MED438

pharmacology
Team 438

Reviewed by Razan AlRabah & Ibrahim AlDakhil

Antimalaria Drugs

Objectives:

By the end of the lecture , you should know:

- 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.
- State the WHO therapeutic strategy for treatment.
- Hint on the CDC recommendations for prophylaxis in travelers to endemic areas.

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Purple: Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

Causes of Human Malaria

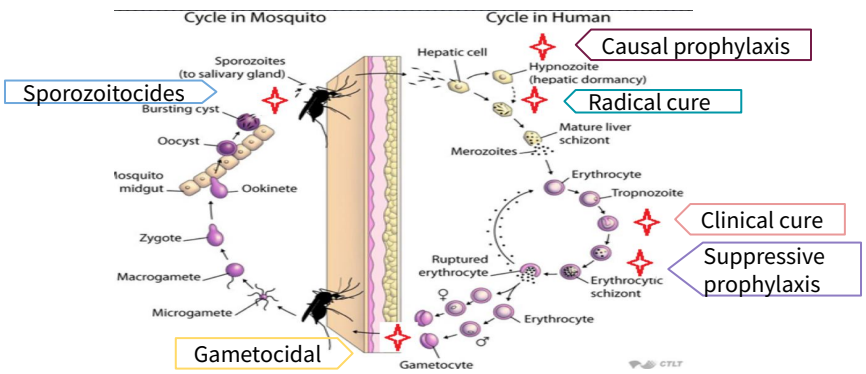
Females slides only

1. Plasmodium falciparum
2. P. vivax
3. P. malariae
4. P. ovale

Classifications of Antimalarial Drugs ★

Classification - Drugs - MOA

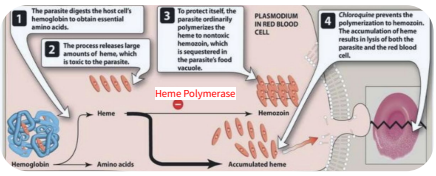
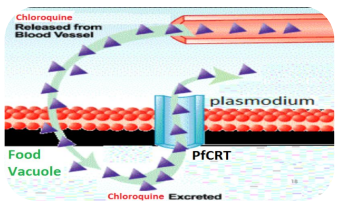
Causal prophylaxis	Primaquine	Destroys parasite in liver cells & prevent invasion of erythrocytes
Suppressive prophylaxis	- Chloroquine - mefloquine - doxycycline	Suppresses the erythrocytic phase & thus attack of malaria fever
Radical cure [1]	Suppressive drug + hypnozoitocidal	Eradicate all forms of vivax from the body
Gametocidal	**against vivax:** - Chloroquine - Quinine **against all species:** Primaquine	Destroys gametocytes & prevent transmission
Sporozoitocides	- Proguanil - pyrimethamine	Destroys sporozoites
Clinical cure (Erythrocytic schizonticide)	**Fast acting, high efficacy:** Chloroquine, quinine, mefloquine, artemisinin **Slow acting, low efficacy:** Pyrimethamine, proguanil, sulfonamides	terminate an episode of malarial fever



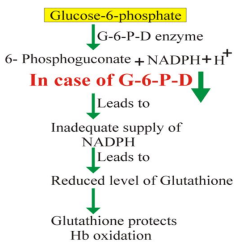
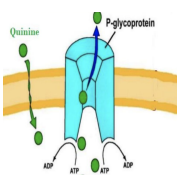
1) Strongest treatment

