ANTI-MALARIAL DRUGS

Points to be covered in this topic

1. INTRODUCTION OF MALARIAL
2. CLASSIFICATION OF ANTIMALARIAL AGENTS
3. CLASSIFICATION OF ANTIMALARIAL AGENTS
4. MOA,PHARMACOKINETICS ,ADR,USES OF DIFFERENT CLASS OF DRUGS
5. TREATMENT OF MALARIAL

❑ INTRODUCTION

- Malaria is an acute infectious disease.
- Causative agent: Plasmodium species & Protozoan parasite

➢ 4 species infecting humans

i. P. falciparum ii. P. vivax iii. P. malariae iv. P. ovale

Transmitted by female Anopheles mosquito is characterized by high fever with rigor, anaemia.

❖ Types of malaria

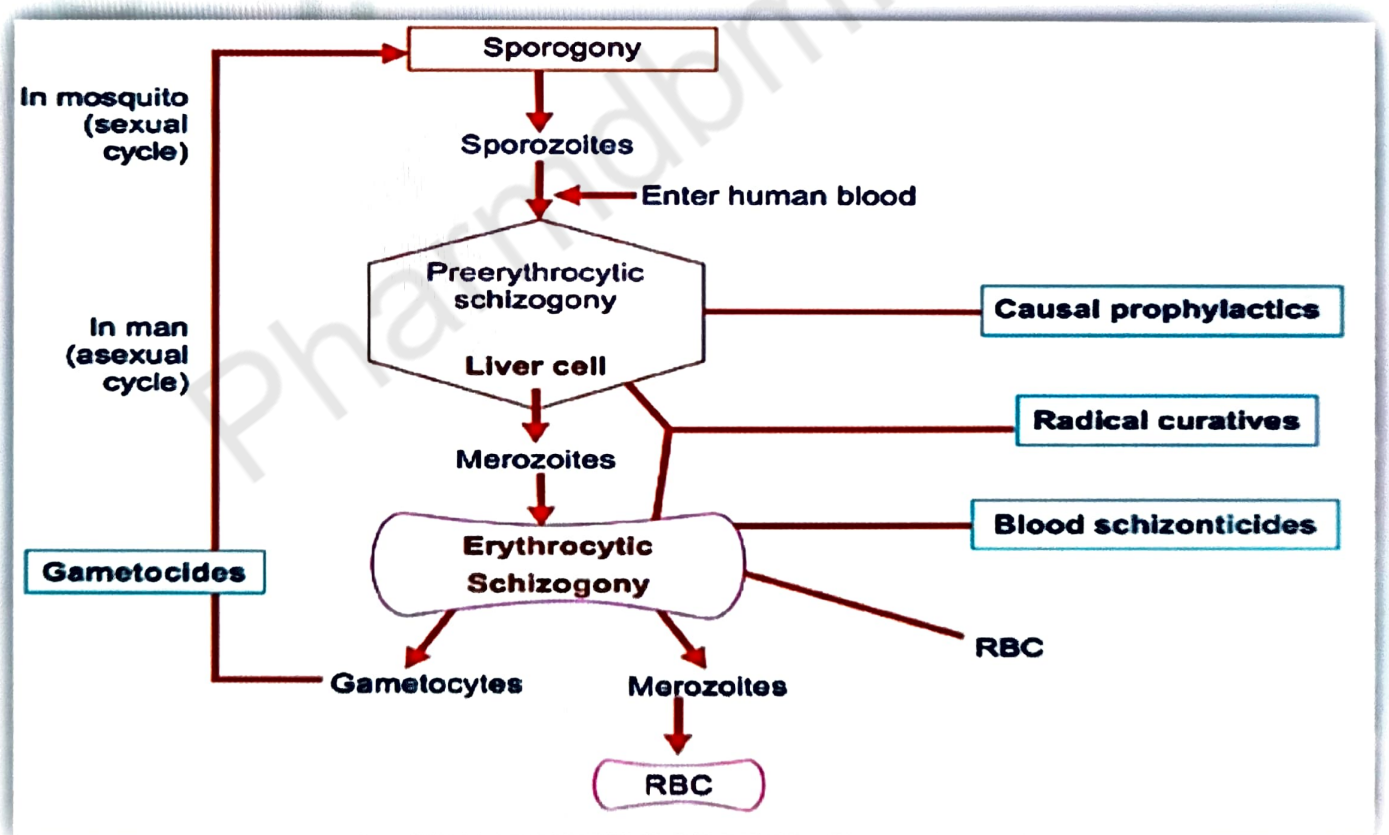
Plasmodium falciparum	Plasmodium vivax	Plasmodium malariae	Plasmodium ovale
• Most dangerous species • causes an acute, rapidly fulminating characterized by persistent high fever disease i.e. orthostatic hypotension, and massive erythrocytosis • capillary obstruction and death treatment is delayed	Causes a milder form of the disease	Common to many tropical regions	rarely encountered

❑ LIFE CYCLE OF MALARIA

1. **Hepatic (Pre erythrocytic) stages** -**parasites localize in liver** -patient is asymptomatic
2. **Erythrocytic stages** -**parasite invade RBCS** -patient develops fever cycle
3. **Development of sexual forms** -occurs in **Anopheles mosquitos**

➢ **Causative organism-** Plasmodium vivax Vector/definitive host - **female anopheles mosquito, intermediate host-man.**

- Life cycle occurs partly inside the mosquito **(sexual sporogony)** & **(asexual schizogony) man**
- **Mosquito bites man- transmits sporozoites to his blood.**
- **Sporozoites** - **liver** and **reproduces asexually** (tissue schizogony) producing **merozoites.**



- Merozoites infect **new RBCS** and **initiate asexual multiplication** in RBC (blood schizogony) - production of more merozoites.
- The **RBC bursts** and starts the **infective cycle.**
- Merozoites develop into **male and female gametes.**

- Some merozoites remain dormant in the liver **(hypnozoites)** which can cause a relapse of infection later **(p. vivax & ovale)**

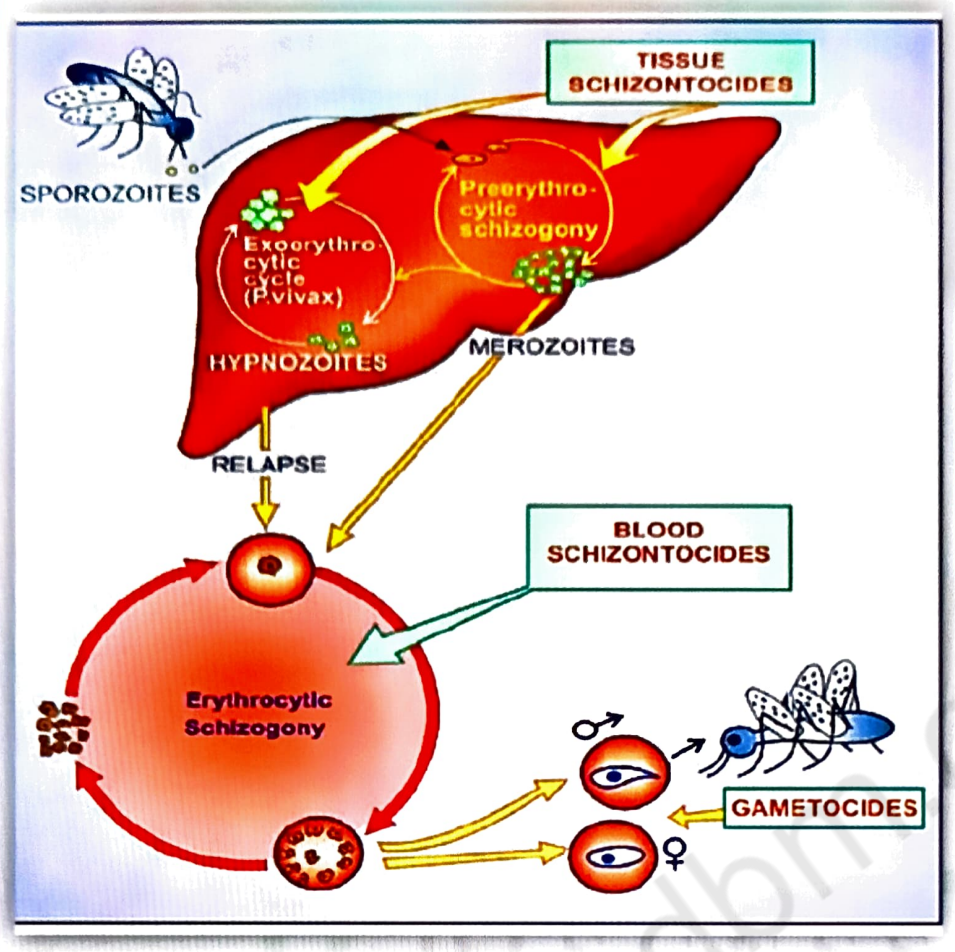


Fig :-life cycle of malarial parasite in man

- When mosquito bites **infected person**, **gametes** are taken up with the **blood.**
- The gametocytes mature in the **mosquito gut and fuse** to form an kinate which develops into **sporozoites.(Sexual sporogony)**
- Sporozoites migrate to **salivary glands** and infect a new host when mosquito bites the person.

