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

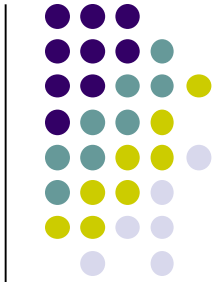
- **Maintain fluid intake using oral rehydration therapy or intravenous fluid therapy.**
- **Antimicrobial agents should not be given until stool analysis is done to specify the etiological agent.**
- **Anti diarrheal drugs**

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



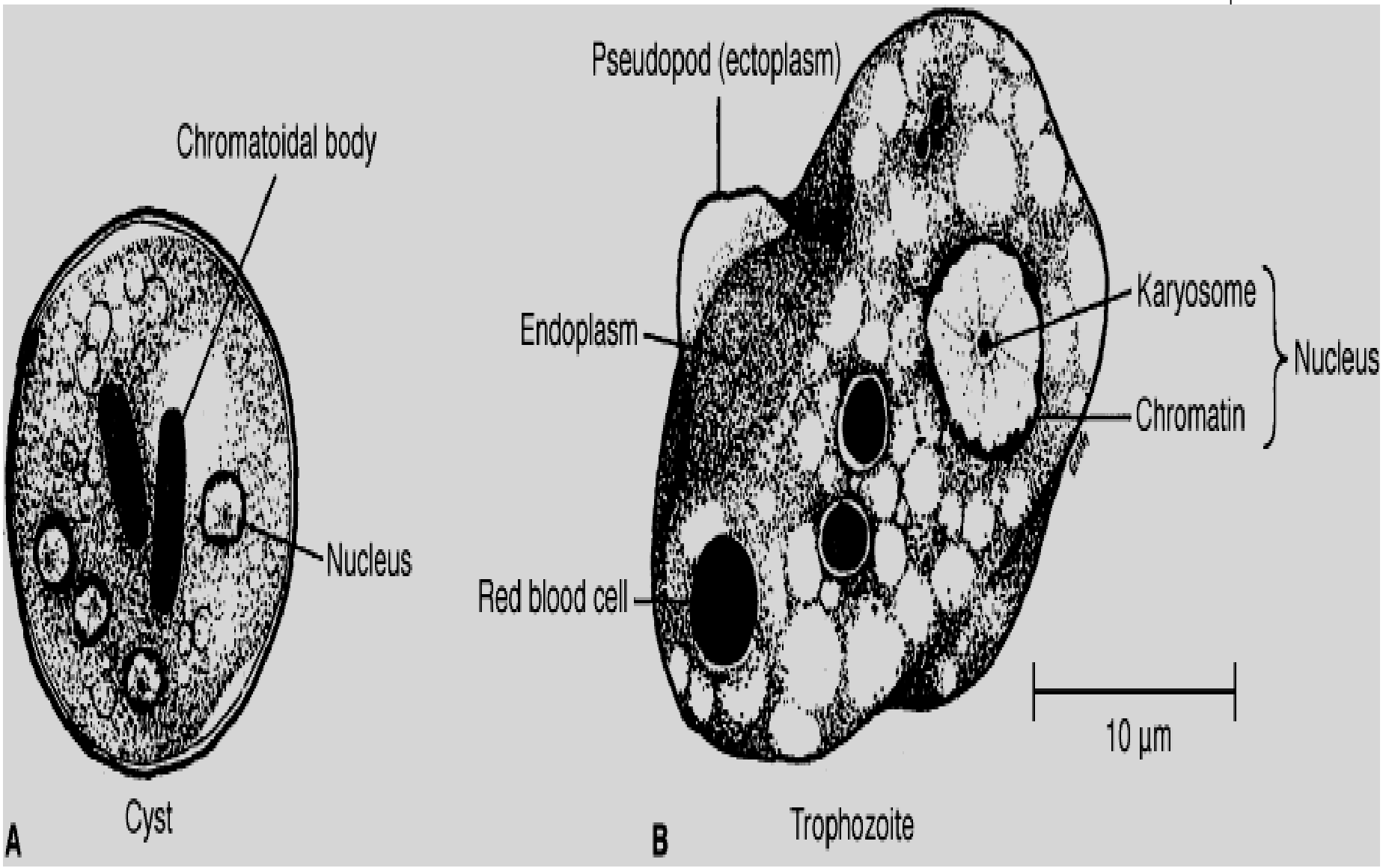
Loperamide

- 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

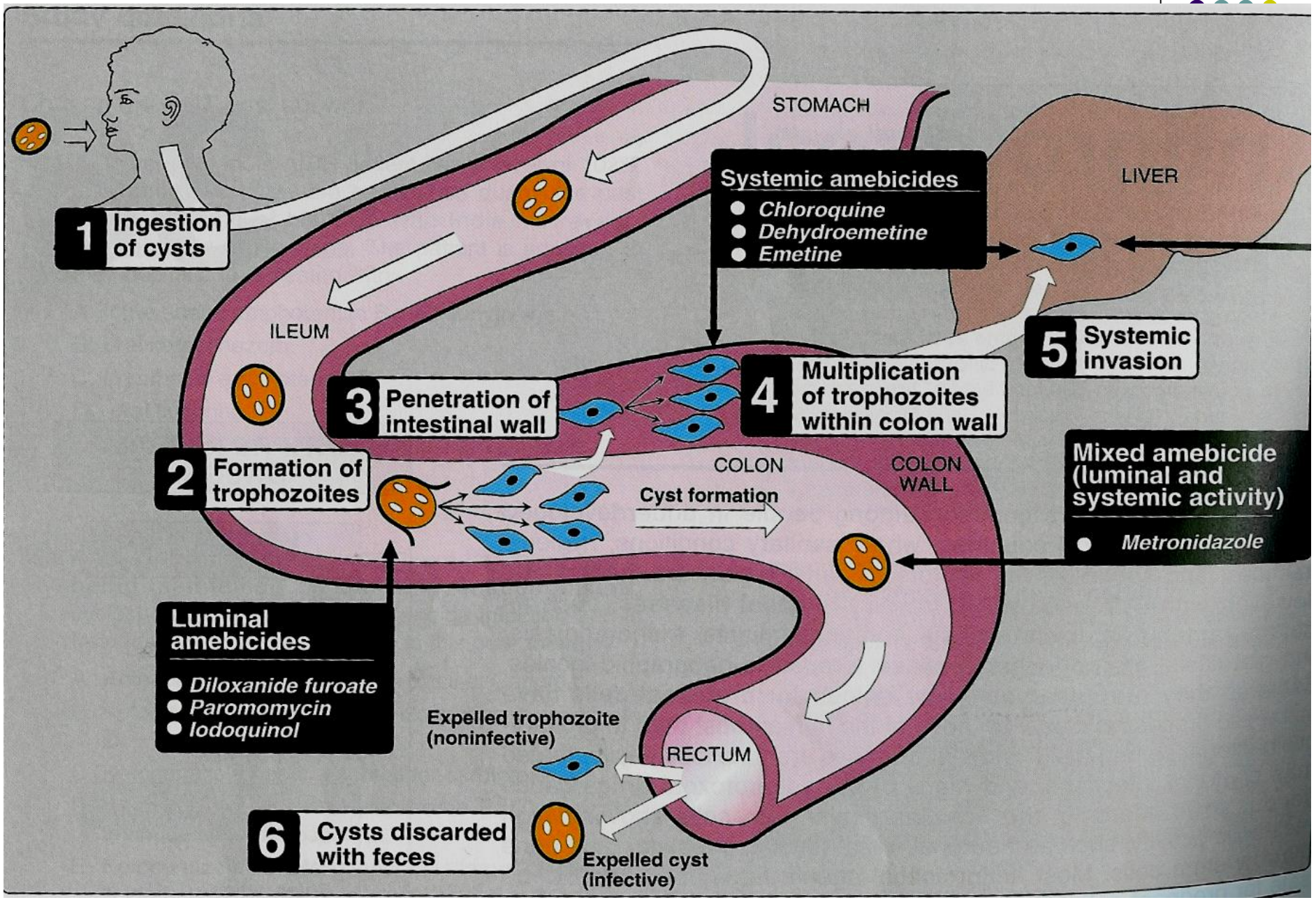
- **Amebiasis is a protozoal infection of intestinal tract.**

