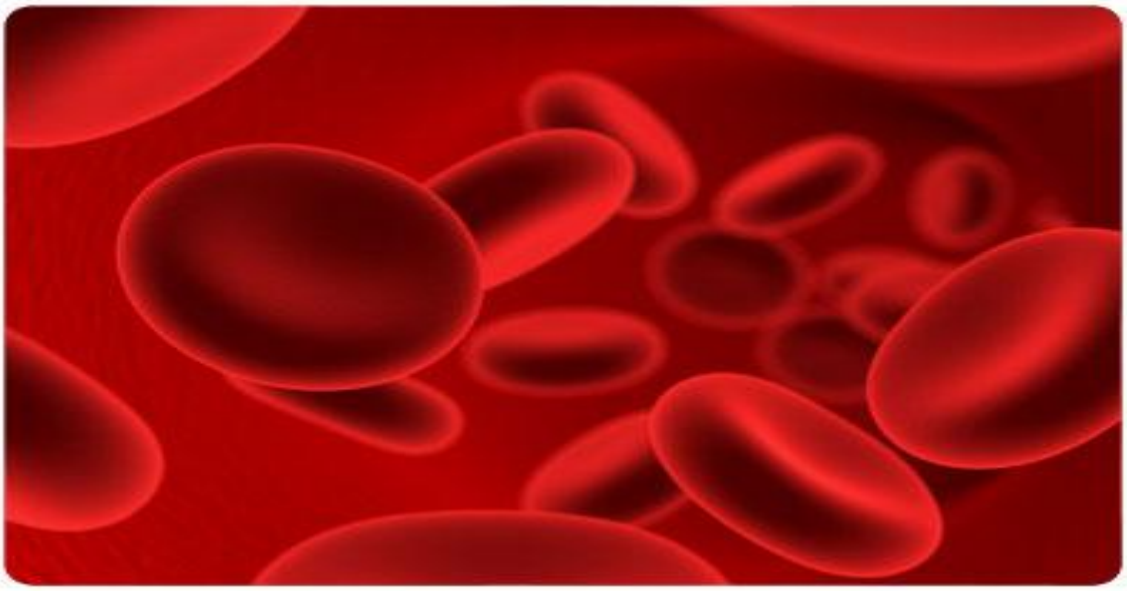
King Saud University
College Of Medicine
Pharmacology Team 430
Hematology Block

Anti-malarial Drugs



Note: the first page is an introduction, and textboxes with **thick maroon** margins are additional info.

