Anti-Malarial Drugs

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- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objectives

- Classify the main antimalarial drugs depending on their goal of therapy
- Detail the pharmacokinetics & dynamics of main drugs used to treat attack or prevent relapses
- Mechanism of action, clinical uses & side effects of main antimalarial drugs
- Mechanisms of drug resistance
- State the WHO therapeutic strategy for treatment
- Hint on the CDC recommendations for prophylaxis in travelers to endemic areas.

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Overview

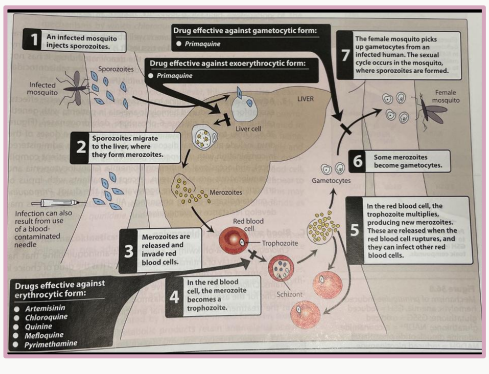
Epidemiology & Etiology

- According to **WHO**:
  - 212 million cases of malaria worldwide in 2015 & 429,000 deaths.
  - 90% of malaria cases & deaths occur in **Africa.**
  - children under 5 are most at risk.
- Four species of plasmodium typically cause human malaria:
  - **Plasmodium falciparum**, P. Vivax, P. Malariae, and P. Ovale.

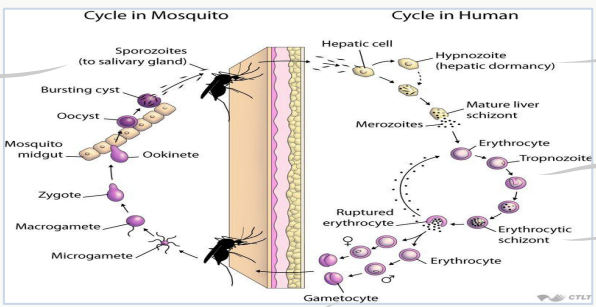
Therapeutic Classification

Sporozoitocides	Proguanil Pyrimethamine	Destroys Sporozoites
Causal Prophylaxis	**Primaquine** Only drug acting on liver sporozoites	Destroys parasite in **liver** cells & prevent invasion of erythrocytes
Radical Cure	Suppressive drug+hypnozoitocidal suppressive & causal prophylaxis	Eradicates all forms of vivax from the body.
Suppressive Prophylaxis	Chloroquine Mefloquine Doxycycline antibiotic	Suppresses the **erythrocytic** phase & thus the attack of malaria fever before symptomatic presentation
Clinical Cure (Erythrocytic schizonticide):	**Fast Acting-High efficacy:** Chloroquine, Quinine, Mefloquine & Artemisinin.	Used to terminate an episode of malarial fever = RBC Schizonts
	Slow Acting Low-efficacy: Pyrimethamine & sulfonamides Proguanil	
Gametocidal	Against Vivax: Chloroquine & Quinine Against All species: Primaquine	Destroys Gametocytes & prevents transmission

Cycle & Drugs' Sites of Action



Sporozoitocides



Causal prophylaxis

Radical cure

Clinical cure

Suppressive prophylaxis

Gametocides

Blood Schizonticide

Artemisinin

Overview

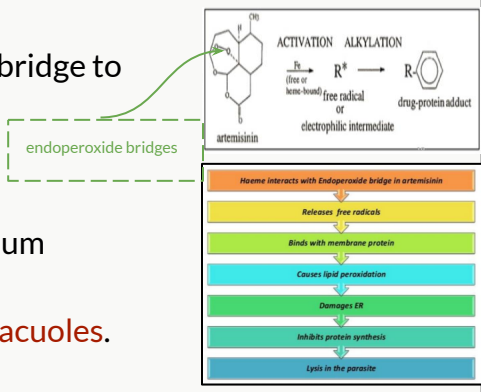
- Artemisinin is the active principle of the plant Artemisia annua (qinghaosu)
- Advantages:
  - Fast acting blood schizonticide.
  - Affects all forms including multidrug resistant P. falciparum.
- Disadvantages:
  - Poorly soluble in water and oil, can only be used orally.
  - Short duration of action.
  - High recrudescence rate after short-course therapy
    = High relapse rate-short DOA; doesn't eradicate all parasites, especially dormant hepatic parasites

