ANTIMALARIAL DRUGS

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Imp. Notes << underlined

Team`s notes << Red

How to study :

1 – U have to know for each drug :

a- **Stage (Hypnozoitocides , Schizontocides , Gametocytocides)**
b- **Strain or species (*P. vivax , P.ovale , P.falciparum ,P.malariae*)**
c- **Type of treatment (prophylactic , acute attack , relapse , spread)**

2- to understand no.1 and memorize it easily , go through next page and read it well .

What are the Aims of Treatment of an infested patient?

Aims	Causation	Therapy	Drugs
To alleviate symptoms	Symptoms are caused by blood forms of the parasite	Blood schizontocidal drugs	chloroquine, quinine, mefloquine, artemisinin, atovaquone, proguanil, pyrimethamine sulphadoxine,
To prevent relapses	Relapses are due to hypnozoites of P. vivax/ P. ovale	Tissue hypnotocidal drugs	Primaquine
To prevent spread	Spread is through the gametocytes	Gametocidal drugs	Primaquine for P. falciparum, Chloroquine for other

What are the Aims of Treatment of an exposed person?

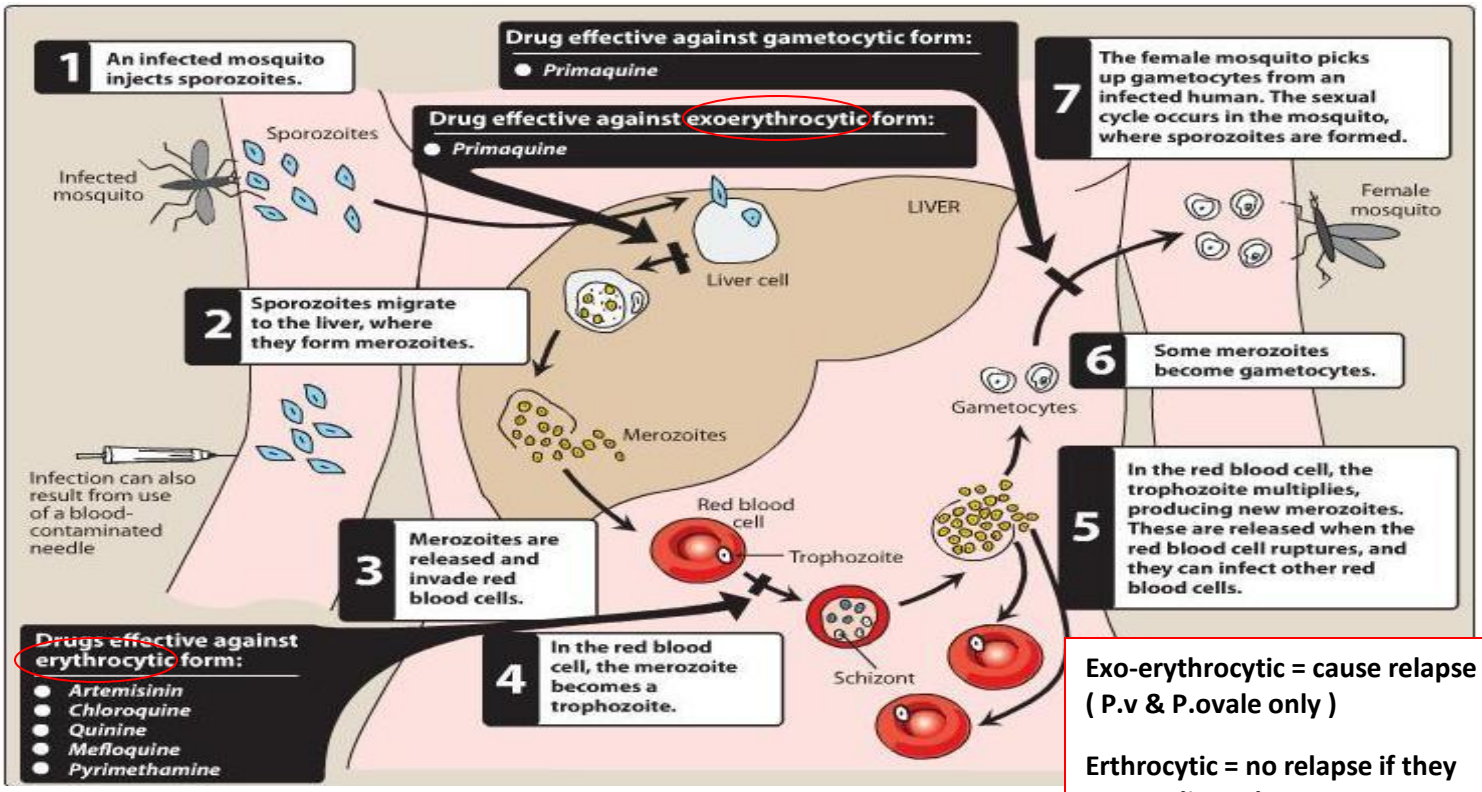
If patient receives sporozoites from an infested mosquito bit ➔ development into tissue schizontozoite ➔ Tissue shizontocidal drugs ➔ Prophylaxsis

