, ganciclovir* is activated through conversion to the nucleoside triphosphate by viral and cellular enzymes, with the actual pathway depending on the virus. CMV is deficient in thymidine kinase and, therefore, forms the triphosphate by another route. The nucleotide competitively inhibits viral DNA polymerase and can be incorporated into the DNA, thereby decreasing the rate of chain elongation.

2. **Pharmacokinetics:** *Ganciclovir* is administered intravenously and distributes throughout the body, including the CSF. Excretion into the urine occurs through glomerular filtration and tubular secretion (Figure 38.13). Like *acyclovir, ganciclovir* accumulates in patients with renal failure. *Valganciclovir* [val-gan-SYE-kloe-veer] is the valyl ester of *ganciclovir*. Like *valacyclovir, valganciclovir* has high oral bioavailability, because rapid hydrolysis in the intestine and liver after oral administration leads to high levels of *ganciclovir*.

3. **Adverse effects:** Adverse effects include severe, dose-dependent neutropenia. [Note: Combined treatment

with *zidovudine, azathioprine*, or *mycophenolate mofetil* can result in additive neutropenia.] *Ganciclovir* is carcinogenic as well as embryotoxic and teratogenic in experimental animals.

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

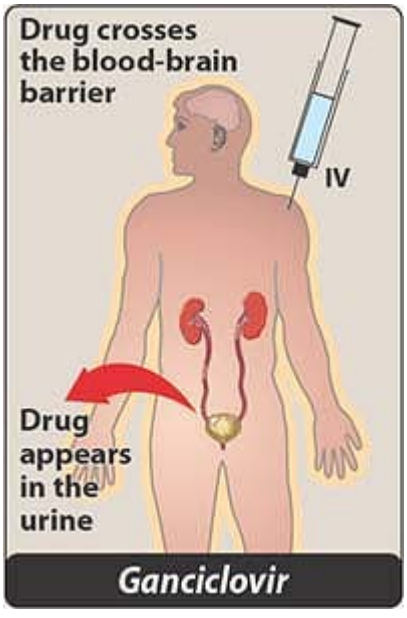


Figure 38.13 Administration and metabolism of *ganciclovir*.

F. Penciclovir and famciclovir

Penciclovir [pen-SYE-kloe-veer] is an acyclic guanosine nucleoside derivative that is active against HSV-I, HSV-2, and VZV. *Penciclovir* is only administered topically (Figure 38.14). It is monophosphorylated by viral thymidine kinase, and cellular enzymes form the nucleoside triphosphate, which inhibits HSV DNA polymerase. Penciclovir triphosphate has an intracellular half-life 20- to 30-fold longer than does acyclovir triphosphate. *Penciclovir* is negligibly absorbed upon topical application and is well tolerated. Both pain and healing are shortened approximately one-half day in duration compared to placebo-treated subjects. *Famciclovir* [fam-SYE-kloe-veer], another acyclic analog of 2'-deoxyguanosine, is a prodrug that is metabolized to the active *penciclovir*. The antiviral spectrum is similar to that of *ganciclovir*, but it is presently approved only for treatment of acute herpes zoster. The drug is effective orally (see Figure 38.14). Adverse effects include headaches and nausea. Studies in experimental animals have shown an increased incidence of mammary adenocarcinomas and testicular toxicity.

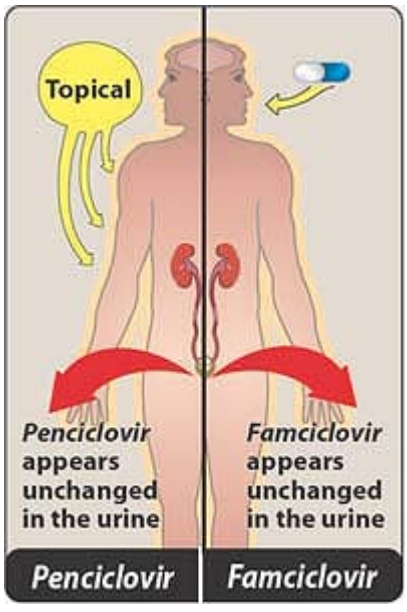


Figure 38.14 Administration and metabolism of penciclovir and *famciclovir*.

G. Vidarabine (ara-A)

Vidarabine [vye-DARE-a-been] (*arabinofuranosyl adenine, ara-A, adenine arabinoside*) is one of the most effective of the nucleoside analogs.

P.445

However, it has been supplanted clinically by *acyclovir*, which is more efficacious and safe. Although *vidarabine* is active against HSV-1, HSV-2, and VZV, its use is limited to treatment of immunocompromised patients with herpetic and vaccinial keratitis and in HSV keratoconjunctivitis. [Note: *Vidarabine* is only available as an ophthalmic ointment.] *Vidarabine*, an adenosine analog, is converted in the cell to its 5'-triphosphate analog (ara-ATP), which is postulated to inhibit viral DNA synthesis. Some resistant HSV mutants have been detected that have altered polymerase.

H. Trifluridine

Trifluridine [trye-FLURE-i-deen] is a fluorinated pyrimidine nucleoside analog. It is structurally very similar to thymidine, the only difference being the replacement of a methyl group on the pyrimidine ring of thymidine with a trifluoromethyl group. Once converted to the triphosphate, the agent is believed to competitively inhibit the incorporation of thymidine triphosphate into viral DNA and, to a lesser extent, to be

P.446

incorporated into viral DNA, leading to the synthesis of a defective DNA that renders the virus unable to reproduce. Trifluridine monophosphate is an irreversible inhibitor of viral thymidine synthase. *Trifluridine* is active against HSV-1, HSV-2, and vaccina virus. It is generally considered to be the drug of choice for treatment of HSV keratoconconjunctivitis and recurrent epithelial keratitis. Because the triphosphate form of trifluridine can also incorporate to some degree into cellular DNA, the drug is considered to be too toxic for systemic use; therefore, the use of *trifluridine* is restricted to topical application as a solution to the eye. A short half-life of approximately 12 minutes necessitates that the drug be applied frequently. Side effects include a transient irritation of the eye and palpebral (eyelid) edema.

Antiviral drug	Mechanism of action	Viruses or diseases affected
Acyclovir	Metabolized to acyclovir triphosphate, which inhibits viral DNA polymerase	Herpes simplex, varicella-zoster, cytomegalovirus
Amantadine	Blockage of the M2 protein ion channel and its ability to modulate intracellular pH	Influenza A
Cidofovir	Inhibition of viral DNA polymerase	Cytomegalovirus; indicated only for virus-induced retinitis
Famciclovir	Same as penciclovir	Herpes simplex, varicella-zoster
Foscarnet	Inhibition of viral DNA polymerase and reverse transcriptase at the pyrophosphate-binding site	Cytomegalovirus, acyclovir-resistant herpes simplex, acyclovir-resistant varicella-zoster
Ganciclovir	Inhibits viral DNA polmerase	Cytomegalovirus
Interferon-α	Induction of cellular enzymes that interfere with viral protein synthesis	Hepatitis B and C, human herpesvirus 8, papilloma virus, Kaposi's sarcoma, hairy-cell leukemia, chronic myelogenous leukemia
Lamivudine	Inhibition of viral DNA polymerase and reverse transcriptase	Hepatitis B (chronic cases), human immunodeficiency virus type 1
Oseltamivir	Inhibition of viral neuramidase	Influenza A
Penciclovir	Metabolized to penciclovir triphosphate, which inhibits viral DNA polymerase	Herpes simplex
Ribavirin	Interference with viral messenger RNA	Lassa fever, hantavirus (hemorrhagic fever renal syndrome), hepatitis C (in chronic cases in combination with *interferon-α* RSV in children and infants
Rimantadine	Blockage of the M2 protein ion channel and its ability to modulate intracellular pH	Influenza A
Valacyclovir	Same as acyclovir	Herpes simplex, varicella-zoster, cytomegalovirus
Vidarabine	inhibits viral DNA synthesis	HSV-1, HSV-2, and VZV; its use is limited to treatment of immunocompromised patients with HSV keratitis
Zanamivir	Inhibition of viral neuramidase	Influenza A

Figure 38.15 Summary of selected antiviral agents.

Figure 38.15 summarizes selected antiviral agents.

V. Overview of the Treatment for HIV Infection

Prior to approval of zidovudine in 1987, treatment of HIV infections focused on decreasing the occurrence of opportunistic infections that caused a high degree of morbidity and mortality in AIDS patients rather than on inhibiting HIV itself. Today, the viral life cycle is understood (Figure 38.16), and a highly active regimen is employed that uses combinations of drugs to suppress replication of HIV and restore the number of CD4+ cells and immunocompetency to the host.[2] This multi drug regimen is commonly referred to as â€œhighly active antiretroviral therapy,â€ or HAART (Figure 38.17). There are five classes of antiretroviral drugs, each of which targets one of four viral processes. These classes of drugs are nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, entry inhibitors and the integrase inhibitors. The current recommendation for primary therapy is to administer two NRTIs with either a protease inhibitor or an NNRTI. Selection of the appropriate combination is based on 1) avoiding the use of two agents of the same nucleoside analog, 2) avoiding overlapping toxicities and genotypic and phenotypic characteristics of the virus, 3) patient factors such as disease symptoms and concurrent illnesses, 4) impact of drug interactions, and 5) ease of adherence to a frequently complex administration regimen. The goals of therapy are to maximally and

durably suppress viral load replication, to restore and preserve immunologic function, to reduce HIV-related morbidity and mortality, and to improve quality of life.

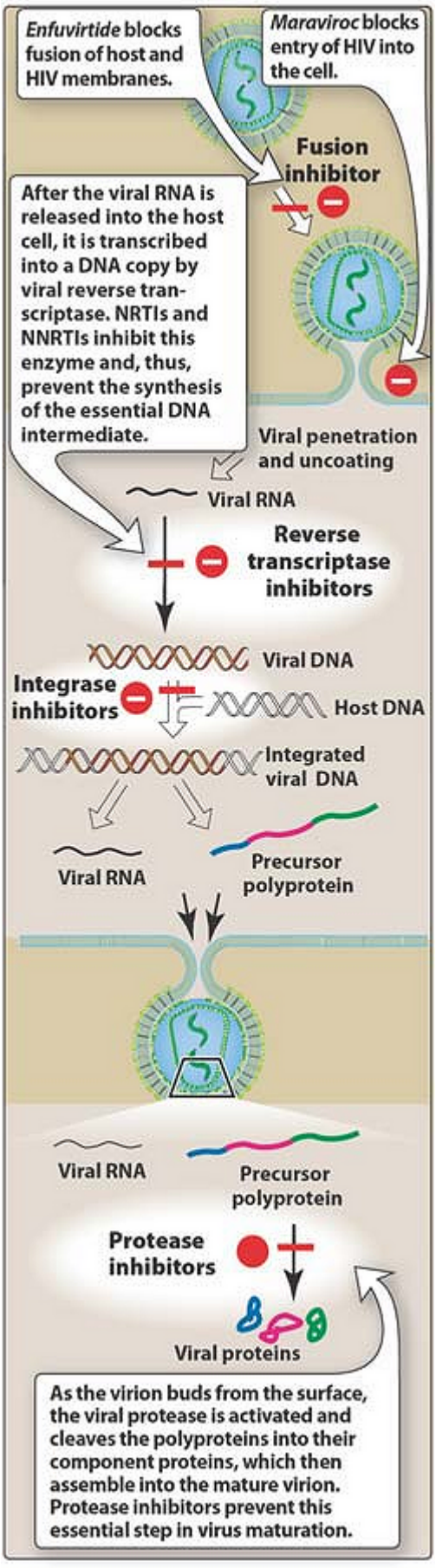

Enfuvirtide blocks fusion of host and HIV membranes.
Maraviroc blocks entry of HIV into the cell.
Fusion inhibitor
After the viral RNA is released into the host cell, it is transcribed into a DNA copy by viral reverse transcriptase. NRTIs and NNRTIs inhibit this enzyme and, thus, prevent the synthesis of the essential DNA intermediate.
Viral penetration and uncoating
Viral RNA
Reverse transcriptase inhibitors
Viral DNA
Integrase inhibitors
Host DNA
Integrated viral DNA
Viral RNA
Precursor polyprotein
Viral RNA
Precursor polyprotein
Protease inhibitors
Viral proteins
As the virion buds from the surface, the viral protease is activated and cleaves the polyproteins into their component proteins, which then assemble into the mature virion. Protease inhibitors prevent this essential step in virus maturation.

Figure 38.16 Drugs used to prevent HIV from replicating. [NRTI = nucleoside and nucleotide reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor.

VI. Nrtis Used to Treat HIV Infection

A. Overview of NRTIs

1. **Mechanism of action:** Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) are analogs of native ribosides (nucleosides or nucleotides containing ribose), which all lack a 3'-hydroxyl group. Once they enter cells, they are phosphorylated by a variety of cellular enzymes to the corresponding triphosphate analog, which is preferentially incorporated into the viral DNA by virus reverse transcriptase. Because the 3'-hydroxyl group is not present, a 3'-5'-phosphodiester bond between an incoming nucleoside triphosphate and the growing DNA chain cannot be formed, and DNA chain elongation

   is terminated. Affinities of the drugs for many host cell DNA polymerases are lower than they are for HIV reverse transcriptase, although mitochondrial DNA polymerase Î³ appears to be susceptible at therapeutic concentrations.

2. **Pharmacokinetics:** The NRTIs are primarily renally excreted, and all require dosage adjustment in renal insufficiency except *abacavir,* which is metabolized by alcohol dehydrogenase and glucuronyl transferase. Dosage adjustment is required when the creatinine clearance drops below 50 mL/min.

3. **Adverse effects**: Many of the toxicities of the NRTIs are believed to be due to inhibition of the mitochondrial DNA polymerase in certain tissues. As a general rule, the dideoxynucleosides, such as *zalcitabine, didanosine*, and *stavudine,* have a greater affinity for the mitochondrial DNA polymerase, leading to such toxicities as peripheral neuropathy, pancreatitis, and lipoatrophy. When more than one NRTI is given, care is taken not to have overlapping toxicities. All the NRTIs have been associated with a potentially fatal liver toxicity characterized by lactic acidosis and hepatomegaly with steatosis.

4. **Drug interactions:** Due to the renal excretion of the NRTIs, there are not many drug interactions encountered with these agents except for *zidovudine* and *tenofovir* (see below).

5. **Resistance:** NRTI resistance is well characterized, and the most common mutation is the mutation at viral codon 184, which confers a high degree of resistance to *lamivudine* but, more importantly, restores sensitivity to zidovudine and tenofovir. Cross-resistance and antagonism occur between agents of the same analog class (thymidine, cytosine, guanosine and adenosine) so concomitant use of agents in the same class is contraindicated (for example, *zidovudine* plus *stavudine*).

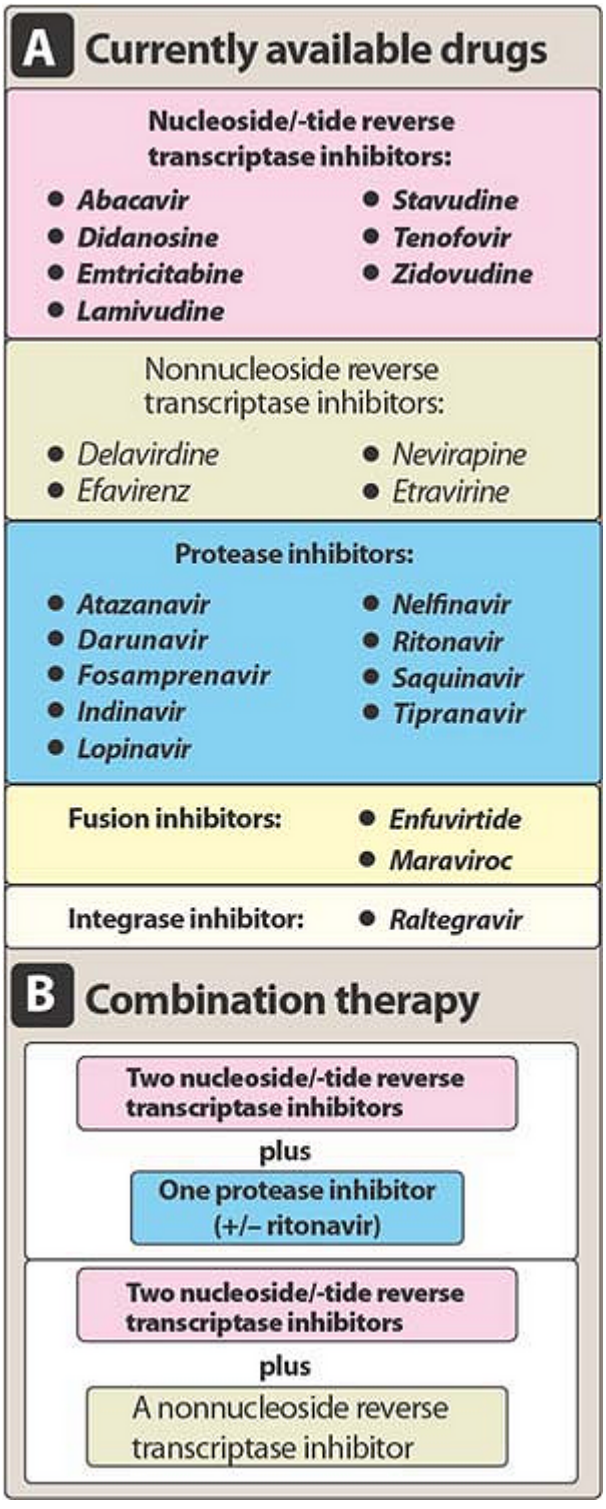


Figure 38.17 Highly active antiretroviral therapy (HAART).

B. Zidovudine (AZT)

Approved in 1987, the first agent available for treatment of HIV infection is the pyrimidine analog, 3'-azido-

3'-deoxythymidine (AZT). AZT has the generic name of zidovudine [zye-DOE-vyoo-deen]. AZT is approved for use in children and adults and to prevent prenatal infection in pregnancy. It is also recommended for prophylaxis in individuals exposed to HIV infection. The drug is well absorbed after oral administration. If taken with food, peak levels may be lower, but the total amount of drug absorbed is not affected. Penetration across the blood-brain barrier is excellent, and the drug has a half-life of 1 hour. The intracellular half-life, however, is approximately 3 hours. Most of the AZT is glucuronylated by the liver and then excreted in the urine (Figure 38.18). In spite of its seeming specificity, AZT is toxic to bone marrow. Headaches are also common. The toxicity of AZT is potentiated if glucuronylation is decreased by coadministration of drugs like probenecid, acetaminophen, lorazepam, indomethacin, and cimetidine. They should be avoided or used with caution in patients receiving AZT. Both stavudine and ribavirin are activated by the same intracellular pathways and should not be given with AZT.

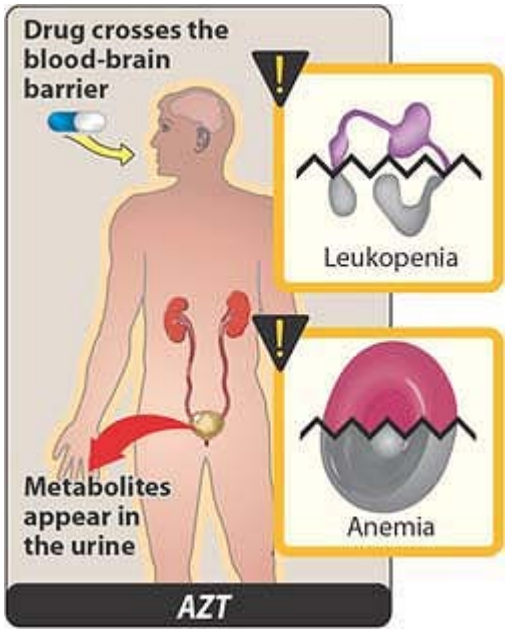


Figure 38.18 Administration, metabolism, and toxicity of *zidovudine (AZT)*.

C. Stavudine (d4T)

Stavudine [STAV-yoo-deen] is an analog of thymidine, in which a double bond joins the 2' and 3' carbons of the sugar. *Stavudine* is a strong inhibitor of cellular enzymes such as the Î² and Î³ DNA polymerases, thus

reducing mitochondrial DNA synthesis, resulting in toxicity. The drug is almost completely absorbed on oral ingestion and is not affected by food. Stavudine penetrates the blood-brain barrier. About half of the parent drug can be accounted for in the urine. Renal impairment interferes with clearance. The major and most common clinical toxicity is peripheral neuropathy along with lipoatrophy and hyperlipidemia.

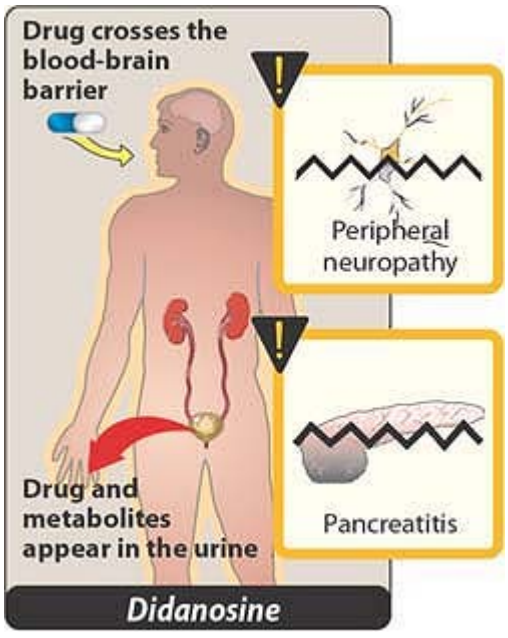


Figure 38.19 Administration, metabolism, and toxicity of *didanosine*.

D. Didanosine (ddI)

The second drug approved to treat HIV-1 infection was didanosine [dye-DAN-oh-seen] (dideoxyinosine, ddI), which is missing both the 2'- and 3'-hydroxyl groups. Upon entry into the host cell, ddI is biotransformed into dideoxyadenosine triphosphate (ddATP) through a series of reactions that involve phosphorylation of the ddI, amination to dideoxyadenosine monophosphate, and further phosphorylation. Like *AZT*, the resulting ddATP is incorporated into the DNA chain, causing termination of chain elongation. Due to its acid lability, absorption is best if *ddI* is taken in the fasting state. The drug penetrates into the CSF, but to a lesser extent than does AZT. About 55 percent of the parent drug appears in the urine (Figure 38.19). Pancreatitis, which may be fatal, is a major toxicity of ddI treatment and requires monitoring of serum amylase. The dose-limiting toxicity of ddI is peripheral neuropathy. Because of its similar adverse effect profile, concurrent use of stavudine is not recommended.

E. Tenofovir (TDF)

Tenofovir [te-NOE-fo-veer] is the first approved drug that is a nucleotide analogâ€”namely, an acyclic nucleoside phosphonate analog of adenosine 5'-monophosphate. It is converted by cellular enzymes to the diphosphate, which is the inhibitor of HIV reverse transcriptase. Cross-resistance with other NRTIs may occur, but some AZT-resistant strains retain susceptibility to tenofovir. Tenofovir should be taken with a meal to increase bioavailability. *Tenofovir* has a long half-life, allowing once-daily dosing. Most of the drug is recovered unchanged in the urine, and elimination is by filtration and active secretion. Serum creatinine must be monitored and doses adjusted in renal insufficiency. Gastrointestinal complaints are frequent and include nausea, diarrhea, and vomiting. (Figure 38.20). *Tenofovir* is the only NRTI with significant drug interactions. *Tenofovir* increases the concentrations of *ddI* to the point that *ddI* dosage reductions are required if the two are given together; however, these two agents are no longer recommended for combined use. *Tenofovir* decreases the concentrations of *atazanavir* such that *atazanavir* must be boosted with *ritonavir* (see p. 452) if given with *tenofovir* to maintain effective *atazanavir* concentrations.

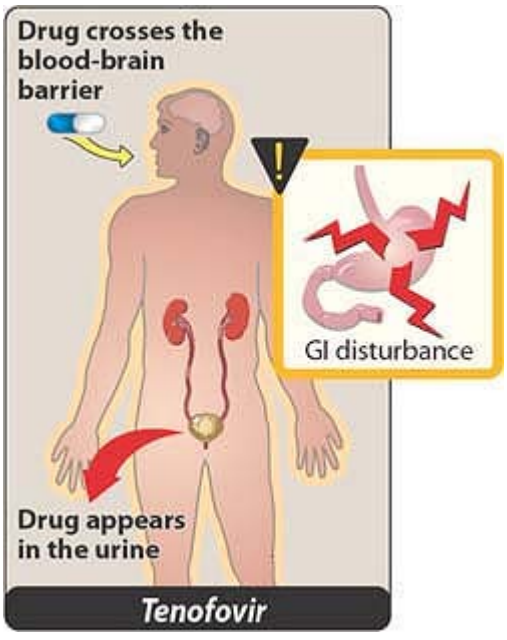


Figure 38.20 Administration, metabolism, and toxicity of *tenofovir*.

F. Lamivudine (3TC)

Lamivudine [la-MI-vyoo-deen] (2'-deoxy-3'-thiacytidine, 3TC) is approved for treatment of HIV in combination with AZT, but it should not be used with other cytosine analogs due to antagonism. *Lamivudine* terminates the synthesis of the proviral DNA chain, and it inhibits the reverse transcriptase of both HIV and HBV. However, it does not affect mitochondrial DNA synthesis or bone marrow precursor cells. It has good bioavailability on oral administration, depends on the kidney for excretion, and is well tolerated.

G. Emtricitabine (FTC)

Emtricitabine [em-tri-SIGH-ta-been], a fluoro-derivative of lamivudine, inhibits both HIV and HBV reverse transcriptase. In a small clinical trial,

it was shown to be at least as effective as lamivudine in the treatment of HIV-infected individuals. Emtricitabine is orally active, with a mean bioavailability of 93 percent. Plasma half-life is about 10 hours, whereas it has a long intracellular half-life of 39 hours. Emtricitabine is eliminated essentially unchanged in the urine. It does not affect cytochrome P450 isozymes, and has no significant interactions with other drugs. Headache, diarrhea, nausea, and rash are its most common adverse effects. Emtricitabine causes hyperpigmentation of the soles and palms, and it has been associated with lactic acidosis, fatty liver, and hepatomegaly. Withdrawal of emtricitabine in HBV-infected patients may result in worsening of the hepatitis.

H. Zalcitabine (ddC)

Zacitabine [zal-SIGH-ta-been], was the first cytosine analog developed; however, due to severe toxicity, it was removed from the market.

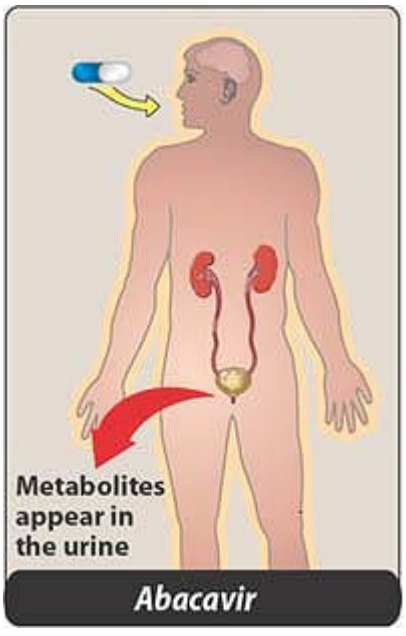


Figure 38.21 Administration and fate of the *abacavir*.

I. Abacavir (ABC)

Abacavir [a-BA-ka-veer] is a guanosine analog. There may be some cross-resistance with strains resistant to AZT and lamivudine. Abacavir is well absorbed orally, and metabolites appear in the urine (Figure 38.21). Most of the drug is metabolized by non-cytochrome P450â€“dependent reactions. A carboxylic acid derivative and a glucuronylated form have been identified. Common side effects include gastrointestinal disturbances, headache, and dizziness. Approximately 5 percent of patients exhibit the â€œhypersensitivity reaction,â€ which is characterized by drug fever, plus one or more of the following symptoms of rash, gastrointestinal symptoms, malaise, and respiratory distress (Figure. 38.22). Sensitized individuals should NEVER be rechallenged because of rapidly appearing, severe reactions that lead to death. There is a newly approved HLA genetic test available to screen patients for the potential of this reaction. Figure 38.23 show some adverse reactions commonly seen with nucleoside analogs.

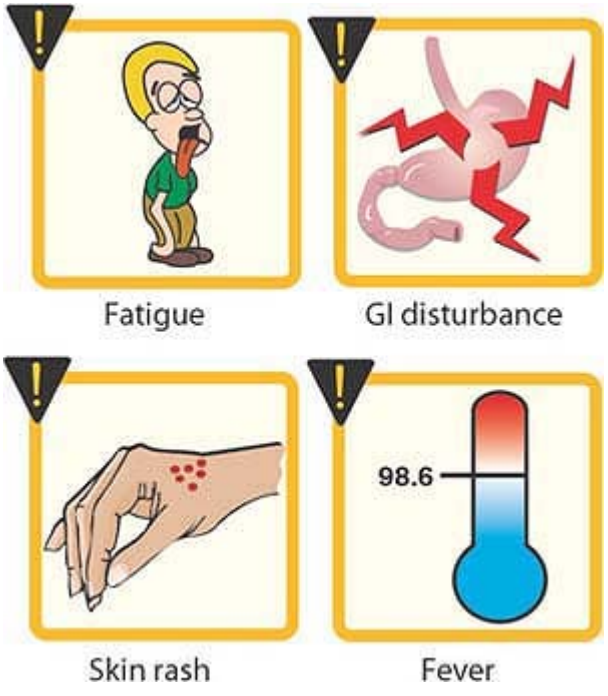


Figure 38.22 Hypersensitivity reactions to *abacavir*.

VII. NNRTIs Used to Treat AIDS

Nonnucleoside reverse transcriptase inhibitors (NNRTIs) are highly selective, noncompetitive inhibitors of HIV-1 reverse transcriptase. They bind to HIV reverse transcriptase at a site adjacent to the active site, inducing a conformational change that results in enzyme inhibition. They do not require activation by cellular enzymes. Their major advantage is their lack of effect on the host blood-forming elements and their lack of cross-resistance with NRTIs. These drugs, however, do have common characteristics that include cross-resistance within the NNRTI class, drug interactions, and a high incidence of hypersensitivity reactions, including rash.

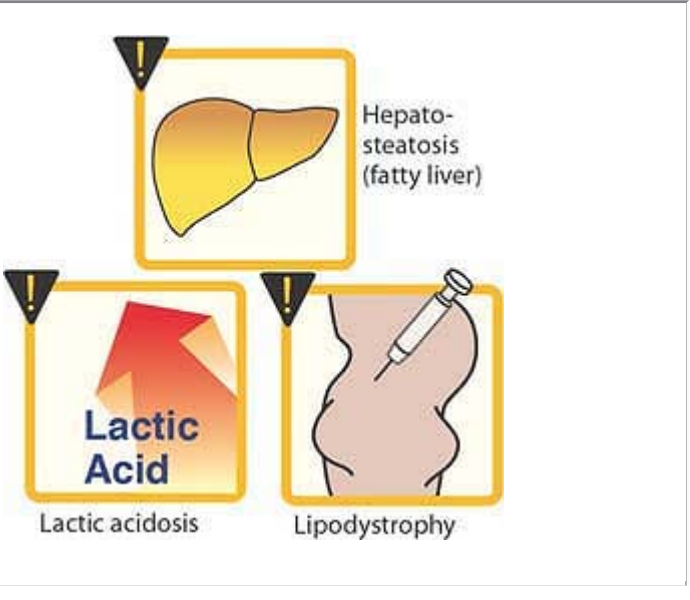


Figure 38.23 Some adverse reactions of nucleoside analogs.

A. Nevirapine (NVP)

Nevirapine [ne-VYE-ra-peen] is used in combination with other antiretroviral drugs for the treatment of HIV-1 infections in adults and children. Due to potential severe hepatotoxicity, *nevirapine* should not be initiated in women with CD4+ T-cell counts of greater than 250 cells/mm^3 or in men with CD4+ T cell counts greater than 400 cells/mm^3. Nevirapine is well absorbed orally, and its absorption is not affected by food and antacids. The lipophilic nature of nevirapine accounts for its entrance into the fetus and mother's milk and for its wide tissue distribution, including the CNS. Nevirapine is dependent upon metabolism for elimination; most of the drug is excreted in the urine as the

glucuronides of hydroxylated metabolites (Figure 38.24). Nevirapine is an inducer of the CYP3A4 family of cytochrome P450 drug-metabolizing enzymes. Nevirapine does increase the metabolism of protease inhibitors, but most combinations do not require dosage adjustment. Nevirapine increases the metabolism of a number of drugs, such as oral contraceptives, ketoconazole, methadone, metronidazole, quinidine, theophylline, and warfarin. The most frequently observed side effects are rash, fever, headache, and elevated serum transaminases and fatal hepatotoxicity. Severe dermatologic effects have been encountered, including Stevens-Johnson syndrome and toxic epidermal necrolysis. A 14-day titration period at half the dose is mandatory to reduce the risk of serious epidermal reactions.

