Antiparasitic Agents

DRUGS FOR THE TREATMENT OF WORM (HELMINTH) INFECTIONS

Mebendazole & Albendazole

I. STRUCTURAL CHARACTERISTICS AND MECHANISM OF ACTION

Mebendazole is the drug of choice to treat most of the common intestinal nematode infections encountered in the U.S. It is a 5-substituted benzimidazole and is the prototypical drug in its class including thiabendazole, albendazole, and flubendazole. Mebendazole binds to the β-subunit of tubulin, preventing microtubule formation. Also effects other parasitic functions such as glucose transport and glycogen depletion.

II. SPECTRUM AND USES

a.) Ascariasis (Roundworm) - *Ascaris lumbricoides*. Infects 1/4 of the world's population. In U.S. it is more prominent in the South, especially in the poor, rural regions. Also seen in inner city populations.

b.) Enterobiasis (Pinworm) - *Enterobius vermicularis*. Most common cause of worm infection in U.S. Symptoms are perianal itching. Easily transmittable.

c.) Hookworm - *Necator americanus, Ancylostoma duodenale* - can lead to anemia

d.) Trichuriasis ( Whipworm) - distributed worldwide in warm humid climates.

e.) Strongyloidiasis - Southern U.S. - difficult to treat. 77% cure rate for albendazole vs. 23% with pyrantel pamoate (97% with ivermectin)

f.) Trichinosis - *Trichinella spiralis* - from undercooked meat, esp. pork. Migrates to muscle. Albendazole is drug of choice (better absorbed than Mebendazole).

g.) Neurocysticercosis - pork tapeworm, *T. solium*. Causes seizures esp. in immigrant Hispanic population (9% of seizures in L.A. Emergency room due to neurocysticercosis)

h.) Cystic Hydatid disease of the liver (Echinococcosis), lung, and peritoneum caused by larval form of dog tapeworm - Albendazole is DOC.

i.) Microspiridiosis

III. DISPOSITION, METABOLISM, AND EXCRETION

- Mebendazole & albendazole are poorly absorbed. Average F = 10-20%.
- Short half-life (1 hr)- not good for systemic treatment.
- High first pass metabolism, approximately 50% of metabolites appear in urine.
- Albendazole is rapidly converted to its sulfoxide metabolite, which is primarily responsible for the systemic anthelmintic activity.
- Biliary excretion of metabolites is extensive.
IV. ADVERSE EFFECTS

a.) Transient abdominal pain and diarrhea.

b.) Embryotoxic in animals. Avoid in pregnancy. Flubendazole is alternative.

c.) Albendazole elevates liver enzymes in 16% of patients. Rarely causes reductions in WBC count (<1%). Should monitor liver enzymes and WBCs every 2-4 weeks.

V. PRODUCTS

Mebendazole - Vermox® (Janssen) - 100 mg chewable tablets.
Trichuriasis, ascariasis, and hookworm - One tablet b.i.d. for 3 days.
Enterobiasis - a single tablet given once. Should re-treat in 3 weeks.

Albendazole - Albenza® (SmithKline Beecham) - 200 mg tablets
Hydatid disease & neurocysticercosis - 400 mg BID with meals.

Pyrantel Pamoate

I. STRUCTURE AND MECHANISM OF ACTION

Pyrantel is a depolarizing neuromuscular blocking agent. Causes paralysis in the worm. It also inhibits cholinesterases. Used as the pamoate salt. Antagonizes the action of piperazine.

II. USES

Considered reasonable alternative to mebendazole for ascariasis, hookworm, and pinworm infections. Should not be given to infants less than 2 yrs old.

III. DISPOSITION

Poorly absorbed from GI tract. ≤7% found in urine as drug and metabolites.

IV. ADVERSE EFFECTS

a.) GI pain, anorexia, nausea, vomiting, diarrhea

b.) Headache, dizziness, fever.

