PHARMACOLOGY

TEAM 432

ANTIMALARIAL DRUGS

Objectives:

- Classify the main antimalarial drugs depending on their target of action
- Detail the pharmacokinetics & dynamics of main drugs used to treat attack or prevent relapses
- Compare the mechanism and major ADRs of adjunctive drugs used in combinations
- State the WHO therapeutic strategy for treatme

Color Guide:

Slides = Black

Females slides = Green

Males slides= Blue

Explanation=Orange

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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 hypnotocidal (schizontocidal) drugs	• Primaquine
To prevent spread	Gametocidal drugs	• Primaquine

N.B. If patient has got infested by sporozoites ➔ we want to protect against progression to Tissue Shizontocides ➔ Primaquine

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TREAT ATTACK

1) ARTEMISININ

Fast acting blood Schizontocide

Affect all forms including multi-drug resistant *P. falciparum*

Preparations	Pharmacokinetics	Mechanism	ADRs
ARTEMISININ (the actual product with **Poor solubility**) **ARTENUSATE** (Water Soluble) **ARTEMETHER** (Water Soluble)	-Derivatives are rapidly absorbed orally - Rapidly biotransform in liver into artenimol➔ active metabolite -Widely distributed **t½ :** **artemisinin ➔ 4hrs** (intermediate-acting) **artesunate ➔ 45min** (fast acting) **IV or IM preparations for severe complicated cases as cerebral malaria (24h) (it's not given for long, only 1st 24h) followed by complete course of ACT** **artemether 4-11hrs** (long-acting, used in combination with other antimalarial drugs)	They have endoperoxidase bridges that are cleaved by haem iorn to yeild carbon-centred free radicals, that will➔ - Alkylate membranes of parasite's food vacuole and mitochondria➔ no energy - Irreversibly bind & inhibit sarco-endoplasmic reticulum Ca^{2+}-ATPase of the parasite, thereby inhibiting its growth -Inhibiting formation of transport vesicles ➔no food vacuoles	- Transient heart block (with parenteral preperation) -↓neutrophil count (for just a briefpart) -Brief episodes of fever -Neuro, hepato and bone marrow toxicity *considered as safe drug as compare to other antimalarial drugs because very seldom to feel it's ADRs.

Resistance ➔

was reported recently in Cambodia-Thailand border

Artemisin-based combination therapies (ACTs): (WHO classical treatment for malaria is the combination of these group of drugs)

- **Artemether + lumefantrine ➢**
- **Artemether + amodiaquine ➢**
- **Artemether + mefloquine ➢**
- **Artemether + sulfadoxine-pyrimethamine ➢**

***Artemisinin and its derivatives should not be used as monotherapy.**

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TREAT ATTACK

2) CHLOROQUINE

Potent blood Schizontocide → Can be active against all forms of the schizonts (***exception is chloroquine-resistant P.f. & P.v.***)

& a Gametoside → ***Against P.v., P.o., P.f.***

Pharmacokinetics

-Rapidly & completely absorbed from the GIT
-Has high volume of distribution(100-1000l/kg)
-Concentrated into parasitized RBCs.
-Released slowly from tissues
-Metabolized in the liver
-Excreted in the urine 70% unchanged
-Initial t½ =2-3days & terminal t ½=1-2months even after the stop of drug.
-It's one of the cumulative drugs
Chloroquine concentrates → 1000-fold in food vacuole of parasite(in RBC).
Why ???

1) Its protonation & ion trapping due to ↓ pH of vacuole
2) Its active uptake by a parasite transporter(s)
3) Its binding to a specific receptor in the food vacuole.

Therapeutic Use:-

Therapeutic Use:-
Used to eradicate blood schizonts of
Plasmodium vivax
Plasmodium vivax resistance evolved in Indonesia, Peru and Oceania
N.B. It is used also in rheumatoid artheritis, SLE,….

