Lecture 10

Antimalarial drugs

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

- Additional Notes
- Important
- Explanation –Extra-

For any correction, suggestion or any useful information
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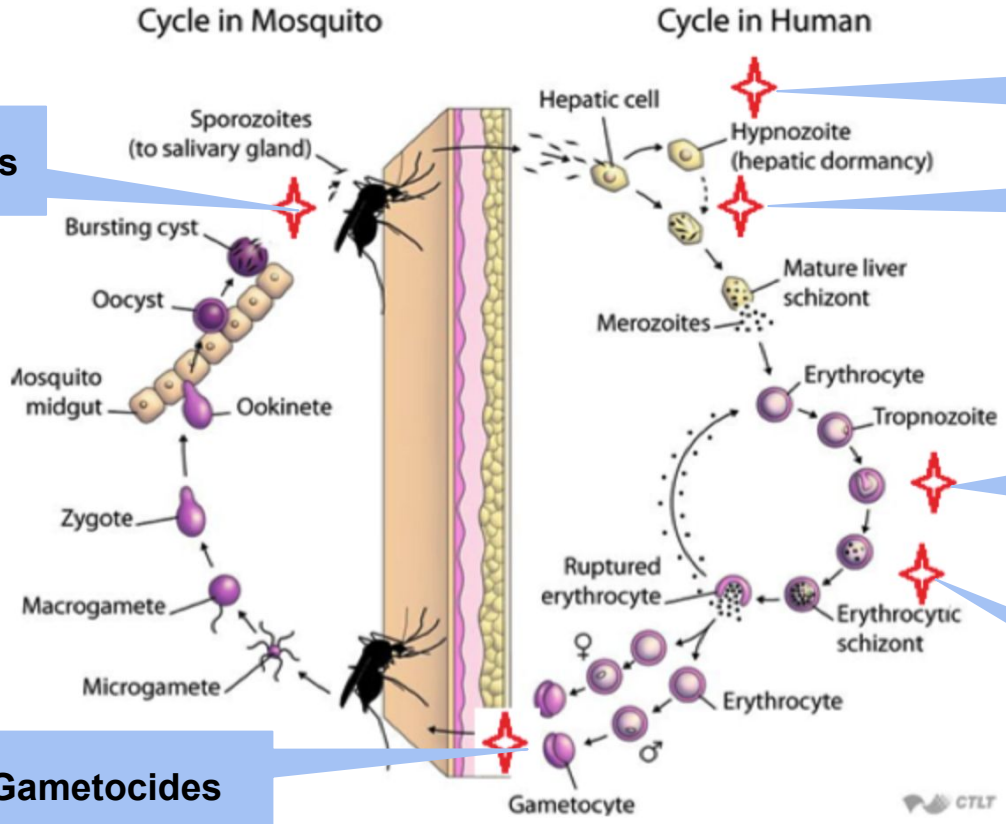
life cycle & Drugs site of action



6-Sporozoitocides

1-causal prophylaxis

4-radical cure

3-clinical cure

2-suppressive prophylaxis

5-Gametocides

Antimalarial drugs

1-causal prophylaxis	2-supressive prophylaxis	3-Clinical cure (erythrocytic schizonicide)		4-radical cure	5-Gametocidal	6-sporozoitocides
destroy parasite in liver cell and prevent invasion of erythrocyte	Suppresses the erythrocytic phase & thus attack of malaria fever	Used to terminate an episode of malarial fever		Eradicate all forms of vivax from the body	Destroys gametocytes & prevent transmission	destroy sporozoites
primaquine	**Chloroquine, mefloquine, doxycycline**	**Fast acting high efficacy: Chloroquine, quinine, mefloquine, artemisinin**	**Slow acting low efficacy: Pyrimethamine, proguanil, sulfonamides**	**Suppressive drug + hypnozoitocidal**	**Chloroquine, quinine** against **vivax** **Primaquine**, **all species**	**Proguanil, pyrimethamine**

it is better to **memorize** this slide after finishing the whole lecture

Artemesinin

Characteristics

- Artemisinin is the active principle of the plant *Artemisia annua* **(qinghaosu).**
- Fast acting **blood Schizontocide.**
- Affect all forms including **multi-drug resistant *P. falciparum.***
- **Short duration of action.**
- High recrudescence rate.
- Poorly soluble in water & oil, can only be used **orally**.

pharmaokinetics

- Rapidly biotransformed in liver into dihydro**artesiminin** active metabolite.
- **Artemisinin ,Artesunate, Artemether** are prodrugs
- Derivatives are rapidly absorbed orally
- Widely distributed

t½ Artemisinin (4hrs)
Dihydro**artemisinin**
(water-soluble;oral administration

t½ Artesunate 45min **(emergency)**
Artesunate (water-soluble; oral, **IV** IM,rectal administration)

t½ artemether 4-11hrs
Artemether (lipid-soluble; oral, IM, and rectal administration)