V. PRODUCTS and DOSING

Oral Suspension: Antiminth® (Pfizer) - Rx only - 50 mg pyrantel pamoate/ml
Liquid: Reese's Pinworm® (Reese) - OTC - 50 mg/ml

Give as single dose of 11 mg/kg (5 mg/lb.). Maximum total dose is 1 g.
DRUGS FOR THE TREATMENT OF CESTODE (TAPEWORM) AND TREMATODE (FLUKE) INFECTIONS

Praziquantel

I. STRUCTURAL CHARACTERISTICS AND MECHANISM OF ACTION

Praziquantel is an isoquinolone analog that is marketed as a mixture of stereoisomers. Praziquantel increases cell membrane permeability in susceptible worms and flukes. This results in loss of intracellular calcium, and paralysis and contractions of the parasite musculature. Phagocytes rapidly attach to the affected parasites resulting in cell death.

II. SPECTRUM AND USES

Praziquantel is the drug of choice for most cestode and nematode infections (see Medical Letter on Antiparasitic Drugs).

a.) Cestodes
   i. Beef and Pork tapeworm - *Teania saganata and T. solium*
   ii. Dog and Fish tapeworm - *Diphyllobothrium canium and D. latum*
   iii. Dwarf tapeworm - *Hymenolepis nana*

b.) Trematodes (Flukes)
   i. Schistosomiasis due to *Schistosoma mansoni* (Africa & Near East, S. America, Caribbean) and *S. haemotobium or japonicum* (Africa, Arabia or S.E. Asia)
   ii. Intestinal flukes (Fasciolopsiasis) - *Fasciolopsis buski* - E. and S.E. Asia
   iii. Liver fluke (Opsiorthchiasis) - *Opisthorchis viverini* - E. Europe, Russia, Thailand
   iv. Chinese liver fluke (Clonorchiasis) - *Clonorchis sinensis* - China, Korea, Indochina
   v. Sheep liver fluke (Fascioliasis) - *Fasciola hepatica* - worldwide
   iv. Lung fluke (Paragonimiasis) - *Paragonimus westermani* - S.E. Asia, N.C. Africa, S. America, animals in N. America

III. ABSORPTION, DISTRIBUTION, AND EXCRETION

- rapidly absorbed (80%). Significant first pass metabolism to inactive metabolites. Metabolites excreted in urine and breast milk.
- CSF levels are 14-20% of plasma levels. half-life = 0.8-1.5 h.

IV. ADVERSE EFFECTS

Generally well tolerated. May cause malaise, headache, dizziness, and GI discomfort.
V. PRODUCTS

Praziquantel - Biltricide® - (Bayer) - 600 mg tablets. Do not chew. Praziquantel is bitter.

Dose for Schistosomiasis - 3 doses of 20 mg/kg at 4-6 hr intervals as a 1 day treatment

Dose for flukes - 3 doses of 25 mg/kg as a 1 day treatment.

**Niclosamide**

I. MECHANISM OF ACTION

Niclosamide inhibits oxidative phosphorylation in the mitochondria of cestodes. The scolex and proximal segments of the tapeworm are killed on contact.

II. SPECTRUM AND USES

Treatment of beef tapeworm, fish tapeworm, and dwarf tapeworm.

III. DISPOSITION & ADVERSE EFFECTS

- Side effects are generally mild - GI: Nausea and vomiting (4.1%); anorexia (3.4%), diarrhea (1.6%). CNS: headache (1.4%), drowsiness, dizziness.

IV. PRODUCTS AND DOSING

Niclosamide - Niclocide® (Miles) - 500 mg chewable tablets

For beef and fish tapeworm - 2g as a single dose for adults for 7 days, Children 11-34 kg 2 tabs (1g) as a single dose on first day, then 1 tab daily for 6 additional days.

