PHARMACOLOGY

TEAM 432

# Treatment of Dysentery & Amoebiasis

## Objectives

1. To understand different causes of dysentery.
2. To describe different classes of drugs used in treatment of both bacillary dysentery and amebic dysentery.
3. To be able to describe actions, side effects of drugs for treating bacillary dysentery.
4. To understand the pharmacokinetics, actions, clinical applications and side effects of antiamebic drugs.
5. To be able to differentiate between three types of antiamebic drugs luminal amebicides, tissue amebicide and mixed amebicides.

## Color Guide

Slides = Black

Females slides = Green

Males slides= Blue

Explanation=Orange

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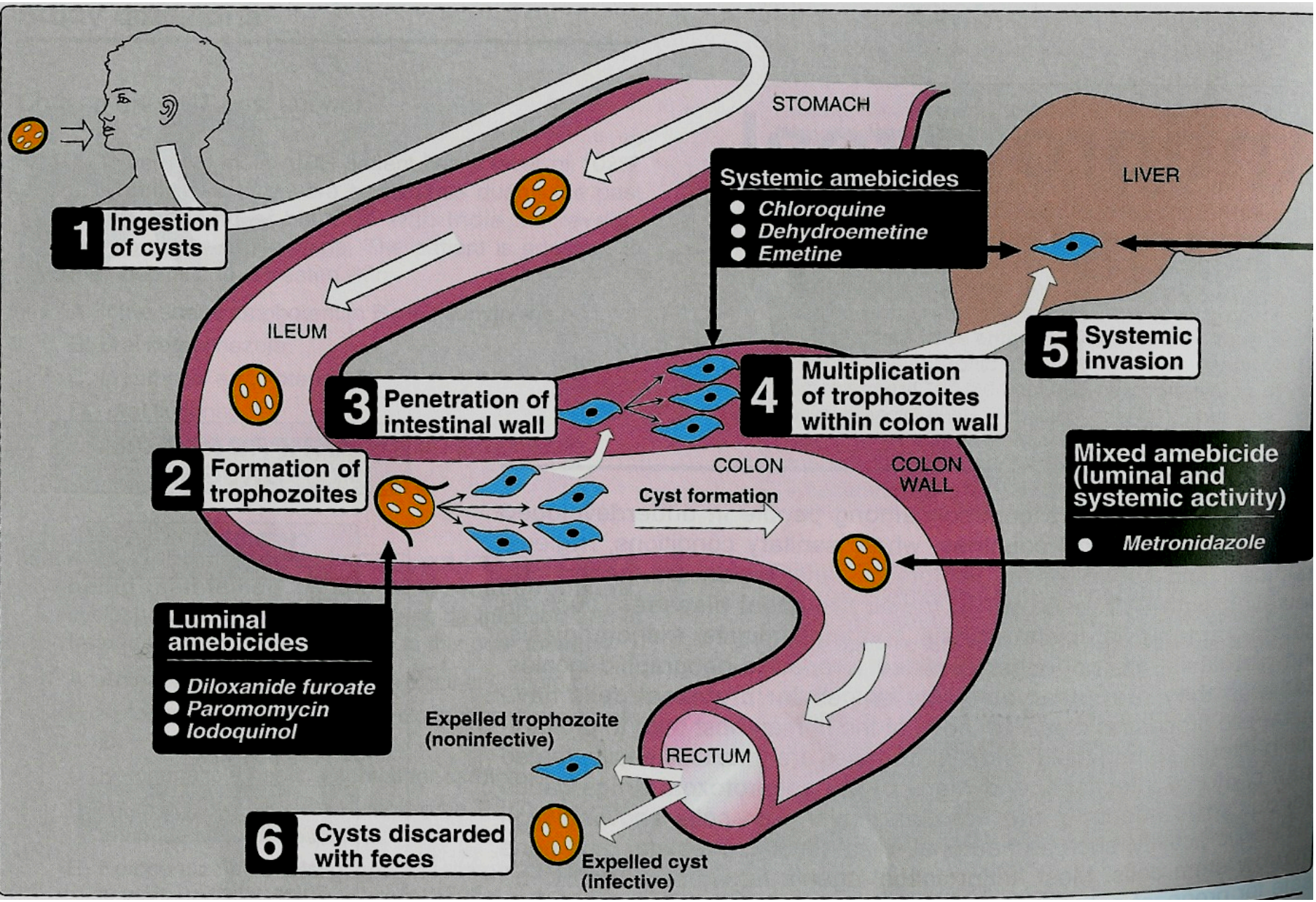
# Dysentery

