Protozoal infections

1. Amebiasis
2. Malaria
3. Giardiasis
4. Leshmaniasis
5. Toxoplasmosis
6. Trypanosomiasis
Protozoal infections

1. Protozoal cells (Eukaryotes) have metabolic processes closer to human host than prokaryotic bacterial pathogens.
2. Difficult to be treated than bacterial infections.
3. Many of antiprotozoal drugs cause toxic effects on the host.
4. Cells with high metabolic processes in the host are susceptible.
5. Bone marrow, renal tubular, intestinal, neuronal.
6. Antiprotozoal are not safe during pregnancy.
Antiprotozoal Drugs

1. Chemotherapy for amebiasis
2. Chemotherapy for malaria
3. Chemotherapy for giardiasis
4. Chemotherapy for leshmaniasis
5. Chemotherapy for toxoplasmosis
6. Chemotherapy for trypanosomiasis
Fig. 46.—Amoebiasis. *E. histolytica*. Trophozoite with ingested erythrocytes to cysts. (From an original drawing by B. Jobling)
Amebiasis occurs due to ingestion of foods contaminated with *Entameba Histolytica* cysts
LIFE CYCLE

Entamoeba histolytica exists in two forms:

1. Cysts (infective):
   - can survive outside the human body.
   - transform to trophozoites.

2. Trophozoites (non-infective; invasive):
   - Reproduce
   - invade wall of large intestine, causing ulceration and may migrate to other tissues, especially the liver.
   - transform to cysts which are excreted in feces.
**LIFE CYCLE**

1. Ingestion of cysts
2. Formation of trophozoites
3. Penetration of intestinal wall
4. Multiplication of trophozoites within colon wall
5. Systemic invasion
6. Cysts discarded with feces

**Systemic amebicides**
- Chloroquine
- Dehydroemetine
- Emetine

**Mixed amebicide (luminal and systemic activity)**
- Metronidazole

**Luminal amebicides**
- Diloxanide furoate
- Paromomycin
- Iodoquinol

Expelled trophozoite (noninfective)
Expelled cyst (infective)
Life Cycle

1. Cysts ingestion.
2. Formation of trophozoites
3. Penetration of intestinal wall
4. Multiplication of trophozoites within colon wall.
5. Systemic invasion.
6. Cyst formation in rectum and excretion in feces.
1. INTRALUMINAL CYSTS
2. INTESTINAL WALL TROPHOZOITES
3. HEPATIC TROPHOZOITES
CLINICAL PRESENTATIONS

- Asymptomatic Intestinal infection (Carriers, passing cysts)
- Mild to moderate intestinal disease (Nondysenteric Colitis)
- Severe Intestinal infection (Dysentery)
- Hepatic abscess
- Ameboma (localized granulomatous lesion of colon)
- Extraintestinal disease (other than hepatic abscess)
ANTIAMEBIC DRUGS

- Luminal Amebicides
- Tissue or systemic amebicides
- Mixed Amebicides
LUMEN AMOEBICIDES

- Acts on the parasites in the lumen of the bowl.
- used for treatment of asymptomatic amebiasis.

**Include**

- Diloxanide Furoate
- **Halogenated Hydroxyquinolines**
  - Iodoquinol
- **Antibiotics**
  - Tetracyclines
  - Paramomycin
  - Erythromycin
Tissue Amoebicides (systemic)

- acts principally in the intestinal wall and liver (or any other extra-intestinal tissue).
- Used for treatment of systemic form of the disease (liver absesses or intestinal wall infection).
- Emetine
- Dehydroemetine
- Chloroquine (liver only)
Luminal amebicides

- Acts on the parasites in the lumen of the bowl.
- Should be used for treatment of asymptomatic amebiasis.
- Include
  - Iodoquinol
  - Diloxanide furoate
  - Paromomycin
Mixed AMOEICIDES

Effective against both luminal and systemic forms of the disease. Although luminal concentration is too low for single drug – treatment.

