

4. ANTINEOPLASTIC – ANTICANCER DRUGS

!! JAY AMBE !!

4. ANTI MALARIAL DRUGS

PREPARED BY

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4. ANTINEOPLASTIC – ANTICANCER DRUGS

MALARIA

- It is a mosquito-borne infectious disease of humans and other animals caused by parasitic protozoans (a type of unicellular microorganism) of the genus *Plasmodium*.
- The disease is transmitted via a bite from an infected female *Anopheles* mosquito, which introduces the organisms from its saliva into the person's circulatory system.
- Five species of *Plasmodium* can infect and be transmitted by humans:
 1. *P. falciparum*
 2. *P. vivax*,
 3. *P. ovale*,
 4. *P. malariae*
 5. The zoonotic species *P. knowlesi*.
- The vast majority of deaths are caused by *P. falciparum* and *P. vivax*.
- *P. ovale*, and *P. malariae* cause a generally milder form of malaria that is rarely fatal.
- The zoonotic species *P. knowlesi*, prevalent in Southeast Asia, causes malaria in macaques (monkey) but can also cause severe infections in humans.

LIFECYCLE OF MALARIA:

Life cycle of malarial parasite depends on two hosts:

1. Human host (Asexual cycle in human):

- When an infected mosquito bites a healthy person, the female *Anopheles* mosquito transmits sporozoite to the blood stream of human.
- The sporozoites circulate in to the blood and reach to liver.
- In the liver follows asexual multiplications and produce thousands of cryptozoites (merozoites).
- Cryptozoites enter in to the red blood cells (RBCs) and follow the following stages:

A) Erythrocytic phase:

In the erythrocyte it follows the following stages:

- a) Trophozoite: Small ring form of cytoplasm
- b) Schizont: The parasite multiplies at the cost of the red blood cells and chromatin is divided into number of cells and mature.
- c) Libration of merozoites (Exoerythrocyte): Later RBCs are ruptured and merozoites are librated and affect fresh RBCs. At these stage symptoms like Fever, Shivering and chills, Anemia, Pain in the joint, Headache, Sever vomiting, Convulsion, Coma were observed.

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B) Gametogony:

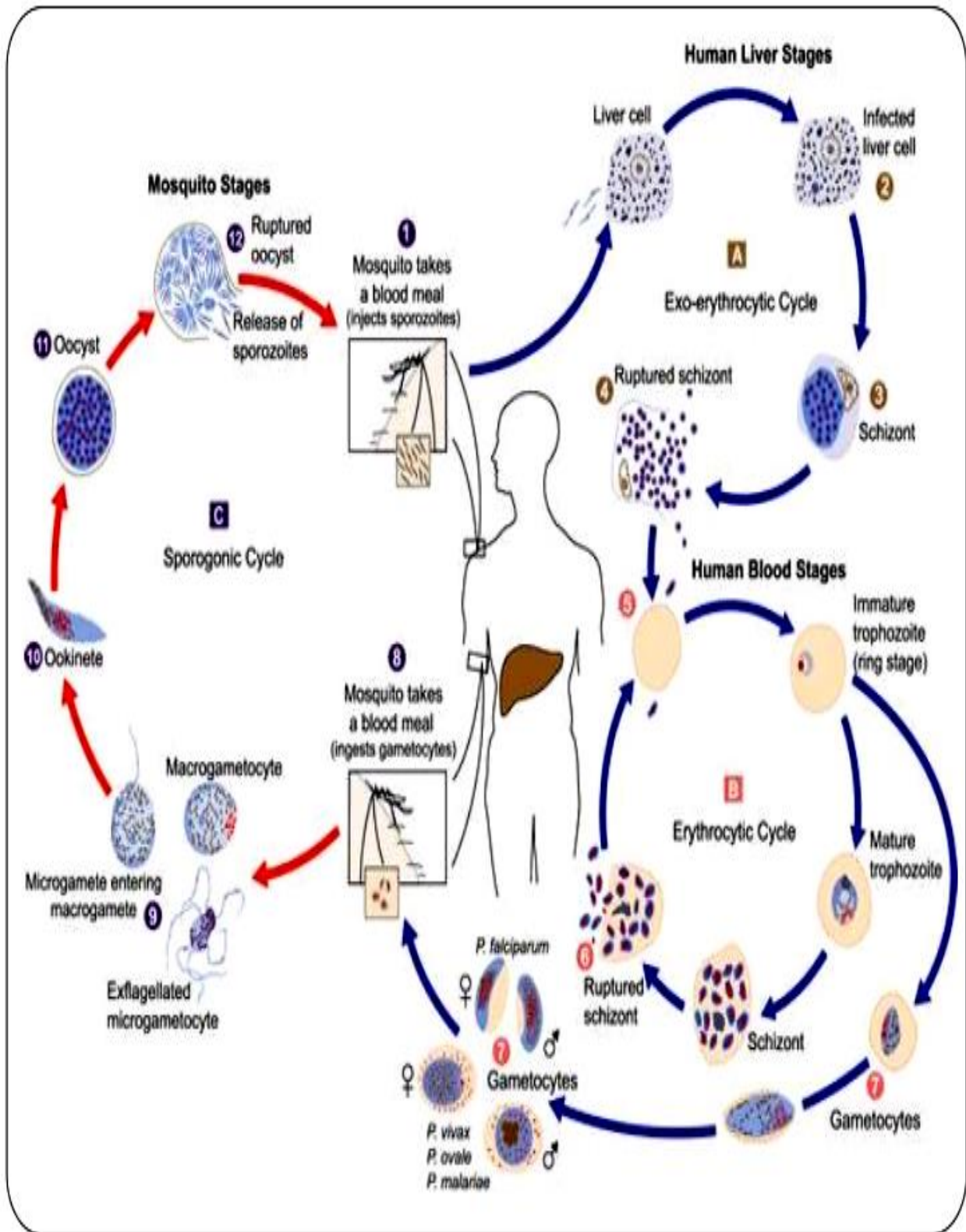
- Some of merozoites undergo meiotic division and form male and female gametes.
- Male gametes are termed as microgametes and
- Female gametes are termed as macrogametes.
- Male and female gametes do not combine in to the human host.

2. Mosquito host (Sexual Phase):

- Female *Anopheles* mosquito bites to infected person, male and female gametes are ingested by the mosquito.
- Games reach to the stomach of mosquito and microgametes fuse in to the macrogametes and produce zygote.
- A cyst is formed around the zygote is known as oocystes. Oocystes undergoes various changes to form elongated bodies known as sporozoites. These sporozoites injected in to human through saliva of mosquito.

	<i>P.vivax</i>	<i>P.ovale</i>	<i>P. malariae</i>	<i>P.falciferum</i>
Period of recurrence	Variable	Variable	Very long	short
Pre-erythrocytic stage (days)	6-8	9	14-16	5.5-7
Erythrocytic cycle (hours)	48 (about)	50	72	48
Incubation period (days)	15 (12-17) or up to 6-12 months	17 (16-18) or longer	28 (18-40) or longer	12 (9-14)

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CLASSIFICATION OF ANTIMALARIAL DRUGS:

1. Therapeutic classification:

A) Causal prophylaxis: (Primary tissue schizonticides)

- Destroy parasite in liver cells and prevent invasion of erythrocytes
E.g. Primaquine, pyrimethamine, proguanil

B) Suppressive Prophylaxis:

- Suppress the erythrocytic phase and related symptoms and thus attack of malarial fever can be used as prophylactics
E.g. Chloroquine, proguanil, mefloquine, doxycycline, pyrimethamine, biguanides

C) Clinical cure:

- Used to terminate an episode of malarial fever
- Act on erythrocytic schizogony and exoerythrocytic schizogony
E.g. Primaquine, pamaquine, pentaquine, , pyrimethamine

D) Suppressive curative:

- Agent completely remove parasite from the body.
E.g. Chloroquine, pyrimethamine

E) Slow acting low efficacy drugs

E.g. Proguanil, pyrimethamine, sulfonamides, tetracyclines

F) Gametocidal:

- Destroy gametocytes and prevent transmission
 - a. Primaquine, artemisinin – against all plasmodia
 - b. Chloroquine, quinine – P.Vivax
 - c. Proguanil, pyrimethamine – Prevent development of sporozoites

2. Chemical classification

A) 4 aminoquinolines:

E.g. Chloroquine, Hydroxychloroquine, Amodiaquine, Pyronaridine

B) 8 aminoquinolines:

E.g. Primaquine, Tafenoquine, Bulaquine

C) Cinchona alkaloids:

E.g. Quinine, Quinidine

D) Quinoline methanol or 4 – Quinoline – carbinolamines:

E.g. Mefloquine, Halofantrine

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- E) Biguanides
E.g. Proguanil, Chlorproguanil
- F) Diaminopyrimidines
E.g. Pyrimethamine
- G) Sulfonamides
E.g. Sulfadoxine, dapsone
- H) Tetracyclines:
E.g. Tetracycline, doxycycline
- I) Naphthoquinone:
E.g. Atovaquone
- J) Sesquiterpene lactones:
E.g. Artesunate, artemether, arteether

➤ CHLOROQUINE:

Mechanism of action:

1. Inside red blood cells, the malarial parasite in its merozoite life cycle stage degrades hemoglobin to acquire essential amino acids, which the parasite requires to construct its own protein and for energy metabolism. Digestion is carried out in a vacuole of the parasitic cell.
During this process, the parasite releases the toxic and soluble molecule heme. The heme moiety consists of a porphyrin ring called Fe(II)-protoporphyrin IX (FP) it is toxic for parasites. To avoid destruction by this molecule, the parasite biocrystallizes heme to form hemozoin, a nontoxic molecule. Hemozoin collects in the digestive vacuole as insoluble crystals.
Chloroquine enters the red blood cell, inhabiting parasite cell, and digestive vacuole by simple diffusion. Chloroquine binds to heme or (Fe(II)-protoporphyrin IX FP) to form the FP-chloroquine complex and prevent formation of hemozoin; this complex is highly toxic to the cell and disrupts membrane function. Action of the toxic FP-chloroquine results in cell lysis and ultimately parasite cell autodigestion. In essence, the parasite cell drowns in its own metabolic products.
2. Depresses oxygen uptake and carbohydrate metabolism
3. Intercalates into DNA
4. Disrupting the parasite's replication and transcription.

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Pharmacological actions:

1. Antimalarial activity:
 - High against erythrocytic forms of vivax, ovale, malariae & sensitive strains of falciparum
 - Gametocytes of vivax
 - No activity against tissue schizonts
 - Resistance develops due to efflux mechanism
2. Other parasitic infections:
 - Giardiasis, taeniasis, extraintestinal amoebiasis
3. Other actions:
 - Depressant action on myocardium, direct relaxant effect on vascular smooth muscles, antiinflammatory, antihistaminic, local anaesthetic, antipyretic.

Pharmacokinetics:

- Absorption: Oral: Rapid (~89%)
- Distribution: Widely in body tissues (eg, eyes, heart, kidneys, liver, lungs) where retention prolonged; crosses placenta; enters breast milk
- Metabolism: Partially hepatic
- Half-life elimination: 3-5 days
- Time to peak, serum: 1-2 hours
- Excretion: Urine (~70% as unchanged drug); acidification of urine increases elimination.

Adverse drug reactions:

- Intolerance:
 - Nausea, vomiting, anorexia
 - Skin rashes, angioneurotic edema, photosensitivity, pigmentation, exfoliative dermatitis
 - Long term therapy may cause bleaching of hair
 - Rarely thrombocytopenia, agranulocytosis, pancytopenia
- Ocular toxicity: High dose prolonged therapy
 - Temporary loss of accommodation
 - Lenticular opacities, subcapsular cataract
 - Retinopathy: constriction of arteries, edema, blue black pigmentation, constricted field of vision.