| Definition | Causes | Treatment |
|---|---|---|
| **Dysentery:** is an inflammatory disorder of the intestine (colon), that results in severe diarrhea containing mucus and/or blood in the feces with fever and abdominal pain. | 1) Viral infections<br>2) Bacterial infections<br>3) parasitic infestations.<br>The two most common causes are:<br>Amebic dysentery *(protozoal infection mainly by Entameba Histolytica).*<br>Bacillary dysentery (or shigellosis) *(bacterial infection mainly by shigella).* | 1) Maintain fluid intake using oral rehydration (due to sever diarrhea) therapy or I.V fluid therapy.<br>أول شي نعطي سوائل !<br>ثم:<br>2) Antimicrobial agents should not be given untill stool analysis is done (emperic therapy should be started after sample of stool taken for analysis).<br>After stool results & detecting the pathogen we give more specific drugs. |

# Amebiasis

| Definition | Clinical presentations | Life Cycle |
|---|---|---|
| **Amebiasis is a protozoal infection of the intestinal tract that occurs due to ingestion of foods or water contaminated with cysts of Entameba Histolytica.not trophozoites**<br><br>**The patients show varying degree of illness from no symptoms to mild diarrhea to severe dysentery.** | **1. Asymptomatic intestinal infection *(Carriers, passing cysts in stool)***<br>**1. Mild to moderate intestinal disease *(colitis)***<br>**2. Severe intestinal infection *(amoebic dysentery)***<br>**3. Ameboma *(localized granulomatous lesion of colon)*.**<br>**4. Hepatic abscess, and other extra-intestinal diseases. (like, liver, brain, lungs, etc…..)** | **1. Cysts ingestion in contaminated food or water.**<br>**2. Liberation of trophozoites in the colon.if carries>stay in the lumen without symptoms but pass cysts with fecess**<br>**3. Invasion & penetration of intestinal wall.**<br>**4. Multiplication of trophozoites within colon wall.**<br>**5. Systemic invasion to liver,lungs and brain.**<br>**6. Cyst formation in rectum and excretion in feces.** |

# LIFE CYCLE


STOMACH
LIVER
ILEUM
COLON
COLON WALL
RECTUM
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
Cyst formation
Expelled trophozoite (noninfective)
Expelled cyst (infective)

# ANTIAMEBIC DRUGS

| Luminal amebicides | Tissue or systemic amebicides (not commonly used). | Mixed amoebicides |
|---|---|---|
| **Acts on the parasites in the lumen of the bowel.** used for treatment of asymptomatic amebiasis (carriers).<br><br>**Include**<br>Diloxanide furoate<br>Iodoquinol<br>**Antibiotics**<br>Paromomycin(antibiotic from aminoglycosides group) | **acts on ameba in the intestinal wall and liver (or any other extra-intestinal tissue).** Used for treatment of systemic form of the disease (intestinal wall infection or liver abscesses).<br><br>**Include**<br>Metronidazole<br>Emetine<br>Dehydroemetine<br>Chloroquine (**liver only**) | Effective against both luminal and systemic forms of the disease. Although luminal concentration is too low for single drug-treatment.<br><br>**Include**<br>Metronidazole<br>Tinidazole |

**Tinidazole** has similar activity but better potency than metronidazole, With longer duration of action (12-14h), a simpler dosing regimen and a better toxicity profile than metronidazole.

