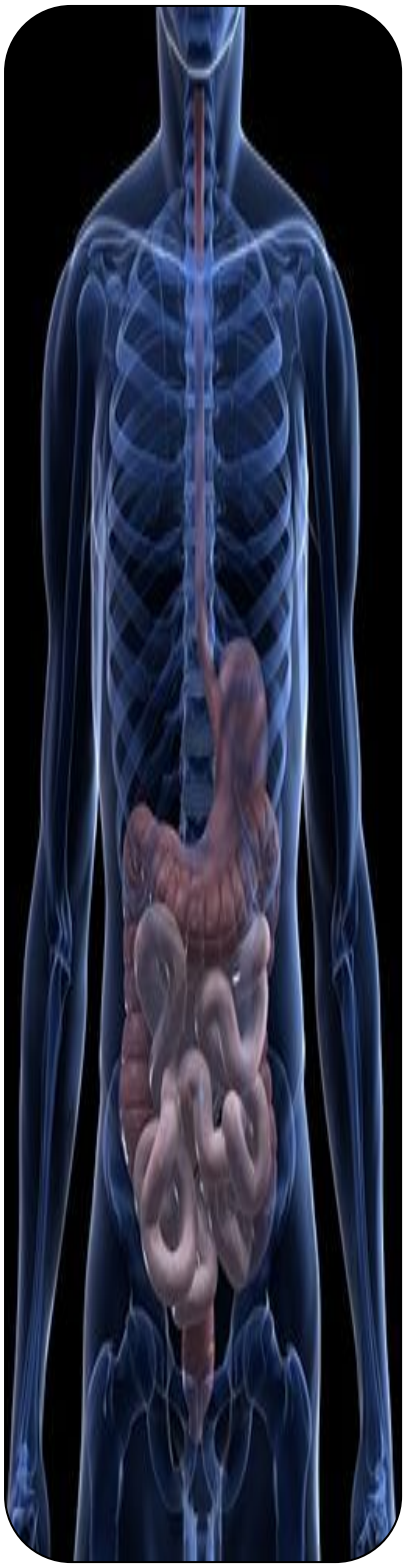
Pharmacology Team

ANTIMALARIAL DRUGS



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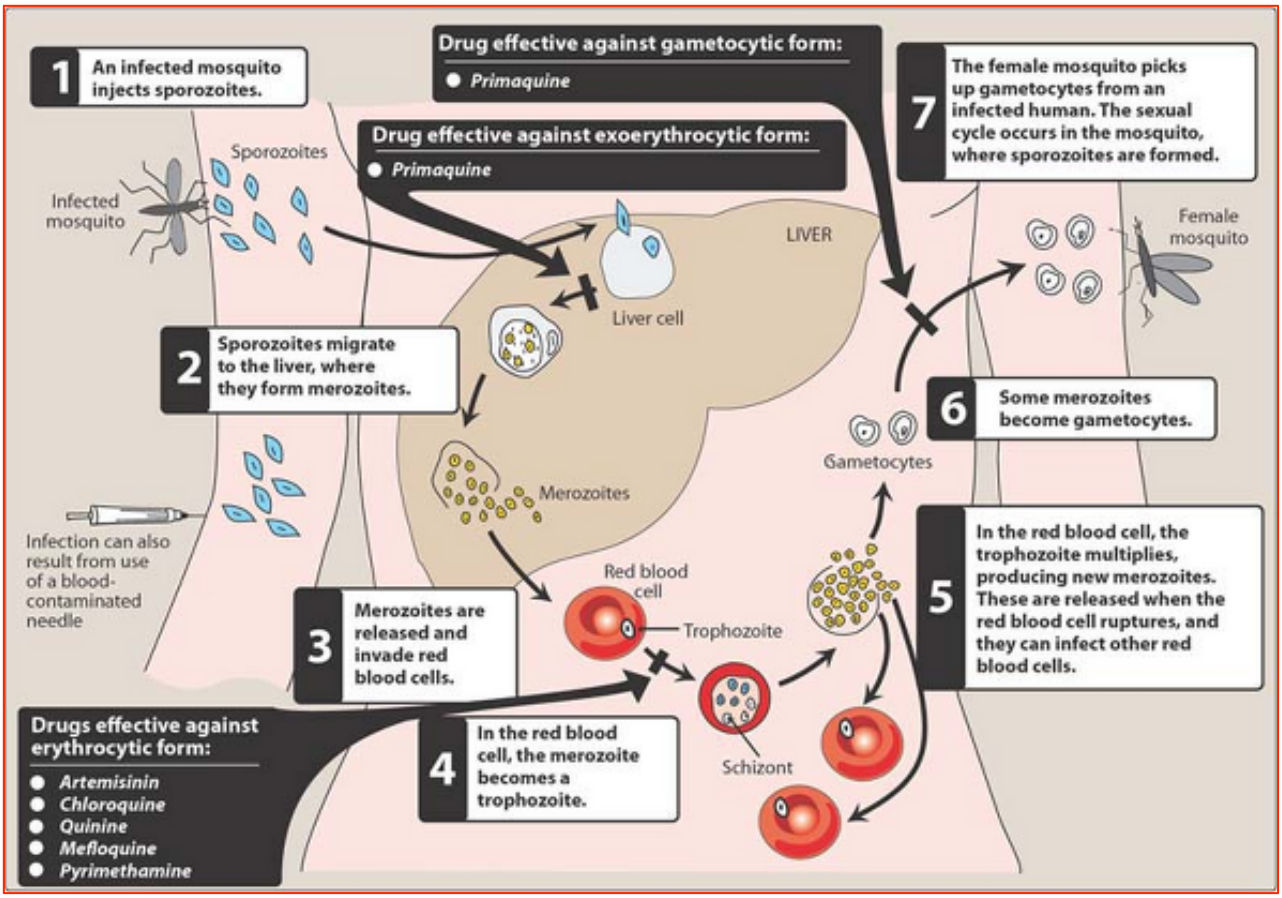
References:
Lippincott's Pharmacology 4th edition
Rang and Dale's Pharmacology Sixth edition

RED = IMPORTANT BLACK=NOT IMPORTANT

Introduction

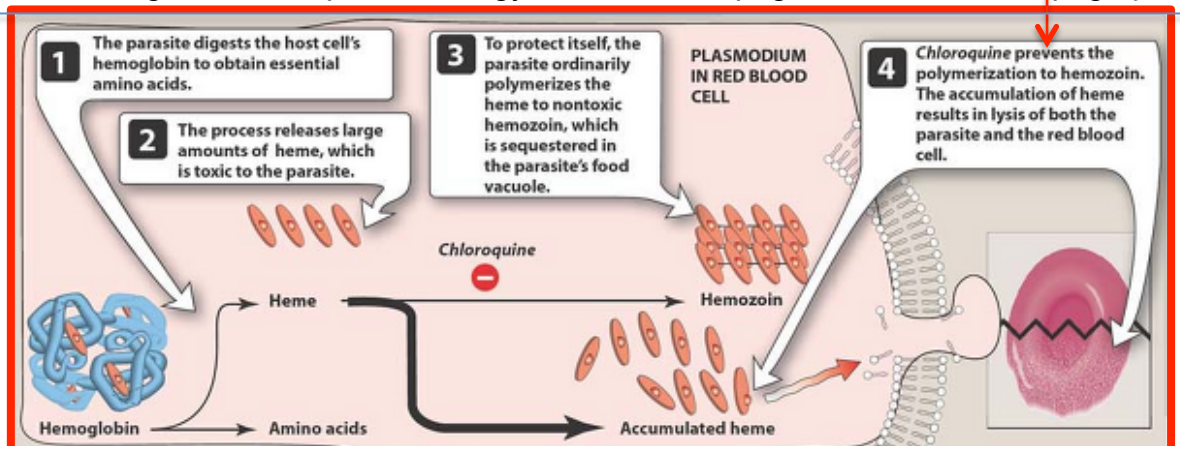
- Malaria is an acute infectious disease caused by four species of the protozoal genus plasmodium.
- **Plasmodium Falciparum**, Plasmodium malariae, Plasmodium Ovale, and **Plasmodium vivax**.
- The parasite is transmitted to humans through the bite of female anopheles mosquito.
- P. Falciparum is the most dangerous species, causing a severe disease. P. vivax causes a milder disease.
- Resistance acquired by the mosquito to insecticides, and by the parasite to drugs, has led to new therapeutic challenges, particularly in the treatment to P. Falciparum.