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

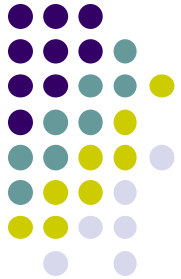
Life Cycle

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.**

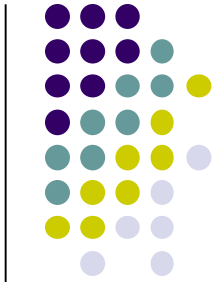
Clinical presentations

- **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

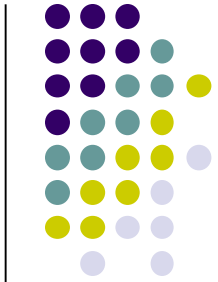
- **Acts on the parasites in the lumen of the bowel.**

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

Include

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

Tissue or systemic amebicides



- **Act on ameba in tissues**

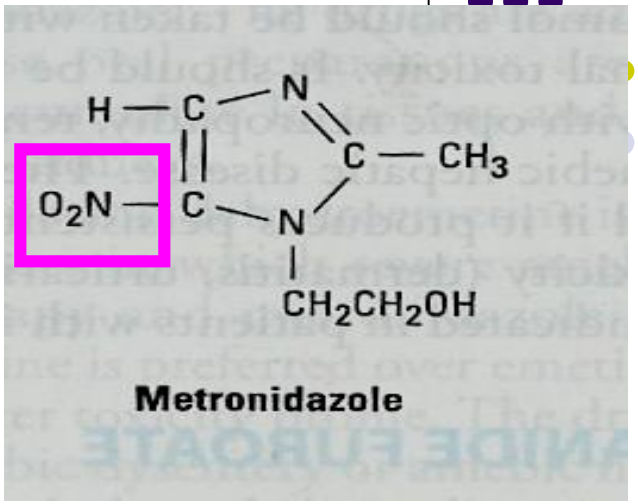
e.g. the intestinal wall and/or other extra-intestinal tissues as liver, brain and lung.

- **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

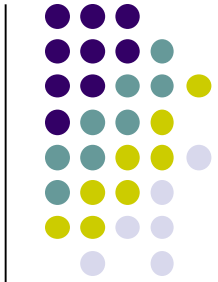


Metronidazole

- **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,**
- **convulsion (IV infusion, rare)**

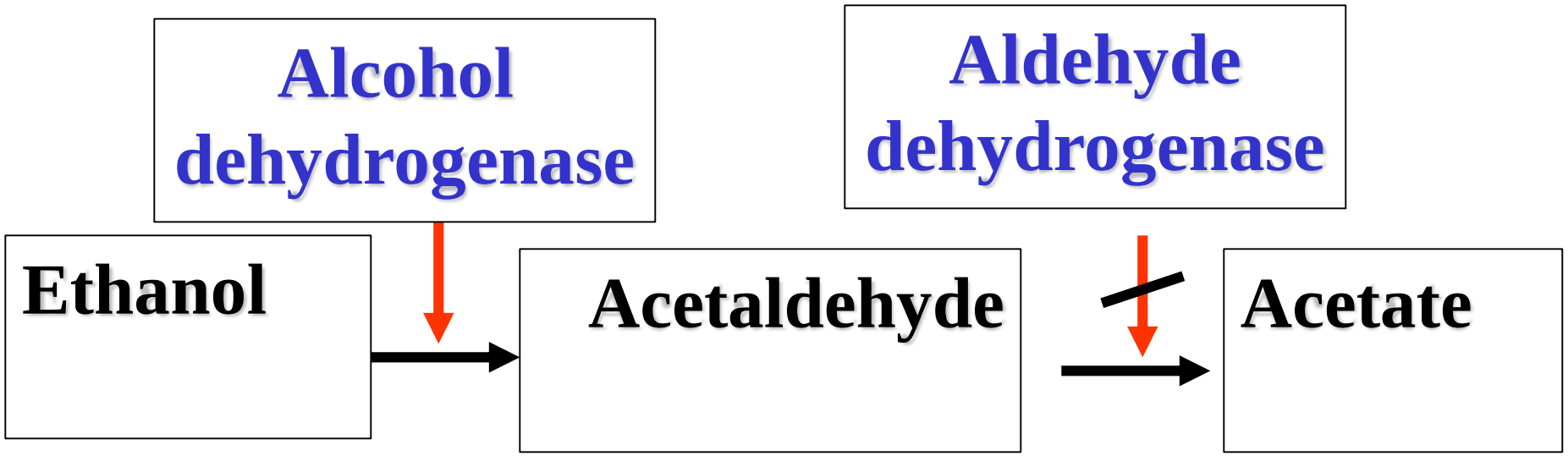
Dysuria, dark urine.

