Treatment of dysentery and amebiasis

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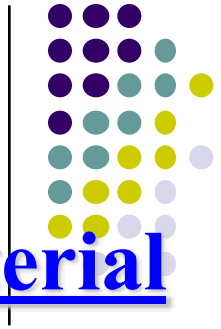
Objectives

- ***To understand different causes of dysentery.***
- ***To describe different classes of drugs used in treatment of both bacillary dysentery and amebic dysentery.***
- ***To be able to describe actions, side effects of drugs for treating bacillary dysentery.***
- ***To understand the pharmacokinetics, actions, clinical applications and side effects of antiamebic drugs.***
- ***To be able to differentiate between types of antiamebic drugs; luminal amebicides, and tissue amebicide.***

Dysentery

Dysentery: is an inflammatory disorder of the intestine, especially of the colon, that results in severe diarrhea containing mucus and/or blood in the feces with fever and abdominal pain caused by any kind of infection.

Causes of Dysentery



Dysentery results from viral infections, bacterial infections, or parasitic infestations.

The two most common causes are:

- **Amebic dysentery *(protozoal infection mainly by Entameba Histolytica).***
- **Bacillary dysentery *(bacterial infection mainly by shigella).***

Treatment of Dysentery

- **Maintain fluid intake using oral rehydration therapy or intravenous fluid therapy.**
- **Antimicrobial agents should not be given until stool analysis is done to specify the etiological agent.**
- **Anti diarrheal drugs**

Antidiarrheal drugs

Diphenoxylate, loperamide

- Treatment should be avoided in
  - the presence of high fever
  - or if the stool is bloody.
  - C. difficile infections
  - are contraindicated because they delay fecal excretion that can prolong fever.
  - as it increases the risk of toxin retention and precipitation of toxic megacolon.

