

دفعه يقين 2025

HLS

PHARMACOLOGY

LECTURE

6

BY

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EDITED

فارما

المحاضرة

إعداد

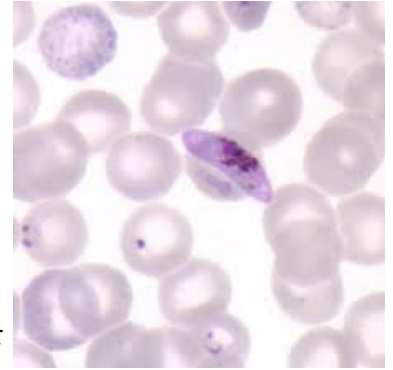
تعديل



#معكم_خطوة_بخطوة

Malaria

- Life-threatening, acute infectious disease (it can be associated with chronic phase)
- **Etiology:**(parasitic disease) **Plasmodium (*P. Falciparum* most dangerous)**
- **Vector: Anopheles**
- Tropical areas
- **Presentation: headache and fatigue, followed by fever, chills, and sweats**
- *P.Falciparum* can lead to capillary obstruction, cerebral malaria,(some time it



can progress to multi organ system failure) and death within days (without treatment)

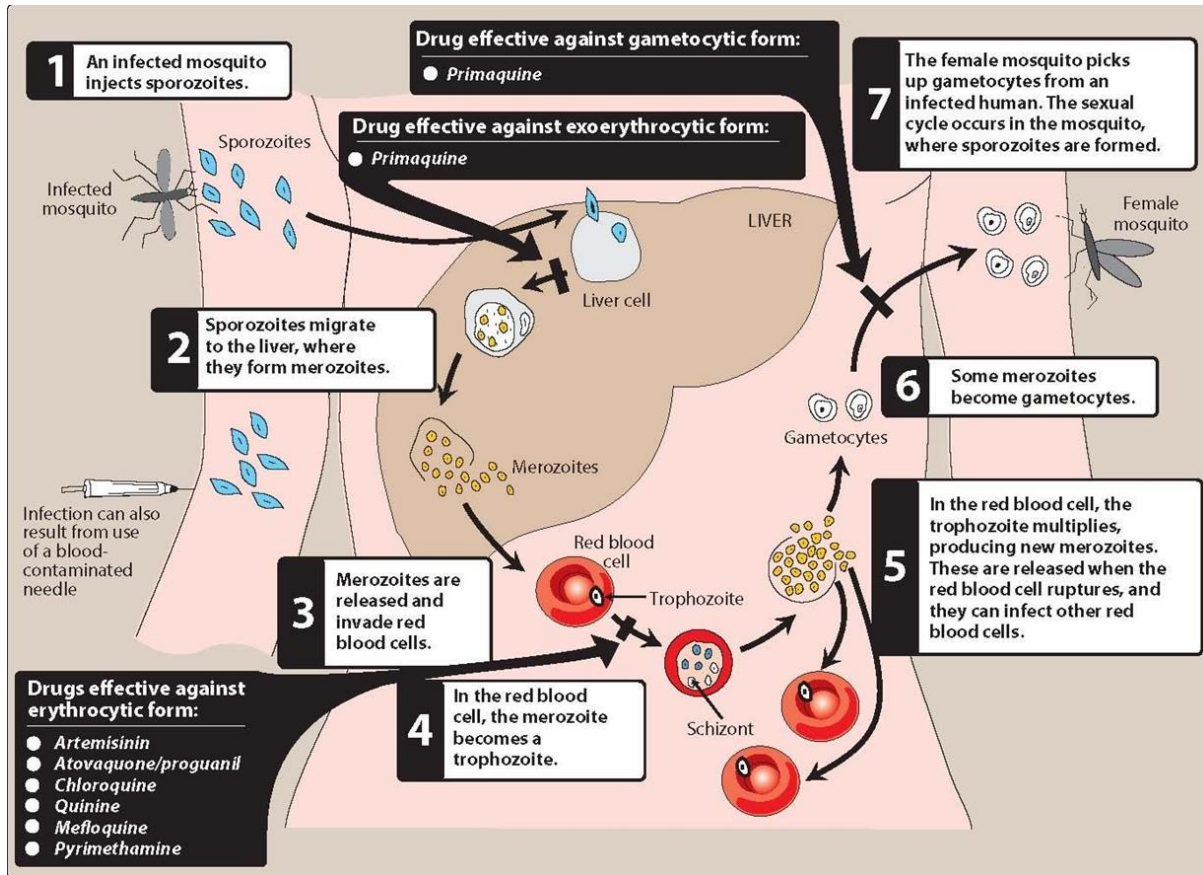
P. Falciparum banana-shaped merozoite

Plasmodium Species

Human Malaria					
Species \ Stages	Ring	Trophozoite	Schizont	Gametocyte	
<i>P. falciparum</i>					<ul style="list-style-type: none"> • Parasitised red cells (pRBCs) not enlarged. • RBCs containing mature trophozoites sequestered in deep vessels. • Total parasite biomass = circulating parasites + sequestered parasites.
<i>P. vivax</i>					<ul style="list-style-type: none"> • Parasites prefer young red cells • pRBCs enlarged. • Trophozoites are amoeboid in shape. • All stages present in peripheral blood.
<i>P. malariae</i>					<ul style="list-style-type: none"> • Parasites prefer old red cells. • pRBCs not enlarged. • Trophozoites tend to have a band shape. • All stages present in peripheral blood
<i>P. ovale</i>					<ul style="list-style-type: none"> • pRBCs slightly enlarged and have an oval shape, with tufted ends. • All stages present in peripheral blood.
