رسالة اليوم :

عندما يمنحك الله بداية جديدة لا تكرر الأخطاء القديمة .

ANTI-PROTOZOAL DRUGS

Prepared by

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1- Describe the infection steps of malaria ?

2- what is special about plasmidum ?

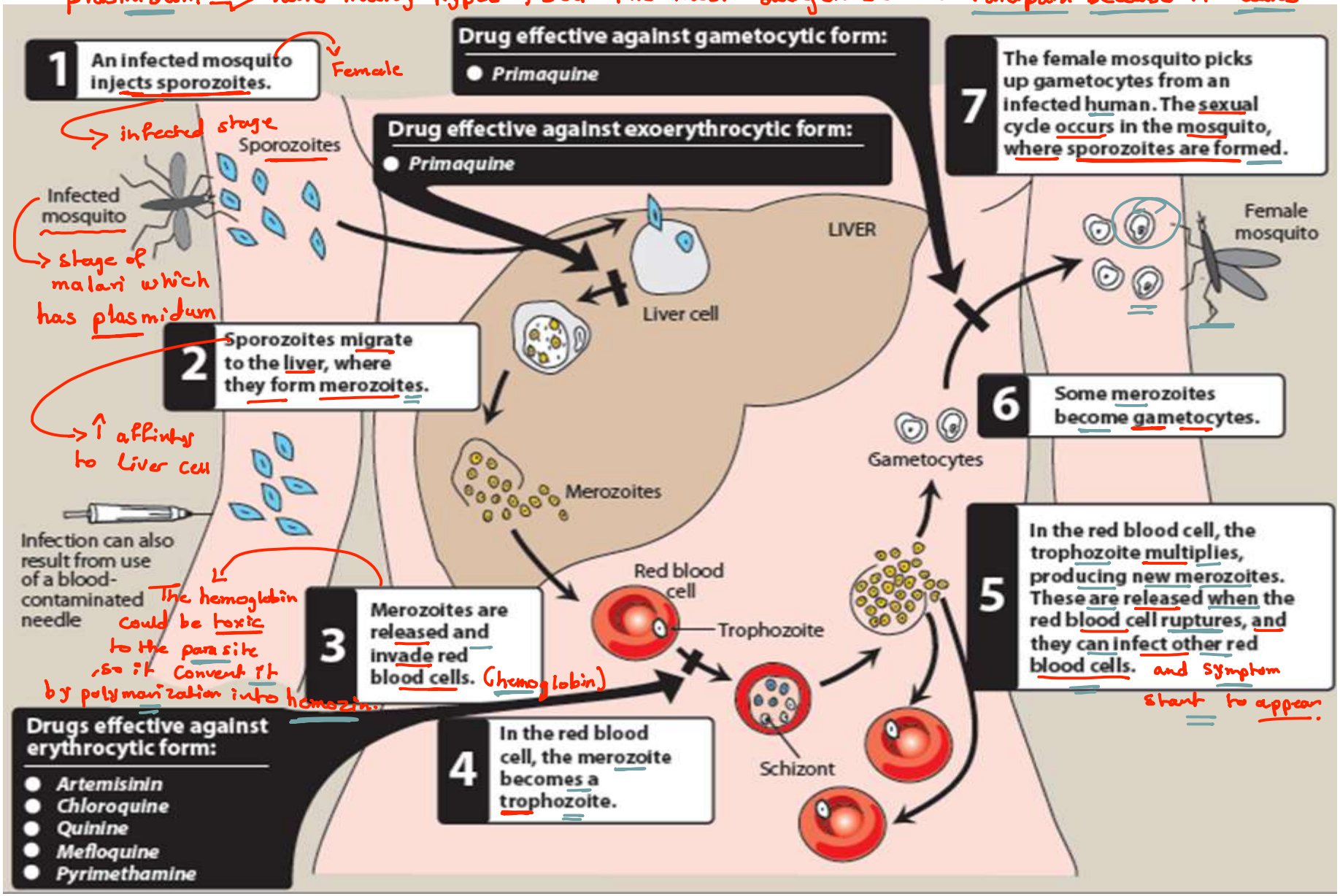
3- what're the classification of anti-malaria ?

Cause death.