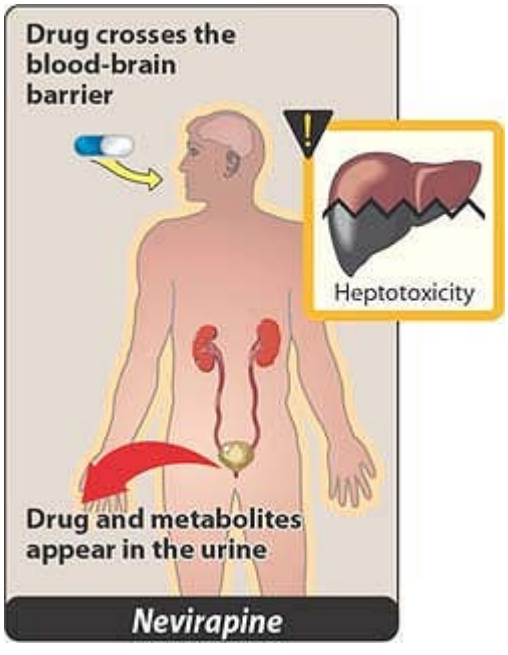


Figure 38.24 Administration, metabolism, and toxicity of *nevirapine*.

B. Delavirdine (DLV)

Delavirdine [de-LA-vir-deen] has not undergone clinical trials as extensive as those of nevirapine and is not recommended as a preferred or alternate agent in the U.S. Department of Health and Human Services (DHHS)

guidelines for initial therapy. Delavirdine is rapidly absorbed after oral administration and is unaffected by the presence of food. Delavirdine is extensively metabolized, and very little is excreted as the parent compound. Fecal and urinary excretion each account for approximately half the elimination. Delavirdine is an inhibitor of cytochrome P450â€“mediated drug metabolism, including that of protease inhibitors. Fluoxetine and ketoconazole increase plasma levels of delavirdine, whereas phenytoin, phenobarbital, and carbamazepine result in substantial decreases in plasma levels of delavirdine. Rash is the most common side effect of delavirdine.

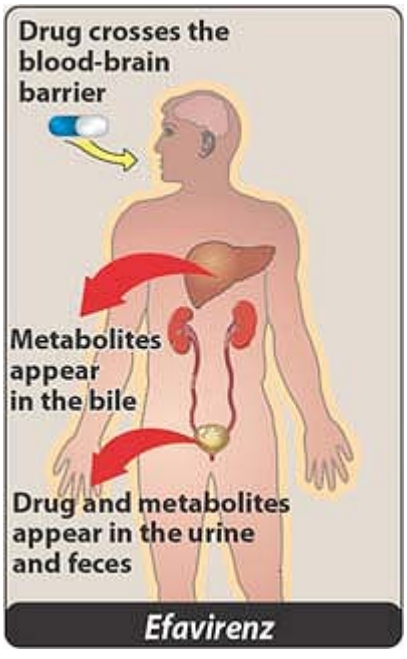


Figure 38.25 Administration and metabolism of *efavirenz*.

C. Efavirenz (EFV)

Efavirenz [e-FA-veer-enz] treatment results in increases in CD4+ cell counts and a decrease in viral load comparable to that achieved by protease inhibitors when used in combination with NRTIs; and therefore, it is the preferred NNRTI on the DHHS guidelines. Following oral administration, efavirenz is well distributed, including to the CNS (Figure 38.25). Bioavailability is enhanced when taken with a high-fat meal. Most of the drug is bound to plasma albumin (99 percent) at therapeutic doses. A half-life of more than 40 hours accounts for its recommended once-a-day dosing. Efavirenz is extensively metabolized to inactive products. Efavirenz is a potent inducer of cytochrome P450 enzymes; therefore, it may reduce the concentrations of drugs that are substrates of the cytochrome P450. Most adverse effects are tolerable and are associated with the CNS, including dizziness, headache, vivid dreams, and loss of concentration (Figure 38.26). Nearly half of the patients experience these complaints, which usually resolve within a few weeks. Rash is the other most common side effect, with an incidence of approximately 25 percent. Severe, life-threatening reactions are rare. *Efavirenz* should be avoided in pregnant women.

See p. 455 for a discussion of the second-generation NNRTI *entravirine*.

VIII. HIV Protease Inhibitors

Inhibitors of HIV protease have significantly altered the course of this devastating viral disease. Within a year of their introduction in 1995, the number of deaths in the United States due to AIDS declined, although the trend

appears to be leveling off (Figure 38.27).

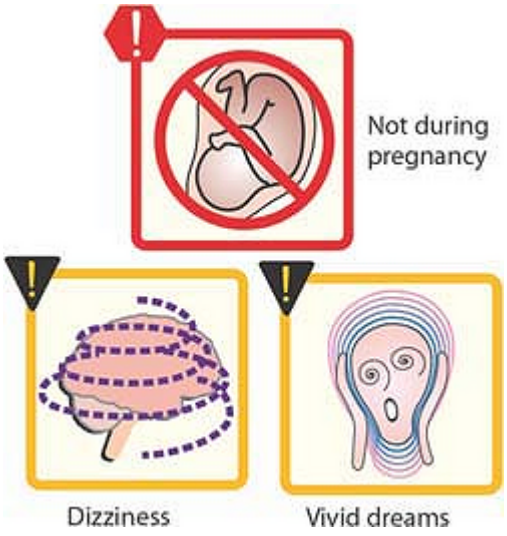


Figure 38.26 Adverse reactions of *efavirenz*.

A. Overview

These potent agents have several common features that characterize their pharmacology.

1. **Mechanism of action:** All the drugs in this group are reversible inhibitors of the HIV aspartyl proteaseâ€"the viral enzyme responsible for cleavage of the viral polyprotein into a number of essential enzymes (reverse transcriptase, protease, and integrase) and several structural proteins. The protease inhibitors exhibit at least a thousand-fold greater affinity for HIV-1 and HIV-2 enzymes than they have for comparable human proteases, such as renin and cathepsin D/E. This accounts for their selective toxicity. The inhibition prevents maturation of the viral particles and results in the production of non-infectious virions. Treatment of antiretrovirally naÃ¯ve patients (that is, patients who have never had HIV therapy) with a protease inhibitor and two NRTIs as recommended by the DHHS guidelines, results in a decrease in the plasma viral load to undetectable levels in 60 to 95 percent of patients. Treatment failures under these conditions are most likely due to a lack of patient adherence.

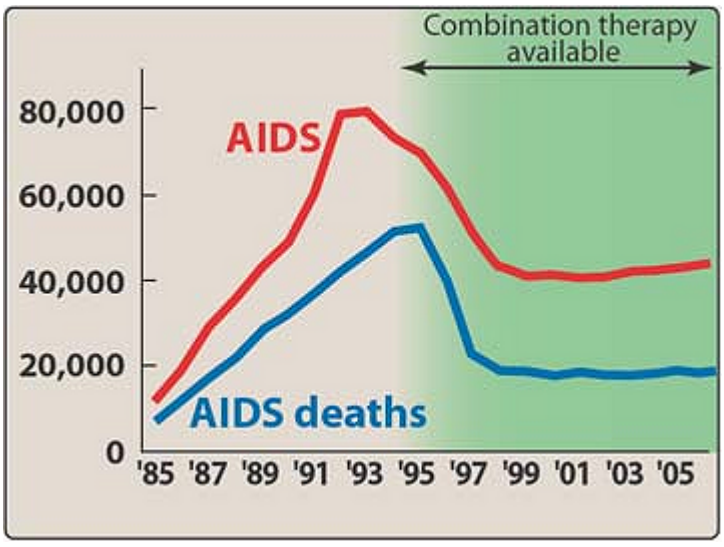


Figure 38.27 Estimated number of AIDS cases and deaths due to AIDS in the United States. Green background indicates years in which combination antiretroviral therapy came into common usage.

2. **Pharmacokinetics:** Most protease inhibitors have poor oral bioavailability. High-fat meals substantially increase the bioavailability of some, such as nelfinavir and saquinavir, whereas the bioavailability of indinavir is decreased and others are essentially unaffected. All are substrates for the CYP3A4 isozyme of cytochrome P450, and individual protease inhibitors are also metabolized by other P450 isozymes. Metabolism is extensive, and very little of the protease inhibitors are excreted unchanged in the urine. Dosage adjustments are unnecessary in renal impairment. Distribution into some tissues may be affected by the fact that the protease inhibitors are substrates for the P-glycoprotein multidrug efflux pump. The presence of this pump in endothelial cells of capillaries in the brain may limit protease inhibitor access to the CNS. The HIV protease inhibitors are all substantially bound to plasma proteins, specifically Î±$_1$-acid glycoprotein. This may be clinically important, because the concentration of Î±$_1$-acid glycoprotein increases in response to trauma and surgery.

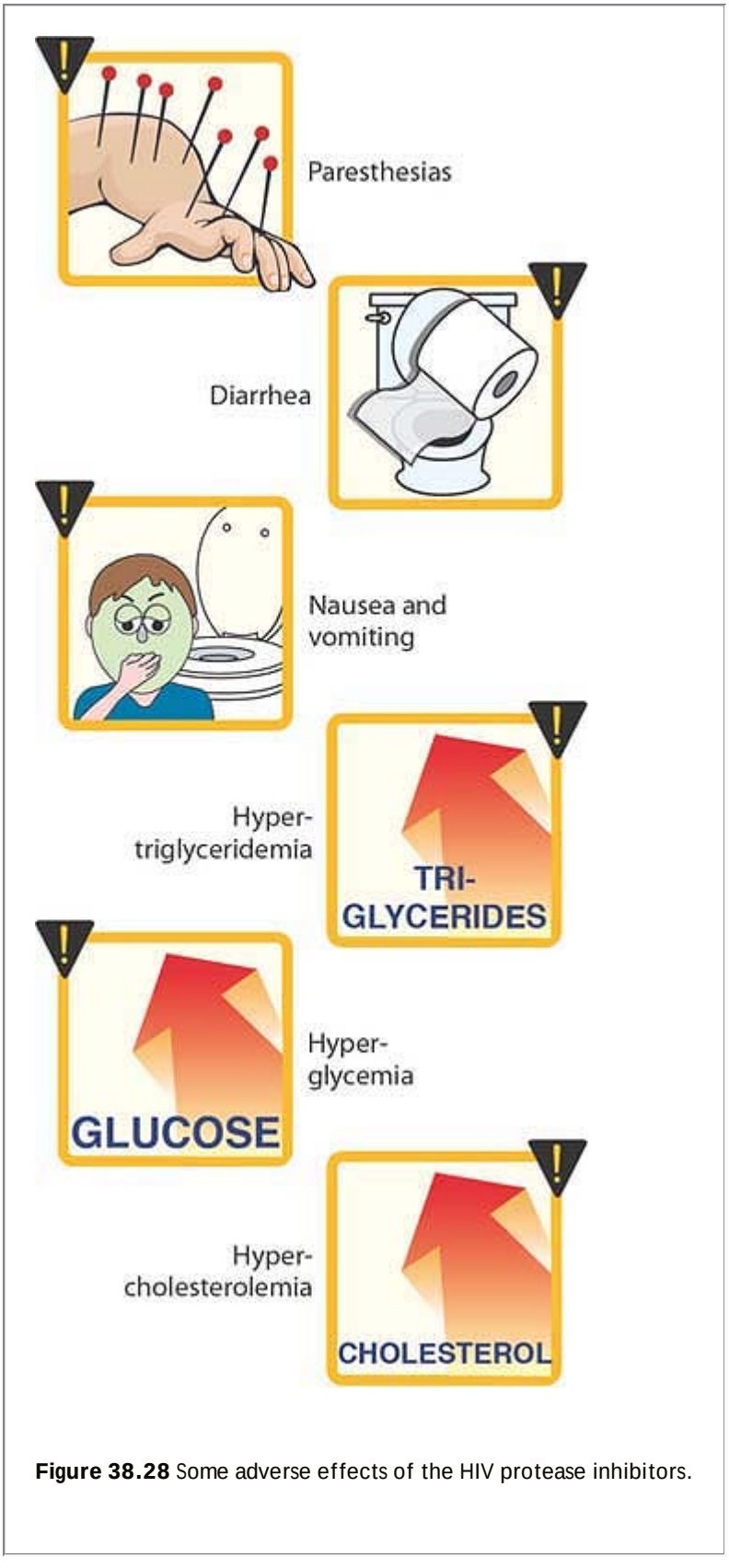


Figure 38.28 Some adverse effects of the HIV protease inhibitors.

3. **Adverse effects:** Protease inhibitors commonly cause parathesias, nausea, vomiting, and diarrhea (Figure 38.28). Disturbances in glucose and lipid metabolism also occur, including diabetes, hypertriglyceridemia, and hypercholesterolemia. Chronic administration results in fat redistribution, including loss of fat from the extremities and its accumulation in the abdomen and the base of the neck (â€œbuffalo humpâ€; Figure 38.29),

and breast enlargement. These physical changes may indicate to others that an individual is HIV positive.

4. **Drug interactions:** Drug interactions are a common problem for all protease inhibitors, because they are not only substrates but also potent inhibitors of CYP isozymes. The inhibitory potency of the compounds lies between that of ritonavir, the most potent, and that of saquinavir, the least potent inhibitor of CYP isozymes. Drug interactions are therefore quite common. Drugs that rely on metabolism for their termination of action may accumulate to toxic levels. Examples of potentially dangerous interactions from drugs that are contraindicated with protease inhibitors include rhabdomyolysis from *simvastatin* or *lovastatin*, excessive sedation from midazolam or

triazolam, and respiratory depression from fentanyl (Figure 38.30). Other drug interactions that require dosage modification and cautious use include *warfarin, sildenafil* and *phenytoin* (Figure 38.31). In addition, inducers of CYP isozymes may result in the lowering of protease plasma concentrations to suboptimal levels, contributing to treatment failures. Thus, drugs such as rifampin and St. John's wort are also contraindicated with protease inhibitors. Meticulous attention must be paid to all these detrimental interactions.

5. **Resistance:** Resistance occurs as an accumulation of stepwise mutations of the protease gene. Initial mutations result in decreased ability of the virus to replicate, but as the mutations accumulate, virions with high levels of resistance to the protease emerge. Suboptimal concentrations result in the more rapid appearance of resistant strains.



Figure 38.29 Accumulation of fat at the base of the neck in a patient receiving a protease inhibitor.

B. Ritonavir (RTV)

Ritonavir [ri-TOE-na-veer] is no longer used as a single protease inhibitor but, instead, is used as a â€œpharmacokinetic enhancer or boosterâ€ of other protease inhibitors. *Ritonavir* is a potent inhibitor of CYP3A, and concomitant ritonavir administration (at low doses) increases the bioavailability of the second protease inhibitor and often allows for longer dosing intervals. The resulting higher Cmin levels of the â€œboosted protease inhibitorsâ€ also help to prevent the development of resistance. Therefore, the â€œboosted protease inhibitorsâ€ are the preferred agents in the DHHS treatment guidelines. Metabolism and biliary excretion are the primary methods of elimination. Ritonavir has a half-life of 3 to 5 hours. Because it is primarily an inhibitor of cytochrome P450 isozymes, numerous drug interactions have been identified. Ritonavir is also a self-inducer of its own metabolism as well as that of some substrates. Nausea, vomiting, diarrhea, headache, and circumoral parethesias are among the more common adverse effects.

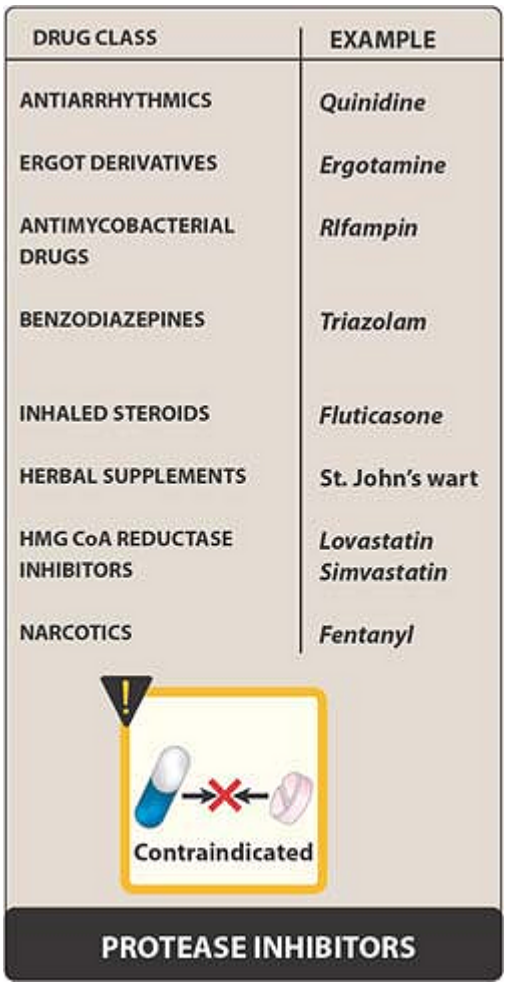


Figure 38.30 Drugs that should not be coadministered with any protease inhibitor.

C. Saquinavir (SQV)

To maximize bioavailability, saquinavir [sa-KWIH-na-veer] is given along with a low dose of ritonavir. High-fat meals also enhance absorption. Elimination of saquinavir is primarily by metabolism, followed by biliary excretion. Its half-life is 7 to 12 hours, requiring multiple daily doses. Drugs that enhance the metabolism of saquinavir, such as rifampin, rifabutin, nevirapine, efavirenz, and other enzyme inducers, should be avoided if possible. The most common adverse effects of saquinavir treatment include headache, fatigue, diarrhea, nausea, and other gastrointestinal disturbances. Increased levels of hepatic aminotransferases have been noted, particularly in patients with concurrent viral hepatitis B or C infections.

D. Indinavir (IDV)

Indinavir [in-DIH-na-veer] is well absorbed orally and, of all the protease inhibitors, is the least protein-bound, at 60 percent. Acidic gastric conditions are necessary for absorption. Absorption is decreased when administered with meals, although a light, low-fat snack is permissible. Ritonavir overcomes this problem and also permits twice-a-day dosing. Metabolism and hepatic clearance account for elimination of indinavir. The dosage should therefore be reduced in the presence of hepatic insufficiency. Indinavir has the shortest half-life of the protease inhibitors, at 1.8 hours. It is well tolerated, with the usual gastrointestinal symptoms and headache predominating. Indinavir

causes nephrolithiasis and hyperbilirubinemia. Adequate hydration is important to reduce the incidence of kidney stone formation, and patients should drink at least 1.5 L of water per day. Fat redistribution is particularly troublesome with this drug.

E. Nelfinavir (NFV)

Nelfinavir [nel-FIN-a-veer] is a non-peptide protease inhibitor. It is well absorbed and does not require strict food or fluid conditions; however, it is usually given with food. Nelfinavir undergoes metabolism by several CYP isozymes. The major metabolite of nelfinavir produced by isozyme CYP2C19 has an antiviral activity equal to that of the parent compound, but it achieves plasma concentrations only 40 percent of those of the parent compound. *Nefinavir* is the only protease inhibitor that cannot be boosted by *ritonavir,* because it is not extensively metabolized by CYP3A. The half-life of nelfinavir is 5 hours. Diarrhea is the most common side effect and can be controlled by loperamide. Like other members of the class, nelfinavir can inhibit the metabolism of other drugs, resulting in required alterations of drug dosage or the prohibition of combined use.

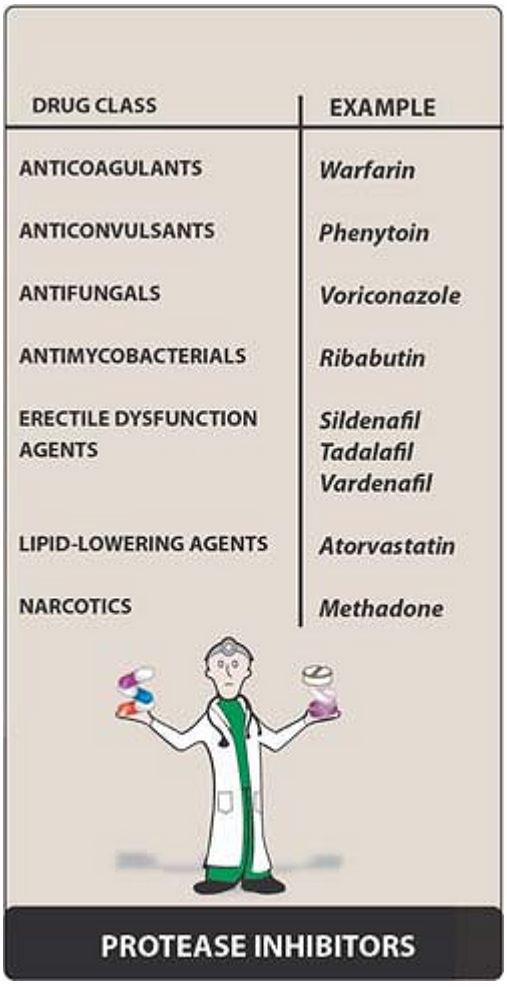


Figure 38.31 Drugs that require dose modifications or cautious use with any protease inhibitor.

F. Fosamprenavir (fAPV)

*Fos*amprenavir [fos-am-PREN-a-veer] is a prodrug that is metabolized to *amprenavir* following oral absorption. Its long plasma half-life permits twice-a-day dosing, and coadministration of ritonavir increases the plasma levels of amprenavir and lowers the total daily dose. *Fosamprenavir* boosted with *ritonavir* is one of the preferred protease inhibitors according to the DHHS treatment guidelines. Nausea, vomiting, diarrhea, fatigue, paresthesias, and headache are common adverse effects. Like other members of the class, fosamprenavir can inhibit the metabolism of other drugs, resulting in required alterations of drug dosage or the prohibition of combined use.

G. Lopinavir (LPVr)

Lopinavir [loe-PIN-a-veer] is a peptidomimetic protease inhibitor. It is one of the preferred protease inhibitors according to the DHHS treatment guidelines. Lopinavir has very poor intrinsic bioavailability, which is substantially enhanced by including a low dose of ritonavir in the formulation. [Note: Only the coformulation known as lopinavir is available in the United States.] Gastrointestinal adverse effects and hypertriglyceridemia are the most common side effects for lopinavir, in addition to the other protease inhibitor class side effects. Like other members of the class, lopinavir can inhibit the metabolism of other drugs, resulting in required alterations of drug dosage or the prohibition of combined use. Enzyme inducers as well as St. John's wort should be avoided, because they lower the plasma concentrations of lopinavir. The oral solution contains alcohol; thus, disulfiram or metronidazole administration can cause unpleasant reactions.

H. Atazanavir (ATV)

Atazanavir [ah-ta-ZA-na-veer] inhibits HIV protease and is structurally unrelated to other HIV protease inhibitors. *Atazanavir* in combination with *ritonavir* are the only once-daily preferred protease inhibitors. Atazanavir is well absorbed orally. Food increases absorption and bioavailability. The drug is highly protein bound (86 percent) and undergoes extensive CYP3A4-catalyzed biotransformation. It is excreted primarily in the bile. Its half-life is about 7 hours, but it only needs to be administered once a day. Atazanavir is a competitive inhibitor of

glucuronyl transferase, and benign hyperbilirubinemia and jaundice are known side effects. In the heart, *atazanavir* prolongs the PR interval and slows the heart rate. *Atazanavir* exhibits a decreased risk of hyperlipidemia, but it is not known if atazanavir is less likely to cause insulin resistance and lipodystrophy, as seen with other protease inhibitors. Like the other protease inhibitors, atazanavir is a potent inhibitor of CYP3A4 and has the potential for many drug interactions. *Atazanavir* is contraindicated with use of prescription doeses of proton-pump inhibitors, and administration must be spaced 12 hours apart from H_2-blockers and antacids.

I. Tipranavir (TPV)

Tipranavir [ti-PRA-na-veer] inhibits HIV protease in viruses that are resistant to the other protease inhibitors. *Tipranavir* is well absorbed when taken with food. The half-life is 6 hours, and it must be administered twice daily in combination with *ritonavir*. *Tipranvir* has a unique action as a *cytochrome P*450 inducer in addition to a substrate that is different from the other protease inhibitors. Side effects are similar to those of the other protease inhibitors with the exception of two â€œblack boxâ€ warnings for severe and fatal hepatitis and rare cases of fatal and nonfatal intracranial hemorrhages. Most patients had underlying comorbidities. *Tipranavir* is useful in â€œsalvageâ€ regimens in patients with multidrug resistance.

J. Darunavir (DRV)

Darunavir [da-RU-na-veer] is the most recently approved protease inhibitor and is also active against HIV protease that is resistant to other protease inhibitors. *Darunavir* is well absorbed when given with food, and the terminal elimination half-life is 15 hours when combined with *ritonavir*. *Darunavir* is extensively metabolized by the CYP3A enzymes and is an inhibitor as well. The side effects are similar to those of the other protease inhibitors with the addition of possible rash. Early reports demonstrate a decreased risk of hyperlipidemia, but it is not known if darunavir is less likely to cause insulin resistance and lipodystrophy, as seen with other protease inhibitors. *Darunavir* is useful in â€œsalvageâ€ regimens in patients with multidrug resistance, and studies are underway in naÃ¯ve patients.

A summary of protease inhibitors is presented in Figure 38.32

IX. Entry Inhibitors

A. Enfuvirtide

Enfuvirtide [en-FU-veer-tide] is the first of new class of antiretroviral drugs known as entry inhibitors. *Enfuvirtide* is a fusion inhibitor. For HIV to gain entry into the host cell, it must fuse its membrane with that of the host cell. This is accomplished by changes in the conformation of the viral transmembrane glycoprotein gp41, which occurs when HIV binds to the host cell surface. Enfuvirtide is a 36-amino-acid peptide that binds to gp41, preventing the conformational change. Enfuvirtide, in combination with other antiretrovirals, is approved for therapy of treatment-experienced patients with evidence of viral replication despite ongoing antiretroviral drug therapy. As a peptide, it must be given subcutaneously. Most of the adverse effects are related to the injection, including

pain, erythema, induration, and nodules, which occur in almost all patients. However, only 3 percent discontinue treatment because of them. Enfuvirtide must be reconstituted prior to administration. It is an expensive medication.

B. Maraviroc

Maraviroc [ma-RA-vi-roc] is the second entry inhibitor. Because it is well absorbed orally, it is formulated as an oral tablet. *Maraviroc* blocks the CCR5 coreceptor that works together with gp41 to facilitate HIV entry through the membrane into the cell. HIV may express either the CCR5 coreceptor or the CXCR4 coreceptor, or both. A test to determine tropism is required to distinguish the CCR5 from the CXCR4 coreceptor as well as mixed and dual tropic virus. Only the CCR5-expressing virus can be treated with *maraviroc*. *Maraviroc* is metabolized by cytochromeP450 liver enzymes, and the dose must be reduced when given with the protease inhibitors. *Maraviroc* is generally well tolerated.

DRUGS	MAJOR TOXICITIES AND CONCERNS
Atazanavir	Nausea, abdominal discomfort, headache, skin rash
Darunavir	Nausea, abdominal discomfort, headache, skin rash
Fosamprenavir	Nausea, diarrhea, vomiting, oral and perioral paresthesia, and rash
Indinavir	Benign hyperbilirubinemia, nephrolithiasis; take 1 hour before or 2 hours after food; may take with skim milk or a low-fat meal; drink >1.5 L of liquid daily
Lopinavir	Gastrointestinal, hyper-lipidemia, insulin resistance
Nelfinavir	Diarrhea, nausea, flatulence, rash
Ritonavir	Diarrhea, nausea, taste perversion, vomiting, anemia, increased hepatic enzymes, increased triglycerides. Requires refrigeration; take with meals; chocolate milk improves the taste
Saquinavir	Diarrhea, nausea, abdominal discomfort, elevated trans-aminase levels. Take with high-fat meal or within 2 hours of a full meal
Tipranavir	Nausea, vomiting,diarrhea, rash, severe hepatotoxicity, intracranial hemorrhage

Figure 38.32 Summary of protease inhibitors. [Note: *Lopinavir* is co formulated with *ritonavir; ritonavir* inhibits the metabolism of *lopinavir*, thereby increasing its level in the plasma.]

X. Integrase Inhibitors

A. Raltegravir (RAL)

Raltegravir [ral TEG ra veer] is the first of new class of antiretroviral drugs known as integrase inhibitors. *Ragtegravir* specifically inhibits the final step in integration of stand transfer of the viral DNA into our own host cell DNA. *Raltegravir* has a half-life of approximately 9 hours and is therefore dosed twice daily. The route of

metabolism is UGT1A1-mediated glucuronidation, therefore drug interactions with CYP450 inducers, inhibitors or substrates do not occur. *Raltegravir* is well-tolerated with nausea, headache and diarrhea as the most common side effects. Raltegravir, in combination with other antiretrovirals, is approved for therapy of treatment-experienced patients with evidence of viral replication despite ongoing antiretroviral drug therapy.

Note added in proof: *Etravirine* [et-ra-VYE-rine] is the first second generation NNRTI. It is active against many of the strains of HIV that are resistant to the first generation NNRTI. HIV strains with the commonn K103N resistance mutation to the first generation of NNRTI's are fully susceptible to *entravirine*. Following oral administration, *etravirine* is well distributed and bioavailability is enhance when taken with a high-fat meal. Although it has a half-life of approximately 40 hours, it is indicated for twice daily dosing. *Etravirine* is extensively metabolized to inactive products. *Etravirine* is a potent inducer of cytochrome P450; therefore, the doses of cytochrome P450 substrates may need to be increased when given with *etravirine*. Rash is the most common side effect. *Etravirine* is otherwsie well tolerated and does not have the CNS side effects that are seen with *efavirenz* and *etravirine* is pregnany category B. *Etravirine* is indicaated for HIV treatment-experienced, multi-drug resistant adult patients who have evidence of ongoing viral replication.

Study Questions

Choose the ONE best answer.

38.1 A 30-year-old male patient with an HIV infection is being treated with a HAART regimen. Four weeks after initiating therapy, he comes to the emergency department complaining of fever, rash, and grastointestinal upset. Which one of the following drugs is most likely the cause of his symptoms?

A. Zidovudine.

B. Nelfinavir.

C. Abacavir.

D. Efavirenz.

E. Darunavir.

View Answer

38.2 Chills, fever, and muscle aches are common reactions to which one of the following antiviral drugs?

A. Acyclovir.

B. Ganciclovir.

C. Oseltamivir.

D. Interferon.

E. Ribavirin

View Answer

38.3 An HIV-positive woman is diagnosed with CMV retinitis. She has been on a HAART regimen containing zidovudine. Which of the following anti-CMV drugs is likely to cause additive myelosuppression with zidovudine?

A. Acyclovir.

B. Ganciclovir.

C. Amantadine.

D. Foscarnet.

E. Ribavirin.

View Answer

38.4 A 25-year-old man is diagnosed with HIV, and therapy is initiated. After the first week of therapy, the patient complains of headaches, irritability, and nightmares. Which one of the following antiretroviral drugs is most likely to be causing these symptoms?

A. Efavirenz.

B. Indinavir.

C. Lamivudine.

D. Nevirapine.

E. Stavudine.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Copyright Â©2009 Lippincott Williams & Wilkins

Chapter 39

Anticancer Drugs

I. Overview

It is estimated that 25 percent of the population of the United States will face a diagnosis of cancer during their lifetime, with 1.3 million new cancer patients diagnosed each year. Less than a quarter of these patients will be cured solely by surgery and/or local radiation. Most of the remainder will receive systemic chemotherapy at some time during their illness. In a small fraction (approximately 10 percent) of patients with cancer representing selected neoplasms, the chemotherapy will result in a cure or a prolonged remission. However, in most cases, the drug therapy will produce only a regression of the disease, and complications and/or relapse may eventually lead to death. Thus, the overall 5-year survival rate for cancer patients is about 65 percent, ranking cancer second only to cardiovascular disease as a cause of mortality. (See Figure 39.1 for a list of the anticancer agents discussed in this chapter.)

II. Principles of Cancer Chemotherapy

Cancer chemotherapy strives to cause a lethal cytotoxic event or apoptosis in the cancer cell that can arrest a tumor's progression. The attack is generally directed toward DNA or against metabolic sites essential to cell replicationâ€”for example, the availability of purines and pyrimidines that are the building blocks for DNA or RNA synthesis (Figure 39.2). Ideally, these anticancer drugs should interfere only with cellular processes that are unique to malignant cells. Unfortunately, most currently available anticancer drugs do not specifically recognize neoplastic cells but, rather, affect all kinds of proliferating cellsâ€”both normal and abnormal. Therefore, almost all antitumor agents have a steep dose-response curve for both toxic and therapeutic effects.