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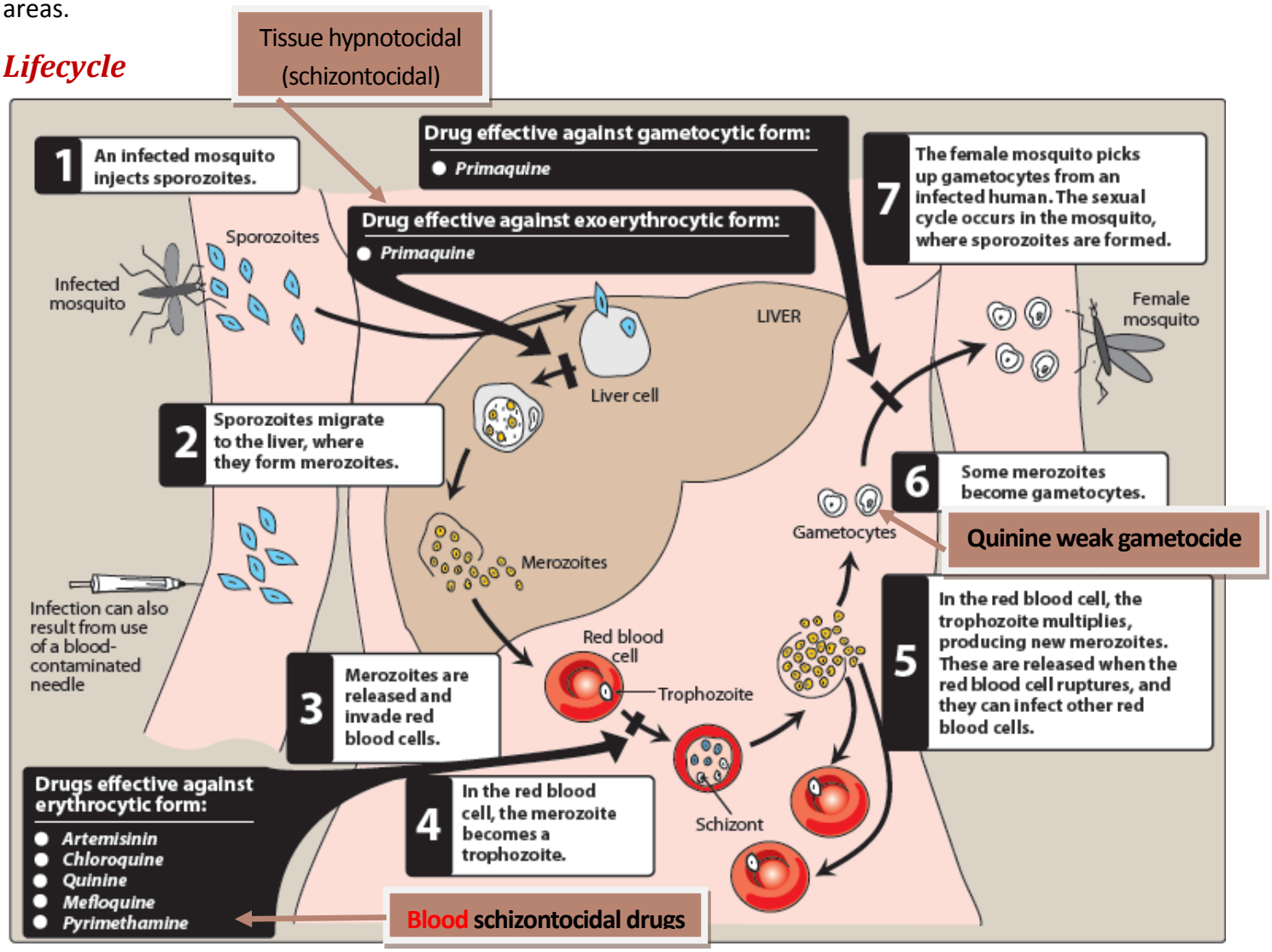
Introduction:

Malaria is an acute infectious disease caused by four species of the protozoal genus Plasmodium. The parasite is transmitted to humans through the bite of a female Anopheles mosquito, which thrives in humid, swampy areas.

Lifecycle



When an infected mosquito bites, it injects Plasmodium **sporozoites** into the bloodstream. The **sporozoites** migrate through the blood to the liver, where they form **cyst-like structures** containing thousands of **merozoites.** Upon release, each **merozoite** invades **a red blood cell**, becoming a **trophozoite** and using **hemoglobin as a nutrient**. The **trophozoites** multiply and become merozoites. Eventually, the infected cell ruptures, releasing heme and merozoites that can enter other erythrocytes. The effectiveness of drug treatment is related to the particular species of infecting plasmodium and the stage of its life cycle that is targeted.

- **Sporozoite:**the infective stage of the malaria parasite that is passed to the human host from the salivary glands of the mosquito. Sporozoites infect liver cells, disappearing from bloodstream within 30 minutes. The mechanism for this amazingly rapid disappearance from the bloodstream to the liver is still unknown.

- **Trophozoite :**The active feeding stage of a protozoal parasite

- **Schizont:** a multinucleate sporozoan (as a malaria parasite) that reproduces by schizogony
- **schizogony :**the asexual reproduction of a sporozoite by multiple fission within the body of the host, giving rise to merozoites.

- **merozoite :**A protozoan cell that arises from the schizogony of a parent sporozoan and may enter either the asexual or sexual phase of the life cycle.
- **Shizontocide :**an agent selectively destructive of the schizont of a sporozoan parasite
- **Gametocyte** - the sexual reproductive stage of the malaria parasite.

What is the Target of treating an infected patient?