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)**

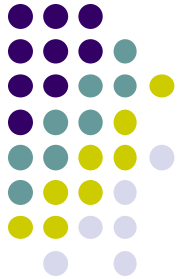
  increase duration of action of metronidazole

- **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.

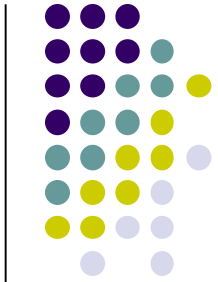
Advantages of tinidazole

- 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.

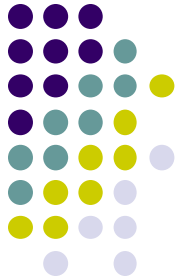
Include

- **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).

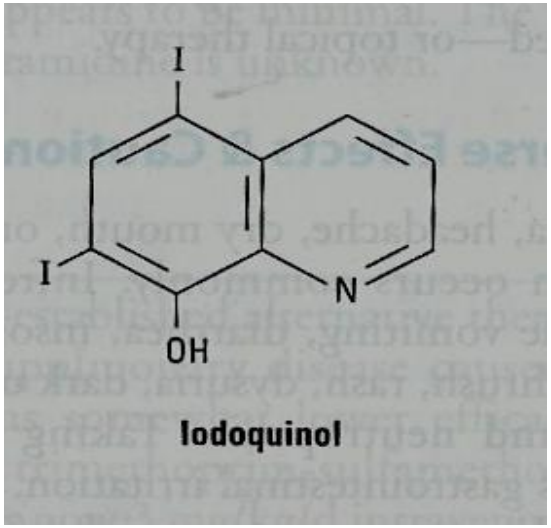
Iodoquinol

- 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

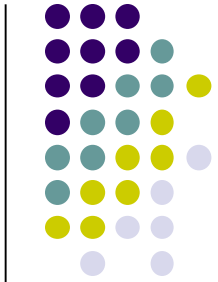
Adverse Effects

- **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).***
- **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.**

USE in diarrhea

- **Bacterial diarrhea**

caused by shigella, salmonella and E coli.

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.

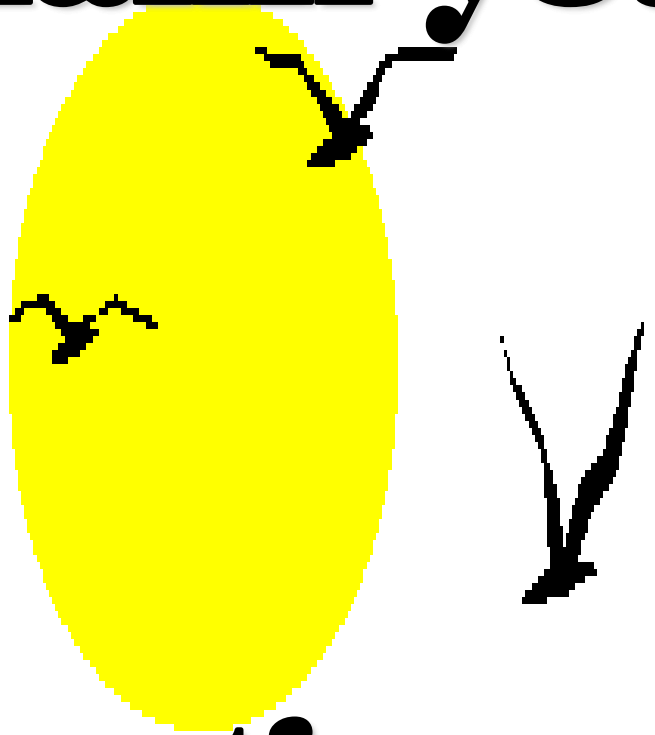
Cephalosporins

- **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 ?