Drug	Artemisinin
MOA	• They have **endoperoxide bridges** that are cleaved by haem iron to yield carbon- centered free radicals in parasite, that will: 1. Alkylate membranes of parasite's food vacuole and mitochondria → **no energy** 2. Irreversibly bind & inhibit sarco-endoplasmic reticulum Ca2+- ATPase of the parasite→ **inhibiting its growth** 3. Inhibiting formation of transport vesicles → **no food vacuoles**
P.K	• Artemisinin is the active principle of the plant Artemisia annua (qinghaosu) • Fast acting **blood** Schizonticide ★ Artemisinin & its analogs are very rapidly acting blood schizonticides against all human malaria parasites **but have no effect on hepatic stages.** • Affect all forms including multi-drug resistant P. falciparum • Disadvantages: ○ Short duration of action ★ High recrudescence[1] rate after short-course therapy ○ Poorly soluble in water & oil, can only be used orally • Artemisinin, Artesunate, Artemether are **prodrugs** ○ Rapidly biotransformed in liver into dihydroartemisinin → active metabolite • Derivatives are rapidly absorbed orally and widely distributed • t1/2: Artemisinin: 4hrs / Artesunate: 45 min / Artemether: 4-11 hrs • Artesunate (water-soluble, given oral, IV, IM, rectal administration) • Artemether (lipid-soluble, given oral, IM, and rectal administration), **Induces its own CYP-mediated metabolism→ ↑ clearance 5 fold so its efficacy will decrease** • Dihydroartemisinin (water-soluble; oral administration)
Uses	• Because Artemisinin derivatives have short t 1/2 : ★ Monotherapy **should be extended** beyond disappearance of parasite to **prevent recrudescence** • By combining the drug with long- acting antimalarial drug e.g:Mefloquine.[2]
ADRs	• Transient heart block.[3] • Decrease neutrophil count • Brief episodes of fever • Resistance → was reported recently in Cambodia- Thailand border.
Pre-paration	★ Artesunate IV or IM preparations for severe complicated cases as cerebral malaria (24h) followed by complete course of ACT. • Artemisinin-based Combination Therapies (ACTs): ○ Artemether + lumefantrine ○ Artemether + amodiaquine ○ Artemether + mefloquine ○ Artemether + (sulfadoxine - pyrimethamine)

1) recurrence of symptoms after a period of remission or quiescence, in which sense it can sometimes be synonymous with **relapse**.
2) This method is also used to prevent the recrudescence of the disease.
3) Thus when given by an injection they're given for 24 hours only (not used chronically).

Drug	Chloroquine
MOA	• Malaria Parasite digest host cell's Hb to utilize globin & obtain amino acids. • Heme is released → **Toxic for the parasite**, so parasite detoxifies it by **heme polymerase**→ Hemozoin (NonToxic) & traps it in food vacuoles. • The parasite digests the host cell's Hb to obtain amino acids, this process releases large amounts of free heme which is toxic to the parasite thus the parasite will use an enzyme called "Heme polymerase" to polymerize the heme to a non toxic product known as "Hemozoin". **Chloroquine prevents the polymerization of heme to hemozoin by inhibiting Heme Polymerase enzyme and the accumulation of heme results in lysis of the parasite.** 
P.K	• Potent **blood** Schizonticide • Active against all forms of the schizonts (except chloroquine-resistant P.f. &P.v.) • Not active against tissue schizonts ★ Gametocide:-Against all species except P. falciparum. • Rapidly & completely absorbed from the GIT, given orally • Has high volume of distribution [1] (100-1000 L/kg); **Released slowly from tissues** and metabolized in liver • Concentrated into parasitized RBCs • Excreted in the urine 70% unchanged • Initial t1/2 = 2-3 days & terminal elimination t1/2=1-2 months.
Uses	★ Used to eradicate **blood** schizonts of Plasmodium. It is given in loading dose to rapidly achieve effective plasma conc. • Hepatic amebiasis • Rheumatoid arthritis (Long use) ★ Safe in pregnancy
ADRs	• Mild headache & visual disturbances • GIT upsets; Nausea, vomiting • Pruritus, urticaria. • Prolonged therapy & high doses: ○ Ocular toxicity [2]: Loss of accommodation, lenticular opacity, retinopathy ○ Ototoxicity [2] ○ Weight loss ○ Bolus injection → hypotension & dysrhythmias
Resis-tance	• Resistance against the drug develops as a result of mutation of the chloroquine resistance transporter (PfCRT) • PfCRT enhances the efflux of chloroquine from the food vacuole. 