CHEMOTHERAPY FOR MALARIA

Fever, hypotension, agregation of RBC's

plasmidum ⇒ have many types, but the most dangerous on is falcipara because it caues



Several classes of antimalarial drugs are available:

1. **Tissue schizonticides (Exoerythrocytic):** Drugs that eliminate developing or dormant liver forms (**Primaquine**)
2. **Blood schizonticides (erythrocytic):** those that act on erythrocytic parasites (**Artemisinin, chloroquine, quinine, mefloquine, pyrimethamine**)
3. **Gametocides:** those that kill sexual stages and prevent transmission to mosquitoes. **(primaquine)**
4. **Radical cure:** eliminate both hepatic and erythrocytic stages. **Primaquine**
5. **Causal prophylactic drugs:** those capable of preventing erythrocytic infection. **Chloroquine and Pyrimethamine**

Anti-malarial drug therapy

- Chloroquine
- Quinine
- Mefloquine
- Primaquine
- Antifolate Drugs
- Other antimalarial drugs

1- what're the roles of pKs for ch.Q ?

2- Describe the normal machanism of parasite to erthrocyte ?

Chloroquine

3- Explain the action of ch.q on parasite ?

4- what're the therapuitic indication ?

5- what's the Adverse effect ?

Pharmacokinetics:

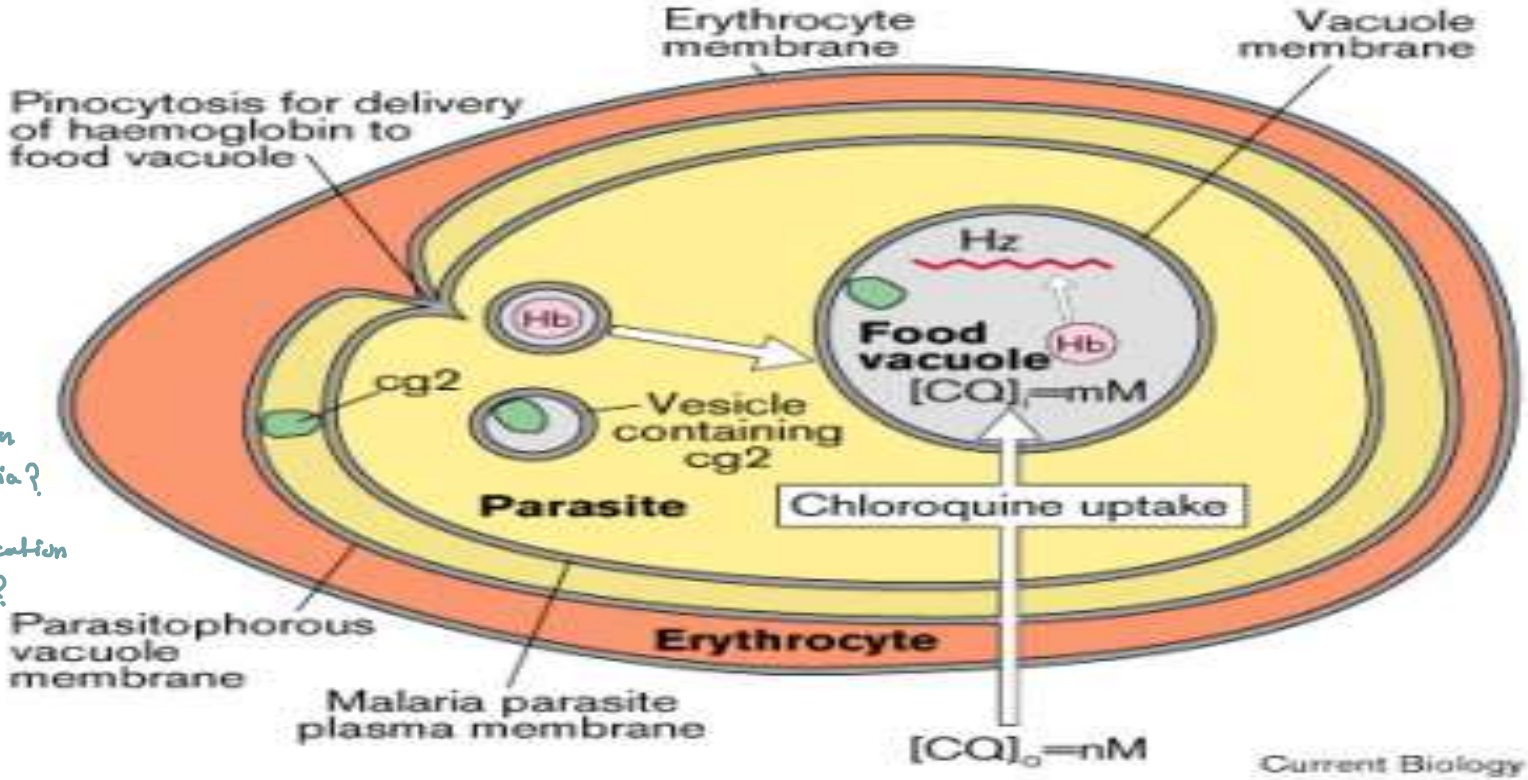
- Well absorbed orally (decreased with antacids). basic drug.... require alkaline media.
- Widely distributed (very large V_d). highly Lipid soluable
- Concentrated in liver & R.B.Cs & other tissues. (milk)
- Parent drug & metabolites are excreted in urine (excretion is enhanced by acidification of urine).