- Well tolerated in Children.

# METRONIDAZOLE

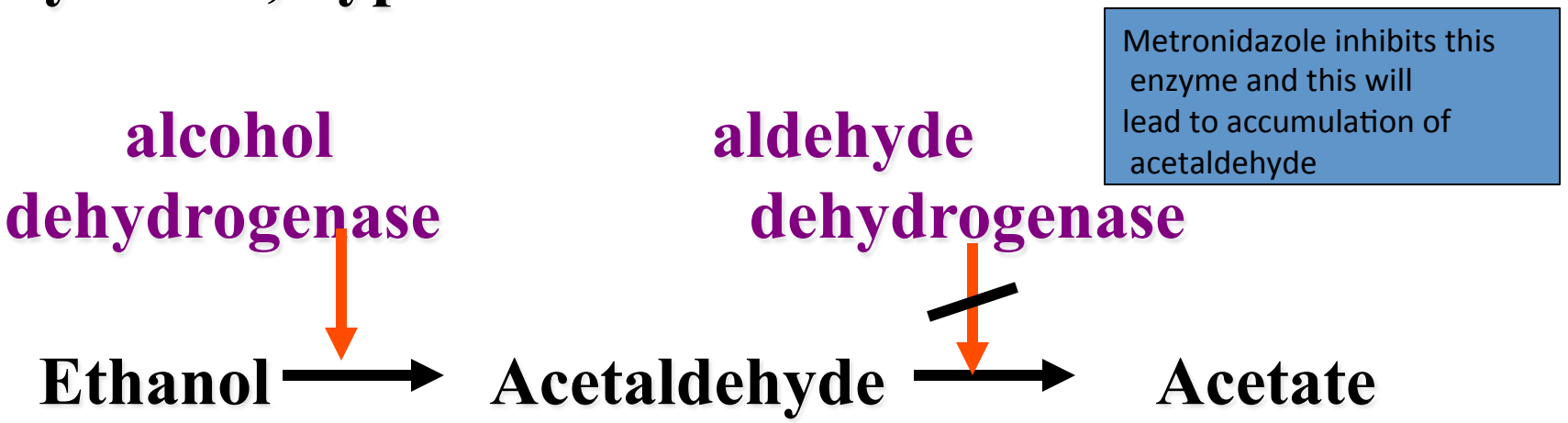
| METRONIDAZOLE | Pharmacokinetics | Clinical Uses |
|---|---|---|
| **Tissue ameobicide**<br>**Mixed amoebicide.**<br>**Drug of choice for treating invasive amebic infections (intestinal & Extra-intestinal).**<br>**Acts on trophozoites.**<br>**Has no effect on cysts.Doesn't eradicate cysts from intestines)so can't be used in luminal only invasive,in male slides they added the mixed info**<br>**Metronidazole inhibits DNA replication.**<br><br>Carriers have the pathogens in their lumen (that why we followed it with luminal amebicide) | **Given orally or IV.**<br>**Plazma half life 8h**<br>**Absorption is rapid and complete.**<br>**▪ Due to rapid absorption from GIT, *not reliably effective against luminal parasites.***<br>**Wide distribution to all tissues and body fluids (CSF, saliva, milk).**<br>**Metabolized in liver by mixed function oxidase → (cytochrome p450 enzyme) followed by glucuronidation (consider drug interactions).**<br>**Excreted in urine.**<br>**Clearance is decreased in liver impairment** | **1)Extra-luminal amoebiasis: is the drug of choice in all tissue amebiasis (*should be combined with luminal amebicide*) to get rid off pathogens from tissue + lumen (not becoming a carrier)**<br>**2)Giardiasis (cause by G. lamblia & common in children)**<br>**3)Broad spectrum of anaerobic bacteria e.g.,**<br>**Helicobacter pylori infection (eradication therapy)**<br>**Pseudo-membranous colitis (Clostridium difficile).**<br>**Dental infection** |

