Al-Mustaqbal University

Pharmacology I

3rd stage

Antiprotozoal Drugs

(191- 201)

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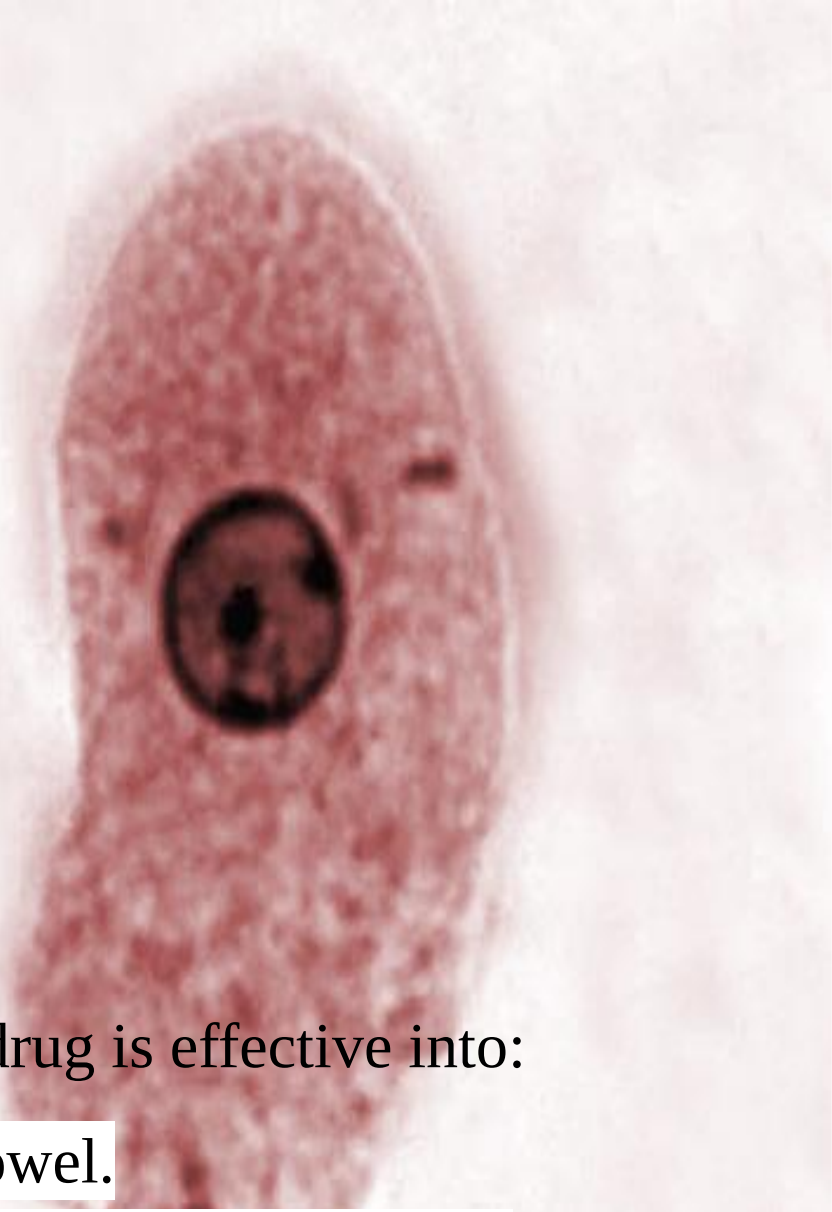
- **Antiprotozoal Drugs**

- Protozoan parasites causing human diseases are widespread in underdeveloped tropical and subtropical regions due to inadequate sanitary conditions and vector

- control.



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

- **Chemotherapy For Amebiasis**

Therapeutic agents are classified according to the site where the drug is effective into:

- **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,

Mixed amebicides (metronidazole and tinidazole)

Metronidazole: Metronidazole, a nitroimidazole, is the mixed amebicide of choice for treating amebic infections.

Metronidazole is also used in the treatment of infections caused by Giardia Lamblia, Trichomonas vaginalis, anaerobic cocci, anaerobic gram-negative bacilli (for example, Bacteroides species), and anaerobic, gram-positive bacilli (for example, Clostridium difficile).