ADRs

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

Prolonged therapy
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???
N.B. Chloroquine concentrates in melanin containing tissues, e.g. the retina (It concentrated in the pigments of skin and eyes).
2. Lichenoid skin eruption, bleaching of hair
3. Weight loss
Bolus injection→ hypotension & dysrrhythmias

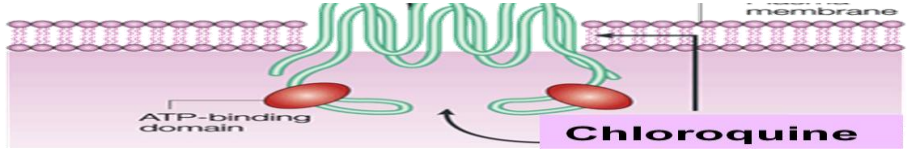
Safe in pregnancy

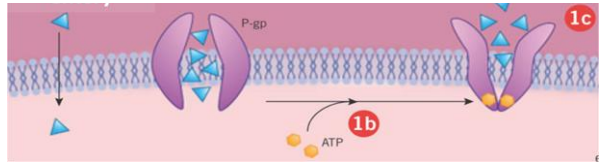
Mechanism

Malaria Parasite digest host cell's Hb to obtain a.a (amino acid).
Heme is released → Toxic
So parasite detoxifies it by *heme polymerase* → Hemozin (NonToxic & safe) & traps it in food vacuole
*heme is a toxic substance, it should not remain inside our tissue, once its released from Hb component it has to be broken down by heme polymerase.

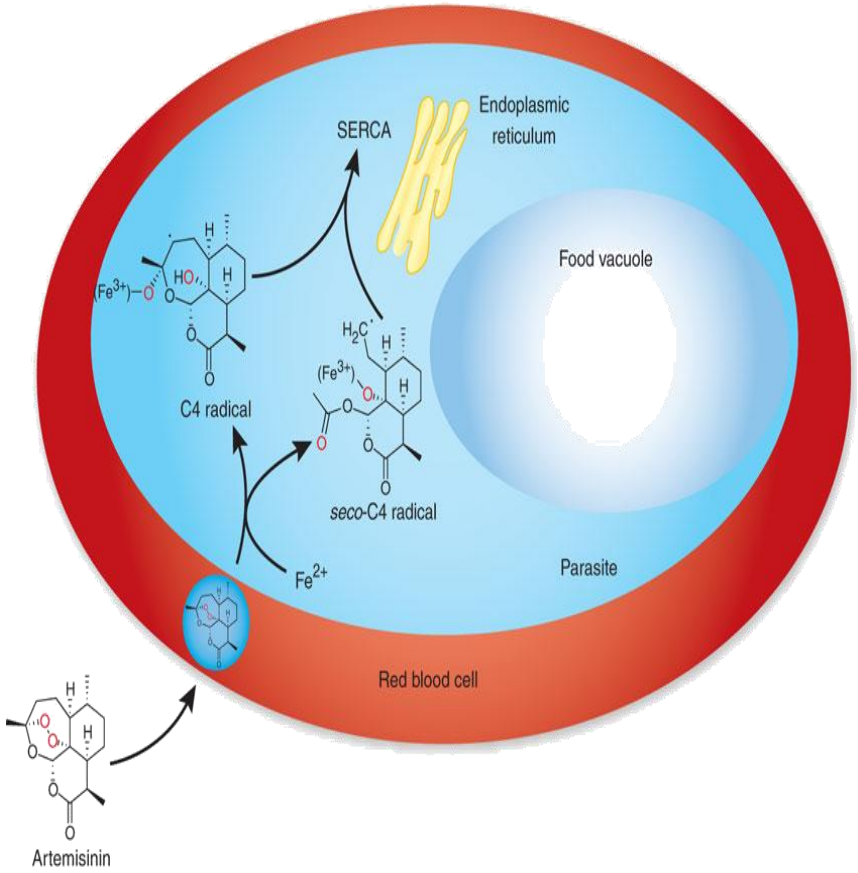
Resistance →

Resistance against the drug develops as a result of enhanced efflux of parasite vesicle →↑expression of the human multi drug resistance transporter P-glycoprotein.