# METRONIDAZOLE

| Adverse effects | Drug interactions | CONTRAINDICATIONS / PRECAUTIONS |
|---|---|---|
| **GIT:**<br>Dry mouth, metallic taste(10-20%)<br>Nausea, vomiting<br>Oral Thrush (Moniliasis, yeast infection).<br>**CNS: Neurotoxicological effect**<br>Insomnia, dizziness peripheral neuropathy, paresthesia encephalopathy, convulsion (*IV infusion, rare*).<br>**Dysuria,** dark urine.<br>**Neutropenia**<br>**Disulfiram-like effect** if taken with alcohol (hot flushes, nausea, vomiting,). | • Enzyme inhibitors *(cimetidine, ketoconazole)*<br>↑ *duration of action of metronidazole bcuz of decrease metabolism*<br><br>• Enzyme inducers *(phenytoin and phenobarbitone antiepiliptic).*<br>↓ *duration of action of metronidazole*<br><br>Metronidazole inhibits CYP 450 family 2C9 & 3A4 so increases anticoagulant effect of warfarin. Increases lithium toxicity. | ▪ Pregnancy and nursing women. (Broad (لأنه)<br>▪ Alcohol intake disulifarm<br>▪ CNS diseases neurotoxological effect<br>▪ Severe hepatic disease metabolized in the liver<br>Severe renal disease excreted in the urine |

# Disulfiram like -effect

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



# Emetine and dehydroemetine

| Emetine and dehydroemetine | Clinical Uses |
| --- | --- |
| **Emetine** is an alkaloid derived from ipeca while **dehydroemetine** is a synthetic analog,<br>▪Both are effective against tissue trophozoites of E. histolytica causing irreversible block of protein synthesis.<br>▪Because of major toxicity concerns **they have been almost completely replaced by metronidazole**<br><br>▪Have erratic oral absorption.<br><br>▪Given preferably subcutaneously but could be given by IM, NEVER I.V.Has long plasma half life about 5 days.<br><br>●Metabolized & excreted slowly via kidney so they have a cumulative effect.Should not be used for more than 10 days (usually 3-5 days).<br><br>●Caution: the drug should not be used in patients with cardiac or renal disease, in young children,or in pregnancy. | Severe forms of amebiasis **acute amoebic dysentery** dehydroemetine is preferable due to less toxicity (3-5 days).<br>Ameobic liver disaeses<br>Intestinal wall infection<br><br>**Adverse effects:**<br><br>Dehydroemetine is less toxic than emetineGIT: nausea, vomiting, diarrhea.Serious toxicities: cardiotoxicityHypotension, cardiac arrhythmias, heart failure |

# Chloroquine

| Chloroquine | Adverse effects |
| --- | --- |
| • Anti-malarial drug<br>• Used in combination with metronidazole or dehydroemetine and luminal amebicide for amebic liver diseases.<br>Now not commonly used in amebeasis. | Adverse effects<br>❖ pruritus is common<br>❖ Nausea, vomiting, abdominal pain, anorexia.<br>❖ Blurring of vision.cuz it accumulates in the eyes<br>❖ Hemolysis in G6PD deficient patients |

# Luminal amoebicides

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

| Diloxanide furoate | Therapeutic Uses | Adverse Effects | Contraindications |
|---|---|---|---|
| Ester of diloxanide + furoic acid . Given orally.<br>It splits in the intestine, most of diloxanide is absorbed, conjugated to form a glucoronide which is excreted in urine (90%).<br>The unabsorbed diloxanide is the **amoebicidal agent (10%).**<br>Direct amoebicidal action against luminal forms<br>*Not active against trophozoites in intestinal wall or extra-intestinal tissues.*<br>Mechanism of action is unknown | Drug of choice for **asymptomatic intestinal infection (drug of choice in cysts passers).**<br>For complete eradication of amebic infections given along with tissue amebicides eg metronidazole.<br>to eradicate cysts of E histolytica after treatment of invasive disease with systemic amebicides. | Flatulence<br>Nausea, vomiting, abdominal cramps.<br>No serious adverse effects | Pregnancy<br>Children (less than 2 years). |

