HEMATOLOGY
&LYMPH SYSTEM

Pharmacology sheet

Number	6
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Malaria and anti-malarial drugs

Malaria is a **mosquito-borne disease** which is responsible for about 3 million deaths a year world-wide. Many of them are children under the age of 5. Currently, there are over 300 million new infections annually.

The disease is caused by several species of the **Plasmodium parasite**:

1. **Plasmodium falciparum**
2. **Plasmodium vivax**
3. **Plasmodium ovale**
4. **Plasmodium malariae**

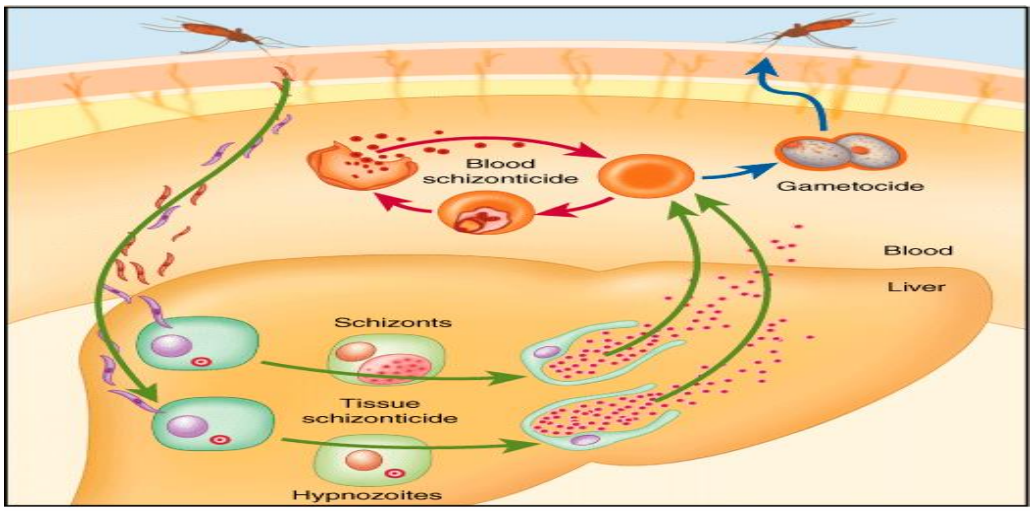
-The two most important are **P. falciparum and P. vivax**.

-The parasite is transmitted by bites from **the female anopheles mosquito**.

P. falciparum causes "**malignant** tertian malaria". "Malignant" because it is **the most severe** form of malaria and can be **fatal**. "Tertian" because it is said to produce fever every third day.

P. vivax produces "**benign** tertian malaria". "Benign" because it is **less severe than falciparum** and is seldom fatal, it is famous for its **latency**. To treat malaria caused by P. vivax, we have to make sure that we cleared the body from latent parasites.

"Malignant" and "benign" refers to the severity of the disease.



The life cycle:

This parasite has two Interdependent life cycles:

-Sexual cycle: in **mosquitos.**

-Asexual cycle: in **human body,** they are transmitted to humans by bites from the female anopheles mosquito, they make their way to the liver where they become **Schizonts (active form)** or **Hypnozoites (latent or sleeping form),** then they make their way to the RBCs where they will live, producing **gametocytes** that can be ingested through the mosquito bite repeating the cycle.

Drugs are only effective during the **asexual cycle** (only in the human body).

Knowledge of the life cycles is essential in understanding antimalarial drug treatment.

We can divide the asexual cycle into two phases according to the location of the parasite:

Exoerythrocytic phase: occurs "**outside**" the erythrocyte

Erythrocytic phase: occurs "**inside**" the erythrocyte

*We have **three types** of drugs that affect this parasite:

1. **Tissue schizonticides**: Drugs that eliminate developing or dormant liver forms.
2. **Blood schizonticides**: Drugs that act on erythrocytic parasites.
3. **Gametocides**: Drugs that kill sexual stages (gametocytes inside human body) and prevent transmission to mosquitoes.

Unfortunately, No single available agent can reliably effect a radical cure (eliminate both hepatic and erythrocytic stages).

