

PHARMACOLOGY

Antimicrobial Agents: Antiprotozoal Drugs

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This group of antiprotozoal drugs includes the drugs effective against plasmodia, entamoeba, giardia, trichomonas and leishmania species etc. These can be classified as: antimalarial drugs, antiameobics, drugs for trichomoniasis, giardiasis, leishmaniasis, antimonials, etc.

Antimalarial Drugs

Anti malarial drugs can be classified according to anti malarial activity and structure.

1. According to antimalarial activity:

- a. **Tissue schizonticides for causal prophylaxis:** These drugs act on the primary tissue forms of the plasmodia which after growth within the liver, initiate the erythrocytic stage. By blocking this stage, further development of the infection can be theoretically prevented. Pyrimethamine and Primaquine have this activity. However since it is impossible to predict the infection before clinical symptoms begins this mode of therapy is more theoretical than practical.
- b. **Tissue schizonticides for preventing relapse:** These drugs act on the hypnozoites of *P. vivax* and *P. ovale* in the liver that cause relapse of symptoms on reactivation. Primaquine is the prototype drug; pyrimethamine also has such activity.
- c. **Blood schizonticides:** These drugs act on the erythrocytic forms of the parasite and thereby terminate clinical attacks of malaria. These are the most important drugs in anti malarial chemotherapy. These include chloroquine, quinine, mefloquine, halofantrine, pyrimethamine, sulfadoxine, sulfones, tetracyclines etc.
- d. **Gametocytocides:** These drugs destroy the sexual forms of the parasite in the blood and thereby prevent transmission of the infection to the mosquito. Chloroquine and quinine have gametocytocidal activity against *P. vivax* and *P. malariae*, but not against *P. falciparum*. Primaquine has gametocytocidal activity against all plasmodia, including *P. falciparum*.
- e. **Sporontocides:** These drugs prevent the development of oocysts in the mosquito and thus ablate the transmission. Primaquine and chloroguanide have this action.

Thus in effect, treatment of malaria would include a blood schizonticide, a gametocytocide and a tissue schizonticide (in case of *P. vivax* and *P. ovale*). A combination of chloroquine and primaquine is thus needed in **ALL** cases of malaria.

2. According to the Structure:

- a. **Aryl amino alcohols:** Quinine, quinidine (cinchona alkaloids), mefloquine, halofantrine.
- b. **4-aminoquinolines:** Chloroquine, amodiaquine.
- c. **Folate synthesis inhibitors:** Type 1 - competitive inhibitors of dihydropteroate synthase - sulphones, sulphonamides
Type 2 - inhibit dihydrofolate reductase - biguanides like proguanil and chloroproguanil; diaminopyrimidine like pyrimethamine
- d. **8-aminoquinolines:** Primaquine, WR238, 605
- e. **Antimicrobials:** Tetracycline, doxycycline, clindamycin, azithromycin, fluoroquinolones
- f. **Peroxides:** Artemisinin (Qinghaosu) derivatives and analogues - artemether, arteether, artesunate, artelinic acid
- g. **Naphthoquinones:** Atovaquone
- h. **Iron chelating agents:** Desferrioxamine

For understanding the activity of various drugs against the plasmodium species, the causative agent of malaria, we must know the life cycle of the malarial parasite. In the figure 1, the life cycle of the parasite is given along with the site of action of various drugs active against this parasite.