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- CNS:
 - Insomnia, transient depression seizures, rarely neuromyopathy & ototoxicity
- CVS:
 - ST & T wave abnormalities, abrupt fall in BP & cardiac arrest in children reported

Therapeutic uses:

1. Hepatic amoebiasis:
2. Giardiasis
3. Clonorchis sinensis
4. Rheumatoid arthritis
5. Discoid Lupus Erythematosus
6. Control manifestation of lepra reaction
7. Infectious mononucleosis

Other derivative:

- **Hydroxy chloroquine:**
 - Less toxic, properties & uses similar
- **Amodiaquine:**
 - As effective as chloroquine
 - Pharmacological actions similar
 - Chloroquine resistant strains may be effective
 - Adverse events: GIT, headache, photosensitivity, rarely agranulocytosis
 - Not recommended for prophylaxis
- **Pyronaridine:**
 - Effective in resistant cases

PRIMAQUINE:

Mechanism of action:

- Primaquine is mainly used to treat the *P. vivax* or *P. ovale* malaria.
- Primaquine is probably derived from hydroxylated metabolites.
- It converts to electrophiles and reactive oxygen species and interferes with oxygen transport system of parasites.

Antimalarial action:

- Active against liver hypnozoites (Parasite infected the hepatic cells).
- Weak action against erythrocytic stage of vivax, so used with suppressive in radical cure

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- No action against erythrocytic stage of falciparum
- It has gametocidal action and is most effective antimalarial to prevent transmission disease against all 4 species

Pharmacokinetics:

- Primaquine is rapidly and nearly completely absorbed after oral administration.
- Its elimination half-life is 5-7 hours.
- Primaquine is extensively metabolized and less than 2% of the dose is excreted unaltered into the urine.

Adverse effects:

- Gastrointestinal:
 - epigastric distress, abdominal cramps ,
- Hemopoetic:
 - mild anemia, methaemoglobinemia, cyanosis, hemolytic anemia in G6PD deficiency
- Avoided during pregnancy.
- A red cell defect, caused by deficiency of glucose-6-phosphate dehydrogenase (G6PD) is responsible for haemolysis in primaquine sensitive individuals. Primaquine may induce methaemoglobinaemia irrespective of the G6PD status of the patient.

Uses:

- Primary use is radical cure of relapsing malaria 15 mg daily for 14 days with dose of chloroquine.
- Falciparum malaria 45 mg of single dose with chloroquine curative dose to kill gametes & cut down transmission of malaria.

Other derivative:

- **Tafenoquine:**
 - More active slowly metabolized analog of primaquine, has advantage that it can be given on weekly basis.
- **Bulaquine:**
 - Congener of primaquine developed in India
 - Comparable antirelapse activity when used for 5 days
 - Partly metabolized to Primaquine
 - Better tolerated in G6PD deficiency

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➤ QUININE:

Mechanism of action:

- The mechanism of action of quinine has not been fully resolved. The most widely accepted hypothesis of its action is based on the well-studied and closely related quinoline drug, chloroquine.
- This model involves the inhibition of hemozoin biocrystallization, which facilitates the aggregation of cytotoxic heme.
- Free cytotoxic heme accumulates in the parasites, causing their deaths.

Pharmacological actions:

1. Antimalarial action:
 - Erythrocytic forms of all malarial parasites including resistant falciparum strains.
 - Gametocidal for vivax & malariae
2. Local irritant effect:
 - Local pain sterile abscess.
3. Cardiovascular:
 - Depresses myocardium, ↓ excitability, ↓ conductivity, ↑ refractory period, profound hypotension IV.
4. Miscellaneous actions:
 - Mild analgesic, antipyretic activity, stimulation of uterine smooth muscle, curare-mimetic effect

Pharmacokinetics:

- Administered orally is completely absorbed
- T_{max} = 1-3 hrs, crosses placental barrier
- Metabolized in liver degradation products excreted in urine $t_{1/2}$ = 10 hrs

Adverse drug reactions:

- Cinchonism:
 - Tinnitus, nausea & vomiting
 - Headache mental confusion, vertigo, difficulty in hearing & visual disturbances
 - Diarrhoea, flushing & marked perspiration