**DRUGS FOR THE TREATMENT OFPROTOZOAL INFECTIONS IN AIDS**

**Drugs for Pneumocystis carinii pneumonia**

I. CHARACTERISTICS OF *Pneumocystis* PNEUMONIA

a.) Single cell organism exists as cystic and extracystic form. Cyst form is 4-6 µ in diameter and is spherical or oval. Up to 8 intracystic cells (sporozoites) occupy the cyst. Extracystic form (trophozoite) is thin walled, pleiomorphic, and varies in size from 2- 5 µ. It appears that the organism is now more closely aligned to the fungi than to protozoa.

b.) *Pneumocystis* is widely distributed. 75% of population have antibodies by age 4.

c.) Opportunistic. Only causes disease in immunosuppressed patients.

d.) *Pneumocystis* pneumonia (plus Kaposi's sarcoma) is the index diagnosis for >60% of AIDS patients. An additional 20% will develop the disease at some point.

e.) Symptoms include cough, shortness of breath, fever, severe tachypnea, dyspnea, chest pain, and cyanosis. Mortality is significant (10-20% of deaths in AIDS). If untreated, mortality rate is 90-100%. Drugs cure about 65% of cases.
II. DRUGS

a.) Trimethoprim-Sulfamethoxazole (see earlier notes) - drug of choice but poorly tolerated in AIDS patients (~50% have severe adverse reactions, usually rash or anemia). For both treatment and prophylaxis.

b.) Atovaquone (see below) - indicated only for treatment

c.) Pentamidine isethionate (see below) - treatment + prophylaxis (aerosolized form)

d.) Dapsone + trimethoprim (see earlier notes) - treatment and prophylaxis (dapsone alone)

e.) Clindamycin + primaquine - alternative treatment

f.) Trimetrexate + leucovorin - alternative treatment

g.) Pyrimethamine + sulfadoxine - alternative treatment

**Atovaquone**

I. STRUCTURE AND MECHANISM OF ACTION

- Atovaquone is an analog of ubiquinone.
- The drug is highly lipophilic with poor water solubility. The mechanism of action is not completely understood but involves inhibition of the mitochondrial electron transport chain. This would ultimately affect ATP synthesis and DNA synthesis.
- Resistance is due to single point mutation in *Plasmodium falciparum* cytochrome B gene.

II. USES

- Treatment of *Pneumocystis carinii* pneumonia- initially indication. Clinical trials demonstrated effectiveness for prophylaxis as well.
- This agent is very expensive (however it is still cheaper than pentamidine). Use only in patients that cannot tolerate TMP-SMX. Since the drug is better tolerated than dapsone, some suggest that this drug may be the prophylactic agent of choice in patients intolerant to TMP-SMX (see NEJM 339:1889-95, 1998).
- Toxoplasmosis - May be a useful alternative
- Malaria prophylaxis – Atovaquone + proguanil (Malarone®). 200X more expensive than chloroquine. Also used in treatment.

III. DISPOSITION, METABOLISM, AND EXCRETION

- Low bioavailability primarily due to poor absorption. Absorption is increased ~2-fold when given with food, especially fatty meals indicating that bile salt micelles may be involved in the absorption of the drug. AIDS patients show 1/3-1/2 the levels of HIV+ persons.
- Pharmacokinetics show a double peak phenomenon. $T_{max}$ is 1-8 hr, with second peak at 24-96 hr indicating significant EHC. Typical plasma concns. of 20-25 µg/ml. Long half-life (2.9 days in volunteers, 2.2 d in AIDS patients). 99.9% protein bound.
- Eliminated primarily in the feces (>94% of the dose). No evidence of metabolism?
III. ADVERSE EFFECTS

63% of patients reported at least one adverse reaction (275 patients). However only 9% had to discontinue therapy. Most common reactions are rash (23%, 4% discontinued), GI problems - nausea (21%), diarrhea (19%), vomiting (14%); headache (16%), fever (14%), insomnia (10%), asthenia (8%).

IV. PRODUCT and DOSING

Atovaquone - Mepron® suspension (Glaxo-SK) – 750 mg/5 ml (yellow, citrus-flavored)

Adult dose: 750 mg administered with food BID for 21 days.

Atovaquone + Proguanil (Malarone®- Glaxo-SK) –250mg/100mg in tablets

Pentamidine Isethionate

I. STRUCTURE and MECHANISM OF ACTION

Pentamidine was originally developed as an antitrypanosomal drug. It is the safest of the diamidine group of antiprotozoals although it still has significant toxicity. The mechanism is unclear, but in trypanosomes it appears to bind to DNA.

