Revised & Approved

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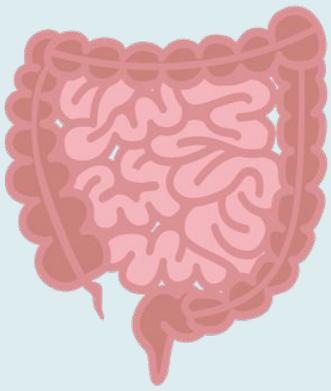
Pharmacology 439

MED439



Gastrointestinal Block

Pharmacology Team 439

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Treatment of Dysentery and 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 types of antiamebic drugs; luminal amebicides, and tissue amebicide

Editing file | Summary

Dysentery

It is an inflammatory disorder of the intestine especially of the Colon that result in severe Diarrhea containing **mucus and/or blood** in the feces with **fever and abdominal pain** caused by any kind of infection.

Causes

Bacillary dysentery
Bacterial infection mainly by **Shigella**

Parasitic infection
Protozoal infection mainly by **Entamoeba Histolytica**

Viral infection

Treatment

Maintain fluid intake using **oral rehydration**
Or by using **IV** fluid therapy

Antimicrobial agents
Should not be given until **stool** analysis
Is done to **specify** the etiological agents

Antidiarrheal Drugs

Antidiarrheal Drugs

Remember IBS-D treatment?

Drug	Loperamide Morphine Derivative	Diphenoxylate + Atropine Not recommended (only seen in developing countries)
MOA	Opioid-receptor agonist	
P.k	• μ-opioid receptors in the myenteric plexus of the large intestine. • Doesn't cross BBB ↓ • **Minimal** liability for **addiction**	• Side effects are mainly due to atropine. This is why we added atropine, to make the patient reluctant to take more medication and ↓ chances of getting addicted due to undesirable side effects • Can cross BBB ↓ • Has **high** liability for **addiction**
Contraindication	Treatment should be avoided in: (Signs of infection) **1.** Presence of high fever **2.** If the stool is bloody. **3.** C. difficile infections They are contraindicated because they **delay fecal excretion** that can prolong fever, as it increases the risk of toxin and source of infection **retention** and precipitation of toxic megacolon.	

Amebiasis

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

Cyst (infective stage)

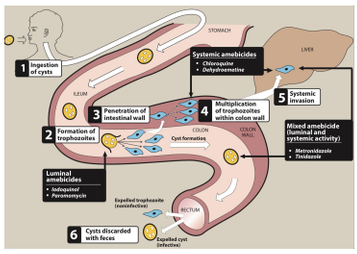
- Can survive outside the human body.
- When ingested, liberate trophozoites in the lumen of the intestine

Exist in two forms

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

Live cycle of Amebiasis



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

Clinical presentation

1. The patients show varying degree of illness from no symptoms to mild diarrhea to severe dysentery
2. **Asymptomatic amebiasis**
   Aka Carriers (passing cysts in stool)
   Cyst only in the colon.
3. **Ameboma**
   (localized granulomatous lesion of colon)
   It has to be treated, if not it can evolve into invasive colitis. Its picture is very similar to colon rectal carcinoma so stool analysis is done to differentiate between them
4. **Amoebic dysentery**
   Severe intestinal infection
5. **Colitis**
   Mild to moderate intestinal disease
6. **Hepatic abscess**, & other extra-intestinal disease

Antiamebic drugs

types	Tissue or systemic amebicides	Luminal amebicides
Site of action	Act on amoeba in tissues E.g. the intestinal wall and/or other extra-intestinal tissues as liver, brain, and lung.	Acts on the parasites in the lumen of the bowel (kills the cysts)
Uses	Treatment of systemic form of the disease (invasive amebiasis) e.g. intestinal wall infection or liver abscesses.	• Treatment of **asymptomatic** amebiasis (carriers). • Eradicate cysts of E.histolytica after treatment of invasive disease (after tissue amebicides).
Drugs	1. Metronidazole/Tinidazole (Same action) 2. Emetine/DehydroEmetine (reduced form) 3. Chloroquine **(liver ONLY)**	1. Diloxanide furoate 2. Iodoquinol 3. Antibiotic: • Paromomycin (Aminoglycoside) • Tetracycline not important