# Luminal amoebicides

| Iodoquinol | Adverse Effects | Uses |
|---|---|---|
| Is given orally<br>Not absorbed (90%), excreted in feces.<br>10% enter circulation, excreted as glucouronide in urine.<br>Mechanism of action is unknown<br>effective against the luminal trophozoites. | **GIT:** Nausea, vomiting, diarrhea.<br>**Peripheral neuropathy** including optic neuritis<br>Enlargement of the thyroid gland.<br>Iodine sensitivity<br>interference with thyroid function tests (increase protein-bound serum iodine, decrease in measured ***($^{131}I$ uptake).***<br><br>**CAUTION** : patients with optic neuropathy, renal or thyroid disease.<br>**discontinued** if it produces persistent diarrhea or signs of iodine toxicity ***(dermatitis, urticaria, pruritus, fever).stop the drug if he has persistant sensitivity*** | luminal amoebicide for<br><br>**asymptomatic amebiasis.** |

# Antibiotics

| Paromomycin Sulphate | Adverse effects | Precautions |
|---|---|---|
| Aminoglycoside antibiotic.<br>It is given orally and Not absorbed from GIT<br>Effective against luminal forms of ameba<br>Has :<br>1)direct amebicidal action ***(causes leakage by its action on cell membrane of parasite).***<br>2)Indirect killing of bacterial flora essential for proliferation of pathogenic amoebae.feeds on flora<br>**USES:** in chronic amebiasis to eliminate cysts (in cysts passers (**Dilaxonide and iodoquinolol are best for this purpose**) | Gastrointestinal distress and diarrhea. | Severe renal disease patients with GIT ulceration<br>Safe in pregnancy |

●Small amount absorbed is excreted unchanged in urine *(may accumulate with renal insufficiency).*

## Tetracyclines

- Very weak direct amoebicidal action.
- Acts mainly ***indirectly*** on bacterial flora.
- Used in severe cases of amoebic dysentery not responding to metronidazole

# Bacillary dysentery (shigellosis)

**Cefixime** Third-generation oral cephalosporin with broad activity against gram-negative bacteria
**Ceftriaxone** Third-generation cephalosporin with broad-spectrum, gram-negative activity. It acts by inhibiting cell wall synthesis

## Treated by:

- First give fluids because it causes diarrhea (dehydration)
- Fluoroquinolones such as ciprofloxacin
- Cotrimoxazole (trimethoprim- sulfamethoxazole)bactericidical although each one alone is bactriostatic
- Children or patient allergic to sulpha drugs parenetral ceftriaxone or oral cefixime (3dr gen cephalosporin) are safe and effective.
- Cotrimoxazole is commonly used in travelers diarrhea.

### Ciprofloxacin

- active against a variety of gram-positive and gram-negative bacteria.
- block bacterial DNA synthesis.
- Used in treatment of

1. Bacterial diarrhoea (caused by shigella, Salmonella and E coli).
2. Urinary tract infections first choice
3. Respiratory tract infections
4. Soft tissues, bones, and joint infections

**CONTRAINDICATED:** in
1) preganancy nursing Mother and Children,
2) Epilepsy, 3)Arrhythmias.
4) Should not be combined with antacids, divalent Cations

**ADVERSE EFFECTS:**
Arthropathy (damage of growing cartilage).
GIT disorders (nausea, vomiting, diarrhea).
CNS disorders (headache, dizziness).
CVS disorder (prolonged QT interval )
Phototoxicity.
Liver toxicity
Tendon related toxicity (ciprofloxacin).