Target of Therapy	Therapeutic Class	Drug Examples
To alleviate symptoms	Blood schizontocidal drugs (kill the blood Shizontocides)	Artemisinin Chloroquine (in **P. vivax** only) Quinine (in pregnancy)
To prevent relapses	Tissue hypnotocidal (schizontocidal) drugs	Primaquine
To prevent spread	Gametocidal drugs (once the parasite become gametocyte it will be infective)	Primaquine

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

Drugs That TREAT the ATTACK :

1-Lactone endoperoxides: e.g artemisinin ,artemether ,artesunate

- **artemisinin** ➔Poor solubility
- **artemether ,artesunate** ➔ Soluble
- **Fast acting (The most rapid acting drugs)** blood Schizontocide (so, it prevents the attack)
- Affect **all forms** including multi-drug **resistant *P. falciparum***

Pharmacokinetics:

- Derivatives are rapidly absorbed orally
- Rapidly biotransform in liver into **artenimol**➔ active metabolite
- Widely distributed
- t½ **artemisinin** ➔ **4hrs** / **artesunate** ➔ **45min (shortest)** / **artemether 4-11hrs**

Artesunate	Artemether
soluble	soluble
Repeated IV dosages	orally
Rapidly acting (short half-life)	Longer half-life
Used in emergency (eg: cerebral malaria)	Used in combination with episode of malaria

Mechanism:

They have **endoperoxidase** bridges that are cleaved **by haeme 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

Note: Its antimalarial action involves the production of **free radicals** within the **plasmodium food vacuole**, following cleavage of the drug's **endoperoxide** bridge by **heme iron** in **parasitized erythrocytes.** It is also believed to covalently bind to and damage specific malarial proteins.

ADRs

- Transient (bradycardia) , heart block
- Transient ↓neutrophil count
- Brief episodes of fever
- Neuro, hepato and bone marrow toxicity (rare)

Note:The first three are the most common and usually transient (eg: decrease the no. of neutrophils for days then return to the normal after short period.)

Resistance **:** was reported recently in Cambodia-Thailand border

Preparations:

- Artesunate IV or IM preparations for severe complicated cases as in cerebral malaria (emergency) (24h) followed by complete course of ACT

Artemisin-based combination therapies (ACTs):

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

Artemisinin and its derivatives should not be used as monotherapy.(to prevent Recrudescence) =Reappearance of a disease after it has been **quiescent (state of inactivity)** .Using it in combination would more effective and would delay the development of resistance .

2-Aminoquinolines derivative

1- : (4-Aminoquinolines)

Potent blood Schizontocide(Can be active **against all forms** of the schizonts (**exception is chloroquine-resistant P.falciparum. & P.vivax.)** & **a has Gametocidal action** (Against ➔P.vivax., P.ovale., P.falcipaum).

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

It has long half-life because it has high concentration in tissue (cumulative effect)

- Initial t½ =2-3days & terminal t ½=1-2months

Chloroquine concentrates ➔ 1000-fold in food vacuole of parasite. Why ???