A. Treatment strategies

1. **Goal of treatment:** The ultimate goal of chemotherapy is a cure (that is, long-term, disease-free survival). A true cure requires the eradication of every neoplastic cell. If a cure is not attainable, then the goal becomes control of the disease (stop the cancer from enlarging and spreading) to extend survival and maintain the best quality of life. This allows the individual to maintain a â€œnormalâ€ existence, with the cancer thus being treated as a chronic disease. In either case, the neoplastic cell burden is initially reduced (debulked), either by surgery and/or by radiation, followed by chemotherapy, immunotherapy, or a combination of these treatment

modalities (Figure 39.3). In advanced stages of cancer, the likelihood of controlling the cancer is far from reality and the goal is palliation (that is, alleviation of symptoms and avoidance of life-threatening toxicity). This means that chemotherapeutic drugs may be used to relieve symptoms caused by the cancer and improve the quality of life, even though the drugs may not lengthen life.

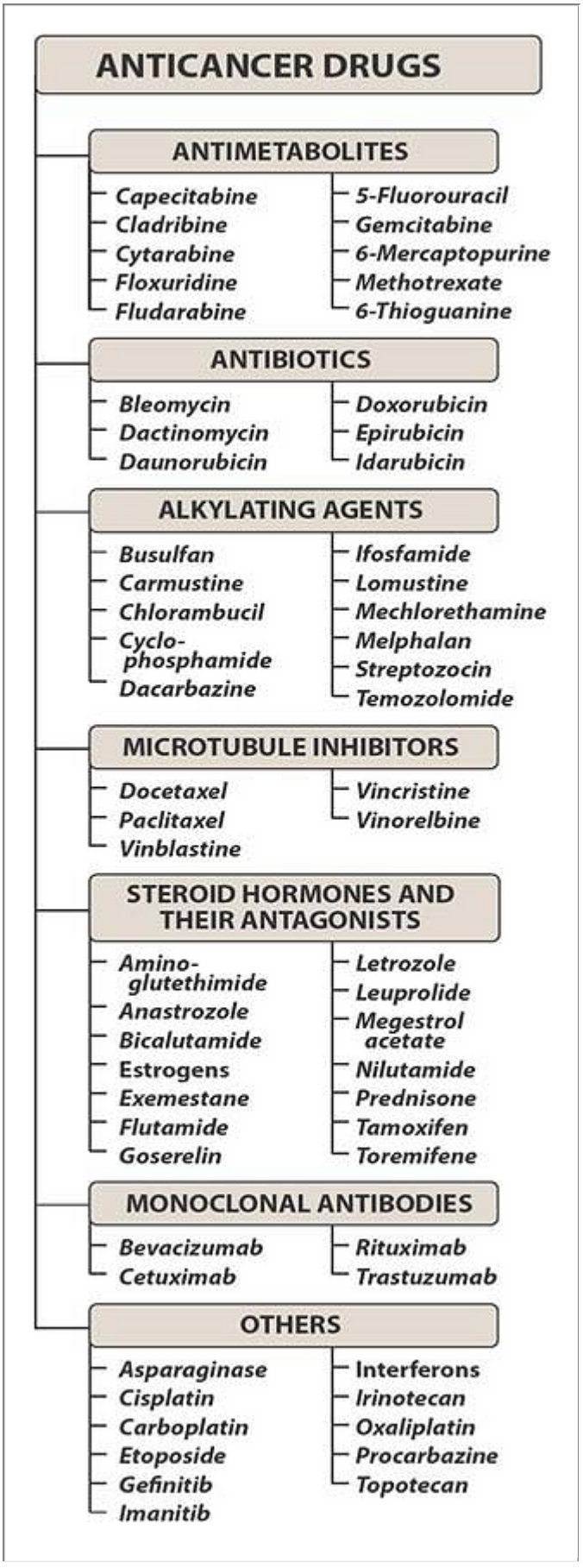

ANTICANCER DRUGS
ANTIMETABOLITES
Capecitabine
Cladribine
Cytarabine
Floxuridine
Fludarabine
5-Fluorouracil
Gemcitabine
6-Mercaptopurine
Methotrexate
6-Thioguanine
ANTIBIOTICS
Bleomycin
Dactinomycin
Daunorubicin
Doxorubicin
Epirubicin
Idarubicin
ALKYLATING AGENTS
Busulfan
Carmustine
Chlorambucil
Cyclo-phosphamide
Dacarbazine
Ifosfamide
Lomustine
Mechlorethamine
Melphalan
Streptozocin
Temozolomide
MICROTUBULE INHIBITORS
Docetaxel
Paclitaxel
Vinblastine
Vincristine
Vinorelbine
STEROID HORMONES AND THEIR ANTAGONISTS
Amino-glutethimide
Anastrozole
Bicalutamide
Estrogens
Exemestane
Flutamide
Goserelin
Letrozole
Leuprolide
Megestrol acetate
Nilutamide
Prednisone
Tamoxifen
Toremifene
MONOCLONAL ANTIBODIES
Bevacizumab
Cetuximab
Rituximab
Trastuzumab
OTHERS
Asparaginase
Cisplatin
Carboplatin
Etoposide
Gefinitib
Imanitib
Interferons
Irinotecan
Oxaliplatin
Procarbazine
Topotecan

Figure 39.1 Summary of chemotherapeutic agents.

2. **Indications for treatment:** Chemotherapy is indicated when neoplasms are disseminated and are not amenable to surgery. Chemotherapy is also used as a supplemental treatment, to attack micrometastases following surgery and radiation treatment in which case it is called adjuvant chemotherapy. Chemotherapy given prior to the surgical procedure in an attempt to shrink the cancer is referred as neoadjuvant chemotherapy, and chemotherapy given in lower doses to assist in prolonging a remission is known as maintenance chemotherapy.

3. **Tumor susceptibility and the growth cycle:** The fraction of tumor cells that are in the replicative cycle (â€œgrowth fractionâ€) influences their susceptibility to most cancer chemotherapeutic agents. Rapidly dividing cells are generally more sensitive to anticancer drugs, whereas slowly proliferating cells are less sensitive to chemotherapy. In general, nonproliferating cells (those in the G_0 phase; Figure 39.4) usually survive the toxic effects of many of these agents.

    a. **Cell-cycle specificity of drugs:** Both normal cells and tumor cells go through growth cycles (see Figure 39.4). However, the number of cells that are in various stages of the cycle may differ in normal and neoplastic tissues. Chemotherapeutic agents that are effective only against replicating cellsâ€”that is, those cells that are cyclingâ€”are said to be cell-cycle specific (see Figure 39.4), whereas other agents are said to be cell-cycle nonspecific. The nonspecific drugs, although having generally more toxicity in cycling cells, are also useful against tumors that have a low percentage of replicating cells.

    b. **Tumor growth rate:** The growth rate of most solid tumors in vivo is initially rapid, but growth rate usually decreases as the tumor size increases (see Figure 39.3). This is due to the unavailability of nutrients and oxygen caused by inadequate vascularization and lack of blood circulation. Reducing the tumor burden through surgery or radiation often promotes the recruitment of the remaining cells into active proliferation and increases their susceptibility to chemotherapeutic agents.

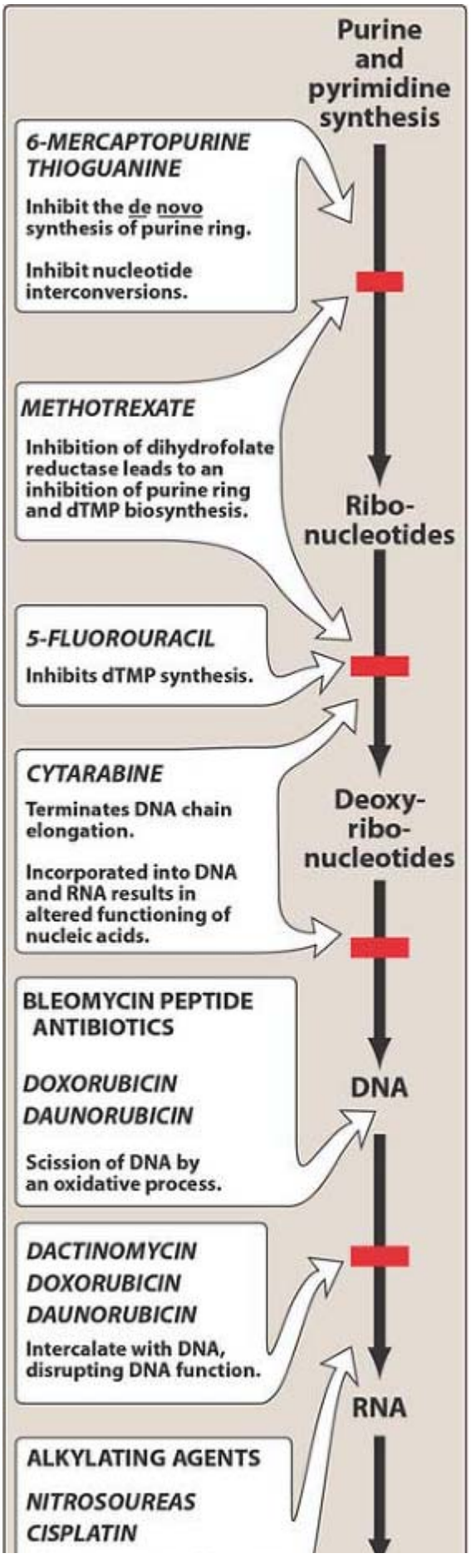

Purine and pyrimidine synthesis
6-MERCAPTOPURINE
THIOGUANINE
Inhibit the de novo synthesis of purine ring.
Inhibit nucleotide interconversions.
METHOTREXATE
Inhibition of dihydrofolate reductase leads to an inhibition of purine ring and dTMP biosynthesis.
Ribo-nucleotides
5-FLUOROURACIL
Inhibits dTMP synthesis.
CYTARABINE
Terminates DNA chain elongation.
Incorporated into DNA and RNA results in altered functioning of nucleic acids.
Deoxy-ribo-nucleotides
BLEOMYCIN PEPTIDE ANTIBIOTICS
DOXORUBICIN
DAUNORUBICIN
Scission of DNA by an oxidative process.
DNA
DACTINOMYCIN
DOXORUBICIN
DAUNORUBICIN
Intercalate with DNA, disrupting DNA function.
RNA
ALKYLATING AGENTS
NITROSOUREAS
CISPLATIN

Figure 39.2 Examples of chemotherapeutic agents affecting the availability of RNA and DNA precursors. dTMP = deoxythymidine monophosphate.

B. Treatment regimens and scheduling

Drugs are usually administered on the basis of body surface area, with an effort being made to tailor the medications to each patient.

1. **Log kill:** Destruction of cancer cells by chemotherapeutic agents follows first-order kinetics; that is, a given dose of drug destroys a constant fraction of cells. The term log kill is used to describe this phenomenon. For example, a diagnosis of leukemia is generally made when there are about 10^9 (total) leukemic cells. Consequently, if treatment leads to a 99.999-percent kill, then 0.001 percent of 10^9 cells (or 10^4 cells) would remain. This is defined as a five-log kill (reduction of 10^5 cells). At this point, the patient will become asymptomatic;

that is, the patient is in remission (see Figure 39.3). For most bacterial infections, a five-log (100,000-fold) reduction in the number of microorganisms results in a cure, because the immune system can destroy the remaining bacterial cells. However, tumor cells are not as readily eliminated, and additional treatment is required to totally eradicate the leukemic cell population.

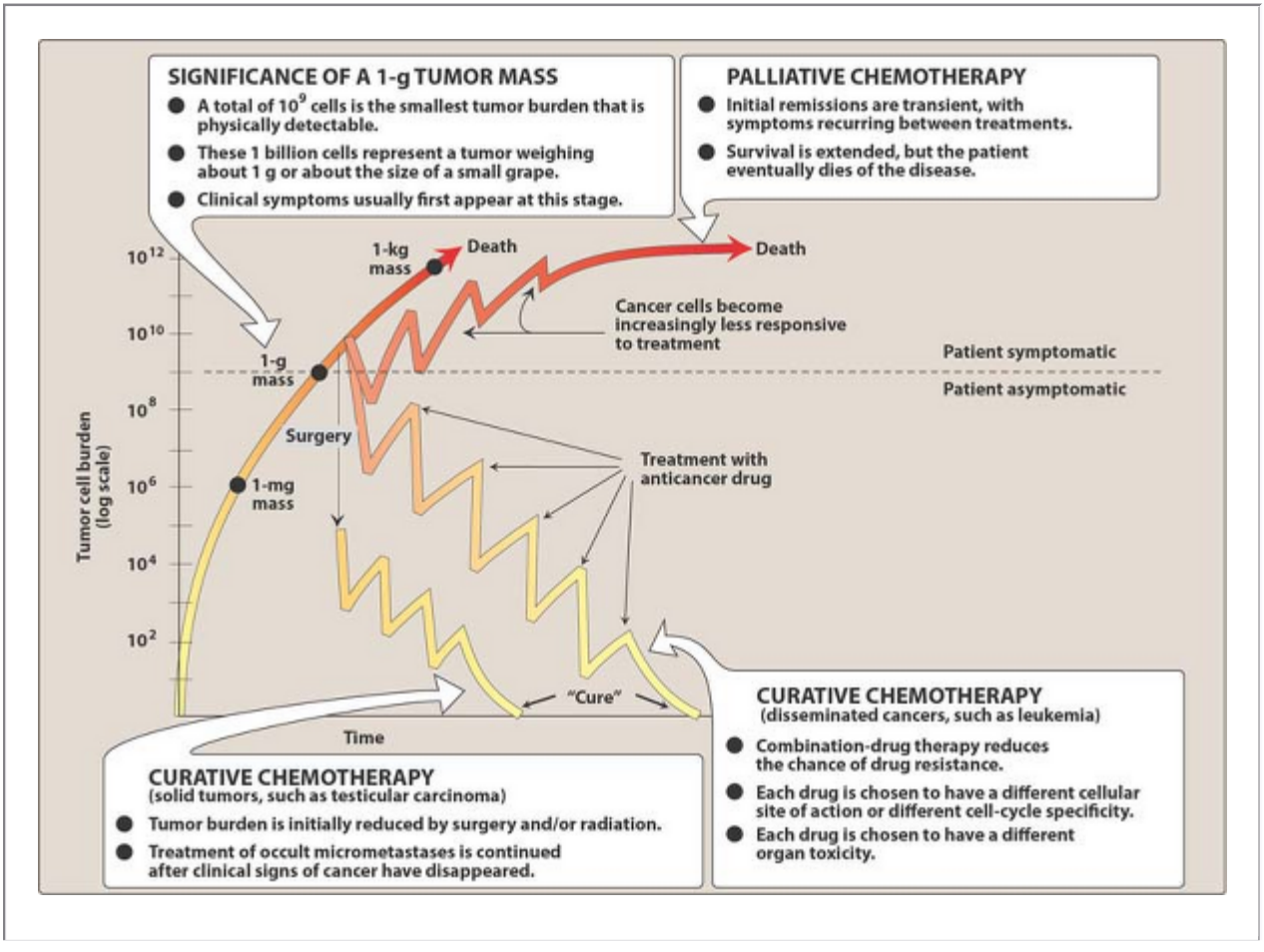


Figure 39.3 Effects of various treatments on the cancer cell burden in a hypothetical patient.

2. **Pharmacologic sanctuaries:** Leukemic or other tumor cells find sanctuary in tissues such as the central nervous system (CNS), where transport constraints prevent certain chemotherapeutic agents from entering. Therefore, a patient may require irradiation of the craniospinal axis or intrathecal administration of drugs to eliminate the leukemic cells at that site. Similarly, drugs may be unable to penetrate certain areas of solid tumors.

3. **Treatment protocols:** Combination-drug chemotherapy is more successful than single-drug treatment in most of the cancers for which chemotherapy is effective.

    a. **Combinations of drugs:** Cytotoxic agents with qualitatively different toxicities, and with different molecular sites and mechanisms of action, are usually combined at full doses.

    This results in higher response rates, due to additive and/or potentiated cytotoxic effects, and nonoverlapping host toxicities. In contrast, agents with similar dose-limiting toxicities, such as myelosuppression, nephrotoxicity, or cardiotoxicity can be combined safely only by reducing the doses of each.

    b. **Advantages of drug combinations**: The advantages of such drug combinations are that they 1) provide maximal cell killing within the range of tolerated toxicity, 2) are effective against a broader range of cell lines in the heterogeneous tumor population, and 3) may delay or prevent the development of resistant cell lines.

    c. **Treatment protocols:** Many cancer treatment protocols have been developed, and each one is applicable to a particular neoplastic state. They are usually identified by an acronym; for example, a common regimen called POMPâ€"used for the treatment of acute lymphocytic leukemiaâ€"consists of p*rednisone*, o*ncovin* (*vincristine*), m*ethotrexate*, and p*urinethol* (*mercaptopurine*). Therapy is scheduled intermittently (approximately 21 days apart) to allow recovery of the patient's immune system, which is also affected by the chemotherapeutic agent, thus reducing the risk of serious infection.

C. Problems associated with chemotherapy

Cancer drugs are toxins that present a lethal threat to the cells. It is therefore not surprising that cells have evolved elaborate defense mechanisms to protect themselves from chemical toxins, including chemotherapeutic agents.

1. **Resistance:** Some neoplastic cells (for example, melanoma) are inherently resistant to most anticancer drugs. Other tumor types may acquire resistance to the cytotoxic effects of a medication by mutating, particularly after prolonged administration of suboptimal drug doses. The development of drug resistance is minimized by short-term, intensive, intermittent therapy with combinations of drugs. Drug combinations are also effective against a broader range of resistant cells in the tumor population. A variety of mechanisms are responsible for drug resistance, each of which is considered separately in the discussion of a particular drug.

2. **Multidrug resistance:** Stepwise selection of an amplified gene that codes for a transmembrane protein (P-glycoprotein for â€œpermeabilityâ€ glycoprotein; Figure 39.5) is responsible for multidrug resistance. This resistance is due to adenosine triphosphateâ€"dependent pumping of drugs out of the cell in the presence of P-glycoprotein. Cross-resistance following the use of structurally unrelated agents also occurs. For example, cells that are resistant to the cytotoxic effects of the vinca alkaloids are also resistant to *dactinomycin*, to the anthracycline antibiotics, as well as to *colchicine*, and vice versa. These drugs are all naturally occurring substances, each of which has a hydrophobic aromatic ring and a positive charge at neutral pH. [Note: P-glycoprotein is normally expressed at low levels in most cell types, but higher levels are found in the kidney, liver, pancreas, small intestine, colon, and adrenal gland. It has been suggested that the presence of P-glycoprotein may account for the intrinsic resistance to chemotherapy observed with adenocarcinomas.]

verapamil) can inhibit the pump and, thus, interfere with the efflux of the anticancer agent. However, these drugs are undesirable because of adverse pharmacologic actions of their own. Pharmacologically inert pump blockers are being sought.

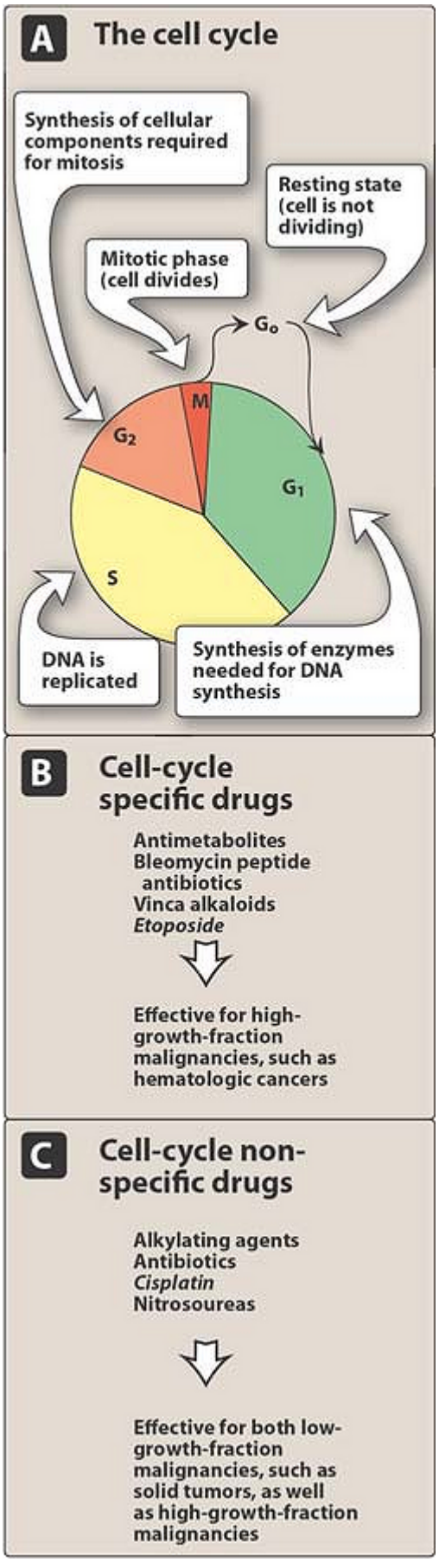

A
The cell cycle
Synthesis of cellular components required for mitosis
Resting state (cell is not dividing)
Mitotic phase (cell divides)
G_o
M
G_2
G_1
S
DNA is replicated
Synthesis of enzymes needed for DNA synthesis
B
Cell-cycle specific drugs
Antimetabolites
Bleomycin peptide antibiotics
Vinca alkaloids
Etoposide
Effective for high-growth-fraction malignancies, such as hematologic cancers
C
Cell-cycle non-specific drugs
Alkylating agents
Antibiotics
Cisplatin
Nitrosoureas
Effective for both low-growth-fraction malignancies, such as solid tumors, as well as high-growth-fraction malignancies

Figure 39.4 Effects of chemotherapeutic agents on the growth cycle of mammalian cells.

3. **Toxicity:** Therapy aimed at killing rapidly dividing cancer cells also affects normal cells undergoing rapid proliferation (for example, cells of the buccal mucosa, bone marrow, gastrointestinal (GI) mucosa, and hair), contributing to the toxic manifestations of chemotherapy.

    a. **Common adverse effects:** Most chemotherapeutic agents have a narrow therapeutic index. Severe vomiting, stomatitis, bone marrow suppression, and alopecia occur to a lesser or greater extent during therapy with all antineoplastic agents. Vomiting is often controlled by administration of antiemetic drugs. Some toxicities, such as myelosuppression that predisposes to infection, are common to many chemotherapeutic agents (Figure 39.6), whereas other adverse reactions are confined to specific agents, such as, cardiotoxicity with doxorubicin and pulmonary fibrosis with *bleomycin*. The duration of the side effects varies widely. For example, alopecia is transient, but the cardiac, pulmonary, and bladder toxicities are irreversible.

    b. **Minimizing adverse effects:** Some toxic reactions may be ameliorated by interventions, such as the use of cytoprotectant drugs, perfusing the tumor locally (for example, a sarcoma of the arm), removing some of the patient's marrow prior to intensive treatment and then reimplanting it, or promoting intensive diuresis to prevent bladder toxicities. The megaloblastic anemia that occurs with *methotrexate* can be effectively counteracted by administering *folinic acid* (*leucovorin, 5-formyltetrahydrofolic acid*; see below). With the availability of human granulocyte colony-stimulating factor (*filgrastim*), the neutropenia associated with treatment of cancer by many drugs can be partially reversed.

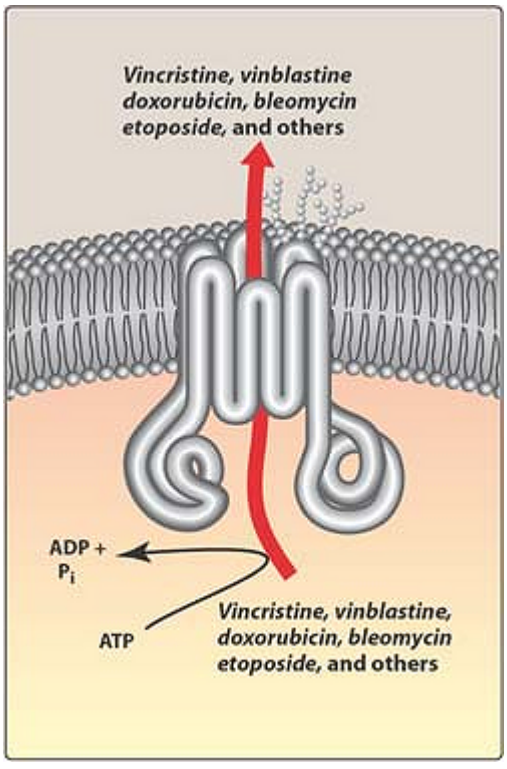


Figure 39.5 The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell.

4. **Treatment-induced tumors:** Because most antineoplastic agents are mutagens, neoplasms (for example, acute nonlymphocytic leukemia) may arise 10 or more years after the original cancer was cured. [Note: Treatment-induced neoplasms are especially a problem after therapy with alkylating agents.]

III. Antimetabolites

Antimetabolites are structurally related to normal compounds that exist within the cell. They generally interfere with the availability of normal purine or pyrimidine nucleotide precursors, either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis. Their maximal cytotoxic effects are in S-phase (and, therefore, cell-cycle) specific.

A. Methotrexate

The vitamin folic acid plays a central role in a variety of metabolic reactions involving the transfer of one-carbon units[1] and is essential for

cell replication. *Methotrexate* [meth-oh-TREK-sate] (*MTX*) is structurally related to folic acid and acts as an antagonist of that vitamin by inhibiting dihydrofolate reductase[2] (DHFR)â€"the enzyme that converts folic acid to its active, coenzyme form, tetrahydrofolic acid (FH_4).

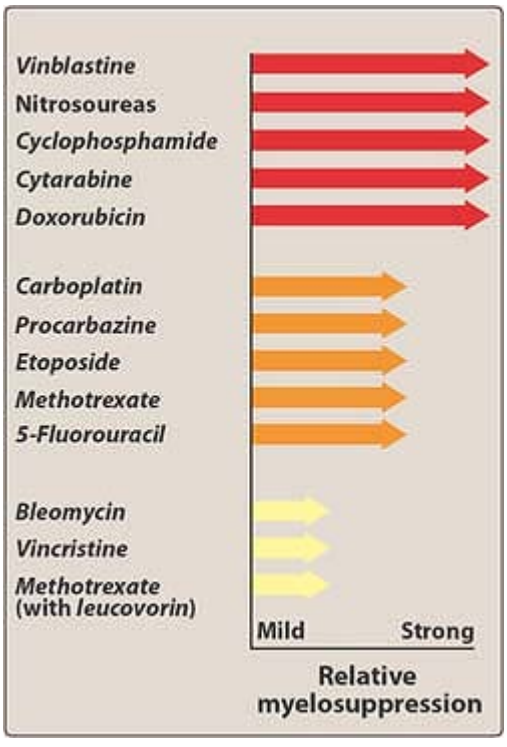


Figure 39.6 Comparison of myelosuppressive potential of chemotherapeutic drugs.

1. **Mechanism of action:** Folic acid is obtained from dietary sources or from that produced by intestinal flora. It undergoes reduction to the tetrahydrofolate form (FH_4) via a reaction catalyzed by intracellular nicotinamide-adenine dinucleotide phosphateâ€“dependent DHFR (Figure 39.7). *MTX* enters the cell by active-transport processes that normally mediate the entry of N^5-methyl-FH_4. At high concentrations, the drug can also diffuse into the cell. *MTX* has an unusually strong affinity for DHFR and effectively inhibits the enzyme. Like tetrahydrofolate itself, *MTX* becomes polyglutamated within the cellâ€”a process that favors intracellular retention of the compound due to increased negative charge. *MTX* polyglutamates also potently inhibit DHFR. This inhibition deprives the cell of folate coenzymes and leads to decreased production of compounds that depend on these coenzymes for their biosynthesis. Although these molecules include the nucleotides adenine, guanine and thymidine and the amino acids methionine and serine, depletion of thymidine is the most prominent effect. This leads to depressed DNA, RNA, and protein synthesis and, ultimately, to cell death (see Figure 39.7). The inhibition of DHFR can only be reversed by a 1000-fold excess of the natural substrate, dihydrofolate (FH_2; see Figure 39.7), or by administration of *leucovorin*, which bypasses the blocked enzyme and replenishes the folate pool. [Note: *Leucovorin*, or *folinic acid*, is the N^5-formyl groupâ€“carrying form of FH_4.] MTX is specific for the S phase of the cell cycle.

2. **Resistance:** Nonproliferating cells are resistant to *MTX*, probably because of a relative lack of DHFR, thymidylate synthase, and/or the glutamylating enzyme. Decreased levels of the *MTX* polyglutamate have been reported in resistant cells and may be due to its decreased formation or increased breakdown. Resistance in neoplastic cells can be due to amplification (production of additional copies) of the gene that codes for DHFR, resulting in increased levels of this enzyme. The enzyme affinity for *MTX* may also be diminished. Resistance can also occur from a reduced influx of *MTX*, apparently caused by a change in the carrier-mediated transport responsible for pumping the drug into the cell.

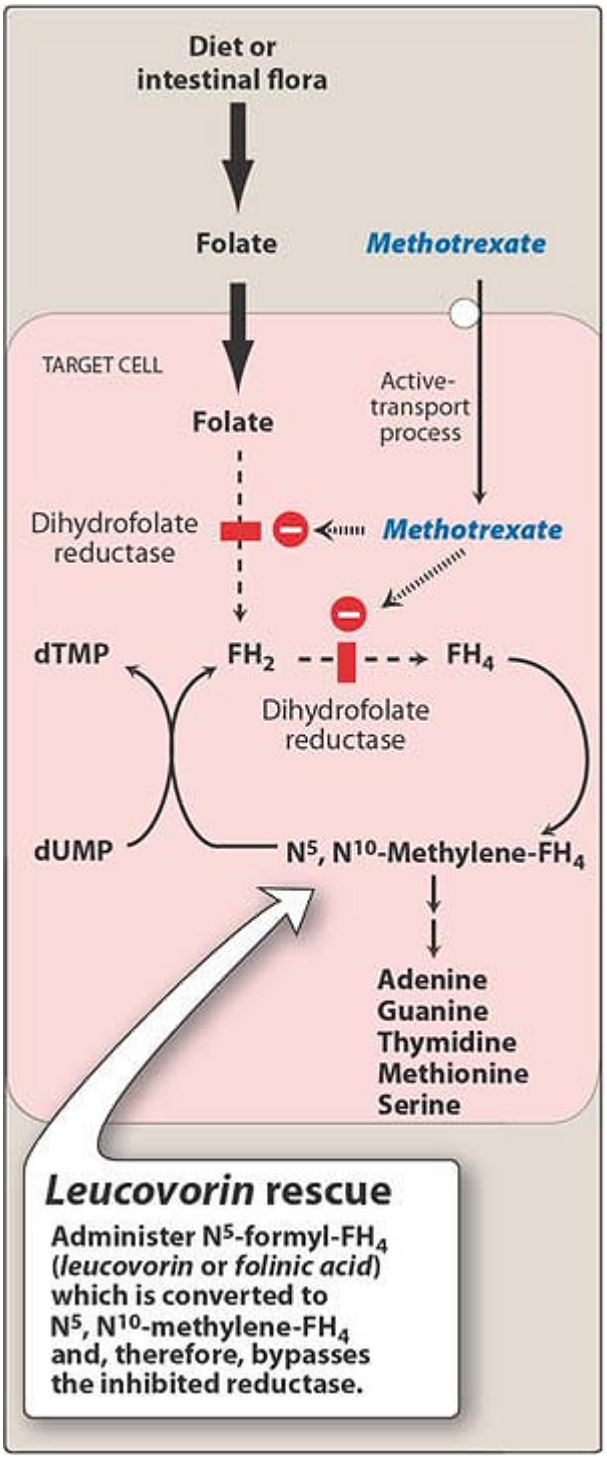


Figure 39.7 Mechanism of action of methotrexate and the effect of administration of leucovorin. FH_2 = dihydrofolate; FH_4 = tetrahydrofolate; dTMP = deoxythymidine monophosphate; dUMP = deoxyuridine mono phosphate.

3. **Therapeutic uses:** *MTX*, usually in combination with other drugs, is effective against acute lymphocytic leukemia, choriocarcinoma, Burkitt's lymphoma in children, breast cancer, and head and neck carcinomas. In addition, low-dose *MTX* is effective as a single agent against certain inflammatory diseases, such as severe

psoriasis and rheumatoid arthritis as well as Crohn's disease. All patients receiving *MTX* require close monitoring for possible toxic effects.

4. **Pharmacokinetics:**

   a. **Administration and distribution:** *MTX* is variably absorbed at low doses from the GI tract, but it can also be administered by intramuscular, intravenous (IV), and intrathecal routes (Figure 39.8). [Note: Because *MTX* does not penetrate the blood-brain barrier, it is administered intrathecally to destroy neoplastic cells that are thriving in the central sanctuary sites.] High concentrations of the drug are found in the intestinal epithelium, liver, and kidney as well as in ascites and pleural effusions. *MTX* is also distributed to the skin.

   b. **Fate:** As previously mentioned, *MTX* is metabolized to polyglutamate derivatives. This property is important, because the polyglutamates, which also inhibit DHFR, remain within the cell even in the absence of extracellular drug. This is in contrast to *MTX* per se, which rapidly leaves the cell as the extracellular drug levels fall. High doses of *MTX* undergo hydroxylation at the 7-position and becomes 7-hyroxymethotrexate. This derivative is much less active as an antimetabolite. It is less water soluble than *MTX* and may lead to crystalluria. Therefore, it is important to keep the urine alkaline and the patient well hydrated to avoid renal toxicity. Excretion of the parent drug and the 7-OH metabolite occurs primarily via the urine, although some of the drug and its metabolite appear in the feces due to enterohepatic excretion.