- Metronidazol
- Tinidazole
METRONIDAZOLE

- Mixed amoebicide.
- Drug of choice for intestinal & extraintestinal amoebiasis.
- Acts on trophozoites.
- Has no effect on cysts.
- Nitro group of metronidazole is reduced by protozoan leading to cytotoxic reduced product that binds to DNA and proteins resulting into parasite death.
Pharmacokinetics

- Given orally or IV.
- Absorption is rapid and complete.
  - Due to rapid absorption from GIT, less effective against parasites in the lumen.
- Wide distribution to all tissues and body fluids (CSF, saliva, milk).
- Plasma protein binding is low (< 20%).
- Plasma half life is 8 h
Pharmacokinetics

- Metabolized by oxidation in liver by mixed function oxidase followed by glucurononylation.
- Excreted in urine as unchanged drug plus metabolites.
- Clearance is decreased in liver impairment.
Clinical Uses

- Amoebiasis (with luminal amebicide).
- Giardiasis (Giardia intestinalis)
- Trichomoniasis (trichomonas vaginalis)
- Broad spectrum of Anaerobic bacteria e.g.,
  - Helicobacter pylori infection (H Pylori)
  - Pseudomembranous colitis (Clostridium difficile).
Adverse effects

Tinidazole has better toxicity profile than metronidazole, but is equally active

1. GIT:
   - Nausea
   - Vomiting
   - Dry mouth
   - Metallic taste
   - Diarrhoea
   - Oral Thrush (Moniliasis, yeast infection).
Adverse effects

2. CNS: Neurotoxicological effect
- Insomnia
- Dizziness
- peripheral neuropathy
  - Numbness or paresthesia in peripheral nervous system
  - ataxia, encphalopathy, convulsion (rare).

3. Dysuria, dark urine.

4. Neutropenia

5. Disulfiram-like effect if taken with alcohol.
disulfiram like -effect

When metronidazole is given with alcohol abdominal distress, nausea, vomiting, flushing, or headache, tachycardia, hyperventilation

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Alcohol</th>
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<tbody>
<tr>
<td>dehydrogenase</td>
<td>dehydrogenase</td>
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<tr>
<td>Ethanol</td>
<td>Acetaldehyde</td>
</tr>
</tbody>
</table>
Drug interactions:

- **Enzyme inhibitors** *(cimetidine, ketoconazole)*
- **Inducers** *(phenytoin and phenobarbitone, rifampin).*
- inhibits CYP family 2C9 & 3A4
- Potentiate anticoagulant effect of warfarin.
- potentiates lithium toxicity.
- disulfiram --- confusional & psychotic states
CONTRAINDICATIONS / PRECAUTIONS:

- Pregnancy and nursing women.
- Alcohol intake
- CNS diseases
- Severe hepatic disease
- Severe renal disease
EMETINE AND DEHYDROEMETINE

Chemistry:
- Emetine hydrochloride is a plant alkaloid derived from ipeca.
- Dehydroemetine is a synthetic analogue

Pharmacokinetics:
- Erratic oral absorption.
- Given preferably subcutaneously but could be given by IM, NEVER I.V.
- Plasma half life is 5 days.
EMETINE

- Concentrated in Liver, Lungs, Spleen, Kidney, Cardiac muscle and Intestinal wall.
- Metabolized & Excreted slowly via kidney so it has a cumulative effect.
- Trace amounts could be detected in urine 1-2 month after last dose.
- Should not be used for more than 10 days (usually 3-5 days).
Pharmacological Actions

- Act on trophozoites causing irreversible block of protein synthesis.
- Depress cardiac conduction & contraction arrhythmia, heart failure and death.
- Antiadrenergic action may lead to hypotension.
- Nausea & vomiting of central origin.
- Decreases serum potassium.
Clinical Uses

- Amoebic liver abscess.
- Intestinal wall infections.
- Severe forms of acute amoebic dysentery dehydroemetine + tetracycline for a short period followed by metronidazole.
Adverse Effects

- Dehydroemetine is less toxic than emetine
- pain at site of injection, abcesses.
- **GIT:** nausea, vomiting, diarrhoea.
- Neuromuscular weakness
- **Serious toxicities:** cardiototoxicity
  - cardiac arrhythmias,
  - Hypotension
  - congestive heart failure
Contraindications

- Heart disease
- Kidney disease
- Pregnancy
- Children
Chloroquine

- Antiamebic drug
- Antimalarial drug
- Used in combination with metronidazole and diloxanide furoate for amebic liver diseases.
LUMEN AMOEBICIDES

- Acts on the parasites in the lumen of the bowl.
- used for treatment of asymptomatic amebiasis.

Include

- Diloxanide Furoate
- Halogenated Hydroxyquinolines
  - Iodoquinol
- Antibiotics
  - Tetracyclines
  - Paramomycin
  - Erythromycin
LUMEN AMOEBCIDES

DILOXANIDE FUROATE

Chemistry

- Dichloroacetamide
- Ester of diloxanide + furoic acid.