Antidiarrheal drugs

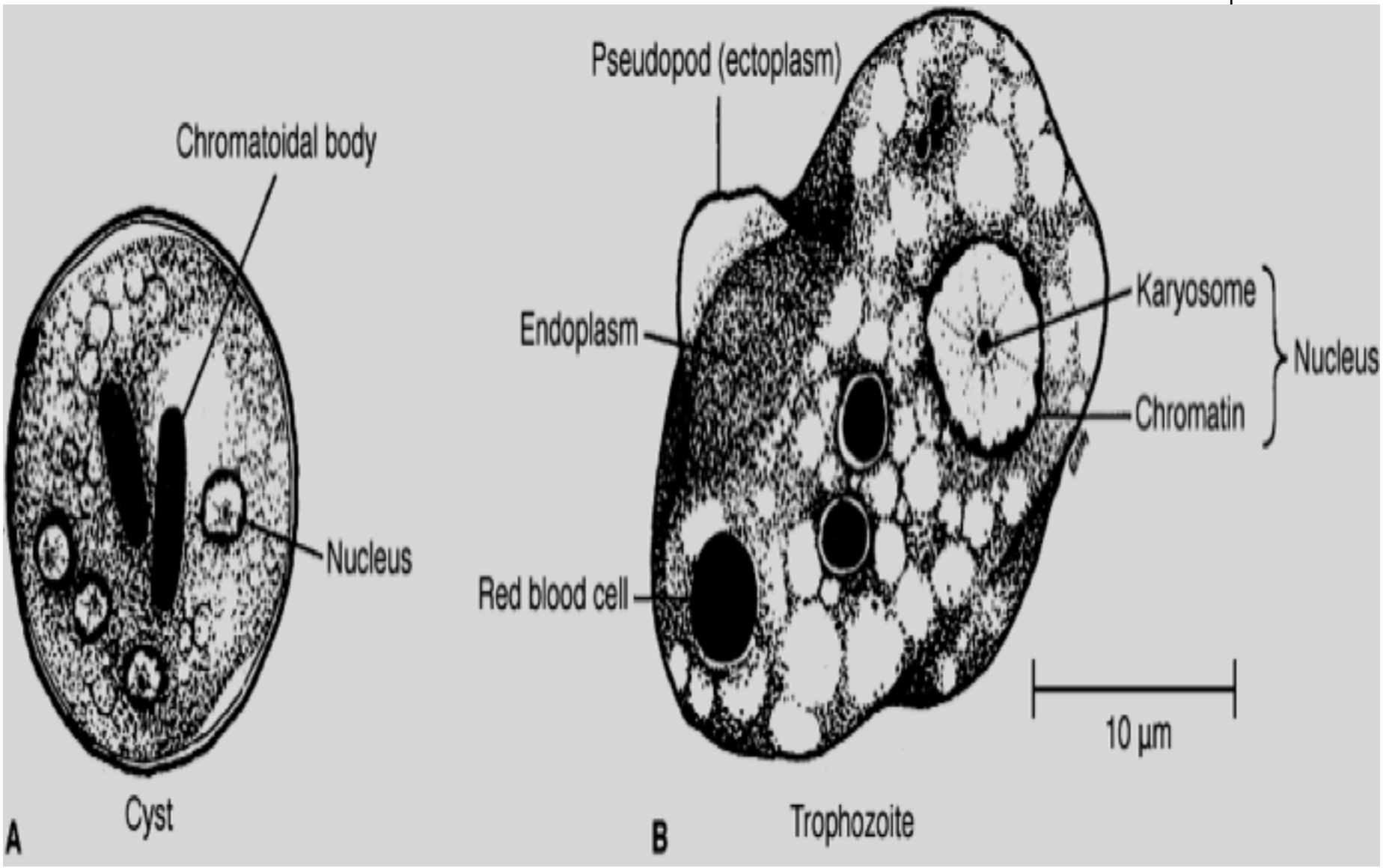
Loperamide

- is an opioid-receptor agonist
- acts on the μ-opioid receptors in the myenteric plexus of the large intestine.
- Do not cross BBB
- Minimal liability for addiction

Diphenoxylate + atropine

- is an opioid-receptor agonist
- Can cross BBB
- Has high liability for addiction
- Side effects are mainly due to atropine.

AMOEBIASIS


Chromatoidal body
Nucleus
A
Cyst
Pseudopod (ectoplasm)
Endoplasm
Red blood cell
Karyosome
Chromatin
Nucleus
10 µm
B
Trophozoite

Amebiasis

- Amebiasis is a protozoal infection of intestinal tract.

- Occurs due to ingestion of foods or water contaminated with cysts of Entameba Histolytica.

Life Cycle

***Entamoeba histolytica* exists in two forms:**

1.Cysts (infective stage):
can survive outside the human body.
When ingested, liberate trophozoites in the lumen of the intestine.