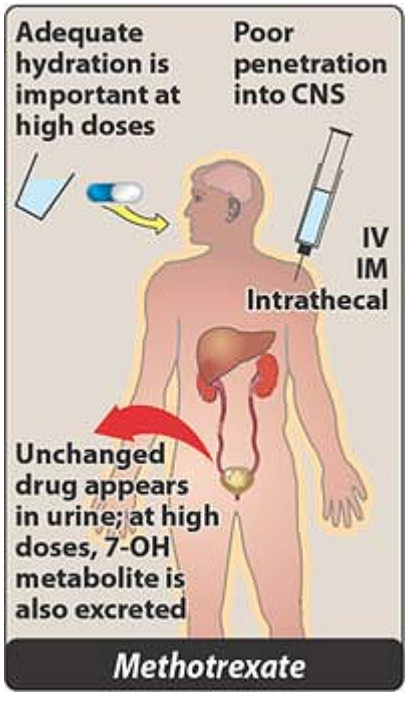


Figure 39.8 Administration and fate of *methotrexate*.

5. **Adverse effects:**

   a. **Commonly observed toxicities:** In addition to nausea, vomiting, and diarrhea, the most frequent toxicities occur in tissues that are constantly renewing. Thus, *MTX* causes stomatitis, myelosuppression, erythema, rash, urticaria, and alopecia. Some of these adverse effects can be prevented or reversed by administering *leucovorin* (see Figure 39.7), which is taken up more readily by normal cells than by tumor cells. Doses of *leucovorin* must be kept minimal to avoid possible interference with the antitumor action of *MTX*.

b. **Renal damage:** Although uncommon during conventional therapy, renal damage is a complication of high-dose *MTX* and its 7-OH metabolite, which can precipitate in the tubules. Alkalinization of the urine and hydration help to prevent this problem.

c. **Hepatic function:** Hepatic function should be monitored. Long-term use of *MTX* may lead to cirrhosis.

d. **Pulmonary toxicity:** This is a rare complication. Children who are being maintained on *MTX* may develop cough, dyspnea, fever, and cyanosis. Infiltrates are seen on radiographs. This toxicity is reversible on suspension of the drug.

e. **Neurologic toxicities:** These are associated with intrathecal administration of *MTX* and include subacute meningeal irritation, stiff neck, headache, and fever. Rarely, seizures, encephalopathy, or paraplegia occur. Long-lasting effects, such as learning

disabilities, have been seen in children who received the drug by this route.

f. **Contraindications:** Because *MTX* is teratogenic in experimental animals and is an abortifacient, it should be avoided in pregnancy. [Note: *MTX* is used with *misoprostol* to induce abortion.]

B. 6-Mercaptopurine

The drug *6-mercaptopurine* [mer-kap-toe-PYOOR-een] (*6-MP*) is the thiol analog of hypoxanthine. *6-MP* and *6-thioguanine* were the first purine analogs to prove beneficial for treating neoplastic disease. [Note: *Azathioprine*, an immunosuppressant, exerts its cytotoxic effects after conversion to *6-MP.*] *6-MP* is used principally in the maintenance of remission in acute lymphoblastic leukemia. *6-MP* and its analog, *azathioprine*, are also beneficial in the treatment of Crohn's disease.

1. **Mechanism of action:**

a. **Nucleotide formation:** To exert its antileukemic effect, *6-MP* must penetrate target cells and be converted to the nucleotide analog, *6-MP*-ribose phosphate (better known as 6-thioinosinic acid, or TIMP; Figure 39.9). The addition of the ribose phosphate is catalyzed by the salvage pathway enzyme, hypoxanthine-guanine phosphoribosyl transferase (HGPRT).[3]

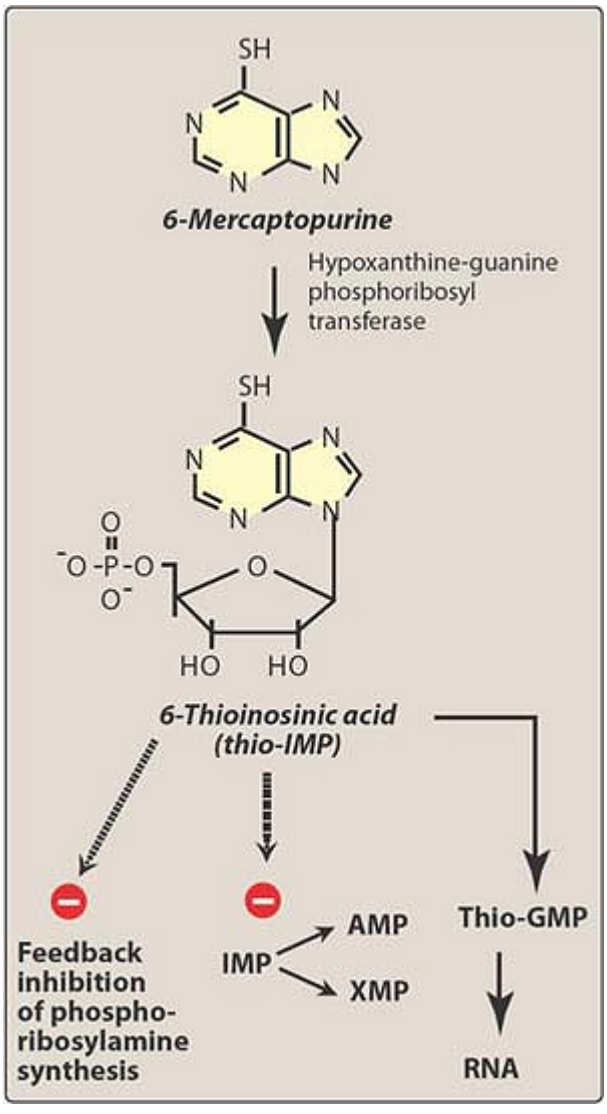


Figure 39.9 Actions of *6-mercaptopurine*.

b. **Inhibition of purine synthesis**: A number of metabolic processes involving purine biosynthesis and interconversions are affected by the nucleotide analog, TIMP. Like adenosine monophosphate (AMP), guanosine monophosphate (GMP), and inosine monophosphate (IMP), TIMP can inhibit the first step of de novo purine-ring biosynthesis (catalyzed by glutamine phosphoribosyl pyrophosphate amidotransferase). TIMP also blocks the formation of AMP and xanthinuric acid from inosinic acid.[4]

c. **Incorporation into nucleic acids:** TIMP is converted to thioguanine monophosphate (TGMP), which after phosphorylation to di- and triphosphates can be incorporated into RNA. The deoxyribonucleotide analogs that are also formed are incorporated into DNA. This results in nonfunctional RNA and DNA.

2. **Resistance:** Resistance is associated with 1) an inability to biotransform *6-MP* to the corresponding nucleotide because of decreased levels of HGPRT (for example, in Lesch-Nyhan syndrome, in which patients lack this enzyme), 2) increased dephosphorylation, or 3) increased metabolism of the drug to thiouric acid or other metabolites.

3. **Pharmacokinetics:** Absorption by the oral route is erratic and incomplete. Once it enters the blood circulation,

the drug is widely distributed throughout the body, except for the cerebrospinal fluid (CSF; Figure 39.10). The bioavailability of *6-MP* can be reduced by the first-pass

metabolism in the liver; while undergoing metabolism in the liver, *6-MP* is converted to to the 6-methylmercaptopurine derivative or to thiouric acid (an inactive metabolite). [Note: The latter reaction is catalyzed by xanthine oxidase.[5]] Because the xanthine oxidase inhibitor, *allopurinol*, is frequently used to reduce hyperuricemia in cancer patients receiving chemotherapy, it is important to decrease the dose of *6-MP* by 75 percent in these individuals to avoid accumulation of the drug and exacerbation of toxicities (Figure 39.11). The parent drug and its metabolites are excreted by the kidney.

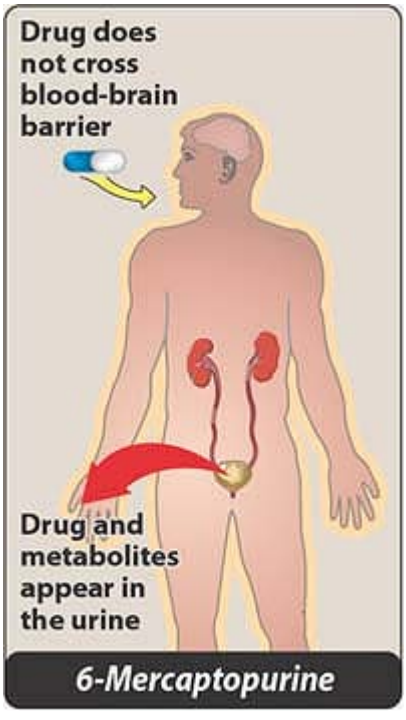


Figure 39.10 Administration and fate of *6-mercaptopurine*.

4. **Adverse effects:** Bone marrow depression is the principal toxicity. Side effects also include anorexia, nausea, vomiting, and diarrhea. Occurrance of hepatotoxicity in the form of jaundice has been reported in about one-third of adult patients.



Figure 39.11 Potential drug interaction between *allopurinol* and *6-mercaptopurine*.

C. 6-Thioguanine

6-Thioguanine [thye-oh-GWAH-neen] (*6-TG*), a purine analog, is primarily used in the treatment of acute nonlymphocytic leukemia in combination with *daunorubicin* and *cytarabine*. Like *6-MP, 6-TG* is converted intracellullarly to TGMP (also called 6-thioguanylic acid) by the enzyme HGPRT. TGMP is further converted to the di- and triphosphates, thioguanosine diphosphate and thioguanosine triphosphate, which then inhibit the biosynthesis of purines and also the phosphorylation of GMP to guanosine diphosphate. The nucleotide form of *6-TG* is incorporated into DNA that leads to cell-cycle arrest.

1. **Pharmacokinetics:** Similar to *6-MP,* the absorption of oral *6-TG* is also incomplete and erratic. The peak concentration in the plasma is reached in 2 to 4 hours after ingestion. When *6-TG* is administered, it is converted the S-methylation product, 2-amino-6-methylthiopurine by thiopurine methyltransferase (TPMT), which appears in the urine. Patients with low or intermediate TPMT activity accumulate higher concentrations of thioguanine cytotoxic metabolites compared to patients with normal TPMT activity. This results in unexpectedly high myelosuppression and has also been associated with the occurrence of secondary malignancies. Approximately three percent of whites and blacks express either a homozygous deletion or mutation of the TPMT gene. An estimated 10 percent of patients may be at increased risk for toxicity because of a heterozygous deletion or mutation of TPMT; therefore, TPMT genotyping is recommended before therapy. To a lesser extent, 6-thioxanthine and 6-thiouric acid are also formed by the action of guanase. Because the deamination product 6-thioanthine is an inactive metabolite, *6-TG* may be administered along with *allopurinol* without any dose reduction.
2. **Adverse effects:** Bone marrow depression is the dose-related adverse effect. *6-TG* is not recommended for maintenance therapy or continuous long-term treatments due to the risk of liver toxicity.

D. Fludarabine

Fludarabine [floo-DARE-a-been] is the 5'-phosphate of 2-fluoroadenine arabinosideâ€”a purine nucleotide analog. It is useful in the treatment of chronic lymphocytic leukemia and may replace *chlorambucil*, the present drug of choice. *Fludarabine* is also effective against hairy-cell leukemia and indolent non-Hodgkin's lymphoma. *Fludarabine* is a prodrug, the phosphate being removed in the plasma to form 2-F-araA, which is taken up into cells and again phosphorylated (initially by deoxycytidine kinase). Although the exact cytotoxic mechanism is uncertain, the triphosphate is incorporated into both DNA and RNA. This decreases their synthesis in the S phase and affects their function. Resistance is associated with reduced uptake into cells, lack of deoxycytidine kinase, and decreased affinity for DNA polymerase plus other mechanisms. *Fludarabine* is administered IV rather than orally, because intestinal bacteria split off the sugar to yield the very toxic metabolite, fluoroadenine. Urinary excretion accounts for partial elimination. In addition to nausea, vomiting, and diarrhea, myelosuppression is the dose-limiting toxicity. Fever, edema, and severe neurologic toxicity also occur. At high doses, progressive encephalopathy, blindness, and death have been reported.

E. Cladribine

Another purine analog, *2-chlorodeoxyadenosine*, or *cladribine* [KLA-dri-been], undergoes reactions similar to those of *fludarabine*; that is, it must be converted to a nucleotide to be cytotoxic. It becomes incorporated at the 3'-terminus of DNA and, thus, hinders elongation. It also affects DNA repair and is a potent inhibitor of ribonucleotide reductase.[6] Resistance may be due to mechanisms analogous to those that affect *fludarabine*,

although cross-resistance is not a problem. *Cladribine* is effective against hairy-cell leukemia, chronic lymphocytic leukemia, and non-Hodgkin's lymphoma. It also has some activity versus multiple sclerosis. The drug is given as a single, continuous infusion. *Cladribine* distributes throughout the body, including into the CSF. Severe bone marrow suppression is a common adverse effect, as is fever. Peripheral neuropathy has also been reported. The drug is teratogenic.

F. 5-Fluorouracil

5-Fluorouracil [flure-oh-YOOR-ah-sil] (*5-FU*), a pyrimidine analog, has a stable fluorine atom in place of a hydrogen atom at position 5 of the uracil ring. The fluorine interferes with the conversion of deoxyuridylic acid to thymidylic acid, thus depriving the cell of thymidine, one of the essential precursors for DNA synthesis. *5-FU* is employed primarily in the treatment of slowly growing solid tumors (for example, colorectal, breast, ovarian, pancreatic, and gastric carcinomas). Adjuvant therapy with *levamisole*â€"a veterinary anthelmintic agentâ€"improves the survival of some patients with colon cancer. When applied topically, *5-FU* is also effective for the treatment of superficial basal cell carcinomas.

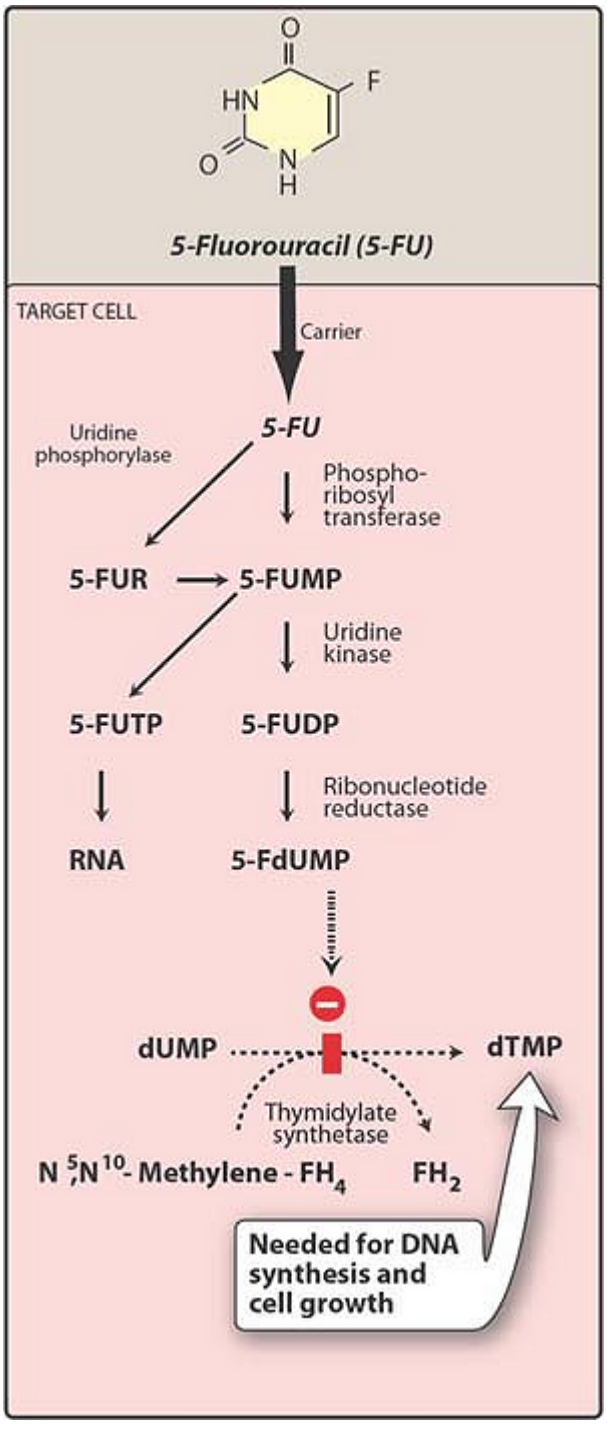


Figure 39.12 Mechanism of the cytotoxic action of *5-FU*. *5-FU* is converted to 5-FdUMP, which competes with deoxyuridine monophosphate (dUMP) for the enzyme thymidylate synthetase. 5-FU = 5-fluorouracil; 5-FUR = 5-fluorouridine; 5-FUMP = 5-fluorouridine monophosphate; 5-FUDP = 5-fluorouridine diphosphate; 5-FUTP = 5-fluorouridine triphosphate; dUMP = deoxyuridine monophosphate; dTMP = deoxythymidine monophosphate. 5-FdUMP = 5-fluorodeoxyuridine monophosphate.

1. **Mechanism of action:** *5-FU* per se is devoid of antineoplastic activity. It enters the cell through a carrier-mediated transport system and is converted to the corresponding deoxynucleotide (5-flurodeoxyuridine

monophosphate (5-FdUMP); Figure 39.12), which competes with deoxyuridine monophosphate for thymidylate synthase.[7]

5-FdUMP acts as a pseudosubstrate and is trapped with the enzyme and its coenzyme N^5,N^{10}-methylene tetrahydrofolic acid (*leucovorin*), in a ternary complex that cannot proceed to release products. DNA synthesis decreases due to lack of thymidine, leading to imbalanced cell growth and â€œthymidine-less deathâ€ of rapidly dividing cells. [Note: *Leucovorin* is administered with *5-FU,* because the reduced folate coenzyme is required in the thymidylate synthase inhibition. Addition of the coenzyme increases the effectiveness of the 5-FU to form a ternary complex and produce an antipyrimidine effect. For example, the standard regimen for advanced colorectal cancer today is *irinotecan* plus *5-FU/leucovorin*.] *5-FU* is also incorporated into RNA, and low levels have been detected in DNA. In the latter case, a glycosylase excises the *5-FU,* damaging the DNA. *5-FU* produces the anticancer effect in the S phase of the cell cycle.

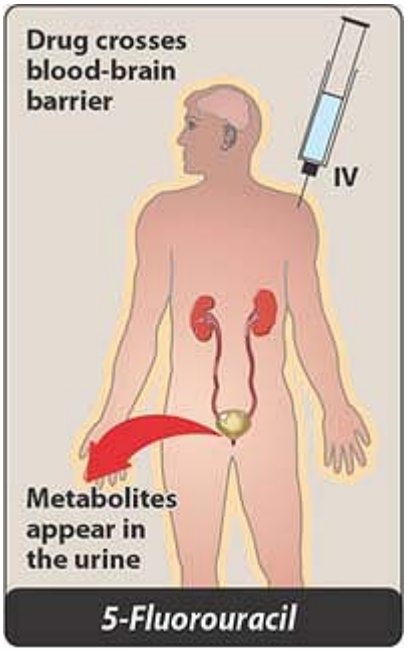


Figure 39.13 Administration and fate of *5-fluorouracil*.

2. **Resistance:** Resistance is encountered when the cells have lost their ability to convert *5-FU* into its active form (5-FdUMP) or when they have altered or increased thymidylate synthase levels.

3. **Pharmacokinetics:** Because of its severe toxicity to the GI tract, *5-FU* is given IV or, in the case of skin cancer, topically (Figure 39.13). The drug penetrates well into all tissues, including the CNS. *5-FU* is rapidly metabolized in the liver, lung, and kidney. It is eventually converted to fluoro-Î²-alanine, which is removed in the urine, and to CO_2, which is exhaled. The dose of *5-FU* must be adjusted in the case of impaired hepatic function. Increased rate of *5-FU* catabolism through elevated levels of dihydropyrimidine dehydrogenase (DPD) can decrease the bioavailability of *5-FU*. The DPD level varies from individual to individual, that may differ by as much as six-fold in the general population. Knowledge about an individual's DPD activity should allow more appropriate dosing of 5-FU.

4. **Adverse effects:** In addition to nausea, vomiting, diarrhea, and alopecia, severe ulceration of the oral and GI mucosa, bone marrow depression (with bolus injection), and anorexia are frequently encountered. An *allopurinol* mouthwash has been shown to reduce oral toxicity. A dermopathy (erythematous desquamation of

the palms and soles) called the â€œhand-foot syndromeâ€ is seen after extended infusions.

G. Capecitabine

Capecitabine [cape-SITE-a-been] is a novel, oral fluoropyrimidine carbamate. It is approved for the treatment of metastatic breast cancer that is resistant to first-line drugs (for example, *paclitaxel* and anthracyclines) and is currently also used for treatment of colorectal cancer.

1. **Mechanism of action:** After being absorbed, *capecitabine,* which is itself nontoxic, undergoes a series of enzymatic reactions, the last of which is hydrolysis to *5-FU*. This step is catalyzed by thymidine phosphorylaseâ€”an enzyme that is concentrated primarily in tumors (Figure 39.14). Thus, the cytotoxic activity of *capecitabine* is the same as that of *5-FU* and is tumor specific. The most important enzyme inhibited by *5-FU* (and, thus, *capecitabine*) is thymidylate synthase.

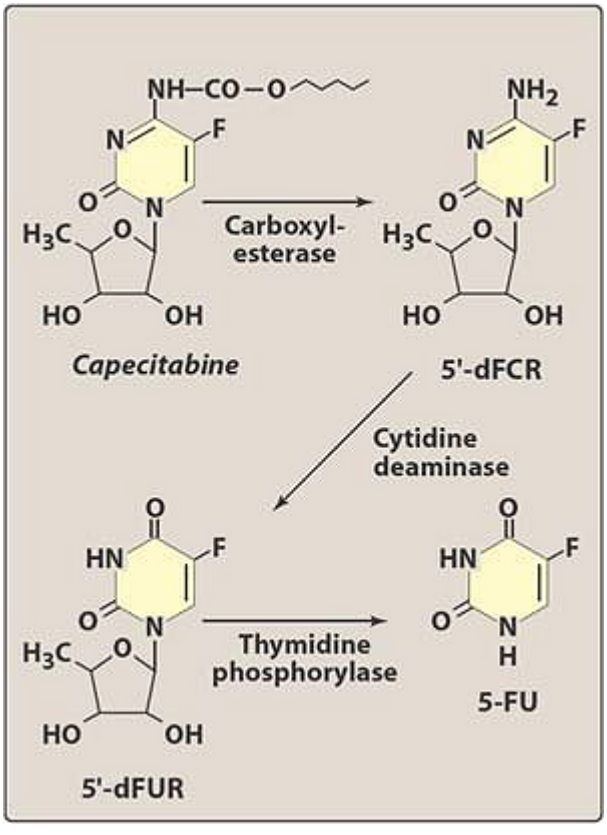


Figure 39.14 Metabolic pathway of *capecitabine* to 5-fluorouracil (5-FU). 5'-dFCR = 5'-deoxy-5-FLuorocytidine; 5'-dFUR = 5'-deoxy-5-fluorouridine.

2. **Pharmacokinetics:** *Capecitabine* has the advantage of being well absorbed following oral administration. It is extensively metabolized to *5-FU* (as described above) and is eventually biotransformed into fluoro-Î²-alanine and CO_2. Metabolites are primarily eliminated in the urine or, in the case of CO_2, it is exhaled.

3. **Adverse effects:** These are similar to those with *5-FU*, with the toxicity occurring primarily in the GI tract. *Capecitabine* should be used cautiously in patients with hepatic or renal impairment. The drug is contraindicated in individuals who are pregnant or are lactating. Patients taking *coumarin* anticoagulants or *phenytoin* should be monitored for coagulation parameters and drug levels, respectively.

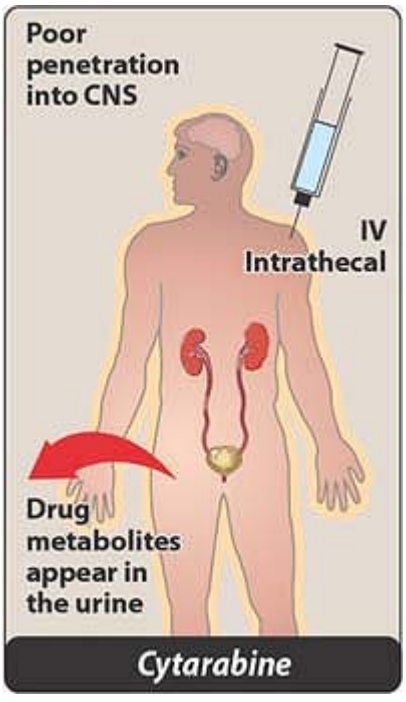


Figure 39.15 Administration and fate of *cytarabine*.

H. Floxuridine

Floxuridine [floks-YOOR-ih-deen] is an analog (floxuridine is 2'-deoxy-5-fluorouridine) of *5-FU*. When given by rapid intra-arterial injection, *floxuridine* is rapidly catabolized in the liver to *5-FU* and produces antimetabolite effects. The primary effect is to interfere with the synthesis of DNA and to a lesser extent inhibit the formation of RNA. The drug is excreted intact and as fluorouracil, urea, and Î±-fluoro-Î²-alanine in the urine. Floxuridine is effective in the palliative management of GI adenocarcinoma that has metastasized to the liver. The common adverse effects are nausea, vomiting, diarrhea, enteritis, stomatitis, and localized erythema.

I. Cytarabine

Cytarabine [sye-TARE-ah-been] (*cytosine arabinoside*, or *ara-C*) is an analog of 2'-deoxycytidine in which the natural ribose residue is replaced by D-arabinose. *Ara-C* acts as a pyrimidine antagonist. The major clinical use of *ara-C* is in acute nonlymphocytic (myelogenous) leukemia in combination with *6-TG* and *daunorubicin*.

1. **Mechanism of action:** *Ara-C* enters the cell by a carrier-mediated process and, like the other purine and pyrimidine antagonists, must be sequentially phosphorylated by deoxycytidine kinase and other nucleotide kinases to the nucleotide form (cytosine arabinoside triphosphate, or ara-CTP) to be cytotoxic. Ara-CTP is an effective inhibitor of DNA polymerase. The nucleotide is also incorporated into nuclear DNA and can retard chain elongation. It is therefore S-phase (and, hence, cell-cycle) specific.
2. **Resistance:** Resistance to *ara-C* may result from a defect in the transport process, a change in phosphorylating enzymes activity (especially deoxycytidine kinase), or an increased pool of the natural dCTP nucleotide. Increased deamination of the drug to ara-U can also cause resistance.
3. **Pharmacokinetics:** *Ara-C* is not effective when given orally, because of its deamination to the noncytotoxic uracil arabinoside (ara-U) by cytidine deaminase in the intestinal mucosa and liver. Given IV, it distributes

throughout the body but does not penetrate the CNS in sufficient amounts to be effective against meningeal leukemia (Figure 39.15). However, it may be injected intrathecally. A new preparation that provides slow release into the CSF is also available. *Ara-C* undergoes extensive oxidative deamination in the body to ara-Uâ€”a pharmacologically inactive metabolite. Both *ara-C* and ara-U are excreted in the urine.

4. **Adverse effects:** Nausea, vomiting, diarrhea, and severe myelosuppression (primarily granulocytopenia) are the major toxicities associated with *ara-C*. Hepatic dysfunction is also occasionally encountered. At high doses or with intrathecal injection, *ara-C* may cause leukoencephalopathy or paralysis.

J. Gemcitabine

Gemcitabine [jem-SITE-ah-been] is an analog of the nucleoside deoxycytidine. It is used for the first-line treatment of locally advanced or metastatic adenocarcinoma of the pancreas. It also is effective against nonâ€“small cell lung cancer and several other tumors.

1. **Mechanism of action:** *Gemcitabine* is a substrate for deoxycytidine kinase, which phosphorylates the drug to 2',2'-difluorodeoxycytidine triphosphate (Figure 39.16). The latter compound inhibits DNA synthesis by being incorporated into sites in the growing strand that ordinarily would contain cytosine. Evidence suggests that DNA repair does not readily occur. Levels of the natural nucleotide, dCTP, are lowered, because *gemcitabine* competes with the normal nucleoside substrate for deoxycytidine kinase. Gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for the generation of deoxynucleoside triphosphates required for DNA synthesis.

2. **Resistance:** Resistance to the drug is probably due to its inability to be converted to a nucleotide, caused by an alteration in deoxycytidine kinase. In addition, the tumor cell can produce increased levels of endogenous deoxycytidine that compete for the kinase, thus overcoming the inhibition.

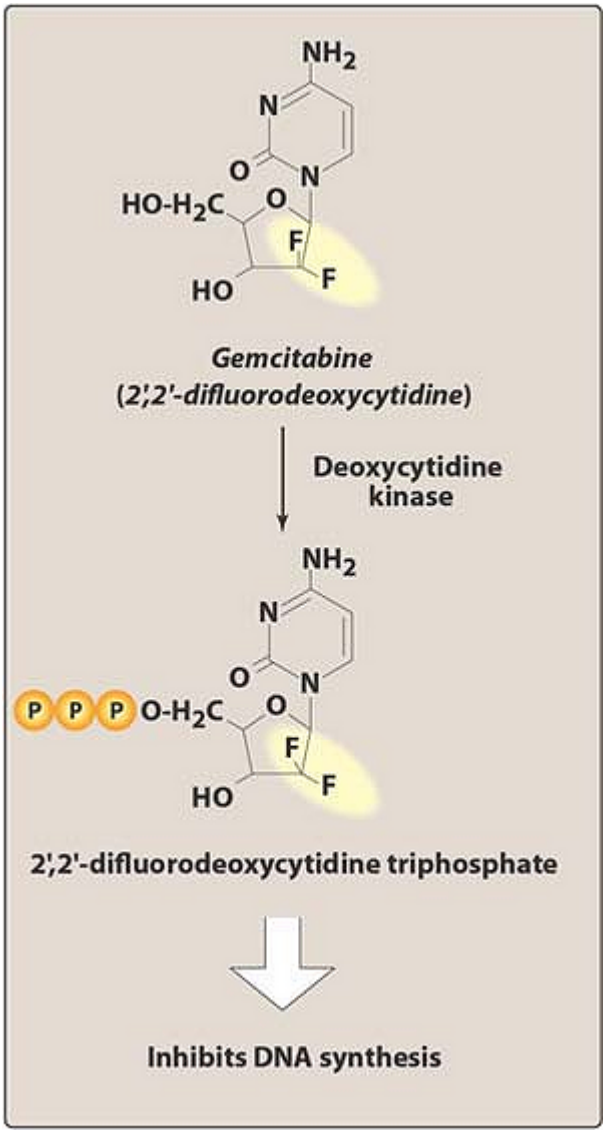


Figure 39.16 Mechanism of action of *gemcitabine*.

3. **Pharmacokinetics:** *Gemcitabine* is infused IV. It is deaminated to difluorodeoxyuridine, which is not cytotoxic, and is excreted in the urine.
4. **Adverse effects:** Myelosuppression is the dose-limiting toxicity of *gemcitabine*. Other toxicities include nausea, vomiting, alopecia, rash, and a flu-like syndrome. Transient elevations of serum transaminases, proteinuria, and hematuria are common.

IV. Antibiotics

The antitumor antibiotics owe their cytotoxic action primarily to their interactions with DNA, leading to disruption of DNA function. In addition to intercalation, their abilities to inhibit topoisomerases (I and II) and produce free radicals also play a major role in their cytotoxic effect. They are cell-cycle nonspecific.

A. Dactinomycin

Dactinomycin [dak-ti-noe-MYE-sin], known to biochemists as *actinomycin D*, was the first antibiotic to find therapeutic application in tumor chemotherapy. *Dactinomycin* is used in combination with surgery and *vincristine* for the treatment of Wilms' tumor. In combination with *MTX, dactinomycin* is effective in the treatment of gestational choriocarcinoma. Some soft-tissue sarcomas also respond.