Mechanism of action: Amebas possess ferredoxin-like, 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 deoxyribonucleic acid (DNA), resulting in death of the E. histolytica trophozoites.

Pharmacokinetics:

Metronidazole is completely absorbed from GIT.

Metronidazole distributes well throughout body tissues and fluids of body even CSF.

The drug accumulates in patients with severe hepatic disease. The parent drug and its metabolites are excreted in the urine.

Adverse effects: The most common adverse effects are nausea, vomiting, epigastric distress, and abdominal cramps. An unpleasant, metallic taste.

Other effects include oral yeast infection and potentially prolong the QT interval, requiring caution when used with drugs that increase QT prolongation.

If taken with alcohol, a disulfiram- like reaction may occur.

Tinidazole: a second-generation nitroimidazole that is similar to metronidazole in spectrum of activity, absorption, adverse effects, and drug interactions.

It is used for treatment of amebiasis, amebic liver abscess, giardiasis, and trichomoniasis.
Tinidazole is as effective as metronidazole, but it is more expensive.
Metabolized by CYP3A4, tinidazole concentrations can be influenced by strong inducers or inhibitors of this enzyme.
Common adverse effects include gastrointestinal upset and a metallic taste, and alcohol consumption should be avoided during therapy.

Luminal amebicides

(luminal agent, such as iodoquinol, diloxanide furoate, or paromomycin).

1. **Iodoquinol:** , is amebicidal agent effective against the luminal trophozoite and cyst forms of E. histolytica .

Adverse effects: rash, diarrhea, and dose-related peripheral neuropathy, including a rare optic neuritis. Long-term use of this drug should be avoided.

2. Paromomycin: an aminoglycoside antibiotic, is only effective against the luminal forms of .E. histolytica, because it is poorly absorbed from the gastrointestinal tract.

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

Adverse effects: Gastrointestinal distress and diarrhea are the principal.

Systemic amebicides

These drugs are useful for treating extraintestinal amebiasis, such as liver abscesses, and intestinal wall infections caused by amebas.

Chloroquine: Chloroquine [KLOR-oh-kwin] is used in combination with metronidazole (or as a substitute for one of the nitroimidazoles in the case of intolerance) to 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.

CLINICAL SYNDROME	DRUG
Asymptomatic cyst carriers	*Iodoquinol* or *paromomycin*
Diarrhea/dysentery Extraintestinal	*Metronidazole* plus *iodoquinol* or *paromomycin*
Amebic liver abscess	*Metronidazole* (or *tinidazole*) plus *iodoquinol* or *paromomycin*

CHEMOTHERAPY FOR MALARIA

Malaria is an acute infectious disease caused by five species of the protozoal genus Plasmodium.

1. Tissue schizonticide

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.

Mechanism of action of primaquine: 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.

Pharmacokinetics of Primaquine:

- Primaquine is well absorbed on oral administration
- It is rapidly oxidized to metabolites which appear in the urine

Adverse effects of Primaquine

- Hemolytic anemia (in patient’s low levels of glucose-6- phosphate)
- Abdominal discomfort (with large doses) especially when administered in combination with chloroquine
- Methemoglobinemia
- Granulocytopenia (rarely)
- Primaquine is contraindicated during pregnancy.
- All Plasmodium species may develop resistance to primaquine

2- Blood schizonticide

Chloroquine it is the drug of choice in the treatment of erythrocytic P. falciparum malaria,
Chloroquine is less effective against Plasmodium vivax malaria.
Chloroquine is highly specific for the asexual form of plasmodia.
It is also effective in the treatment of extraintestinal amebiasis.

Pharmacokinetics of Chloroquine
Chloroquine is rapidly and completely absorbed following oral administration.
4 days of therapy suffice to cure the disease.
The drug concentrates in erythrocytes, liver, spleen, kidney, lung, melanin-containing tissues, and leukocytes.
Some metabolic products have antimalarial activity. The excretion by urine rate is enhanced as is acidified.

Adverse effects:

Higher doses, many more toxic effects occur, such as gastrointestinal upset, pruritus, headaches, and blurring of vision.

Discoloration of the nail beds and mucous membranes may be seen on chronic administration.
Electrocardiographic changes (because it has a quinidine-like effect).
Dermatitis produced by gold or phenylbutazone therapy.
Patients with psoriasis or porphyria should not be treated with chloroquine, because an acute attack may be provoked.