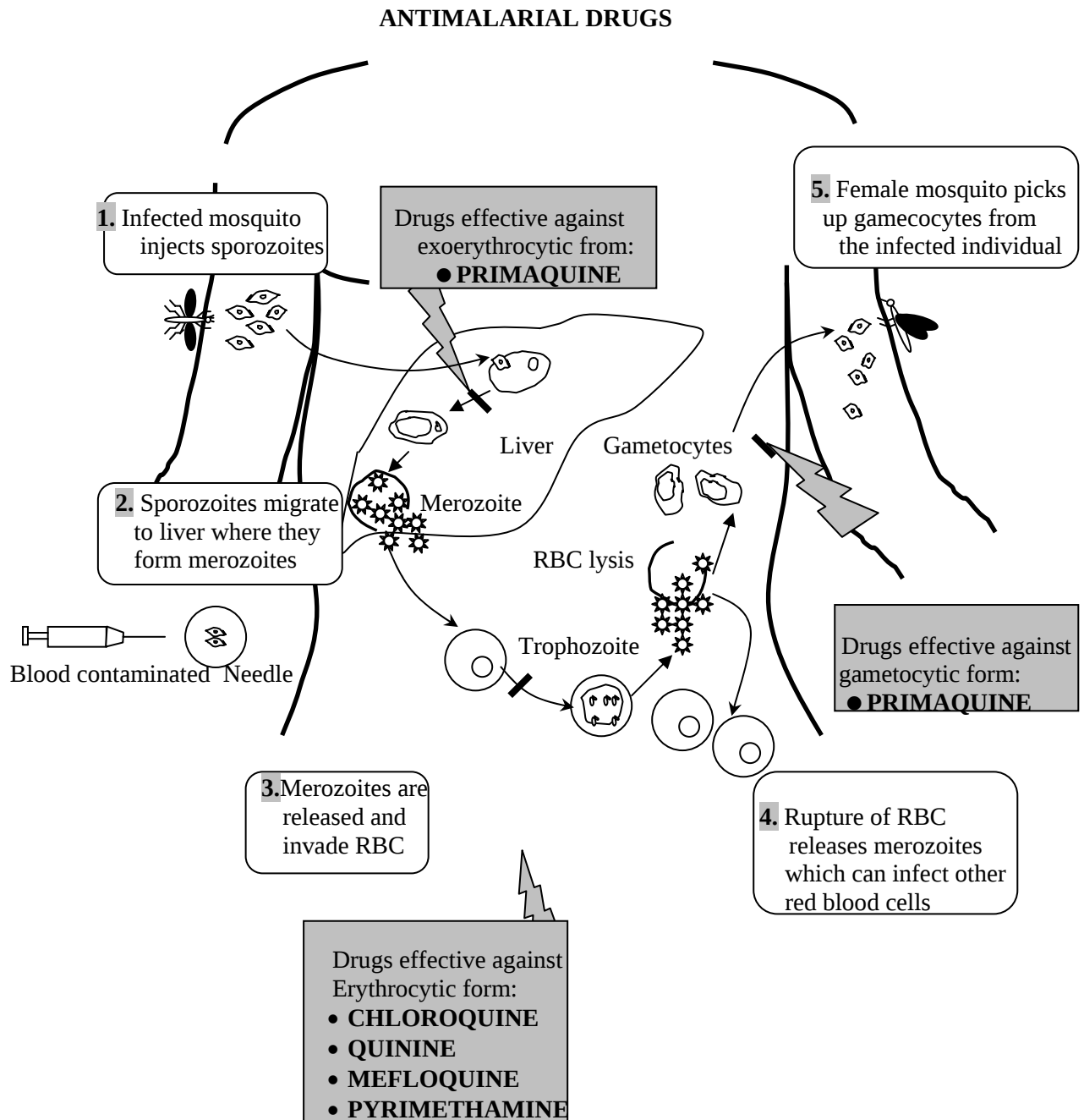


Fig.1. Life cycle of malarial parasite with site of action of some drugs

1. Chloroquine: Chloroquine is a 4-aminoquinoline that has marked and rapid schizonticidal activity against all infections of *P. malariae* and *P. ovale* and against chloroquine-sensitive infections of *P. falciparum* and *P. vivax*. It is also gametocytocidal against *P. vivax*, *P. malariae* and *P. ovale* as well as immature gametocytes of *P. falciparum*. It is not active against intrahepatic forms, and should therefore be used with primaquine to effect radical cure of *P. vivax*. and *P. ovale* .

Use: The use of chloroquine as a single first-line drug treatment is now increasingly limited following the evolution of chloroquine-resistant *P. falciparum*. In some areas chloroquine use could potentially be extended by its combination with other antimalarial drugs, in order to take continuing advantage of its antipyretic and anti-inflammatory effect and for its action against vivax malaria. Resistance of *P. vivax* to chloroquine was first documented in 1989 in Papua New Guinea and is now also confirmed in Indonesia and Myanmar. Clinical attacks of chloroquine-resistant *P. vivax* can be treated with mefloquine or quinine.

Recommended treatment: Children and adults, for whom the use of chloroquine is indicated, should receive a full treatment dose of 25 mg of chloroquine base per kg given over 3 days. The pharmacokinetically superior regimen consists of 10 mg of base per kg followed by 5 mg/kg 6-8 h later and 5 mg/kg on each of the following 2 days. A more practical regimen used in many areas consists of 10 mg/kg on the first and second days and 5 mg/kg on the third. Both these regimens provide a total dose of 25 mg/kg (e.g. 1 500 mg of base for a 60-kg adult).

Recommended Chemoprophylaxis:

5 mg of base per kg weekly in a single dose,
or

10 mg of base per kg weekly, divided into 6 daily doses.

Chloroquine alone is recommended as a prophylactic drug in some of the areas where only *P. vivax* is present or where *P. falciparum* is still sensitive to the drug. Chloroquine may also be recommended in areas of moderate levels of *P. falciparum* resistance to chloroquine if combined with 200 mg of proguanil daily. This combination provides substantial protection, although less than mefloquine.

Other Uses: Giardiasis, Rheumatoid Arthritis, Extraintestinal Ameobiasis, Discoid Lupus Erythromatosis, Lepra Reaction, Infectious Mononucleosis, Photogenic Reactions.

Pharmacokinetics: Chloroquine is absorbed efficiently when administered orally, peak plasma concentrations being achieved within 3 h (range 2-12 h). The drug has a high capacity for binding to tissues, particularly the melanin-containing tissues of the skin and eye. It is preferentially concentrated in erythrocytes and this concentration is enhanced in parasitized erythrocytes.

