Chapter 36 part 2

half-lives preclude their use in chemoprophylaxis. They are metabolized in the liver and are excreted primarily in 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.

**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 plasmo- dial dihydrofolate reductase3 at much lower concentrations than those needed to inhibit the mammalian enzyme. The inhibition deprives the protozoan of tetrahydrofolate, 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 African sleeping sickness and American sleeping sickness, two chronic and, eventually, fatal diseases caused by species of Trypanosoma (Figure 36.13). In African sleeping sickness, the causative organisms, T. brucei gambiense and T. 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 T. cruzi and occurs in South America.

1. **Melarsoprol**

Melarsoprol [mel-AR-so-prol] is a derivative of mersalyl oxide, a trivalent arsenical. Its use is limited to the treatment of trypanosomal infections (usually in the late stage with CNS involvement), 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 are protected from its toxic effects. Trypanosomal resistance may also be due to decreased permeability of the drug.

**2. Pharmacokinetics**: Melarsoprol usually is slowly administered intravenously through a fi ne 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, whereas pentamidine does not penetrate the CSF. 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 in 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. In rare cases, however, it may 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.

**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 eff ective in the treatment of systemic blastomycosis (caused by the fungus Blastomyces dermatitidis) and in treating infections caused by Pneumocystis jiroveci (formerly called Pneumocystis carinii, the name now used to refer to the organism in animals). [Note: It is now considered to be a fungus, but it is not sus- ceptible to antifungal drugs. Trimethoprim-sulfamethoxazole is pre- ferred in the treatment of P. jiroveci infections. However, pentamidine is an alternative 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. jiroveci-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 immunodefi ciency virus, pentamidine has assumed an important place in chemotherapy.] Pentamidine is also an alternative drug to stibogluconate in the treatment of leishmaniasis.

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

**2. Pharmacokinetics:** Fresh solutions of pentamidine are administered intramuscularly or as an aerosol (Figure 36.15). [Note: The IV 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 β 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 peroxide4 (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 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.

**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 dehydrogenase6), 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 and RNA synthesis in 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 trans- mitted 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 diffi cult, 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 form7 of the organism).

1. **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.

1. **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 reaction8 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 urine (Figure 36.17). Adverse effects include pain at the injection site, gastro- intestinal 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 a combination of sulfadiazine and pyrimethamine. Leucovorin is commonly 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.]

**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 stools. Although some infections are asymptomatic, severe diarrhea can occur, which can be very serious in immune-suppressed patients. The treatment of choice is met- ronidazole for 5 days. One alternative agent is tinidazole, which is equally effective as metronidazole in the treatment of giardiasis but with a much shorter course of therapy (2 grams given once). Nitazoxanide [nye-ta-ZOX- a-nide], a nitrothiazole derivative structurally similar to aspirin, was recently approved for the treatment of giardiasis. Nitazoxanide is also equally efficacious as metronidazole and, in comparison, has a two-day-shorter course of therapy.