Artemesinin

mechanism (artemesinin)	They have endoperoxide bridges → - cleaved by **haem** iron to yield carbon- centered free radicals, that will:(so heam will cleave endoperoxide bridges of drug→ the effects below) ★ **Alkylate membranes** of parasite's food vacuole and mitochondria- → no energy. ★ **Irreversibly** bind & inhibit sarco-endoplasmic reticulum Ca^{2+}-ATPase of the parasite→ - inhibiting its growth. ★ Inhibiting formation of **transport vesicles** → - no food vacuoles
adrs	1)Transient heart block. (if parenteral). 2) ↓Neutrophil count. 3)Brief episodes of fever. Resistance → - was reported recently in Cambodia- Thailand border.
Clinical uses	**Because artemisinin derivatives have short t½ :** 1. monotherapy should be extended beyond disappearance of parasite to prevent recrudescence 2. by combining the drug with long- acting antimalarial drug
preparations (artemesinin)	**Artemisin-based combination therapies (ACTs):**(this combination will be used in some cases → last slides) **Artemether + lumefantrine .** **Artemether + mefloquine.** **Artemether + amodiaquine .** **Artemether + sulfadoxine-pyrimethamine.**

chloroquine

characteristic	•Potent blood Schizontocidal. •Active against all forms of the schizonts (except chloroquine-resistant P.f. & P.v.) •Effect against all Gametoside species except falciparum •No activity against ***liver*** shizonts (not used for causal prophylaxis → slide 2) •Safe in pregnancy
pharmacokinetics	•Given orally •Rapidly & completely absorbed from the GIT •Has high volume of distribution(100-1000l/kg) •Concentrated into parasitized RBCs •Released slowly from tissues that why it has long duration of action •Metabolized in the liver •Excreted in the urine 70% unchanged •(Initial t½ =2-3 days & terminal t ½=1- 2 months) *
MOA	Prevent polymerization of heme → accumulation of heme inside parasite and RBC leading to lysis both of them ***for better understanding:*** malaria Parasite digest host cell's Hb to obtain amino acids → Heme is released which is toxic to the parasite So parasite detoxifies it by ***heme polymerase*** → Hemozoin (NonToxic) & traps it in food vacuole

*Initial t½ : for distribution of drug from central compartment to the peripheral compartment.

*terminal t ½: for elimination of drug from central and peripheral compartments.

Cont. chloroquine

Side effects	• **For short period:** **•Mild headache and visual disturbances** **•Gastro-intestinal upsets; Nausea, vomiting** **•Pruritus, urticaria.**	**•For prolonged periods (as in case of Rheumatoid arthritis):** **•Ocular toxicity** **•Ototoxicity** **•Weight loss** **•Bolus injection→hypotension & dysrrhythmias**
Mechanism of resistance	**the resistance develop as a result of mutation of protein called plasmodium flaciparum chloroquine resistance transporter *(PfCRT)* , found in food vacuole of the plasmodium leading to efflux of chloroquine from food vacuole of plasmodium**	
Uses	**•eradicate blood schizonts of Plasmodium** **•Hepatic amoebiasis** **•Rheumatoid arthritis**	

we know that it has **high distribution** and **chloroquine** loves the pigmented tissue like retina

QUININE

characteristic	•It is quinidine isomer, both extracted from cinchona bark so it has some side effects of quinidine as depression of myocardium, reduce excitability & conductivity. •Mild analgesic, antipyretic, stimulation of uterine smooth muscle, curaremimetic effect (neuromuscular blocking effect) •Safe in pregnancy
pharmacokinetics	•Administered: orally for 7 day course or by slow IV for severe P. falciparum infection •Rapidly & completely absorbed from the GIT •Peaks Plasma concentration 1-3 hrs •5% excreted in the urine unchanged •t½ = 10 hrs but longer in case of sever falciparum infection(18hrs) •Metabolized in the liver & excreted in urine
MOA & resistance	Same as chloroquine
uses	•Parenteral treatment of severe falciparum malaria •Oral treatment of falciparum malaria

Side effects

★ **therapeutic dose** → poor compliance → bitter taste

★ **Higher doses :**

- Cinchonism syndrome : (tinnitus, deafness, headaches, nausea & visual disturbances)
- Abdominal pain & diarrhea
- Hypotension & arrhythmias
- Rashes, fever, hypersensitivity reactions
- Blood dyscarasis: anaemia, thrombocytopenic purpura & hypoprothrombinaemia
- Blackwater fever (Most series effect) , a fatal condition in which acute haemolytic anaemia is associated with renal failure
- 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 (curaremimetic effect)
- Hypersensitivity
- Optic Neuritis, auditory problems
- Dose should be reduced in renal insufficiency