# Summary for treatment of amebiasis

| | |
|---|---|
| Asymptomatic cyst carriers | *Iodoquinol* or *Paromycin* or *Diloxanide furoate* |
| Diarrhea/dysentery<br>Extraintestinal | *Metronidazole* plus *Iodoquinol* or *Paromycin* or *Diloxanide furoate* |
| Amebic liver absess | Metronidazole, Tinidazole,<br>or choloroquine |

# SUMMARY

- **Maintain *fluid* intake (oral rehydration therapy or Intravenous fluid therapy).**
- **asymptomatic luminal amebiasis is treated by luminal amebicides (diloxanide furoate, or paromomycin ).**
- **Intestinal and extra-intestinal amebiasis is treated by tissue amebicides (metronidazole is drug of choice usually being given first, followed by luminal amebicides to ensure complete eradication).**
- **Ciprofloxacin is the drug of choice in bacillary dysentery. In childrn and pregnancy ceftriaxone or cefixime is the choice. Cotrimoxazole is good in travelers diarrhea.**

Treatment of bacillary dysentery by: **Fluoroquinolones such as ciprofloxacin, Cotrimoxazole (trimethoprim- sulfamethoxazole)**

| Drug | MOA | Pharmacokinetics | ADRs |
|---|---|---|---|
| Ciprofloxacin:<br>Contraindicated:<br>• Children, pregnancy, nursing mother<br>• Epilepsy<br>• Arrhythmias.<br>Should not be combined with antacids, divalent cations. | Block bacterial DNA synthesis<br>Uses<br>- Bacterial diarrhea (caused by shigella, salmonella and E coli).<br>- Urinary tract infections<br>- Respiratory tract infections<br>- Soft tissues, bones, and joint infections | Active against a variety of gram-positive and gram-negative bacteria. | • Arthropathy (damage of growing cartilage).<br>• GIT disorders (nausea, vomiting, diarrhea).<br>• CNS disorders (headache, dizziness).<br>• CVS disorder (prolonged QT interval )<br>• Phototoxicity.<br>• Liver toxicity<br>TOXICITY: GIT, CNS and Tendon related |

## Treatment of dysentery and amebiasis :

| Drug | MOA+Uses | Pharmacokinetics | ADRs |
|---|---|---|---|
| **1] Luminal Amebicides:** | | | |
| **A)Diloxanide furoate:.**<br>**Drug of choice for asymptomatic intestinal infection.**<br><br>**Contraindications:**<br>• **Pregnancy.**<br>• **Children (less than 2 years).** | **Mechanism of action is unknown** | **-Ester of diloxanide + furoic acid .**<br>**-Given orally.**<br>**-It splits in the intestine, most of diloxanide is absorbed, conjugated to form a glucoronide which is excreted in urine (90%).**<br>**-The unabsorbed diloxanide is the amoebicidal agent (10%).** | (GIT as all luminal ambecides)<br>• **Flatulence**<br>• **Nausea, vomiting, abdominal cramps.**<br>• **No serious adverse effects** |
| **B)Iodoquinol:**<br>**Precautions:**<br>**-Iodoquinol should be used with caution in patients with optic neuropathy, renal or thyroid disease.**<br>**-discontinued if it produces persistent diarrhea or signs of iodine toxicity *(dermatitis, urticaria, pruritus, fever).*** | **Mechanism of action is unknown** | • **Is given orally**<br>• **Not absorbed (90%), excreted in feces.**<br>• **10% enter circulation, excreted as glucouronide in urine. (Same as Diloxanide furoate)** | • **GIT: Nausea, vomiting, diarrhea.**<br>• **Peripheral neuropathy including optic neuritis**<br>• **Enlargement of the thyroid gland.**<br>• **Iodine sensitivity.**<br>• **Interference with thyroid function tests (increase protein-bound serum iodine, decrease in measured *($^{131}I$ uptake).*** |
| C)Antibiotics | | | |
| 1- Paromomycin Sulphate: | **-Has direct amebicidal action *(causes leakage by its action on cell membrane of parasite).***<br>**-Indirect killing of bacterial flora essential for proliferation of pathogenic amoebae.** | • **Aminoglycoside antibiotic.**<br>• **It is given orally**<br>• **Not significantly absorbed from GIT**<br>**Small amount absorbed is excreted unchanged in urine *(may accumulate with renal insufficiency).*** | **Gastrointestinal distress and diarrhea.**<br><br>**Contraindications:**<br>• **Severe renal disease**<br>• **patients with GIT ulceration** |