Adverse effects: Serious adverse reactions to chloroquine are rare at the usual antimalarial dosages, but pruritus, which may be intolerable, is common among dark-skinned people. Transient headaches, nausea, vomiting, gastrointestinal symptoms and "blurred vision" may also be experienced following chloroquine administration. Irreversible visual impairment resulting from accumulation of chloroquine in the retina is a rare but recognized complication of long-term, high-dosage therapy.

Over dosage: Chloroquine has a low safety margin. Acute chloroquine poisoning is extremely dangerous and death may occur within a few hours. Poisoning may result after oral ingestion by adults of a single amount of 1.5-2.0 g, i.e. 2-3 times the daily treatment dose. Symptoms include headache, nausea, diarrhoea, dizziness, muscular weakness and blurred vision, which may be dramatic with loss of vision. However, the main effect of over dosage is cardiovascular toxicity with hypotension and cardiac arrhythmias progressing to cardiovascular collapse, convulsions, cardiac and respiratory arrest, and death.

If the patient is seen within a few hours of the event, emesis must be induced or gastric lavage undertaken as rapidly as possible. If not, treatment is symptomatic and directed particularly to sustaining cardiovascular and respiratory function.

2. Amodiaquine: Amodiaquine is a 4-aminoquinoline antimalarial drug similar in structure and activity to chloroquine. Like chloroquine, it also possesses antipyretic and anti-inflammatory properties.

Use: Evidence has thus accumulated, particularly in Africa (using 35 mg/kg amodiaquine in West Africa) that supports the use of amodiaquine in the treatment of uncomplicated falciparum malaria, with the provision that monitoring of efficacy and toxicity are continued. It has been suggested that amodiaquine is less toxic than sulfadoxine-pyrimethamine in HIV-positive patients. Amodiaquine has the advantage over chloroquine of being more palatable and therefore easier to administer to children.

Chemoprophylaxis: Amodiaquine is no longer recommended for chemoprophylaxis because of the risk of severe adverse reactions

Use in pregnancy: There is no evidence to contraindicate the use of amodiaquine for treatment of malaria during pregnancy.

Adverse effects : Adverse reactions to the standard doses of amodiaquine used for malaria treatment are generally similar to those to chloroquine, the most common being nausea, vomiting, abdominal pain, diarrhoea and itching; a less common effect is bradycardia. There is some evidence that itching may be less common with amodiaquine than with chloroquine. In contrast to chloroquine, however, amodiaquine can induce toxic hepatitis and fatal agranulocytosis following its use for malaria chemoprophylaxis. The toxicity of amodiaquine seems to be related to the immunogenic properties of the quinone imine produced by auto-oxidation of the parent drug.

Contraindications: Amodiaquine is contraindicated:

- in persons with known hypersensitivity to amodiaquine,
- in persons with hepatic disorders,
- for chemoprophylaxis.

3. Quinine: Quinine is normally effective against falciparum infections that are resistant to chloroquine and sulfa drug-pyrimethamine combinations.

Use: Quinine is the drug of choice for severe falciparum malaria. It should only be used for uncomplicated malaria when alternatives are unavailable. Quinine may be a useful first-line treatment in multidrug-resistant malaria i.e. where *P. falciparum* does not respond to chloroquine, sulfa drug- pyrimethamine combinations, and mefloquine.

Injectable quinine given by the intramuscular route can be a valuable initial treatment for a patient with uncomplicated malaria who is repeatedly vomiting and therefore unable to take oral drugs. Once vomiting has stopped, oral treatment with an appropriate drug should be resumed.

Quinine can be used as a second-line treatment for patients who fail to respond to the standard first-line therapy and/or are hypersensitive to sulfa drugs. When used in this way, quinine should always be accompanied by another drug. To improve compliance and maintain its efficacy, quinine is usually combined with tetracycline or doxycycline. Since these drugs are contraindicated in children and pregnant women, clindamycin can be used for these groups. Quinine can be given by the oral, intravenous or intramuscular routes. Quinine should not be given alone for the treatment of malaria as short courses, e.g. 3 days, owing to the possibility of recrudescence.

Use in pregnancy: Quinine is safe in pregnancy.

Adverse effects : Cinchonism, a symptom complex characterized by tinnitus, hearing impairment, and sometimes vertigo or dizziness, occurs in a high proportion of treated patients. Symptoms appear when the total plasma concentration of quinine is about 5 mg/l, i.e. at the lower limit of the therapeutic range of the drug, which is 5-15 mg/l. The symptoms that are usually reversible generally develop on the second or third day of treatment and alone rarely constitute a reason for withdrawing the drug.

Dose-related cardiovascular, gastrointestinal and central nervous system effects may arise following excessive infusion or from accumulation following oral administration. Severe hypotension may develop if the drug is injected too rapidly. Quinine may enhance the effects of cardiosuppressant drugs and should be prescribed with caution in individuals taking drugs such as beta-adrenergic blocking agents, digoxin and calcium channel blocking agents, especially in those with cardiac disease. Enhanced cardiac toxicity may occur if quinine therapy is administered to individuals who have taken mefloquine for malaria chemoprophylaxis.