1. **Mechanism of action:** The drug intercalates into the minor groove of the double helix between guanine-cytosine base pairs of DNA,[8] forming a stable *dactinomycin*-DNA complex. The complex interferes primarily with DNA-dependent RNA polymerase, although at high doses, *dactinomycin* also hinders DNA synthesis. The drug also causes single-strand breaks, possibly due to action on topoisomerase II or by generation of free radicals.
2. **Resistance:** Resistance is due to an increased efflux of the antibiotic from the cell via P-glycoprotein. DNA repair may also play a role.
3. **Pharmacokinetics:** The drug, administered IV, distributes to many tissues but does not enter the CSF (Figure 39.17). The drug is minimally metabolized in the liver. Most of the parent drug and its metabolites are excreted via the bile, and the remainder are excreted via the urine.
4. **Adverse effects:** The major dose-limiting toxicity is bone marrow depression. The drug is immunosuppressive. Other adverse reactions include nausea, vomiting, diarrhea, stomatitis, and alopecia. Extravasation during injection produces serious problems. *Dactinomycin* sensitizes to radiation, and inflammation at sites of prior radiation therapy may occur.

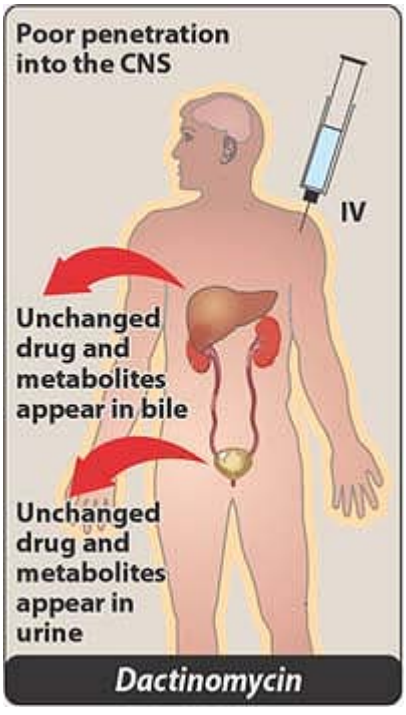


Figure 39.17 Administration and fate of *dactinomycin*.

B. Doxorubicin and daunorubicin

Doxorubicin [dox-oh-ROO-bi-sin] and *daunorubicin* [daw-noe-ROO-bi-sin] are classified as anthracycline antibiotics. *Doxorubicin* is the hydroxylated analog of *daunorubicin*. *Idarubicin* [eye-da-RUE-bi-sin], the 4-demethoxy analog of

daunorubicin, and *epirubicin* [eh-pee-ROO bih-sin] are also available. Applications for these agents differ despite their structural similarity and their apparently similar mechanisms of action. *Doxorubicin* is one of the most important and widely used anticancer drugs. It is used in combination with other agents for treatment of sarcomas and a variety of carcinomas, including breast and lung, as well as for treatment of acute lymphocytic leukemia and lymphomas. *Daunorubicin* and *idarubicin* are used in the treatment of acute leukemias.

1. **Mechanism of action:** The anthracyclines have three major activities that may vary with the type of cell. All three are effective in the S and G_2 phases.

    a. **Intercalation in the DNA:** The drugs insert nonspecifically between adjacent base pairs and bind to the sugar-phosphate backbone of DNA. This causes local uncoiling and, thus, blocks DNA and RNA synthesis. Intercalation can interfere with the topoisomerase IIâ€“catalyzed breakage/reunion reaction of supercoiled DNA strands, causing irreparable breaks.

    b. **Binding to cell membranes:** This action alters the function of transport processes coupled to phosphatidylinositol activation.[9]

    c. **Generation of oxygen radicals:** Cytochrome P450 reductase (present in cell nuclear membranes) catalyzes reduction of the anthracyclines to semiquinone free radicals. These in turn reduce molecular O_2, producing superoxide ions and hydrogen peroxide, which mediate single-strand scission of DNA (Figure 39.18). Tissues with ample superoxide dismutase or glutathione peroxidase activity are protected.[10] Tumors and heart tissue are generally low in SOD. In addition, cardiac tissue lacks catalase and, thus, cannot effectively scavenge hydrogen peroxide. Lipid peroxidation therefore may explain the cardiotoxicity of anthracyclines.

2. **Pharmacokinetics:** All these drugs must be administered IV, because they are inactivated in the GI tract. Extravasation is a serious problem that can lead to tissue necrosis. The anthracycline antibiotics bind to plasma proteins as well as to other tissue components, where they are widely distributed. They do not penetrate the blood-brain barrier or the testes. All these drugs undergo extensive hepatic metabolism. The bile is the major route of excretion, and the drug dose must be modified in patients with impaired hepatic function (Figure 39.19). Some renal excretion also occurs, but the dose generally need not be adjusted in patients with renal failure. Because of the dark red color of the anthracycline drugs, the veins may become visible surrounding the site of infusion, and the drugs also impart a red color to the urine.

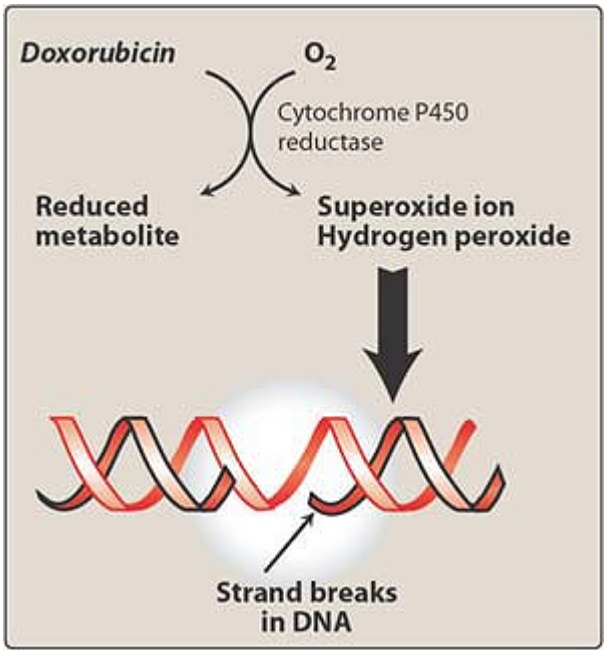


Figure 39.18 *Doxorubicin* interacts with molecular oxygen, producing superoxide ions and hydrogen peroxide, which cause single-strand breaks in DNA.

3. **Adverse effects:** Irreversible, dose-dependent cardiotoxicity, apparently a result of the generation of free radicals and lipid peroxidation, is the most serious adverse reaction and is more common with *daunorubicin* and *doxorubicin* than with *idarubicin* or *epirubicin*. Irradiation of the thorax increases the risk of cardiotoxicity. Addition of *trastuzumab* to protocols with *doxorubicin* or *epirubicin* increases congestive heart failure. There has been some success with the iron-chelator *dexrazone* in protecting against the cardiotoxicity of *doxorubicin*. [Note: A new liposomal-encapsulated *doxorubicin* has been reported to be less cardiotoxic than the usual formulation.] As with *dactinomycin*, both *doxorubicin* and *daunorubicin* also cause transient bone marrow suppression, stomatitis, and GI tract disturbances. Increased skin pigmentation is also seen. Alopecia is usually severe. Occurrence of multidrug resistance is common; however, it is less frequent than with plant alkaloids.

C. Bleomycin

Bleomycin [blee-oh-MYE-sin] is a mixture of different copper-chelating glycopeptides that, like the anthracycline antibiotics, cause scission of DNA by an oxidative process. *Bleomycin* is cell-cycle specific and causes cells to accumulate in the G_2 phase. It is primarily employed in the treatment of testicular cancers in combination with *vinblastine* or *etoposide*. Response rates are close to 100 percent if *cisplatin* is added to the regimen. *Bleomycin* is also effective, although not curative, for squamous cell carcinomas and lymphomas.

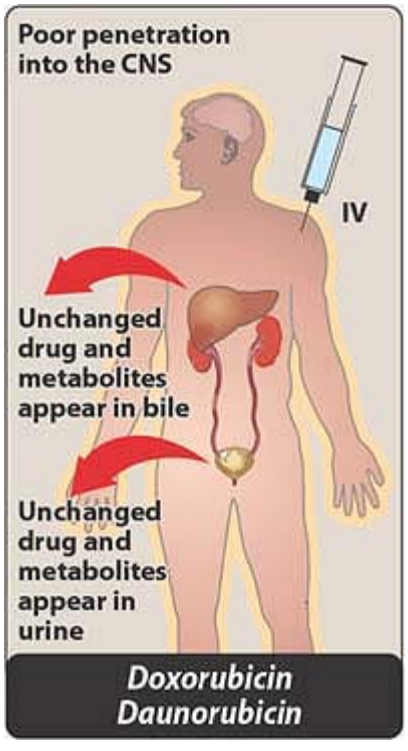


Figure 39.19 Administration and fate of doxorubicin and *daunorubicin*.

1. **Mechanism of action**: A DNA-*bleomycin*-Fe^{2+} complex appears to undergo oxidation to *bleomycin*-Fe^{3+}. The

liberated electrons react with oxygen to form superoxide or hydroxyl radicals, which in turn attack the phosphodiester bonds of DNA, resulting in strand breakage and chromosomal aberrations (Figure 39.20).

2. **Resistance:** Although the mechanisms of resistance have not been elucidated, experimental systems have implicated increased levels of *bleomycin* hydrolase (or deamidase), glutathione-S-transferase, and possibly, increased efflux of the drug. DNA repair also may contribute.

3. **Pharmacokinetics:** *Bleomycin* is administered by a number of routes, including subcutaneous, intramuscular, IV, and intracavitary. The *bleomycin*-inactivating enzyme (a hydrolase) is high in a number of tissues (for example, liver and spleen) but is low in lung and is absent in skin (accounting for the drug's toxicity in those tissues). Most of the parent drug is excreted unchanged into the urine by glomerular filtration, necessitating dose adjustment in patients with renal failure.

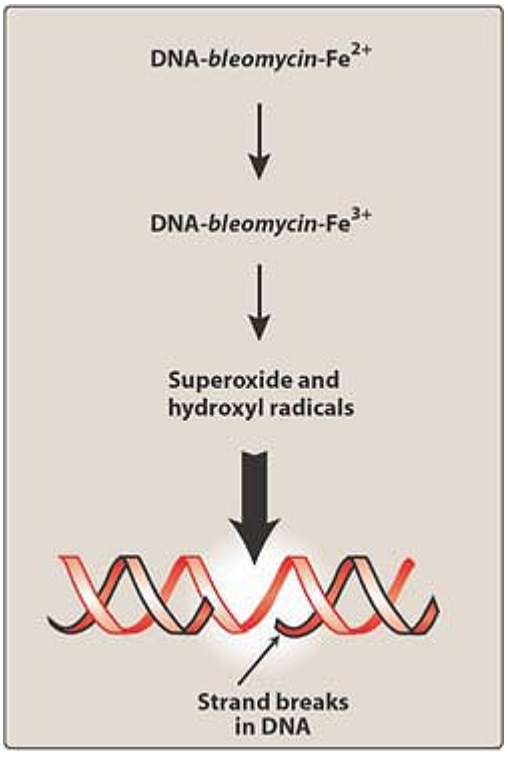


Figure 39.20 *Bleomycin* causes breaks in DNA by an oxidative process.

4. **Adverse effects:** Pulmonary toxicity is the most serious adverse effect, progressing from rales, cough, and infiltrate to potentially fatal fibrosis. The pulmonary fibrosis that is caused by *bleomycin* is often referred as â€œ*bleomycin* lung.â€ Mucocutaneous reactions and alopecia are common. Hypertrophic skin changes and hyperpigmentation of the hands are prevalent. There is a high incidence of fever and chills and a low incidence of serious anaphylactoid reactions. *Bleomycin* is unusual in that myelosuppression is rare.

V. Alkylating Agents

Alkylating agents exert their cytotoxic effects by covalently binding to nucleophilic groups on various cell constituents. Alkylation of DNA is probably the crucial cytotoxic reaction that is lethal to the tumor cells. Alkylating agents do not discriminate between cycling and resting cells, but they are most toxic for rapidly dividing cells. They are used in combination with other agents to treat a wide variety of lymphatic and solid cancers. In addition to being cytotoxic, all are mutagenic and carcinogenic and can lead to second malignancies, such as acute leukemia.

A. Mechlorethamine

Mechlorethamine [mek-lor-ETH-ah-meen] was developed as a vesicant (nitrogen mustard) during World War I. Its ability to cause lymphocytopenia led to its use in lymphatic cancers. Because it can covalently attach to two separate nucleotides, such as guanine on the DNA molecules, it is called a â€œbifunctional agent.â€ *Mechlorethamine* was used primarily in the treatment of Hodgkin's disease and may find use in the treatment of some solid tumors.

1. **Mechanism of action:** *Mechlorethamine* is transported into the cell, where the drug forms a reactive intermediate that alkylates the N^7 nitrogen of a guanine residue in one or both strands of a DNA molecule (Figure 39.21). This alkylation leads to cross-linkages between guanine residues in the DNA chains and/or depurination, thus facilitating DNA strand breakage. Alkylation can also cause miscoding mutations. Although alkylation can occur in both cycling and resting

cells (and, therefore, is cell-cycle nonspecific), proliferating cells are more sensitive to the drug, especially those in the G_1 and S phases.

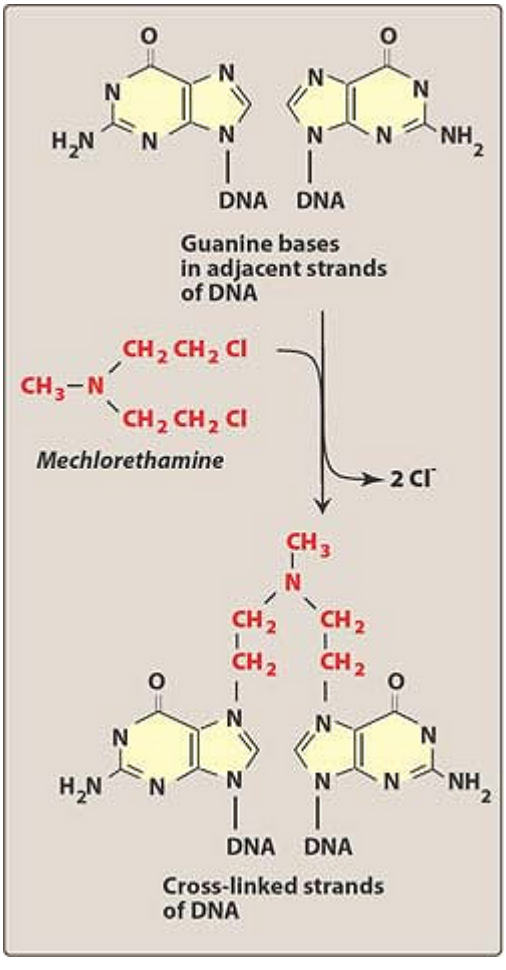


Figure 39.21 Alkylation of guanine bases in DNA is responsible for the cytotoxic effect of *mechlorethamine*.

2. **Resistance:** Resistance has been ascribed to decreased permeability of the drug, increased conjugation with

thiols such as glutathione, and possibly, increased DNA repair.

3. **Pharmacokinetics:** *Mechlorethamine* is very unstable, and solutions must be made up just prior to administration. *Mechlorethamine* is also a powerful vesicant (blistering agent) and is only administered IV. Because of its reactivity, scarcely any drug is excreted.

4. **Adverse effects:** The adverse effects caused by *mechlorethamine* include severe nausea and vomiting (centrally mediated). [Note: These effects can be diminished by pretreatment with *ondansetron, granisetron,* or *palonosetron* with *dexamethasone*.] Severe bone marrow depression limits extensive use. Latent viral infections (for example, herpes zoster) may appear because of immunosuppression. Extravasation is a serious problem. If it occurs, the area should be infiltrated with isotonic *sodium thiosulfite* to inactivate the drug.

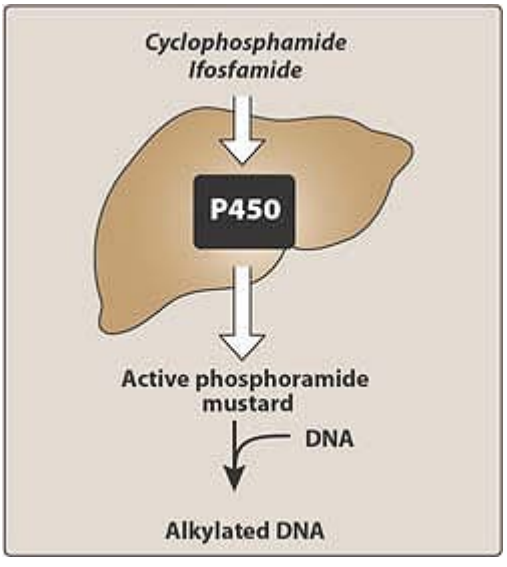


Figure 39.22 Activation of *cyclophosphamide* and *ifosfamide* by hepatic cytochrome P450.

B. Cyclophosphamide and ifosfamide

These drugs are very closely related mustard agents that share most of the same primary mechanisms and toxicities. They are unique in that they can be taken orally and are cytotoxic only after generation of their alkylating species, which are produced through hydroxylation by cytochrome P450. These agents have a broad clinical spectrum, being used either singly or as part of a regimen in the treatment of a wide variety of neoplastic diseases, such as Burkitt's lymphoma and breast cancer. Non-neoplastic disease entities, such as nephrotic syndrome and intractable rheumatoid arthritis, are also effectively treated with low doses of *cyclophosphamide*.

1. **Mechanism of action:** *Cyclophosphamide* [sye-kloe-FOSS-fah-mide] is the most commonly used alkylating agent. Both *cyclophosphamide* and *ifosfamide* [eye-FOSS-fah-mide] are first biotransformed to hydroxylated intermediates primarily in the liver by the cytochrome P450 system (Figure 39.22). The hydroxylated intermediates then undergo breakdown to form the active compounds, phosphoramide mustard and acrolein. Reaction of the phosphoramide mustard with DNA is considered to be the cytotoxic step.

2. **Resistance:** Resistance results from increased DNA repair, decreased drug permeability, and reaction of the drug with thiols (for example, glutathione). Cross-resistance does not always occur.

3. **Pharmacokinetics:** Unlike most of the alkylating agents, *cyclophosphamide* and *ifosfamide* can be administered by the oral route (Figure 39.23). After oral administration, minimal amounts of the parent drug are excreted into

the feces (after biliary transport) or into the urine by glomerular filtration.

4. **Adverse effects:** The most prominent toxicities of both drugs (after alopecia, nausea, vomiting, and diarrhea) are bone marrow depression, especially leukocytosis, and hemorrhagic cystitis, which can lead to fibrosis of the bladder. The latter toxicity has been attributed to acrolein in the urine in the case of *cyclophosphamide* and to toxic

metabolites of *ifosfamide*. [Note: Adequate hydration as well as IV injection of MESNA (sodium 2-mercaptoethane sulfonate), which neutralizes the toxic metabolites, minimizes this problem.] Other toxicities include effects on the germ cells, resulting in amenorrhea, testicular atrophy, aspermia, and sterility. Veno-occlusive disease of the liver is seen in about 25 percent of the patients. A fairly high incidence of neurotoxicity has been reported in patients on high-dose *ifosfamide*, probably due to the metabolite, chloroacetaldehyde. Secondary malignancies may appear years after therapy.

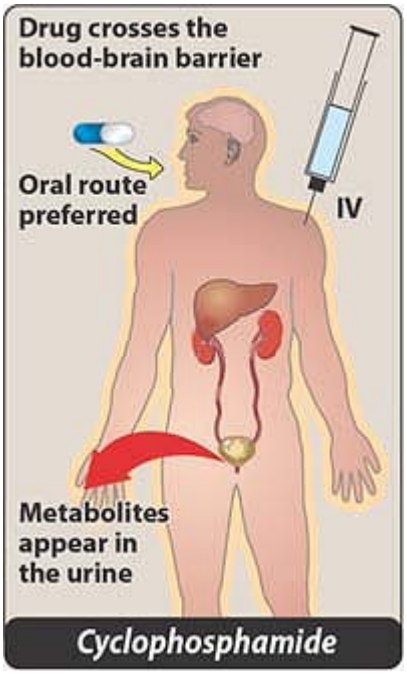


Figure 39.23 Administration and fate of *cyclophosphamide*.

C. Nitrosoureas

Carmustine [KAR-mus-teen] and *lomustine* [LOE-mus-teen] are closely related nitrosoureas. Because of their ability to penetrate into the CNS, the nitrosoureas are primarily employed in the treatment of brain tumors. They find limited use in the treatment of other cancers. [Note: *Streptozocin* [STREP-toe-zoe-sin] is another nitrosourea that is specifically toxic to the Î² cells of the islets of Langerhans, hence its use in the treatment of insulinomas.]

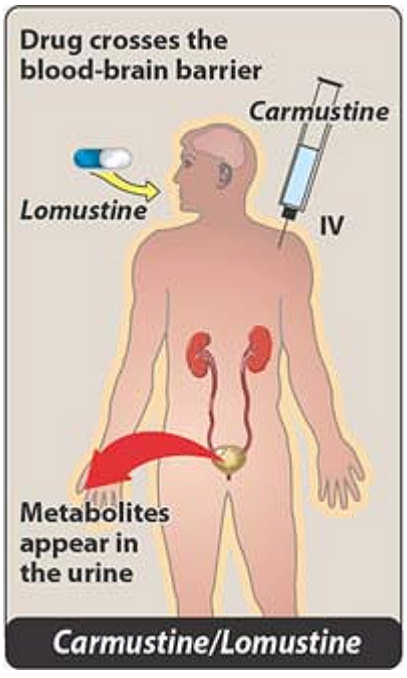


Figure 39.24 Administration and fate of *carmustine/lomustine*.

1. **Mechanism of action:** The nitrosoureas exert cytotoxic effects by an alkylation that inhibits replication and, eventually, RNA and protein synthesis. Although they alkylate DNA in resting cells, cytotoxicity is expressed primarily on cells that are actively dividing. Therefore, nondividing cells can escape death if DNA repair occurs. Nitrosoureas also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins in the targeted cells.
2. **Resistance:** Although the true nature of resistance to nitrosoureas is unknown, it probably results from DNA repair and reaction of the drugs with thiols.
3. **Pharmacokinetics:** In spite of the similarities in their structures, *carmustine* is administered IV, whereas *lomustine* is given orally. Because of their lipophilicity, they distribute widely in the body to many tissues, but their most striking property is their ability to readily penetrate into the CNS. The drugs undergo extensive metabolism. *Lomustine* is metabolized to active products. The kidney is the major excretory route for the nitrosoureas (Figure 39.24).
4. **Adverse effects:** These include delayed hematopoietic depression, which may be due to metabolic products. An aplastic marrow may develop on prolonged use. Renal toxicity and pulmonary fibrosis related to duration of therapy is also encountered. [Note: *Streptozotocin* is also diabetogenic.]

D. Dacarbazine

Dacarbazine [dah-KAR-bah-zeen]â€”an agent that has found use in the treatment of melanoma, is an alkylating agent that must undergo biotransformation to an active metabolite, methyltriazenoimidazole carboxamide (MTIC). This metabolite is responsible for the drug's activity as an alkylating agent by forming methylcarbonium ions that can attack the nucleophilic groups in the DNA molecule. Thus, similar to other alkylating agents, the cytotoxic action of dacarbazine has been attributed to the ability of its metabolite to methylate DNA on the O^6 position of guanine. *Dacarbazine* is administered by IV. Its major adverse effects are nausea and vomiting. Myelosuppression (thrombocytopenia

and neutropenia) occur later in the treatment cycle. Hepatotoxicity with hepatic vascular occlusion may also occur in long-term treatments.

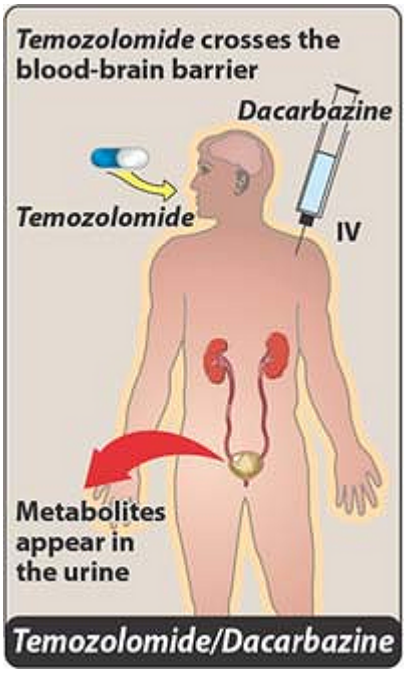


Figure 39.25 Administration and fate of *temozolomide/dacarbazine*.

E. Temozolomide

The treatment of tumors in the brain is particularly difficult. Recently, *temozolomide* [te-moe-ZOE-loe-mide], a triazene agent, has been approved for use against treatment-resistant gliomas and anaplastic astrocytomas. *Temozolomide* is related to *dacarbazine,* because both must undergo biotransformation to an active metabolite, MTIC, which probably is responsible for the methylation of DNA on the 6 position of guanine. Unlike *dacarbazine, tomozolomide* does not require cytochrome P450 system for metabolic transformation; it undergoes chemical transformation under normal physiological pH. *Temozolomide* also has the property of inhibiting the repair enzyme, O^6-guanine-DNA-alkyltransferase. A property that distinguishes *temozolomide* from *dacarbazine* is the former's ability to cross the blood-brain barrier. *Temozolomide* is taken orally and has excellent oral bioavailability. The parent drug and metabolites are excreted in the urine (Figure 39.25). *Temozolomide* is taken for five consecutive days and repeated every 28 days. Similar to *dacarbazine,* its major initial toxicities are nausea and vomiting. Myelosuppression (thrombocytopenia and neutropenia) occur later in the treatment cycle.

F. Other alkylating agents

Melphalan [MEL-fah-lan], a phenylalanine derivative of nitrogen mustard, is used in the treatment of multiple myeloma. This is a bifunctional alkylating agent that can be given orally. Although *melphalan* can be given orally, the plasma concentration differs from patient to patient due to variation in intestinal absorbtion and metabolism. The dose of *melphalan* is carefully adjusted by monitoring the platelet and white blood cell counts. *Chlorambucil* [clor-AM-byoo-sil] is another bifunctional alkylating agent that is used in the treatment of chronic lymphocytic leukemia. Both *melphalan* and *chlorombucil* have moderate hematologic toxicities and upset the GI tract. *Busulfan* [byoo-SUL-fan] is another oral agent that is effective against chronic granulocytic leukemia. *Busulfan* is also a

bifunctional alkylating agent that can cause myelosuppression. In aged patients, *busulfan* can cause pulmonary fibrosis. Like other alkylating agents, all these agents are leukemogenic.

VI. Microtubule Inhibitors

The mitotic spindle is part of a larger, intracellular skeleton (cytoskeleton) that is essential for the movements of structures occurring in the cytoplasm of all eukaryotic cells. The mitotic spindle consists of chromatin plus a system of microtubules composed of the protein tubulin. The mitotic spindle is essential for the equal partitioning of DNA into the two daughter cells that are formed when a eukaryotic cell divides. Several plant-derived substances used as anticancer drugs disrupt this process by affecting the equilibrium between the polymerized and depolymerized forms of the microtubules, thereby causing cytotoxicity.

A. Vincristine and vinblastine

Vincristine [vin-KRIS-teen] (*VX*) and *vinblastine* [vin-BLAS-teen] (*VBL*) are structurally related compounds derived from the periwinkle plant, Vinca rosea. They are therefore referred to as the vinca alkaloids. A structurally

related, new (and less toxic) agent is *vinorelbine* [vye-NOR-el-been] (*VRB*). Although the vinca alkaloids are structurally very similar to each other, their therapeutic indications are different. They are generally administered in combination with other drugs. *VX* is used in the treatment of acute lymphoblastic leukemia in children, Wilms' tumor, Ewing's soft-tissue sarcoma, Hodgkin's and non-Hodgkin's lymphomas, as well as some other rapidly proliferating neoplasms. [Note: *VX* (trade name, O*ncovin*) is the â€œOâ€ in the POMP regimen for leukemia and the MOPP regimen for Hodgkin's lymphoma. Due to relatively milder bone-suppressing ability, *VX* is used in a number of other protocols.] *VBL* is administered with *bleomycin* and *cisplatin* for the treatment of metastatic testicular carcinoma. It is also used in the treatment of systemic Hodgkin's and non-Hodgkin's lymphomas. *VRB* is beneficial in the treatment of advanced nonâ€“small cell lung cancer, either as a single agent or with *cisplatin*.

1. **Mechanism of action:** *VX* and *VBL* are both cell-cycle specific and phase specific, because they block mitosis in metaphase (M phase). Their binding to the microtubular protein, tubulin, is GTP dependent and blocks the ability of tubulin to polymerize to form microtubules. Instead, paracrystalline aggregates consisting of tubulin dimers and the alkaloid drug are formed. The resulting dysfunctional spindle apparatus, frozen in metaphase, prevents chromosomal segregation and cell proliferation (Figure 39.26).

2. **Resistance:** Resistant cells have been shown to have an enhanced efflux of *VX, VBL,* and *VRB* via P-glycoprotein in the cell membrane. Alterations in tubulin structure may also affect binding of the vinca alkaloids.

3. **Pharmacokinetics:** Intravenous injection of these agents leads to rapid cytotoxic effects and cell destruction. This in turn can cause hyperuricemia due to the oxidation of purines that are released from fragmenting DNA molecules, producing uric acid. The hyperuricemia is ameliorated by administration of the xanthine oxidaseâ€“inhibitor *allopurinol*. The vinca alkaloids are concentrated and metabolized in the liver by the cytochrome P450 pathway. They are excreted into bile and feces. Doses must be modified in patients with impaired hepatic function or biliary obstruction.

4. **Adverse effects:** Both *VX* and *VBL* have certain toxicities in common. These include phlebitis or cellulitis, if the drugs extravasate during injection, as well as nausea, vomiting, diarrhea, and alopecia. However, the adverse effects of *VX* and *VBL* are not identical. *VBL* is a more potent myelosuppressant than *VX*, whereas peripheral neuropathy (paresthesias, loss of reflexes, foot drop, and ataxia) is associated with *VX*. Constipation is more frequently encountered with *VX*, which can also cause inappropriate antidiuretic hormone secretion. The anticonvulsants *phenytoin, phenobarbital*, and *carbamazepine* can accelerate the metabolism of *VX*, whereas the azole antifungal drugs can slow its metabolism. Granulocytopenia is dose limiting for *VRB*.

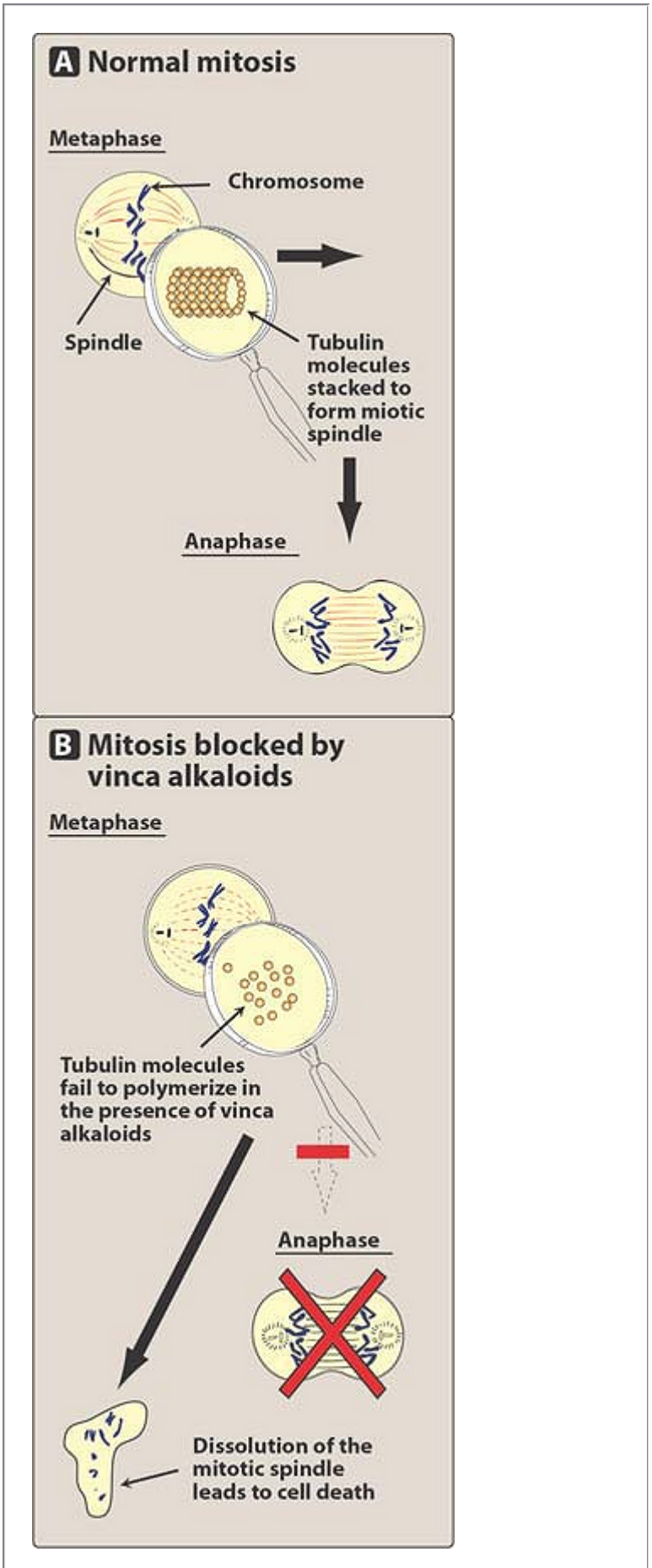

A Normal mitosis
Metaphase
Chromosome
Spindle
Tubulin molecules stacked to form miotic spindle
Anaphase
B Mitosis blocked by vinca alkaloids
Metaphase
Tubulin molecules fail to polymerize in the presence of vinca alkaloids
Anaphase
Dissolution of the mitotic spindle leads to cell death

Figure 39.26 Mechanism of action of the microtubule inhibitors.