<i>P. knowlesi</i>					<ul style="list-style-type: none"> • pRBCs not enlarged. • Trophozoites, pigment spreads inside cytoplasm, like <i>P. malariae</i>, band form may be seen • Multiple invasion & high parasitaemia can be seen like <i>P. falciparum</i> • All stages present in peripheral blood.

dormant in the human body عندهم القدرة انهم يضلهم و malaria usually mild to moderate يعملوا p.vivax and p.ovale for a long period of time to cause recurrent malaria later on

Malaria



اثناء ال merozoites phase ممكن جزء منهم يضلهم dormant inside the liver cells

Antimalaria Agents

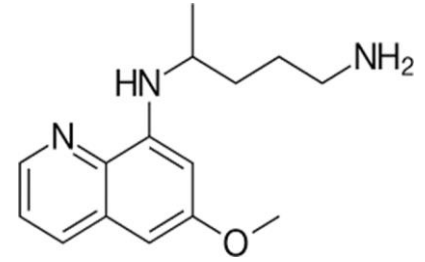
MALARIA	
Artemether/lumefantrine	COARTEM
Atovaquone-proguanil	MALARONE
Chloroquine	ARALEN
Mefloquine	LARIAM
Primaquine	
Pyrimethamine	DARAPRIM
Quinine/Quinidine	QUALAQUIN, QUINIDINE GLUCONATE

كلهم quinolone derivatives

الوحيد هو الخيار الوحيد for the treatment of exoerythrocytic forms

Primaquine

- 8-aminoquinoline
- Oral
- Effective against:
 - primary exoerythrocytic (liver) forms of plasmodia
 - Hypnozoites (dormant form of the parasite in the liver) of recurring malarial (*P. vivax* and *P. ovale*) (ONLY AGENT)
 - Sexual (gametocytic) forms of all plasmodia
- NOT effective against the erythrocytic stage of malaria



Primaquine

Mechanism of action

- Not fully understood
- Metabolites are oxidants → disrupt plasmodial mitochondria

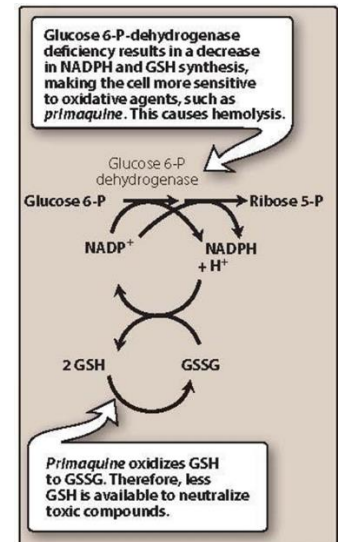
Adverse effects

- Drug-induced hemolytic anemia (in patients with G6PD)