- drugs destroy the sexual forms of the parasite in the blood and thereby prevent transmission of the infection to the mosquito = gametocytocidal drugs (e.g chloroquine + primaquine)

- drugs act on the hypnozoites of P. vivax and P. ovale in the liver that prevent relapse = tissue hypnotocidal drugs (e.g primaquine)

- drugs act on the blood forms of the parasite and thereby terminate clinical attacks of malaria= Blood schizonticidal drugs (e.g chlroquine , quinine , mefloquine , artemisinin)

- drugs prevent acute attack (Bld schizonticidal) & against the sporozoite to prevent the parasite becoming established in the liver (tissue schizonticidal) << prophylactic drugs (e.g chloroquine & mefloquine)



Exo-erythrocytic = cause relapse (P.v & P.ovale only)

Erthrocytic = no relapse if they are eradicated .

1-CHLOROQUINE (example of 4-Aminoquinolines) <<(TREAT ATTACK)

imp. Potent blood Schizontocide & a Gametoside

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

Against ➔ P.v., P.o.

Pharmacokinetics :

- Rapidly & completely absorbed from the GIT
- Has high volume of distribution
- 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

imp. Kinetics:

- it is a long standing cumulative drug
- real action : it stays in tissue up to 2 months

But disappears from circulation in 2-3 days.

(long half life because of high concentration in tissues.)

- it is storage mainly in the RBCs (inside the food vacuole of plasmodium)

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

- Its protonation & ion trapping due to ↓ pH of vacuole (acidity of food vacuole trap it)
- Its active uptake by a parasite transporter(s)
- Its binding to a specific receptor in the food vacuole (high affinity to receptor in food vacuole).

Mechanism of CHLOROQUINE :

• malaria parasite breaks down the Hb Into:

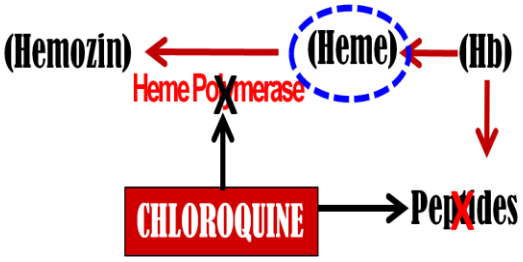
{ Globin
Heme (toxic for malaria & RBCs)

1- to obtain the protein (globin) and nourish on AA.

2-Then, it will release hemepolymerase to convert heme into hemozin (not toxic)

• CHLOROQUINE blocks these 2 steps >> the parasite will not have nourishment + it will be killed by the toxicity of the heme .

(Chloroquine is hemepolymerase inhibitor)



Uses:

- In Malaria; ➔ Acute attack

  ➔ In prophylaxis (prevent it's growing inside any patient who receive the infection)

- In rheumatoid artheritis, SLE,….etc
- ***safe in pregnancy***
- used in amebic liver disease.
- **Resistance** against the drug develops as a result of enhanced efflux of parasite vesicle →↑expression of the human multi drug resistance transporter **P-glycoprotein** . MCQ

(high resistant against CHLOROQUINE)

ADRs :

Short-term:

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

Prolonged therapy (more selective):

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 and skin .*

2. Lichenoid skin eruption, bleaching of hair (no color of patient hair)
3. Weight loss
4. Ototoxicity (cochleovestibular paresis in fetal life)
5. Bolus injection→ hypotension & dysarrhythmias

2-QUININE (example of Aminoquinolines DERIVATIVE) << (TREAT ATTACK)

MCQ

Potent blood Schizontocide (***Against all species → Ideal for P. falciparum***) & **weak Gametoside** ***Against →P.v. & P.m)***

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 days course or by slow IV(To avoid arrhythmia) for severe *P.falciparum* infection

Mechanism

Same as chloroquine → ↓heme polymerase → suppress heme deactivation → accumulate → ↑ parasite & RBC lysis

Other Pharmacological Actions :

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

Uses

In Malaria:

* Drug of choice → acute attack of falciparum malaria

* In prophylaxis for individuals returning from an area where malaria is endemic

Resistance → develops like chloroquine by efflux through p-glyco-protein MDR transporter

(but less than chloroquine)

Not used in pregnancy .

Contraindications

- Prolonged QT Interval
- Glucose-6-Phosphate Dehydrogenase Deficiency
- Myasthenia Gravis
- Hypersensitivity
- Optic Neuritis, auditory problems
- Dose should be reduced in renal insufficiency

Interactions

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

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 dyscarasis** ; anaemia, thrombocytopenic purpura & hypoprothrombinaemia
- **Black water fever**, 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