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- Still higher doses , exaggerated symptoms with delirium , fever, tachypnoea, respiratory depression , cyanosis.
- Idiosyncrasy : Similar to cinchonism but occurs in therapeutic doses and produce allergic reaction.
- Cardiovascular toxicity: Cardiac arrest, hypotension ,fatal arrhythmias
- Black water fever:
 - Hemolysis and hemoglobinuria
 - Dark urine
 - Azotemia
 - Intra vascular coagulation
 - Renal failure
 - Uremia
- Hypoglycemia

Pharmacokinetics (quinine and quinidine):

- Quinine is rapidly and completely absorbed.
- The clearance of quinine varies between 1.2-4 ml/min/kg and the mean elimination half-life is 10- 12 hours. Clearance may be reduced in the elderly, smokers and in patients with malaria.
- Quinine is cleared primarily by hepatic metabolism. The systemic clearance of total drug and renal elimination (15-40%) is higher for quinidine (2.5-5 ml/min/kg) than quinine.

➤ MEFLOQUINE:

- Quinoline methanol derivative developed to deal with chloroquine resistant malaria
- Rapidly acting erythrocytic schizonticide , slower than chloroquine & quinine
- Effective against chloroquine sensitive & resistant plasmodia
- Mechanism of action similar to chloroquine.
- Mefloquine resistance among plasmodium falciparum has become common in Thailand, cambodia and myanmar, as it has not been used extensively in india mefloquine resistance is not a problem over here. But due to its long half life chances of selection of resistant strains are high; mefloquine resistant isolates have been reported from gujrat and andhra pradesh.
- Resistance to mefloquine confers resistance to quinine and halofantrine

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Pharmacokinetics:

- Good but slow oral absorption
- High protein binding
- Concentrated in liver, lung, intestine.
- Extensive metabolism in liver, primarily secreted in bile, undergoes enterohepatic circulation
- Long $t_{1/2} = 2 - 3$ weeks

Adverse events:

- GIT:
 - Bitter in taste, nausea, vomiting, abdominal pain, diarrhoea
- Neuropsychiatric disturbances:
 - Anxiety, hallucinations, sleep disturbances, psychosis, errors in operating machinery, convulsions
- CVS:
 - Bradycardia, sinus arrhythmia, & QT prolongation
- Teratogenicity:
 - Avoided in first trimester
- Miscellaneous:
 - Allergic skin reactions, hepatitis & blood dyscrasias.
 - Disturbed sense of balance, ataxia, neuropsychiatric reactions are dose related and subside in 1-3 weeks

Uses:

- Effective drug for MDR falciparum
 - T/t of uncomplicated falciparum in MDR malaria should be used along with artesunate (ACT)
 - Prophylaxis in MDR areas 250 mg per week started 2-3 weeks before to assess side effects
- Due to fear of development of drug resistance mefloquine should not be used as drug for prophylaxis in residents of endemic area.
- It cannot be given parenterally and is not used in complicated cerebral malaria.

Other derivative:

- Halofantrine

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- It is quinoline methanol derivatives.
- Used in chloroquine resistant malaria since 1980
- Erratic bioavailability, lethal cardiotoxicity & cross resistance to mefloquine limited its use
- Now a day used only when no other alternative available
- **Adverse events:** Nausea, vomiting, QT prolongation, diarrhoea, itching, rashes
- **Contraindicate:** Along with quinine, chloroquine, antidepressants, antipsychotics.

➤ ATOVAQUONE

- Synthetic naphthoquinone
- Rapidly acting erythrocytic schizonticide for *Plasmodium falciparum* & other plasmodia.
- Proguanil potentiates action of atovaquone and prevents development of resistance

Mechanism of action:

- Collapses mitochondrial membrane & interferes ATP production.

➤ BIGUANIDE DERIVATIVES:

- Proguanil (chloroguanide, chloroguanide) is a prophylactic antimalarial drug.
- When taken, it is converted to the active metabolite cycloguanil.
- Proguanil is effective against sporozoites.

Mechanism of action:

It works by stopping the malaria parasites, *Plasmodium falciparum* and *Plasmodium vivax*, from reproducing once they are inside red blood cells, by inhibiting the enzyme dihydrofolate reductase, which catalyzes the formation of tetrahydrofolate, the main one-carbon unit carrier in the body, required for Thymidine monophosphate and purine base synthesis.

