

ANTI-AMOEBIIC DRUGS

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AMOEBIASIS

- ▶ infection with *Entamoeba histolytica*.
- ▶ transmitted through GIT.
- ▶ has two stages of development: **cyst and trophozoite.**

Cysts → small intestine → little trophozoites (ileocecum)

AMOEBIASIS



cysts (colon) — asymptomatic intestinal infection, source of infection



trophozoites (tissues) — intestinal amoebiasis

→ extra intestinal infection



Intestinal amoebiasis :

amoebic ulcers → a/c dysentery (blood, mucus in stools)

C/c int. amoebiasis → vague abd. symptoms, amoeboma

Extra intestinal d/s

Liver abscess

Rare- lung, spleen, kidney, brain

CLASSIFICATION

➤ Tissue Amoebiasis

* Both intestinal & extra intestinal

Nitroimidazoles – Metronidazole , Tinidazole , Secnidazole , Ornidazole

Alkaloids - Emetine , Hydroemetine

* Extra intestinal amoebiasis only - Chloroquine

➤ Luminal amoebiasis

Amide – Diloxanide furoate

8-Hydroxy quinolones – Quinidochlor

Antibiotics – Tetracycline, Paromomycin



Metronidazole

- ▶ Prototype drug introduced in 1959
- ▶ Bactericidal against **Giardia lamblia**, anaerobic bacteria - **Bacteroides fragilis**, **Fusobacterium**, **Clostridium perfringens/difficile**, **Helicobacter pylori**, **Anaerobic Streptococci**.
- ▶ Does not affect aerobic bacteria.



➤ MOA

- Not clearly understood
- Enters microorganism by diffusion - Nitro group reduced to a highly reactive nitro radical - DNA damaged Cytotoxicity.
- High selective anaerobic action – interference with electron transportation from NADPH or other reduced substrates
- • Also inhibits cell mediated immunity
- • Induce mutagenesis
- • Cause radio-sensitization



Metronidazole



Pharmacokinetics

- Completely absorbed from intestine
- Wide distribution in body. $t_{1/2}$ - 8hrs.
- Therapeutic concentrations in -Vaginal secretions, Semen, Saliva, CSF
- Route of administration – oral & parenteral

Metronidazole

- Broad spectrum cidal action for protozoa
 1. **Anti-amoebiasis:** kills *E histolytic* trophozoites but not cysts. Treatment of all tissue infections with *E histolytic*. No effect against luminal parasites and *so must be used with a luminal amoebicide to ensure eradication of the infection.*
 2. **Anti-trichomoniasis**
 3. **Anti-anaerobic bacteria**
 4. **Anti-giardiasis**



Metronidazole

- Pseudomembranous colitis, Ulcerative gingivitis, H.pylori, Peptic ulcer disease, Guinea worm infestation.
- Adverse Drug Reactions
 - **Frequent** - Anorexia, nausea, *METALLIC TASTE*, abdominal cramps, *disulfiram reaction*.
 - **Less frequent** - Headache, glossitis, dry mouth, dizziness, rashes, transient neutropenia.
 - **On prolonged administration** - *Peripheral neuropathy*, CNS effects.

Tinidazole

- ▶ long $t_{1/2}$, slower metabolism, long DOA, OD dosing.
- ▶ Higher cure rates in amoebiasis.
- ▶ Lower s/e → metallic taste, nausea, rash.

USES -

- Amoebiasis – 2g od X 3 d
- Tricho, giardiasis- 2g single dose
- Anaerobic infection –
 - Px -2 g single dose for colorectal surgeries
 - Tx – 2g → 0.5 g bd X 5 days
- H pylori- 500 mg bd X 2 wks in triple therapy



➤ Secnidazole : **longest t ½** [17-29 hrs]

2 g single dose but for hepatic amoebiasis 1.5 gm
od X5 days

➤ Ornidazole – long t ½ ,similar to Tinidazole

➤ Satranidazole –

better tolerability

No disulfiram reaction

No acetamide metabolite [weak carcinogen]

Emetine and Dehydroemetine

- Emetine - alkaloid from *Cephaelis ipecacuanha*.
- Dehydroemetine - a semisynthetic analog [less cardiotoxic, less cumulative]
- are effective against tissue trophozoites of *E histolytica*.