Mechanism of action:

- Blood schizonticide only RBc's in blood.
- The parasite digests hemoglobin and releases soluble heme, which is toxic to the parasite.
- Normally, the parasite polymerizes heme to hemozoin (a pigment), which is isolated in the parasite's food vacuole

- Chloroquine (weak base) is concentrated in the acidic food vacuole by ion trapping.
- Chloroquine binds to heme, preventing its polymerization to hemozoin → intracellular accumulation of heme → lysis of the parasite.

→ so it become ionized and digested in Vacuole lead to



1- How does it given during the malaria?

2- what're the indication during malaria?

we detect the malari by blood film, in which the plasmidum occur.

Therapeutic uses: Duration of treatment = 3 days.

1- Malaria: (1g at 0 and 24 hours, then 0.5 g at 48 hours)

- Drug of choice for treatment of:

- **Non-falciparum malaria** (in P ovale & P vivax, it should be followed by primaquine).

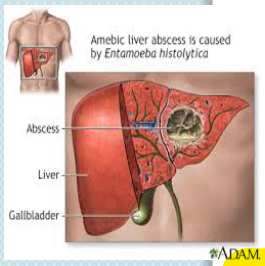
have a role in dormant stage in liver ± parasite ± especially

For 14 days, to ensure the killed of all

- **Chloroquine-sensitive falciparum malaria**.

  - Drug of choice for chemoprophylaxis of malaria in areas without resistant falciparum strains (500mg once/week; started 1-2 weeks before travelling & continued for 4 weeks after leaving the endemic area).

before 2 weeks.



2- Amoebic liver abscess. ⇒ because the chloraquin diposted in liver so it cure the infections

3- Anti-inflammatory action → rheumatoid arthritis

Treated by large does with long duration.

- **Adverse effects:**
- ***Small doses*** for a short time (in malaria): minimal adverse effects.
- ***Large dose*** for long time (as anti-inflammatory) causing:

1- Headache & pruritis.

2- GIT: Nausea-vomiting and diarrhea.

3- C.V.S.: quinidine-like action (hypotension & arrhythmia).

4- Eye: blurred vision & retinopathy (routine ophthalmologic examination should be done).

5- Irreversible ototoxicity & psychosis.

6- Myopathy & peripheral neuropathy.

7- Large intramuscular injections or rapid intravenous infusions can result in severe hypotension and respiratory and cardiac arrest.

- **N.B.** Parenteral administration of chloroquine is best avoided, but if other drugs are not available for parenteral use, it should be infused slowly

Contraindications & precautions

1. Patients with psoriasis or porphyria (it may precipitate acute attacks).
2. Not used in patients with retinal or visual field abnormalities.

- Not used in patients with myopathy. Used with caution in patients with a history of liver disease or neurologic disorders.
- Its absorption is impaired by the antidiarrheal agent kaolin & antacids.

N.B. Chloroquine is safe in pregnancy and for young children

1- What's the combination of it? what does it work?

Amodiaquine

- Similar to chloroquine.
- **Combined with** Artesunate or sulfadoxine-pyrimethamine for treatment of resistant falciparum malaria. (Active form)
- **Not used for prophylaxis???**

2- why

because long-term use causes → a- agranulocytosis, b- aplastic anemia (→ Bone marrow depression.), and c- hepatotoxicity).