Pharmacokinetics

- Given orally.
- Split in the intestine, most of diloxanide is absorbed, conjugated to form a glucoronide which is excreted in urine (90%).
- The unabsorbed moiety being the amoebicidal agent (10%).
Pharmacodynamics:

- Unknown mechanism of action
- Direct amoebicidal action against luminal forms.
- Not active against tissue trophozoites.
Therapeutic Uses

- Drug of choice for asymptomatic Intestinal infection
- For eradication of infection given along with tissue amoebicide (metronidazole).
- Dose: 500 mg three times/day for 10 days.
Adverse Effects

- Flatulence
- Nausea, vomiting, abdominal cramps.
- No serious adverse effects

Contraindications:
- Pregnancy
- Children (less than 2 years).
Paromomycin Sulphate

- Aminoglycoside, not absorbed.
- Effective against luminal forms of ameba

**Mechanism of action**

- Direct amebicidal action (causes leakage by its action on cell membrane of parasite).
- Indirect killing of bacterial flora essential for proliferation of pathogenic amoebae.
Kinetics

- Orally
- Not significantly absorbed from the GIT
- Small amount absorbed is excreted unchanged in urine (may accumulate with renal insufficiency).
Adverse effects

- Gastrointestinal distress and diarrhea.

Precautions

- Severe renal disease
- patients with GIT ulceration
Tetracyclines

- Very weak direct amoebicidal action.
- Mainly act *indirectly* on bacterial flora.
- Used in severe cases of amoebic dysentery not responding to metronidazole combined with dehydroemetine.
HALOGENATED HYDROXYQUINOLINES

- Iodoquinol
- Cliquinol

Mechanism of action

- Unknown
- Effective against organisms in GIT only. Not effective against organisms in the intestinal wall or liver.

Pharmacokinetics

- Absorption is poor (90%), excreted in feces.
- 10% enter circulation, excreted as glucouronide in urine.
- Half life is 11-14 h
Uses

- lumen amoebicide.

- For eradication of infection given along with tissue amoebicide (metronidazole).
Adverse Effects

- Peripheral neuropathy including optic neuritis
- GIT: Nausea, vomiting, diarrhoea.
- Enlargement of the thyroid gland.
- Agranulocytosis.
- Iodine sensitivity.
- Drug interfere with thyroid function tests (increase protein-bound serum iodine, decrease in measured $^{131}$I uptake).
Contraindications

- Optic neuropathy
- Thyroid disease
- Sensitivity to iodine
- Severe liver disease
- Severe kidney disease
- **discontinued** if it produces persistent diarrhea or signs of iodine toxicity (dermatitis, urticaria, pruritus, fever)
<table>
<thead>
<tr>
<th>Clinical Syndrome</th>
<th>Drug</th>
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<tr>
<td>Asymptomatic cyst carriers</td>
<td>Iodoquinol or Paromycyn or Diloxanide furoate</td>
</tr>
<tr>
<td>Diarrhea/dysentery</td>
<td>Metronidazole plus Iodoquinol or Paromycyn or Diloxanide furoate</td>
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<tr>
<td>Extraintestinal</td>
<td></td>
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<tr>
<td>Amebic liver abscess</td>
<td>Chloroquine plus Metronidazole or Emetine</td>
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<tr>
<td>Clinical Setting</td>
<td>Drugs of Choice and Adult Dosage</td>
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<tr>
<td>Asymptomatic intestinal infection</td>
<td>Luminal agent: Diloxanide furoate, 500 mg 3 times daily for 10 days or Iodoquinol, 650 mg 3 times daily for 21 days or Paromomycin, 10 mg/kg 3 times daily for 7 days</td>
</tr>
<tr>
<td>Mild to moderate intestinal infection</td>
<td>Metronidazole, 750 mg 3 times daily (or 500 mg IV every 6 hours) for 10 days plus Luminal agent (see above)</td>
</tr>
<tr>
<td>Severe intestinal infection</td>
<td>Metronidazole, 750 mg 3 times daily (or 500 mg IV every 6 hours) for 10 days plus Luminal agent (see above)</td>
</tr>
<tr>
<td>Hepatic abscess, ameboma, and other extraintestinal disease</td>
<td>Metronidazole, 750 mg 3 times daily (or 500 mg IV every 6 hours) for 10 days plus Luminal agent (see above)</td>
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