Mefloquine

An effective single agent for suppressing and curing infections caused by multidrug-resistant forms of P. falciparum.

MOA: damage the parasite's membrane,

- It 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.

Quinine and quinidine

Interfere with heme polymerization, resulting in death of the erythrocytic form of the plasmodial parasite.

For These drugs are reserved severe infestations and for malarial strains that are resistant to other agents, such as chloroquine.

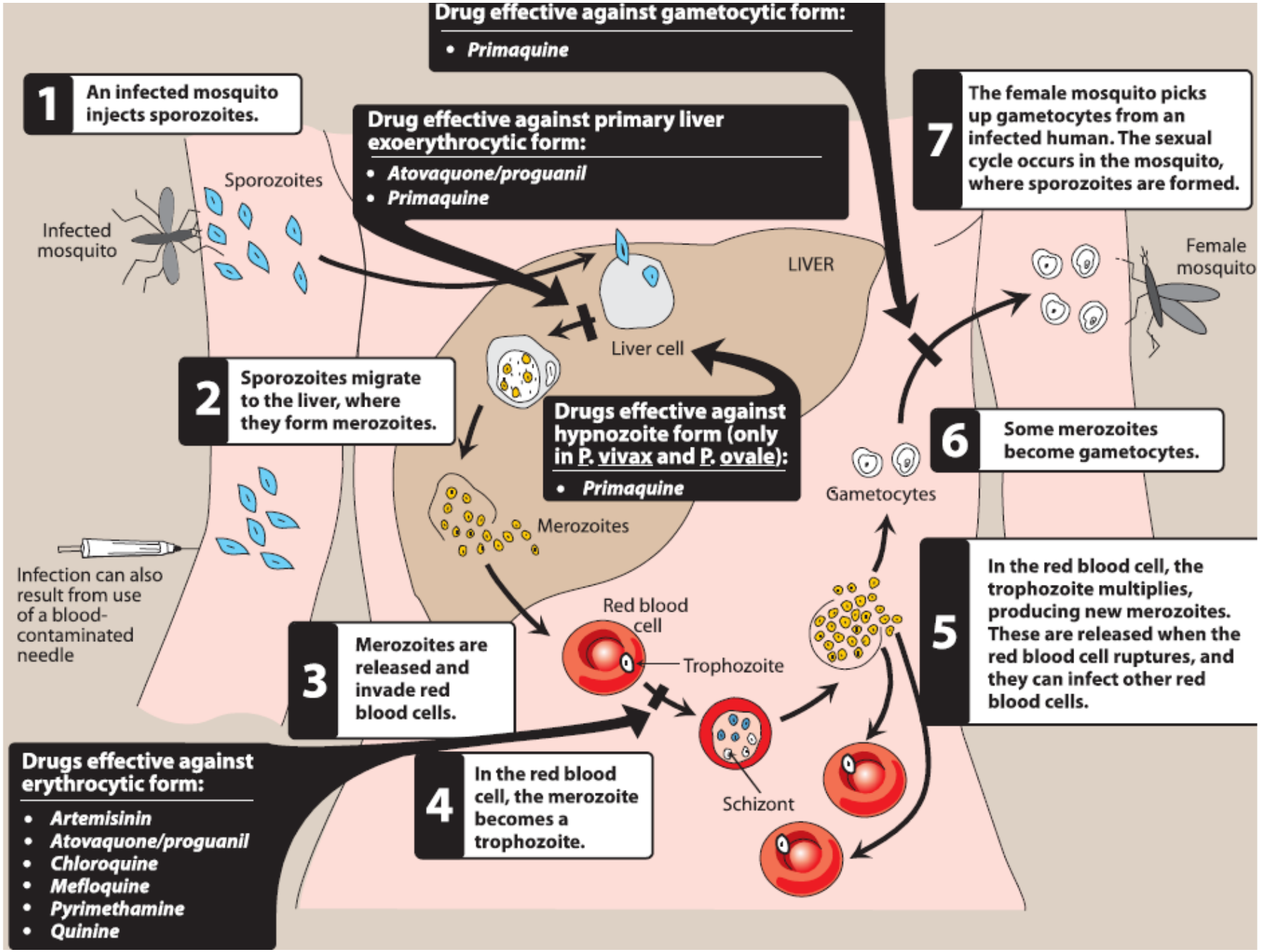
Taken orally, quinine is well distributed throughout the body and can reach the fetus. Alkalinization of the urine decreases its excretion.