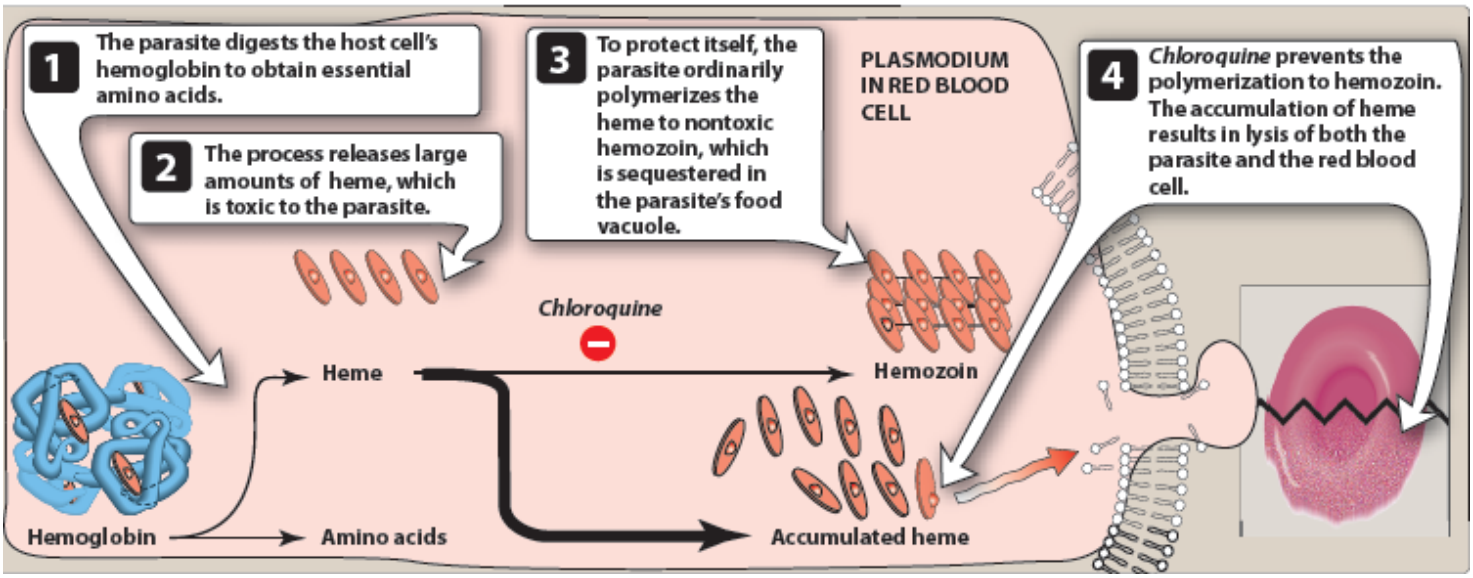
- Its protonation & ion trapping due to ↓ pH of vacuole (the drug like the acidic media)
- Its active uptake by a parasite transporter(s)
- Its binding to a specific receptor in the food vacuole.

Mechanism:

- Malaria Parasite digest host cell's Hb to obtain a.a (for feeding and growth).
- Heme is released ➔ Toxic
- So parasite detoxifies it by heme polymerase ➔ Hemozin

N.B. It is used also in rheumatoid artheritis, SLE, and extraintestinal amebiasis.

So the chloroquine inhibit the mechanism of parasite feeding by inhibiting heme polymerase



Additional Note: After traversing the erythrocytic and plasmodial membranes, *chloroquine* (a diprotic weak base) is concentrated in the organism's acidic food vacuole, primarily by ion trapping. It is in the food vacuole that the parasite digests the host cell's hemoglobin to obtain essential amino acids. However, this process also releases large amounts of soluble heme (ferriprotoporphyrin IX), which is toxic to the parasite. To protect itself, the parasite ordinarily polymerizes the heme to hemozoin (a pigment), which is sequestered in the parasite's food vacuole. *Chloroquine* specifi cally binds to heme, preventing its polymerization to hemozoin. The increased pH and the accumulation of heme result in oxidative damage to the membranes, leading to lysis of both the parasite and the red blood cell.

ADR:-

Short-term

- Mild headache and visual disturbances
- Gastro-intestinal upsets; Nausea, vomiting
- Pruritus, urticaria.

Prolonged therapy

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??? (the commonest ADRS) Note: An ophthalmologic examination should be routinely performed.]

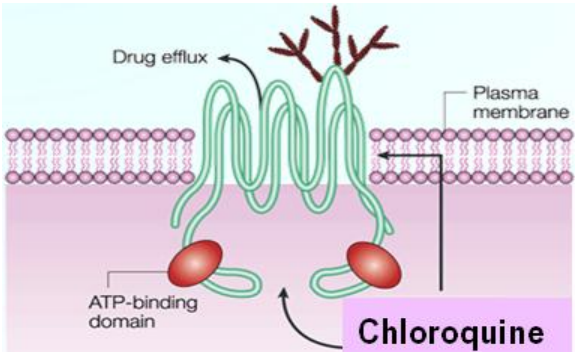
- Lichenoid skin eruption, bleaching of hair
- Weight loss
- ✱ Bolus injection→ hypotension & dysrhythmias