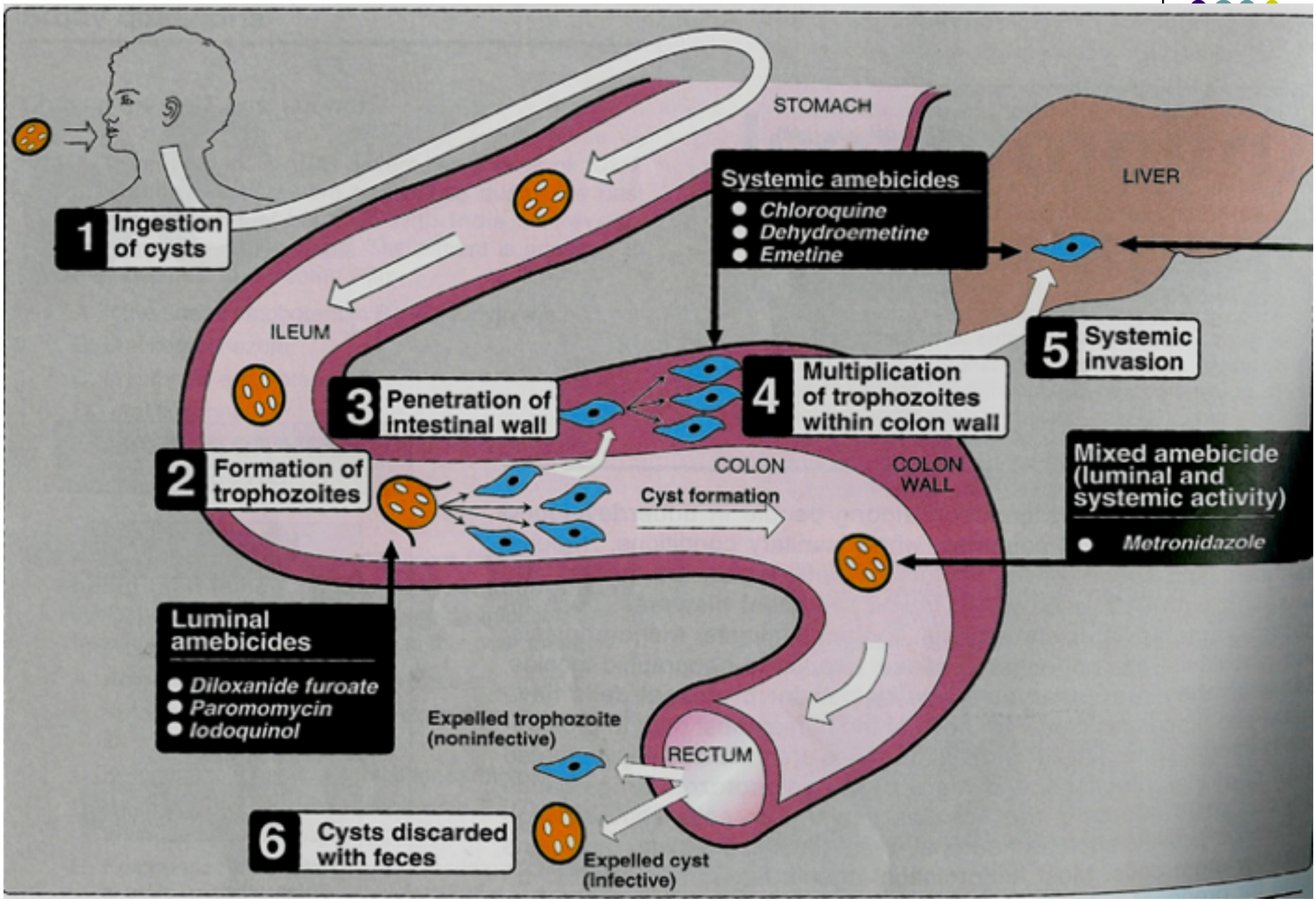
2.Trophozoites (non-infective; invasive stage):

- Multiply and feed on intestinal bacterial flora.
- They may invade and ulcerate wall of large intestine or may migrate to liver or other tissues.
- **In rectum,** trophozoites transform to cysts and are excreted in feces.

Life Cycle

1. Cysts ingestion in contaminated food or water.
2. Liberation of trophozoites in the colon.
3. Invasion of intestinal wall.
4. Multiplication of trophozoites within colon wall.
5. Systemic invasion to other organs (liver, lungs, brain).
6. Cyst formation in rectum and excretion in feces.

LIFE CYCLE


STOMACH
LIVER
Systemic amebicides
Chloroquine
Dehydroemetine
Emetine
1 Ingestion of cysts
ILEUM
3 Penetration of intestinal wall
4 Multiplication of trophozoites within colon wall
5 Systemic invasion
2 Formation of trophozoites
COLON
COLON WALL
Cyst formation
Mixed amebicide (luminal and systemic activity)
Metronidazole
Luminal amebicides
Diloxanide furoate
Paromomycin
Iodoquinol
Expelled trophozoite (noninfective)
RECTUM
6 Cysts discarded with feces
Expelled cyst (infective)

Clinical presentations

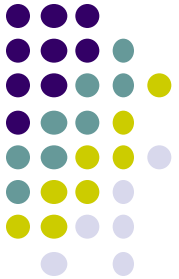
- **The patients show varying degree of illness from no symptoms to mild diarrhea to severe dysentery.**

Clinical presentations

- Asymptomatic amebiasis = Carriers

  (passing cysts in stool)
- Mild to moderate intestinal disease (colitis)
- Severe intestinal infection (amoebic dysentery)
- Ameboma (localized granulomatous lesion of colon).
- Hepatic abscess, and other extra-intestinal diseases.