The major adverse effect of quinine

1. Cinchonism (syndrome causing nausea, vomiting, tinnitus, and vertigo).
2. Positive Coombs' test for hemolytic anemia occurs (Quinine)
3. Quinine is fetotoxic

Drug interactions of quinine

- Potentiation of neuromuscular-blocking agents
- Elevation of digoxin levels if taken concurrently with quinine
- Quinine absorption is retarded when the drug is taken with aluminumcontaining antacids.


Drug effective against gametocytic form:
• Primaquine
1 An infected mosquito injects sporozoites.
Drug effective against primary liver exoerythrocytic form:
• Atovaquone/proguanil
• Primaquine
7 The female mosquito picks up gametocytes from an infected human. The sexual cycle occurs in the mosquito, where sporozoites are formed.
Sporozoites
Infected mosquito
LIVER
Female mosquito
Liver cell
2 Sporozoites migrate to the liver, where they form merozoites.
Drugs effective against hypnozoite form (only in P. vivax and P. ovale):
• Primaquine
6 Some merozoites become gametocytes.
Gametocytes
Merozoites
Infection can also result from use of a blood-contaminated needle
Red blood cell
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.
3 Merozoites are released and invade red blood cells.
Drugs effective against erythrocytic form:
• Artemisinin
• Atovaquone/proguanil
• Chloroquine
• Mefloquine
• Pyrimethamine
• Quinine
4 In the red blood cell, the merozoite becomes a trophozoite.
Schizont

Pyrimethamine

• Inhibits plasmodial dihydrofolate reductase at much lower concentrations than those needed to inhibit the mammalian enzyme.

• The inhibition deprives the protozoan of tetrahydrofolate cofactor required in the de-novo biosynthesis of purines and pyrimidines.

• It is also used against P. malariae and toxoplasma gondii.
• If megaloblastic anemia occurs with pyrimethamine treatment, it may be reversed with leucovorin.

CHEMOTHERAPY FOR TRYPANOSOMIASIS

African trypanosomiasis (sleeping sickness) and American trypanosomiasis (Chagas disease) are two chronic and, eventually, fatal diseases caused by species of Trypanosoma.

Pentamidine

Pentamidine is active against a variety of protozoal infections, including African trypanosomiasis due to T. brucei gambiense, for which it is used to treat the early stages of disease (hemolymphatic stage without CNS involvement). Pentamidine is also an alternative drug for the treatment of leishmaniasis.

MOA: T. brucei concentrates pentamidine by an energy-dependent, high-affinity uptake system and interfering with parasite synthesis of RNA, DNA, phospholipids, and proteins.

Pentamidine is administered intramuscularly or intravenously.
However, it carries risks of serious reversible renal dysfunction upon discontinuation, as well as adverse effects such as hyperkalemia, hypotension, pancreatitis, ventricular arrhythmias, and hyperglycemia. Monitoring plasma glucose is crucial due to the potential for lifethreatening hypoglycemia.

Suramin

Suramin [SOO-ra-min] is used primarily in the early stage (without CNS involvement) of African trypanosomiasis.
It inhibits many enzymes of energy metabolism, which correlated with trypanocidal activity.
Suramin must be injected intravenously.
suramin binds to plasma proteins, poorly penetrates the blood-brain barrier, and exhibits a prolonged elimination half-life (over 40 days) and is mainly excreted unchanged in the urine.

Adverse reactions include nausea and vomiting, shock and loss of consciousness, acute urticaria, blepharitis, and neurologic problems, such as paresthesia, photophobia, and hyperesthesia of the hands and feet.

Renal insufficiency may occur but tends to resolve with discontinuation of treatment.

Acute hypersensitivity reactions may occur, and a test dose should be given prior to drug administration.

Melarsoprol

Melarsoprol a trivalent arsenical compound, is the only medication available for treatment of late stages of African trypanosome infections (CNS involvement) concentrations appear in the CSF.