Hypoglycaemia may be caused by quinine since the drug stimulates secretion of insulin from pancreatic beta-cells. Hypoglycaemia is particularly likely to develop after intravenous infusion of quinine in pregnancy, since beta-cells are more susceptible to a variety of stimuli at that time.

4. Mefloquine: Mefloquine is a 4-quinoline methanol chemically related to quinine. It is a potent long-acting blood schizonticide active against *P. falciparum* resistant to 4-aminoquinolines and sulfa drug-pyrimethamine combinations. It is also highly active against *P. vivax* and, *P. malariae* and most probably *P. ovale*. It is not gametocytocidal and is not active against the hepatic stages of malaria parasites. Owing to its long elimination half-life and consequent long-lived subtherapeutic concentrations in the blood, the development of resistance is to be expected especially in areas of high transmission. *P. falciparum* resistance to mefloquine is accompanied by cross-resistance to halofantrine and reduced sensitivity to quinine.

Use: Mefloquine can be used both for therapy (**15 mg or 25 mg of mefloquine base per kg**) and chemoprophylaxis (**5 mg of mefloquine base per kg weekly**). It should not be used for treatment where chloroquine or sulfa drug-pyrimethamine combinations are effective because of its potential toxicity, cost and long elimination half-life.

Use in pregnancy : Mefloquine is given for both chemoprophylaxis and treatment during the second and third trimesters of pregnancy, but it should be used with caution during the first trimester.

Adverse effects: *Frequent adverse effects* include dizziness, mild to moderate nausea, vomiting, diarrhoea and abdominal pain (self-limiting but may be severe in some users).

Neuropsychiatric adverse reactions included affective disorders, anxiety disorders, hallucinations, sleep disturbances including nightmares and, in a few people, overt psychosis, toxic encephalopathy, convulsions and acute brain syndrome.

Concomitant administration of mefloquine with other related compounds such as quinine, quinidine and chloroquine may produce ECG abnormalities and increase the risk of convulsions. The use of halofantrine after mefloquine causes significant lengthening of the QTc interval

Rare Haematological events, elevation of hepatic transaminases and dermatological events (Stevens-Johnson syndrome, toxic epidermal necrolysis), have been reported with mefloquine use.

Contraindications: The use of mefloquine is contraindicated in persons:

- with a history of allergy to mefloquine,
- with a history of severe neuropsychiatric disease,
- receiving halofantrine treatment,
- who have received treatment with mefloquine in the previous 4 weeks,

5. Halofantrine: Halofantrine, a phenanthrene methanol, is a blood schizonticide that is active against all malaria parasites. It is active against *P. falciparum* infections that are resistant to chloroquine and to sulfa drug-pyrimethamine combinations. Halofantrine is not active against gametocytes or the hepatic stages of malaria parasites.

Use: Halofantrine has no place in malaria control programmes because of its high cost, its variable bioavailability, its cross-resistance to mefloquine and the fact that fatal cardiotoxicity has been reported in certain risk groups following standard therapy. It may be used on an individual basis in patients known to be free from heart disease in areas where multiple drug resistance is prevalent and no other effective antimalarial is available.

Adverse effects : Adverse effects include nausea, abdominal pain, diarrhoea, pruritis and skin rashes. Prolongation of the QTc interval and rare cases of serious ventricular dysrhythmias, sometimes fatal, have also been reported.

6. Antifolate Drugs: The only useful combinations of antifolate drugs for the treatment of malaria are synergistic mixtures that act against the parasite-specific enzymes, dihydropteroate synthetase and dihydrofolate reductase. Available combinations include the sulfa drug-pyrimethamine combinations, sulfadoxine-pyrimethamine and sulfalene-pyrimethamine, the former being more widely available.

Cotrimoxazole, the co-formulated combination of sulfamethoxazole and trimethoprim, has weak antimalarial properties because trimethoprim has a much lower affinity than pyrimethamine for the parasite dihydrofolate reductase enzyme. Cotrimoxazole should not be used for the treatment of malaria.

The use of sulfa drug-pyrimethamine combinations for chemoprophylaxis is no longer recommended because of the risk of severe skin reactions.

Formulations

Sulfadoxine-pyrimethamine:

- Tablets containing 500 mg of sulfadoxine and 25 mg of pyrimethamine.
- Ampoules containing 500 mg of sulfadoxine and 25 mg of pyrimethamine in 2.5 ml of injectable solution.

Sulfa drug-pyrimethamine combinations are highly active blood schizonticides against *P. falciparum* but are less effective against other Plasmodium species. There is no cross-resistance with the 4-aminoquinolines, mefloquine, quinine, halofantrine or the artemisinin derivatives. The combinations do not have gametocidal activity but have been shown to be sporontocidal in animal models.