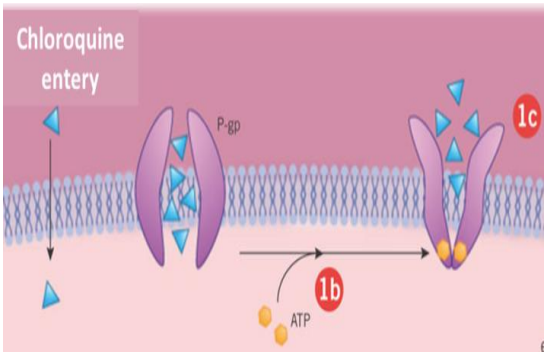
N.B. Chloroquine concentrates in melanin containing tissues, e.g. the retina

N.B. Safe in pregnancy : (**Late pregnancy**)

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

Note:The resistant strains effectively neutralize the drug via a mechanism that **drains chloroquine away from the digestive vacuole .**





Therapeutic Use:-

Used to eradicate blood schizonts of **Plasmodium vivax .**

Plasmodium vivax resistance evolved in Indonesia, Peru and Oceania (so it's less or not effective against this type of malaria)

2-QUININE

Aminoquinolines derivative : Arylaminoalccohols

- Quinoline methanols: quinine, quinidine & mefloquine
- Phenanthrene methanols: halofantrine.

QUININE :

- Is a the main alkaloid in cinchona bark
- Potent blood **Schizontocide** & **weak Gametocide**

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** for **severe P. falciparum infection**

Mechanism : As Anti-malarial ➔ Same as chloroquine (because they are from the same family)

Other Actions :

- Quinidine – like action (antiarrhythmic drug)
- Mild oxytoxic effect on pregnant uterus
- Slight neuromuscular blocking action
- Weak antipyretic action

oxytoxic effect: it resembles the oxytocin hormone in the body(stimulate uterus contraction to deliver the fetus). IN LATE PREGNANCY

Resistence: like chloroquine by efflux through **p-glycoprotein MDR** transporter

ADRS:

With therapeutic dose : poor compliance ➔ **bitter taste**. (No ADRS)

Higher doses :

- **Cinchonism** ➔ *(tinnitus, deafness, headaches, nausea & visual disturbances)* (most common)
- Abdominal pain & diarrhea
- Rashes, fever, hypersensitivity reactions
- Hypotension & arrhythmias
- **Blood dyscarasis** :anaemia, thrombocytopenic purpura &hypoprothrombinaemia
- Blackwater fever: a fatal condition in which acute haemolytic anaemia is associated with renal failure (dark urine)
- IV ➔ neurotoxicity ➔ tremor of the lips and limbs, delirium, fits, stimulation followed by depression of respiration & coma

N.B. Safe in pregnancy : **(early pregnancy)**

Contraindications :

- Prolonged QT Interval (because it can cause arrhythmia)
- Glucose-6-Phosphate Dehydrogenase Deficiency (because it cause hemolytic anemia)
- Myasthenia Gravis (because it has neuromuscular blocking effect)
- Hypersensitivity (because it initiate hypersensitivity reaction)
- Optic Neuritis, auditory problems (because it cause cinchonisim)
- Dose should be reduced in renal insufficiency

Interactions :

- **Antacids :** Antacids containing aluminum &/or magnesium may **delay or decrease absorption** of quinine. (increase its level → toxicity)
- (CYP3A4 inhibitor): Cimetidine – Mefloquine - Erythromycin
- **Quinine can raise plasma levels of warfarin and digoxin.**

Drugs that PREVENT RELAPSES

Note: *Primaquine* is the only agent that can lead to radical cures of the **P. vivax and P. ovale** malarias, which may remain in the liver in the **exoerythrocytic (tissue)** form after the **erythrocytic (blood) form** of the disease is eliminated.