Drug interactions

- Antacids: Antacids containing aluminum &/or magnesium may delay or decrease absorption of quinine
- Mefloquine because it prolong QT interval
- Quinine can raise plasma levels of warfarin and digoxin

PRIMAQUINE

Characteristics	**-Hypnozotiocides** → against liver hypnozoites and gametocytocidal -Radical cure of **P. Ovale** and **P. Vivax** -Prevents spread of all forms -RESISTANCE: is rare when combined with chloroquine -Avoid in pregnancy and G6PD deficiency
Pharmacokinetics	-Well absorbed orally -t1/2 is 3-6 hours
Mechanism of action	**Either, or:** **-Generates ROS** (damages lipids, proteins, and nucleic acids) -Interferes with the **electron transport** in the parasite -Inhibits formation of **transport vesicles** (no food vacuoles)
Clinical Uses	• **Radical cure** of relapsing malaria • In Falciparum malaria

Cont. Primaquine

ADRS	**At regular doses:** -G6PD deficient patients→hemolytic anemia	**At larger doses:** • Epigastric distress, Abdominal Cramps • Mild Anemia, cyanosis, methemoglobinemia • **Severe Methemoglobinemia** >> patients with deficiency of NADH methomoglobin reductase (rare) • Granulocytopenia, agranulocytosis (rare)

important

WHO treatment guidelines

In P. Vivax	**Sensitive:** • **Chloroquine**(3 days) • followed by **Primaquine** (14 days)	**Resistant:** • **ACT** (3 days) • followed by **Primaquine** (14 days)

cont, WHO treatment guidelines

	Uncomplicated:	Complicated:	Special Risk Groups:
In Falciparum (all show resistance)	-ACT	**Artesunate** (IV for 24 hours) followed by:- ***ACT** or **[Artemether/Quinine]** + **[clindamycin/doxycyline]**	**-Quinine + Clindamycin** (pregnancy 1st trimester) **-ACT** (Pregnancy 2nd, 3rd trimesters, lactating women, infants, and young children)

important

Prophylaxis in travellers

Chloroquine	Areas without resistant P. Falciparum	Begin 1-2 weeks before departure (except doxycycline 2 days prior) continue for 4 weeks after leaving endemic area
Mefloquine	Areas with chloroquine-resistant P. Falciparum	
Doxycycline	Areas with multidrug-resistant P. Falciparum	

MCQs

1. **A 23-year-old recent college graduate has plans to go to Africa to work for a year in the Peace Corps before returning to start medical school. He visits his family physician for a prescription for appropriate malarial prophylaxis. He brings a map from the Centers for Disease Control that shows that the area he will be in has a high incidence of chloroquine resistance. Which antimalarial should he take?**
   a. Primaquine
   b. Doxycycline
   c. Mefloquine
   d. Pyrimethamine
   e. Quinine
2. **Which of the following can be given in acute attack and given IV?**
   a. Artesunate
   b. Artemisinin
   c. Artemether
3. **The mechanism of action of chloroquine?**
   a. generating ROS
   b. it prevent the polymerization of heme molecules
   c. bind and inhibit sarco-endoplasmic reticulum Ca+2 -atpase of the parasite
   d. inhibiting the the formation of transport vesicles
4. **Patient developed tinnitus, deafness,and visual disturbances, and blackwater fever after being treated with one of the antimalarial drugs. What is the name of that drug?**
   a. chloroquine
   b. quinine
   c. doxycycline
   d. primaquine
5. **25 years old pregnant women had a normal medical history except she had G6PD deficiency, diagnosed with malaria and treated with one of the antimalaria drugs. Which drug should not be used in this case?**
   a. Quinine
   b. Primaquine
   c. Cholroquine
   d. ACT
6. **In case of sensitive plasmodium vivax you should treat with :**
   a. Chloroquine for 3days then primaquine for 14 days.
   b. ACT followed with primaquine
   c. ACT ONLY
   d. Artesunate ONLY

MCQs

7. **Which of the following drugs is recommended for the treatment of severe, multidrug-resistant Plasmodium falciparum malaria?**
   a. Artemisinin
   b. Chloroquine
   c. Sodium dtibogluconate
   d. Quinine

8. **Which of the following is contraindicated in case of myasthenia gravis patient with malaria?**
   a. Quinine
   b. Artemisinin
   c. Chloroquine
   d. melarsoprol

Answers : 1.C 2.A 3.B 4. B 5.B 6.A 7. A 8.A

Good luck!

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