Adverse effects:

- Stomatitis, mouth ulcers, larger doses depression of myocardium, megaloblastic anemia
- **Causal prophylaxis:** 100 – 200 mg daily

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➤ PYRMETHAMINE:

- Diaminopyrimidine more potent than proguanil & effective against erythrocytic forms of all species.
- Tasteless so suitable for children
- Sequential blockade
- Sulfadoxine 500 mg + Pyrimethamine 25 mg, 3 tablets once for acute attack
- Not recommended for prophylaxis
- High affinity for plasmodial enzyme 2000 times greater than for mammalian enzyme.

Mechanism of action:

- Pyrimethamine interferes with tetrahydrofolic acid synthesis from folic acid by inhibiting the enzyme dihydrofolate reductase (DHFR).
- Tetrahydrofolic acid is needed for DNA and RNA synthesis in many species, including protozoa.
- It has also found to inhibit superoxide dismutase (SOD), a key protein involved in Amyotrophic Lateral Sclerosis (ALS).

Pharmacokinetics:

- Pyrimethamine is well absorbed after oral administration.
- The elimination half-time ($t_{1/2}$) in healthy adults is between 46.1 and 150 hours.

Use:

- Single dose treatment of uncomplicated chloroquine resistant falciparum malaria
- Patients intolerant to chloroquine
- First choice treatment for toxoplasmosis

Adverse events:

- Megaloblastic anemia, Thrombocytopenia, Agranulocytosis.

➤ ARTEMISININ:

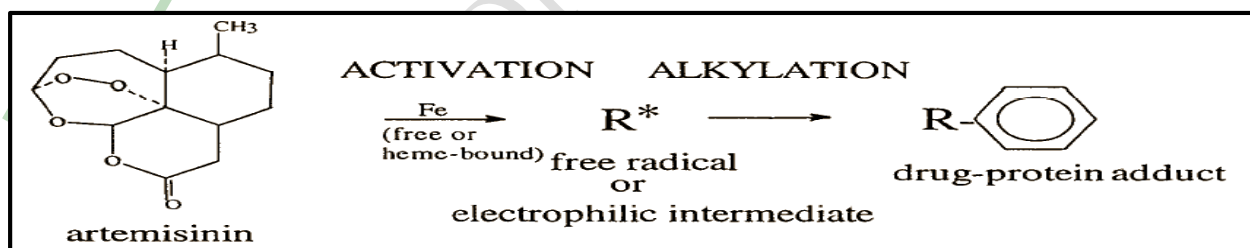
- Artemisinin is the active principle of the plant artemisia annua
- Used in chinese traditional medicine as quinghauso as elicit quicker defervescence and clearing of parasitemia in 48 hours
- Sesquiterpine lactone derivative
- Do not kill hypnozoites but have some action on gametocytes of falciparum
- Short duration of action
- High recrudescence rate