طبيب مهو ال parasite يعمل hemolysis والدوا ممكن يعمل hemolysis طبعا هاي risk بس we

adverse effects ال need to eliminate the parasitic infection

- Methemoglobinemia
- Abdominal discomfort
- Avoided in pregnant women



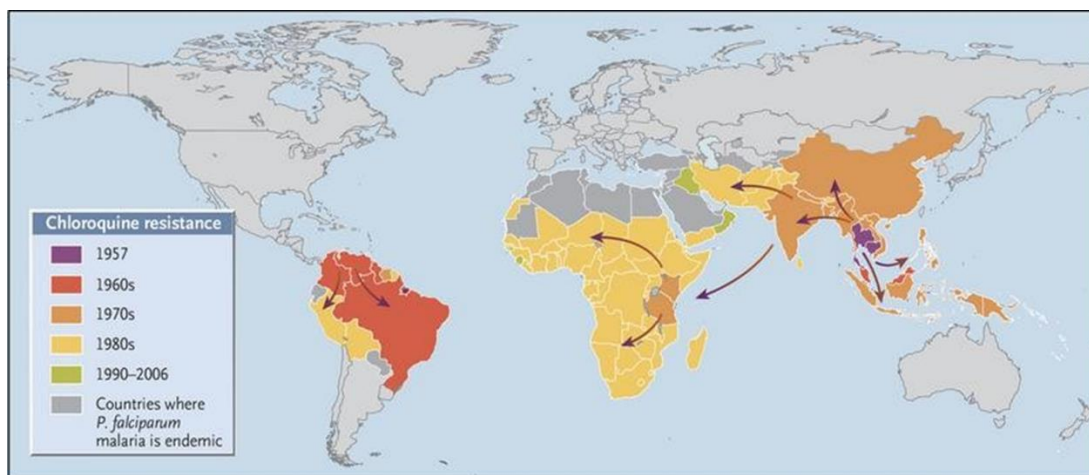
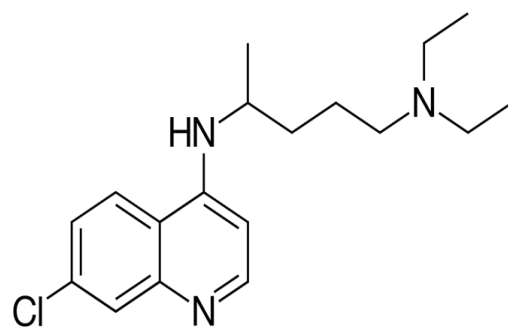
Chloroquine

- Synthetic 4-aminoquinoline
- Used to be mainstay of antimalarial therapy (drug of choice in the treatment of erythrocytic *P.Falciparum* malaria)

❖ High resistance in endemic areas

- Used in the prophylaxis of malaria for travel to areas with known chloroquine-sensitive malaria
- Effective in the treatment of extraintestinal amebiasis

كان ال first line لفترة طويلة جدا وهو اللي قلل من تأثير ال malaria بشكل كبير



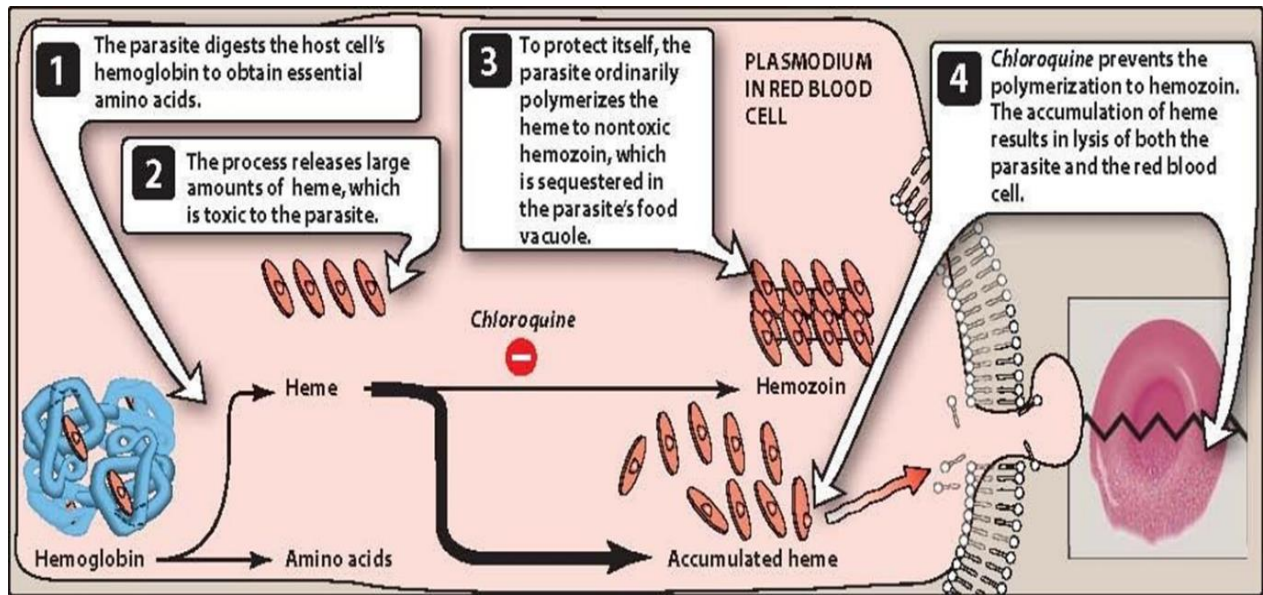
History of Chloroquine-Resistant *P. falciparum* Malaria.