1- what's the mechanism of action?
2- what're the indication uses?
3- what're the Adverse effect?

Quinine

The target is :- chloraquin Resistance P.alciparm

Treatment and proptylaxis

- **Mechanism of action:**

Blood schizonticide

It binds to double-stranded DNA → prevents strand separation → blocks of DNA replication and transcription to RNA. ⇒ Death.

- **Used in:**

Treatment of chloroquine-resistant falciparum.

Treatment of severe falciparum infection (quinidine I.V). N.B. Not used in prophylaxis (too toxic).

effect SN node. + contractility of heart.

- **Adverse effects:**

1. ***Cinchonism*** (Gastrointestinal distress, headache, vertigo, blurred vision, and tinnitus).
2. Hypersensitivity.
3. Quinidine-like action (hypotension & arrhythmia).
4. Visual & auditory disturbances.
5. Hemolysis in patients with G6PD deficiency. ... Hemolytic anemia
6. Black water fever (marked hemolysis and hemoglobinuria) ... hemoglobin in urine. due to
7. Quinine is contraindicated in pregnancy (Oxytocic effect).

1-what're the Therapeutic indications ?

Mefloquine

First Line drug for prophylaxis in chloroquin-resistance area

Blood schizonticide.

- **Therapeutic uses:**

1. First-line drug given weekly for prophylaxis in chloroquine-resistant areas.
2. Alternative to quinine in chloroquine-resistant falciparum infections.

- **Advsers effects:**

1. Commonly : gastrointestinal distress, skin rash, headache, and dizziness.
2. High doses → arrhythmia, psychiatric disorders, neurologic symptoms, and seizures.

1- whats the machanism of action ?
2- what're the the indications ?
3- what're the Adverse effect?

Primaquine

Mechanism of action: act as cellular oxidants

- Tissue schizonticide and Gametocide (Prevents transmission of disease to mosquito).

Kill the sexual stages.

Therapeutic uses:

Radical cure of relapsing malaria (P ovale & P vivax). in dormant stage.

a- b-

Eradicates liver stages of P ovale & P vivax. Should be given after a blood schizonticide.

Terminal prophylaxis of relapsing malaria. It should be given after leaving the endemic area to ensure that the dormant forms in liver (hypnozoites) are eradicated.

Alternaive for primary prophylaxis

Pneumocystis jiroveci infection: combined with clindamycin.

- **Adverse effects:**

1. Gastrointestinal distress.
2. Pruritus, headaches.
3. Hemolytic anemia (in G6PD deficiency).
4. Methaemoglobinaemia.
5. Contraindicated during pregnancy (the fetus is relatively deficient in G6PD).