Life cycle of malaria:

When an infected mosquito bites, it injects Plasmodium sporozoites into the bloodstream. The sporozoites migrate through the blood to the liver, where they form cyst-like structures containing thousands of merozoites. Upon release, each merozoite invades a red blood cell, becoming a trophozoite and **using hemoglobin as a nutrient**. The trophozoites multiply and become merozoites. Eventually, the infected cell ruptures, releasing heme and merozoites that can enter other erythrocytes. Alternatively, released merozoites can become **gametocytes, which are picked up by the mosquitoes from the blood they ingest**. The cycle thus begins again, with the gametocytes becoming sporozoites in the insect.

IMPORTANT*: Infections with **P.falciparum** and P.malariae **have no exoerythrocytic stage**
Infections with **P.vivax** and P.ovale **have exoerythrocytic stage**
(* the source: Rang and dale's pharmacology- sixth edition- page704 "see the last page")



Plasmodium uses hemoglobin as a nutrient:
It is in the food vacuole that parasite digest the host cell's hemoglobin to obtain essential amino acids. However, this process releases large amounts of heme, which is toxic to the parasite. To protect itself, the parasite ordinarily polymerizes the heme to hemozine, which is nontoxic, with the use of heme polymerase. Some drugs interfere with this process such as chloroquine.

Symptoms of malaria:
Fever, shivering, pain in the joints, headache, repeated vomiting, generalized convulsions, and coma.

Antimalarial drugs

Some drugs can be used prophylactically to prevent malaria, while others are directed towards treating acute attacks. In general, antimalarial drugs are classified in terms of the action against the different stages of the life cycle of the parasite

A) *Blood* schizonticidal agents:
Are used to treat the acute attack. They act on the erythrocytic forms of the plasmodium.
- Atremisinin
- Chloroquine
- Quinine

***B) Tissue* schizonticidal agents:**
Have a radical cure effect by acting on the parasites in the liver, these drugs also destroy gametocytes and thus reduce the spread of infection.
- Primaquine

Target of Therapy	Therapeutic Class	Drug Examples
To alleviate symptoms	**Blood schizontocidal drugs**	• **Artemisinin** • **Chloroquine (in vivax only)** • **Quinine (in pregnancy)**
To prevent Relapses	**Tissue schizontocidal drugs**	• **Primaquine**
To prevent Spread	**Gametocidal drugs**	• **Primaquine**

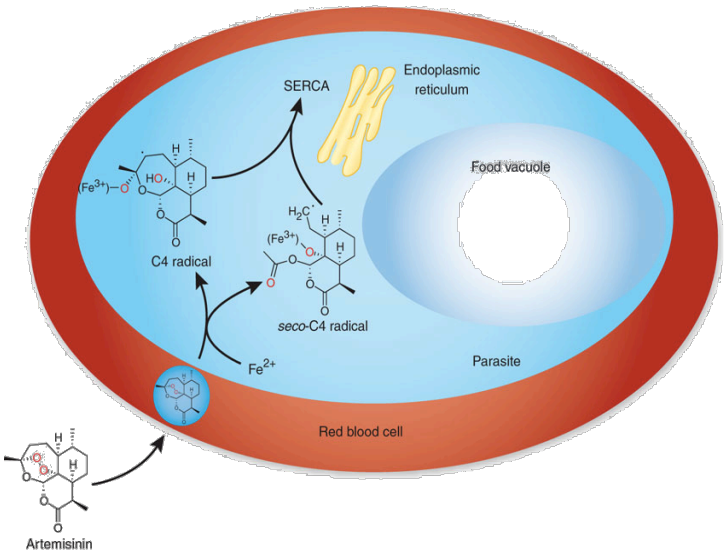
1- Atremisinin:

- Important drug because plasmodium have not developed resistance to it yet.
- Another preparations are available with better solubility: **Artensuate**, and **artemether**.