B. Paclitaxel and docetaxel

Better known as *Taxol, paclitaxel* [PAK-li-tax-el] is the first member of the taxane family to be used in cancer chemotherapy. A semisynthetic *paclitaxel* is now available through chemical modification of a precursor found in the needles of Pacific yew species. Substitution of a side chain

has resulted in *docetaxel* [doe-see-TAX-el], which is the more potent of the two drugs. *Paclitaxel* has shown good activity against advanced ovarian cancer and metastatic breast cancer. Favorable results have been obtained in nonâ€“small cell lung cancer when administered with *cisplatin. Docetaxel* is showing impressive benefits, with fewer side effects, in these conditions.

1. **Mechanism of action:** Both drugs are active in the G_2/M phase of the cell cycle. They bind reversibly to the Î²-tubulin subunit, but unlike the vinca alkaloids, they promote polymerization and stabilization of the polymer rather than disassembly (Figure 39.27). Thus, they shift the depolymerization-polymerization process to accumulation of microtubules. The overly stable microtubules formed are nonfunctional, and chromosome desegregation does not occur. This results in death of the cell.

2. **Resistance:** Like the vinca alkaloids, resistance has been associated with the presence of amplified P-glycoprotein or a mutation in the tubulin structure.

3. **Pharmacokinetics:** These agents are infused and have similar pharmacokinetics. Both have a large volume of distribution, but neither enters the CNS. Hepatic metabolism by the cytochrome P450 system and biliary excretion are responsible for their elimination into the stool. Thus, dose modification is not required in patients with renal impairment, but doses should be reduced in patients with hepatic dysfunction.

4. **Adverse effects:** The dose-limiting toxicity of *paclitaxel* and *docetaxel* is neutropenia. [Note: Patients with fewer than 1500 neutrophils/mm^3 should not be given these agents.] Treatment with granulocyte colony-stimulating factor (*Filgrastim*) can help to reverse neutropenia and prevent the problems associated with this condition. Peripheral neuropathy can develop with either of these drugs. A transient, asymptomatic bradycardia is sometimes observed with *paclitaxel*, and fluid retention is seen with *docetaxel*. The latter drug is contraindicated in patients with cardiac disease. Alopecia occurs, but vomiting and diarrhea are uncommon. Because of serious hypersensitivity reactions (including dyspnea, urticaria, and hypotension), a patient who is to be treated with *paclitaxel* is premedicated with *dexamethasone* and *diphenhydramine* as well as with an H_2 blocker.

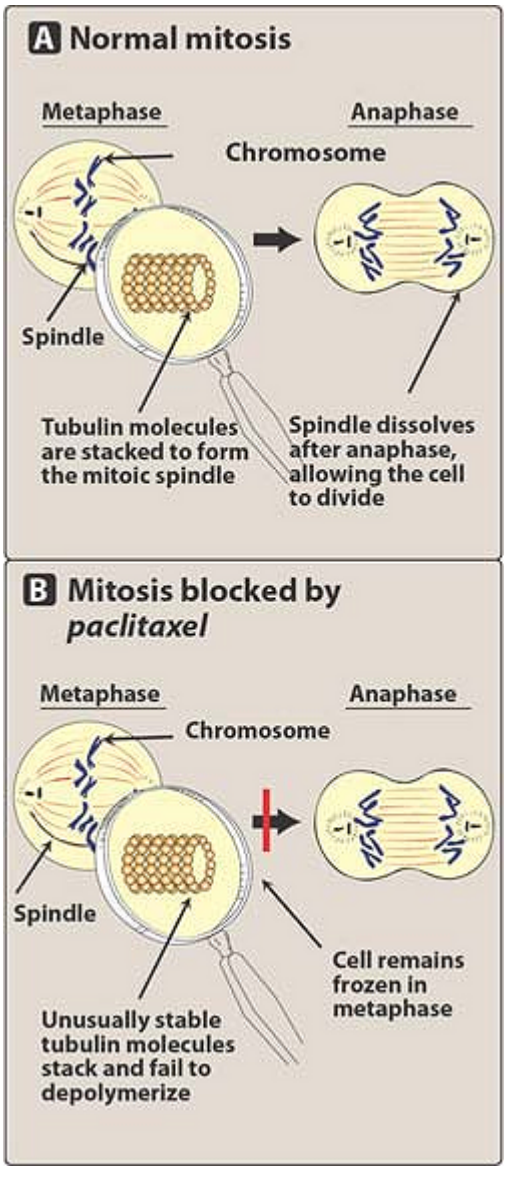


Figure 39.27 *Paclitaxel* stabilizes microtubules, rendering them nonfunctional.

VII. Steroid Hormones and Their Antagonists

Tumors that are steroid hormoneâ€“sensitive may be either 1) hormone responsive, in which the tumor regresses following treatment with a specific hormone; 2) hormone dependent, in which removal of a hormonal stimulus causes tumor regression; or 3) both. Hormone treatment of responsive tumors usually is only palliative, except in the case of the cytotoxic effect of glucocorticoids at higher doses (for example, *prednisone*) on lymphomas. Removal of hormonal stimuli from hormone-dependent tumors can be accomplished by surgery (for example, in the case of orchiectomy for patients with advanced prostate cancer) or by drugs (for example, in breast cancer, for which treatment with the antiestrogen *tamoxifen* is used to prevent estrogen stimulation of breast cancer cells). For a steroid hormone to influence a cell, that cell must have intracellular (cytosolic) receptors that are specific for that hormone (Figure 39.28A).

A. Prednisone

Prednisone [PRED-ni-sone] is a potent, synthetic, anti-inflammatory corticosteroid with less mineralocorticoid activity than *cortisol*. The use of this compound in the treatment of lymphomas arose when it was observed that patients with Cushing's syndrome, which is associated with hypersecretion of cortisol, have lymphocytopenia and decreased lymphoid mass. [Note: At high doses, *cortisol* is also lymphocytolytic and leads to hyperuricemia due to the breakdown of lymphocytes.] *Prednisone* is primarily employed to induce remission in patients with acute lymphocytic leukemia and in the treatment of both Hodgkin's and non-Hodgkin's lymphomas.

1. **Mechanism of action:** *Prednisone* itself is inactive and must first be reduced to *prednisolone* by 11-Î²-hydroxysteroid dehydrogenase.[11] This steroid then binds to a receptor that triggers the production of specific proteins (see Figure 39.28A).
2. **Resistance:** Resistance is associated with an absence of the receptor protein or a mutation that lowers receptor affinity for the hormone. However, in some resistant cells, a receptor-hormone complex is formed, although a stage of gene expression is apparently affected.
3. **Pharmacokinetics:** *Prednisone* is readily absorbed orally. Like other glucocorticoids, it is bound to plasma albumin and transcortin. It undergoes 11-Î²-hydroxylation to *prednisolone* in the liver. *Prednisolone* is the active drug. The latter is glucuronidated and excreted into the urine along with the parent compound.
4. **Adverse effects:** *Prednisone* has many of the adverse effects associated with glucocorticoids. It can predispose to infection (due to its immunosuppressant action) and to ulcers and pancreatitis. Other effects include hyperglycemia, cataract formation, glaucoma, osteoporosis, and change in mood (euphoria or psychosis).

B. Tamoxifen

Tamoxifen [tah-MOX-ih-fen] is an estrogen antagonist. It is structurally related to the synthetic estrogen *diethylstilbestrol* and is used for first-line therapy in the treatment of estrogen receptorâ€“positive breast cancer. *Tamoxifen* has weak estrogenic activity, and it is classified as a selective estrogen-receptor modulator (SERM). Another SERM that has been approved for advanced breast cancer in postmenopausal women is *toremifene* [tore-EM-ih-feen]. It also finds use prophylactically in reducing breast cancer occurrence in women who are at high risk. However, because of possible effects stimulating premalignant lesions due to its estrogenic properties, *tamoxifen* is presently approved only for 5 years of use.

1. **Mechanism of action:** *Tamoxifen* binds to the estrogen receptor, but the complex is transcriptionally not productive. That is, the complex fails to induce estrogen-responsive genes, and RNA synthesis does not ensue (Figure 39.28B). The result is a depletion (down-regulation) of estrogen receptors, and the growth-promoting effects of the

natural hormone and other growth factors are suppressed. [Note: Estrogen competes with *tamoxifen*. Therefore, in premenopausal women, the drug is used with a gonadotropin-releasing hormone (GnRH) analog such as *leuprolide*, which lowers estrogen levels.] The action of *tamoxifen* is not related to any specific phase of the cell cycle.

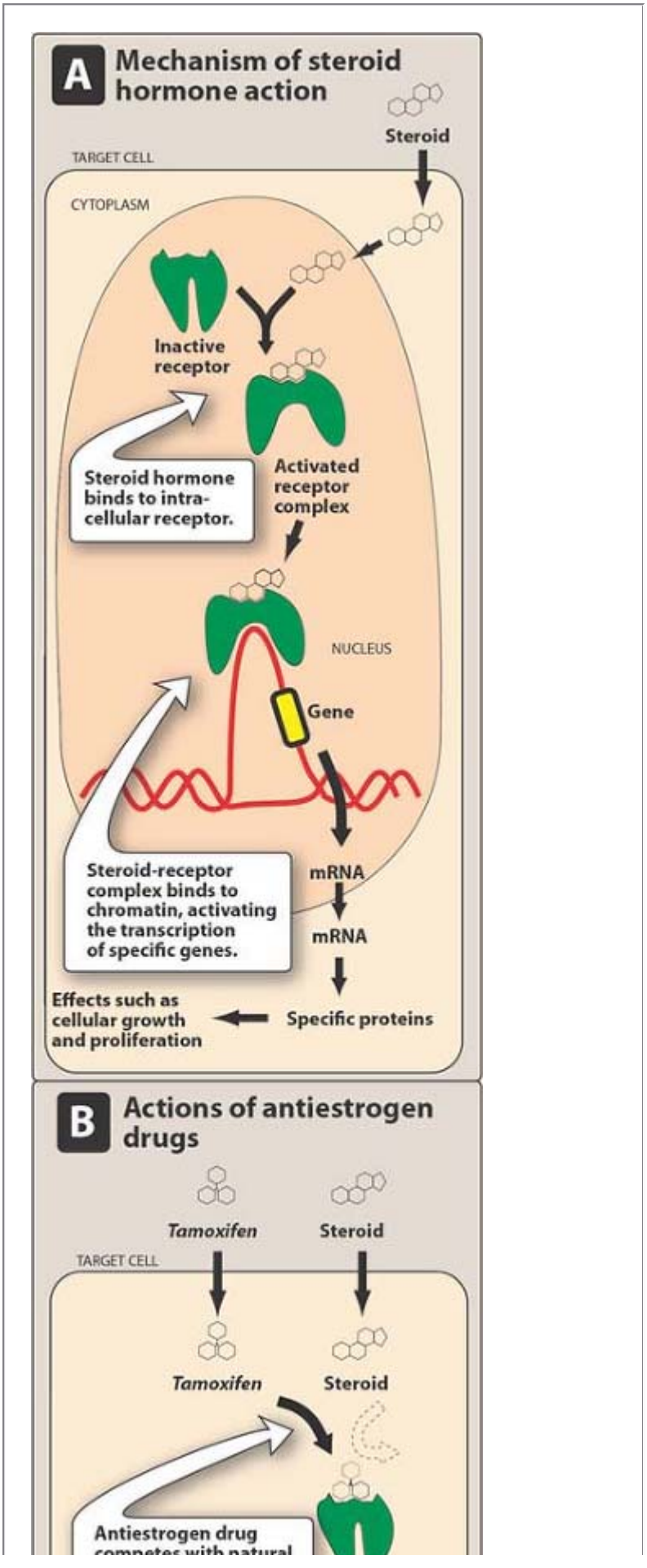

A
Mechanism of steroid hormone action
Steroid
TARGET CELL
CYTOPLASM
Inactive receptor
Steroid hormone binds to intra-cellular receptor.
Activated receptor complex
NUCLEUS
Gene
Steroid-receptor complex binds to chromatin, activating the transcription of specific genes.
mRNA
mRNA
Effects such as cellular growth and proliferation
Specific proteins
B
Actions of antiestrogen drugs
Tamoxifen
Steroid
TARGET CELL
Tamoxifen
Steroid
Antiestrogen drug

Figure 39.28 Action of steroid hormones and antiestrogen agents.

2. **Resistance:** Resistance is associated with a decreased affinity for the receptor or the presence of a dysfunctional receptor.

3. **Pharmacokinetics:** *Tamoxifen* is effective on oral administration. It is partially metabolized by the liver. Some metabolites possess antagonist activity, whereas others have agonist activity. Unchanged drug and its metabolites are excreted predominantly through the bile into the feces (Figure 39.29).

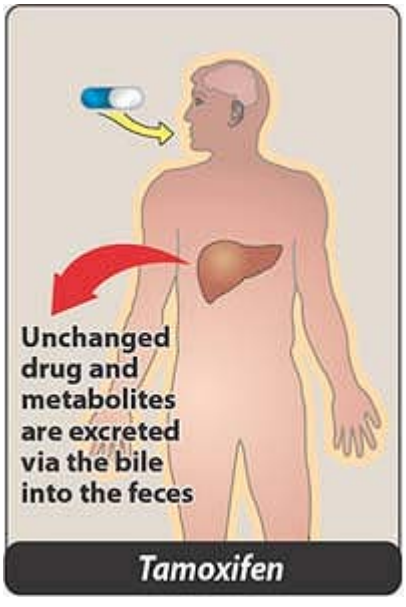


Figure 39.29 Administration and fate of *tamoxifen*.

4. **Adverse effects:** Side effects caused by *tamoxifen* are similar to the effects of natural estrogen, including hot flashes, nausea, vomiting, skin rash, vaginal bleeding, and discharge (due to some slight estrogenic activity of the drug and some of its metabolites). Hypercalcemia requiring cessation of the drug may occur. *Tamoxifen* can also lead to increased pain if the tumor has metastasized to bone. *Tamoxifen* has the potential to cause endometrial cancer. Other toxicities include thromboembolism and effects on vision. [Note: Because of a more favorable adverse effect profile, aromatase inhibitors are making an impact in the treatment of breast cancer.]

C. Aromatase inhibitors

The aromatase reaction is responsible for the extra-adrenal synthesis of estrogen from androstenedione, which takes place in liver, fat, muscle, skin, and breast tissue, including breast malignancies. Peripheral aromatization is an important source of estrogen in postmenopausal women. Aromatase inhibitors decrease the production of estrogen in these women.

1. **Aminoglutethimide:** *Aminoglutethimide* [ah-mee-noe-glue-TETH-ih-mide] was the first aromatase inhibitor to be identified for the treatment of metastatic breast cancer in postmenopausal women. *Aminoglutethimide* was shown to inhibit both the adrenal synthesis of pregnenolone (a precursor of estrogen) from cholesterol as well

as the extra-adrenal synthesis. Because the drug also inhibits hydrocortisone synthesis, which evokes a compensatory rise in adrenocorticotropic hormone secretion sufficient to overwhelm the blockade of the adrenal, the drug is usually taken with *hydrocortisone*. Due to its nonselective properties and unfavorable side effects, as well as the need to concomitantly administer *hydrocortisone* (*cortisol*), newer aromatase inhibitors (described below) have been developed.

2. **Anastrozole and letrozole:** The imidazole aromatase inhibitors, such as *anastrozole* [an-AS-troe-zole] and *letrozole* [LE-troe-zole], are nonsteroidal. They have gained favor in the treatment of breast cancer because 1) they are more potent (they inhibit aromatization by greater than 96 percent, compared to less than 90 percent with *aminoglutethimide*), 2) they are more selective than *aminoglutethimide*, 3) they do not need to be supplemented with hydrocortisone, 4) they do not predispose to endometrial cancer, and 5) they are devoid of the androgenic side effects that occur with the steroidal

aromatase inhibitors. Although *anastrozole* and *letrozole* are considered to be second-line therapy after *tamoxifen* for hormone-dependent breast cancer in the United States, they have become first-line drugs in other countries for the treatment of breast cancer in postmenopausal women. They are orally active and cause almost a total suppression of estrogen synthesis. They are cleared primarily by liver metabolism.

3. **Exemestane:** A steroidal, irreversible inhibitor of aromatase, *exemestanei* [ex-uh-MES-tane], is orally well absorbed and widely distributed. Hepatic metabolism is by the CYP3A4 isozyme, but to date, no interactions have been reported. Because the metabolites are excreted into the urine, doses of the drug must be adjusted in patients with renal failure. Its major toxicities are nausea, fatigue, and hot flashes. Acne and hair changes also occur.

D. Progestins

Megestrol [me-JESS-trole] *acetate* was formerly the progestin used most widely in treating metastatic hormone-responsive breast and endometrial neoplasms. It is orally effective. Other agents are usually compared to it in clinical trials. However, the aromatase inhibitors are replacing it in therapy.

E. Leuprolide and goserelin

Gonadotropin-releasing hormone is normally secreted by the hypothalamus and stimulates the anterior pituitary to secrete the gonadotropic hormones, luteinizing hormone (LH; the primary stimulus for the secretion of testosterone by the testes), and follicle-stimulating hormone (FSH; which stimulates the secretion of estrogen). The synthetic nonapeptides, *leuprolide* [loo-PROE-lide] and *goserelin* [GOE-se-rel-in], are analogs of GnRH. As GnRH agonists, they occupy the GnRH receptor in the pituitary, which leads to its desensitization and, consequently, inhibition of release of FSH and LH. Thus, both androgen and estrogen syntheses are reduced (Figure 39.30). Response to *leuprolide* in prostatic cancer is equivalent to that of orchiectomy (surgical removal of one or both testes), with regression of tumor and relief of bone pain. These drugs have some benefit in premenopausal women with advanced breast cancer and have largely replaced estrogens in therapy for prostate cancer. *Leuprolide* is available 1) as a sustained-release preparation, 2) subcutaneous, or 3) as a depot intramuscular injection to treat metastatic carcinoma of the prostate. *Goserelin acetate* is implanted intramuscularly. Levels of androgen may initially rise but then fall to castration levels. The adverse effects of these drugs, including impotence, hot flashes, and tumor flare, are minimal compared to those experienced with estrogen treatment.

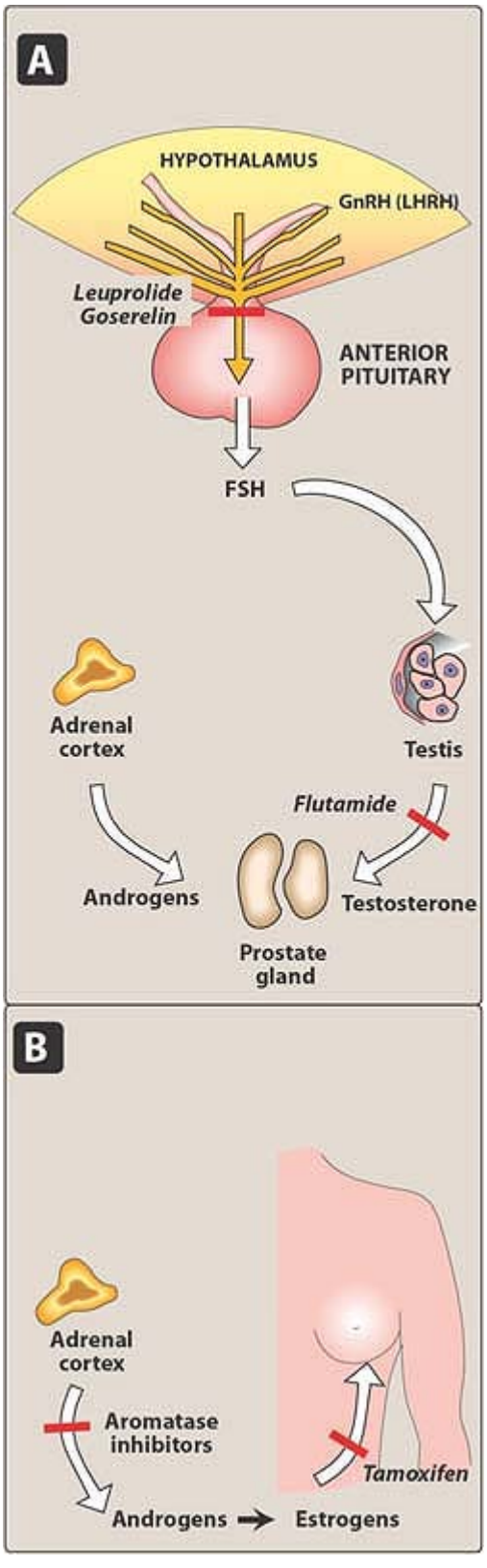

A
HYPOTHALAMUS
GnRH (LHRH)
Leuprolide
Goserelin
ANTERIOR
PITUITARY
FSH
Adrenal
cortex
Testis
Flutamide
Androgens
Testosterone
Prostate
gland
B
Adrenal
cortex
Aromatase
inhibitors
Tamoxifen
Androgens
Estrogens

Figure 39.30 Effects of some anticancer drugs on the endocrine system. A. In therapy for prostatic cancer. B. In therapy of postmenopausal breast cancer. FSH = follicle-stimulating hormone; GnRH (LHRH) = gonadotropin- releasing hormone (leuteinizing hormone-releasing hormone).

F. Estrogens

Estrogens, such as *ethinyl estradiol* or *diethylstilbestrol*, had been used in the treatment of prostatic cancer. However, they have been largely replaced by the GnRH analogs because of fewer adverse effects. Estrogens inhibit the growth of prostatic tissue by blocking the production of LH, thereby decreasing the synthesis of androgens in the testis. Thus, tumors that are dependent on androgens are affected. Estrogen treatment can cause serious complications, such as thromboemboli, myocardial infarction, strokes, and hypercalcemia. Men who are taking estrogens may experience gynecomastia and impotence.

G. Flutamide, nilutamide, and bicalutamide

Flutamide [FLOO-tah-mide], *nilutamide* [nye-LOO-ta-mide], and *bicalutamide* [bye-ka-LOO-ta-mide] are synthetic, nonsteroidal antiandrogens used in the treatment of prostate cancer. They compete with the natural hormone for binding to the androgen receptor and prevent its translocation into the nucleus (see Figure 39.30). *Flutamide* is metabolized to an active hydroxy derivative that binds to the androgen receptor. *Flutamide* blocks the inhibitory effects of testosterone on gonadotropin secretion, causing an increase in serum LH and testosterone levels. Therefore, *flutamide* is always administered in combination with *leuprolide* or *goserelin* which can desensitize the hypothalamus-pituitary axis. These antiandrogens are taken orally. [Note: *Flutamide* requires dosing three times a day and the others once a day.] These agents are cleared through the kidney. Side effects include gynecomastia and GI distress and, in the case of *flutamide*, liver failure could occur. *Nilutamide* can cause visual problems.

VIII. Monoclonal Antibodies

Monoclonal antibodies have become an active area of drug development for anticancer therapy and other nonneoplastic diseases, because they are directed at specific targets and often have fewer adverse effects. They are created from B lymphocytes (from immunized mice or hamsters) fused with â€œimmortalâ€ B-lymphocyte tumor cells. The resulting hybrid cells can be individually cloned, and each clone will produce antibodies directed against a single antigen type. Recombinant technology has led to the creation of â€œhumanizedâ€ antibodies that overcome the immunologic problems previously observed following administration of mouse (murine) antibodies. Currently, several monoclonal antibodies are available in the United States for the treatment of cancer. *Trastuzumab, rituximab, bevacizumab,* and *cetuximab* are described below. Others include *gemtuzumab ozogamicin,* which is a monoclonal antibody conjugated with a plant toxin that binds to CD33â€”a cell-surface receptor that is present on the leukemia cells of 80 percent of patients with acute myelocytic leukemia; *alemtuzumab,* which is effective in treatment of B-cell chronic lymphocytic leukemia that no longer responds to other agents; and I^{131}-*tositumomab*, which is used in relapsed non-Hodgkin's lymphoma.

A. Trastuzumab

In patients with metastatic breast cancer, overexpression of transmembrane human epidermal growth factorâ€“receptor protein 2 (HER2) is seen in 25 to 30 percent of patients. *Trastuzumab* [tra-STEW-zoo-mab], a recombinant DNAâ€“produced, humanized monoclonal antibody, specifically targets the extracellular domain of the HER2 growth receptor that has intrinsic tyrosine kinase activity. The drug, usually administered with *paclitaxel*, can cause regression of breast cancer and metastases in a small percentage of these individuals. [Note: At least 50 tyrosine kinases mediate cell growth or division by phosphorylating signaling proteins. They have been implicated in

the development of many neoplasms by an unknown mechanism.] *Trastuzumab* binds to HER2 sites in breast cancer tissue and inhibits the proliferation of cells that overexpress the HER2 protein, thereby decreasing the number of cells in the S phase.

1. **Mechanism of action:** How the antibody causes its anticancer effect remains to be elucidated. Several mechanisms have been proposedâ€"for example, down-regulation of HER2-receptor expression, an induction of antibody-dependent cytotoxicity, or a decrease in angiogenesis due to an effect on vascular endothelial growth factor. Efforts are being directed toward identifying those patients with tumors that are sensitive to the drug.
2. **Pharmacokinetics:** *Trastuzumab* is administered IV. *Trastuzumab* does not penetrate the blood-brain barrier.
3. **Adverse effects:** The most serious toxicity associated with the use of *trastuzumab* is congestive heart failure. The toxicity is worsened if given in combination with *anthracycline*. Extreme caution should be exercised when giving the drugs to patients with preexisting cardiac dysfunction. Other adverse effects include infusion-related fever and chills, headache, dizziness, nausea, vomiting, abdominal pain, and back pain, but these effects are well tolerated. Cautious use of the drug is recommended in patients who are hypersensitive to the Chinese hamster ovary (CHO) cell components of the proteins or to benzyl alcohol (in which case sterile water can be used in place of the bacteriostatic solution provided for preparation of the injection).

B. Rituximab

Rituximab (ri-TUCX-ih-mab) was the first monoclonal antibody to be approved for the treatment of cancer. It is a genetically engineered, chimeric monoclonal antibody directed against the CD20 antigen that is found on the surfaces of normal and malignant B lymphocytes. CD20 plays a role in the activation process for cell-cycle initiation and differentiation. The CD20 antigen is expressed on nearly all B-cell non-Hodgkin's lymphomas, but not in other bone marrow cells. *Rituximab* has proven to be effective in the treatment of posttransplant lymphoma and in chronic lymphocytic leukemia.

1. **Mechanism of action:** The Fab domain of *rituximab* binds to the CD20 antigen on the B lymphocytes, and its Fc domain recruits immune effector functions, inducing complement and antibody-dependent, cell-mediated cytotoxicity of the B cells. The antibody is commonly used with other combinations of anticancer agents, such as *cyclophosphamide, doxorubicin, vincristine (Oncovin),* and *prednisone* (CHOP).
2. **Pharmacokinetics:** *Rituximab* is infused IV and causes a rapid depletion of B cells (both normal and malignant). The fate of the antibody has not been described.
3. **Adverse effects:** Severe adverse reactions have been fatal. It is important to infuse *rituximab* slowly. Hypotension, bronchospasm, and angioedema may occur. Chills and fever frequently accompany the first infusion, especially in patients with high circulating levels of neoplastic cells, because of rapid activation of complement, which results in the release of tumor necrosis factor Î± and interleukins. Pretreatment with *diphenhydramine, acetaminophen*, and bronchodilators can ameliorate these problems. Cardiac arrhythmias can also occur. Tumor lysis syndrome has been reported within 24 hours of the first dose of *rituximab*. This syndrome consists of acute renal

failure that may require dialysis, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatasemia (an abnormally high content of alkaline phosphatase in the blood). Leukopenia, thrombocytopenia, and neutropenia have been reported in less than 10 percent of patients.

C. Bevacizumab

The monoclonal antibody, *bevacizumab* [be-vah-SEE-zoo-mab] is the first in a new class of anticancer drugs called antiangiogenesis agents. *Bevacizumab* is approved for use as a first-line drug against metastatic colorectal cancer and is given with *5-FU* based chemotherapy. *Bevacizumab* is infused IV. It attaches to and stops vascular endothelial growth factor from stimulating the formation of new blood vessels. Without new blood vessels, tumors do not

receive oxygen and essential nutrients necessary for growth and proliferation. The most common adverse effects of this treatment are hypertension, stomatitis, and diarrhea. Less common are bleeding in the intestines, protein in the urine, and heart failure. Among the rare serious side effects are bowel perforation, opening of healed wounds, and stroke.

D. Cetuximab

Cetuximab [see-TUX-i-mab] is another chimeric monoclonal antibody that has recently been approved to treat colorectal cancer. It is believed to exert its antineoplastic effect by targeting the epidermal growth factor receptor on the surface of cancer cells and interfering with their growth. It is usually combined with *irinotecan* during treatment. Like other antibodies, it is administered IV. *Cetuximab* has caused difficulty breathing and low blood pressure during the first treatment, and interstitial lung disease has been reported. Other side effects include rash, fever, constipation, and abdominal pain.

IX. Other Chemotherapeutic Agents

A. Platinum coordination complexes

Cisplatin [SIS-pla-tin] was the first member of the platinum coordination complex class of anticancer drugs, but because of its severe toxicity, *carboplatin* [KAR-boe-pla-tin] was developed. The mechanisms of action of the two drugs are similar, but their potency, pharmacokinetics, patterns of distribution, and dose-limiting toxicities differ significantly. *Cisplatin* has synergistic cytotoxicity with radiation and other chemotherapeutic agents. *Oxaliplatin* [ox-AL-ih-pla-tin], a new member of this class of drugs, is a closely related analog of *carboplatin*. *Cisplatin* has found wide application in the treatment of solid tumors, such as metastatic testicular carcinoma in combination with *VBL* and *bleomycin*, ovarian carcinoma in combination with *cyclophosphamide*, or alone for bladder carcinoma. *Carboplatin* is employed when patients cannot be vigorously hydrated, as is required for *cisplatin* treatment, or if they suffer from kidney dysfunction or are prone to neuro- or ototoxicity. *Oxaliplatin* is showing excellent activity against advanced colorectal cancer.

1. **Mechanism of action:** The mechanism of action for this class of drugs is similar to that of the alkylating agents. In the high-chloride milieu of the plasma, *cisplatin* persists as the neutral species, which enters the cell and loses its chlorides in the low-chloride milieu. It then binds to the N^7 of guanine in DNA, forming inter- and intrastrand

cross-links. The resulting cytotoxic lesion inhibits both DNA replication and RNA synthesis. Similarly, the chemical moieties that replace the chlorides in the *carboplatin* structure are removed hydrolytically to form the active drug. Cytotoxicity can occur at any stage of the cell cycle, but cells are most vulnerable to the actions of these drugs in the G_1 and S phases. Both drugs can also bind proteins and other compounds containing thiol (â€“SH) groups.

2. **Resistance:** Sensitivity to these agents is decreased if cells have elevated glutathione levels or increased DNA repair or if metallothionein (a protein rich in â€“SH groups) is induced. Decreased cellular uptake has also been implicated. Cross-resistance between *cisplatin* and *carboplatin* is not invariable. However, there is none with *oxaliplatin*.

3. **Pharmacokinetics:** These agents are administered IV in saline solution. They can also be given intraperitoneally for ovarian cancer and intra-arterially to perfuse other organs. More than 90 percent of *cisplatin* is covalently bound to plasma proteins, but the binding of *carboplatin* to plasma proteins is very low. The highest concentrations of the drugs are found in the liver, kidney, and intestinal, testicular, and ovarian cells, but little penetrates into the CSF. The renal route is the main avenue for excretion (Figure 39.31).

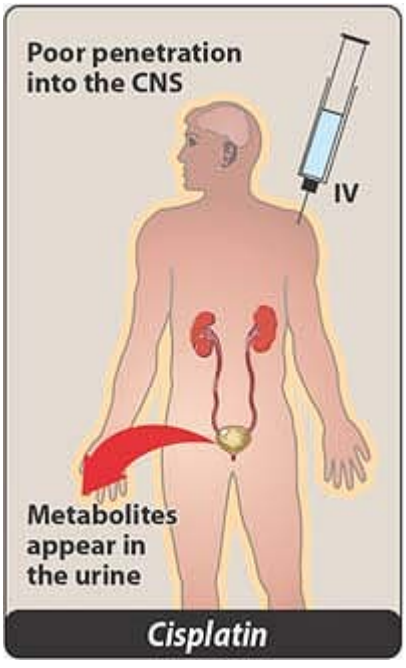


Figure 39.31 Administration and fate of *cisplatin*.