➤ MOA

- Inhibiting peptidyl-tRNA translocation → inhibiting elongation of peptide chain → **inhibiting protein synthesis** → interfering cleavage and breeding of trophozoites
- No action on cysts

PK


- Administered s/c (preferred) or im. (but never i.v.)

Uses

- kills *E histolytic* trophozoites of histolytic tissues but no effect against luminal cysts -- + luminal amoebicide
- Rapid action.
- Given only till a/c sx subside (not > 10 days)
- **Cumulative** in liver, kidney, spleen, lungs– 2nd course only after 6 weeks
- Reserve drug for severe cases or metronidazole resistant or intolerant.
- Also for liver fluke infection.

Adverse Effects

- low selectivity → also inhibits protein synthesis of eukaryote.
 - Toxicity increase with length of therapy.
1. **Local irritant**: pain and tenderness in the area of injection.
 2. **GIT** : nausea, vomiting (central and direct), abdominal cramps ,diarrhoea.




3. Cardiac toxicity: arrhythmias, congestive heart failure, hypotension, ECG changes—to avoid strict bed rest during therapy, no exercise X 2mnths

4. Neuromuscular blockade: muscle weakness and discomfort— myositis like

- Not be used in patients with cardiac or renal disease, in young children, or in pregnancy.



Chloroquine

- Kills trophozoites .
- Chloroquine reaches high liver concentrations
→ treatment of **amoebic liver abscess**.
- **Not effective in the treatment of intestinal or other extrahepatic amoebiasis.**
- nor in controlling the luminal cycle (cyst passers). completely absorbed from the upper intestine

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- Efficacy similar to emetine, but duration of treatment is longer and relapses frequent.
 - **No resistance** detected.
 - Dose for amoebic liver abscess: 600 mg (base) for 2 days → 300 mg daily for 2-3 weeks.

DILOXANIDE

- Diloxanide furoate is a dichloroacetamide derivative.
- **Highly effective luminal amoebicide:** directly kills trophozoites responsible for production of cysts
- Hydrolyzed in intestine → released Diloxanide is absorbed. Diloxanide(weaker amoebicide): no systemic antiamoebic activity despite its absorption.
- primarily metabolized by glucuronidation → urine.

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- **Effective for asymptomatic luminal infections and cyst passers.**
 - used with a tissue amoebicide, usually metronidazole.
 - **Adverse Effects**: flatulence, nausea, abdominal cramps, rashes etc.
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NITAZOXANIDE

- Salicylamide congener of anthelmintic Niclosamide.
- **Spectrum**
 - *Cryptosporidium parvum*
 - *G. intestinalis*, *E. histolytica*, and *T. vaginalis* , other protozoans.
 - **Intestinal helminths:** *Hymenolepis nana*, *Trichuris trichiura*, *Ascaris lumbricoides*, *Enterobius vermicularis*, *Ancylostoma duodenale*, *Strongyloides stercoralis*, and the liver fluke *Fasciola hepatica*.
 - **Anaerobic bacteria**, including *Clostridium* spp. and *H. pylori*.
 - **Antiviral activity** → now undergoing clinical trials for the treatment of hepatitis C.



PK

- Prodrug → tizoxanide
- **PFOR inhibitor** [essential enzyme p/w of electron transport metabolism in anaerobic organisms]
- Conjugated in liver → bile and urine

USE

- Amoebic dysentery as **luminal amoebicide**
- Giardiasis, Cryptosporidiosis

ADR

Abd pain, vomiting, head ache...