II. USES

a.) Treatment and prophylaxis (aerosolized form) of *Pneumocystis carinii* pneumonia. Appears to be less effective for prophylaxis than TMP-SMX.

b.) Prophylaxis of East and West African Sleeping Sickness - *Trypanosoma gambiense*. May also be useful for visceral leishmaniasis.

III. DISPOSITION, METABOLISM, AND EXCRETION

– not well absorbed orally. Can be given I.V. or I.M.

– plasma levels are low (peak at 600 ng/ml after a 2 h infusion of 4 mg/kg i.v.) - 2.6 ng/ml in bronchial lavage fluid 18-24 h later. Extensive tissue distribution. When given in the aerosolized form, peak plasma levels were only 2.3 ng/ml, whereas levels in bronchial lavage fluid were 23 ng/ml 18-24 hrs after inhalation.

– approximately 1/3 of dose excreted unchanged in urine. half-life = 6.4 ± 1.3 h.

IV. ADVERSE EFFECTS

Approximately 60% of patients have an adverse reaction to pentamidine. Some fatalities have occurred due to hypotension or hypoglycemia.

a.) Severe hypotension. ~1% incidence (<60 mm Hg). May develop after a single IV or IM dose. Patients should receive slow infusion (over 60 min) in supine position. Monitor blood pressure closely.

b.) Hypoglycemia - associated with necrosis of pancreatic islet cells coupled with high insulin concentrations. 2.4% have blood glucose < 25mg/dl. Hyperglycemia may also occur even after therapy has ended. Monitor blood glucose.

c.) Blood dyscrasias - severe leukopenia (<1000 cu mm) (2.8%), thrombocytopenia (1.7%), moderate leukopenia in 7.5%
c.) Renal dysfunction - 23% have elevated serum creatinine. 0.5% have acute renal failure.

e.) Liver dysfunction - elevated transaminases in 8.7%

f.) Hypocalcemia

g.) Bronchospasm is common with aerosol form (~15% incidence). Cough 30-50%. Decreased appetite (50-70%).

V. PRODUCTS and DOSING

Injection: Pentam 300® (Lyphomed) - 300 mg per vial dissolved in Sterile Water for Injection or 5% Dextrose.

Dose: 4 mg/kg once a day for 14 d administered deep IM or IV. Correct dose in renal failure.

Aerosol: NebuPent® (Lyphomed) - 300 mg vial

Dose: every 4 weeks administered via the Respirgard® II nebulizer by Marquest. Deliver dose over 30-45 min at 5-7 ml/min. Reconstitute only in Sterile Water. Pentamidine precipitates in normal saline.

Costs for 21 days of Treatment : TMP-SMX = $10, Atovaquone = $400, Pentamidine = $1200

Costs for Prophylaxis: 30 d of DS TMP-SMX = $19, Pentamidine = $99/300 mg vial + $3 for nebulizer + administrative and supervisory costs
Drugs for Toxoplasmosis

CHARACTERISTICS OF *Toxoplasma gondii* INFECTIONS

a.) *Toxoplasma gondii* is an obligate intracellular protozoa. The parasite may exist as tachozoites, in tissue cysts, and as oocysts. Tachozoites are crescent- to oval-shape (4-8 µ) that stain with Wright’s and Giemsa stains. Usually found in vacuoles of host cells. Tissue cysts can vary in size from 10-200 µ and may contain as many as 3000 organisms. Tissue cysts are found in any organ but usually in brain, heart, and skeletal muscle. Oocysts are 10-12 µ in diameter and found only in the intestines of cats.

b.) *Toxoplasma gondii* is widely distributed in nature. Definitive hosts are in the cat family. Oocysts are shed in cat feces. Can infect any animal and even some invertebrates (roaches, worms, slugs). 15-68% of adults in U.S. and >90% in France and Europe - latent.

c.) Causes disease (toxoplasmosis) only in immunocompromised hosts. Only 10-20% of cases are symptomatic (higher in AIDS). 3-40% of all HIV+ patients.

d.) Acute infections are usually presented as lymphadenopathy with fever, night sweats, malaise, sore throat, maculopapular rash. May be difficult to distinguish from cytomegalovirus or "mono". Symptoms usually resolve in a few months.

e.) Major problem in AIDS and transplant patients is infection of the CNS. Brain lesions can usually be detected by CAT scan as a single or multiple lesion. Neurological problems may be the presenting sign. May also infect heart, esp. in transplant patients.

f.) *Toxoplasma gondii* is also an important cause of chorioretinitis in U.S. and Europe, usually as a result of congenital infection (from the mother). Often asymptomatic until later in life. Symptoms are blurred vision, pain, photophobia, and loss of central vision. Relapses are frequent.