❖ Antimalarial drugs

- **17th Century - Cinchona Tree in Peru**
- **1820 till 1942 - Cinchona Bark**
- **WW I and WW II- Java blocked**
- **1926- Mepacrine 1945- Proguanil**
- **Proguanil, Pyrimethamine**

❖ OBJECTIVES AND USE OF ANTIMALARIAL DRUGS

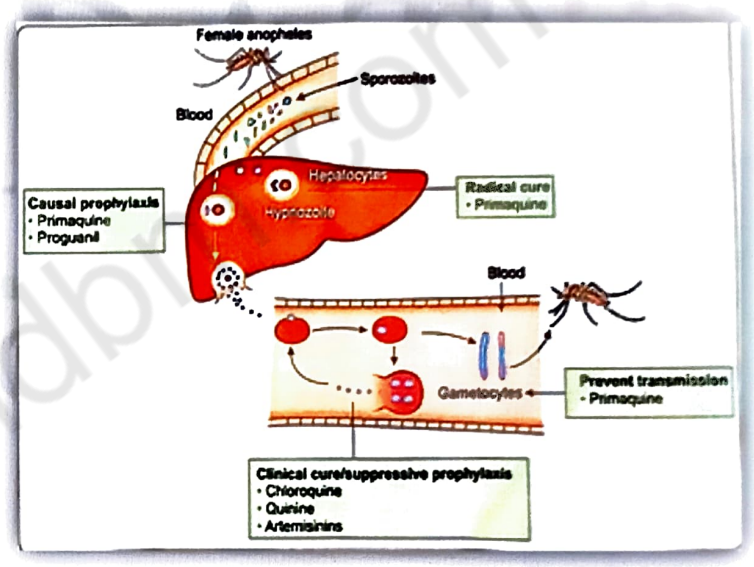
The aims of using drugs in relation to malarial infection are:

- To prevent **clinical attack of malaria (prophylactic).**
- To treat clinical attack of malaria **(clinical curative).**
- To completely eradicate the parasite from the patient's **body (radical curative).**
- To cut down human-to-mosquito transmission **(gametocidal).**

❖ Forms of Antimalarial Drugs

Clinically malarial infections can be controlled by the drugs used in following ways:

1. Causal prophylaxis
2. Suppressive prophylaxis
3. Clinical cure
4. Radical cure
5. Gametocidal



1. Causal prophylaxis

- Drugs **prevent the maturation of or destroy the sporozoites** within the **infected hepatic cell-** thus prevent **erythrocytic invasion**
- **Primaquine-** for all species of malaria but **not used due to its toxic potential**
- **Proguanil-** primarily for **P. falciparum** and not effective **against P. vivax (weak activity), rapid development of resistance**

2.Suppressive prophylaxis

- Schizontocides **inhibit erythrocyte phase** and **prevent the rupture of the infected erythrocytes**, lead to freedom from rigors and pyrexia

- Includes **quinine, chloroquine, proguanil, pyrimethamine,artemicinin and tetracycline**

3.Clinical cure

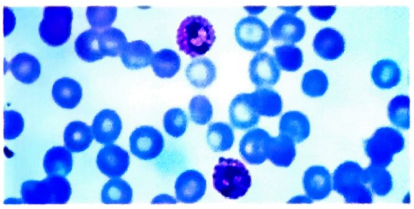
- **Erythrocytic schizontocides** are used to **terminate episodes of malarial fever**

➢ **Fast acting high efficacy drugs**

- **Chloroquine, Quinine, Mefloquine , Halofantrine , Artemicin**
- Used singly to treat malaria fever
- Faster acting, preferably used in **falciparum malaria** where **delayed treatment may lead to death** even if parasites are **clear from blood**

➢ **Slow acting low efficacy drugs**

- **Proguanil, Pyrimethamine, sulfonamides, tetracyclines**
- Used only in combination



4. Radical cure

- Drug attack **exoerythrocytic stage (hypnozoites)** given with clinical curative for the total eradication of the parasite from the patient's body
- **Radical cure of the P. falciparum malaria** can be achieved by suppressive only for **radical cure of P.vivax infection, primaquine and proguanil are effective**

5.Gametocidal

- **Removal of male and female gametes of Plasmodia** formed in the **patient's blood**
- It has no benefit for treated patient.
- **Primaquine and artemisinins** are highly effective against gametocytes of all species

❑ ANTI-MALARIAL AGENTS

These are drugs used for **prophylaxis**, treatment and prevention of relapses of malaria

❑ CLASSIFICATION OF ANTI-MALARIAL AGENTS

CLASS	DRUGS
4-aminoquinolones	Chloroquine, Amodiaquine , Piperaquine
8-Aminoquinolones	Bulaquine, Primaquine, Tafenoquine
Biguanides	Proguanil (Chloroguanide)
Cinchona Alkaloids	Quinine
Napthyridine	Pyronaridine
Diamino Pyrimidines	Pyrimethamine
Napthoquinone	Atovaquone
Amino alcohol	Halofantrine, Lumefantrine
Quinoline methanol	Mefloquine
Antibiotics	Clindamycin , Doxycycline

1. 4-aminoquinolines

Chloroquine, amodiaquine, piperaquine

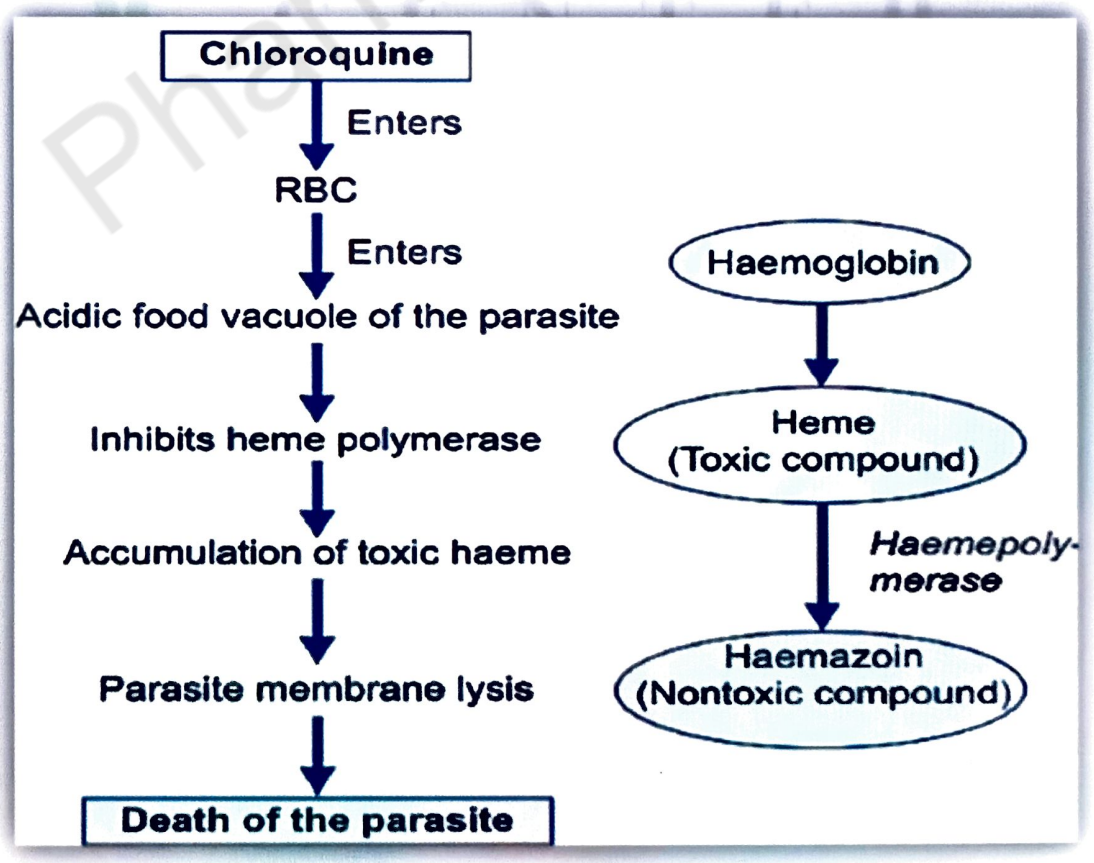
1.Chloroquine

- Chloroquine is a **4-aminoquinoline.**
- It is very effective against P. vivax, P. ovale, P. malariae and **chloroquine-sensitive strains of *P. falciparum.***
- primary drug in the treatment and prevention of malaria since **1940.**

❖ Mechanism of action

- Chloroquine is a basic drug, which is taken up by the **acidic food vacuoles of susceptible plasmodia and inhibits the conversion** of **heme to hemozoin.**
- The **'drug–heme'** complex is **toxic** and **kills** the **parasite.**
- Resistance to chloroquine is common with *P. falciparum.*

Hemoglobin ⟶ Heme (toxic) ⟶ Hemozoin (non-toxic)



❖ Antimalarial Actions

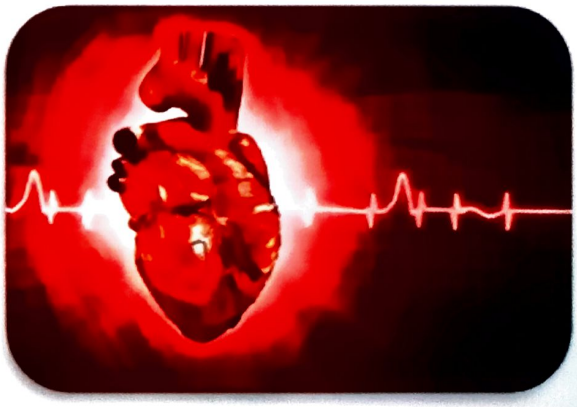
- Chloroquine is a **highly effective blood schizonticide** with activity against all 5 species of the plasmodia.
- It **completely cures sensitive falciparum malaria**.
- It is **rapidly acting** —patients become a febrile in 24–48 hr.
- **Chloroquine** also destroys gametocytes of ***P. vivax, P. ovale*** and ***P. malariae,*** but has **no effect on the hypnozoites in the liver.**
- Chloroquine is safe in pregnancy

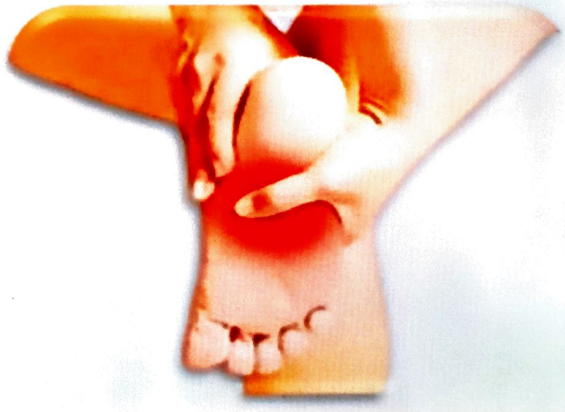
❖ Pharmacokinetics

- Chloroquine is commonly administered by **oral route**, but it can also be given by **I.M.** and **slow I.V. routes.**
- It is well absorbed after **oral** and **parenteral administration.**
- It has **strong affinity for melanin-containing tissues.**
- It gets concentrated in **liver, spleen, kidney, lungs, skin**, etc.
- Chloroquine is **metabolized in the liver** and **slowly excreted in urine.**

❖ Adverse effects

- **Nausea, vomiting, skin rashes, itching, headache and visual disturbances.**
- **Parenteral administration can cause hypotension, confusion, cardiac arrhythmias, convulsions and even cardiac arrest.**
- **Ototoxicity, retinopathy, myopathy, neuropathy**
- **Psychiatric disturbances.**





❖ Uses

1. Chloroquine is the drug of choice for the treatment of **acute attack** of malaria caused by ***P. vivax, P. ovale, P. malariae*** **and chloroquine-sensitive** ***P. falciparum***

2. Other uses are as follows:

- Rheumatoid arthritis
- Extraintestinal amoebiasis
- Discoid lupus erythematosis
- Lepra reaction
- Infectious mononucleosis
- Photogenic reactions
- Malaria
- Giardiasis

✓ Mnemonic :-

RED LIP Mahatma Gandhi

- **Rheumatoid arthritis**
- **Extraintestinal amoebiasis**
- **Discoid lupus erythematosis**
- **Lepra reaction**
- **Infectious mononucleosis**
- **Photogenic reactions**
- **Malaria**
- **Giardiasis**

ii. Amodiaquine

- Similar mechanism of action , pharmacokinetics ,ADR of chloroquinine
- It may be used in **uncomplicated falciparum malaria.**

iii. Piperaquine

- Piperaquine is a bisquinoline congener of CQ
- It is **more active against CQ-resistant P. falciparum** and retains **equal activity against CQ sensitive organisms.**
- Similar mechanism of action , pharmacokinetics ,ADR of chloroquinine

2. 8-Aminoquinolones

Primaquine, Bulaquine, Tafenoquine

i. Primaquine

- Primaquine is a poor **erythrocytic schizontocide.**
- It has **weak action** on *P. vivax*, but blood forms of ***P. falciparum*** are totally insensitive.