P.K

- Artemisinin, Artesunate, & Artemether are prodrugs:
  - Rapidly biotransformed in liver into dihydroartemisinin (active metabolite)
  - Derivatives are rapidly absorbed orally and widely distributed
  - T ½:
    1. Artemisinin: 4 hrs
    2. Artesunate: 45 min (water soluble; oral, IV, IM, rectal administration)
    3. Artemether: 4-11 hrs, (lipid-soluble;oral, IM, rectal administration)
       Artemether induces its own CYP-mediated metabolism → ↑ clearance 5 fold

M.O.A

- Artemisinin & its analogs are very rapidly acting blood schizonticides against all human malaria parasites. No effect on hepatic stages.
- They have endoperoxide bridges, Haem iron cleaves this bridge to yield carbon-centered free radicals in parasite, that will:
  - Alkylate membranes of parasites' food vacuole and mitochondria → no energy.
  - Irreversibly bind and inhibit sarco-endoplasmic reticulum Ca^{2+}-ATPase of the parasite → inhibiting its growth.
  - Inhibiting formation of transport vesicles → no food vacuoles.



Clinical uses

- Because artemisinin derivatives have short t½:
  - Monotherapy should be extended beyond disappearance of parasite to prevent recrudescence . Prolong the therapy even if the symptoms disappear (to prevent the relapse)
  - Or Combine the drug with long-acting antimalarial drugs. (Ex. mefloquine).

Preparations

- For severe complicated cases as cerebral malaria:
  - IV or IM Artesunate (24h) + complete course of ACT

***ACT = Artemisinin*-based combination therapies** oral preparations :

- Artemether + lumefantrine
- Artemether + amodiaquine
- Artemether + mefloquine
- Artemether + sulfadoxine - pyrimethamine.

Anti malarial drugs with long DOA

ADRs

- Transient heart block.
- ↓ neutrophil count (rare).
- Brief episodes of fever confused with malarial fever
- **Resistance** → was reported recently in Cambodia-Thailand border

Blood Schizonticides & Gametocides

Chloroquine

Overview

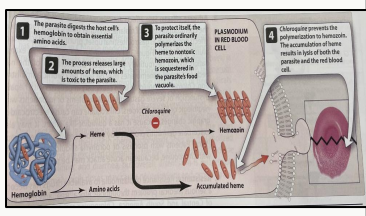
- Potent blood Schizonticide Not active against tissue schizonts (Hepatic stages)
  - Active against all forms of the schizonts
  - Exception : chloroquine-resistant P.falciparum and P.vivax
- Gametocide: Against all species (except P. falciparum we use primaquine).

P.K

- Rapidly and completely absorbed from the GIT, given PO orally
- Disadvantage: Has high volume of distribution (100-1000 L/kg) & Released slowly from tissues and metabolized in liver.
- **Concentrated into parasitized RBCs.**
- Excreted in the urine 70% unchanged.
- Initial t½ = 2-3 days and terminal elimination t½ = 1-2 months due to the high volume of distribution

M.O.A

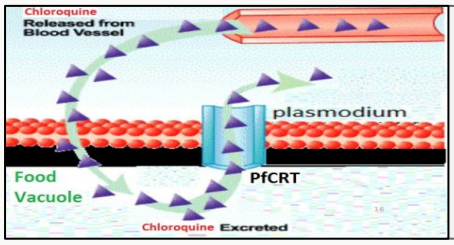
- **Malaria Parasite** digest host cell's Hb to utilize globin and obtain amino acids.
- Heme is released (Toxic to the parasite), so parasite detoxifies it by:
  - **Heme polymerase** → Hemozoin (Non Toxic) & traps it in food vacuoles.
  - Heme polymerase is inhibited by chloroquine, heme accumulation results in lysis of the parasite & the RBC



MOA? detoxification of heme by inhibition/block heme polymerase

Resistance

- Resistance against the drug develops as a result of ***mutation*** of the chloroquine resistance transporter (**PfCRT**)
  - Mutated **PfCRT enhances the efflux of chloroquine from the food vacuole**



Chloroquine يمسك ب Food vacuole
ويدخل للبارا سايت عن طريق PFCRT
البارا سايت بعد فتره تغير تركيب PFCRT ف مابيقدر يدخل
chloroquine with the food vacuole
Therefore the Parasite will develop resistance against the drug

Therapeutic uses

- Used to eradicate **blood** schizonts of Plasmodium. It is given in loading dose to rapidly achieve effective plasma concentration. (Cure & prophylactic)
- **Safe in pregnancy**
- Hepatic amebiasis.
- Rheumatoid arthritis.