1) Highly bound to tissue.
2) Because the drug accumulates and stays trapped within the tissue for months

Drug	Quinine
MOA	• **Same as chloroquine**
P.K	• The main alkaloid in cinchona bark • Potent **blood** Schizonticide of all malarial parasites & gametocide for P. vivax & ovale but not falciparum. **It is Not active against liver stage parasites.** • Depresses the myocardium, reduce excitability & conductivity ★ Mild analgesic, antipyretic, stimulation of uterine smooth muscle,**curare mimetic effect** [1]**.** • Rapidly & completely absorbed from the GIT • Peaks after 1-3 hours • Metabolized in the liver & excreted in urine • 5-20% excreted in the urine unchanged • t1⁄2 = 10 hrs but longer in severe falciparum infection (18 hrs) • Given orally in a 7 day course or by slow IV for severe P. falciparum infection
Uses	• Parenteral treatment of **severe** falciparum malaria • Oral treatment of falciparum malaria • Nocturnal leg cramps [5] ★ Safe in pregnancy [2]
ADRs	• With therapeutic dose: poor compliance⟶ bitter taste • Higher doses: Cinchonism ⟶ (tinnitus, deafness, headaches, nausea & visual disturbances) • Abdominal pain & diarrhea • Rashes, fever, hypersensitivity reactions • Hypotension & arrhythmias, hypoglycemia • Blood dyscrasias; **anaemia**, thrombocytopenic purpura & 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 • If given IV it causes neurotoxicity ⟶tremor of the lips & limbs, delirium, fits,stimulation followed by depression of respiration & coma [3]
C.I	• Prolonged QT Interval [4] ★ Glucose-6-Phosphate Dehydrogenase deficiency & pregnancy • Myasthenia Gravis [5] • Hypersensitivity • Optic Neuritis, auditory problems • Dose should be reduced in renal insufficiency 
Drug Inter-actions	• Antacids: Antacids containing aluminum &/or magnesium may delay or decrease absorption of quinine • Mefloquine [6] • Quinine can raise plasma levels of warfarin & digoxin [7]
Resistance	• Like chloroquine, by mutation of chloroquine resistance transporter • Also increased expression of P-glycoprotein transporter 

1) Curare is a muscle relaxant.
2) **Quinine can be used in the 1st trimesters but contraindicated in the 2nd and 3rd trimester (can induce mild contractions).**
3) Needs monitoring if given I.V or if used prolongedly.
4) C.I in arrhythmia
5) Due to its anti-muscular - relaxant - effects
6) should have 1 month gab before using it (it Prolongs Q-T interval leading to heart block if both drugs were used together)
7) By displacing them from plasma proteins and by decreasing their excretion.

Drug	Primaquine
MOA	• Not well understood. It may be acting by: ★ **Generating ROS** → can damage lipids, proteins & nucleic acids in the parasite • Interfering with the electron transport in the parasite → no energy • Inhibiting formation of transport vesicles → no food vacuoles • Primaquine → Converted to electrophiles → Generate reactive oxygen species (interferes with oxygen transport)
P.K	• Well absorbed orally • Rapidly metabolized to etaquine and tafenoquine[1] → more active forms • (t1/2 → 3-6h)
P.D	★ Hypnozoitocides → **against liver** hypnozoites & gametocytocides, **against the 4 human malaria species** • Radical cure of P. ovale & P. vivax • Prevent spread of all forms (chemoprophylaxis)
Uses	• Radical cure of relapsing malaria, 15mg/day for 14 days • In falciparum malaria: a single dose (45mg) to kill gametes & cut down transmission • Effective against dormant infection.
Doses	• G-6-PD **normal** → 15 mg\day **for 14 days** • G-6-PD **deficiency** (**mild**-moderate African form) → 45 mg\week **for 8 weeks** • G-6-PD **deficiency** (more **sever** mediterranean variety) → 30 mg\week **for 30 weeks**
ADRs	**At regular doses:** ★ patients with G-6-PD deficiency → hemolytic anemia. ○ Oxidation of Primaquine produces free radicals, free radicals will cause oxidative damage of RBCs → Hemolysis ○ H2O2 oxidized GSH ○ **GSH Maintains integrity of RBCs** **At larger doses:** • Epigastric distress & abdominal cramps • Mild anemia, cyanosis & methemoglobinemia • Severe methemoglobinemia → rarely in patients with deficiency of NADH methemoglobin reductase. • Granulocytopenia & agranulocytosis (rare)
C.I	★ Should be avoided in pregnancy (the fetus is relatively G6PD-deficient and thus at risk of hemolysis) ★ G6PD deficiency patients
Resistance	• Rare when Primaquine and chloroquine are combined