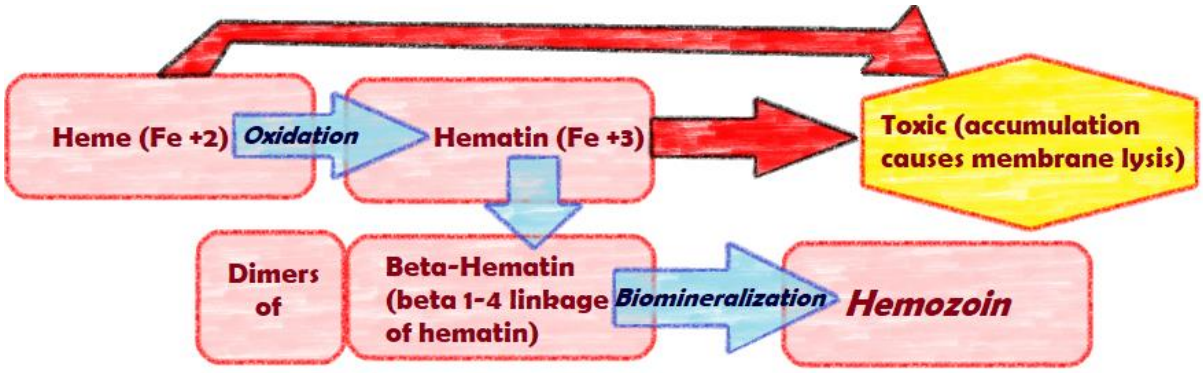
Chloroquine:

old drug, It is potent **blood schizontocidal drug** effective against **all four types of clinically important plasmodium species**.

Its mechanism of action is complex and not fully understood.

*It is accumulated in parasite lysosomes, inhibiting the digestion of hemoglobin by the parasite, thus reducing the parasite's supply of amino acids.

*It also **inhibits heme-polymerase**, which is the enzyme that crystalizes toxic free heme (under several conditions such as the low pH of the vacuole) to the **innocuous hemozoin,** in a process known as **biomineralization**.



Biomineralization of Beta-hematin happens by conjugating it with histidine-rich proteins and phospholipids.

Chloroquine is the drug of choice in the treatment of erythrocytic falciparum malaria, **except in resistant strains**. And it **is less effective** against P. vivax malaria.

It is effective in the treatment of **extraintestinal amebiasis**.

Chloroquine is used for the treatment of malaria in pregnancy.

***Adverse effects** of Chloroquine (high toxic doses):

1- gastrointestinal upset
2- pruritus
3- headaches
4- **visual disturbances** (an ophthalmological examination should be routinely performed).
5- Hypotension, cardiac arrhythmia and convulsions **if given parentally**.

Contraindication:

We don't give Chloroquine to patients with **psoriasis** or **porphyria.**

The development of resistance to drugs poses one of the greatest threats to malaria control.

chloroquine resistance has spread to nearly all areas of the world rendering this drug ineffective except in chloroquine sensitive areas like Egypt Algeria Turkey and Iraq .

*the doctor didn't talk about slide 11.

Quinine and Quinidine:

Are **rapid-acting, highly effective blood schizonticides** against the four species of human malaria parasites (like Chloroquine).

Those drugs have a **gametocidal activity against P. vivax and P. ovale**, but not P.falciparum. It is **not active against liver stage parasites**.

Quinine and quinidine remain first-line therapies for **falciparum malaria** — especially severe cases—although **toxicity** may complicate therapy.

Quinine is **more toxic and less effective** than chloroquine against malarial parasites susceptible to both drugs (it is better to use chloroquine unless the parasite is chloroquine-resistant).

Therapeutic dosages of quinine and quinidine commonly cause **cinchonism**, which is a **collection of symptoms** that include:

tinnitus, headache, nausea, dizziness, flushing, and visual disturbances.

Therapeutic doses may cause hypoglycaemia through stimulation of insulin release (pregnant patients).

Quinine can raise plasma levels of **warfarin(because it affects cyp2c19)** and **digoxin (because it affects cytochrome p450)** .

