Antiprotozoal Drugs

• 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.

• With increased world travel, protozoal diseases are no longer confined to specific geographic locales.

• Because they are unicellular eukaryotes, the protozoal cells have metabolic processes closer to those of the human host than to prokaryotic bacterial pathogens.

• Therefore, protozoal diseases are 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.

• Most antiprotozoal agents have not proven to be safe for pregnant patients.
## Antiprotozoal Drugs

### Amebiasis
- Chloroquine *ARALEN*
- Dehydroemetine *DEHYDROEMETINE*
- Iodoquinol *YODOXIN*
- Metronidazole *FLAGYL*
- Paromomycin *HUMATIN*
- Tinidazole *TINDAMAX*

### Malaria
- Artemether/lumefantrine *COARTEM*
- Atovaquone-proguanil *MALARONE*
- Chloroquine *ARALEN*
- Mefloquine *LARIAM*
- Primaquine
- Pyrimethamine *DARAPRIM*
- Quinine/Quinidine *QUALAQUIN, QUINIDINE GLUCONATE*
# Antiprotozoal Drugs

## Trypanosomiasis
- Benznidazole **RADANIL**
- Eflornithine
- Melarsoprol
- Nifurtimox
- Pentamidine **NEBUPENT**
- Suramin **GERMANIN**

## Leishmaniasis
- Miltefosine **IMPAVIDO**
- Sodium stibogluconate

## Toxoplasmosis
- Pyrimethamine **DARAPRIM**

## Giardiasis
- Metronidazole **FLAGYL**
- Nitazoxanide **ALINIA**
- Tinidazole **TINDAMAX**
Chemotherapy 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 varying degrees of illness, from no symptoms to mild diarrhea to fulminating dysentery.
- The diagnosis is established by isolating E. histolytica from feces.
- Therapy is indicated for acutely ill patients and asymptomatic carriers, since dormant E. histolytica may cause future infections in the carrier and be a potential source of infection for others.
- Therapeutic agents for amebiasis are classified according to the site of action as:
  - **Luminal amebicides** act on the parasite in the lumen of the bowel.
  - **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.
Life cycle of Entamoeba histolytica

1. Ingestion of cysts
2. Formation of trophozoites
3. Penetration of intestinal wall
4. Multiplication of trophozoites within colon wall
5. Systemic invasion
6. Cysts discarded with feces

Systemic amebicides:
- Chloroquine
- Dehydroemetine

Mixed amebicide (luminal and systemic activity):
- Metronidazole
- Tinidazole

Luminal amebicides:
- Paromomycin
- Iodoquinol

Expelled trophozoite (noninfective)
Expelled cyst (infective)
Mixed Amebicides

- **Tinidazole:**

- **Metronidazole:**
  - Metronidazole a nitroimidazole, is the mixed amebicide of choice for treating **amebic infections**.
  - The drug of choice for the treatment of **pseudomembranous colitis** caused by the anaerobic, gram-positive bacillus Clostridium difficile.

- **Mechanism of action:**
  - Amebas possess ferredoxin-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 death of the E. histolytica trophozoites.
Pharmacokinetics

- **Metronidazole** is completely and rapidly absorbed after oral administration.
- 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%.
- 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 **glucuronidation**.
- The drug accumulates in patients with severe hepatic disease.
- The parent drug and its metabolites are excreted in the urine.
Adverse Effects:

- Nausea
- GI disturbance
- Metallic taste
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 the asymptomatic colonization state.

• **Iodoquinol**: a halogenated 8-hydroxyquinolone, is amebicidal against *E. histolytica* and is effective against the luminal trophozoite and cyst forms.

• **Paromomycin**: Paromomycin an aminoglycoside antibiotic, is only effective against the intestinal (luminal) forms of *E. histolytica*, because it is not significantly absorbed from the gastrointestinal tract.

• Paromomycin is directly amebicidal and also exerts its antiamebic actions by reducing the population of intestinal flora.
Systemic Amebicides

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

- **Chloroquine**: is used in combination with metronidazole treat amebic liver abscesses.

- It eliminates trophozoites in liver abscesses, but it is not useful in treating luminal amebiasis. Therapy should be followed with a luminal amebicide.

- **Chloroquine** is also effective in the treatment of **malaria**.

- **Dehydroemetine**: Dehydroemetine is an alternative agent for the treatment of amebiasis.

- The drug inhibits protein synthesis by blocking chain elongation.

- Intramuscular injection is the preferred route, since it is an irritant when taken orally.

- The use of this ipecac alkaloid is limited by its toxicity, and it has largely been replaced by metronidazole.

- **Adverse effects** include pain at the site of injection, nausea, cardiotoxicity (arrhythmias and congestive heart failure), neuromuscular weakness, dizziness, and rash.
Chemotherapy of Malaria

- Malaria is an acute infectious disease caused by four species of the protozoal genus Plasmodium.
- It is transmitted to humans through the bite of a female Anopheles mosquito.
- 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, reddish limbs).
- P. falciparum infection can lead to capillary obstruction and death without prompt treatment.
- 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.
Life cycle of the malarial parasite Plasmodium falciparum:

1. An infected mosquito injects sporozoites.
2. Sporozoites migrate to the liver, where they form merozoites.
3. Merozoites are released and invade red blood cells.
4. In the red blood cell, the merozoite becomes a trophozoite.
5. In the red blood cell, the trophozoite multiplies, producing new merozoites. These are released when the red blood cell ruptures, and they can infect other red blood cells.
6. Some merozoites become gametocytes.
7. The female mosquito picks up gametocytes from an infected human. The sexual cycle occurs in the mosquito, where sporozoites are formed.