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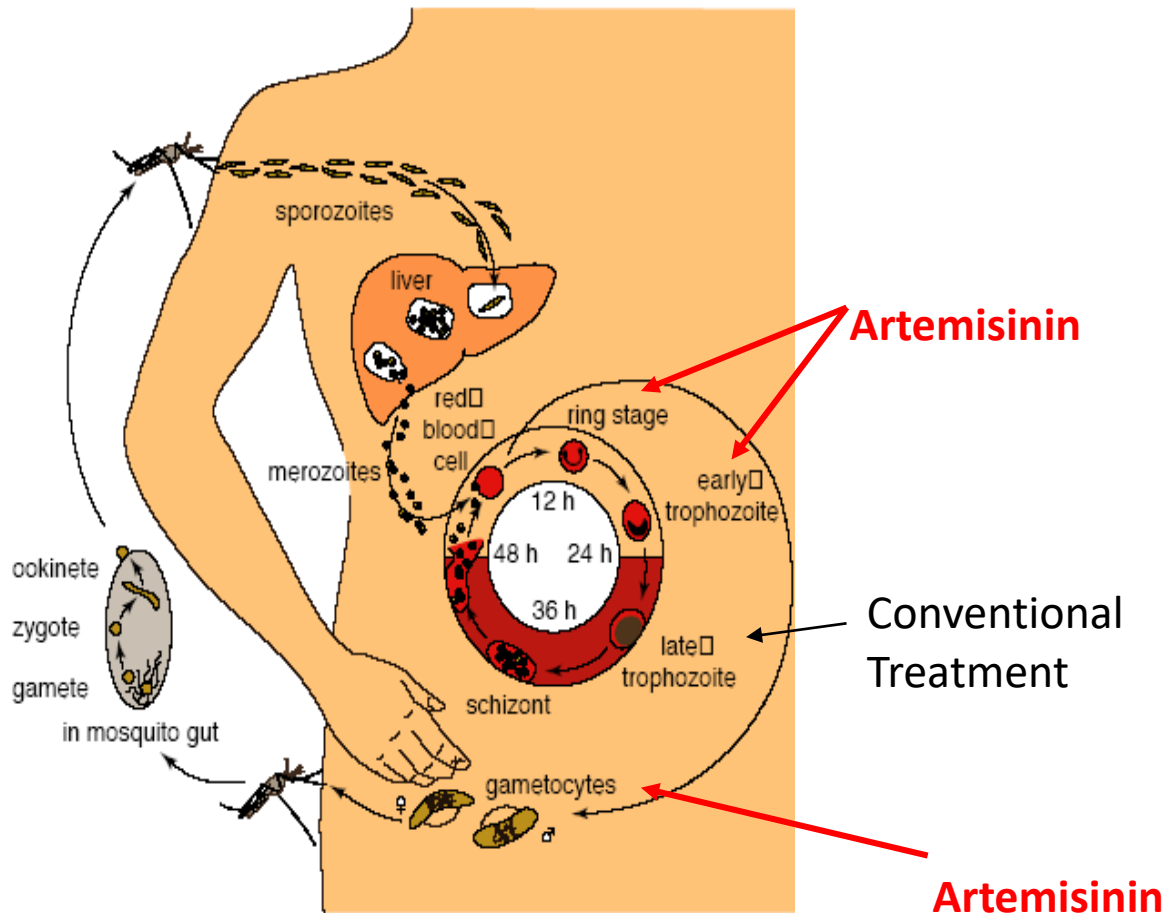
- Poorly soluble in water & oil
- Artemisinin compounds are shorter acting drugs
- Monotherapy needs to be extended beyond disappearance of parasite to prevent recrudescence
- This can be prevented by combining 3-5 day regimen of artemisin compounds with one long acting drug like:
 - Artesunate – Sulfadoxine, pyrimethamine: ARTESUNATE 100 mg BD for 3 days with S-P, 3 tablets
 - Artesunate Mefloquine: Artesunate 100 mg BD for 3 days, + mefloquine 750 mg on second day & 500 mg on third day
- Indicated by WHO in acute uncomplicated resistant falciparum malaria

Mechanism of action:

- These compounds have presence of endoperoxide bridge
- Endoperoxide bridge interacts with heme in parasite
- Heme iron cleaves this endoperoxide bridge
- There is generation of highly reactive free radicals which damage parasite membrane by covalently binding to membrane proteins



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Use:

- These compounds are mainly schizonticides and are effective against plasmodium vivax as well as chloroquine resistant and sensitive strains of plasmodium falciparum.
- They are useful in cerebral malaria and MDR malaria

Adverse events:

- Leucopenia
- Hypersensitivity: Drug fever, itching
- GIT: nausea, vomiting, abdominal pain (common)
- ECG changes: ST-T changes, QT prolongation
- Abnormal bleeding, dark urine
- Reticulocytopenia

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➤ SESQUITERPENE LACTONES:

- **Artesunate:**

- Water soluble ester of dihydroartemisinin
- Dose: can be given oral, IM, IV, rectal
 - Oral
 - 100 mg BD on day 1
 - 50 mg BD day 2 to day 5
 - Parenteral
 - 120 mg on day 1 (2.4 mg/kg BD)
 - 60 mg OD (2.4 mg/kg) for 7 days

- **Artemether:**

- Methyl ether of dihydroartemisinin
- Dose:
 - Oral & IM
 - 80 mg BD on day 1 (3.2 mg/kg)
 - 80 mg OD (1.6 mg/kg) for 7 days