*this drug has **a low therapeutic index**, thus it is not commonly used.

Atovaquone-proguanil (Malarone):

A combination of two drugs (Atovaquone and proguanil) so it can work on two mechanisms at the same time, **reducing the chances of developing resistance against this drug.**

Malarone is the drug of choice to be used prophylactically against malaria.

***Atovaquone** is like chloroquine.

***Proguanil (Chloroguanide):**

slow-acting erythrocytic schizonticide, also inhibits the pre-erythrocytic stage of P. Falciparum.

Mechanism of action:

It is cyclized in the body to **cycloguanil** which inhibits plasmodial **Dihydrofolate reductase (DHFRase)** in preference to the mammalian enzyme.

Current use of proguanil is restricted to **prophylaxis** of malaria in **combination with chloroquine** (the combined drug is called **Malarone**, which is the drug of choice in prophylaxis) in areas of low level chloroquine resistance among P.falciparum.

*The drug is safe to use during pregnancy.

Mefloquine:

Mefloquine is an effective therapy for **many chloroquine-resistant strains of P.falciparum and other species.**

Although toxicity is a concern, mefloquine is **one of the recommended chemoprophylactic drugs for use in most malaria-endemic regions with chloroquine-resistant strains.**

Its mechanism of action appears to be associated **with inhibition of the heme-polymerase (same as chloroquine).**

Side effects of this drug are usually bad.

Weekly dosing with mefloquine for chemoprophylaxis may cause:

Nausea, vomiting, dizziness, sleep and behavioural disturbances, epigastric pain, diarrhea, abdominal pain, headache, rash, dizziness and **Neuropsychiatric toxicities.**

Mefloquine is **contraindicated in a patient** with a history of:

Epilepsy, psychiatric disorders, arrhythmia, cardiac conduction defects.

Primaquine:

Destroys **primary and latent hepatic stages of P. vivax and P. ovale (tissue schizonticide).**

thus has great clinical value for **preventing relapses of P. vivax or P. ovale** malaria (Standard therapy).

*exert a marked **gametocidal effect** against **all four species of plasmodia** that infect humans, especially **P. falciparum,** so we use it to reduce spreading of the malaria.

Because of its lack of activity against the erythrocytic schizonts, **primaquine is often used in conjunction with a blood schizonticide.**

Primaquine can be used in **post-prophylaxis** (prophylaxis after being in areas where malaria are common).

*Primaquine **causes induced hemolytic anemia** in patients with genetically low levels of glucose-6-phosphate dehydrogenase **(G6PD deficiency).**

*Patients should be tested for **G6PD deficiency** before primaquine is prescribed.

Adverse effects off primaquine:

Nausea, epigastric pain, abdominal cramps, and headache.

*Note: symptoms are more common with **higher dosages** and when the drug is taken on an **empty stomach**.

*Primaquine should be avoided in:

1- Patients with a history of **granulocytopenia** or **methemoglobinemia**
2- In those receiving potentially **myelosuppressive drugs** (e.g. quinidine).
3- **Pregnancy**
4- **G6PD deficiency**

Remember:
-When treating about **P. falciparum** we should **use blood schizonticides**.
-When treating **P. Vivax** we should **combine blood schizonticides with tissue schizonticides.**

All of those were the old drugs for malaria, now let's discuss the new drugs:

Artemisinin derivatives:

Artemether / Arteether / Artesunate

-Artemisinin is a **very potent** and rapidly acting **blood schizonticides** that have **peroxide configuration** which is responsible for its action.