The long half-life of sulfa drug-pyrimethamine combinations provides a potent selective pressure for parasite resistance in areas of high transmission. Sulfa drug-pyrimethamine combinations have low efficacy against *P. vivax*. The combination of sulfa drug-pyrimethamine plus chloroquine can therefore be used, not because of a hypothetical effect on the development of resistance, but because it offers an inexpensive and effective option for treatment in areas where chloroquine-resistant, sulfa drug-pyrimethamine-sensitive *P. falciparum* and chloroquine-sensitive *P. vivax* coexist. Such combinations may, however, increase the risk of adverse skin reactions.

Use: Sulfa drug-pyrimethamine combinations have been successfully used in areas with highly developed *P. falciparum* resistance to chloroquine and during malaria epidemics. Compliance is high since they offer single-dose therapy. Sulfadoxine-pyrimethamine is the most widely used formulation, sulfalene- pyrimethamine has been largely used in the Indian subcontinent. It is generally assumed that these two formulations are equipotent although there are no comparative data to support this assumption.

There is evidence that folic acid, even in physiological doses, administered concurrently with sulfadoxine-pyrimethamine, can antagonize the action of sulfadoxine. It has been suggested that folic acid supplements should be delayed for one week after sulfa drug-pyrimethamine treatment to avoid an inhibitory effect on antimalarial efficacy. However, there are as yet no clinical data to substantiate this.

Recommended treatment: Sulfadoxine-pyrimethamine and sulfalene-pyrimethamine are recommended as single adult doses of 1500 mg of sulfa drug plus 75 mg pyrimethamine (25 mg of the sulfa component per kg as a single dose). This comprises 3 tablets.

Chemoprophylaxis: Sulfa drug-pyrimethamine combinations are no longer recommended for chemoprophylaxis in travellers because of the risk of severe adverse reactions.

Use in pregnancy: There is no clinical evidence that the use of sulfa drug-pyrimethamine combinations for malaria treatment in pregnant women has any effect on the fetus. Although there is a theoretical risk of jaundice among premature babies born to mothers given sulfa drugs late in the third trimester, there does not appear to be an increased risk of kernicterus.

Adverse effects : Sulfa drug-pyrimethamine combinations are generally well tolerated when used at the recommended doses for malaria therapy. The most serious events are associated with hypersensitivity to the sulfa component, involving the skin and mucous membranes and normally occurring after repeated administration. There have been isolated reports of a

transient increase in liver enzymes as well as hepatitis occurring after administration of sulfadoxine-pyrimethamine. Haematological changes including thrombocytopenia, megaloblastic anaemia and leukopenia have also been observed.

Contraindications: The use of sulfadoxine- or sulfalene-pyrimethamine combinations is contraindicated:

- in persons with known hypersensitivity to sulfa drugs or pyrimethamine,
- for chemoprophylaxis,
- in persons with severe hepatic or renal dysfunction (except when benefits exceed the risks involved),
- in infants in the first two months of life.

7. Proguanil: Proguanil is a synthetic biguanide derivative of pyrimidine with a marked effect on the primary tissue stages of *P. falciparum*, *P. vivax* and *P. ovale*. Its effect on the primary exoerythrocytic forms of *P. malariae* is unknown. It has some causal prophylactic effect against sensitive strains in contrast to the suppressive prophylactic activity shown by pyrimethamine. Proguanil does not affect hypnozoites and therefore does not have antirelapse activity.

Proguanil also exhibits weak blood schizonticidal activity and, while it is not currently used for treatment, a 3-day regimen of a combination of proguanil with atovaquone, a hydroxynaphthoquinone, has been shown to be effective against multidrug-resistant *P. falciparum*.

Proguanil is a dihydrofolate reductase inhibitor acting primarily through its major metabolite, cycloguanil.

Use: Proguanil is currently used only for chemoprophylaxis (as a combination with chloroquine in areas with a low prevalence of chloroquine-resistant *P. falciparum*) and for treatment of malaria as a component of the combination proguanil- atovaquone.

Adverse effects : Proguanil is remarkably safe and few adverse reactions have been observed, although there are reports indicating that mouth ulcers and hair loss may occur following prophylactic use.

Contraindications: The use of proguanil is contraindicated in persons with liver or kidney dysfunction.

8. Artemisinin and Its Derivatives: Artemisinin (*qinghaosu*) is the antimalarial principle isolated by Chinese scientists from *Artemisia annua* L. It is a sesquiterpene lactone with a peroxide bridge linkage. Its various derivatives include artemether, arteether, artesunate, dihydroartemisinin and artelinic acid. Artemisinin is poorly soluble in oils or water but the parent compound has yielded dihydroartemisinin, the oil-soluble derivatives artemether and arteether, and the more water-soluble derivatives sodium artesunate and artelinic acid. These derivatives have more potent blood schizonticidal activity than the parent compound and are the most rapidly effective antimalarial drugs known. They are used for the treatment of severe and uncomplicated malaria. They are not hypnozoiticidal but gametocytocidal activity has been observed.