The drug interacts with sulfhydryl groups of various substances. affecting pyruvate kinase enzymes in both the organism and host.
Some resistance by decreased transporter uptake of the drug.

Melarsoprol is administered by slow IV injection.

CNS toxicity (encephalopathy) which can be fatal in 10% of cases. Co-administration of corticosteroids can help mitigate the risk of encephalopathy. Other adverse effects include peripheral neuropathy, hypertension, hepatotoxicity, and albuminuria. hypersensitivity reactions, and febrile reactions post-injection.

Hemolytic anemia has been seen in patients with glucose-6-phosphate dehydrogenase deficiency.

Eflornithine

Eflornithine is a crucial component in the treatment of late-stage African trypanosomiasis when combined with nifurtimox.
The intravenous form is used, but frequent dosing is required due to its short half-life. Additionally, topical eflornithine is employed to manage unwanted facial hair in women. Potential adverse reactions include anemia, thrombocytopenia, seizures, and temporary hearing loss.

Nifurtimox

The drug, when combined with eflornithine, is employed to treat advanced infections of T. brucei gambiense and T. cruzi (Chagas disease). Functioning as a nitroaromatic compound, it undergoes reduction, generating toxic oxygen radicals that are detrimental to T. cruzi. Administered orally, the drug excreted through urine. adverse effects including hypersensitivity reactions, gastrointestinal problems, and peripheral neuropathy.

Benznidazole

Benznidazole, a nitroimidazole derivative akin to nifurtimox, is the preferred treatment for Chagas disease due to its improved tolerability compared to nifurtimox.

Adverse effects, such as dermatitis, peripheral neuropathy, insomnia, and anorexia, are common. Both benznidazole and nifurtimox are cautioned against during pregnancy due to the potential risk of harm to the fetus.

CHEMOTHERAPY FOR LEISHMANIASIS

Leishmaniasis is a protozoal infection caused by various species of the genus Leishmania.

There are three manifestations of leishmaniasis: cutaneous, mucocutaneous, and visceral. [Note: In the visceral type (liver and spleen}, the parasite is in the bloodstream and if untreated is fatal.]

Sodium stibogluconate

The pentavalent antimonial sodium stibogluconate [stib-o-GLOO-koenate] is a prodrug which is reduced to the active trivalent antimonial compound. Administered parenterally, Metabolism is minimal, and the drug is excreted in urine.

Miltefosine

Miltefosine [mil-te-FOE-zeen] is the first orally active drug for visceral leishmaniasis and can also treat cutaneous and mucocutaneous forms of the disease.

MOA: interferes with phospholipids and sterols in the parasitic cell membrane to induce apoptosis. The drug is teratogenic and should be avoided in pregnancy.

Adverse reactions for both treatments include various side effects such as injection site pain, gastrointestinal upset, and cardiac arrhythmias.

CHEMOTHERAPY FOR TOXOPLASMOSIS

An infected pregnant woman can transmit T. gondii to her fetus.

The treatment of choice for this condition is a combination of sulfadiazine and pyrimethamine.

Leucovorin is commonly administered to protect against folate deficiency.

[Note: At the first appearance of a rash, pyrimethamine should be discontinued, because hypersensitivity to this drug can be severe.]

Pyrimethamine with clindamycin or the combination of trimethoprim and sulfamethoxazole are alternative treatments.
Trimethoprim/sulfamethoxazole is used for prophylaxis against toxoplasmosis (as well as P jirovecii) in immunocompromised patients.

CHEMOTHERAPY FOR GIARDIASIS

Infections involve trophozoites in the small intestine, occasionally forming cysts passed in stools. While some cases are asymptomatic, severe diarrhea, particularly in immunocompromised individuals, can occur. The preferred treatment is a single oral dose of tinidazole, with oral metronidazole as an alternative for 5 days. Nitazoxanide [nye-ta-ZOX-a-nide], oral therapy for treatment of giardiasis. The anthelmintic drug albendazole may also be efficacious for giardiasis, and paromomycin is sometimes used for treatment of giardiasis in pregnant patients.

References

Lippincott Illustrated Reviews: Pharmacology. 7TH ed, Wolters Kluwer.

Thank you