DRUGS

a.) Pyrimethamine + sulfadiazine (or sulfamethoxazole) - 40-70% have ADR. 80% relapse.

b.) Clindamycin + pyrimethamine - 1° alternative in patients who can't tolerate sulfas

c.) Azithromycin (possibly clarithromycin) - better vs. tissue cysts

d.) Atovaquone - limited experience but clinical improvement in 7/8 in one trial.

e.) Investigational: arprinocid (a purine), trimetrexate, dapsone

f.) gamma-interferon, interleukin 2

d.) Corticosteroids for eye infections (prednisone 1-2 mg/kg) may be helpful
I. STRUCTURE AND MECHANISM OF ACTION

Pyrimethamine is an analog of trimethoprim. It has a much higher affinity for the dihydrofolate reductase of *Plasmodium* (malaria) and *Toxoplasma* than for mammalian or bacterial DHFR.

II. USES

a.) Toxoplasmosis (considered drug of choice in combination with sulfadiazine)

b.) Chemoprophylaxis of sensitive malaria - *Plasmodium falciparum* (see Antimalarial notes)

c.) Treatment of chloroquine or mefloquine-resistant malaria (usually administered as a fixed combination with sulfadoxine - Fansidar®) - may also combine with quinine or quinidine.

III. ABSORPTION, DISTRIBUTION, AND EXCRETION

- well absorbed orally. \( T_{\text{max}} = 2-6 \) h
- half-life = 4 days, 87% bound to plasma proteins
- metabolized extensively in liver. Metabolites are excreted in urine.

IV. ADVERSE EFFECTS

a.) GI effects: nausea and vomiting (large doses). Vomiting \( \square \) with meals and lower doses.

b.) Hematologic effects: may cause megaloblastic anemia at high doses - treat with folinic acid (leucovorin). Rare leukopenia, thrombocytopenia. May precipitate hemolytic anemia in G6PD deficiency.

V. PRODUCT and DOSING

Darapim® (Glaxo-Wellcome) - 25 mg tablets. Take with food or meals.

*Toxoplasmosis:* Adults - 50-75 mg daily with 1-4 g of a sulfa (usually sulfadiazine). Continue for 1-3 weeks. Reduce dose by one-half and continue for additional 4-5 weeks. Pediatric dose is 1-2 mg/kg day divided in 2 equal doses. After 2-4 days, reduce dose by one-half and continue for an additional month.

*Prophylaxis of malaria:* Adults and children > 10 yrs - 25 mg once weekly. Children 4-10 - 12.5 mg once weekly. Children <4 - 6.25 mg once weekly.

*Treatment of acute malaria:* – use only in areas where plasmodia are sensitive. Combine with fast-acting agent such as chloroquine or mefloquine.

Fansidar® (Roche) - 500 mg of sulfadoxine + 25 mg pyrimethamine
For prophylaxis of malaria in adults: 1 tablet per week or 2 tablets once every 2 weeks.
Drugs for *Cryptosporidium sp.*

I. CHARACTERISTICS OF CRYPTOSPORIDIOSIS

a.) *Cryptosporidium parvum* life cycle is as follows: Healthy hosts are infected with an oocyst. The oocyst open and four motile sporozoites are released that invade the epithelial cells of the small intestine. These are invaginated and develop into eight merozoites in the vacuoles at the apex of the enterocytes. The merozoites will rupture the cell and reinvade adjacent cells to spread. Eventually, sporulated oocysts will be shed into the feces.

b.) Cryptosporidiosis is described by a watery and often cholera-like diarrhea. The stool volume of AIDS patients may reach up to 17L per day! Infects 10-15% of AIDS pop.