Drugs effective against erythrocytic form:
- Artemisinin
- Atovaquone/proguanil
- Chloroquine
- Quinine
- Mefloquine
- Pyrimethamine

Drug effective against gametocytic form:
- Primaquine
Primaquine

- **Primaquine**
  - an 8-aminoquinoline, is an oral antimalarial drug that eradicates primary exoerythrocytic (tissue) forms of plasmodia.
  - The sexual (gametocytic) forms of all four plasmodia are destroyed in the plasma or are prevented from maturing later in the mosquito, thereby interrupting transmission of the disease.
  - Primaquine is not effective against the erythrocytic stage of malaria and, therefore, is used in conjunction with agents to treat the erythrocytic form (for example, chloroquine and mefloquine).
Mechanism of Action

- While not completely understood, metabolites of primaquine are believed to act as oxidants that are responsible for the schizonticidal action.
- Primaquine is well absorbed after oral administration and is not concentrated in tissues.
- It is rapidly oxidized to many compounds, primarily the deaminated drug. Which compound possesses the schizonticidal activity has not been established.
- The drug is minimally excreted in the urine.
Adverse Effects

• **Hemolytic anemia** in patients with glucose-6-phosphate dehydrogenase deficiency

• Large doses of the drug may cause **abdominal discomfort** (especially when administered in combination with chloroquine).

• Primaquine should not be used during pregnancy.

• All Plasmodium species may develop resistance to primaquine.
Glucose 6-P-dehydrogenase deficiency results in a decrease in NADPH and GSH synthesis, making the cell more sensitive to oxidative agents, such as *primaquine*. This causes hemolysis.

*Primaquine* oxidizes GSH to GSSG. Therefore, less GSH is available to neutralize toxic compounds.

**Figure 43.6**

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

- Chloroquine 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 used in the prophylaxis of malaria for travel to areas with known chloroquine-sensitive malaria.

- Hydroxychloroquine is an alternative to chloroquine for the prophylaxis and treatment of chloroquine-sensitive malaria.

- It is also effective in the treatment of extraintestinal amebiasis.
Mechanism of Action

• Although the mechanism of action is not fully understood.
• After traversing the erythrocytic and plasmodial membranes, chloroquine (a diprotic weak base) is concentrated in the acidic food vacuole of the malarial parasite, primarily by ion trapping.
• In the food vacuole, the parasite digests the host cell’s hemoglobin to obtain essential amino acids.
• However, this process also releases large amounts of soluble heme, which is toxic to the parasite.
• To protect itself, the parasite polymerizes the heme to hemozoin (a pigment), which is sequestered in the 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 phospholipid membranes, leading to lysis of both the parasite and the red blood cell.
Figure 43.7
Action of chloroquine on the formation of hemozoin by *Plasmodium* species.
Adverse effects

• Side effects are minimal at low prophylactic doses.
• At higher doses, gastrointestinal upset, pruritus, headaches, and blurred vision may occur.
• 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, severe gastrointestinal problems, or neurologic disorders.
• Patients with psoriasis or porphyria should not be treated with chloroquine, because an acute attack may be provoked.
Figure 43.8
Some adverse effects commonly associated with chloroquine.
Quinine

- Quinine originally isolated from the bark of the cinchona tree.
- Interferes with heme polymerization, resulting in death of the erythrocytic form of the plasmodial parasite.
- It is reserved for severe infestations and for chloroquine-resistant malarial strains.
- Quinine is usually administered in combination with doxycycline, tetracycline, or clindamycin.
- Taken orally, quinine is well distributed throughout the body.
- The major adverse effect of quinine is cinchonism, a syndrome causing nausea, vomiting, tinnitus, and vertigo.
- These effects are reversible and are not reasons for suspending therapy.
- Quinine treatment should be suspended if hemolytic anemia occurs.
- Drug interactions include potentiation of neuromuscular-blocking agents and elevation of digoxin levels if taken concurrently.
- Quinine absorption is reduced by aluminum-containing antacids.
Artemisinin is derived from the sweet wormwood plant, which has been used in traditional Chinese medicine for many centuries.

Artemisinin and its derivatives are recommended first-line agents for the treatment of multidrug-resistant P. falciparum malaria.

To prevent the development of resistance, these agents should not be used alone.

The antimalarial action involves the production of free radicals resulting from cleavage of the drug’s endoperoxide bridge by heme iron in the parasite food vacuole.

These agents may also covalently bind to and damage specific malarial proteins.

Oral, rectal, and intravenous (IV) preparations are available.

Adverse effects include nausea, vomiting, and diarrhea. High doses may cause prolongation of the QT interval.

Hypersensitivity reactions and rash have occurred.