A) Tissue or Systemic Amebicides

Drug	Metronidazol
MOA	A Tissue amoebicide that acts on (tissue form) **trophozoites** by: - Inhibiting DNA replication (like fluoroquinolones) - Doesn't eradicate **cysts** from intestine because it has good oral absorption, so it doesn't reach intestine
P.K	● Given orally or IV ● Absorption is rapid and complete ● Wide distribution to all tissues and body fluids (CSF, saliva, milk). ● Plasma half life is (8h). You have to give it frequently (no need to memorize it) ● **Metabolized in liver (by CYP-450**) by mixed function oxidase followed by glucuronidation (consider drug interactions). ● Clearance is decreased in liver impairment. ● Excreted in urine. **Remember**: It has absorption distribution (CSF, saliva, milk)
Uses (DOC for all)	● Drug of choice for treating invasive amebic infections (intestinal & extraintestinal amebiasis) **Should be followed by luminal amebicides** to eradicate cysts ● Giardiasis ● Trichomoniasis ● Anaerobic bacterial infections (only when there's parasitic infection, because it has many ADRs) ○ Peptic ulcer (Helicobacter pylori) triple therapy. ○ Pseudomembranous colitis (Clostridium difficile)
ADRs Mnemonic **(METHOD)**: Metallic taste Encephalopathy Tint urine brown, Headache, Oral thrush Disulfiram like effect	**CNS: Neurotoxic effects:** ● Insomnia, dizziness ● Peripheral neuropathy, paresthesia. ● Encephalopathy, convulsion (IV infusion, rare but important). **GIT:** ● Dry mouth, metallic taste (because of salivary excretion) ● Nausea, vomiting, diarrhea (reduced by taking it after a meal). ● Oral Thrush because it kills normal mouth flora. (Moniliasis, yeast infection). **Other ADRs:** ● **Disulfiram-like** effect if taken with alcohol ● Dysuria, dark urine, neutropenia.
C.I	● Severe **renal** disease ● Severe **hepatic** disease ● CNS diseases. ● Alcohol intake ● Pregnancy (to avoid malformation in infants) and breastfeeding women.
Drug Interaction Refer to CYP lecture	**Enzyme inhibitor** E.g. cimetidine, ketoconazole → increase duration of action of Metronidazole **Enzyme inducers** E.g phenytoin, phenobarbitone → decreased duration of action of Metronidazole **It inhibits CYP-450 (2C9 & 3A4):** ● Increases anticoagulant effect of warfarin (Low TI) ● Increases lithium (anti-manic) toxicity
Alcohol Interaction (Disulfiram-like)	Combining metronidazole & alcohol causes (nausea, vomiting, abdominal distress, flushing, headache, tachycardia, hyperventilation). Remember #CNS? Ethanol —(Alcohol dehydrogenase)→ Acetaldehyde —(Aldehyde dehydrogenase ✖)→ Acetate

A) Tissue or Systemic Amebicides, cont.

Drug	**Tinidazole** **Dr Ishfaq: T for long Time**
MOA	Similar activity to metronidazole but **better potency**
P.K	**Advantages of tinidazole:** ○ **Longer** duration of action (12-14h) ↓ frequency of admin. ○ Simpler dosing regimen ○ Better **toxicity** profile than metronidazole

Drug	**Emetine,** Dehydro**Emetine**
MOA	Both are effective against tissue **trophozoites** of E. histolytica causing irreversible block of protein synthesis.
P.K	● Emetine is an alkaloid derived from ipecac عرق الذهب (emetic plant) while dehydroemetine is a synthetic analog. ● Have erratic oral absorption. ● Given preferably subcutaneously (minimize ADRs) but could be given IM, **Never given as I.V** (causes immediate arrhythmia and CVS toxicity) ● Long plasma half life about 5 days ● Should not be used for more than 10 days (usually 3-5 days) ● Metabolized & excreted slowly via kidney so they have a **cumulative effect:** build up of drug in plasma with every dose causing toxicity, accumulates in body. ● Because of major toxicity concerns they have been almost completely replaced by metronidazole
Uses	● Amoebic liver abscess ● Intestinal wall infections ● Severe forms of amebiasis: acute amoebic dysentery, dehydroemetine is preferable due to less toxicity (3-5 days)
ADRs	● **Dehydroemetine is less toxic** than Emetine ● Serious toxicity: **cardiotoxicity** (Hypotension, cardiac arrhythmias, heart failure) ● GIT: nausea, vomiting, diarrhea
C.I	● Patients with cardiac or renal disease ● Pregnancy ● Young children