The antimalarial activity of artemisinin and its derivatives is extremely rapid and most patients show clinical improvement within 1-3 days after treatment. However, the recrudescence rate is high when the drugs are used in monotherapy. Treatment for < 7 days gave unacceptably high recrudescence rates. These compounds are not recommended for use in the treatment of malaria due to *P. vivax*, *P. malariae* or *P. ovale* since other effective antimalarial drugs are available for this purpose.

Use in pregnancy: Artemisinin and its derivatives are the drugs of choice for severe malaria and can be used for treatment of uncomplicated malaria during the second and third trimester of pregnancy in areas of multiple drug resistance. Owing to lack of data, their use in the first trimester is not recommended.

Adverse effects : There is some concern about cerebellar dysfunction, and prolonged or repetitive treatment with artemisinin and its derivatives, which may occur in areas of high transmission, must be viewed with caution.

9. Primaquine: Primaquine is an 8-aminoquinoline highly active against the gametocytes of all malaria species found in humans and against hypnozoites of the relapsing malarial parasites, *P. vivax* and *P. ovale*. It is the only drug currently used for the treatment of relapsing malaria, although another 8-aminoquinoline, CDRI 80/53 (bulaquine) has recently completed phase III clinical trials and another, tafenoquine, is still undergoing clinical trials.

Use

Antirelapse treatment in *P. vivax* and *P. ovale* infections.: Primaquine may be given concurrently with an active blood schizonticide, such as chloroquine, from the first day of treatment. Antirelapse treatment of vivax malaria with primaquine at doses of 0.5 mg/kg for 14 days has been recommended.

Gametocytocidal drug in *P. falciparum* infections: Single dose of 0.75 mg of base per kg base (adults; 45 mg of base); the same dose may be repeated once, one week later.

Use in pregnancy : Primaquine is contraindicated during pregnancy because of the risk of haemolysis in the fetus, which is relatively deficient in G6PD.

Adverse effects: Primaquine may cause anorexia. Other adverse effects include nausea, vomiting, abdominal pain and cramps. These symptoms are dose related. Primaquine has also been known to cause weakness, uneasiness in the chest, anaemia, methaemoglobinaemia, leukopenia and suppression of myeloid activity.

Drug interactions : Primaquine should not be administered with any other drug that may induce haematological disorders.

9. Antibiotics Used As Antimalarial Drugs

a. Doxycycline: Doxycycline is derived from and related to oxytetracycline, and has an identical spectrum of activity. It differs from tetracyclines in that it is more completely absorbed and more lipid-soluble; it also has a longer plasma half-life.

Use

Doxycycline, like tetracyclines, can be used for therapy in combination with quinine in areas where reduced susceptibility to quinine has been reported.

In contrast to tetracycline, doxycycline can also be used for chemoprophylaxis. Experience with this indication is limited but increasing. Doxycycline prophylaxis is recommended in areas of mefloquine-resistant falciparum malaria and for those visiting high-risk areas who are unable to take mefloquine.

Use in pregnancy: Doxycycline is contraindicated in pregnancy and in nursing mothers since the risks of its use are similar to those with tetracycline (see below).

Adverse effects: Adverse effects include gastrointestinal irritation, phototoxic reactions (increased vulnerability to sunburn), transient depression of bone growth (largely reversible) and discoloration of teeth and enamel hypoplasia (permanent). Aggravation of renal impairment may occur but is less likely than with tetracyclines.

Contraindications: Doxycycline is contraindicated in:

- persons with known hypersensitivity to tetracyclines,
- children under 8 years of age,
- pregnant and nursing mothers,
- persons with hepatic dysfunction.

b. Clindamycin : Clindamycin is a semi-synthetic antibiotic derived from lincomycin. Like tetracycline, it is an efficient blood schizonticide with a relatively slow action and a similar spectrum of activity. Along with tetracycline and doxycycline, it is an option for use in combination with quinine for treatment of falciparum malaria when decreased susceptibility to quinine has been reported. However, it is more toxic and costly than tetracycline and doxycycline and should therefore only be used when these drugs are contraindicated or unavailable. It should not be used alone for the treatment of malaria because of its slow action. It is not suitable for chemoprophylaxis.

Adverse effects : Nausea, vomiting, abdominal pain or cramps have been reported and some patients (2-20%) may experience diarrhoea. Pseudomembranous colitis, a potentially fatal condition caused by *Clostridium difficile* toxin, may develop in some cases. Hypersensitivity reactions, including skin rashes and urticaria, and neutropenia and thrombocytopenia occur rarely.

c. Azithromycin: Azithromycin belongs to a new class of macrolide antibiotics. It is structurally similar to erythromycin but is better tolerated, has a broader antimicrobial spectrum of action, and provides prolonged tissue levels. It is an efficient blood schizonticide but has a relatively slow action.

Combinations of Drugs for Malaria

1. Atovaquone-Proguanil: Atovaquone was originally developed as an antimalarial compound, but was registered for the treatment of opportunistic infections caused by *Pneumocystis carinii* and *Toxoplasma gondii* associated with AIDS. Atovaquone alone has weak antimalarial activity and recrudescence of parasitaemia occurs in one-third of patients with *P. falciparum* when used alone. In combination with proguanil, however, a synergistic effect is seen. Atovaquone-proguanil is highly efficacious against *P. falciparum*, including strains that are resistant to chloroquine and mefloquine, with cure rates of 94-100%. For adults, 1 g of atovaquone plus 400 mg of proguanil (4 tablets) daily for 3 days.