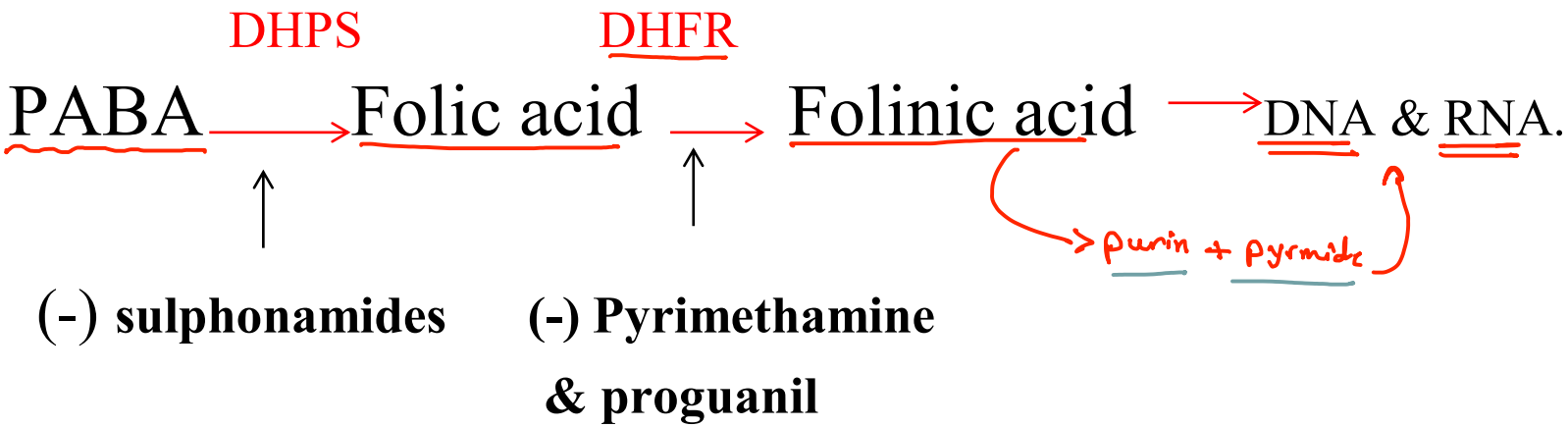
Antifolate Drugs

Pyrimethamine - Proguanil - Sulfadoxine.

- Blood schizonticides.
- Sporonticide in the mosquito's gut.

Mechanism of action:

- **Sulfonamides** inhibit the synthesis of folate by competition with PABA.
- **Pyrimethamine & proguanil** inhibit dihydrofolate reductase → inhibit the conversion of folic to folinic acid → inhibit the synthesis of DNA& RNA.



- **Fansidar**

Good combination. = 2 small doses to avoid Adverse effect

Pyrimethamine + sulfadoxine → Synergistic antimalarial effects through the sequential blockade of 2 steps in folic acid synthesis.

Therapeutic uses:

1. Treatment of chloroquine resistant falciparum (fansidar plus quinine).
2. Chemoprophylaxis of chloroquine-resistant malaria (Proguanil + atovaquone "Malarone" can be used daily).
3. Toxoplasmosis (pyrimethamine + sulfadiazine).

- ***Side effects***

small does .... parasite.
large does ... human.

Sulfonamides:

- GIT upset.
- Hypersensitivity.
- Hemolytic anemia (in G6PD deficiency).
- Drug interactions (competition for plasma protein binding)

Pyrimethamine

- Megaloblastic anemia (folate deficiency).

only in multidrug resistance. / chloraquin falciparum Resistance.

Other antimalarial drugs

1. **Doxycycline** (tetracycline antibiotic).
2. **Atovaquone**(quinine derivative, a component of Malarone): effective in both treatment & prophylaxis of falciparum malaria.
3. **Halofantrine:** Blood schizonticide.

Effective against chloroquine-resistant falciparum.

Not used in prophylaxis (Quinidine-like cardiotoxicity).

4. **Lumefantrine**→ less cardiotoxic (can be used in prophylaxis).
5. **Artemisinin derivatives (e.g. Artesunate):**

Effective against multidrug-resistant falciparum malaria.

The only drugs effective against quinine-resistant falciparum infection.

Not used for chemoprophylaxis (short half-lives of 1–3 h).

Best used in combination with other agents.

Choice of Treatment

	1st choice	Altenative
Chloroquine-sensitive P falciparum & P malariae infections	Chloroquine ***(blood schizonticide)***	
P vivax and P ovale infections	Chloroquine (blood schizonticide)Then: Primaquine (tissue schizonticide) → to prevent relapses	
Chloroquine-resistant P falciparum	Quinine; **Plus:** Doxycycline ***or*** Clindamycin ***or*** Pyrimethamine-sulfadoxine	Mefloquine ***OR*** Malarone (atovaquone + proguanil)
Severe or complicated infections with P falciparum	Quinidine I.V. (ECG monitoring is needed)***OR*** Artesunate IV followed by oral doxycycline or clindamycin.	

Prevention of Malaria in Travelers

- ***Chloroquine-sensitive geographic areas:*** Chloroquine (500 mg weekly).

  Started 1-2 weeks before travelling & continued for 4 weeks after leaving the endemic area.
- ***Chloroquine-resistant geographic areas:*** Mefloquine (250 mg weekly).

Started 1-2 weeks before travelling & continued for 4 weeks after leaving the endemic area.

- ***Areas with multidrug-resistant malaria:*** Doxycycline or Malarone (daily).

  Started 2 days before travelling & continued for (4 weeks for doxycycline or 1 week for malarone) after leaving the endemic area.
- ***Terminal prophylaxis of P vivax and P ovale infections:*** Primaquine (daily for 14 d).