Drug	**Chloroquine**
MOA	Anti-malarial drug.
Uses	Alone/Combination with metronidazole or dehydroemetine for **amebic liver diseases.**
ADRs	● Pruritus is common ● Blurring of vision (sign of toxicity of chloroquine) deposits in retina, Remember #CNS Eye? ● **Hemolysis in G6PD deficient patients** (because it has **oxidative** property) ● Nausea, vomiting, abdominal pain, anorexia (avoided if taken with food)

B) Luminal Amebicides

Drug	Diloxanide furoate
MOA	• MOA is unknown • Direct* amoebicidal action against luminal forms **(Cyst)** *has to come in contact with cyst • Not effective against trophozoites in intestinal wall or extra-intestinal tissues.
P.K	• **Ester** of diloxanide + Furoic acid • Given orally • Splits in the intestine liberating diloxanide • The little **unabsorbed diloxanide is the amoebicidal agent**, i.e. furoate has no effect • The absorbed portion (very little) is excreted in urine
Uses	• Drug of choice for **asymptomatic** intestinal infection (cyst passers) • To **eradicate** cysts of E. histolytica after treatment of invasive disease with systemic amebicides
ADRs	• Flatulence • Nausea, vomiting, abdominal cramps.
C.I	Because there are no studies on them so it's not safe: • Pregnancy • Children (less than 2 years).

Drug	Iodoquinol
MOA	• M.O.A is unknown • Effective against the luminal forms of amebiasis
P.K	• Given orally • Poorly absorbed, excreted in feces.
Uses	Luminal amoebicide for asymptomatic amebiasis
ADRs Mostly due to iodine	• GIT: Nausea,vomiting, diarrhea. • **Peripheral neuropathy** including optic neuritis (pain in the eye and temporary vision loss. If patient complains of vision loss we should stop the drug). • Enlargement of the **thyroid** gland • Iodine sensitivity • Interference with thyroid function tests - Increase protein-bound serum iodine, decrease in measured (I^{131} uptake).
C.I	• 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)

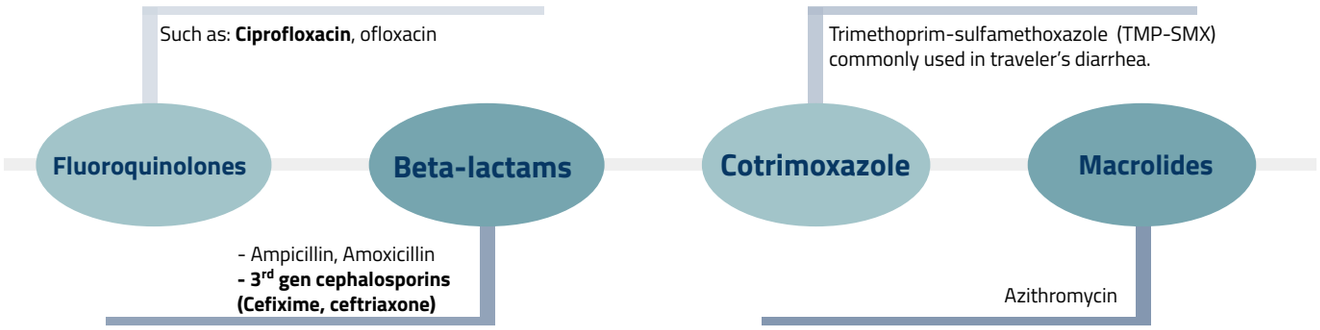
B) Luminal Amebicides

Drug	Paromomycin sulphate
MOA	• **Aminoglycoside** antibiotic • **Direct** amebicidal action: causes leakage by its action on cell membrane of parasite • **Indirect** effect: killing of bacterial flora essential for proliferation of pathogenic amoebae
P.k	• Effective only against luminal forms of ameba • Given orally • Not significantly absorbed from GIT • Small amount absorbed is excreted unchanged in urine (may accumulate with renal insufficiency)
Uses	Chronic amebiasis to eliminate cysts (in cysts passers)
ADRs	Gastrointestinal distress and diarrhea
C.I	• Severe renal disease (Nephrotoxicity, accumulation of the drug can cause renal damage). • Patients with GIT ulceration