Chemoprophylaxis For adults, 250 mg of atovaquone plus 100 mg of proguanil (one tablet) daily.

Use in pregnancy: Atovaquone alone and atovaquone-proguanil are not teratogenic in rats. Proguanil is safe during pregnancy but there is insufficient information on the safety of atovaquone or the combination drug in pregnant or lactating women.

Adverse effects: Adverse effects include abdominal pain, nausea, vomiting, diarrhoea, headache, anorexia and coughing.

2. Artemether-Lumefantrine: Lumefantrine is an aryl amino alcohol similar to quinine, mefloquine and halofantrine. Biochemical studies suggest that its antimalarial effect involves lysosomal trapping of the drug in the intra-erythrocytic parasite, followed by binding to toxic haemin that is produced in the course of haemoglobin digestion. This binding prevents the polymerization of haemin to non-toxic malaria pigment. Artemether-lumefantrine can be used for the treatment of uncomplicated infections with *P. falciparum*, including strains from multidrug-resistant areas. This drug is not recommended for chemoprophylaxis. This drug should not be used in pregnant women. Safety of its use in pregnancy has not yet been established.

Adverse effects : The following adverse effects have been reported: dizziness and fatigue, anorexia, nausea, vomiting, abdominal pain, palpitations, myalgia, sleep disorders, arthralgia, headache and rash.

In children and adults treated with this combination, the frequency and degree of QTc prolongations was lower than with chloroquine, mefloquine or halo-fantrine. Studies show no indication of cardiotoxicity.

3. Mefloquine-Sulfadoxine-Pyrimethamine: The combination of mefloquine-sulfadoxine-pyrimethamine was developed for therapeutic use on the basis of the observation that its components display at least additive activity and that their combination might delay the emergence of parasite resistance. It has not been recommended for general use by malaria control programmes for either chemoprophylaxis or treatment since 1990 because of concerns of the risk of severe adverse reactions to the sulfadoxine component, and because it did not appear to be justified to introduce mefloquine on a large scale to areas where sulfa drug-pyrimethamine was still effective.

Antiamoebics

Amoebiasis is an infection caused by the protozoa *Entamoeba histolytica*. About 90% of the patients are asymptomatic and the remaining produce a spectrum of clinical syndrome ranging from dysentery to abscesses of the liver and other organs.

Classification

1. Tissue amoebicides

- Nitroimidazole: Metronidazole, Tinidazole, Secnidazole, Ornidazole, Satrinidazole
- Alkaloids: Emetine, Dehydroemetine
- Others: Chloroquine

2. Luminal amoebicides

- Amide – Diloxanide furoate
- 8-Hydroxyquinolines – Quiniodochlor, Diiodohydroxyquinoline
- Antibiotic: Tetracycline, Paromomycin

Metronidazole: It is the prototype nitroimidazole for the treatment of amoebiasis.

MOA: It is reduced by anaerobic metabolism, and the metabolites act as electron sink, depriving cells of reducing equivalent. It has been found to inhibit Cell Mediated Immunity (CMI), causes radiosensitization.

Pharmacokinetics: It is completely absorbed orally, plasma protein binding is around 20%, $t_{1/2}$ is 7.5 hrs. Its clearance is decreased in patients of liver disease.

Uses: Amoebiasis, Giardiasis, Trichomoniasis, Anaerobic infections, Pseudomembranous enterocolitis, IBD (Inflammatory bowel disease)- Ulcerative colitis and Crohn's disease, H. pylori – induced peptic ulcer, as Radiosensitiser.

Side effects

- a. Nausea, vomiting, headache, metallic taste, neutropenia
- b. Weakness, vertigo, dizziness, paraesthesia
- c. Pancreatitis, seizures, encephalopathy
- d. On i.v. injection peripheral neuropathy.
- e. Its metabolites are mutagenic, so it should be avoided in pregnancy.
- f. Disulfiram like reaction when taken with alcohol

Contraindications: Pregnancy, blood dyscrasias, neurological disease, chronic alcoholism

Preparations: Tab. – Metrogyl, Flagyl 400 mg, 200 mg
Inj. - Metrogyl, Flagyl 500 mg/100ml

Tinidazole – It is a congener of metronidazole similar to it in every respect, except

- Less side effects, better tolerability
- Longer $t_{1/2}$ (12 hr), so once daily dosing can be done.
-

Secnidazole: A newer congener of metronidazole has the same spectrum and potency except: Longer half life (26 hrs), so a single dose of 2 g has comparable result with metronidazole and tinidazole.

Satrinidazole: Same as metronidazole, except

- Longer $t_{1/2}$ (14 hrs)
- Less side effects,
- No neurological, mutagenic and disulfiram like reactions.