ANTIAMEBIC DRUGS



- **Luminal amebicides**
- **Tissue or systemic amebicides**

Luminal amebicides

- **Acts on the parasites in the lumen of the bowel.**

- **used for treatment of asymptomatic amebiasis (carriers).**

Include

- **Diloxanide furoate**
- **Iodoquinol**
- **Paromomycin**

Tissue or systemic amebicides

- Act on ameba in tissues

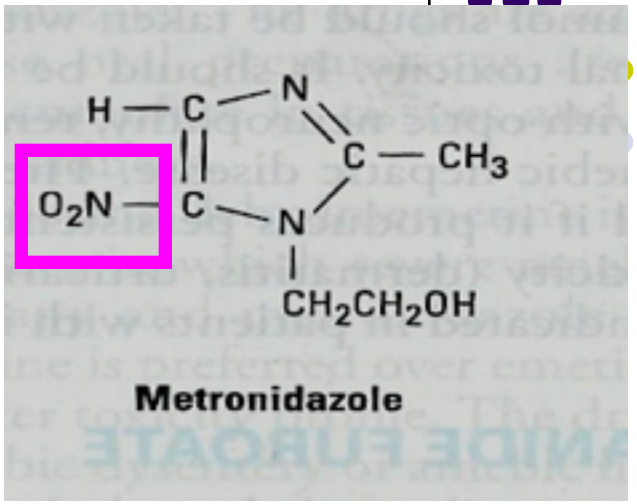
e.g. the intestinal wall and/or other extra-intestinal tissues as liver, brain and lung.

- Used for treatment of systemic form of the disease (invasive amebiasis) e.g. intestinal wall infection or liver abscesses.

Include

- Metronidazole/ tinidazole
- Emetine / dehydroemetine
- Chloroquine (liver only)

METRONIDAZOLE



- Tissue amoebicide.
- Acts on trophozoites.
- Metronidazole inhibits DNA replication.
- Does not eradicate cysts from intestine
- Drug of choice for treating

  invasive amebic infections (intestinal & extra-intestinal amebiasis).

Pharmacokinetics

- Given orally or IV.
- Absorption is rapid and complete.
- Wide distribution to all tissues and body fluids (CSF, saliva, milk).
- Plasma half life is (8 h)
- Metabolized in liver by mixed function oxidase followed by glucuronidation (consider drug interactions).
- Excreted in urine.
- Clearance is decreased in liver impairment

Clinical Uses

- **is the drug of choice in all tissue amebiasis**
  - Extra-luminal amoebiasis
  - N.B. should be followed by luminal amebicides
- **Giardiasis**
- **Trichomoniasis**
- **Anaerobic bacterial infections**
- **Pseudo-membranous colitis (Clostridium difficile).**
- **Peptic ulcer (Helicobacter pylori)**

Side effects

GIT:

- **Dry mouth, metallic taste**
- **Nausea, vomiting, diarrhea (*NVD*)**
- **Oral Thrush (Moniliasis, yeast infection).**

CNS: Neurotoxicological effect

- **Insomnia, dizziness**
- **Peripheral neuropathy, paresthesia**
- **Encephalopathy, convulsion (IV infusion, rare)**

