Lecture 3

Treatment Of dysentery and amoebiasis

Learning 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

- Additional Notes
- Explanation –Extra-
- Important

before starting, please check our GIT block correction

For any correction, suggestion or any useful information
do not hesitate to contact us: Pharmacology434@gmail.com

Dysentery

Definition: 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

Causes :

Dysentery results from:

1. Viral infection
2. bacterial infection
3. parasitic infection

The two most common causes are:

- Amebic dysentery: protozoal infection mainly by Entameba Histolytica).

Entamoeba histolytica exists in two forms:

1.Cysts (infective stage): can survive outside the human body

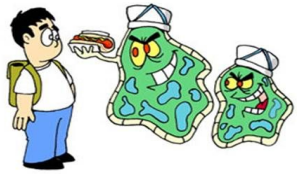
2.Trophozoites (non-infective; invasive stage)

- Bacillary dysentery (or shigellosis):bacterial infection mainly by shigella

Treatment:

- 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.

Amebiasis



Amebiasis

Is a protozoal infection of the intestinal tract that occurs due to ingestion of foods or water contaminated with cysts of Entameba Histolytica.

- The patients show varying degree of illness from:

No symptoms TO mild diarrhea TO severe dysentery.

Clinical presentations :

- Asymptomatic intestinal infection (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

Life Cycle

Cysts ingestion in contaminated food or water 1

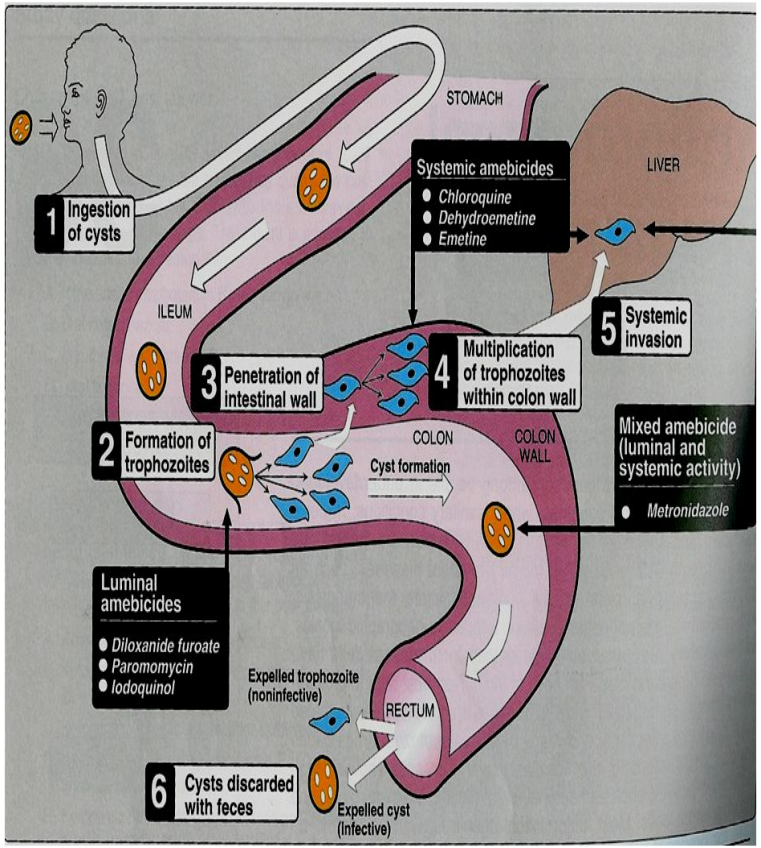
Liberation of **trophozoites** in the colon. 2

Invasion of intestinal wall 3

Multiplication of trophozoites within colon wall 4

Systemic invasion to other organs (liver, lungs, brain). 5

Cyst formation in rectum and excretion in feces 6



ANTI-AMEBIC DRUGS

Drug	Luminal amebicides	Tissue or systemic amebicides
Act on	Acts on the parasites in the lumen of the bowel.	Act on ameba in tissues e.g. the intestinal wall and/or other extra-intestinal tissues as liver, brain and lung.
Uses	Treatment of asymptomatic amebiasis (carriers).	Treatment of systemic form of the disease (invasive amebiasis) e.g. intestinal wall infection or liver abscesses
Include	❑ **Diloxanide furoate** ❑ **Iodoquinol** ❑ **Paromomycin**	❑ **Metronidazole/ tinidazole** ❑ **Emetine / dehydroemetine** ❑ **Chloroquine (liver only)**