4. **Adverse effects:** Severe, persistent vomiting occurs for at least 1 hour after administration of *cisplatin* and may continue for as long as 5 days. Premedication with antiemetic agents is usually helpful. The major limiting toxicity is dose-related nephrotoxicity, involving the distal convoluted tubule and collecting ducts. This can be ameliorated by aggressive hydration and diuresis. Hypomagnesemia and hypocalcemia usually occur concurrently. [Note: It is important to correct calcium levels before correcting magnesium levels.] Other toxicities include ototoxicity with high-frequency hearing loss and tinnitus, mild bone marrow suppression, some neurotoxicity characterized by paresthesia and loss of proprioception, and hypersensitivity reactions ranging from skin rashes to anaphylaxis. Patients concomitantly receiving aminoglycosides are at greater risk for nephrotoxicity and ototoxicity. Unlike *cisplatin, carboplatin* causes only mild nausea and vomiting, and it is not nephro-, neuro-, or ototoxic. Its dose-limiting toxicity is myelosuppression.

B. Irinotecan and topotecan

Irinotecan [eye-rin-oh-TEE-kan] and *topotecan* [toe-poe-TEE-kan] are semisynthetic derivatives of an earlier, more toxic drug, *camptothecin* [camp-toe-THEE-sin]. They have a complicated multiring structure containing a lactone ring that is essential for activity. *Topotecan* is employed in metastatic ovarian cancer when primary therapy has failed and also in the treatment of small-cell lung cancer. *Irinotecan* is used as a first-line drug together with *5-FU* and *leucovorin* for the treatment of colon or rectal carcinoma.

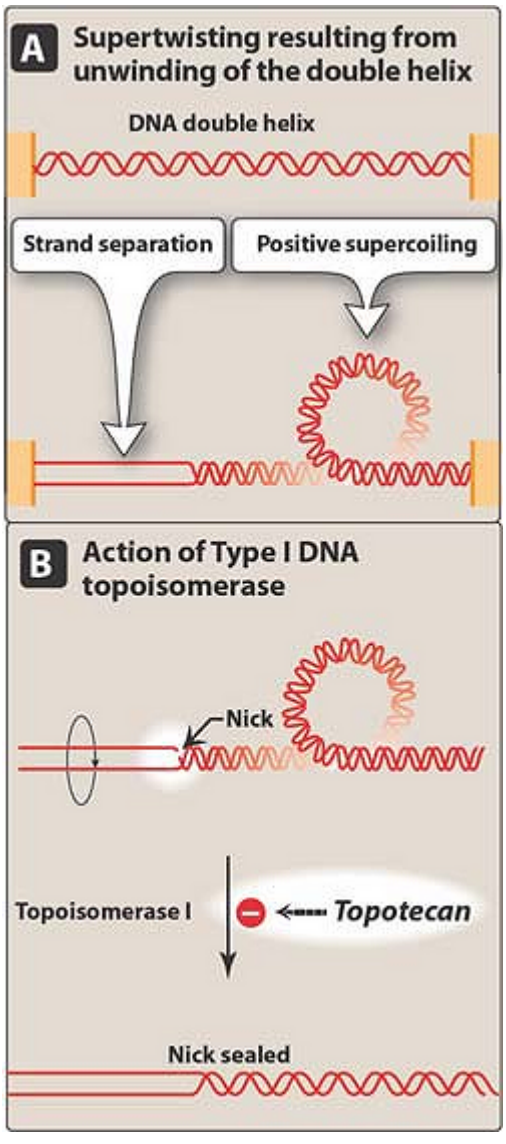


Figure 39.32 Action of Type I DNA topoisomerases.

1. **Mechanism of action:** These drugs are S-phase specific. They inhibit topoisomerase I, which is essential for the replication of DNA in human cells (Figure 39.32). Unlike *etoposide*, which inhibits the related enzyme topoisomerase II (see below), *topotecan* was the first clinically useful topoisomerase I inhibitor. SN-38 (the active metabolite of *irinotecan*) is formed from *irinotecan* by carboxylesterase-mediated

cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as *irinotecan* as an inhibitor of topoisomerase I. The topoisomerases relieve torsional strain in DNA by causing reversible, single-strand breaks. By binding to the enzyme-DNA complex, *topotecan* or SN-38 prevent religation of the single-strand breaks.

2. **Resistance:** Several mechanisms may explain resistance. Among them are the ability to transport the drugs out of the cell, decreased ability to convert *irinotecan* to the active SN-38 metabolite, or a down-regulation or mutation in topoisomerase I.

3. **Pharmacokinetics:** *Topotecan* and *irinotecan* are infused IV. Hydrolysis of the lactone ring destroys the activity

of these drugs. Both the drugs and their metabolites are eliminated in the urine. Therefore, the dose may have to be modified in patients with impaired kidney function.

4. **Adverse effects:** Bone marrow suppressionâ€"particularly neutropeniaâ€"is the dose-limiting toxicity for *topotecan*. Frequent peripheral blood counts should be performed on patients taking this drug. [Note: *Topotecan* should not be used in patients with a baseline neutrophil count of less than 1500 cells/mm^3. Doing so could result in infection and death.] Other hematologic complications, including thrombocytopenia and anemia, may also occur. Nonhematologic effects include diarrhea, nausea, vomiting, alopecia, and headache. Myelosuppression is also seen with *irinotecan*, and delayed diarrhea may be severe and require treatment with *loperamide*.

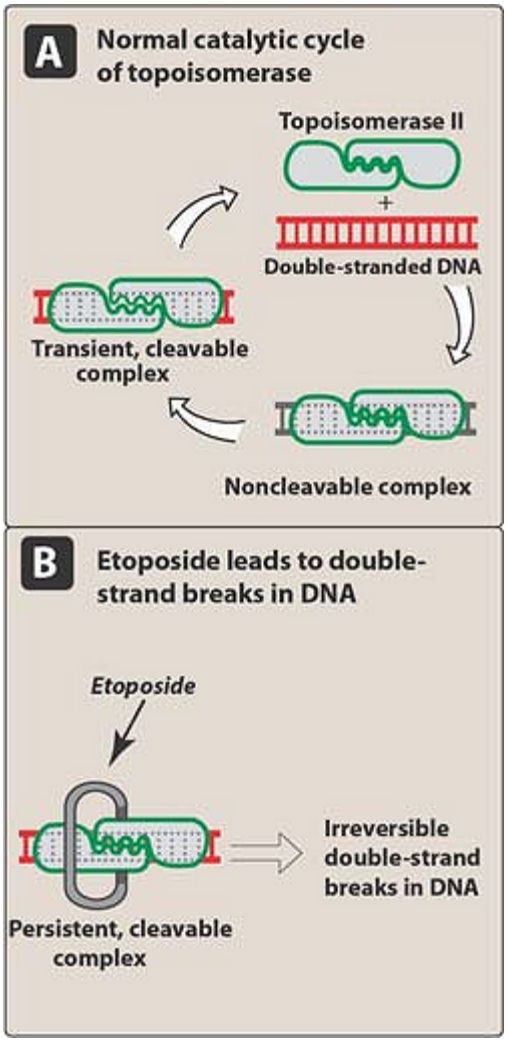


Figure 39.33 Mechanism of action of *etoposide*.

C. Etoposide (VP-16)

Etoposide [e-toe-POE-side] and its analog, *teniposide* [ten-i-POE-side], are semisynthetic derivatives of the plant alkaloid, podophyllotoxin. They block cells in the late S to G_2 phase of the cell cycle. Their major target is topoisomerase II. Binding of the drugs to the enzyme-DNA complex results in persistence of the transient, cleavable form of the complex and, thus, renders it susceptible to irreversible double-strand breaks (Figure 39.33). Resistance

to topoisomerase inhibitors is conferred either by presence of the multidrug-resistant P-glycoprotein or by mutation of the enzyme. *Etoposide* finds its major clinical use in the treatment of oat-cell carcinoma of the lung and in combination with *bleomycin* and *cisplatin* for testicular carcinoma. *Teniposide* is used as a second-line agent in the treatment of acute lymphocytic leukemia. *Etoposide* may be administered either IV or orally, whereas *teniposide* is only administered IV. They are highly bound to plasma proteins and distribute throughout the body, but they enter the CSF poorly. Despite this, *teniposide* has shown effectiveness against gliomas and neuroblastomas. Metabolites are converted to glucuronide and sulfate conjugates and are excreted in the urine. Drugs that induce the cytochrome P450 system lead to an acceleration of *teniposide* metabolism. Dose-limiting myelosuppression (primarily leukopenia) is the major toxicity for both drugs. Leukemia may develop in patients who were treated with *etoposide*. Other toxicities are alopecia, anaphylactic reactions, nausea, and vomiting.

D. Imatinib

Imatinib [i-MAT-in-ib] *mesylate* is used for the treatment of chronic myeloid leukemia in blast crisis, as well as GI stromal tumor. It acts as a signal

transduction inhibitor, used specifically to inhibit tumor tyrosine kinase activity. A deregulated BCR-ABL kinase is present in the leukemia cells of almost every patient with chronic myeloid leukemia. In the case of GI stromal tumor, an unregulated expression of tyrosine kinase is associated with a growth factor. The ability of *imatinib* to occupy the â€œkinase pocketâ€ prevents the phosphorylation of tyrosine on the substrate molecule and, hence, inhibits subsequent steps that lead to cell proliferation. *Imatinib* has the advantage over *interferon-Î±* in that it can be given orally. It also has a more rapid hematologic response than *interferon-Î±* plus *cytarabine*. Studies of cell lines indicate that resistance may occur by amplification of the BCR-ABL gene and/or by increased efflux due to increased multidrug-resistance protein. The drug is very well absorbed orally. It undergoes metabolism by the cytochrome P450 system to several compounds, of which the N-demethyl derivative is active. Excretion is predominantly through the feces. Adverse effects include fluid retention and edema, hepatotoxicity, thrombocytopenia or neutropenia, as well as nausea and vomiting.

E. Gefitinib (Iressa)

Gefitinib [ge-FIN-ih-tib] targets the epidermal growth factor receptor. It is approved for the treatment of nonâ€“small cell lung cancer that has failed to respond to other therapy, and it is effective in 10 to 20 percent of patients with this cancer. *Gefitinib* is usually used as a single agent. *Gefitinib* is absorbed after oral administration and undergoes extensive metabolism in the liver by the cytochrome P450 enzyme CYP3A4. At least five metabolites have been identified, only one of which has significant antitumor activity. The major route of excretion of the drug and its metabolites is the feces. The most common adverse effects are diarrhea, nausea, and acne-like skin rashes. A rare but potentially fatal adverse effect is interstitial lung disease, which presents as acute dyspnea with cough.

F. Procarbazine

Procarbazine [proe-KAR-ba-zeen] is used in the treatment of Hodgkin's disease and other cancers. *Procarbazine* rapidly equilibrates between the plasma and the CSF after oral or parenteral administration. It must undergo a series of oxidative reactions to exert its cytotoxic action that causes inhibition of DNA, RNA, and protein synthesis. Metabolites and the parent drug are excreted via the kidney. Bone marrow depression is the major toxicity, and nausea, vomiting, and diarrhea are common. The drug is also neurotoxic, causing symptoms ranging from drowsiness to hallucinations to paresthesias. Because it inhibits monoamine oxidase, patients should be warned against ingesting foods that contain tyramine (for example, aged cheeses, beer, and wine). Ingestion of alcohol leads to a disulfiram-type reaction). *Procarbazine* is both mutagenic and teratogenic. Nonlymphocytic leukemia has developed in patients treated with the drug.

G. L-Asparaginase

L-Asparaginase [ah-SPAR-a-gi-nase] catalyzes the deamination of asparagine to aspartic acid and ammonia. The form of the enzyme used chemotherapeutically is derived from bacteria. *L-Asparaginase* is used to treat childhood

and *prednisone*. Its mechanism of action is based on the fact that some neoplastic cells require an external source of asparagine because of their limited capacity to synthesize sufficient amounts of that amino acid to support growth and function. *L-Asparaginase* hydrolyzes blood asparagine and, thus, deprives the tumor cells of this amino acid, which is needed for protein synthesis (Figure 39.34). Resistance to the drug is due to increased capacity of tumor cells to synthesize asparagine. The enzyme must be administered either IV or intramuscularly, because it is destroyed by gastric enzymes. Toxicities include a range of hypersensitivity reactions (because it is a foreign protein), a decrease in clotting factors, liver abnormalities, pancreatitis, seizures, and coma due to ammonia toxicity.

H. Interferons

Human interferons have been classified into three typesâ€"Î±, Î², and Î³â€"on the basis of their antigenicity. The Î± interferons are primarily leukocytic, whereas the Î² and Î³ interferons are produced by connective tissue fibroblasts and T lymphocytes, respectively. Recombinant DNA techniques in bacteria have made it possible to produce large quantities of pure interferons, including two species designated *interferon*-Î±-*2a* and -*2b* that are employed in treating neoplastic diseases. *Interferon*-Î±-*2a* is presently approved for the management of hairy-cell leukemia, chronic myeloid leukemia, and acquired immunodeficiency syndrome (AIDS)â€"related Kaposi sarcoma. *Interferon-Î±-2b* is approved for the treatment of hairy-cell leukemia, melanoma, AIDS-related Kaposi's sarcoma, and follicular lymphoma.

1. **Mechanism of action:** Interferons secreted from producing cells interact with surface receptors on other cells, at which site they exert their effects. Bound interferons are neither internalized nor degraded. The Î± and Î² interferons compete with each other for binding and, therefore, presumably bind at the same receptor or in close proximity; the Î³ interferons bind at different receptors. As a consequence of the binding of interferon, a series of complex intracellular reactions take place. These include synthesis of enzymes, suppression of cell proliferation, activation of macrophages, and increased cytotoxicity of lymphocytes. However, the exact mechanism by which the interferons are cytotoxic is unknown
2. **Pharmacokinetics:** Interferons are well absorbed after intramuscular or subcutaneous injections. An IV form of *interferon-Î±-2b* is also available. Interferons undergo glomerular filtration and are degraded during reabsorption, but liver metabolism is minimal.

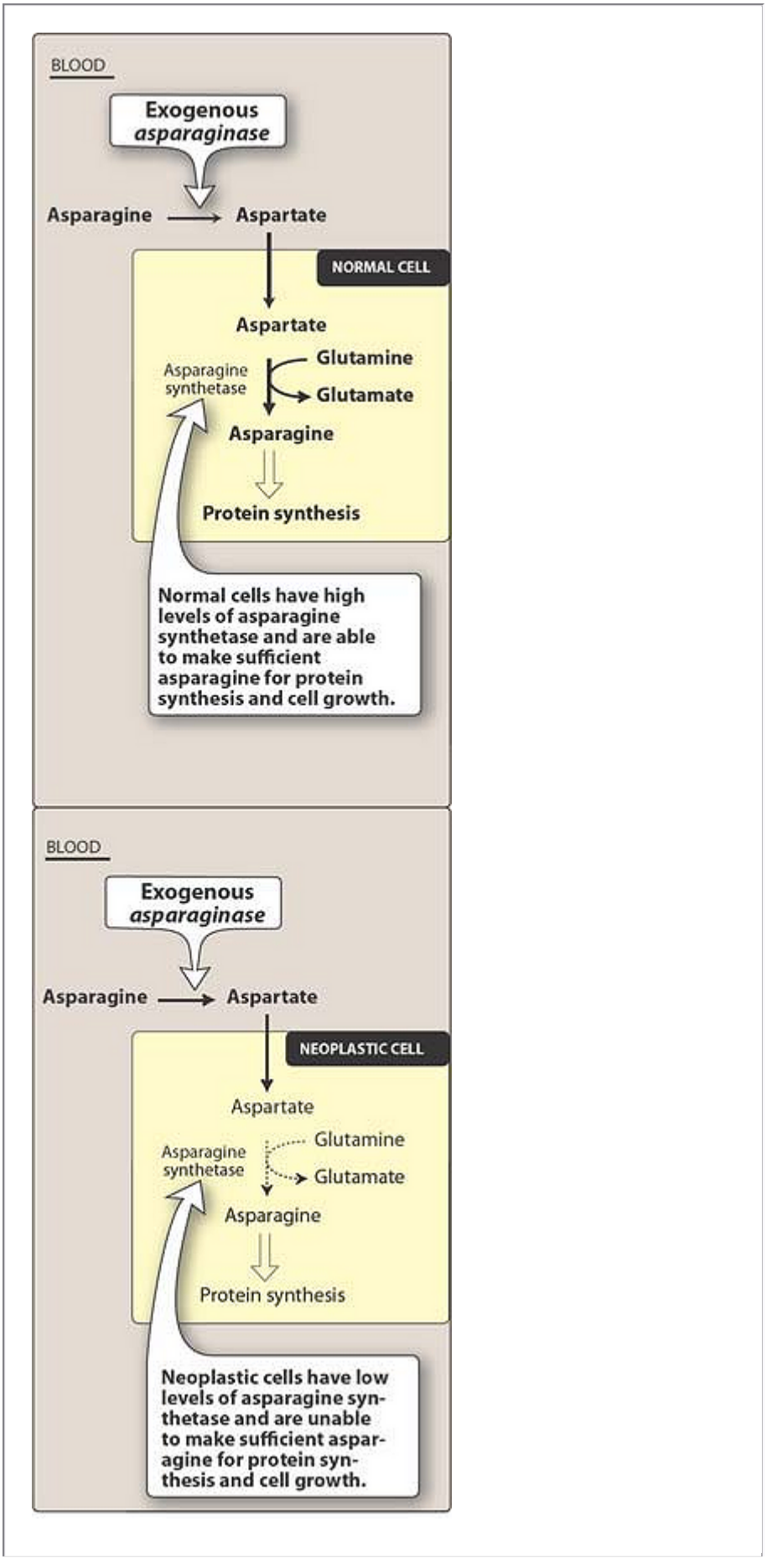

BLOOD
Exogenous asparaginase
Asparagine
Aspartate
NORMAL CELL
Aspartate
Asparagine synthetase
Glutamine
Glutamate
Asparagine
Protein synthesis
Normal cells have high levels of asparagine synthetase and are able to make sufficient asparagine for protein synthesis and cell growth.
BLOOD
Exogenous asparaginase
Asparagine
Aspartate
NEOPLASTIC CELL
Aspartate
Asparagine synthetase
Glutamine
Glutamate
Asparagine
Protein synthesis
Neoplastic cells have low levels of asparagine synthetase and are unable to make sufficient asparagine for protein synthesis and cell growth.

Figure 39.34 Activity of asparagine synthetase in normal and neoplastic cells.

Study Questions

Choose the ONE best answer.

39.1 A patient with colonic cancer is being treated with 5-FU as well as leucovorin (N^5,N^{10}-methylene tetrahydrofolate). The rationale for administering the coenzyme depends on it being essential for:

A. Conversion of 5-FU to fluorodeoxyuridylic acid (FdUMP).

B. Protection against the anemia caused by 5-FU treatment.

C. The inhibition of thymidylate synthase by FdUMP.

D. Prolongation of the antitumor effect of 5-FU.

View Answer

39.2 Neutropenia develops in a patient undergoing cancer chemotherapy. Administration of which one of the following agents would accelerate recovery of neutrophil counts?

A. Leucovorin.

B. Filgrastim.

C. Prednisone.

D. Vitamin B_{12}.

View Answer

39.3 Hydration and/or diuresis can prevent the renal toxicity associated with:

A. Cisplatin.

B. Chlorambucil.

C. Tamoxifen.

D. Gemcitabine.

E. MTX.

View Answer

39.4 A patient is being treated with allopurinol to control hyperuricemia resulting from chemotherapy. Which of the following would have to have its dose reduced to prevent toxicity?

A. 5-FU.

B. 6-MP.

C. 6-TG.

D. Fludarabine.

E. Cytarabine.

View Answer

Editors: **Finkel, Richard; Clark, Michelle A.; Cubeddu, Luigi X.**
Title: *Lippincott's Illustrated Reviews: Pharmacology, 4th Edition*

Copyright Â©2009 Lippincott Williams & Wilkins

Chapter 40

Immunosuppressants

I. Overview

The importance of the immune system in protecting the body against harmful foreign molecules is well recognized. However, in some instances, this protection can result in serious problems. For example, the introduction of an allograft (that is, the graft of an organ or tissue from one individual to another who is not genetically identical) can elicit a damaging immune response, causing rejection of the transplanted tissue. Transplantation of organs and tissues (for example, kidney, heart, or bone marrow) has become routine due to improved surgical techniques and better tissue typing. Also, drugs are now available that more selectively inhibit rejection of transplanted tissues while preventing the patient from becoming immunologically compromised (Figure 40.1). Earlier drugs were nonselective, and patients frequently succumbed to infection due to suppression of both the antibody-mediated (humoral) and cell-mediated arms of the immune system. Today, the principal approach to immunosuppressive therapy is to alter lymphocyte function using drugs or antibodies against immune proteins. Because of their severe toxicities when used as monotherapy, a combination of immunosuppressive agents, usually at lower doses, is generally employed. [Note: Immunosuppressive therapy is also used in the treatment of autoimmune diseases; for example, corticosteroids can control acute glomerulonephritis.] Immunosuppressive drug regimens usually consist of anywhere from two to four agents with different mechanisms of action that disrupt various levels of T-cell activation. The immune activation cascade can be described as a three-signal model. Signal 1 constitutes T-cell triggering at the CD3 receptor complex by an antigen on the surface of an antigen-presenting cell (APC). Signal 2, also referred to as costimulation, occurs when CD80 and CD86 on the surface of APCs engage CD28 on T cells. Both Signals 1 and 2 activate several intracellular signal transduction pathways, one of which is the calcium-calcineurin pathway, which is targeted by *cyclosporine* and *tacrolimus.* These pathways trigger the production of cytokines such as interleukin (IL)-2, IL-15, CD154, and CD25. IL-2 then binds to CD25 (also known as the IL-2 receptor) on the surface of other T cells to activate mammalian target of *rapamycin* (mTOR), providing Signal 3, the stimulus for T-cell proliferation. Immunosuppressive drugs can be categorized according to their mechanisms of action: 1) Some agents interfere with cytokine production or action; 2) others disrupt cell metabolism, preventing lymphocyte proliferation; and 3) mono- and polyclonal antibodies block T-cell surface molecules.

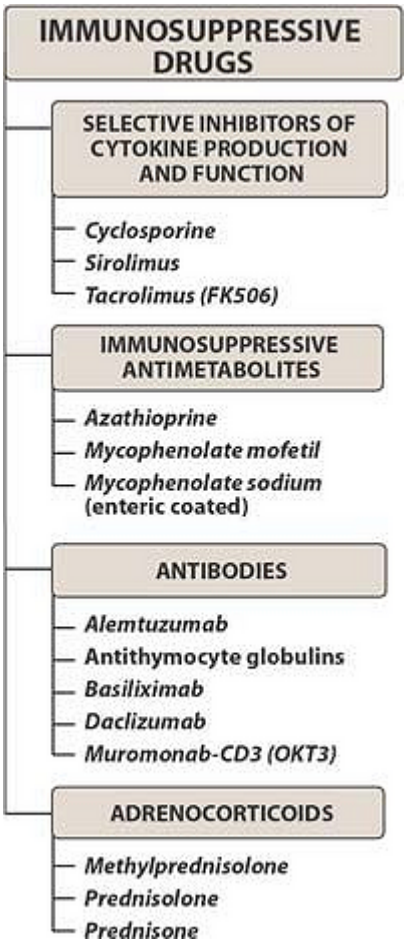
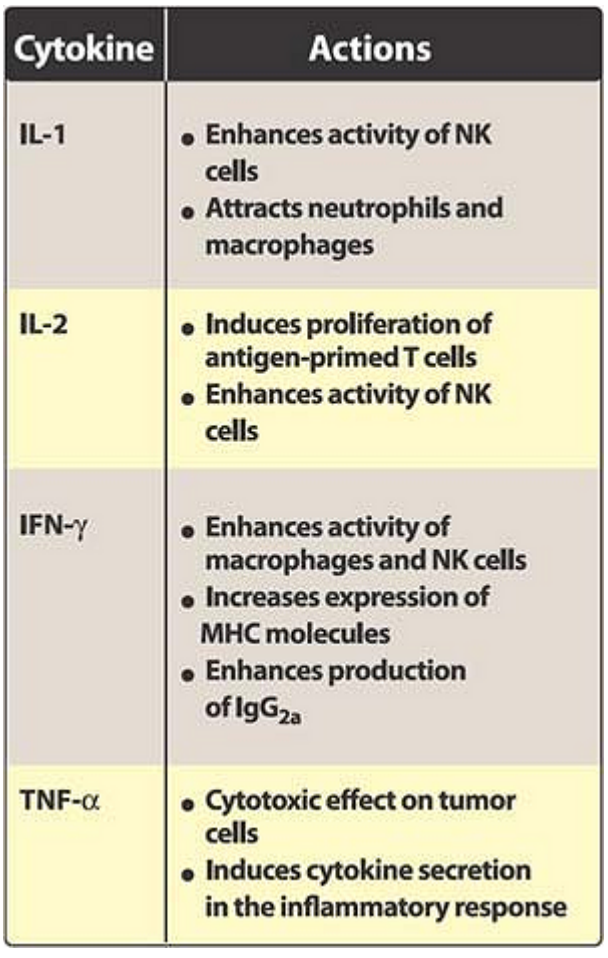


Figure 40.1 Immunosuppressant drugs.

II. Selective Inhibitors of Cytokine Production and Function

Cytokines are soluble, antigen-nonspecific, signaling proteins that bind to cell surface receptors on a variety of cells. The term cytokine includes the molecules known as ILs, interferons (IFNs), tumor necrosis factors (TNFs), transforming growth factors, and colony-stimulating factors. Of particular interest when discussing immunosuppressive drugs is IL-2â€"a growth factor that stimulates the proliferation of antigen-primed (helper) T cells, which subsequently produce more IL-2, IFN-Î³, and TNF-Î² (Figure 40.2). These cytokines collectively activate natural killer cells, macrophages, and cytotoxic T lymphocytes. Clearly, drugs that interfere with the production or activity of IL-2, such as *cyclosporine*, will significantly dampen the immune response and, thereby, decrease graft rejection.



Cytokine	Actions
IL-1	• Enhances activity of NK cells • Attracts neutrophils and macrophages
IL-2	• Induces proliferation of antigen-primed T cells • Enhances activity of NK cells
IFN-γ	• Enhances activity of macrophages and NK cells • Increases expression of MHC molecules • Enhances production of IgG_{2a}
TNF-α	• Cytotoxic effect on tumor cells • Induces cytokine secretion in the inflammatory response

Figure 40.2 Summary of selected cytokines.

A. Cyclosporine

Cyclosporine [sye-kloe-SPOR-een] (*CsA*) is a lipophillic cyclic polypeptide composed of 11 amino acids (several are methylated on the peptidyl nitrogen). The drug is extracted from a soil fungus. *CsA* is used to prevent rejection of kidney, liver, and cardiac allogeneic transplants. *CsA* is most effective in preventing acute rejection of transplanted organs when combined in a double-drug or triple-drug regimen with corticosteroids and an antimetabolite such as *mycophenolate mofetil*. *CsA* is an alternative to *methotrexate* for the treatment of severe, active rheumatoid arthritis. It can also be used for patients with recalcitrant psoriasis that does not respond to other therapies.

1. **Mechanism of action:** *Cyclosporine* preferentially suppresses cell-mediated immune reactions, whereas humoral immunity is affected to a far lesser extent. After diffusing into the T cell, *CsA* binds to a cyclophilin (more generally called an immunophilin) to form a complex that binds to calcineurin (Figure 40.3). The latter is responsible for dephosphorylating NFATc (**c**ytosolic **N**uclear **F**actor of **A**ctivated **T** cells). The *CsA*-calcineurin complex cannot perform this reaction; thus, NFATc cannot enter the nucleus to promote the reactions that are required for the synthesis of a number of cytokines, including IL-2. The end result is a decrease in IL-2â€"the primary chemical stimulus for increasing the number of T lymphocytes.
2. **Pharmacokinetics:** *Cyclosporine* may be given either orally or by intravenous infusion. Oral absorption is variable. Interpatient variability may be due to metabolism by a cytochrome P450 (CYP3A4) in the

gastrointestinal tract, where the drug is metabolized. About 50 percent of the drug is associated with the blood fraction. Half of this is in the erythrocytes, and less than one-tenth is bound to the lymphocytes. *CsA* is extensively metabolized, primarily by hepatic CYP3A4. [Note: When other drug substrates for this enzyme are given concomitantly, many drug interactions have been reported.] It is not clear whether any of the 25 or more metabolites have any activity. Excretion of the metabolites is through the biliary route, with only a small fraction of the parent drug appearing in the urine.

3. **Adverse effects:** Many of the adverse effects caused by *CsA* are dose dependent; therefore, it is important to monitor blood levels of the drug. Nephrotoxicity is the most common and important adverse effect of *CsA*. It is therefore critical to monitor kidney function. Reduction of

the *CsA* dosage can result in reversal of nephrotoxicity in most cases, although nephrotoxicity may be irreversible in 15% of patients. [Note: Coadministration of drugs that also can cause kidney dysfunction (for example, the aminoglycoside antibiotics) and anti-inflammatories, such as *diclofenac*, *naproxen*, or *sulindac,* can potentiate the nephrotoxicity of *CsA*.] Hepatotoxicity can also occur; therefore, liver function should be periodically assessed.] Infections in patients taking *CsA* are common and may be life-threatening. Viral infections due to herpes group and cytomegalovirus (CMV) are prevalent. Lymphoma may occur in all transplanted patients due to the net level of immunosuppression and has not been linked to any one particular agent. Anaphylactic reactions can occur on parenteral administration. Other toxicities include hypertension, hyperlipidemia, hyperkalemia (it is important not to use K^+-sparing diuretics in these patients), tremor, hirsutism, glucose intolerance, and gum hyperplasia.

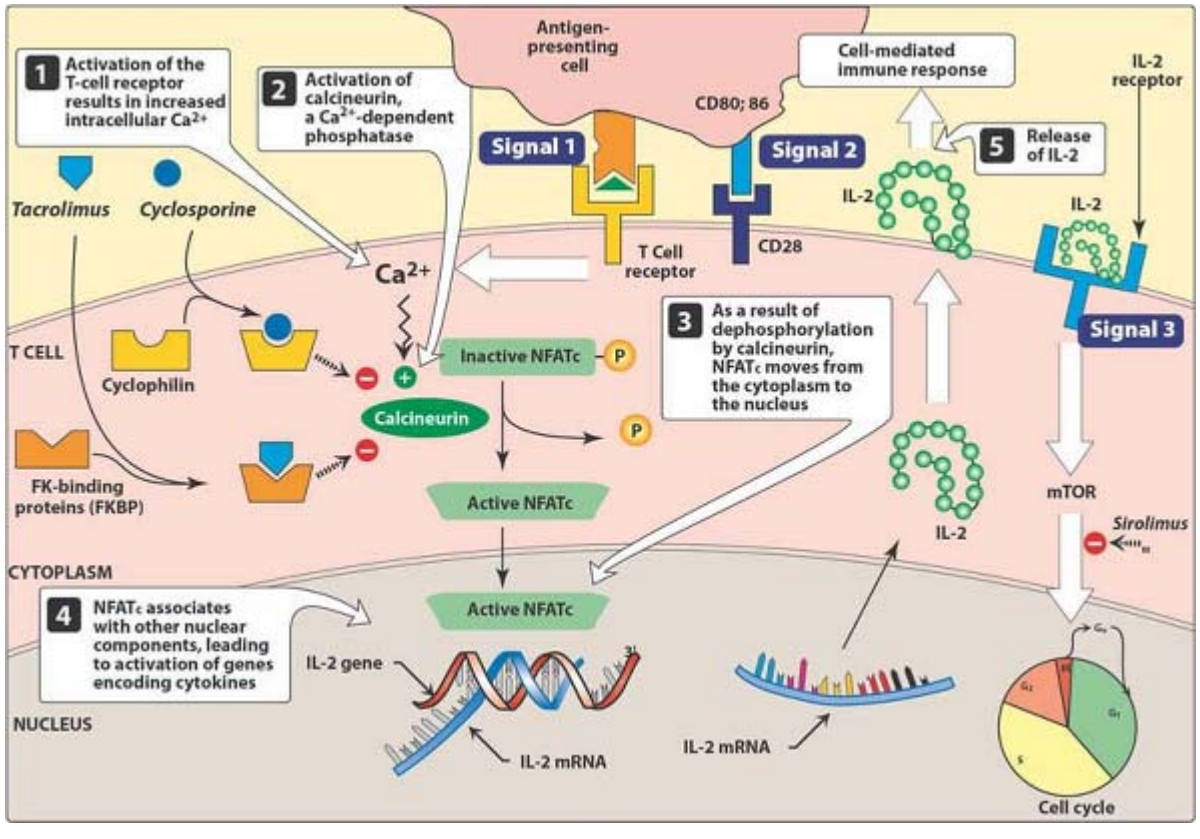


Figure 40.3 Mechanism of action of *cyclosporine* and *tacrolimus*. Il-2 = interleukin-2; mTOR = mammalian target of rapamycin; NFATc = cytosolic nuclear factor of activated T cells.