c.) Other symptoms include crampy abdominal pain, fatigue, anorexia, nausea, and vomiting.

d.) Prolonged diarrhea in immunocompromised patients may lead to severe malnutrition, wasting, and eventually death.

e.) May also cause a self-limiting diarrhea (usually 2-3 weeks) in general population (25-35% seroprevalence in U.S). Contaminates the water supply and is resistant to chlorination. Endemic in farm animals. Famous endemic episode in Milwaukee in Spring 1993.

f.) *Cryptosporidium* may also invade the bile ducts of ~10% of AIDS patients. Has rarely been found in lungs.

g.) Diagnosis is usually by acid fast staining of feces. Oocysts stain red, whereas yeasts and fecal debris stain blue or green. A monoclonal antibody test and an ELISA assay are also available.

h.) Important to differentiate from other GI infections in immunocompromised hosts such as CMV, *Mycobacterium avium* complex, *Microsporidium*, *Isospora belli*, *Shigella*, *Salmonella*, *Campylobacter jejuni*, *C. difficile*, *Giardia*, and *Entamoeba*.

II. Treatment of Cryptosporidiosis

a.) Non-specific treatment - antidiarrheal agents (opiates, loperamide, diphenoxylate). Octreotide diacetate (somatostatin analog) has been tried but a recent multicenter trial was negative. Also requires nutritional management and administration of fluids. May require TPN.

b.) Hyperimmune bovine colostrum - led to a marked abatement of symptoms. Currently in clinical trials.

c.) Over 90 drugs have been tried without success. Some promising agents are listed below:

i. Azithromycin - in clinical trials at 4 centers. Preliminary data shows effectiveness in some patients. Is effective in animal models of the disease.

ii. Paromomycin - a non-absorbable aminoglycoside used for amebiasis may be effective. Uncontrolled trials in San Francisco did not demonstrate efficacy and nephrotoxicity was observed.

iii. Nitazoxanide – seems to provide relief in ~40-50% of patients. Application for approval was rejected by FDA due to lack of data. Still in clinical trials.

iii. Diclazuril (a static drug that is used for treatment of the gut epithelial parasite *Eimeria*) and a better absorbed congener, Letrazuril, are also in clinical trials.
ANTIMALARIAL DRUGS

LIFE CYCLE OF *Plasmodium* sp.

There are currently four species of Plasmodia that infect man. These are *Plasmodium vivax*, *P. falciparum*, *P. malariae*, and *P. ovale*. Approximately 1/3 of the world's population is infected causing 2 million deaths per year. Approximately 4% of U.S. citizens travel to countries where malaria is endemic. In the life cycle of this obligate parasite, asexual reproduction occurs in humans and sexual reproduction occurs in the female *Anopheles* mosquito. The life cycle is described and illustrated shown below:

1. **Sporozoites** from the saliva of the *Anopheles* mosquito are injected into human bloodstream.
2. Sporozoites enter the liver & mature into **schizonts** in 2 weeks.
3. Schizonts rupture releasing 10,000-40,000 **merozoites**
4. Merozoites circulate in blood for a few minute and then enter the red blood cells.
5. In the erythrocytes, an asexual reproduction takes place. The merozoites mature into a ring form, and then to a **trophozoite**, and finally into an erythrocyte **schizont**.
6. The erythrocytic schizont can burst and release more merozoites. This cycle may continue for months or even years.
7. Some merozoites go on to initiate a sexual stage, maturing to form male and female **gametocytes**.
8. The gametocytes are ingested by a feeding mosquito. In the mosquito gut, the male gametocyte exflagellates to form a **microgamete**. This fertilizes the female gametocyte to form the **zygote**.
9. The zygote invades the gut mucosa, where it develops into an **oocyst**.
10. The oocyst bursts, releasing thousands of **sporozoites** in the gut, that then migrate to the salivary gland of the mosquito, where the cycle can begin again in a fresh target.
Antimalarial Drugs

- Quinine
- Chloroquine
- Hydroxychloroquine
- Mefloquine
- Quinacrine
- Primaquine
- Pyrimethamine
- Sulfadoxine
- Dapsone
Choroquine

