Antiparasitic Agents: 
Antiprotozoals, Anthelmintics and Others

Reading Assignment: Chapter 49 (Chapters 50-53 optional but suggested and informative)

I. Antiprotozoal Agents

Protozoa are one-celled eukaryotes which typically afford disease as a consequence of replicating in large numbers in the host.

See tables 50.1 and 51.1 for lists of the major blood, tissue, intestinal and vaginal protozoa.

A) Antimalarial Agents

-Malaria is caused by a class of red blood cell parasites (protozoa) called Plasmodium (P falciparum, P malariae, P. vivax, P. ovale, >100 other minor strains). P. falciparum most common and severe.

-Mosquitoes pass sporozoites to humans where they enter the blood stream and travel to the liver where hepatocytes are infected (we will not discuss life cycle and replication)

-Resistance to antimalarial agents, particularly Chloroquine, is a problem

1. Quinine and 4-Quinoline Methanols

-Quinine original from Cinchona bark
  (used by Inca's pre 16th century)
-Quinidine gluconate and sulfate salts given IV and may be used alone or in combination with other agents where chloroquine resistance occurs.

-Mefloquine approved in 1989: is a synthetic analog of quinine
-Kills Plasmodia at 'blood stage' of life cycle
-Not prescribed to patients with history of depression, psychosis, convulsions.
-Used for Prophylaxis where chloroquine resistance to P. falciparum occurs.

2. Aminoquinolines

-Chloroquine is the most versatile (oral)
-used to treat acute attacks and prophylactic where resistance not reported.

-Primaquine used to prevent relapse (more adverse effects)

"Other agents developed/used because of resistance to chloroquine"

3. 9-Methanthrene Methanols (Halofantrine)
4. Mechanism of Action for the Quinoline-Based Antimalarials

Exact mechanism is not known: A number of molecular mechanisms are proposed for how these agents act and whether they have 'identical' or just similar mechanisms of action. Generally, the following is accepted.

These agents are weak bases which are uncharged at neutral pH. When the agents enter the protozoa and subsequently the lysosomes, a more acidic environment, the agents are converted to their 'charged' salt form and trapped in the lysosome. Thus, high concentration of drug are accumulated in the protozoa food vacuoles (lysosomes). It is then believed that when the parasite feeds on hemoglobin in red blood cells the digestion of protein results in an insoluble precipitate in the lysosome. (eg. Chloroquine complexes with these protein digest products (heme)) In the end, degradation of hemoglobin by the malaria parasite is adversely effected by these agents and the ultimate result is their death. Exactly how this happens is still debated.

This general mechanism also explains why resistance to these agents is associated with impaired uptake of the drug by the malarial protozoa and that cross-resistance has been observed among these agents.

5. Diaminopyrimidine/Dihydrotriazine Antimalaria Agents
(Inhibitors of folate metabolism, DHFR)

Pyrimethamine

- Pyrimethamine is not used alone but is used in combination with sulfadoxine against chloroquine resistant organisms.

Chloroguanide (Proguanil)

Liver Metabolism

- also has broad antiprotozoal activity

Cycloquanil

Active form of drug

These agents inhibit dihydrofolate reductase, which interferes with folic acid synthesis, and thus ultimately as a folic acid antagonist results in interference of nucleotide synthesis. High affinity for Plasmodia DHFR and low affinity for human DHFR.

6. Other Agents with Antimalarial Activity
- sulfa drugs as shown above for combination therapy with DHFR inhibitors (synergistic)
  - Artemisinin
  - tetracycline, chloramphenicol

B) Other Antiprotozoal Agents

There are many other agents with a variety of mechanisms of action to treat protozoal infections such as trypanosomiasis, leishmaniasis, amebiasis, giardiasis, trichomoniasis and others.

See tables 50.1 and 51.1 for lists of the major blood, tissue, intestinal and vaginal protozoa; the text briefly discusses treatment options for individual protozoal infections.

See The Medical Letter volume 37 (issue 961) November 10, 1995

1. Metronidazole

- Metronidazole is metabolically reduced to reactive metabolites in the protozoa. These reactive metabolites bind DNA of the protozoa affording a lethal effect.
- Generally low toxicity in humans.
- widely used for variety of protozoal infections in North America
- Adverse Effects: nausea, dry mouth, metallic taste, disulfuram-like reaction with alcohol

2. Other agents typically used in North America

- Paromycin (aminoglycoside)
- Combinations of sulfa drugs (sulfamethazole) and DHFR inhibitors (trimethoprim/pyrimethamine)
- Tetracycline

2. Other agents available from CDC (for Leishmaniasis, Trypanosomiasis and other protozoal infections not common in North America)

Pentamidine, Suramin, Sodium Stibogluconate, melarsoprol, nifurtimox

II. Anthelminthic Agents

Helminths (worms) are multicellular animals that are much larger than protozoa. Many types of worms (tapeworms, roundworms and flatworms (flukes))
See tables 52.2 and 53.1 for lists of the major blood, tissue and intestinal helminths.

1. **The Benzimidazoles**

   ![Mebendazole](image1)
   ![Albendazole](image2)

   - Mebendazole (Vermox) used in the U.S.
   - Cimetidine may inhibit liver metabolism of Mebendazole
   - (roundworms and tapeworms)

   **Mechanism of Action:**

   The benzimidazoles bind to beta-tubulin which results in the inhibition of microtubule assembly involved in cell division. Therefore, cell division processes are arrested. Glucose uptake is also depleted. The benzimidazoles have high affinity for beta-tubulin in the parasite (worm) but low affinity for mammalian beta-tubulin affording 'selective toxicity'.

2. **Pyrantel**

   ![Pyrantel](image3)

   Pyrantel pamoate acts on the nervous system of pinworm, roundworm and hookworm. It is a depolarizing neuromuscular blocking agent that causes spastic paralysis in susceptible helminths.

3. **Niclosamide (a salicylanilide)**

   - used for tapeworms
   - kills on contact by uncoupling oxidative phosphorylation (energy depletion)

4. **Praziquantel**

   - Broad spectrum
   - well tolerated

   - **Mechanism of Action:** Appears to effect helminth membranes ultimately
stimulating the action of hosts antibodies. (expose/release antigen(s))

5. Other Antihelminths with various applications

- Ivermectin
- Diethylcarbamazine
- Piperazine

III. Pediculocides and Miticides (Lice and Scabies)

1. Lindane (Kwell®)

![Lindane structure]

- Effect on insects is similar to DDT but lower toxicity to humans
- Adverse effects: rash, conjunctivitis (rare: convulsions, aplastic anemia)
- Insecticidal against lice

2. Malathion

Another insecticide that has limited use for lice. (local irritation and foul smelling)

3. Pyrethrins

- Pyrethrins are natural extracts from Chrysenthemum (A-200, RID, Pronto)
- Only major adverse effect is possible allergic reaction
- for lice (pyrethrin + piperonyl butoxide)

Permethrin is a synthetic pyrethrin which is chemically more stable

![Permethrin structure]

- Mechanism of Action: Disrupts sodium conductance of nerve cell membranes of the parasite.
- Adverse Effects: burning, numbness, rash

(Eliminate®) 5% permethrin for scabies, alternative is 1% lindane or 10% crotamilton
(Nix®) 1% permethrin for lice

4. Crotamiton

Scabicide (Eurax®)