Anti-amebiasis

Clinical picture:

bloody diarrhea --- in adults

•Amebiasis (also called amebic dysentery) is an infection of the intestinal tract caused by Entamoeba histolytica.

The diagnosis is established by isolating E. histolytica from fresh feces.

Amebiasis may be in the form of:

1) Asymptomatic intestinal infection
2) Mild to moderate colitis
3) Severe intestinal infection (dysentery)

Extra-intestinal infection: Ameboma, liver abscess

AIM OF THERAPY:

•Therapy is aimed not only at the acutely **ill patient** but also at those who are **asymptomatic carriers**, because dormant E. histolytica may cause future infections in the carrier and be a potential source of infection for others

Clinical Classification Antiamoebic Drugs

Mixed amebicides : both systemic and luminal

- **Metronidazole** ... anaerobic infections.
- **Tinidazole**

Luminal amebicides

- treatment of the asymptomatic colonization state.
- **Iodoquinol,**
- **Paromomycin**
- **diloxanide furoate**

systemic amebicides

- These drugs are useful for treating liver abscesses and intestinal wall infections caused by amebas
- **Chloroquine**
- **Emetine**
- **Dehydroemetine**

A- Mixed amebicides
(metronidazole and tinidazole)

Metronidazole: a nitroimidazole, is the mixed amebicide of choice for treating amebic infections and kills the E. histolytica trophozoites.

For the treatment of amebiasis, it is usually administered with a luminal amebicide, such as iodoquinol or paromomycin.

This combination provides cure rates of greater than 90 %

Pharmacokinetics:

- Metronidazole is completely and rapidly absorbed after oral administration
- Metabolism of the drug depends on hepatic oxidation of the metronidazole side chain by mixed-function oxidase, followed by glucuronidation. The parent drug and its metabolites are excreted in the urine
- distributes well throughout body tissues and fluids. Therapeutic levels can be found in vaginal and seminal fluids, saliva, breast milk, and cerebrospinal fluid (CSF).

Mechanism of action:

- It is a prodrug which is activated by the reduction of its nitro group in anaerobes. Disruption of DNA structure & function → cell death.

Highly effective tissue amoebicide & partially effective luminal amoebicide affect trophozoites not cysts (due to decreased luminal concentration as it is completely absorbed).

Clinical uses of metronidazole:

1.Protozoal infections:

Amebiasis (metronidazole or tinidazole are the drugs of choice in treatment of all tissue infections with E. histolytica).

Others: giardiasis - urogenital trichomoniasis (trichomonas vaginalis).

2.Anaerobic bacterial infections:

Pseudomembranous colitis due to clostridium difficile

Adverse effects:

1-The most common adverse effects are those associated with the gastrointestinal tract, including nausea, vomiting, epigastric distress, and abdominal cramps, unpleasant, metallic taste is commonly experienced.

2-Oral moniliasis (yeast infection of the mouth)

3- Neurotoxicologic problems, such as dizziness, vertigo, and numbness or paresthesias in the peripheral nervous system. [Note: The latter are reasons for discontinuing the drug.]

4-Dark urine, dysuria

5-Teratogenic (contraindicated in pregnancy)

Drug interactions:

1- if used with enzyme inducers, such as phenobarbital, enhances the rat e of metabolism. Conversely, if with enzyme inhibitors, such as cimetidi ne, prolong the plasma half-life of metronidazole. The drug accumulates in patients with severe hepatic disease.

2-If taken with alcohol, a disulfiram-like effect occurs. → patient is flashed and has tachycardia.

2- Tinidazole: is a second-generation nitro-imidazole that is similar to metronidazole, but :

More effective.

Longer t1/2. / short duration.

Less teratogenic.

B. Luminal amebicides

After treatment of invasive intestinal or extra-intestinal amebic disease is complete, a luminal agent, such as iodoquinol, diloxanide furoate, or paromomycin, should be administered for treatment of the asymptomatic colonization state.

Luminal amebicides :

1-Diloxanide Furoate

2-Iodoquinol: alternative to diloxanide.

3-Antibiotic amebicides:

Paromomycin: direct amebicide.

Diloxanide furoate:

In the gut, diloxanide furoate is split into diloxanide and furoic acid; about 90% o f the diloxanide is rapidly absorbed and then conjugated to form the glucuronide, which is promptly excreted in the urine. The unabsorbed diloxanide is the active a ntiamebic substance.