- Mechanism of action of primaquine is not known

❖ Resistance

- Acquired **resistance to hypnozontocidal** and **gametocytocidal action** of primaquine has not been observed.

❖ Pharmacokinetics

- Primaquine is readily absorbed after **oral ingestion.**
- It is **oxidized in liver** with a **plasma t½ of 6–8 hrs**
- Excreted in urine within 24 hours.

❖ Adverse effects

- **Epigastric distress**
- **weakness or uneasiness in chest**

❖ Uses

i. **Radical cure of P. vivax and P. ovale malaria**
ii. **Gametocidal effects**
iii. **Terminal prophylaxis**
iv. **Chemoprophylaxis of malaria**
v. **Pneumocystis jiroveci**
vi. **Falciparum malaria**

ii. Bulaquine

- It is an **analog of primaquine** developed in India and is claimed that patients require fewer days **(5 days)** of **antirelapse therapy** and is better tolerated when compared to primaquine.

iii. Tafenoquine

- Tafenoquine is **highly active against vivax hypnozoites.**
- It is **activity against asexual erythrocytic stages of P.v. and P.f.** (including CQ-resistant strains), but clearance of fever and parasitaemia were slow.

- **8-aminoquinoline** is used as a single dose antirelapse drug for vivax malaria.
- Tafenoquine has a long plasma **t½ of 14–19 days**
- (t½ of primaquine is 6–8 hours).

❖ Side effects

- **Incidents of anaemia**
- **Haemolysis**
- **Methaemoglobinemia**

3. Biguanides

i. Proguanil (Chloroguanide)

- It is a relatively **slow-acting erythrocytic schizonticide** For both **P.f. and P.v.**

❖ Mechanism of action

- Proguanil is cyclized in the body to a **triazine derivative (cycloguanil)** which **inhibits plasmodial DHFRase thymidylate synthase** in preference to the **mammalian DHFRase.**

❖ Resistance

- Resistance to proguanil develops rapidly due to mutational changes in the plasmodial **DHFRase-thymidylate synthase enzyme.**
- There is partial cross-resistance between proguanil and pyrimethamine, which is a directly acting plasmodial DHFRase inhibitor

❖ Pharmacokinetics

- Absorption of oral proguanil is slow.
- It is partly **metabolized and excreted in urine.**
- **t½ is 16–20 hr.**

- **Side effects :- Vomiting, Occasional stomatitis , Haematuria, Rashes and transient loss of hair**

❖ Uses

i. vivax malaria

4. Cinchona Alkaloids

i. Quinine

- Quinine is the **levo rotatory alkaloid** obtained from **cinchona bark,** the oldest **antimalarial** still in use.
- Its ***d*-isomer quinidine** is used as an **antiarrhythmic.**
- Quinine is an **erythrocytic schizontocide** for all species of **plasmodia,** but **less effective** and **more toxic than CQ.**
- It is rapidly acting and is often effective even in **chloroquine-resistant strains of *P. falciparum*.**
- It is also **gametocytocidal** for three species of the malarial parasite **except for *P. falciparum***
- Quinidine, the **d-isomer of quinine**, can be used in place of **quinine.**

❖ Mechanism of action

- Quinine may act like chloroquine by **inhibiting the enzyme haeme polymerase.**

❖ Pharmacokinetics

- Quinine is rapidly and completely absorbed **orally.**
- It is **70% bound to plasma proteins**, especially **α1 , acid glycoprotein** which increases during acute malarial infection.
- CSF concentrations are **low.**
- Metabolized in the liver by **CYP3A4** and excreted in **urine** with a **t½ of 10–12 hours**

❖ Adverse effects

- **Gastric irritant** —causes **nausea, vomiting and epigastric pain**

Cinchonism

- A large single dose or higher therapeutic doses taken for a few days produce a syndrome called **'cinchonism'.**
- It consists of **ringing in ears, nausea, vomiting** (due to both gastric irritation and CTZ stimulation), **headache, mental confusion, vertigo, difficulty in hearing** and **visual defects** (due to direct **neurotoxicity** as well as constriction of **retinal** and **auditory vessels**).
- **Diarrhoea, flushing.**

❖ Uses

1. **Malaria**

a) Uncomplicated resistant falciparum malaria

Quinine may be used **orally** as an alternative to **ACT in uncomplicated CQ-resistant falciparum Malaria**

b) **Complicated falciparum malaria and cerebral Malaria**

- Quinine is used in the treatment of **resistant falciparum malaria and cerebral malaria**
- Quinine also has **mild analgesic** and **antipyretic activity.**
- It is a **myocardiac depressant**.
- Quinine is a **skeletal muscle relaxant.**

5. Napthyridine

Pyronaridine

i. Pyronaridine

- Pyronaridine is a **water soluble .**
- **Mannich base** resembling structurally to **amodiaquine .**
- It is an **erythrocytic schizontocide with high efficacy**
- Mechanism of action similar to CQ.

- It is **active against both CQ-sensitive and CQ-resistant *p. Falciparum*.**
- The onset of action is slower and duration long.
- It is **concentrated in RBCS** and metabolized with a terminal **t½ of 7 days.**
- **Weak analgesic-antipyretic** action is produced at **higher doses**

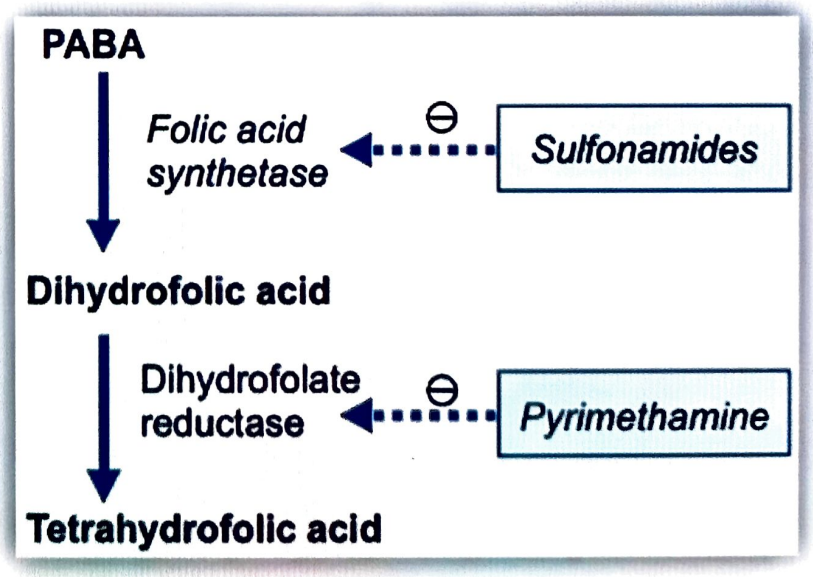
6. Diamino Pyrimidines

i. Pyrimethamine

- It is a directly acting **inhibitor of plasmodial DHFRase** (does not require conversion to a cyclic triazine, as is the case with proguanil).

❖ Mechanism of action

- Pyrimethamine is a **dihydrofolate reductase inhibitor.**
- Pyrimethamine preferentially **binds plasmodial dihydrofolate reductase** with about 2000 times higher affinity than mammalian enzymes.
- When **sulfadoxine is given with Pyrimethamine** , together they produce sequential **blockade resulting in inhibition of nuclear division.**
- This mode of action makes them slow acting.
- The **combination** (SP) **is synergistic** and the development of resistance is slower.
- Pyrimethamine can also be combined with dapsone which acts like sulfonamides



❖ Resistance

- P. falciparum has to a large extent and P. vivax to some extent developed resistance to **Pyrimethamine + sulfadoxine** and the resistance is quite widespread.
- **Mutation in DHFR and folate synthetase** leads to resistance

❖ Pharmacokinetics

- Absorption of Pyrimethamine from g.i.t. is good but slow.
- Certain organs like **liver, spleen, kidney** and **lungs** concentrate pyrimethamine.
- It is metabolized and **excreted in urine** with a **t½ of 4 days.**
- Prophylactic concentrations remain in blood for 2 weeks

❖ Adverse effects

- Nausea and rashes.
- Folate deficiency is rare; **megaloblastic anaemia** and **granulocytopenia** May occur with higher doses, especially in those with **marginal folate stores.**

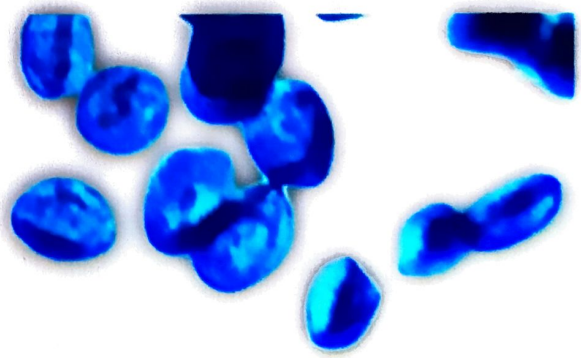
❖ Uses

i. Pyrimethamine is used only in combination with a **sulfonamide as sulfa-Pyrimethamine (S/P)** or dapsone (see below) for treatment of **falciparum malaria.**

ii. **Chemoprophylaxis**

iii. **Toxoplasmosis**

iv. **Pneumocystosis**



7. Napthoquinone

i. Atovaquone

- This synthetic **naphthaquinone** is a rapidly acting **erythrocytic schizontocide** as well as **active against Pre erythrocytic stage of *P. falciparum* and other plasmodia.**
- **Pneumocystis jiroveci** and **Toxoplasma gondii** are also susceptible to atovaquone. It collapses plasmodial mitochondrial membranes and interferes with ATP production.
- **Proguanil potentiates** its antimalarial action and prevents emergence of resistance..
- Atovaquone is used as a **second line drug** for opportunistic infections with ***P. jiroveci* and *T. gondii*** in AIDS patients.