T1/2:

Artemisinin (4hrs)
Artesunate (45min)
Artemether (4-11hrs)

MOA: by production of **free radicals** within the plasmodium vacuole, following cleavage of the drug's endoperoxide bridge by heme iron in parasitized erythrocyte. These free radicals will attack the lipids, membranes and the structures of the organism, and inhibit its growth by inhibiting enzyme called sarco-endoplasmic reticulum Ca2+-ATPas (SERCA).



*Artemisinin **and its derivatives should not be used as monotherapy?? →** Because it has got short half-life, so if we use alone recrudescent will happen "recurrence of the symptoms" and also to prevent resistance and delay its development to give better results.

ADRs:

- Transient heart block
- ↓ neutrophil count
- Brief episodes of fever
- Neuro, hepato and bone marrow toxicity

→ Overall, the drug is considered safe

Preparations:

1- Artesunate IV or IM preparations for severe complicated cases as cerebral malaria (24h) followed by complete course of **ACT.**

2- Artemisin-based combination therapies (ACTs):
   - Artemether + lumefantrine
   - Artemether + amodiaquine
   - Artemether + mefloquine
   - Artemether + sulfadoxine-pyrimethamine

- These combinations are used in mild to moderate malaria alone
- in case of severe malaria the treatment is initiated by artesunate for 24 hours then we continue the treatment with ACT.

2- Chloroquine:

- Effective in the treatment of extraintestinal amebiasis (especially amebic liver abscess).
- It has anti-inflammatory action, therefore, can be used in rheumatoid arthritis and SLE.
- Used in sensitive vivax malria ONLY
- Resistence to it has developed (especially chloroquine-resistant P.falciparum).

MOA:

As mentioned in the introduction, malaria parasite digest host cell's Hemoglobin RBC to obtain amino acids. Heme is released (which is Toxic to the parasite) So parasite detoxifies it by heme polymerase to Hemozin (which is non toxic to the parasite).

chloroquine prevents polymerization of heme to hemozoin ,leading to death of the parasite.

Pharmacokinetics:

Chloroquine concentrates 1000-fold in food vacuole of parasite. Why ?
1- Its protonation & ion trapping due to ↓ pH of vacuole (=because it is acidophilic and food vacuoles have low PH)
2-Its active uptake by a parasite transporter(s)
3- Its binding to a specific receptor in the food vacuole

- Has high volume of distribution
- Concentrated in food vacuoles of parasites, in erythrocytes, in melanin containing tissues "pigments", and other tissues.
- Released slowly from tissues
- Initially t1/2=2-3days, terminal t1/2=1-2months

ADRs:

Because drug is concentrated in melanin containing tissues like retina and skin…

❖ **in Short-term use "as in malaria":**

1. Mild headache and visual disturbances.
2. Gastro-intestinal upsets; Nausea, vomiting .
3. Pruritus, urticaria "allergy".

❖ **Prolonged therapy "as in Rheumatoid arthritis":**

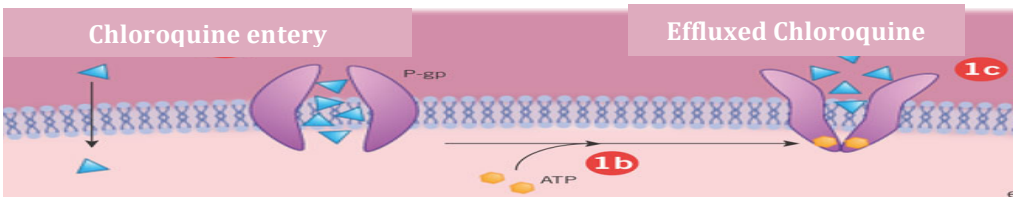
1. **Retinopathy**, characterized by loss of central visual acuity, macular pigmentation and retinal artery constriction. Progressive visual loss is halted by stopping the drug, but is not reversible.
2. Lichenoid skin eruption, bleaching of hair.
3. Weight loss
4. Hemolytic anemia in patients with G6PD deficiency (not mentioned in the slides nor during the lecture)

Bolus injection→ hypotension & dysrrhythmias

Chloroquine Resistance: (IMP!!)