1) more potent , longer duration

Prophylaxis in travellers "CDC recommendations"

Chloroquine	Mefloquine	Doxycycline
Areas without resistant P. falciparum	Areas with chloroquine resistant P. falciparum	Areas with multidrug-resistant P. falciparum

Begin 1-2 weeks before departure (except for doxycycline 2 days) & continue for 4 weeks after leaving the endemic area

In P. vivax:

Sensitive :

- Chloroquine for 3 days followed by Primaquine for 14 days [1]

Resistant:

- ACT for 3 days followed by Primaquine for 14 days

WHO treatment guidelines

In P. falciparum:

- In falciparum (All show Resistance)

Uncomplicated:

- ACT

Complicated:

- IV Artesunate for 24 hrs followed by ACT
- Or Artemether + [Clindamycin or Doxycycline]
- Or Quinine + [Clindamycin or Doxycycline]

Special risk group:

01

ACT for :

1.Pregnancy; 2nd & 3rd trimester
2.Lactating women [2]
3.Infants & young children

02

Quinine + Clindamycin (7 days) for:
Pregnancy; 1st trimester

1) During the first 3 days of the treatment a blood test should be done on the patient to exclude G6PD deficiency or any blood disorders e.g. hemolysis then Primaquine can be used.
2) **After lactation, Primaquine SHOULD be used.**

Quiz

MCQ

1- A patient on warfarin was given anti-malarial drug, the effect of the drug is prolonged. Which of the following drugs was he given?

(A)Artemether (B) Doxycycline (C)Chloroquine (D)Quine

2- A patient on warfarin was given anti-malarial drug, the effect of the drug is shorted. Which of the following drugs was he given?

(A)Artemether (B) Doxycycline (C)Chloroquine (D)Quine

3- A patient was prescribed an antimalarial drug , later he experienced headaches , nausea, visual disturbances and tinnitus. Which anti-malarial drug is associated with these ADRs?

(A)Artemether (B) Doxycycline (C)Chloroquine (D)Quine

4- which of the following is appropriate anti-malarial therapy for a pregnant women in her 1st trimester?

(A)Artemether + Doxycycline (B) Artemether + lumefantrine
(C)Chloroquine primaquine (D)Quinine + Clindamycin

5- Which one of the following antimalarial drugs can cause Blackwater fever as serious adverse effect ?

(A)Quinine (B) Chloroquine (C) Primaquine (D) lumefantrine

SAQ

A 27-year- patient was was infected with malaria and the doctor prescribed him Primaquine.

1-Mention the MOA of the drug?
2-Enumerate ADRs.
3-Mention 2 Contraindications.

A patient with severe falciparum malaria.

4- What drug should be prescribed?
5- Enumerate the contraindications.

Answers:

MCQ

Q1	D
Q2	A
Q3	D
Q4	D
Q5	A

SAQ

Q1	Mentioned in Pg6
Q2	Hemolytic anemia-Epigastric distress-Cyanosis
Q3	Pregnancy - G6PD deficiency patients
Q4	Quinine
Q5	Prolonged QT Interval-Myasthenia Gravis- Optic Neuritis- G6PD deficiency

Share with us your ideas !

Good Luck , Future Doctors!

Team Leaders:

May Babaeer Zyad Aldosari

This Amazing Work Was Done By:

Njoud AlMutairi Nouf AlShammari