I. STRUCTURAL CHARACTERISTICS AND MECHANISM OF ACTION

Chloroquine is a 4-aminoquinilone. The 4-aminoquinolones act by intercalation into the DNA of parasites. These drugs are selective because they accumulate in erythrocytes. DNA intercalation is not the only mechanism of action of quinolones as mefloquine and primaquine do not interact strongly with the DNA structure. It has also been suggested that when the drug concentrates within parasite vesicles it raises intracellular pH and thus inhibits growth. Another proposed mechanism involves breakdown of hemoglobin by the parasite and binding of chloroquine to ferriprotoporphyrin IX causing membrane damage.

II. USES

• **Malaria** - Chloroquine is drug of choice for prophylaxis and treatment of *Plasmodium* in areas where the organism is sensitive.
• Chloroquine-resistance is widespread in S.E. Asia and India. Resistance to chloroquine is now becoming more common in Sub-Saharan Africa.
• Recently, Malawi abandoned chloroquine as the first line treatment for malaria. Other nations are sure to follow.
• Still OK in the Middle East and Central and S. America.

III. DISPOSITION AND ADVERSE EFFECTS

– very widely distributed with extensive tissue binding. Concentrations in liver, spleen, and kidney are 200-700 times higher than in plasma.
– generally well tolerated when used for prolonged suppressive therapy. OK in pregnancy.
– when used to treat acute malaria may cause nausea and vomiting. Rare irreversible retinal damage in patients receiving high doses. Report visual disturbances to physician.
– Overdose in children and infants may be fatal at relatively low doses (250 mg in infants or toddlers, 2 g in adults)

IV. PRODUCTS AND DOSING

Chloroquine phosphate - 250 mg tablets  
Aralen Phosphate® (Sanofi-Winthrop) - 500 mg tablets (contains 300 mg free base)

Hydroxychloroquine sulfate - Plaquenil® 200 mg tabs. = 250 mg chloroquine phosphate.

*Suppressive therapy* (for travelers to malarious areas that are chloroquine-sensitive). Adults: 300 mg (base) weekly, on the same day each week. Begin 1-2 weeks prior to exposure and continue for 6 weeks after leaving endemic area.

<table>
<thead>
<tr>
<th>Children's Chloroquine</th>
<th>Dose Based on Age</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>Chloroquine base equivalent</td>
</tr>
<tr>
<td>&lt;1</td>
<td>37.5 mg</td>
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<tr>
<td>1 to 3</td>
<td>75 mg</td>
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<tr>
<td>4 to 6</td>
<td>100 mg</td>
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<tr>
<td>7 to 10</td>
<td>150 mg</td>
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<tr>
<td>11 to 16</td>
<td>225 mg</td>
</tr>
</tbody>
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Note: compliance with these regimens is notoriously poor (<50%). Approximately 1200 cases of acute malaria in U.S. per year are primarily in travelers who are non-compliant. Cost of chloroquine prophylaxis for a family of four is about $350.

Mefloquine

Mefloquine is a quinolinemethanol. Mechanism of action is unknown, but it kills the blood schizont. It is now the drug of choice for chloroquine-resistant or Fansidar-resistant malaria. Mefloquine-resistance is becoming a major problem in Thailand and other countries in S.E. Asia.

I. USES

a.) Mefloquine is the current drug of choice for prophylaxis for travelers to endemic areas with chloroquine-resistant *Plasmodium falciparum*
b.) Treatment of mild to moderate acute malaria infections due to susceptible strains of *P. falciparum* or *P. vivax*.

II. DISPOSITION AND ADVERSE EFFECTS

- high volume of distribution (20 L/kg). 98% protein bound. Concentrates in RBCs.
- long terminal half-life (15-33 days).
- Mefloquine is teratogenic and embryotoxic in rats and rabbits at high doses. No adequate controlled studies in pregnant women. Should warn women of child-bearing age traveling to endemic areas to use contraception. Low concentrations (3-4% of plasma levels) excreted in breast milk.
- Safety in children not established. After a single 20-30 mg/kg dose, mefloquine was effective but nausea and vomiting occurred in 10-20% and dizziness in 40% of children.
- generally well tolerated in adults. May cause dizziness. Vomiting (3%).