Data are from the Worldwide Antimalarial Resistance Network Packard RM. *The origins of antimalarial-drug resistance. New England Journal of Medicine. 2014 Jul 31;371(5):397-9.*

Chloroquine

Mechanism of action

- CQ (a weak base) concentrates in the acidic food vacuoles of the parasite
- CQ binds to heme, preventing its polymerization to hemozoin

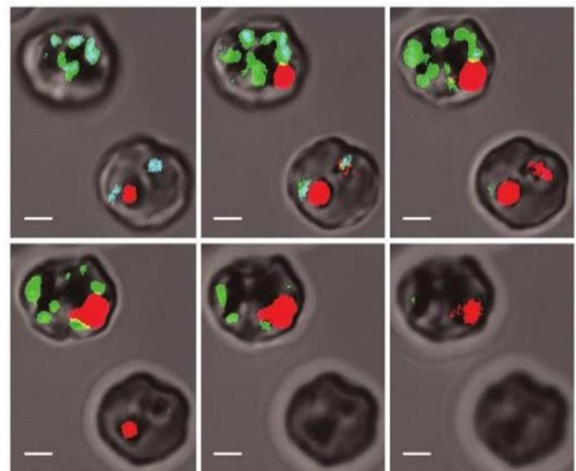


ال parasite يكسر ال hemoglobin molecule و بصير في 4 hemes وبتكون toxic لل parasite ال فيعمل ال parasite ال polymerization لل heme و بحوله ل other non toxic substance وبتخزنه بال parasitic food vacuole
 قال chloroquine بصير له concentration بال parasitic food vacuole و يمنع ال parasite من انها convert heme to hemozoin
 فبصير ال accumulation لل heme اللي هو toxic لل parasite

Chloroquine

Pharmacokinetics

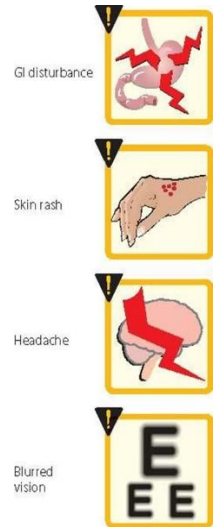
- Oral
- Large volume of distribution
- Concentrates and persists in erythrocytes (also spleen, lung, kidneys)
- Penetrates to placenta and CNS (which could be useful for treat cerebral malaria (advanced stage of malaria))
- Hepatic metabolism
- Renal excretion



Chloroquine

Adverse effects

- Gastrointestinal upset
- Headache
- Blurred vision, retinopathy (for a prolonged period of time) (routine ophthalmologic examination must be done)
- Discoloration of nail beds
- Contraindicated in patients with porphyria or psoriasis
- Can prolong QT interval

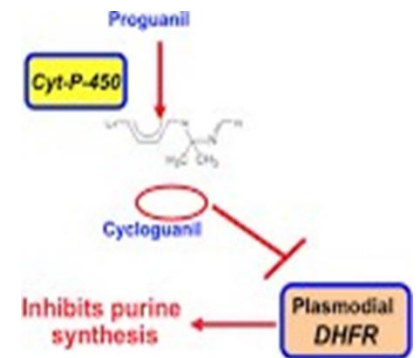


Atovaquone–proguanil

Tow drugs بنعطيهما دائما chloroquine resistant وهي الحل لل

- Effective for chloroquine-resistant strains of *P. falciparum*
- Used in the prevention and treatment of malaria
- **MOA of atovaquone:** Inhibits mitochondrial processes
فهو بمنعوا من انو يطلع its own energy and ATP
such as electron transport, as well as ATP and pyrimidine biosynthesis

- **MOA of proguanil**



Mefloquine

• Uses:

1. effective agent for prophylaxis from all plasmodia
2. treatment when used in combination with an **artemisinin derivative** for infections caused by multidrug-resistant forms of *P. falciparum*

- **MOA:** not understood
- Oral
- Long half-life (20 days)

- **Adverse effects:** nausea, vomiting, and dizziness to disorientation, hallucinations, and depression

avoided عشان هيك او usually use at lower doses او in combination with other drugs او حتى

- Reserved for treatment of malaria when other agents cannot be used (because of risk of neuropsychiatric reactions)

Quinine

A very old substance derived from cinchona tree

- interferes with heme polymerization, resulting in death of the erythrocytic form of the plasmodial parasite
- reserved for severe infestations and for chloroquine-resistant malarial strains
- administered in combination with doxycycline, tetracycline, or clindamycin
- Can cause cinchonism (nausea, vomiting, tinnitus, and vertigo)



cinchona tree

Artemisinin

- First-line agent for the treatment of multidrug-resistant *P. falciparum* malaria
 - **Artemisinin-based combination therapy (ACT):** artemisinin + another antimalarial
- e.g., a tablet with artemether coformulated with lumefantrine



Sweet wormwood

عشان نزيد فعالية ال treatment ونقلل ال rate of resistant

- **MOA:** production of free radicals resulting from cleavage of the drug's endoperoxide bridge by heme iron in the parasite food vacuole.

ال parasitic vacuole غالباً بتكون ال target لمعظم ال antimalaria drugs لانو هي المكان اللي ال parasite

بعطل فيه ال function تبع ال heme

Pyri methamine

- Inhibits plasmodial dihydrofolate reductase required for the synthesis of tetrahydrofolate

Very strong in elimination the erythrocytic form of malaria

- a blood schizonticide and a strong sporonticide
- usually administered with other agents, such as artemisinin derivatives
- Pyrimethamine in combination with sulfadiazine is also used against *Toxoplasma gondii*

Summary of Antimalarial Chemotherapy

All Plasmodium species except chloroquine-resistant <i>P. falciparum</i>
<i>Chloroquine</i>
Chloroquine-resistant <i>P. falciparum</i>
<i>Atovaquone-proguanil, Artemether/lumefantrine</i> Alternate: <i>Mefloquine, Quinine plus; Doxycycline or clindamycin</i>
Prevention of relapses: <i>P. vivax</i> and <i>P. ovale</i> only
<i>Primaquine</i>
Prevention of malaria
Chloroquine-sensitive geographic areas
<i>Chloroquine</i>
Chloroquine-resistant geographic areas
<i>Atovaquone-proguanil, Doxycycline, Mefloquine</i>
In pregnancy
<i>Chloroquine or mefloquine</i>

6th edition

TREATMENT OF MALARIA	
Uncomplicated malaria/ <i>P. falciparum</i> or species not identified	<i>Atovaquone-proguanil*</i> <i>Artemether-lumefantrine†</i> <i>Mefloquine</i> or <i>Quinine plus</i> <i>Doxycycline, tetracycline, or clindamycin</i>
Chloroquine-resistant or unknown resistance	<i>Quinine plus</i> <i>Doxycycline, tetracycline, or clindamycin</i>
Uncomplicated malaria/ <i>P. falciparum</i> or species not identified	<i>Chloroquine</i> Alternative: <i>Hydroxychloroquine</i>
Chloroquine-sensitive region	<i>Chloroquine + primaquine</i> Alternative: <i>hydroxychloroquine + primaquine</i>
Uncomplicated malaria/ <i>P. vivax</i> or <i>P. ovale</i>	<i>Chloroquine + primaquine</i> Alternative: <i>hydroxychloroquine + primaquine</i>
Uncomplicated malaria/ <i>P. malariae</i> or <i>P. knowlesi</i>	<i>Chloroquine</i> Alternative: <i>Hydroxychloroquine</i>
Severe malaria	<i>Artesunate†</i> plus <i>Atovaquone-proguanil, mefloquine, sulfadoxine-pyrimethamine, or doxycycline</i> or <i>Quinine plus</i> <i>Doxycycline, tetracycline, or clindamycin</i>
PREVENTION OF MALARIA	
Chloroquine-sensitive region	<i>Chloroquine</i>
All other regions	<i>Atovaquone-proguanil</i> <i>Doxycycline</i> <i>Mefloquine</i>
During pregnancy	<i>Chloroquine or mefloquine</i>

7th edition