❖ Side effects—

- **Diarrhoea, vomiting.**
- **Headache, rashes, fever, and is contraindicated during pregnancy.**

8. Amino alcohol

Halofantrine & Lumefantrine

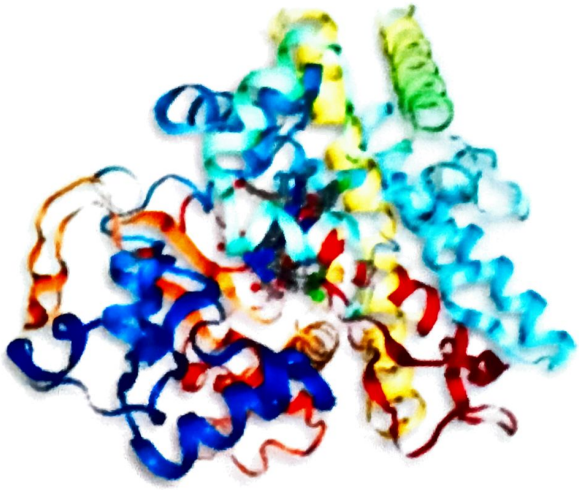
- **Halofantrine** and **lumefantrine** are **schizontocidal against erythrocytic** forms of all *plasmodium* species including MDR strains of p. Falciparum.
- Mechanism of action is not exactly known but it is thought to act like **chloroquine by inhibiting heme polymerase in the parasite.**
- Binds to haeme and this complex may be damaging the parasite membranes

❖ Pharmacokinetics

- Lumefantrine is highly **lipophilic; absorption** starts after 2 hours

Of **ingestion** and **peaks at 6–8 hours.**

- Antimalarial action is **slower than CQ.**
- **Plasma protein binding is 99%,**
- It is **metabolized by CYP3A4.**
- Excreted in the **stools.**
- **Terminal t½ is 2–3 days,.**

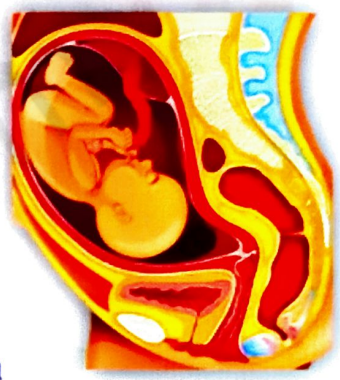


❖ Adverse effects

i. Halofantrine can cause **gastrointestinal disturbances, headache, rashes, pruritus and Cardiotoxicity including prolongation of QT interval and arrhythmias.**

ii. It is also **contraindicated in pregnancy.**

iii. Lumefantrine **is less toxic.**



❖ Uses

i. Halofantrine was used in **MDR strains of falciparum**

9.Quinoline methanol

i. Mefloquine

- Mefloquine (MQ) is a **quinoline methanol.**
- In a single dose given orally **mefloquine is highly effective against erythrocytic** forms of the malaria parasite including the **multi-drug resistant (MDR) strains of *P. falciparum.***
- Mefloquine gets concentrated in the **acidic vacuoles** of the parasite.

❖ Mechanism of action :- inhibiting heme polymerase in the parasite.

- Some strains of **P. falciparum** have developed **resistance to mefloquine in parts of Asia.**

❖ Pharmacokinetics

- It is **well absorbed when given orally**

- It is **not given parenterally.**
- It is **excreted through the gut.**

❖ Adverse effects

- **Nausea, vomiting, dizziness, confusion, headache, abdominal pain, sleep disturbances** are common. .
- CNS effects like **ataxia, disorientation, visual and auditory disturbances, seizures, encephalopathy .**
- when given IV. Mefloquine can **depress cardiac conduction** resulting in **bradycardia** and **arrhythmias.**

❖ Uses

i. **Uncomplicated MDR strains of falciparum malaria —mefloquine used with artesunate.**

ii. **Prophylaxis of MDR malaria in travellers— Mefloquine 250 mg/week.**

❖ Contraindications

- Mefloquine should be avoided in patients with **arrhythmias, conduction defects in the heart, epileptics, and in psychiatric patients.**
- Mefloquine should not be combined with **quinine** and **halofantrine.**

10.Antibiotics

Clindamycin , Doxycycline

i. Clindamycin

- **Clindamycin** has **activity against erythrocytic forms** of the malarial parasite—may be used as an alternative to doxycycline following administration of **quinine** or **artemisinin.**
- Clindamycin against all species of plasmodia including **multidrug resistant strains of p. Falciparum**
- **Liver stages** and **gametocytes are not affected**

- Clindamycin is a **second choice drug to doxycycline** for adding to quinine or to artesunate for the **treatment of multidrug resistant falciparum malaria, or CQ-resistant vivax malaria**
- it can be used in **children and pregnant women**. However, **clindamycin is not used for prophylaxis of malaria**,

ii. Doxycycline

- This antibiotic has **slowly acting** and **weak erythrocytic schizontocidal** action against all plasmodial species including ***P. falciparum*** **resistant to CQ, MQ and S/P.**
- Doxycycline can also be used in the **chemoprophylaxis of falciparum malaria**
- **Gametocytes and vivax hypnozoites are also not killed.**
- Doxycycline is **never used alone** to treat malaria, but only in **combination with quinine** for the **treatment of CQ-resistant malaria (falciparum or vivax)**
- **Doxycycline 200 mg/day** has also been combined with **artesunate to treat Mefloquine/chloroquine/S/P-resistant**
- **Doxycycline 100 mg/day** is used as a **2nd line prophylactic for short-term travellers to CQ-resistant *P. falciparum*** areas.
- It is not to be given to children and pregnant women.

iii. Tetracycline has **weak activity against erythrocytic forms** of the malaria parasites.

iv. Sulfadoxine is used in **combination with Pyrimethamine.**

v. Fluoroquinolones and **azithromycin** have also been found to have **antimalarial activity.**

11.Sesquiterpine lactone

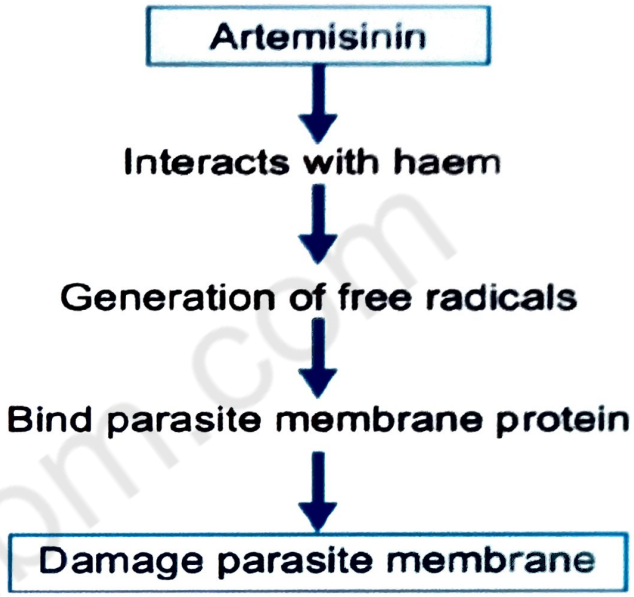
Artesunate, Artemether, Arteether, Dihydroartemisinin , arterolane

❖ Artemisinin

Artemisinin, a highly bitter compound, is a **sesquiterpene lactone** obtained from the plant **Artemisia annua**

❖ Mechanism of action

Artemisinin **interacts with haem** resulting in the **generation of free radicals** that **bind to the macromolecules** as well as **membrane proteins and damage the macromolecules and the parasite membrane.**



- Artemisinin is a potent, rapidly acting, **erythrocytic schizonticide effective** against all the 5 plasmodial species, including MDR P. falciparum.
- It is also **effective against gametocytes (but not the liver stages).**
- It is useful in **cerebral malaria.**

❖ Pharmacokinetics

Artemisinin is poorly soluble in water and oil.

The derivatives are suitable for administration by different routes.

- ✓ **Artesunate — water soluble— oral, IM, IV, rectal.**
- ✓ **Artemether —lipid soluble— oral, IM and rectal.**
- ✓ **Dihydroartemisinin —water soluble—oral.**
- ✓ **Arteether—longer—IM.**

❖Adverse effects

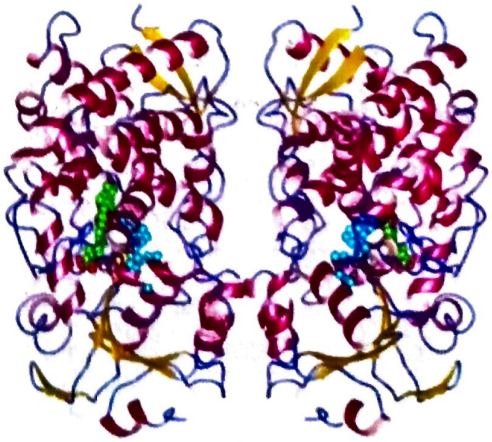
- **Mild gastrointestinal symptoms, fever, and bradycardia.**
- They can also cause **itching, rashes, other allergic reactions** and rarely **raised serum Transaminases.**
- **Bone marrow toxicity with anaemia, haemolysis, neutropenia** and **decrease in reticulocyte count**

i. Artesunate

- The sodium salt of artesunate is **water-soluble** and is administered by **oral, I.M. or I.V. routes.**
- After **oral ingestion**, absorption is incomplete but fast, reaching peak in **<60 min.**
- It is rapidly converted to the **active metabolite Dihydroartemisinin** (DHA) .
- The **t½ of DHA is 1–2 hours.**
- Metabolism by **CYP2B6** and **CYP3A4.**
- Intravenous artesunate is the **1st choice drug for severe malaria.**

ii. Artemether

- It is **lipid-soluble** and is administered **orally or I.M., But not I.V.**.
- **First pass metabolism** and is **converted to DHA**
- Metabolism by **CYP3A4** .
- **t½ of 5–8 hours.**
- For **severe malaria, it is a 2nd choice option when I.V.**
- Oral artemether is used in **combination with lumefantrine** .