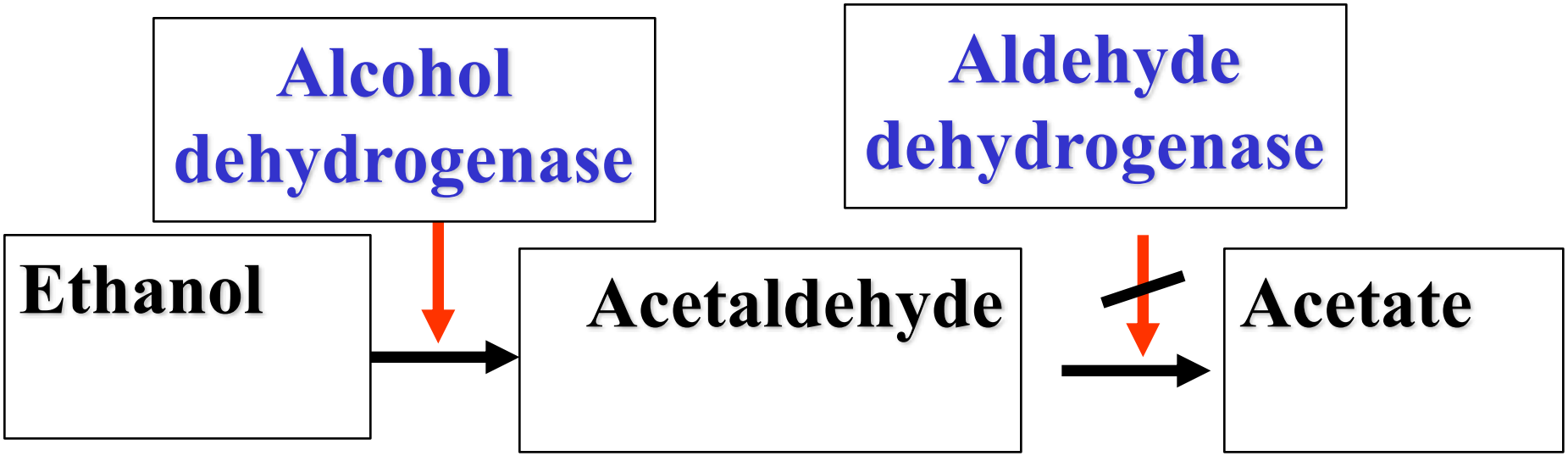
Dysuria, dark urine.

Neutropenia

Disulfiram-like effect if taken with alcohol.

Drug – Alcohol Interaction
Disulfiram like-effect of metronidazole

Combining metronidazole and alcohol causes nausea, vomiting, abdominal distress, flushing, headache, tachycardia, hyperventilation.

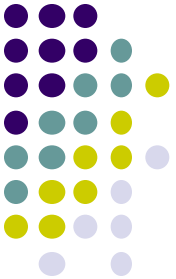


Drug interactions:

- Enzyme inhibitors (cimetidine, ketoconazole) increase duration of action of metronidazole
- Inducers (phenytoin and phenobarbitone). decrease duration of action of metronidazole

- Metronidazole inhibits CYP-450 (2C9 & 3A4) so
  - increases anticoagulant effect of warfarin.
  - Increases lithium toxicity.

CONTRAINDICATIONS / PRECAUTIONS:



- Pregnancy and breast feeding women.
- Alcohol intake
- CNS diseases
- Severe renal disease
- Severe hepatic disease

Tinidazole

Tinidazole has similar activity to metronidazole but better potency.

Advantages of tinidazole

- has longer duration of action (12-14h)
- a simpler dosing regimen
- a better toxicity profile than metronidazole.

Emetine and dehydroemetine

- **Emetine is an alkaloid derived from ipeca while dehydroemetine is a synthetic analog.**
- **Both are effective against tissue trophozoites of *E. histolytica* causing irreversible block of protein synthesis.**
- **Because of major toxicity concerns they have been almost completely replaced by metronidazole.**

Emetine and dehydroemetine

- **Have erratic oral absorption.**
- **Given preferably subcutaneously but could be given by IM, NEVER I.V.**
- **Has long plasma half life about 5 days.**
- **Metabolized & excreted slowly via kidney so they have a cumulative effect.**
- **Should not be used for more than 10 days (usually 3-5 days).**

Clinical Uses

- **Intestinal wall infections.**
- **Amoebic liver abscess.**
- **Severe forms of amebiasis acute amoebic dysentery, dehydroemetine is preferable due to less toxicity (3-5 days).**

Adverse Effects

Dehydroemetine is less toxic than emetine

- **GIT: nausea, vomiting, diarrhea.**
- **Serious toxicities: cardiotoxicity**

  Hypotension, cardiac arrhythmias, heart failure

  Caution: the drug should not be used in patients with cardiac or renal disease, in young children, or in pregnancy.

Chloroquine

- Anti-malarial drug
- Used in combination with metronidazole or dehydroemetine for amebic liver diseases.

Adverse effects

- Pruritus is common
- Nausea, vomiting, abdominal pain, anorexia.
- Blurring of vision.
- Hemolysis in G6PD deficient patients.