- **Arteether:**

- Ethyl ether of dihydroartemisinin
- Therapeutically equivalent to quinine in cerebral malaria
- A longer $t_{1/2}$ & more lipophilic than artemether favouring accumulation in brain
- **Dose:** 3.2 mg/kg on day 1 followed by 1.6 mg/kg daily for next 4 days

➤ TETRACYCLINES:

- Slow but potent action on erythrocytic stage of all MP & Pre-erythrocytic stage of falciparum
- Always used in combination with quinine or Sulfadoxine-pyrimethamine for treatment of chloroquine resistant malaria

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MANAGEMENT OF MALARIA

PROPHYLAXIS OF MALARIA:

- **Duration:** 1-2 weeks before to 4 weeks after returning from endemic area
- **Drug regimens:**
 - After returning home a traveller who has been heavily exposed to malaria and not G6PD deficient should be treated with primaquine 15 mg base daily for 14 days in order to eliminate hepatic forms of plasmodium vivax and ovale: causal prophylaxis.
 - Chloroquine resistant malaria:
 - Mefloquine 250 mg once a week ,
 - Doxycycline 100 mg daily ,
 - Atovaquone + proguanil daily
- **Drugs not allowed for prophylaxis:**
 - Quinine , artemisinin compounds
 - Shorter acting, higher toxicity
 - Pyrimethamine sulfadoxine
 - Amodiaquine

ACUTE ATTACK OF CHLOROQUINE SENSITIVE MALARIA:

- Tab. Chloroquine phosphate 250 mg
 - Contains 150 mg of base
 - Give 4 tablets stat , 2 tablets after 8 hours and , 1 tablet BD for 2 days
- Patients who cannot take orally
 - 3.5 mg/kg IM every 6 hrs for 3 days
- Tab primaquine 15 mg OD for 14 days in Plasmodium vivax, ovale
- Primaquine 45 mg single dose for falciparum after chloroquine (gametocidal)

ACUTE ATTACK OF CHLOROQUINE RESISTANT MALARIA:

- **Patient who can take orally:**
 - 3 tablets of (Pyrimethamine + sulfadoxine) single dose followed by quinine 600 mg TDS for 2 days or
 - Tab Quinine 600 mg TDS X 3 days with Cap doxycycline 100 mg BD for 7 days or
 - Quinine 3 days with mefloquine or
 - (Atovaquone 250 mg + proguanil 100 mg) 4 tab(Single dose) for 3 days or

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- artesunate 100 mg BD x 3 days with Sulfadoxine-pyrimethamine or mefloquine
- **Patient who cannot take orally**
 - Inj Quinine Hcl 20 mg/kg in 500 ml dextrose saline over 4 hrs then
 - 10 mg/kg in dextrose saline over 2 hrs every 8 hrly till patient is able to swallow
 - Then quinine 600 mg TDS for 7 days & tetracycline/ doxycycline or artemether / arteether injection

RESISTANCE SHOULD BE SUSPECTED:

- All patients with complication
- Any patient who has already received chloroquine last 1 month
- Hb continues to fall in absence of bleeding & asexual forms persist along with symptoms after 48 hrs of treatment.

MALARIA IN CHILDREN:

- Quinine parenteral high toxicity / oral well tolerated
- Primaquine avoided in neonates
- Mefloquine not used in children below 15 kg weight

ACUTE MALARIA IN PREGNANT WOMEN

- Chloroquine in usual doses
- Mefloquine C/I in first trimester
- Primaquine/ tetracycline avoided
- Anemia: folic acid & iron

PRACTICE POINTS:

- Most antimalarials are bitter in taste give along with milk or fruit juice
- If vomiting occurs within hour of drug repeat full dose, in case of mefloquine repeat half dose
- If vomiting after 1 hour no need to repeat
- Postural hypotension : quinine, chloroquine

DRUGS USED IN CHLOROQUINE RESISTANT MALARIA:

- Mefloquine
- Quinine
- Sulfadoxine pyrimethamine
- Artemisinin compounds