- The mechanism of action of diloxanide furoate is unknown.
- Adverse effect: May cause flatulence

Iodoquinol:

a halogenated 8-hydroxy quinolone is amebicidal against E. histolytica and is effect ive against the luminal trophozoite and cyst forms.

- It is used in GiardiasisSide effects:

1. GIT upset: nausea, vomiting, diarrhea.
2. Neurotoxicity: subacute myelo-optic neuropathy (SMON).
3. Thyroid enlargement

3-Paromomycin:

an aminoglycoside antibiotic, is only effective against the intestinal (luminal) forms of E. histolytica and tapeworm,

- Mechanism of action:
- Because it is not significantly absorbed from the gastrointestinal tract. Paramomycin is directly amebicidal and also exerts its antiamebic actions by reducing the populati on of intestinal flora. Its direct amebicidal action is probably due to the effects it has on cell membranes, causing leakage. Very little of the drug is absorbed on oral inges tion, but that which is absorbed is excreted in urine.
- Adverse effects:

Gastrointestinal distress and diarrhea

C. Systemic amebicides

•These drugs are useful for treating liver abscesses and intestinal wall infections caused by amebases.

1-Chloroquine: is used in combination-

with metronidazole and diloxanide furoate to treat and prevent amebic liver abscesses. It elimina tes trophozoites in liver abscesses, but it is not useful in treating luminal amebiasis. Chloroquine is also effective in the treatment of malaria.

2. Emetine and dehydroemetine:

•are alternative agents for the treatment of amebiasis.

Mechanism of action:

They inhibit protein synthesis by blocking chain elongation. Intramuscular injection is the prefer red route. Emetine is concentrated in the liver, where it persists for a month after a single dose. I t is slowly metabolized and excreted, and it can accumulate. Its half-life in plasma is 5 days.

Adverse effects:

1-Pain at the site of injection,

2-Cardiotoxicity (for example, arrhythmias and congestive heart failure), neuromuscular weakn ess

3-Dizziness

4-Rashes.

Their use is limited by their toxicities (dehydroemetine is less toxic than emetine), and close cli nical observation is necessary when these drugs are administered. They should not be taken for more than 5 days.

Drug choice of amebiasis

TABLE 52–2 Drugs used in the treatment of amebiasis.

Disease Form	Drug(s) of Choice	Alternative Drug(s)
Asymptomatic, Intestinal infection	Diloxanide furoate	Iodoquinol, paramomycin
Mild to moderate intestinal infection	Metronidazole *plus* luminal agent (see above)	Tinidazole, *or* tetracycline, *or* erythromycin *plus* luminal agent
Severe intestinal infection	Metronidazole *or* tinidazole *plus* luminal agent	Tetracycline *or* emetine *or* dihydroemetine *plus* luminal agent
Hepatic abscess and other extraintestinal disease	Metronidazole *or* tinidazole *plus* luminal agent	Emetine *or* dihydroemetine *plus* choroquine (for liver abscess) *plus* luminal agent

Adapted, with permission, from Katzung BG, editor: *Basic & Clinical Pharmacology*, 11th ed. McGraw-Hill, 2009.

CHEMOTHERAPY FOR GIARDIASIS

- Giardia lamblia
- Although some infections are asymptomatic, severe diarrhea can occur, which can be very serious in immune-suppressed patients.

Treatment :

1. Metronidazole for 5 days Or

2. Tinidazole, which is equally effective as metronidazole in the treatment of giardiasis but with a much shorter course of therapy (2 grams given once).

CHEMOTHERAPY FOR LEISHMANIASIS

- There are three types of leishmaniasis: cutaneous, mucocutaneous, and visceral.
- Pentavalent antimonials, such as sodium stibogluconate, are the conventional therapy used in the treatment of leishmaniasis.

Sodium stibogluconate

- Given daily by IV or IM injections or topically in cutaneous lesions.

CHEMOTHERAPY FOR TOXOPLASMOSIS

- Toxoplasma gondii, is transmitted to humans when they consume raw or inadequately cooked infected meat.
- An infected pregnant woman can transmit the organism to her fetus.

Treatment:

- A combination of **sulfadiazine and pyrimethamine**.
- **Folinic acid** is commonly administered to protect against folate deficiency