Emetine & dehydroemetine: Emetine is an alkaloid, dehydroemetine is a synthetic product. They are not used nowadays because of high systemic toxicity. They act by inhibiting translocation of t-RNA-amino acid complex. These drugs can not be given orally because of their erratic absorption. They are only given parenterally. They provide faster relief than metronidazole in acute dysentery, but not used because of high toxicity.

Side effects:

- Nausea, vomiting, headache and diarrhoea
- Cardiac side effects like myocarditis, tachycardia are the most serious ones
- Stiffness of muscles, a myositis like condition
-

Contraindications:

- Pregnancy
- Cardiac/Renal diseases.

Chloroquine: It is used for extraintestinal amoebiasis. It is active against trophozoites of *Entamoeba histolytica* only. Chloroquine has very high volume of distribution. Since, it is concentrated in the liver so it is effective only against hepatic amoebiasis.

Diloxanide Furoate: It is an effective luminal amoebicide but not active tissue amoebicide. It is hydrolysed in the intestine to its furoate ester. Diloxanide is rapidly absorbed from the intestine and is conjugated to form the glucuronide which is promptly excreted in urine. Furoic acid is not absorbed and is more powerful amoebicide than diloxanide. Most common adverse effect is flatulence. It is drug of choice for asymptomatic cyst passer.

8-Hydroxyquinoline: These are halogenated hydroquinoline. These are highly effective luminal amoebicide which were used in the past. Their absorption is quite erratic, only 10-20% of the drug is absorbed.

Side effect: Common side effects are diarrhea, goiter, pruritis, subacute myeloptic neuropathy. It should be cautiously used in patients of optic neuropathy.

Contraindication: Hypersensitivity to Iodine. Used in the past for:

- Travellers' diarrhoea
- Amoebiasis

Drug for Trichomoniasis

Trichomonas is a flagellated protozoan which causes vulvovaginitis. Many drugs are available to treat it like:

- 1) Metronidazole – 400 mg TDS for 7 days.
- 2) Secnidazole – 2 g single dose
- 3) Nimorazole – 2 g single dose
- 4) Quiniodochlor – 200 mg vaginal pessaries may be used for 2 weeks at night.
- 5) Natamycin/Hamycin – Their vaginal pessaries are also available which can be used at night time.

Note: Drugs should be given for both the partners.

Drugs for Giardiasis

Giardia lamblia is a flagellate protozoan, commensal in the intestine of man. It may cause malabsorption and diarrhea in man.

- 1) Metronidazole – 15 mg/kg for 7 days
- 2) Secnidazole – 2 g single dose
- 3) Furazolidone – may also be used
- 4) Quiniodochlor – 100 mg TDS for five days should be given.

Drugs for Leishmaniasis

Classification

a) Antimonials

- a. Sodium stibogluconate
- b. Meglumine antimonate

b) Diamidine

- a. Pentamidine

c) Miscellaneous

- a. Amphotericin B
- b. Ketoconazole
- c. Miltefosine
- d. Paromomycin sulfate
- e. Allopurinol

Antimonials: Sodium stibogluconate and meglumine antimonate are the pentavalent antimonial compounds containing $1/3^{\text{rd}}$ antimony by weight.

MOA: They inhibit SH group of enzymes i.e. it interfere with energy supply of the parasite.

Pharmacokinetics: Not absorbed orally, must be given by i.v. or i.m. route. It is excreted via two phases one rapid (2 hrs) and other longer (24 hrs). Treatment is given in a dose of 200 mg/kg for 20 days.

Side effects: Nausea, vomiting, metallic taste, cough, pancreatitis, Q-T prolongation, cardiac arrhythmias, hemolytic anemia. Serious liver, kidney and cardiac effects are rare.

Pentamidine: It is an aromatic diamidine derivative effective against Leishmania, Pneumocystis and Trypanosoma. It is only available as parenteral preparation.

MOA: it interferes with the kinetoplast DNA of the parasite and also inhibits bioenergetics of the parasite.

Pharmacokinetics: It is not absorbed orally, only administered parenterally. Its $t_{1/2}$ is 6 hr, while elimination $t_{1/2}$ is 12 hr.

Uses:

- 1) Trypanosomiasis
- 2) Leishmaniasis
- 3) Pneumonia- caused by Pneumocystitis carinii in AIDS patients

Others

Paromomycin sulfate: It is an aminoglycoside antibiotic, now the drug of choice for Kala-Azar. It is not significantly absorbed from the GI tract. The amount absorbed is excreted by glomerular filtration.

Side effects: Renal damage, abdominal pain, diarrhea, GI ulcerations.

Uses:

- 1) Kala azar
- 2) Luminal amebicide

Miltefosine: It is an alkylphosphocholine analog that has been approved by the FDA for the treatment of Leishmaniasis. It is given in a dose of 2.5 mg/kg for 28 days orally and has produced excellent results. Vomiting, diarrhea, elevation of liver enzymes is the main side effects. The drug is teratogenic and should be cautiously used during pregnancy.