Summary of Treatment of Amebiasis (Dr's Slides)

Asymptomatic dysentery (cyst carriers)	**Luminal amebicides:** Diloxanide or iodoquinol or Paromomycin
Amebic colitis & dysentery. Ameboma, & Extra-intestinal disease	Metronidazole or Tinidazole followed by **luminal amebicides**
Hepatic abscess	Metronidazole or Tinidazole or Dehydroemetine or Chloroquine

Bacillary dysentery treated by:



- Resistance to ampicillin, amoxicillin and sulfonamides has been reported worldwide, and these agents are not recommended as empirical therapy
- Antimicrobial therapy is typically administered for 5 days (one or two drugs according to the severity of the disease).

Drug	Ciprofloxacin
MOA	• Active against a variety of gram-positive and gram-negative bacteria • Block bacterial DNA synthesis and growth (DNA gyrase and topoisomerase)
Uses	• Fluoroquinolones are first-line treatment for shigellosis • Bacterial diarrhea caused by shigella, salmonella and E coli • Drug of choice for bacillary dysentery • Urinary tract infections • Respiratory tract infections • Soft tissues, bones, and joint infections
ADRs	• Arthropathy (damage of growing cartilage) • Phototoxicity • Liver toxicity (make sure there is no liver issues before prescribing) • GIT disorder (nausea, vomiting, diarrhea) • CNS disorders (headache, dizziness) • CVS disorders (prolong QT interval⟶ may cause torsades de pointes) Most Serious
C.I	• Children, pregnancy, nursing mother. • Epilepsy • **Shouldn't be combined with antacids** because they contain divalent cations like Mg^{++} and Ca^{++} which cause complexation of these drugs which obstructs absorption (contains cations like Mg^{++} & Ca^{++} that binds to the drug causing reduction in its efficacy) • Arrhythmias

Drug	Cephalosporins (Cefixime, Ceftriaxone)
MOA	Act by inhibiting cell wall synthesis interfering with synthesis of peptidoglycan (major structural component of bacterial cell wall)
P.K	Oral cefixime or parenteral ceftriaxone are safe and effective
Uses	• 3rd generation cephalosporins are second line therapy • In case of children or patient allergic to sulfonamides, cephalosporins or azithromycin may be used. • Drug of choice in case of pregnancy or children (cotrimoxazole and ampicillin are also safe, used depending on sensitivity)

Summary

Type	Drug	MOA	Uses	ADRs
Tissue or Systemic Amebicides	**Metronidazole**	Acts on trophozoites by Inhibiting DNA replication	- Drug of choice for treating invasive (tissue) amebic infections (intestinal & extraintestinal amebiasis) - Broad spectrum of anaerobic bacterial infections	**GIT:** - Dry mouth, metallic taste. - Oral Thrush (yeast infection). **CNS:** (Neurotoxicological) **Other: Disulfiram-like** effect with alcohol intake
	Tinidazole			
	Emetine & dehydroemetine	Against tissue trophozoites causing irreversible block of protein synthesis	- Amoebic liver abscess - Intestinal wall infections - Severe forms of amebiasis: acute amoebic dysentery **dehydroemetine** is preferable	Serious cardiotoxicity Because of major toxicity concerns, they have been almost completely replaced by metronidazole.
	Chloroquine	Anti-malarial drug	Amebic liver diseases, in combination with Metronidazole & dehydroemetine	- Pruritus - Blurring of vision. - Hemolysis in G6PD deficient patients.
Luminal Amebicides	**Diloxanide furoate**	Unknown	- DOC for asymptomatic intestinal infection (cyst passers) - To eradicate cysts of E. histolytica	Flatulence, Nausea, vomiting, abdominal cramps.
	Iodoquinol		Luminal amoebicide for asymptomatic amebiasis.	- **Peripheral Neuropathy** (Optic neuritis) - Thyroid gland enlargement - Interference with thyroid function tests
	Aminoglycoside (Paromomycin sulphate)	**Direct** amebicidal: leakage by its action on cell membrane of parasite **Indirect**: killing of bacterial flora essential for proliferation	Chronic amebiasis to eliminate cysts (in cysts passers).	Gastrointestinal distress and diarrhea **CI:** Severe renal disease, GIT ulceration
Bacillary Dysentery	**Fluoroquinolone** (Ciprofloxacin)	Block bacterial DNA synthesis and growth. (DNA gyrase and topoisomerase)	- Bacterial diarrhea caused by shigella, salmonella and E coli. - UTI, RTI - Soft tissues, bones, & joint infections	- Arthropathy - Phototoxicity **C.I:** - Children, pregnancy, nursing mother. - Epilepsy, arrhythmia - Shouldn't be combined with antacids, divalent cations
	Cephalosporins (cefixime, ceftriaxone)	Inhibits cell wall synthesis	- 3rd Gen are second line - In case or patient allergic to sulfonamides - DOC in case of pregnancy and children	