Resistance against the drug develops as a result of enhanced efflux of parasite vesicle → because of increased expression of the human multi drug resistance transporter P-glycoprotein = MDR T P-GP

In another way, this means: once the drug enters the parasite cell, and before it starts its action, the parasite is able to identifies it as a drug that is toxic. As a defensive mechanism, the parasite will get rid of the drug and throw it out of the cell by the help of MDR T P-GP. When there is upregulation and increase expression of this protein, the parasite will develop resistance to the drug.



3-Quinine

MOA + Resistance mechanism: Same as chloroquine

Other Actions:

- Antiarrhythmic as well = quinidine like action.
- Mild oxytoxic effect on pregnant uterus
- Slight neuromuscular blocking action
- Weak antipyretic action

Oxytoxic effect: stimulate uterus contraction to deliver the fetus. In late pregnancy , it has a similar action to the natural the oxytocin hormone in the body.

Major ADRs:

❖ **In therapeutic does:**

- Bitter taste => poor compliance "patient may not take it regulatory or stop because of its tastes"

❖ **In Higher doses:**

- **Cinchonism (tinnitus, deafness, headaches, nausea & visual disturbances)** "it's called cinchonism reffering to its origin plant cinchona bark."
- Abdominal pain & diarrhea
- Rashes, fever, hypersensitivity reactions
- Hypotension & arrhythmias
- Blood dyscarasis; anaemia, thrombocytopenic purpura & hypoprothrombinaemia
- Blackwater fever, a fatal condition in which acute haemolytic anaemia is associated with renal failure.

Cinchonism: a syndrome causing nausea and vomiting, tinnitus, and vertigo

If given IV => neurotoxicity => tremor of the lips and limbs, delirium, fits, stimulation followed by depression of respiration & coma.

Contraindications:

- Prolonged QT Interval.
- Glucose-6-Phosphate Dehydrogenase Deficiency.
- Myasthenia Gravis. "because of neuromuscular blocking action"
- Hypersensitivity.
- Optic Neuritis, auditory problems.
- Dose should be reduced in renal insufficiency.

Interactions

- Antacids: Antacids containing aluminum &/or magnesium may delay or decrease absorption of quinine.
- Erythromycin (CYP3A4 inhibitor)
- Cimetidine
- Mefloquine.
- Quinine can raise
- plasma levels of warfarin and digoxin.

Both Erythromycin and cimetidine are inhibitors of Quinine metabolism.

*** **Less resistance than chloroquine**

4- Primaquine:

MOA: Not well understood. Many theories. Believed to act as oxidant.

ADRs:

- **in regular doses:**
- **Drug induced hemolytic anemia in patients with G6PD deficiency**
  how? Primaquine oxidizes the glutathione => no enough NADPH => RBCs lysis by oxidants.

- **In large doses:**
  - Epigastric distress & abdominal cramps.
  - Mild anemia, cyanosis & methemoglobinemia
  - Severe methemoglobinemia!rarely in patients with deficiency of NADH methemoglobin reductase.
  - Granulocytopenia & agranulocytosis => rare

Other drugs used in combination (=Other drugs that we can use to combine with the previous main drugs)

DRUG	MECHANISM	ADR
Lumefantrine	**↓heme polymerase**	
Amodiaquine	**↓heme polymerase**	
Mefloquine	**↓heme polymerase**	
Sulfadoxine-pyrimethamine	**Sequential block of dihydropteroate synthase & dihydrofolate reductase therefore ↓ DNA synthesis**	→ Allergy and Bone marrow suppression
Clindamycin	**inhibits parasite apicoplast (which is needed for survival & successful host invasion)**	→ Pseudomembranous colitis
Doxycycline	**Inhibit protein synthesis by binding to 30S subunit of ribosome**	→ Bone deformities and teeth discoloration

* Which one of the 4 main drugs that can be used in patients with G6PD deficiency??
Atremisinin

WHO treatment Guidelines:

P.vivax infection
If sensitive →
give Chloroquine for 3 days,
followed by **Primaquine** for 14 days.