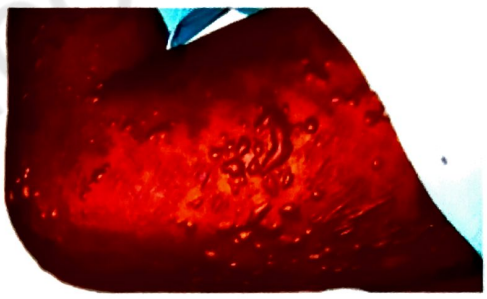
iii. Arteether

- This compound is available for **I.M.**
- Administration only to **adults for complicated malaria**.
- Because of its longer elimination **t½ (23 hours)**.
- It is advised in a **3 day schedule**, but is considered **less dependable** in **severe/complicated malaria.**

12. Sulfonamide and Sulfone

i. Sulfadoxine and sulfamethopyrazine

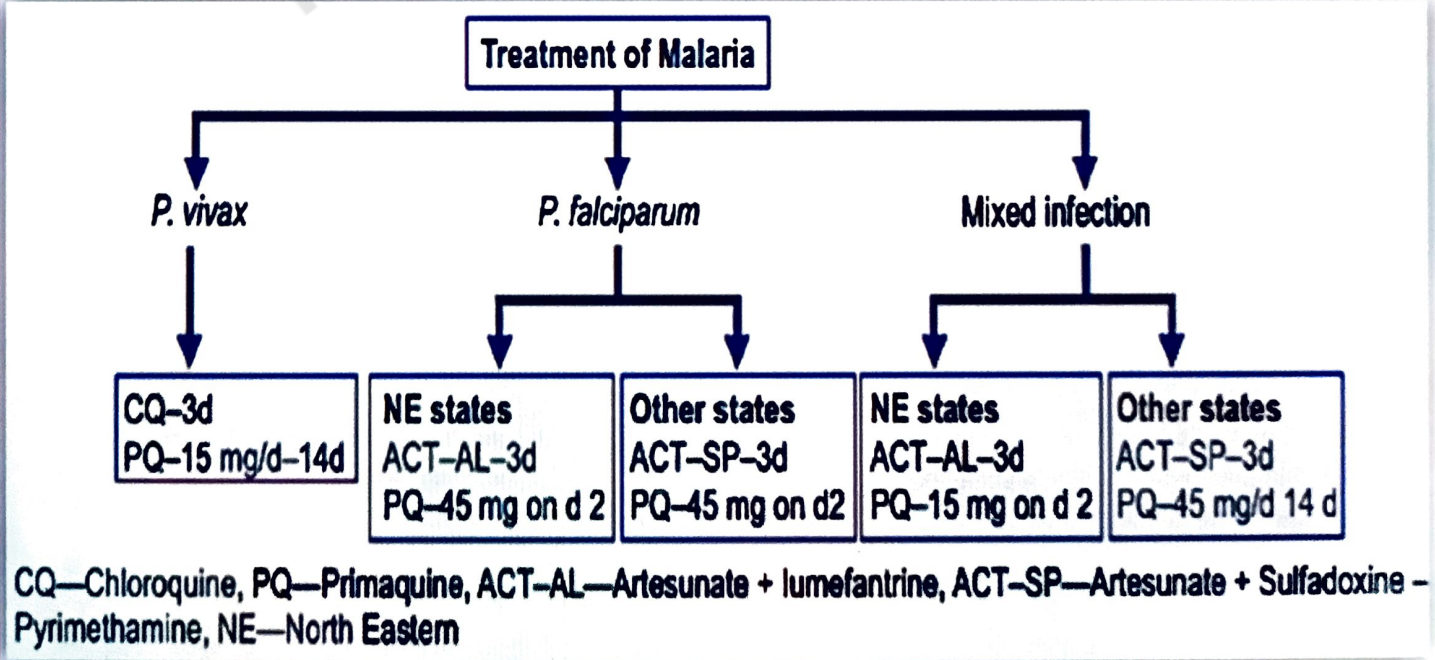
- Sulfadoxine & sulfamethopyrazine **ultralong acting** sulfonamides
- They attain **low blood concentrations**, but are able to synergise with pyrimethamine which also has **long t½.**



❖ Adverse effects

- **Exfoliate dermatitis**
- **Stevens-johnson syndrome**
- Due to the sulfonamide. Therefore, use is restricted to single dose treatment of **uncomplicated CQ resistant falciparum malaria**.

❑ TREATMENT OF MALARIA



CQ—Chloroquine, PQ—Primaquine, ACT–AL—Artesunate + lumefantrine, ACT–SP—Artesunate + Sulfadoxine – Pyrimethamine, NE—North Eastern

TREATMENT AND PROPHYLAXIS OF MALARIA (NATIONAL GUIDELINES ACCORDING TO NBVDCP)

Treatment of Uncomplicated malaria			
Parasite	Males and Non-pregnant females	Pregnancy (1st trimester)	Pregnancy (2nd and 3rd trimester)
P. vivax (or P. ovale)	Chloroquine+ Primaquine[a,b]	Chloroquine	Chloroquine
P. falciparum (or P. malariae)	ACT + Primaquine[d]	Quinine	ACT[c]
Mixed	ACT + Primaquine[d]	Quinine	ACT[c]
Treatment of severe/complicated malaria			
P. falciparum	Artesunate followed by oral ACT	Artesunate followed by oral ACT	Artesunate followed by oral ACT

WHO Recommended ACTs include

Artemether-Lumefantrine	Artesunate- Amodiaquine
Artesunate- Mefloquine	Artesunate-Sulfadoxine-Pyrimethamine
Dihydroartemisinln - Piperaquine	

CHEMOPROPHYLAXIS OF MALARIA

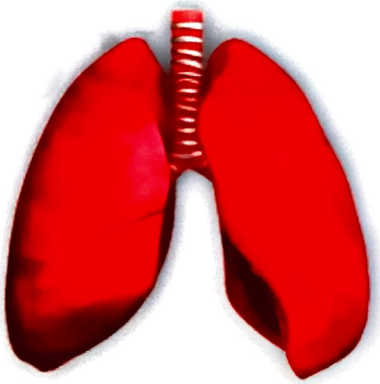
Short-term(< 6weeks)	Doxycycline
long-term (> 6 weeks)	Mefloquine'

ANTI-AMOEBIC DRUGS

Points to be covered in this topic

1. INTRODUCTION
2. CLASSIFICATION OF ANTI- AMOEBIC DRUGS
3. MOA,PHARMACOKINETICS ,ADR,USES OF DIFFERENT CLASS OF DRUGS
4. TREATMENT OF ANTI- AMOEBIC DRUGS

❑ INTRODUCTION



- Amoebiasis caused by the protozoan *Entamoeba Histolytica.*
- It spreads by faecal contamination of **food and water.**
- Though it primarily affects colon, other organs like **liver**, **lungs** and **brain** are the secondary sites.

- Acute amoebiasis is characterised by **bloody mucoid stools** and **abdominal pain.**
- **Infective stage :- Trophozoite**
- Chronic amoebiasis manifests as **anorexia**, **abdominal pain**, **intermittent diarrhoea** and **constipation.**

❖ Life cycle of Entamoeba histolytica

➢ Entamoeba histolytica exists in two forms:

1. **Cysts form** (That can survive out side the body).
2. **Trophozoites form** (That are labile and don't persist outside the body).

✓ Life cycle consists of following steps:

1. **Ingestion of cysts :-** Cysts are ingested through feces, contaminated food or water.
2. **Formation of trophozoites:-** Cysts are passed into the lumen of intestine, where the trophozoites are liberated.

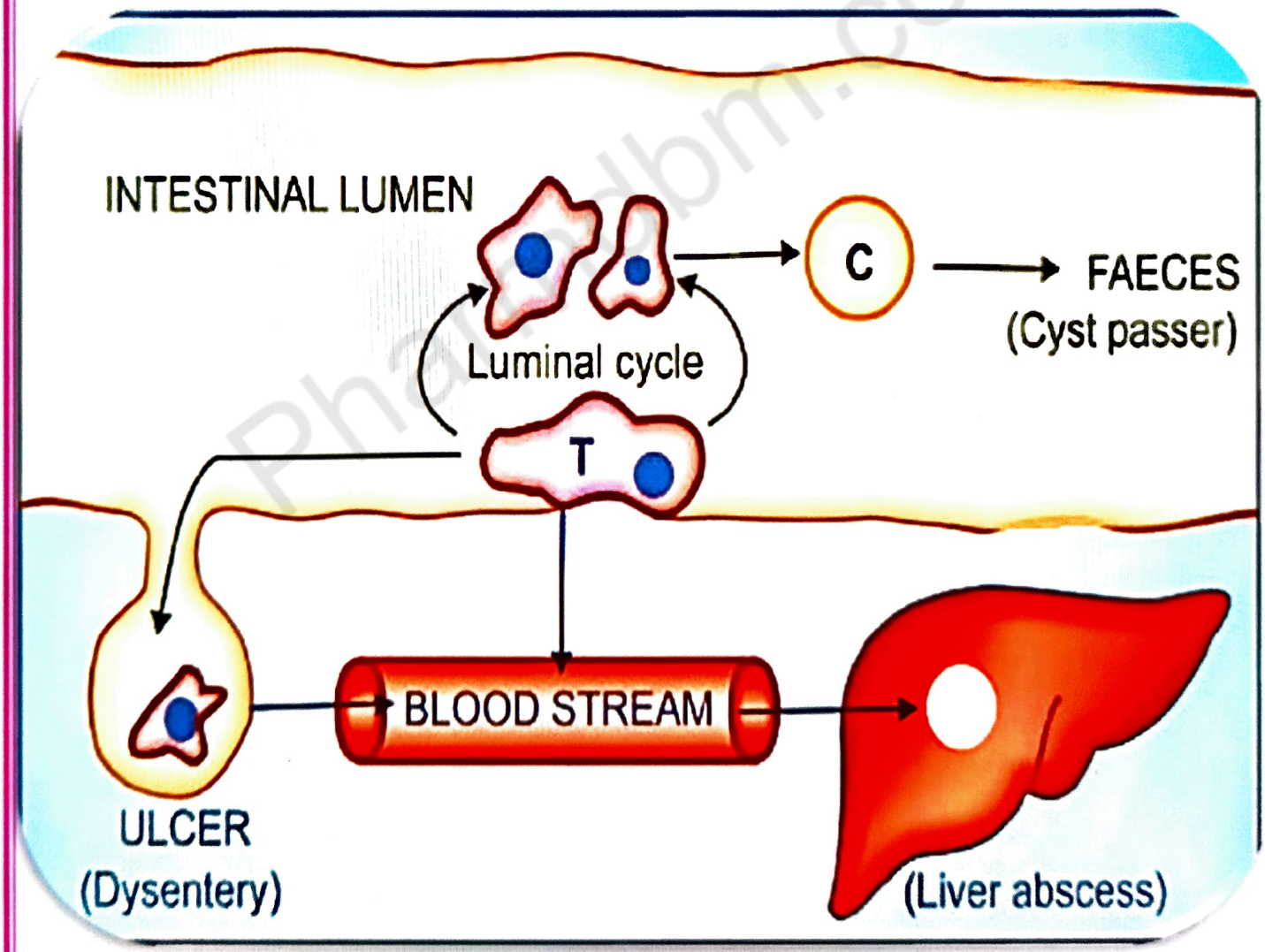


Fig :- The luminal cycle and invasive forms of amoebiasis. T-trophozoite , C-cyst

3. Penetration and multiplication of trophozoites

- Trophozoites are **penetrated in intestinal wall** and **multiply within colon wall.**
- They either invade and ulcerate the mucosa of large intestine or simply feed on intestinal bacteria.