MCQs

Q1: Which of the following can't be given orally?			
A- metronidazole	B-cefixime	C-paromomycin	D-ceftriaxone
Q2: 17-year-old girl who is suffering from schizophrenia had bacterial diarrhea caused by salmonella refused to take the antibiotic you gave to her because she was worried from the side effects. which of the following is NOT one of the side effects of the antibiotic you gave to her?			
A- Arthropathy	B-urinary retention	C-phototoxicity	D-liver toxicity
Q3: Which one of the following antiamoebic drug can not be used if we have patient with cardiac disease?			
A-iodoquinol	B- tinidazole	C- cefixime	D-emetine
Q4: Tinidazole is different from Metronidazole by which of the following?			
A- has less duration of action	B-has less potency	C-has long duration of action	D-has caustic taste
Q5: What is the Drug of choice for invasive amebic infection?			
A-ciprofloxacin	B-emetin	C-metronidazole	D-cefixime
Q6: Which one of the following can not be used in patient with hemolytic anemia due to genetic defect in glucose phosphate dehydrogenase in his RBCs?			
A- chloroquine	B-emetin	C-metronidazole	D-tinidazole
Q7: 26 years old male who came to the hospital for routine test with no symptoms or diarrhea, the stool analyze was done also. Which shown that he has many cysts of Entameba Histolytica. Which one of the following antiamoebic drug can be used in his case?			
A- metronidazole	B-diloxanide furoate	C-dehydroemetine	D-chloroquine
Q8: Which of the following drugs interferes with thyroid function tests?			
A- diloxanide furoate	B-emetin	C-tinidazole	D-iodoquinol
Q9: A 25-year-old patient presents to the Emergency Department suffering from bloody diarrhoea and pain in his right abdomen for the past 2 weeks. He just returned from a holiday in the tropics. Entamoeba histolytica is detected in a stool sample.Which of the following medications would be most appropriate therapy?			
A- Erythromycin	B-vancomycin	C-Mebendazole	D- Metronidazole
Q10: Depending on your answer in the previous question, The patient would develop:			
A- Metallic taste	B-Angina	C-Disulfiram like effect	D- A and C

1	2	3	4	5	6	7	8	9	10
D	B	D	C	C	A	B	D	D	D

SAQ

Q1) list 3 side effects of chloroquine

Q2) mention MOA of Cephalosporins

Q3) mention 4 Pharmacokinetics of metronidazole

Q4) mention 4 uses of ciprofloxacin

Q5) 29 year old mother of 2 children came to the ER with hypotension and cardiac arrhythmia after asking her husband if she suffers from any diseases he told you she has heart failure and she is currently being treated from an E.histolytica infection.

A) What drug did she take ?
B) What the is the mechanism of action of the drug she is using ?
C) list other 2 side effects of this drug

Answers

A1) 1- blurred vision 2- pruritus 3- nausea, vomiting

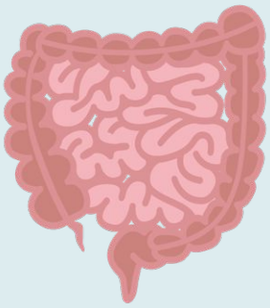
A2) Act by inhibiting cell wall synthesis interfering with synthesis of peptidoglycan (major structural component of bacterial cell wall)

A3) 1- given orally or IV 2- absorption is rapid and complete 3- plasma half-life is (8h) 4- excreted in urine

A4) 1- urinary tract infection 2- respiratory tract infection 3- drug of choice for bacillary dysentery 4- soft tissue, bones, joint infection

A5) A) dehydroemetine B) irreversible block of protein synthesis C) nausea and diarrhea

Feedback Form



Gastrointestinal Block

Pharmacology Team 439

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