III. PRODUCTS AND DOSING

*Lariam*® (Roche) - 250 mg mefloquine HCl tablets.

*Malaria prophylaxis* - Adults: 250 mg once weekly for 4 weeks, then 250 mg every other week. CDC recommends a single dose weekly starting one week prior to travel and continue for 4 weeks after returning. Children: 15-19 kg - 1/4 tablet, 20-30 kg - 1/2 tablet, 31-45 kg - 3/4 tablet, >45 kg - 1 tablet.

*Treatment of mild to moderate acute malaria*: Adults: 5 tablets (1250 mg) as a single dose. Administer with a full glass of water. Note: patients with *P. vivax* malaria are at high risk for relapse because mefloquine does not eliminate hepatic phase parasites. To avoid relapse, follow up treatment with primaquine.
**Primaquine**

I. STRUCTURE AND MECHANISM OF ACTION

Primaquine is an 8-aminoquinoline. While it is structurally related to the 4-aminoquinolines, it acts in a different manner and on different forms of the parasite. Primaquine disrupts parasite mitochondrial function and also binds to DNA. Primaquine inhibits the gametocyte and the exoerythrocytic forms of the parasite (liver trophozoites). This prevents the development of blood forms responsible for relapses with *P. vivax* malaria.

II. USES

a.) For the radical cure of vivax malaria (in combo with chloroquine or mefloquine)

b.) Prevention of relapse of *P. vivax* malaria

c.) Follow up of chloroquine phosphate prophylaxis in *P. vivax* endemic areas.

III. DISPOSITION AND ADVERSE EFFECTS

– much lower volume of distribution than the 4-aminoquinolines.

– rapidly metabolized to a carboxylic acid metabolite. Some metabolites are active. <1% excreted unchanged in urine. half-life is about 4 hours.

– main adverse effects are GI upset with nausea and vomiting.

– may cause moderate to severe hematologic problems, esp. in persons with G6PD or NADH-methemoglobin reductase deficiency. Reactions are manifested by hemolytic anemia, leukopenia, or methemoglobinemia. Discontinue if urine is darkened.

IV. PRODUCTS

Primaquine Phosphate (Sanofi-Winthrop) - 26.3 mg tablets (equivalent to 15 mg free base).

CDC Treatment schedule: Begin dosing during last 2 weeks of, or following a course of, suppression with chloroquine or mefloquine. Adults: 26.3 mg (15 mg base) daily for 14 days. Children: 0.5 mg/kg /day x 14 days.

Aralen phosphate with Primaquine Phosphate (Winthrop) - Tablets contain 500 mg of chloroquine phosphate (+300 mg of chloroquine free base) + 79 mg of primaquine phosphate (= 45 mg free base)

Prophylaxis: Start at least one day before entering endemic area. Adults: Take one tablet weekly on the same day each week. Continue for 8 weeks after leaving the endemic area. For dosing of children, prepare a liquid by crushing one tablet in 40 ml (may use chocolate syrup to prepare a suspension) and dose according to weight.
Other Antimalarial Drugs

a.) Fansidar® - pyrimethamine + sulfadoxine (see section on Toxoplasmosis)

b.) Doxycycline - current drug of choice for prophylaxis in mefloquine resistant areas. Adult dose is 100 mg day (see Tetracycline section).

c.) Quinine - blood schizonticide, primarily used for treatment of acute malarial attacks

d.) Amiodaquone - 4-aminoquinolone that is more active than chloroquine. Not available in U.S.

e.) Halofantrine - new antimalarial blood schizonticide developed by U.S. Army that may be useful in resistant malaria. Structurally related to mefloquine. Not currently available in U.S.

f.) Artemesinin (qinghaosu) - from the Chinese medicinal herb *Artemesia*. Several more potent analogs are being tested – artemunate, arteether, artmetether. Artesunate is most common drug in S.E. Asia. Used primarily for treatment of mefloquine-resistant strains