4. Systemic invasion

- **Large numbers of trophozoites** within **the colon wall** can also lead to **systemic invasion** and caused **liver abscess.**

5. Cysts discarded

- The trophozoites within the intestine are slowly carried toward the rectum, where they return to **cyst form** and are **excreted in feces**

➢ Classification of amoebicidal drugs

According to the site where the drug is effective the amoebicidal drugs are classified as:

i. **Luminal amoebicides** (Act on parasite in the **lumen of bowel)**

ii. **Systemic amoebicides** (Against amebas in **intestinal wall & liver)**

iii. **Mixed amoebicides** (Against both the **luminal and systemic form of diseases)**

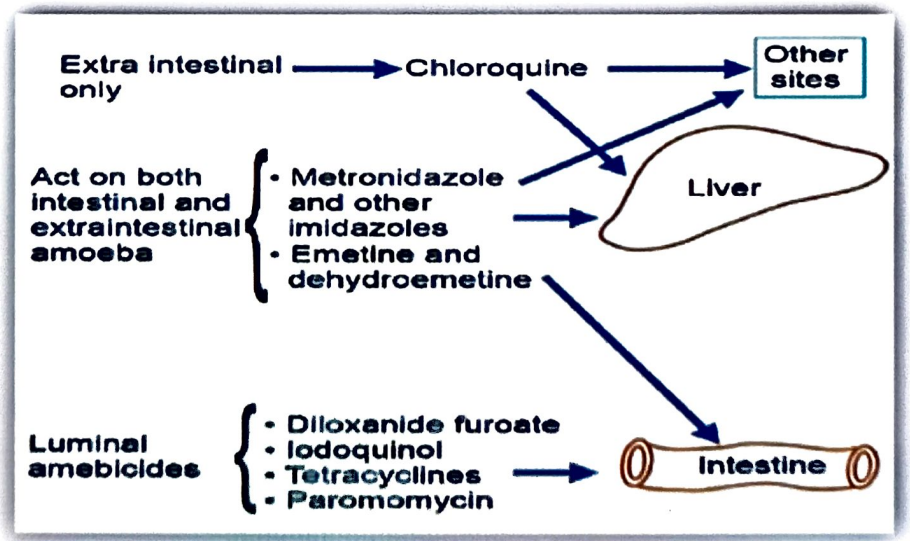


Fig :- Sites of action of antiamoebic drugs

❑ CLASSIFICATION ON ANTIAMOEBIC DRUGS

CLASS	SUB-CLASS		DRUGS
Tissue amoebicides	For intestinal + extra intestinal Amoebiasis	Nitroimidazole	Metronidazole, Tinidazole, Secnidazole Ornidazole Satrinidazole
		Alkaloids	Emetin, Dehydroemetin
	For extra intestinal Amoebiasis only	4-aminoquinoline	Chloroquine
Luminal amoebicides	Amides		Diloxanide furoate Nitazoxanide
	8- hydroxyquinolines		Quiniodochlor Diiodohydroxyquin
	Antibiotics		Tetracyclines Paromomycin

I. TISSUE AMOEBICIDES

a. Nitroimidazole:- Metronidazole, Tinidazole, Secnidazole, Ornidazole, Satrinidazole

i. Metronidazole

- It is the prototype **Nitroimidazole** introduced in **1959** for trichomoniasis.
- It has **broad-spectrum cidal activity** against anaerobic protozoa, including **Giardia lamblia, E. histolytica, Trichomonas vaginalis**
- It helps in the extraction of guinea worm **(Dracunculus medinensis)**

❖ Mechanism of action

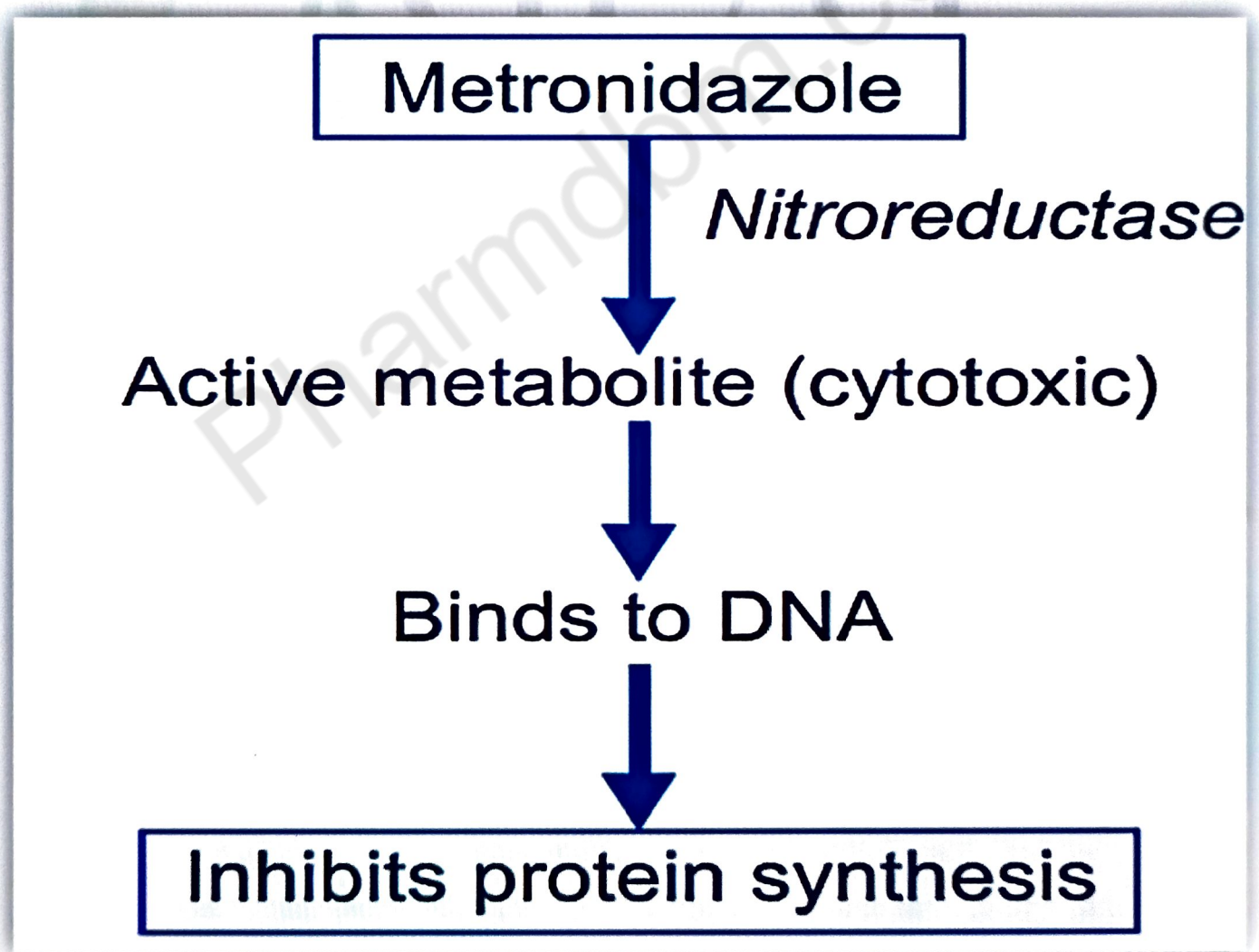


Fig :- Mechanism of action of Metronidazole

- Metronidazole is a **prodrug**.
- Microorganisms including **anaerobic bacteria** and certain protozoa reduce the nitro group of metronidazole by a **nitroreductase** and convert it to a **cytotoxic derivative**.
- This derivative **binds to DNA and inhibits protein synthesis**.
- **Aerobic bacteria lack this nitroreductase** and are, therefore, not susceptible to metronidazole.

❖ Pharmacokinetics

- Metronidazole is **well-absorbed,** is widely distributed, penetrates all tissues and reaches adequate concentrations in the **CSF.**
- It has a **plasma t½ of 8 hr.**
- It is metabolised in the **liver** by **oxidation** and **glucuronide conjugation.**

❖ Adverse effect

- **Anorexia, abdominal crams, alcohol intolerance**
- **Glossitis & giddiness**
- **Taste - Metallic, thrombophlebitis**
- **Headache, stomatitis, furry tongue; dizziness ,steven -Johnson syndrome**
- **Insomnia, ataxia, vertigo, carcinogenic, mutagenic. Reddish brown colour urine**

❖ Drug interactions

- Metronidazole potentiates the anticoagulant effect of warfarin and other oral **coumarins by inhibiting** their **metabolism.**
- There is **prolongation of prothrombin time**; hence, **reduction of warfarin** dose may be needed.
- Metronidazole may potentiate **lithium toxicity by decreasing** the renal clearance of lithium.

❖ **Uses**

i. **Metronidazole is used in the treatment of alveolar abscess, pericoronitis, periodontitis, etc**
ii. **Amoebiasis**
iii. **Giardiasis**
iv. **Trichomonas vaginitis**
v. **Anaerobic bacterial infections Anaerobic**
vi. **Acute necrotizing ulcerative gingivitis (ANUG)**
vii. **Pseudomembranous enterocolitis**

ii. Tinidazole

Tinidazole is a second-generation nitroimidazole that is similar to metronidazole in spectrum of activity, absorption, adverse effects and drug interactions.

- Metabolism is slower; **t½ is ~12 hr.**
- Duration of action is longer; dosage schedules are simpler.
- Thus, it is more suited for **single dose or once daily therapy**.

❖ **Side effects** :- **metallic taste (2%), nausea (1%), rash (0.2%).**

iii. Secnidazole

- Metronidazole, secnidazole is a **Nitroimidazole derivative.**
- **Plasma t½ of 17–29 hours**
- The spectrum, side effects and mechanism of action of secnidazole are similar to metronidazole.
- **Secnidazole** is longer-acting and can be given as a **single 2 g dose** for most indications of metronidazole

iv. Ornidazole

- It has activity similar to metronidazole, but it is slowly metabolized—has **longer t½ (12–14 hr).**

- Dose and duration of regimens for **amoebiasis, giardiasis, trichomoniasis, anaerobic infections** and **bacterial vaginosis** resemble those for tinidazole.
- **In chronic intestinal amoebiasis and asymptomatic cyst passers 0.5 twice daily for 5 to 7 days** used.

v. Satrinidazole

- **Satranidazole** is **more potent** than **tinidazole** and also does not cause **disulfiram-like antabuse reactions.**

❖ **Side effect :- nausea, metallic taste and peripheral neuropathy.**

I (b) Alkaloids

b. Alkaloids :- Emetine, Dehydroemetin

i. Emetine

- It is an alkaloid from ***Cephaelis ipecacuanha***.
- Emetine is a potent and **directly acting amoebicide—kills trophozoites** but has no effect on cysts.