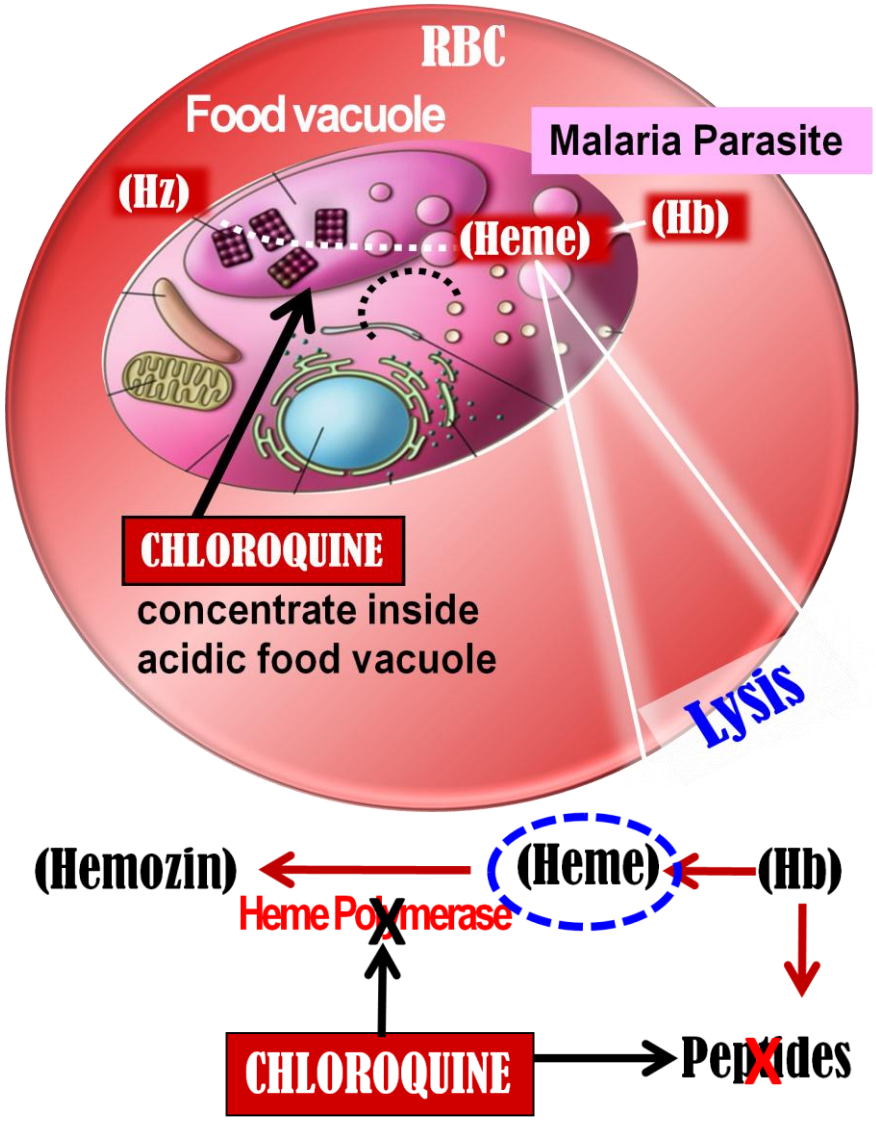




ARTEMISININ mechanism:



CHLOROQUINE mechanism:



TREAT ATTACK

3) QUININE

-Quinoline methanols; quinine, quinidine & mefloquine
Phenanthrene methanols; halofantrine
-Is a the main alkaloid in cinchona bark
-Potent blood Schizontocide & weak Gametoside
Quinine and Quinidine both cause cinchonism

ADRs

1-**With therapeutic dose:** poor compliance →bitter taste.

2- **Higher doses:**

-Cinchonism ototoxicity: (tinnitus, deafness, headaches, nausea & visual disturbances)

-Abdominal pain & diarrhea

-Rashes, fever, hypersensitivity reactions

-Hypotension & arrhythmias

- Blood Dyscrasia *; anaemia, thrombocytopenic purpura & Hypoprothrombinaemia

-Blackwater fever: a fatal condition in which acute haemolytic anaemia precipitating of hemoglobin in renal tubules causing renal failure, so it is associated with renal failure

IV : 1- neurotoxicity ➔ tremor of the lips and limbs, delirium, fits, stimulation followed by depression of respiration & coma.

2- arrhythmias

pharmacokinetics:

-Rapidly & completely absorbed from the GIT
-Peaks after 1-3 hrs
-Metabolized in the liver
-5% excreted in the urine unchanged
-t½ = 10 hrs but longer in sever falciparum infection
N.B. Administered: orally in a 7 day course or by slow IV (if giving fast it may cause heart block by increasing PR interval)for severe P. falciparum infection

Mechanism:

Anti-Mlarial: Same as chloroquine
Other Actions:
-Quinidine – like action
-Mild oxytoxic effect on pregnant uterus
-Slight neuromuscular blocking action(Muscle relaxant)
-Weak antipyretic action