PRIMAQUINE : 8-AMINOQUINOLINES:

Hypnozoitocides ➔ against liver hypnozoites (***Radical cure of P. ovale & P. vivax***) & gametocytocides (*Prevent spread of all forms*)

Pharmacokinetics:

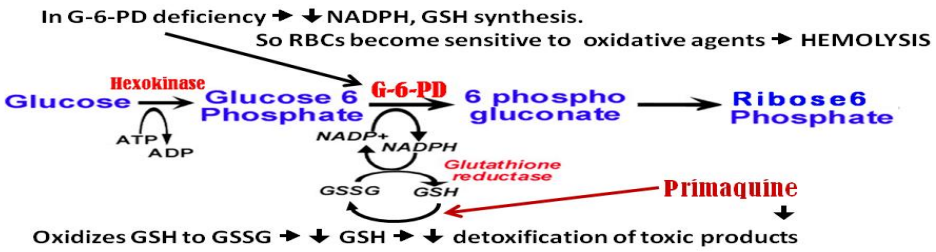
- Well absorbed orally
- Rapidly metabolized to etaquine & tafenoquine ➔ more active
- t½ ➔ 3-6h

Mechanism : 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: Rare when primaquine & chloroquine ➔ combine

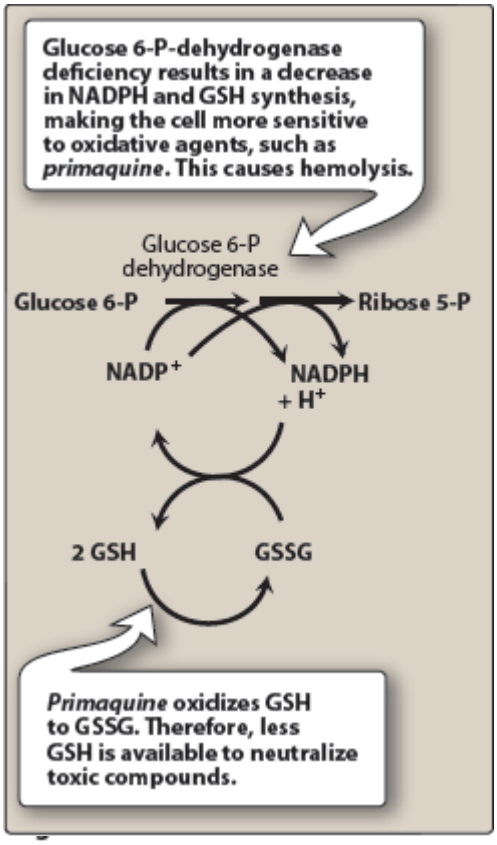
ADRS;



At regular doses : patients with G-6-PD deficiency ➔ hemolytic anemia.