ADRs

- Mild headache & visual disturbances
- GIT upsets; nausea, vomiting
- Pruritus & urticaria

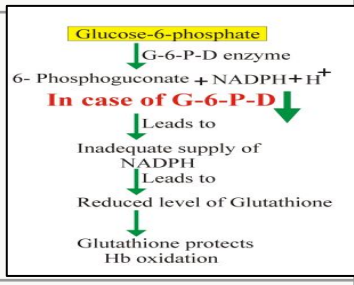
- **Prolonged therapy & high doses** like for rheumatoid
  - Ocular toxicity :- loss of accommodation, lenticular opacity & retinopathy.
  - Ototoxicity
  - Weight loss

- **Bolus injection**
  - Hypotension & Dysrhythmias

Blood Schizonticides & Gametocides

Quinine

Overview	1. Potent blood schizonticide of all malarial parasites 2. Gametocide for P. Vivax & Ovale but not falciparum. 3. It is not active against liver stage parasites. - Affects Na channels: Depresses the myocardium, reduce excitability & conductivity - Mild analgesic, antipyretic, stimulation of uterine smooth muscle, curare mimetic effect (curare= neuromuscular blockade) - The main alkaloid in cinchona bark
P.K	• Administered: orally in a 7 day course or by slow IV for severe p.falciparum infection • Rapidly and completely absorbed from the GIT • Peaks after 1-3 hours. • Metabolized in the liver and excreted in urine • 5-20% excreted in the urine unchanged. • T½ = 10 hrs but longer in severe falciparum infection (18 hrs).
M.O.A	• Same as chloroquine: inhibits heme polymerase
Resistance	• Like chloroquine, by mutation of the chloroquine resistance transporter (PfCRT), also increased expression of P-glycoprotein transporter → *efflux of drug*.
Clinical uses	1. Parenteral treatment of severe falciparum malaria 2. Oral treatment of falciparum malaria (schizonticide) 3. Nocturnal leg cramps. **-Safe in pregnancy**
ADRs	- With therapeutic dose > Poor compliance → bitter taste. - **Higher doses:** • Cinchonism → tinnitus, deafness, headaches, nausea and visual disturbances • Abdominal pain and diarrhea, • Rashes, fever, hypersensitivity reactions • Hypotension and arrhythmias • Hypoglycemia (injection) • Blood dyscrasias ; anaemia, thrombocytopenic purpura and hypoprothrombinemia (mild) • Blackwater fever: a fatal condition in which acute haemolytic anaemia is associated with renal failure due to a hypersensitivity reaction to the drug. • IV > neurotoxicity → tremor of the lips and limbs, delirium, fits, stimulation followed by depression of respiration and coma.
C.I	• Prolonged QT Interval • G6PD deficiency. • Myasthenia Gravis. Due to its muscle relaxant effects • Hypersensitivity. • Optic Neuritis, auditory problems. Due to cinchonism • Dose should be reduced in renal insufficiency.
Drug interactions	• Antacids: containing aluminum &/or magnesium may delay or decrease absorption of quinine. • Mefloquine both prolong QT interval • Quinine can raise plasma levels of warfarin and digoxin since they already have Narrow Therapeutic Index NTI



Hypnozoitocide & Gametocides

Primaquine

Overview	• Hypnozoitocides, the only one against liver hypnozoites & gametocytocides against the 4 human malaria species. • Radical cure of P. ovale and P. vivax. • Prevents spread of all forms (chemoprophylaxis).
P.K	• Well absorbed orally • Rapidly metabolized to etaquine & tafenoquine > more active forms • T½. > 3-6 hrs.
M.O.A	• Not well understood, It may be acting by:- – Generating ROS (electrophiles) → can damage lipids, proteins and nucleic acids in the parasite. - Interfering with the electron transport → no energy. - Inhibiting formation of transport vesicles → no food vacuoles.
Clinical uses	• Radical cure of relapsing malaria, 15 mg/day for 14 days. • In falciparum malaria: a single dose (45 mg) to kill gametes the only benefit with p. Falciparum and cut down transmission.
C.I	• Should be avoided in G6PD deficiency & pregnancy (the fetus is relatively G6PD deficient & thus at risk of hemolysis).
Doses	• G6PD normal → 15 mg/day for 14 days. • G6PD deficiency (mild-moderate African form) → 45 mg\week for 8 weeks. • G6PD deficiency (more severe mediterranean variety) → 30 mg\week for 30 weeks.
Resistance	• Rare, when Primaquine & Chloroquine are combined
ADRs	**1. At regular doses:** • Patients with G6PD deficiency → hemolytic anemia. • Oxidation of primaquine produces free radicals → Free radicals will cause oxidative damage of RBCs → Hemolysis. • H_2O_2 oxidizes GSH (GSH Maintains integrity of RBCs) 2. **At larger doses:** • Epigastric distress and abdominal cramps. • Mild anemia, cyanosis and methemoglobinemia. ➔ Severe methemoglobinemia in patients with deficiency of NADPH methemoglobin reductase (rarely) . • Granulocytopenia and agranulocytosis → rare.