Drug	Use and pharmacodynamics	Pharmacokinetics	Side effects	Precautions/ comments
Mefloquine	Used for prophylaxis and acute treatment of drug-resistant malaria (especially *P. falciparum*) Schizonticidal in the blood but not on tissue form Mechanism → ↓heme polymerase The same mech. as two previous drugs	Acute treatment: oral dosing Hepatic metabolism with enterohepatic circulation $t_{1/2}$ is 14–22 days Very long acting (similar to chloroquine)	Gastro-intestinal disturbances are common (up to 50% of cases) CNS – hallucinations, psychosis, fits	Not used in pregnancy or in patients with neuropsychiatric disorders Do not use in patients with renal or hepatic dysfunction Potentiates bradycardia of beta-blockers and quinine potentiates its toxicity contraindicated in cardiac anomalies **MCQ**

4-ARTEMISININ (ex. Of LACTONE ENDOPEROXIDES) << (TREAT ATTACK)

Fast acting blood Schizontocide (Affect all forms of multi-drug resistant *P. falciparum*)

Pharmacokinetics

- Derivative are rapidly absorbed orally
- Rapidly biotransform in liver into artenimol→ active metabolite
- Widely distributed
- t½ artemisinin → 4hrs / artesunate → 45min / artemether 4-11hrs (short t½ indicates no accumulation of the drug)

ADRs

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

Mechanism

They have endoproxidase bridges that are cleaved by heme iron into 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

Uses

- In acute attack including chloroquine resistant & cerebral malaria.
  (It terminates acute attacks but recrudesces happen due to short t½.. MCQ..)
- Resistance → not recorded

5-PRIMA

Hypnozoitocides ➔ **against liver hypnozoites ((*prevent relapse)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

Uses

***In Malaria: It is the* essential co-drug with chloroquine in treating all cases of malaria**

- **The only known drug to cure both acute & relapsing malaria**
- ***May be used prophylactically***

Resistance; ➔ Rare when primaquine & chloroquine are combined

Uses :

- ✓ Drug of choice to be combined with chloroquine.
- ✓ Drug of choice in **relapsing malaria.**

ADRs

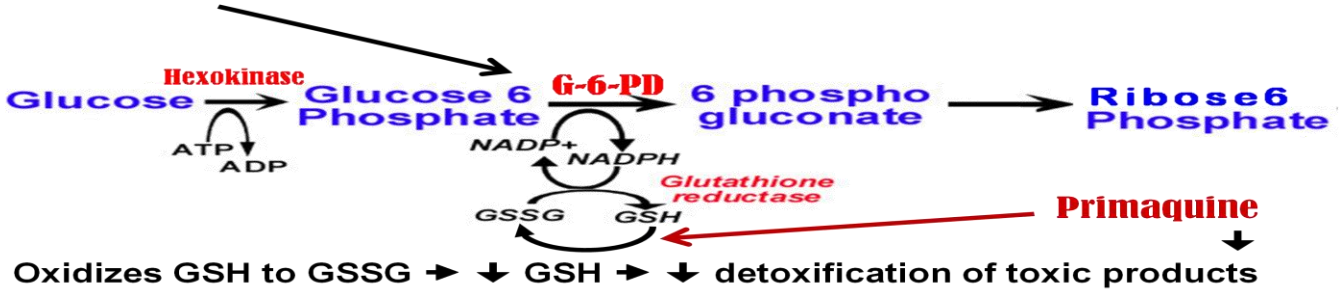
At regular doses ➔ patients with G-6-PD deficiency ➔ hemolytic anemia.

The drug most associated with hemolytic anemia in G6PD deficiency is: Primaquine .. MCQ

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**

!! In G-6-PD deficiency ➔ ↓NADPH, GSH synthesis. So RBCs become sensitive to oxidative agents ➔ HEMOLYSIs



PROPHYLAXIS (to prevent clinical attack)

- **ALL TRAVELLERS to an endemic area should be aware**
- **Use appropriate measures to avoid mosquito bites (e.g repellents, appropriate cover at night, mosquito nets).**
- **The choice of chemoprophylaxis regimen is dependent on the dominant local parasite species and its drug resistance profile.**

Commonly used drugs are CHLOROQUINE, MEFLOQUINE

Areas endemic for chloroquine sensitive strains

Areas endemic for chloroquine resistant strains

- **Chemoprophylaxis must start before (2w), and continue after (4w), travel to & from an endemic area.**
- **Full compliance with the chemoprophylaxis regimen is necessary.**
- **Drug choice & doses may need to be altered in patients with renal or hepatic dysfunction.**
- **Prophylaxis is not 100% effective.**

RESISTANCE

Resistance of *P. falciparum* to chloroquine, sulfodoxin-pyrimethamin & amodiaquine is the major problem of ↑ malaria morbidity & mortality

Treating resistant strains → by ARTEMISININ Compounds → alone (7dys) or in combination with other drugs (3dys) is the current choice →↓gametocyte carriage

- Chloroquine and quinine have gametocytocidal activity against P.v , P.m (quinine weaker than chloro .) , but not against P. falciparum.

-Primaquine has gametocytocidal activity against all plasmodia, including P. falciparum.

- preventing relapse: **PRIMAQUINE**

- Rapidly acting blood schizontocides : Artemisinin, Chloroquine, Quinine , Atovaquone.

- Primaquine , Proguanil and Pyrimethamine are tissue schizontocides.