B. Tacrolimus

Tacrolimus [ta-CRAW-lih-mus] (*TAC*, originally called *FK506*) is a macrolide that is isolated from a soil fungus. *TAC* is approved for the prevention of rejection of liver and kidney transplants and is given with a corticosteroids and/or an antimetabolite. This drug has found favor over

CsA, not only because of its potency and decreased episodes of rejection (Figure 40.4) but also because lower doses of corticosteroids can be used, thus reducing the likelihood of steroid-associated adverse effects. An ointment preparation has been approved for moderate to severe atopic dermatitis that does not respond to conventional therapies.

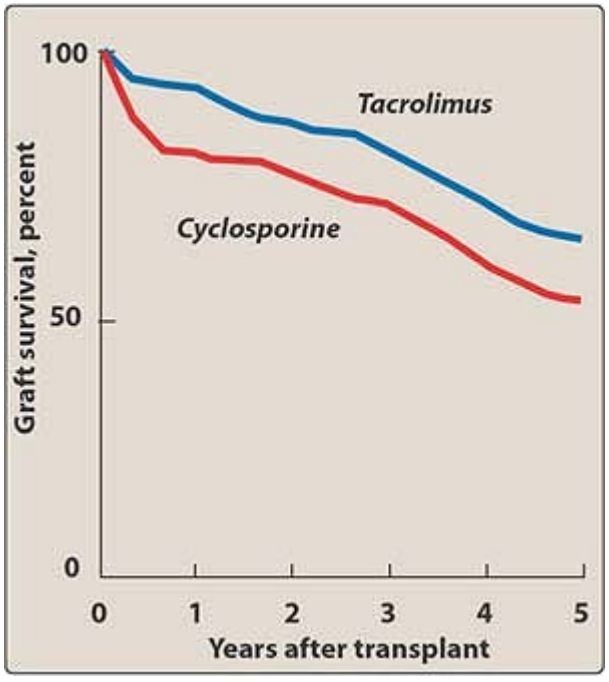


Figure 40.4 Five-year renal allograft survival in patients treated with *cyclosporine* or *tacrolimus*.

1. **Mechanism of action:** *TAC* exerts its immunosuppressive effect in the same manner as *CsA*, except that it binds to a different immunophilin, FKBP-12 (FK-**b**inding **p**rotein; Figure 40.5).

2. **Pharmacokinetics:** *TAC* may be administered orally or intravenously. The oral route is preferable, but as with *CsA*, oral absorption of *TAC* is incomplete and variable, requiring tailoring of doses. Absorption is decreased if the drug is taken with high-fat or high-carbohydrate meals. *TAC* is from 10- to 100-fold more potent than *CsA*. It is highly bound to serum proteins and is also concentrated in erythrocytes. Like *CsA*, *TAC* undergoes hepatic metabolism by the CYP3A4 isozyme; thus, the same drug interactions occur. At least one metabolite of *TAC* has been shown to have immunosuppressive activity. Renal excretion is very low, and most of the drug and its metabolites are found in the feces.

3. **Adverse effects:** Nephrotoxicity and neurotoxicity (tremor, seizures, and hallucinations) tend to be more severe in patients who are treated with *TAC* than in patients treated with *CsA*, but careful dose adjustment can minimize this problem. Development of posttransplant, insulin-dependent diabetes mellitus is a problem, especially in black and Hispanic patients. Other toxicities are the same as those for *CsA*, except that *TAC* does not cause hirsutism or gingival hyperplasia. Compared with *CsA*, *TAC* has also been found to have a lower

incidence of cardiovascular toxicities such as hypertension and hyperlipidemia, both of which are common disease states found in kidney transplant recipients. Anaphylactoid reactions to the injection vehicle have been reported. The drug interactions are the same as those described for *CsA*.

C. Sirolimus

Sirolimus [sih-ROW-lih-mus] (*SRL*) is a recently approved macrolide obtained from fermentations of a soil mold. The earlier nameâ€"and one that is sometimes still usedâ€"is *rapamycin*. *SRL* is approved for use in renal transplantation, to be used together with *CsA* and corticosteroids, thereby allowing lower doses of those medications to be employed and, thus, lowering their toxic potential. The combination of *SRL* and *CsA* is apparently synergistic because *SRL* works later in the immune activation cascade. To limit the long-term side effects of the calcineurin inhibitor, *SRL* is often utilized in calcineurin inhibitor withdrawal protocols in patients who remain rejection free during the first 3 months posttransplant. The antiproliferative action of *SRL* has found use in cardiology. *SRL*-coated stents inserted into the cardiac vasculature inhibit restenosis of the blood vessels by reducing proliferation of the endothelial cells. In addition to its immunosuppressive effects, *SRL* also inhibits proliferation of cells in the graft intimal areas and, thus, is effective in halting graft vascular disease.

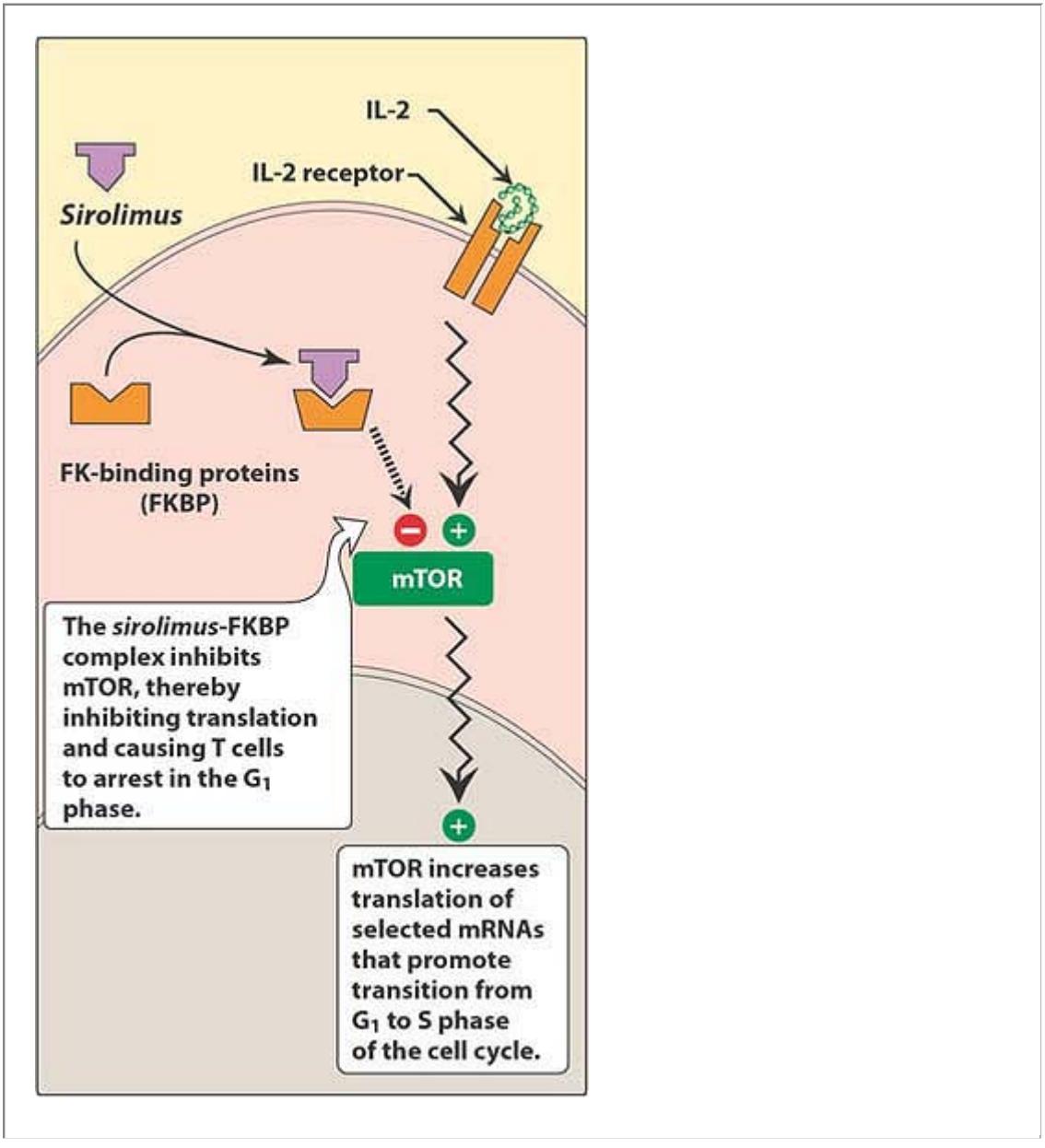


Figure 40.5 Mechanism of action of *sirolimus*. mTOR = molecular target of *rapamycin (sirolimus)*.

1. **Mechanism of action:** *SRL* and *TAC* bind to the same cytoplasmic FK-binding protein, but instead of forming a complex with calcineurin, *SRL* binds to mTOR interfering with Signal 3). The latter is a serine-threonine

kinase. [Note: TOR proteins are essential for many cellular functions, such as cell-cycle progression, DNA repair, and as regulators involved in protein translation.] Binding of *SRL* to mTOR blocks the progression of activated T cells from the G_1 to the S phase of the cell cycle and, consequently, the proliferation of these cells (see Figure 40.5). Unlike *CsA* and *TAC*, *SRL* does not owe its effect to lowering IL-2 production but, rather, to inhibiting the cellular responses to IL-2.

2. **Pharmacokinetics:** The drug is available only as oral preparations. Although it is readily absorbed, high-fat meals can decrease the drugâ€"s absorption. *SRL* has a long half-life compared to those of *CsA* and *TAC,* and a loading dose is required at the time of initiation of therapy. Like both *CsA* and *TAC*, *SRL* is metabolized by the CYP3A4 isozyme and interacts with the same drugs as do *CsA* and *TAC*. *SRL* also increases the drug concentrations of *CsA,* and careful blood level monitoring of both agents must be employed to avoid harmful drug toxicities. The parent drug and its metabolites are predominantly eliminated in the feces.

3. **Adverse effects:** A frequent side effect of *SRL* is hyperlipidemia (elevated cholesterol and triglycerides), which can require treatment. The combination of *CsA* and *SRL* is more nephrotoxic than *CsA* alone due to the drug interaction between the two; therefore, lower doses are initiated. Although the administration of *SRL* and *TAC* appears to be less nephrotoxic, *SRL* can still potentiate the nephrotoxicity of *TAC,* and drug levels of both must be monitored closely. Other untoward problems are headache, nausea and diarrhea, leukopenia, and thrombocytopenia. Impaired wound healing has been noted with *SRL* in obese patients and those with diabetes; this can be especially problematic immediately following the transplant surgery and in patients receiving corticosteroids.

III. Immunosuppressive Antimetabolites

Immunosuppressive antimetabolite agents are generally used in combination with corticosteroids, and the calcineurin inhibitors, *CsA* and *TAC*.

A. Azathioprine

Azathioprine [ay-za-THYE-oh-preen] was the first agent to achieve widespread use in organ transplantation. It is a prodrug that is converted first to *6-mercaptopurine* (*6-MP*) and then to the corresponding nucleotide, thioinosinic acid. The immunosuppressive effects of *azathioprine* are due to this nucleotide analog. Because of their rapid proliferation in the immune response and their dependence on the de novo synthesis of purines required for cell division, lymphocytes are predominantly affected by the cytotoxic effects of *azathioprine*. [Note: The drug has little effect on suppressing a chronic immune response.] Its major nonimmune toxicity is bone marrow suppression. Concomitant use with angiotensin-converting enzyme inhibitors or *cotrimoxazole* in renal transplant patients can lead to an exaggerated leukopenic response. *Allopurinol*, an agent used to treat gout, significantly inhibits the metabolism of *azatihioprine*; therefore, the dose of *azathioprine* must be reduced by 60 to 75 percent. Nausea and vomiting are also encountered. (See p. 464 for a discussion of the mechanism of action, resistance, and pharmacokinetics of *6-MP*.)

B. Mycophenolate mofetil (MMF)

Azathioprine has for the most part been replaced by *mycophenolate mofetil* [mye-koe-FEN-oh-late MAW-feh-til] (MMF) because of the latterâ€"s safety and efficacy in prolonging graft survival. It has been successfully used in

heart, kidney, and liver transplants. As an ester, it is rapidly hydrolyzed in the gastrointestinal tract to mycophenolic acid (MPA), which is a potent, reversible, uncompetitive inhibitor of inosine monophosphate dehydrogenase, blocking the de novo formation of guanosine phosphate. Thus, like *6-MP*, it deprives the rapidly proliferating T and B cells of a key component of nucleic acids (Figure 40.6). [Note: Lymphocytes lack the salvage pathway for purine synthesis and, therefore, are dependent on de novo purine production.] MPA is quickly and almost completely absorbed after oral administration. Both MPA and its glucuronidated metabolite are highly bound (greater than 90 percent) to plasma albumin, but no displacement-type interactions have been reported. The glucuronide is excreted predominantly in the urine. The most common adverse effects include diarrhea, nausea, vomiting, abdominal pain, leukopenia, and anemia. Higher doses of *MMF* (3 g/day) were associated with a higher risk of CMV infection. [Note: MPA is less mutagenic or carcinogenic than *azathioprine*.] Concomitant administration with antacids containing magnesium or aluminum, or with *cholestyramine*, can decrease absorption of the drug.

C. Enteric-coated mycophenolate sodium

In an effort to minimize the gastrointestinal effects associated with *MMF*, enteric-coated mycophenolate sodium (EC-*MPS*) was developed. The active drug (MPA) is contained within a delayed-release formulation designed to release in the neutral pH of the small intestine. EC-MPS at 720 mg and *MMF* at 1000 mg contain equivalent amounts of MPA. In Phase III studies, the new formulation was found to be equivalent to MMF in the prevention of acute rejection episodes in kidney transplant recipients. However, the rate of gastrointestinal adverse events was similar to that with MMF.

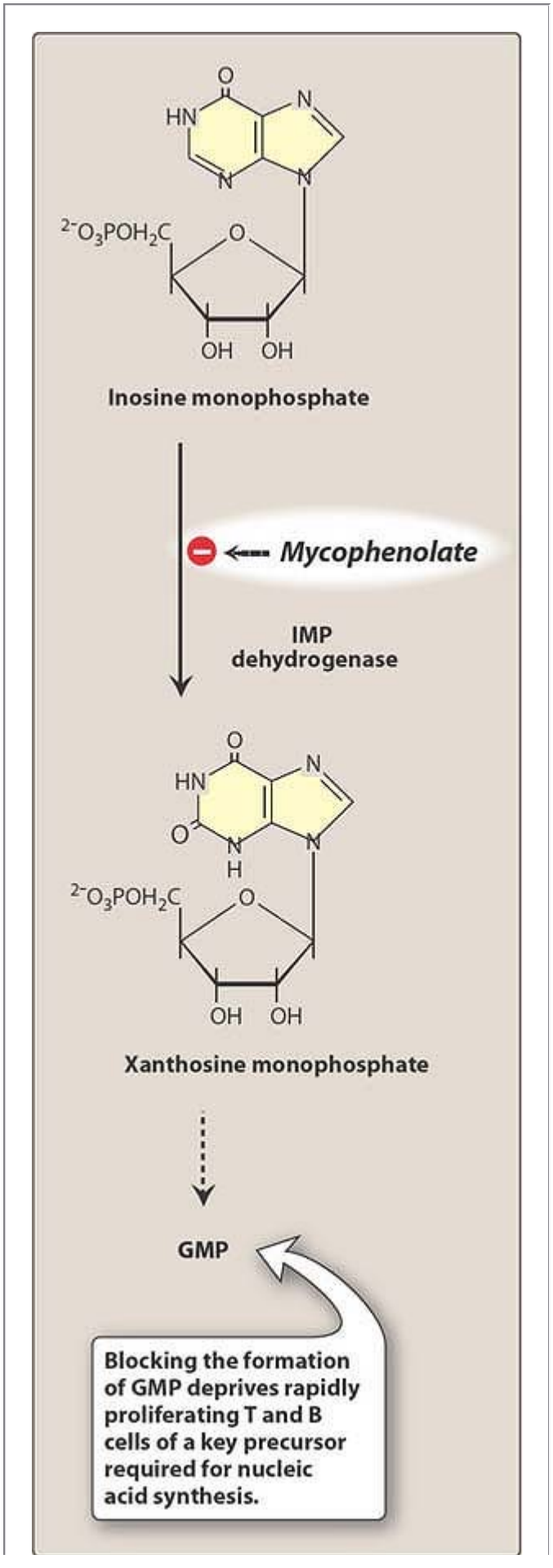

Inosine monophosphate
Mycophenolate
IMP dehydrogenase
Xanthosine monophosphate
GMP
Blocking the formation of GMP deprives rapidly proliferating T and B cells of a key precursor required for nucleic acid synthesis.

Figure 40.6 Mechanism of action of *mycophenolate*.

IV. Antibodies

The use of antibodies plays a central role in prolonging allograft survival. They are prepared either by immunization of rabbits or horses with human lymphoid cells (producing a mixture of polyclonal antibodies directed against a number of lymphocyte antigens), or by hybridoma technology (producing antigen-specific, monoclonal antibodies). [Note: Hybridomas are produced by fusing mouse antibody-producing cells with immortal, malignant plasma cells (Figure 40.7). Hybrid cells are selected and cloned, and the antibody specificity of the clones is determined. Clones of interest can be cultured in large quantities to produce clinically useful amounts of the desired antibody. Recombinant DNA technology can also be used to replace part of the mouse gene sequence with human genetic material, thus â€œhumanizingâ€ the antibodies produced, making them less antigenic.] The names of monoclonal antibodies conventionally contain â€œmuroâ€ if they are from a murine (mouse) source and â€œxiâ€ or â€œizâ€ if they are humanized (see Figure 40.7). The suffix â€œmabâ€ (monoclonal antibody) identifies the category of drug. The polyclonal antibodies, although relatively inexpensive to produce, are variable and less specific, which is in contrast to monoclonal antibodies, which are homogeneous and specific.

A. Antithymocyte globulins

Thymocytes are cells that develop in the thymus and serve as T-cell precursors. The antibodies developed against them are prepared by immunization of large rabbits or horses with human lymphoid cells and, thus, are polyclonal. They are primarily employed, together with other immunosuppressive agents, at the time of transplantation to prevent early allograft rejection, or they may be used to treat severe rejection episodes or corticosteroid-resistant acute rejection. Rabbit formulations of polyclonal antithymocyte globulin are more commonly used over the horse preparation due to greater potency. The antibodies bind to the surface of circulating T lymphocytes, which then undergo various reactions, such as complement-mediated destruction, antibody-dependent cytotoxicity, apoptosis, and opsonization. The antibody-bound cells are phagocytosed in the liver and spleen, resulting in lymphopenia and impaired T-cell responses. The antibodies are slowly infused intravenously, and their half-life extends from 3 to 9 days. Because the humoral antibody mechanism remains active, antibodies can be formed against these foreign proteins. [Note: This is less of a problem with the humanized antibodies.] Other adverse effects include chills and fever, leukopenia and thrombocytopenia, infections due to CMV or other viruses, and skin rashes.

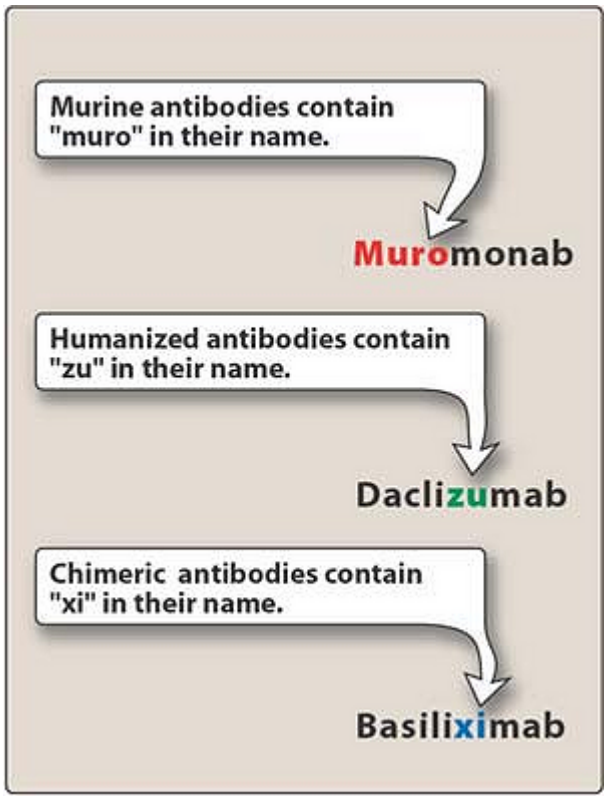


Figure 40.7 Conventions for naming monoclonal antibodies. [Note: *Muromonab* was named before the convention was adopted to make the last three letters in their names *mab*.]

B. Muromonab-CD3 (OKT3)

Muromonab-CD3 [myoo-roe-MOE-nab] is a murine monoclonal antibody that is synthesized by hybridoma technology and directed against the glycoprotein CD3 antigen of human T cells. *Muromonab-CD3* is used for treatment of acute rejection of renal allografts as well as for corticosteroid-resistant acute allograft rejection in cardiac and hepatic transplant patients. It is also used to deplete T cells from donor bone marrow prior to transplantation.

1. **Mechanism of action:** Binding to the CD3 protein results in a disruption of T-lymphocyte function, because access of antigen to the recognition site is blocked. Circulating T cells are depleted; thus, their participation in the immune response is decreased. Because *muromonab-CD3* recognizes only one antigenic site, the immunosuppression is less broad than that seen with the polyclonal antibodies. T cells usually return to normal within 48 hours of discontinuation of therapy.

2. **Pharmacokinetics:** The antibody is administered intravenously. Initial binding of *muromonab-CD3* to the antigen transiently activates the T cell and results in cytokine release (cytokine storm). It is therefore customary to premedicate the patient with *methylprednisolone*, *diphenhydramine*, and *acetaminophen* to alleviate the cytokine release syndrome.

3. **Adverse effects:** Anaphylactoid reactions may occur. Cytokine release syndrome may follow the first dose. The symptoms can range from a mild, flu-like illness to a life-threatening, shock-like reaction. High fever is common. Central nervous system effects, such as seizures, encephalopathy, cerebral edema, aseptic meningitis, and headache, may occur. Infections can increase, including some due to CMV. *Muromonab-CD3* is contraindicated in patients with a history of seizures, in those with uncompensated heart failure, in pregnant women, and in

those who are breast-feeding. Because of these adverse effects and the improved tolerability of thymoglobulin and the IL-2 receptor antagonists, *muromonab-CD3* is rarely used today.

C. IL-2-receptor antagonists

The antigenicity and short serum half-life of the murine monoclonal antibody have been averted by replacing most of the murine amino acid sequences with human ones by genetic engineering. *Basiliximab* [bah-si-LIK-si-mab] is said to be â€œchimerizedâ€ because it consists of 25 percent murine and 75 percent human protein. *Daclizumab* [dah-KLIZ-yoo-mab] is 90 percent human protein, and is designated â€œhumanized.â€ Both agents have been approved for prophylaxis of acute rejection in renal transplantation in combination with *CsA* and corticosteroids. They are not used for the treatment of ongoing rejection.

1. **Mechanism of action:** Both compounds are anti-CD25 antibodies and bind to the Î± chain of the IL-2 receptor on activated T cells. They thus interfere with the proliferation of these cells. *Basiliximab* is about 10-fold more potent than *daclizumab* as a blocker of IL-2 stimulated T-cell replication. Blockade of this receptor foils the ability of any antigenic stimulus to activate the T cellâ€“response system.
2. **Pharmacokinetics:** Both antibodies are given intravenously. The serum half-life of *daclizumab* is about 20 days, and the blockade of the receptor is 120 days. Five doses of *daclizumab* are usually administeredâ€”the first at 24 hours before transplantation, and the next four doses at 14-day intervals. The serum half-life of *basiliximab* is about 7 days. Usually, two doses of this drug are administeredâ€”the first at 2 hours prior to transplantation, and the second at 4 days after the surgery.
3. **Adverse effects:** Both *daclizumab* and *basiliximab* are well tolerated. Their major toxicity is gastrointestinal. No clinically relevant antibodies to the drugs have been detected, and malignancy does not appear to be a problem.

D. Alemtuzumab

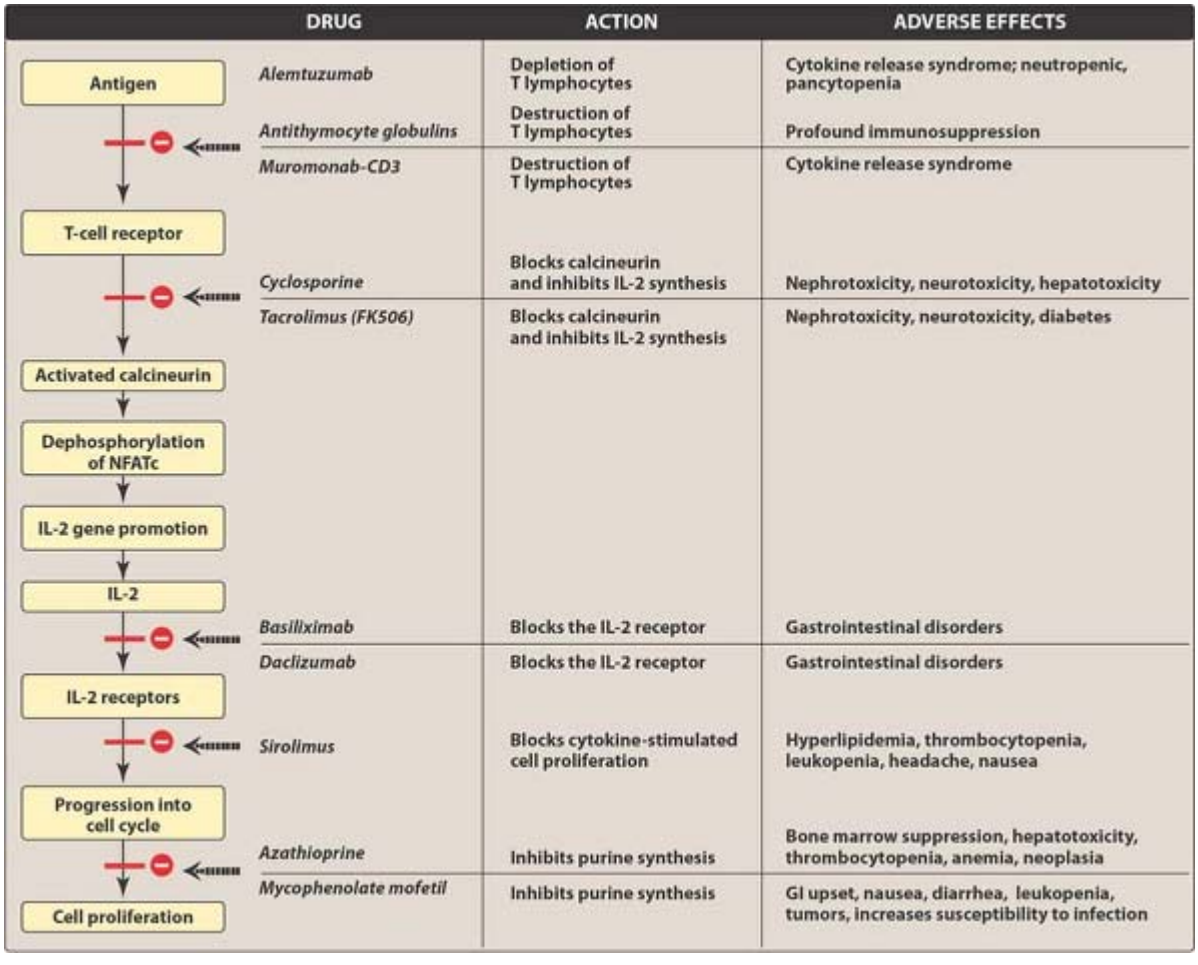
Alemtuzumab [al-em-TOOZ-oo-mab], a humanized monoclonal antibody directed against CD52, exerts its effects by causing profound depletion of T cells from the peripheral circulation. This effect may last for up to 1 year. *Alemtuzumab* is currently approved for the treatment of refractory B-cell chronic lymphocytic leukemia. Although it is not currently approved for use in organ transplantation, it is being utilized in combination with *SRL* and low-dose calcineurin inhibitors in corticosteroid avoidance protocols at many transplant centers. Preliminary results are promising, with low rates of rejection with a *prednisone*-free regimen. Side effects include first-dose cytokine-release syndrome, requiring premedication with *acetaminophen*, *diphenhydramine*, and corticosteroids. Adverse effects include neutropenia, anemia, and rarely, pancytopenia. Early results have not shown an increase in opportunistic infections or lymphomas with *alemtuzumab* despite its potent immunosuppressive activity. A summary of the major immunosuppressive drugs is presented in Figure 40.8

V. Corticosteroids

The corticosteroids were the first pharmacologic agents to be used as immunosuppressives both in transplantation and in various autoimmune disorders. They are still one of the mainstays for attenuating rejection episodes. For transplantation, the most common agents are *prednisone* or

methylprednisolone, whereas *prednisone* or *prednisolone* are employed for autoimmune conditions. [Note: In transplantation, they are used in combination with agents described previously in this chapter.] The steroids are used to suppress acute rejection of solid organ allografts and in chronic graft-versus-host disease. In addition, they are effective against a wide variety of autoimmune conditions, including refractory rheumatoid arthritis, systemic lupus erythematosus, temporal arthritis, and asthma. The exact mechanism responsible for the immunosuppressive action of the corticosteroids is unclear. The T lymphocytes are affected most. The steroids are able to rapidly reduce lymphocyte populations by lysis or redistribution. On entering cells, they bind to the glucocorticoid

receptor. The complex passes into the nucleus and regulates the translation of DNA. Among the genes affected are those involved in inflammatory responses. **The use of these agents is associated with numerous adverse effects. For example, they are diabetogenic, and they can cause hypercholesterolemia, cataracts, osteoporosis, and hypertension on prolonged use. Consequently, efforts are being directed toward reducing or eliminating the use of steroids in the maintenance of allografts.**



DRUG	ACTION	ADVERSE EFFECTS
Alemtuzumab	Depletion of T lymphocytes	Cytokine release syndrome; neutropenic, pancytopenia
Antithymocyte globulins	Destruction of T lymphocytes	Profound immunosuppression
Muromonab-CD3	Destruction of T lymphocytes	Cytokine release syndrome
Cyclosporine	Blocks calcineurin and inhibits IL-2 synthesis	Nephrotoxicity, neurotoxicity, hepatotoxicity
Tacrolimus (FK506)	Blocks calcineurin and inhibits IL-2 synthesis	Nephrotoxicity, neurotoxicity, diabetes
Basiliximab	Blocks the IL-2 receptor	Gastrointestinal disorders
Daclizumab	Blocks the IL-2 receptor	Gastrointestinal disorders
Sirolimus	Blocks cytokine-stimulated cell proliferation	Hyperlipidemia, thrombocytopenia, leukopenia, headache, nausea
Azathioprine	Inhibits purine synthesis	Bone marrow suppression, hepatotoxicity, thrombocytopenia, anemia, neoplasia
Mycophenolate mofetil	Inhibits purine synthesis	GI upset, nausea, diarrhea, leukopenia, tumors, increases susceptibility to infection

Figure 40.8 Sites of action of immunosuppressants. Il-2 = interleukin-2. NFATc = cytosolic nuclear factor of activated T cells.

Study Questions

Choose the ONE best answer.

40.1 A 45-year-old male who received a renal transplant 3 months previously and is being maintained on methylprednisolone, cyclosporine, and mycophenolate mofetil is found to have increased creatinine levels, indicating possible rejection. Which of the following courses of therapy would be appropriate?

A. Increased dose of methylprednisolone.

B. Hemodialysis.

C. Treatment with muromonab-CD3.

D. Treatment with sirolimus.

E. Treatment with azathioprine.

View Answer

40.2 A 23-year-old female suffering from grand mal epilepsy is being controlled with phenytoin. She is a candidate for a renal transplant. Which agent might exacerbate the seizures in this patient?

A. Mycophenolate mofetil.

B. Sirolimus.

C. Cyclosporine.

D. Tacrolimus.

View Answer

40.3 Which of the following drugs used to prevent allograft rejection can cause hyperlipidemia?

A. Azathioprine.

B. Basiliximab.

C. Tacrolimus.

D. Mycophenolate mofetil.

E. Sirolimus.

View Answer

40.4 Which of the following drugs specifically inhibit calcineurin in the activated T lymphocytes?

A. Daclizumab.

B. Tacrolimus.

C. Prednisone.

D. Sirolimus.

E. Mycophenolate mofetil.

View Answer