❖ Mechanism of action

- It acts by **inhibiting protein synthesis in amoebae** by arresting intraribosomal translocation of **tRNA-amino acid complex.**

❖ Pharmacokinetics

- Emetine **cannot be given orally** because it will be **vomited out.**
- It is administered by **S.C. or I.M. injection.**

❖ Adverse effect

- Nausea, vomiting (due to CTZ stimulation and gastric irritation)

- **Abdominal cramps, diarrhoea, weakness, stiffness of muscles, myositis Hypotension , ECG changes** and **myocarditis.**
- Cardiotoxicity including **arrhythmias, hypotension and cardiac failure** can occur.

❖ Uses

- Emetine is used for acute amoebic dysentery or for **amoebic liver abscess.**
- A **luminal amoebicide** must always follow **emetine to eradicate the cyst forming trophozoites.**
- It is also effective in **liver fluke infestation**

ii. Dehydroemetin

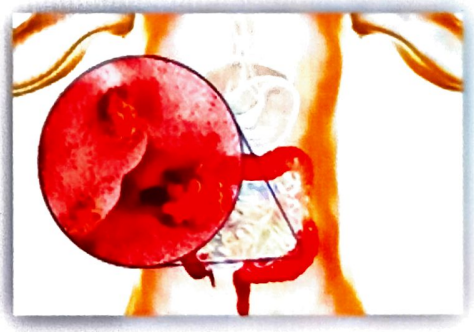
- It is **equally effective but less cumulative and less toxic to the heart** Thus, it is usually preferred over emetine.
- **Similar to emetine.**

2. For extra intestinal Amoebiasis only

4-aminoquinoline :- Chloroquine

i. Chloroquine

- **Chloroquine attains high concentration in the liver,** is directly toxic against trophozoites
- It is useful in **hepatic amoebiasis.**
- It kills trophozoites of **E. histolytica**



❖ Pharmacokinetics

- chloroquine is completely **absorbed from the small intestines,** it is not **effective against amoebae in the colon.**
- It is used **(300 mg base/day for 21 days)** as an alternative to metronidazole in hepatic amoebiasis.

II. LUMINAL AMOEBICIDES

1. Amides :- Nitazoxanide , Diloxanide furoate

i. Nitazoxanide

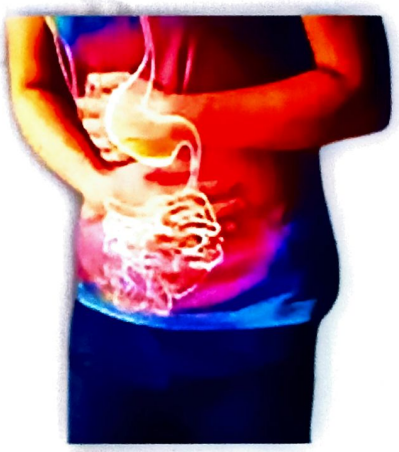
- Salicylamide congener of the **anthelmintic niclosamide**.
- Introduced for the treatment of **giardiasis** and **cryptosporidiosis** is also active against many other protozoa including e. **Histolytica, T. Vaginalis, and helminths , ascaris, H. Nana, etc.**

❖ **Mechanism of action** :- It is a **prodrug** which on **absorption is converted to the active form tizoxanide**, an **inhibitor of PFOR enzyme** that is an essential **pathway of electron transport energy metabolism in anaerobic organisms.**

❖ **Pharmacokinetics**

- Tizoxanide generated from nitazoxanide is **glucuronide conjugated** and excreted in **urine** as well as **bile** . Metabolized in **liver**

❖ **Adverse effect**



- **Abdominal pain**
- **Vomiting**
- **Headache**
- **Greenish tint to the urine**

❖ **Uses**

- It is also indicated in **giardiasis**, and may be used as an alternative **luminal amoebicide in amoebic dysentery.**
- Nitazoxanide is the most effective drug for **Cryptosporidium parvum** infection

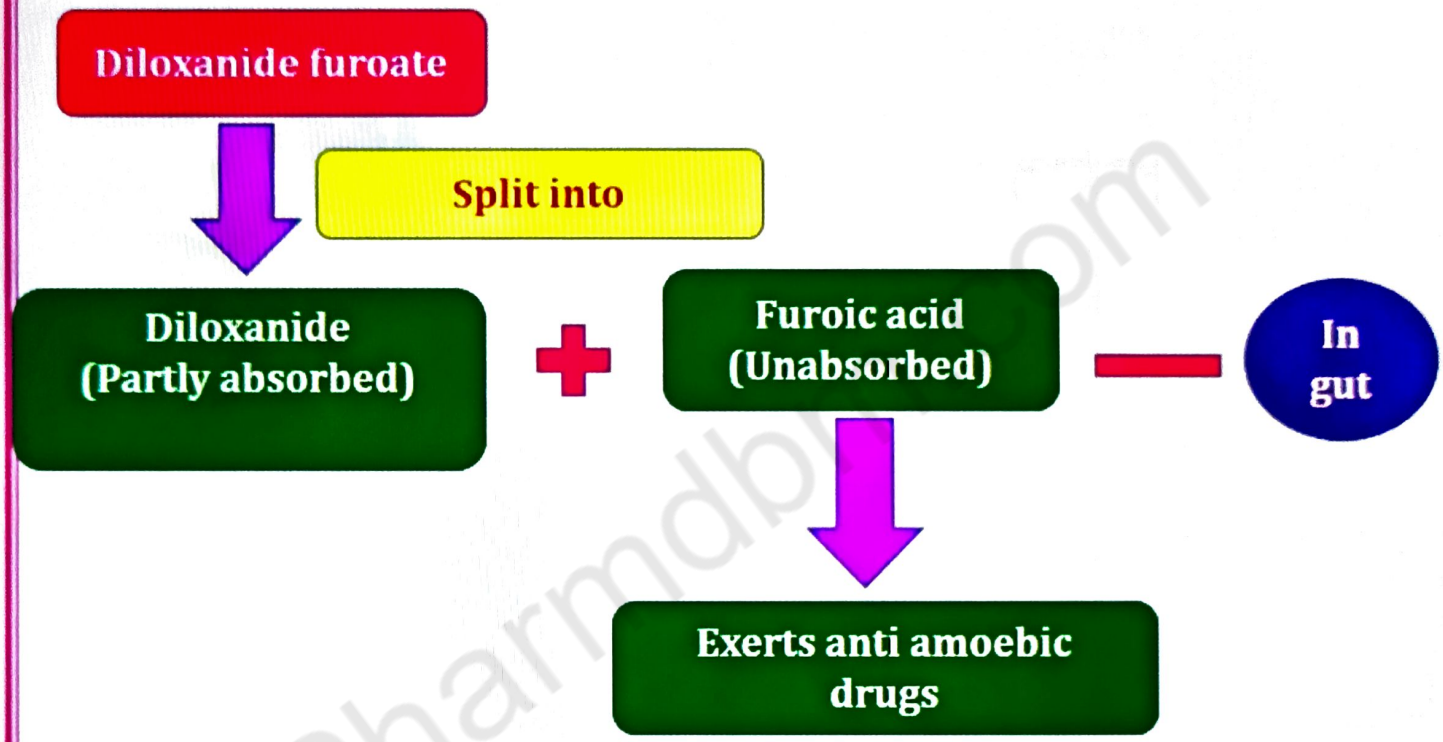
❖ **Contraindication** :- **should be avoided in pregnancy.**

ii. Diloxanide furoate

It is a **highly effective luminal amoebicide** which **directly kills trophozoites** responsible for **production of cysts.**

❖ Mechanism of action

- Diloxanide furoate is directly amoebicidal.
- It is split in the intestines to diloxanide and furoic acid.
- It acts on the parasite in the intestines but not in the tissues.



❖ Pharmacokinetics

- It is primarily metabolized by **glucuronidation**
- Excreted in **urine.**

❖ Side effects :- Flatulence, occasional nausea, itching and rarely urticaria

❖ Uses

- Diloxanide is used along with a nitroimidazole for the cure of **amoebiasis, as diloxanide eradicates cysts**
- It can be used alone in **asymptomatic cyst passers, mild intestinal amoebiasis.**

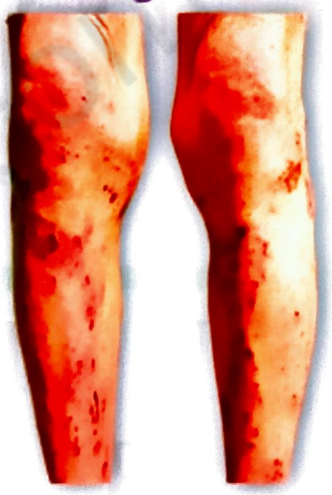
2. 8- hydroxyquinolines :- Quiniodochlor , Diiodohydroxyquin

i. Quiniodochlor & Diiodohydroxyquin

- **8-hydroxyquinolines** including **Quiniodochlor** and **Iodoquinol.**
- They are **active against Entamoeba Giardia, Trichomonas. Giardia,**
- **Trichomonas, some fungi (dermatophytes, Candida)**
- They **kill the cyst forming amoebic trophozoites in the intestine**, but do not have tissue **amoebicidal action.**

❖ **Pharmacokinetics**

- The absorbed fraction is **conjugated in liver with glucuronic acid** and sulfate
- **Excreted in urine; t½ is ~12 hours.**



❖ **Side effects**

i. **Nausea**

ii. **loose and green stools**

iii. **pruritus**

❖ **Uses**

- Used for the **prophylaxis** and treatment of nonspecific **diarrhoeas, traveller's diarrhoea, dietary indiscretion, etc**
- Other uses **are—giardiasis , local treatment of monilial and trichomonas vaginitis, fungal and bacterial skin infections.**

3. Antibiotics :- Tetracyclines ,Paromomycin

i. Tetracyclines

- Tetracyclines have modest **direct inhibitory action on Entamoeba.**
- Tetracyclines are incompletely **absorbed in the small intestine**, reach the **colon in large amounts and inhibit the bacterial flora** with which entamoebae live symbiotically

- The **luminal cycle** with little **mucosal invasion**.

ii. Paromomycin

- Paromomycin is active against many protozoa like **emtamoeba, giardia, cryptosporidium, trichomonas, leishmania** and some tape worms, in addition to having antibacterial spectrum like neomycin.
- In the **1960s** an oral formulation of paromomycin was introduced as a **luminal amoebicide.**
- Paromomycin is being **used in resistant kalaazar** .
- **Orally** administered paromomycin acts only in the **gut lumen**.
- It is neither absorbed nor degraded in the intestines.
- Eliminated unchanged in the **faeces.**
- Paromomycin is an efficacious **luminal amoebicide,**
- Paromomycin is an alternative drug for **giardiasis,** especially during **1st trimester of pregnancy** when metronidazole and other drugs are contraindicated.

