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

CLASSFICATION

- **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 perfringes/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 ½ - 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 ½ ,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

- 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 dichoroacetamide 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.

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

NITAZOXANIDE

- Salicylamide congener of anthelminthic **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

- 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 iodohydroxyquine 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.

- 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.

- 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.