**2- Tetracyclines:** Used in **severe cases of amoebic** dysentery not responding to **metronidazole combined with dehydroemetine.**
-Very weak direct amoebicidal action.

## 2-Tissue (Systemic) Amebicides:

**A) Emetine & Dehydroemetine:**
Emetine is an alkaloid derived from ipecac, while dehydroemetine is a synthetic analog.

Because of major toxicity concerns they have been almost completely replaced by metronidazole.

irreversible block of protein synthesis.

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

- Have erratic oral absorption. (Not preferred)
- 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.
- 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).

- Dehydroemetine is less toxic than emetine
- Pain at site of injection, abscesses.
- GIT: nausea, vomiting, diarrhea.
- Serious toxicities: Cardiotoxicity, Hypotension, cardiac arrhythmias, heart failure

**Contraindications:**
- Cardiac Disease.
- Renal Disease.
- Pregnancy.
- Young children

**B) Chloroquine:** (Anti-malarial drug.)
Used in combination with metronidazole or dehydroemetine and luminal amebicide for amebic liver diseases.

**B)Tinidazole:** has similar activity to metronidazole BUT has longer duration of action (12-14h), a simpler dosing regimen (once a day ) and a better toxicity profile than metronidazole.

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

## 3-Mixed Amebicides:

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

**A)Metronidazole:**
Drug of choice for treating amebic infections (intestinal & Extra-intestinal).

**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 family 2C9 & 3A4
*increases anticoagulant effect of warfarin.
*Increases lithium toxicity

Nitro group of metronidazole is reduced by protozoan leading to cytotoxic reduced product that binds to DNA and proteins resulting into parasite death.

**Uses:**
- Extra-luminal amoebiasis: is the drug of choice in all tissue amebiasis (*should be combined with luminal amebicide*).
- Giardiasis
- Trichomoniasis
- Broad spectrum of anaerobic bacteria e.g., Helicobacter pylori infection + Pseudo-membranous colitis

**Contraindications:**
Pregnancy and nursing women.
Alcohol intake
CNS diseases
Severe hepatic disease
Severe renal disease

- Acts on trophozoites,h as no effect on cysts.
- Given orally or IV.
- Absorption is rapid and complete (Due to rapid absorption from GIT, *not reliably effective against luminal parasites*)
- 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.
- Excreted in urine.
- Clearance is decreased in liver impairment

**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*).

**Other:**
- Dysuria, dark urine.
- Neutropenia (Abnormally low neutrophils)
- Disulfiram-like effect if taken with alcohol.

# MCQs

**Q1) Example for enzyme inhibitor drug:**
**A)Metronidazole**
**B)Emetine**
**C)Dehydroemetine**
**D)Chloroquine**

**Q2) Which drug we should be cautious in give to patient with thyroid enlargement:**
**A)Iodoquinol**
**B)Diloxanide**
**C)Chloroquine**
**D)Emetine**

**Q3) which drug we use when there is hepatic abcesses:**
**A)Paromycine**
**B)Emetine**
**C)Dehydroemetine**
**D)Chloroquine**

**Q1) A Q2) A Q3) D**

PHARMACOLOGY

TEAM 432

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