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

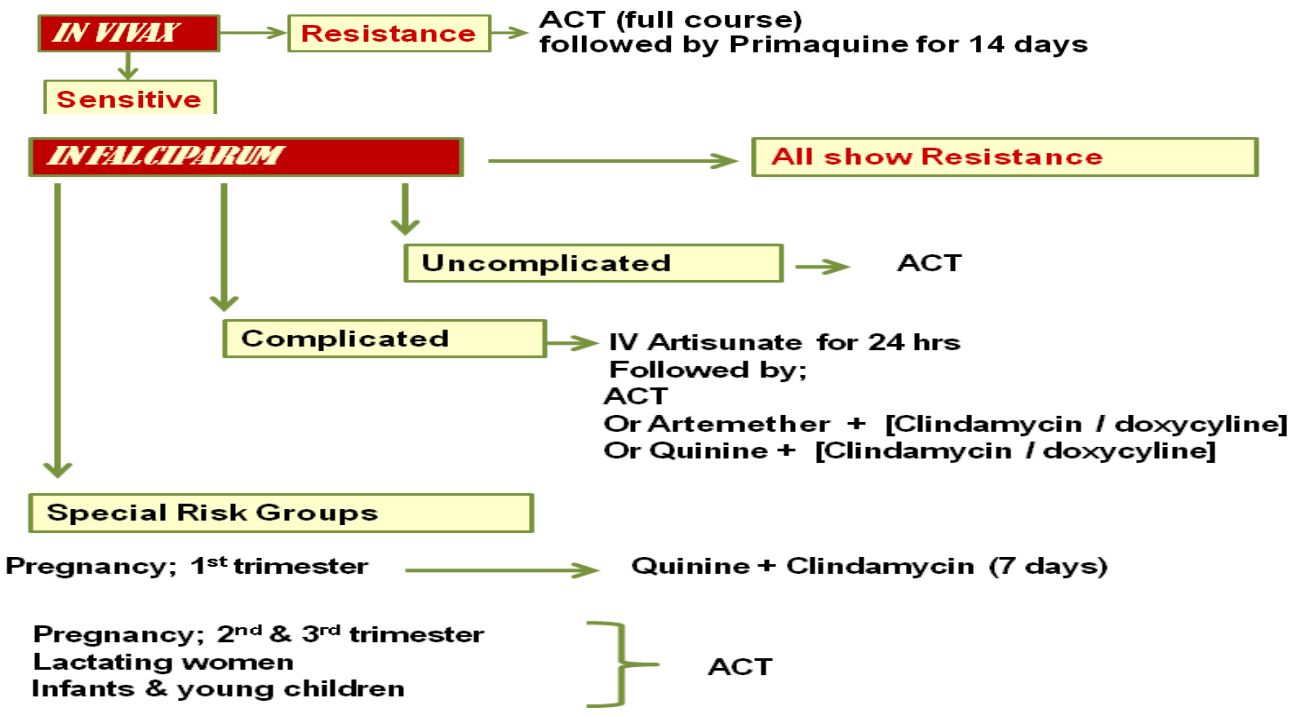


Mechanism of *primaquine*-induced hemolytic anemia. GSH = reduced glutathione; GSSG = oxidized glutathione; $NADP^+$ = nicotinamide adenine dinucleotide phosphate; NADPH = reduced nicotinamide adenine dinucleotide phosphate.

DRUGS USED IN COMBINATIONS with Artemether:

DRUG	MECHANISM	ADRs
Lumefantrine	↓heme polymerase [like chloroquine]	Palpitation, dizziness,allergic reaction, hepatotoxicity
Amodiaquine	↓heme polymerase [like chloroquine]	Nausea, vomiting, itching, stomach upset & headache.
Mefloquine	↓heme polymerase [like chloroquine]	neuropsychiatric disorders
Sulfadoxine-pyrimethamine	Sequential block of dihydropteroate synthase & dihydrofolate reductase ↓ DNA synthesis(then the parasite die)	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:



Summary

- **Artemisinin ,Chloroquine ,Quinine** are drugs of choice to abort the attack (Blood schizontocidal drugs)
- **Primaquine** is Tissue (schizontocidal) and Gametocidal drug used as preventive therapy
- **Artesunate IV or IM** is used in cerebral malaria
- **Artemisin** never used alone ->Artemisin-based combination therapies (ACTs) is the base standered in treatment of malaria
- Artesunate and Artemisin Have endoperoxidase bridges that yield free radicals which destroy the parasites
- The common Artemisin ADRs are Transient heart block,↓neutrophil count and fever

- **Chloroquine** concentrates ➔ 1000-fold in food vacuole of parasite

- The common ADRs of chloroquine are Retinopathy , Lichenoid skin eruption

- **QUININE** have no ADRs in the therapeutic dose except it's bitter taste however in larger doses it causes Cinchonism ,Blood dyscarasis and Blackwater fever
- **QUININE** is Safe in pregnancy and it has many intraction with Antacids and CYP3A4 inhibitors

- **Primaquine** ADRs At regular doses ➔ hemolytic anemia however At larger doses it cause Epigastric distress ,Mild anemia, cyanosis & methemoglobinemia

- **Sulfadoxine-pyrimethamine** is one of the drug which used in compination with **Artemisin** and it dose Sequential block of dihydropteroate synthase & dihydrofolate reductase so↓ DNA synthesis

- **In vivax** if it sensitive we use **Chloroquine** for 3 days followed by **Primaquine** for 14 days however If it was resistance **ACT (full course)** followed by Primaquine for 14 days
- **In falciparum** if it is uncomplicated ➔**ACT** and if it's complicated we can use IV Artisunate for 24 hrs followed **by ACT**