WHO Treatment Guidelines

In Plasmodium Vivax

- If Sensitive: **Chloroquine** for 3 days followed by **Primaquine** for 14 days.
- If Resistant: **ACT/3 days followed by primaquine for 14 days.**

In plasmodium Falciparum all show resistance

- If Uncomplicated: **ACT**
- If Complicated:
  - **Quinine+Clindamycin /Doxycycline**
  - **Artemether+Clindamycin/Doxycycline**
  - **IV artesunate for 24 hrs followed by ACT**

Special Risk Groups In falciparum

- **Pregnancy 1st trimester: Quinine & Clindamycin *7 *days***
- Pregnancy 2nd & 3rd trimester/Lactating women/Infants & young children : **ACT**

Follow with primaquine to kill dormant hepatic sporozoites

Prophylaxis in Travellers (CDC Recommendations)

Begins 1-2 weeks before departure (except Doxycycline 2 days) & continue 4 weeks after leaving the endemic area.

- **Chloroquine :** Areas without resistant P. Falciparum
- **Mefloquine:** Areas with chloroquine-resistant P. Falciparum
- **Doxycycline:** Areas with multi-drug resistant P. Falciparum

MCQ

1.A male patient with severe malaria was treated with an IV drug. Later he developed hypoglycemia. What is the medication he was treated with?			
A.Chloroquine	B.Quinine	C.Clindamycin	D.Ceftriaxone
2.Which of the following drugs is an anti gametocide for p.falciparum?			
A.Proguanil	B.Quinine	C.Chloroquine	D.Primaquine
3.A 20 year old photographer with moderate G6PD deficiency went to West Africa. He came back with symptoms of chills and fever. On investigation, they found Plasmodium Vivax. What medication should be given to manage his case?			
A.ACT followed by Primaquine for 14 days	B.ACT followed by Primaquine for 8 weeks	C.ACT followed by Chloroquine for prophylaxis	D.ACT followed by Mefloquine for prophylaxis
4.A 30 old pregnant (1st trimester) women came back from East Africa. With a major complaint of fever, headache and photophobia. Giemsa blood staining shows plasmodium vivax. When she was asked, she said I took chloroquine prior to the journey for prophylaxis. What is the best treatment for her condition?			
A.Quinine+Clindamycin	B.Artemisinin	C.Primaquine	D.Doxycycline
5.A semi-comatose patient presented to the hospital and he was diagnosed with cerebral malaria. which of the following drugs should be administered immediately?			
A.Artesunate	B.Artemether - mefloquine	C.Artemether - amodiaquine	D.Artemether-clindamycin
6.How does resistance develop against chloroquine?			
A.By enhanced efflux through the p-glycoprotein transporter	B.Secondary to binding to a receptor in food vacuole	C.Through the increasing the ph of food vacuole	D.Via decreasing glutathione that detoxifies toxic products
7.A patient currently on warfarin was treated with an antimalarial drug. After few days the PT greatly prolonged .Which antimalarial drug was used?			
A.chloroquine	B.Quinine	C.Primaquine	D.Artemisinin

1:B ,2:D ,3:B ,4:A ,5:A ,6:A ,7:B

SAQ

01

What is the mechanism of action of primaquine?

may be acting by:

- Generating ROS (electrophiles) → can damage lipids, proteins and nucleic acids in the parasite.
- Interfering with the electron transport → no energy.
- Inhibiting formation of transport vesicles → no food vacuoles.

02

Mention 3 ADRs and 3 C.I. of Quinine

ADR: Blackwater fever, cinchonism, hypoglycemia
C.I: G6PD deficiency, prolonged QT interval, Myasthenia Gravis

03

Mention 3 uses of Chloroquine

- Used to eradicate blood schizonts of Plasmodium.
- Hepatic amebiasis.
- Rheumatoid arthritis.

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