If resistance →
Give ACT, followed by **Primaquine**

P.Falciparum infection → always show resistance to Chloroquine.
Uncomplicated "mild to moderate" → give ACT.

Complicated "severe" →
IV OR IM Artesunate for 24 hrs,
followed by
-ACT
-Or Artemether + [Clindamycin / doxycyline]
-Or Quinine + [Clindamycin / doxycyline]

in Pregnancy
Pregnancy; 1st trimester → Quinine + clindamycin

Pregnancy; 2nd & 3rd trimester
Lactating women
Infants & young children
→ ACT

- **Why quinine can be given in 1st trimester only?**
  Because of the oxytoxic effect.
- **Chloroquine is safe in pregnancy, but yet not given. Why?** Because if I give it and the pregnant lady has P.falciparum infection, she will die from the infection not the drug. So we must give another drug that is both safe and can attack all parasites whether sensitive or resistance.

MCQs:

Q1: A patient is infested by plasmodium ovale and is suffering from repeated relapses. Which ONE of the following drugs can be used to prevent relapses?

A. chloroquine
B. Quinine
C. Artenisinin
D. primaquine

Q2: Which one of the following is the most probable mechanism of plasmodial resistance to cloroquine?

A. change in the receptor structre.
B. increse expressone of p-glycoprotein
C.increase in the activty of DNA repair mechanism.
D. Induction of inactivating enzyme.

Q3: Which one of the following is the drug to use in acute attack (by P.Falciparum):

A. chloroquine
B. Quinine
C. Mefloquine
D. primaquine

Q4: Which of the following drugs can cause cinchonism?

A. chloroquine
B. Quinine
C. Artenisinin
D. primaquine

Q5: Which of the following drugs kill the organisms by producing free radicals?

A. chloroquine
B. Quinine
C. Artenisinin
D. primaquine

Q6: Primaquine, a tissue schizonticidal, is NOT used in which of the following cases:

A. Resistant p.vivax
B. Resistant p.ovale
C. Sensitive p.vivax
D. Sensitive P.faliparum

Q7: which on e of the following antimalarial drugs can be given to a patient with G6PD deficiency
A. chloroquine
B. Quinine
C. Artenisinin
D. primaquine

Rang and dale's pharmacology- sixth edition- page704

antimalarial drugs are classified in terms of the action against the different stages of the life cycle of the parasite (Fig. 49.1).

Drugs used to treat the acute attack

Blood schizonticidal agents (Fig. 49.1, site A) are used to treat the acute attack—they are also known as drugs that produce a 'suppressive' or 'clinical' cure. They act on the erythrocytic forms of the plasmodium. In infections with *P. falciparum* or *P. malariae*, which have no exoerythrocytic stage, these drugs effect a cure; with *P. vivax* or *P. ovale*, the drugs suppress the actual attack, but exoerythrocytic forms can re-emerge later to cause relapses.

This group of drugs includes *quinoline–methanols* (e.g. **quinine** and **mefloquine**), various *4-aminoquinolines* (e.g. **chloroquine**), the phenanthrene **halofantrine**, and agents that interfere either with the synthesis of folate (e.g. **sulfones**) or with its action (e.g. **pyrimethamine** and **proguanil**), as well as the hydroxy-naphthoquinone compound **atovaquone**. Combinations of these agents are frequently used. Some antibiotics, such as **tetracycline** and **doxycycline** (see Ch. 46), have proved useful when combined with the above agents. Compounds derived from *qinghaosu*, for example **artemether**, **arteflene** and **artesunate**, have also proved effective.

For a brief summary of currently recommended treatment regimens, see the *Antimalarial drugs* box and Table 49.2. A more detailed coverage of the treatment of malaria is given by Newton & White (1999) and Baird (2005).

Drugs that effect a radical cure

Tissue schizonticidal agents effect a 'radical' (in the sense of striking at the root of the infection) cure by acting on the parasites in the liver (Fig. 49.1, site B). Only the 8-aminoquinolines