-**Combination therapy**: Used in combination with other **drugs to protect emergence of resistance to partner drug** (ACT- Artemisinin Combination Therapy)

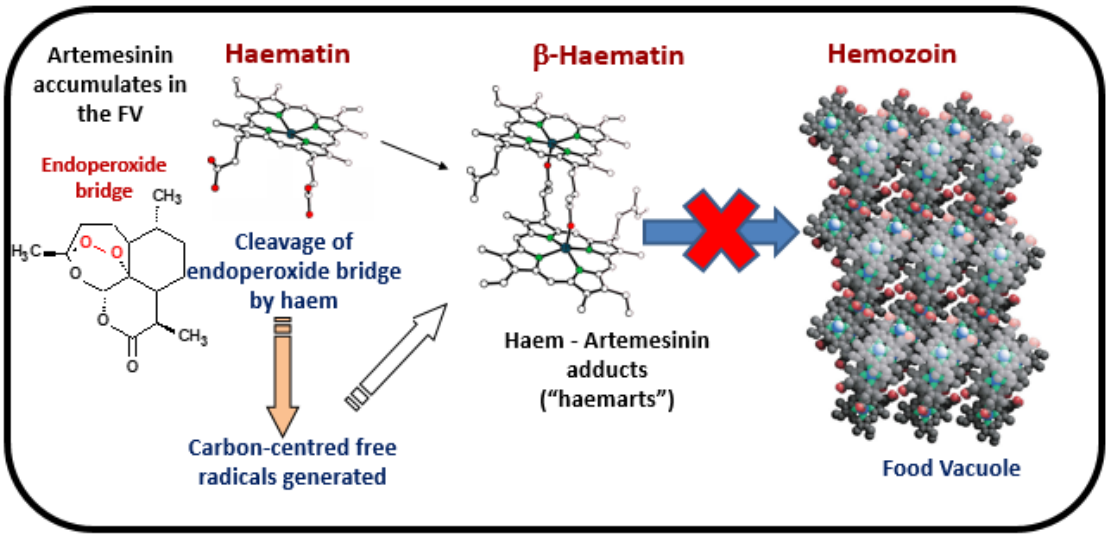
-Duration of action is **short**

-Recrudescence rate is **high** when used **alone** in **short courses**.

-Used **only** in **combination(ACT).**

-Artemisinin **reduces parasite burden rapidly.**

-It was discovered in the plant ***Artemisia annua – sweet wormwood.***



Possible targets of artemisinin free radicals:
TCTP (translationally controlled tumour protein homolog)
SERCA (sarco/endoplasmic reticulum Ca^{2+} ATPase)
Cysteine proteases

-**Mechanism of action:** instead of forming beta-hematin dimers, this drug will form Heme-Artemesinin adducts (Haemarts) which cannot be biomineralized to Hemozoin, causing toxicity.

Pyrimethamine - sulphonamide and antibiotics:

Pyrimethamine inhibits plasmodial dihydrofolate reductase at much lower concentrations than those that inhibit the mammalian enzyme.

Tetracycline and doxycycline are active against erythrocytic schizonts of all human malaria parasites. They are not active against liver stages.

Doxycycline is used in the treatment of falciparum malaria in conjunction with quinine, allowing a shorter and better-tolerated course of that drug.

Drug	Use	Adult Dosage[3]
Chloroquine	**Areas without resistant P falciparum**	**500 mg weekly**
Atovaquone-proguanil (Malarone)	**Areas with chloroquine-resistant P falciparum (drug of choice in highly infected area)**	**1 tablet (250 mg atovaquone/100 mg proguanil) daily**
Mefloquine	**Areas with chloroquine-resistant P falciparum**	**250 mg weekly**
Doxycycline	**Areas with multidrug-resistant P falciparum**	**100 mg daily**
Primaquine	**Terminal prophylaxis of P vivax and P ovale infections; alternative for primary prevention**	**52.6 mg (30 mg base) daily for 14 days after travel; for primary prevention 52.6 mg (30 mg base) daily**

Clinical Setting	Drug Therapy	Alternative Drugs
Severe or complicated infections with P falciparum	Artesunate, 2.4 mg/kg IV, every 12 hours for 1 day, then daily for two additional days; follow with 7 day oral course of doxycycline or clindamycin or full treatment course of mefloquine or Malarone	Artemether, 3.2 mg/kg IM, then 1.6 mg/kg/d IM; follow with oral therapy as for Artesunate
	Or… Quinidine gluconate,2 10 mg/kg IV over 1–2 hours, then 0.02 mg/kg IV/min	
	Or… 15 mg/kg IV over 4 hours, then 7.5 mg/kg IV over 4 hours every 8 hours	