❖ Side effects

- **Nausea, vomiting, Abdominal cramps, diarrhoea; rarely rashes, renal impairment**

❑ TREATMENT OF AMOEBIASIS

Acute intestinal amoebiasis: One of the following can be given.

- ✓ **Metronidazole 400–800 mg TDS for 5–7 days or 2.4 g OD for 3 days**
- ✓ **Tinidazole 2 g OD for 3 days**
- ✓ **Secnidazole 2 g single dose**

Alternatively **ornidazole/satranidazole/ benznidazole** may be used.

diloxanide furoate 500 mg TDS for 10 days to eradicate the cysts.

2. Chronic amoebiasis and asymptomatic cyst passers

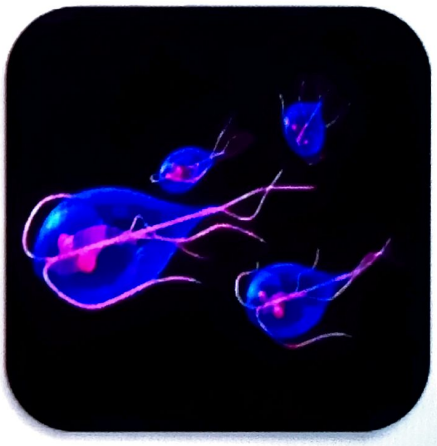
- ✓ Diloxanide furoate 500 mg TDS for 10 days or tetracycline 250 mg QID for10 days.
- ✓ The alternatives are iodoquinol (650 mg TDS for 21 days) or paromomycin (10 mg/kg TDS for 7 days).

3. Hepatic amoebiasis

- A course of **metronidazole 600– 800 mg TDS for 10 days or tinidazole** are the **first-line drugs.**
- A course of **diloxanide furoate 500 mg TDS for 10 days** should follow in order to eradicate the cysts.

DRUGS FOR GIARDIASIS

Many drugs useful in **amoebiasis** are also effective in **giardiasis**.



1. Metronidazole

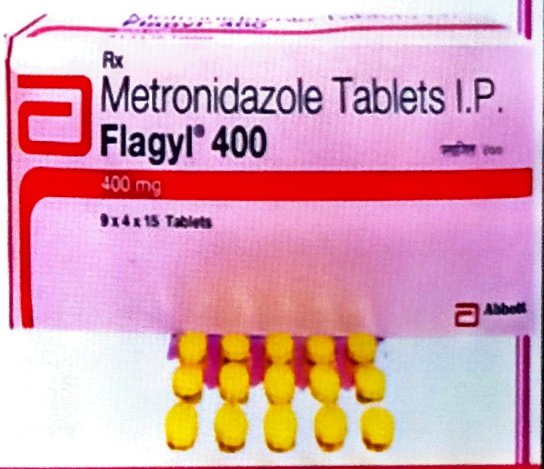
400 mg TDS (children 15 mg/kg/day) for 5–7 days or 2 g daily for 3 days,

Or

Tinidazole 0.6 g daily for 7 days or 2 g single dose,

Or

Secnidazole 2 g single dose



These may be considered as the drugs of choice, but ~ **10% patients may not be cured**, and a **second course or alternative drug** may be needed.

2. Nitazoxanide

- This **prodrug of the PFOR enzyme inhibitor tizoxanide** has become available for the treatment of diarrhoea and dysentery caused by **Cryptosporidium parvum , Giardia lamblia and E. histolytica.**
- The dosage schedule is **convenient—500 mg (children 7.5 mg/kg) twice daily for 3 days. Efficacy (~80% cure)** approaches that of metronidazole.

3. Quiniodochlor 250 mg TDS for 7 days

4. Furazolidone

- It is a **nitrofuran compound** active against many **gram-negative bacilli** including **salmonella and shigella, also giardia** and **trichomonas.**

✓ For **giardiasis 100 mg TDS for 5–7 days has** been used, but is inferior to metronidazole or tinidazole.

- It has also been used in **bacterial enteritis,** but is not a first line treatment.
- Furazolidone is partly absorbed from **intestines** and **excreted** in **urine** which **turns orange .**

❖ **Side effects** : **Nausea, Headache, Dizziness**

DRUGS FOR TRICHOMONIASIS

1. Drugs used orally

Metronidazole 400 mg TDS for 7 days or 2 g single dose, or Tinidazole 600 mg daily for 7 days or 2 g single dose or Secnidazole 2 g single dose, are the drugs of choice.

2. Drugs used intra vaginally

i. **Diiodohydroxyquin 200 mg** inserted intra-vaginally at bed time for 1-2weeks

FLORAQUIN 100 mg vaginal pessaries.

ii. **Quiniodochlor 200 mg** inserted in the vagina every night for 1–3 weeks.

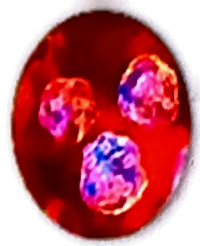
GYNOSAN 200 mg vaginal tab.

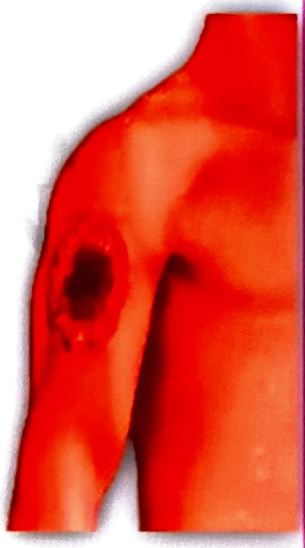
iii. **Povidone-iodine 400 mg** inserted in the vagina daily at night for 2 weeks.

BETADINE VAGINAL 200 mg

DRUGS FOR LEISHMANIASIS

- Leishmaniasis is caused by **protozoa of the genus leishmania.** Kala-azar or visceral leishmaniasis is caused by **leishmania donovan.**
- Oriental sore by l. Tropica and mucocutaneous leishmaniasis by **L. Braziliensis.**





CLASS	DRUGS
Antimonials	Sod. Stibogluconate, Meglumine antimonate
Diamidine	Pentamidine
Others	Amphotericin B, Ketoconazole, Allopurinol, Miltefosine, Paramomycin

i. Sodium stibogluconate

- It is a pentavalent antimonial is the most effective drug in **kala-azar.**
- It is also effective in **mucocutaneous and cutaneous leishmaniasis.**
- It is given as a **4% solution** in the dose of 10–20 mg/kg IM (gluteal region) or IV for 20 days.

- **Adverse effects**

i. **Metallic taste in the mouth**

ii. **Nausea**

iii. **Vomiting, diarrhoea , headache**

iv. **Myalgia, arthralgia, pain at the injection site, bradycardia, skin rashes**

v. **Haematuria and jaundice.**

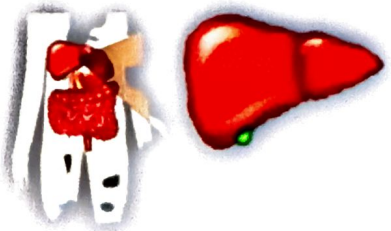
ii. Meglumine antimonate and ethyl stibamine can also be used in all forms of **leishmaniasis.**

iii. Pentamidine is an aromatic Diamidine effective against **Leishmania donovani, trypanosomes, Pneumocystis, jiroveci** and some fungi.

Given intramuscularly the drug is **rapidly absorbed** but very little reaches the **CNS.**

❖ Adverse effects

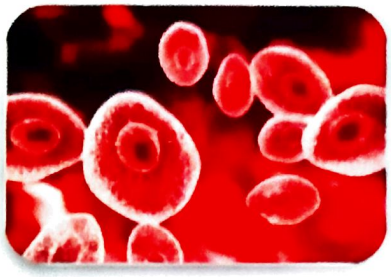
- **Vomiting, diarrhoea, flushing, pruritus, rashes**
- **tachycardia and hypotension apart from pain at the injection site.**
- **Hepatotoxicity**
- **renal impairment**
- **ECG changes and in some patients diabetes mellitus May be precipitated.**



❖ **Uses**

i. **Leishmaniasis**

ii. **Pneumocystis**



iv. Miltefosine

- Miltefosine is the first drug that can be used orally in **leishmaniasis.**
- It has a high efficacy against both **visceral** and **cutaneous leishmaniasis**.
- It is effective also in **leishmania resistant to stibogluconate**.
- It is approved for use in India in visceral **leishmaniasis—700 mg/kg/day for 4 weeks.**
- It is **contraindicated in pregnancy.**

v. Amphotericin B has been tried in leishmaniasis in the endemic areas where antimonials may be ineffective.

vi. Ketoconazole inhibits ergosterol synthesis in the leishmania and is effective in cutaneous leishmaniasis.

AMB is also useful in mucocutaneous and dermal leishmaniasis

viii. Allopurinol

- In leishmania, allopurinol is converted to a metabolite which inhibits protein synthesis.
- It may be used along with antimonials.

DRUGS FOR TRYPANOSOMIASIS

Trypanosomiasis is caused by protozoa of the genus Trypanosoma.

i. **Suramin sodium**

ii. **Melarsoprol**

iii. **Eflornithine**

i. Suramin sodium

- It is the drug of choice for early stages of **trypanosomiasis.**
- It **does not cross the BBB**
- It is also useful for the **prophylaxis** but pentamidine is preferable.
- Suramin is given **IV.**
- It is extensively **bound to plasma proteins.**
- Suramin is also effective in **eradicating** adult forms of **Onchocerca volvulus.**

❖ Adverse effect

i. **Vomiting, shock**

ii. **Rash, neuropathies**

iii. **Haemolytic anaemia**

iv. **Agranulocytosis**

ii. Melarsoprol is the preferred drug in later stages of trypanosomiasis which is associated with **encephalitis** and **meningitis.**

iii. Eflornithine

- It is used in **CNS trypanosomiasis.**
- **Nifurtimox** and **benznidazole** are useful in **CHAGAS' DISEASE (American trypanosomiasis).**