PAROMOMYCIN

- Aminoglycoside antibiotic.
- Not significantly absorbed from the GIT.
- **Only as a luminal amoebicide** and has no effect against extra intestinal amoebic infections.
- inhibiting protein synthesis → kill trophozoites.
- inhibiting symbiosis flora → indirectly inhibiting amoeba protozoa.

Uses

- DOC for treating intestinal colonization with *E. histolytica*.
- **Giardiasis in pregnant women**, especially during the first trimester, when metronidazole is contraindicated and as an alternative agent for metronidazole-resistant isolates of *G. intestinalis*.
- **Dose** - 500 mg orally three times daily for 10 days

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- 6.25% cream has been used to treat **vaginal trichomoniasis** in patients who had failed metronidazole therapy or could not receive metronidazole.
 - **Leishmaniasis.**

Adverse effects

- abdominal pain and cramping, epigastric pain, nausea and vomiting, steatorrhea, and diarrhea. Rarely, rash and headache.

8-HYDROXYQUINOLINES

- against *Entamoeba*, *Giardia*, *Trichomonas*, some fungi (dermatophytes, *Candida*) and some bacteria.

USE

- Intestinal amoebiasis as alternatives to Diloxanide furoate.
- Other uses are--giardiasis; local treatment of monilial and trichomonas vaginitis, fungal and bacterial skin infections.
- Diarrhoeal diseases
- Di iodoxyhydroxyquine safer drug




➤ ADR

- Nausea, transient loose and green stools, pruritus etc. **Goiter** → prolonged medication.
- **Iodism** (furunculosis, inflammation of mucous membranes) --due to chronic iodine overload.
- Prolonged/repeated use of high doses of quiniodochlor caused a neuropathic syndrome called '**subacute myelo-optic neuropathy**' (SMON)
- India **banned only** for pediatric patients, [blindness]. Banned in other countries.

Tetracyclines

- Directly inhibit amoebae at high concentrations.
- Older tetracyclines are incompletely absorbed in the small intestine, reach the colon in large amounts and inhibit the bacterial flora with which *Entamoebae* live symbiotically.


Thus, they indirectly reduce proliferation of **entamoebae in the colon** and are used in chronic, difficult to treat cases with **only the luminal cycle** and little mucosal invasion.

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- They are not good for acute dysentery and for hepatic amoebiasis
 - **Tetracyclines** lessen risk of
 - *opportunistic infections*
 - *perforation*
 - *peritonitis*
- when given along with systemic amoebicide.

TREATMENT OF AMOEBIASIS

1. Invasive intestinal amoebiasis

- **Metronidazole/ Tinidazole** are DOC.
- Secnidazole, ornidazole, satranidazole are the alternatives.
- Adjuvant measures for diarrhea and abdominal pain.

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- ▶ Dehydroemetine is rarely used for most severe cases → faster symptomatic relief. discontinued as soon as acute symptoms are controlled (2-3 days) and metronidazole started.
 - ▶ Emetine may also be needed when metronidazole is contraindicated or produces rashes/neurotoxicity.
 - ▶ **This should be followed by a luminal amoebicide to eradicate *and to prevent carrier (cyst passing) state.***

2. Chronic intestinal amoebiasis/ asymptomatic cyst passers

- Diloxanide furoate –DOC
- Metronidazole/ Tinidazole- cure any latent hepatic infection.
- A single course of a hydroxyquinoline not > 2 weeks may be used as third choice.
- A tetracycline with tissue amoebicide in cases which fail to clear completely.

3. Hepatic amoebiasis

- Complete eradication of trophozoites from the liver is essential to avoid relapses.
- **Metronidazole / Tinidazole** are the first choice drugs.
- Dehydroemetine is to be used only if metronidazole cannot be given for one reason or the other.
- **Abscess → aspirated.**
- A luminal amoebicide must be given later to finish the intestinal reservoir of infection.



THANK YOU