Tissue or systemic amebicides

1-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

- Extra-luminal amoebiasis: is **the drug of choice in all tissue amebiasis**(*should be followed by luminal amebicides*.): to get rid off pathogens from tissue + lumen (not becoming a carrier)
- Giardiasis
- Trichomoniasis
- Broad spectrum of anaerobic bacterial infections

e.g. 1) Peptic ulcer *(Helicobacter pylori)* 2) Pseudo-membranous colitis *(Clostridium difficile).*

cont. 1-METRONIDAZOLE

Adverse 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

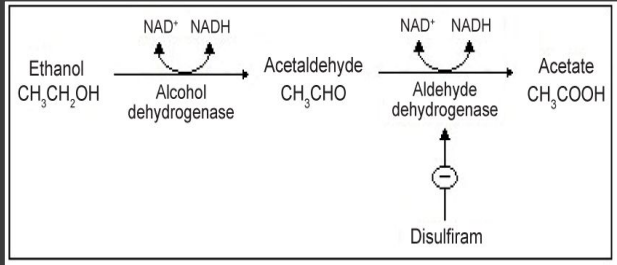
Disulfiram-like effect if taken with alcohol

Combining of :

metronidazole + alcohol =

causes nausea, vomiting, abdominal distress, flushing, headache, tachycardia, hyperventilation.

*Metronidazole inhibits this enzyme and this will lead to accumulation of acetaldehyde



Contraindications

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

Drug interactions

- ↑ **Enzyme inhibitors** (cimetidine, ketoconazole) duration of action of metronidazole
- ↓ **Enzyme Inducers** (phenytoin and phenobarbitone). duration of action of metronidazole
- **Metronidazole inhibits** CYP-450 (2C9 & 3A4) so:

*Increases anticoagulant effect of warfarin *Increases lithium toxicity

Tinidazole

Tinidazole has similar activity to metronidazole but better potency.

Advantages of tinidazole

- Has longer duration of action (12-14h)
- A simpler dosing regimen
- Better toxicity profile than metronidazole.

Tissue or systemic amebicides

Emetine and dehydroemetine

(natural source – basic in character – lipid soluble)

Pharmacodynamic and Kinetic	- Emetine is an alkaloid derived from ipeca (عرق الذهب) while dehydroemetine (Emetine without H+) is a synthetic analog. - Because of major toxicity (CV toxicity) concerns they have been almost completely replaced by metronidazole. - Have erratic (not dependable) oral absorption. - Given preferably subcutaneously but could be given by IM, NEVER I.V. (because it causes CV toxicity) - Has long plasma half life about 5 days. (1 dose will stay 5 days) - Metabolized & excreted slowly via kidney so they have a cumulative effect. (يعني الجرعه تقعد تتجمع بالجسم) - Should not be used for more than 10 days (usually 3-5 days). (because of the cumulative effect)
MOA	- Both are effective against tissue trophozoites of *E. histolytica* causing irreversible block of protein synthesis. (interfere with multiplication of E. h. trophozoites)
Uses	- Amoebic liver abscess. - Intestinal wall infections. - Severe forms of amebiasis acute amoebic dysentery dehydroemetine is preferable due to less toxicity (3-5 days).

Tissue or systemic amebicides

cont. Emetine and dehydroemetine

Adverse Effect	Dehydroemetine is less toxic than emetine. - GIT: nausea, vomiting, diarrhea.- - Serious toxicities: cardiotoxicity - Hypotension, cardiac arrhythmias, heart failure
C.I.	- the drug should not be used in patients with cardiac or (renal because its stays there for 5days) disease, in (young children especially less than 2 years because they're in developing stage) , or in pregnancy. * (No. 1 is metronidazole but if we are obligatory to use them both are effective but dehydroemetine is preferable because its less toxic)

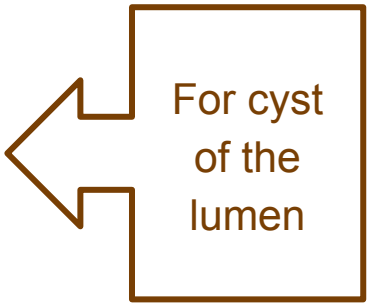
Chloroquine
(derivative from planet)

Uses	- Anti-malarial drug - Used in combination with metronidazole or dehydroemetine for only amebic liver diseases.
Adverse Effect	- Pruritus is common - Nausea, vomiting, abdominal pain, anorexia. - Blurring of vision. (because it get deposit in the eye) - Hemolysis in G6PD(Glucose 6 Phosphate Dehydrogenase) deficient patients. (Because its oxidizing drug and any oxidizing drug cause hemolytic anemia in G6PD deficient patients because they have vulnerable RBC cell membrane and the oxidizing drug destroy it)