Resistance

like chloroquine by efflux through p-glycoprotein MDR transporter

Contraindication

-Prolonged QT Interval
-Glucose-6-Phosphate Dehydrogenase Deficiency
Because those patients have the tendency to develop hemolytic anemia and the drug itself causes hemolytic anemia as a side effect.
-Myasthenia Gravis (neuromuscular blocking action)
-Hypersensitivity
-Optic Neuritis, auditory problems
-Dose should be reduced in renal insufficiency

Interaction

-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.**
*Warfarin and digoxin causes toxicity when giving with quinine

N.B. Safe in **pregnancy**
But it has an oxytoxic effect on pregnant uterus which is cause contraction of the uterus, so be careful in the last weeks of pregnancy before labor

*a diseased state of the blood usually one in which the blood contains permanent abnormal cellular elements; all blood cells are abnormal

Prevent relapses

4) PRIMAQUINE

- Hypnozoitocides → against liver hypnozoites (Radical cure of P. ovale & P. vivax)& gametocytocides (Prevent spread of all forms)	**Pharmacokinetics:**	**Mechanism:**
	Well absorbed orally Rapidly metabolized to etaquine & tafenoquine more active t½ : 3-6h	**Not well understood.** It may be acting by: -Generating ROS: can damage lipids, proteins & nucleic acids -Interfering with the electron transport in the parasite no energy -Inhibiting formation of transport vesicles: no food vacuoles
Resistance:	**ADRS:**	
Rare when primaquine & chloroquine → combine When giving with Quinine → decreases the resistance of quinine It's a good drug! It's the best dug in preventing relapses	**1-at regular doses:** Patients with G-6-PD deficiency → hemolytic anemia. In G-6-PD deficiency → ↓NADPH, GSH synthesis. So RBCs become sensitive to oxidative agents → HEMOLYSIS. Oxidizes GSH to GSSG → ↓ GSH → ↓ detoxification of toxic products. **Contraindicated in G6PD** **2-at higher doses:** • Epigastric distress & abdominal cramps . • Mild anemia, cyanosis & methemoglobinemia Severe methemoglobinemia → rarely in patients with deficiency of NADH methemoglobin reductase • Granulocytopenia & agranulocytosis. rare	

Combined with artemether

prphylaxis

Drugs used in combination		
drug	**Mechanism**	**ADRS**
Lumefantrine	heme polymerase inhibitors [like chloroquine]	Palpitation, dizziness,allergic reaction, **hepatotoxicity**
Amodiaquine		Nausea, vomiting, itching, stomach upset & headache.
Mefloquine		**neuropsychiatric disorders**
Sulfadoxine-pyrimethamine	Sequential block of dihydropteroate synthase & dihydrofolate reductase. decrease DNA synthesis	Allergic skin reactions, Agranulocytosis; aplastic anemia
Clindamycin	inhibits parasite apicoplast (needed for survival & successful host invasion)	Skin rash, **Pseudo-membranous colitis**
Doxycycline	Inhibit protein synthesis by binding to 30S subunit of ribosome	Yellowish discoloration of teeth, dental carries, bone deformity, vertigo, hypersensitivity

WHO treatment guidelines				
In Vivax		In FALCIPARUM (all show resistance)		
Resistance	**Sensitive**	**uncomplicated**	**Complicated**	**Special risk groups**
ACT athermeter combined therapy (full course) followed by Primaquine for 14 days	Chloroquine for 3 days followed by Primaquine for 14 days	ACT	-IV Artisunate for 24 hrs Followed by; ACT Or -Artemether + [Clindamycin / doxycyline] Or -Quinine + [Clindamycin / doxycyline]	-pregnancy 1st trimester: Quinine + Clindamycin (7 days) -Pregnancy; 2nd & 3rd trimester, lactating women, infants & young children: ACT

Questions

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 structure..

B. increase expression of p-glycoprotein!!

C. increase in the activity 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 one of the following antimalarial drugs can be given to a patient with G6PD deficiency

A. chloroquine

B. Quinine

C. Artenisinin

D. primaquine

Q8: A 36-year-old male of Lebanese ancestry is being treated for Plasmodium vivax malaria. He experiences sever fatigue, back pain, and darkened urine. Which one of the following drugs is most likely to cause his symptoms?

A-Pytimethamine

B-Artemisin

C-Chloroquine

D-Quinine

E-Primaquine

Q9: Titinus, dizziness, blurred vision, and headache are indicative of toxicity to which one of the following anti-malarial?

A-primaquine

B-Quinine

Answers	
1	D
2	B
3	B
4	B
5	C
6	D
7	C
8	E
9	B

PHARMACOLOGY TEAM 432

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