Luminal amoebicides

- used to eradicate cysts of *E histolytica* after treatment of invasive disease.

Include

- **Diloxanide furoate**
- **Iodoquinol**
- **Antibiotics**
  - **Paromomycin**
  - **Tetracycline**

Diloxanide furoate

- Ester of diloxanide + furoic acid .
- Given orally.
- It splits in the intestine liberating diloxanide
- The unabsorbed diloxanide is the amoebicidal agent .
- The absorbed portion is excreted in urine .

Diloxanide furoate

- Mechanism of action is unknown
- Direct amoebicidal action against luminal forms
- Not active against trophozoites in intestinal wall or extra-intestinal tissues.

Therapeutic Uses

- **Drug of choice for asymptomatic intestinal infection (cysts passers).**
- **to eradicate cysts of *E histolytica* after treatment of invasive disease with systemic amebicides.**

Adverse Effects

- **Flatulence**
- **Nausea, vomiting, abdominal cramps.**

Contraindications:

- Pregnancy

- Children (less than 2 years).

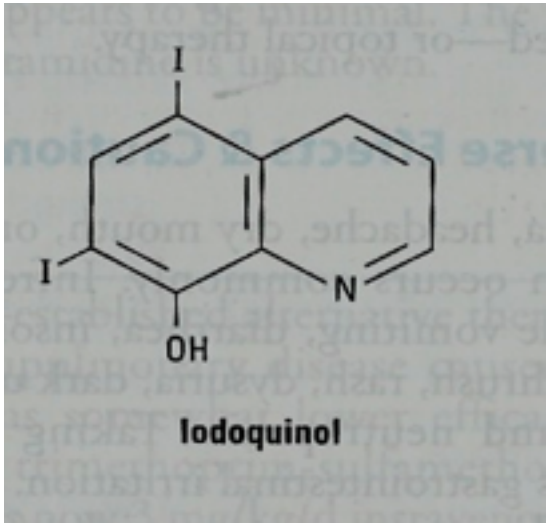
Iodoquinol

- Is given orally
- Poorly absorbed, excreted in feces.
- Mechanism of action is unknown
- effective against the luminal forms of amebiasis

Uses

- Luminal amoebicide for

  asymptomatic amebiasis.



Iodoquinol

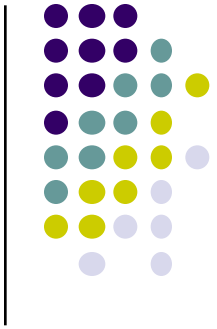
Adverse Effects

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

- **Iodoquinol should be used with caution in patients with optic neuropathy, or thyroid disease.**

- **Discontinued if it produces persistent diarrhea or signs of iodine toxicity (dermatitis, urticaria, pruritus, fever).**

Paromomycin Sulphate



- **Aminoglycoside antibiotic.**
- **Given orally**
- **Not significantly absorbed from GIT**
- **Effective only against luminal forms of ameba**
- **Has direct amebicidal action *(causes leakage by its action on cell membrane of parasite).***
- **Indirect killing of bacterial flora essential for proliferation of pathogenic amoebae.**
- **Small amount absorbed is excreted unchanged in urine *(may accumulate with renal insufficiency).***

Paromomycin Sulphate

- Use in chronic amebiasis to eliminate cysts (in cysts passers).

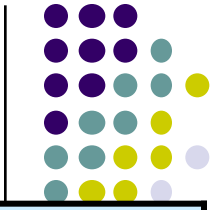
Adverse effects

- Gastrointestinal distress and diarrhea.

Precautions

- Severe renal disease
- patients with GIT ulceration

Summary for treatment of amebiasis



Asymptomatic dysentery (**cyst carriers**)	**Luminal amebicides** Diloxanide or iodoquinol or Paromomycin
Amebic colitis and dysentery ameboma, and extra-intestinal disease	Metronidazole or tinidazole followed by luminal amebicides
Hepatic abscess	Metronidazole or tinidazole or choroquine or dehydroemetine

Bacillary dysentery

Treated by:

- **Fluoroquinolones such as ciprofloxacin, ofloxacin**
- **Beta-lactams: Ampicillin, amoxicillin, third-generation cephalosporins (cefixime, ceftriaxone)**
- **Macrolides: Azithromycin**
- **Cotrimoxazole (trimethoprim-sulfamethoxazole) (TMP-SMX) commonly used in traveler's diarrhea.**
- **Antimicrobial therapy is typically administered for 5 days.**

Bacillary dysentery

- **Resistance to ampicillin, amoxicillin and sulfonamides, has been reported worldwide, and these agents are not recommended as empirical therapy.**
- **Fluoroquinolones are first-line treatment for shigellosis.**
- **Second line therapy include third generation cephalosporins.**

Fluoroquinolones

Ciprofloxacin

- Active against a variety of gram-positive and gram-negative bacteria.
- block bacterial DNA synthesis and growth (DNA gyrase & topoisomerases).
- Fluoroquinolones are first-line treatment for shigellosis.

USES

- **Bacterial diarrhea**

caused by shigella, salmonella and E coli.

- **Urinary tract infections**
- **Respiratory tract infections**
- **Soft tissues, bones, and joint infections**

Adverse effects

- **Arthropathy** (damage of growing cartilage).
- **GIT disorders** (nausea, vomiting, diarrhea).
- **CNS disorders** (headache, dizziness).
- **CVS disorder** (prolonged QT interval).
- **Phototoxicity.**
- **Liver toxicity.**

Contraindicated in:

- Children, pregnancy, nursing mother.
- Epilepsy
- Arrhythmias.
- Should not be combined with antacids, divalent cations.

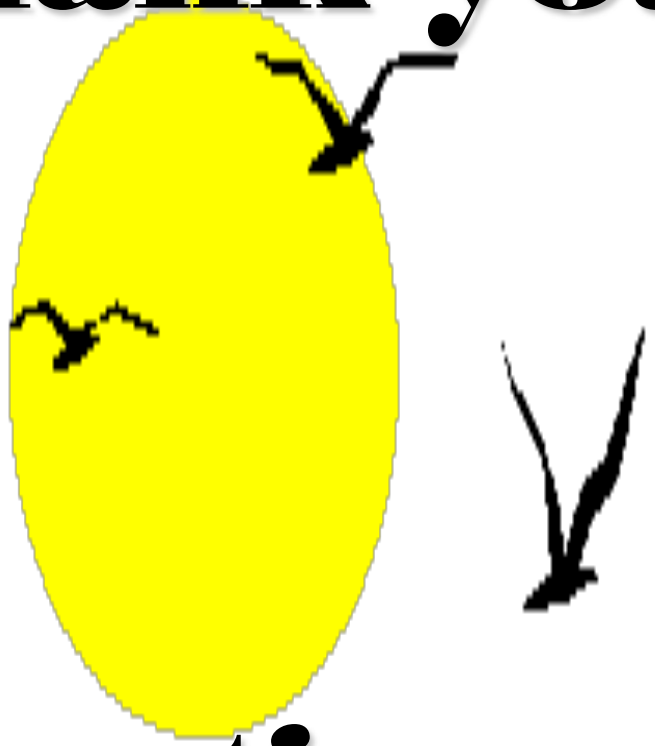
Cephalosporins

- **Oral cefixime or parenetral ceftriaxone are safe and effective.**
- **They are 3rd generation cephalosporin.**
- **Act by interfering with synthesis of peptidoglycan, a major structural component of bacterial cell wall.**
- **In case of children or patient allergic to sulfonamides, cephalosporins or azithromycin may be used.**

SUMMARY

- **Maintain *fluid* intake (oral rehydration therapy or Intravenous fluid therapy).**
- **asymptomatic luminal amebiasis is treated by luminal amebicides (diloxanide, or iodoquinol or paromomycin).**
- **Metronidazole** is the mainstay of therapy for invasive amebiasis (intestinal amebiasis) (**followed by luminal amebicides to prevent relapse).**
- Chloroquine has also been used for patients with hepatic amebiasis.
- Dehydroemetine is useful but not preferable due to CVS toxicity
- **Ciprofloxacin is the drug of choice in bacillary dysentery. In children and pregnancy, ceftriaxone or cefixime is the choice.**

Thank you



Questions ?