Luminal Amebicides

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

❖ **Include:**
- **Diloxanide furoate***
- **Iodoquinol***



- **Antibiotics:**

- **Paromomycin**
- **Tetracycline**

Luminal Amebicides

1- Diloxanide Furoate

Pharmacodynamic and Kinetic	- Ester of diloxanide + furoic acid . - Given orally. - It splits in the intestine liberating diloxanide. (has absorbable and unabsorbed form) - The unabsorbed diloxanide is the amoebicidal agent . - The absorbed portion is excreted in urine.
MOA	- Mechanism of action is unknown - Direct amoebicidal action against luminal forms. (يعني against cyst but HOW is unknown) - Not active against trophozoites in intestinal wall or extra-intestinal tissues.
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 Effect	* (because its not absorbed only small amount is absorbed so most of the adverse effect are GIT) - Latulence - Nausea, vomiting, abdominal cramps.
C.I.	- Pregnancy. (affect fetus growing tissue) - Children (less than 2 years). (affect growth stage)

Iodoquinol
(has iodine)

Pharmacodynamic and Kinetic	- Is given orally - Poorly absorbed, excreted in feces.
MOA	- Mechanism of action is unknown - Effective against the luminal forms of amebiasis (against cyst)
Uses	- Luminal amoebicide for asymptomatic amebiasis. (Same as Diloxanide furoate)
Adverse Effect *(BY THE ABSORBED FORM WHILE THE UNABSORBED FORM DOES THE ACTION OF THE DRUG)*	- 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).*
C.I.	- 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	
Pharmacodynamic and Kinetic	- Aminoglycoside antibiotic. - Given orally - Not significantly absorbed from GIT - Small amount absorbed is excreted unchanged in urine ***(may accumulate with renal insufficiency).***
MOA	- 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 (because the bacterial flora is its food).
Uses	- Use in chronic amebiasis to eliminate cysts (in cysts passers).
Adverse Effect	- Gastrointestinal distress and diarrhea.
C.I.	- Severe renal disease - patients with GIT ulceration (because the drug itself can cause irritation)

Bacillary dysentery

(due to shigella infection)

Treated by:

- **Fluoroquinolones such as ciprofloxacin. (antibiotic)**
- **Cotrimoxazole* (CO means when combine it's bactericidal but if we used one alone it will be bacteriostatic) (trimethoprim-sulfamethoxazole) commonly used in traveler's diarrhea. (sulfonamide)**
- **In case of children or patient allergic to sulfonamides, cephalosporins can be used.**
- **Oral cefixime or parenteral ceftriaxone are safe and effective.**
- **They are 3rd generation cephalosporin.**
- **Act by inhibiting cell wall synthesis.**

*(use of it less because of resistance)

Ciprofloxacin

MOA	- Active against a variety of gram-positive and gram-negative bacteria. - Block bacterial DNA synthesis.
Uses	In treatment of: - Bacterial diarrhea (caused by shigella, salmonella and E coli). - Urinary tract infections - Respiratory tract infections - Soft tissues, bones, and joint infections
Adverse Effect	- Arthropathy (damage of growing cartilage). (so C.I. in children and pregnancy) - GIT disorders (nausea, vomiting, diarrhea). - CNS disorders (headache, dizziness). - CVS disorder (prolonged QT interval). - Phototoxicity. - Liver toxicity.
C.I.	- Children, pregnancy, nursing mother. - Epilepsy (because of CNS disorders) - Arrhythmias. (because of CV irregularities) - Should not be combined with antacids, divalent cations. (because the effect of it will be less)

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 (**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.**

Summary for treatment of amebiasis

Asymptomatic dysentery (cyst carriers)	**Luminal amebicides** **Diloxanide or iodoquinol or Paromomycin**
When symptoms range from mild to sever : **Amebic colitis and dysentery** **ameboma,** **and extra-intestinal disease**	**Metronidazole or tinidazole followed by luminal amebicides**
Hepatic abscess	**Metronidazole or tinidazole** if it doesn't respond we use **choroquine or dehydroemetine** but we don't give emetine because of its CV toxicity.

MCQs:

1-B).
2-A).
3-D).
4-C).
5-G).

1- which one of these drugs has half life of 5 days:
A)Diloxanide
B)Dehydroemetine
C)Iodoquinol
D)Paromomycin

2- which one of these drugs are used in only amebic liver diseases:
A)Chloroquine
B) Ceftriaxone
C) Cefixime
D) Ciprofloxacin

3- which one of these Luminal amoebicides should not be used in a Pregnant lady:
A) Iodoquinol
B) Paromomycin
C) Tetracycline
D) Diloxanide furoate

4- which one of these Luminal amoebicides should not be used in a patient with optic neuritis:
A) Tetracycline
B) Paromomycin
C) Iodoquinol
D) Diloxanide furoate

5- 2 years child has bacillary dysentery. which one of these drugs is the most suitable:
E) Ciprofloxacin
G) ceftriaxone

Good luck!

Done by Pharmacology team

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