Revised By
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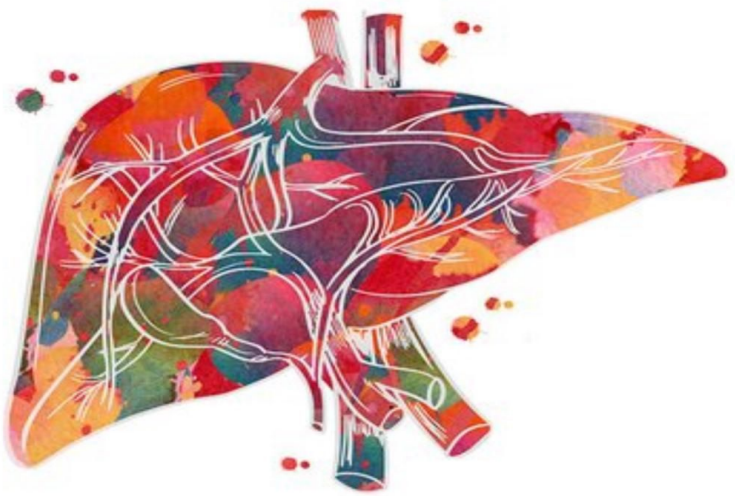
Pharmacology
Team 437

MED437
KING SAUD UNIVERSITY



Treatment of dysentery and amoebiasis

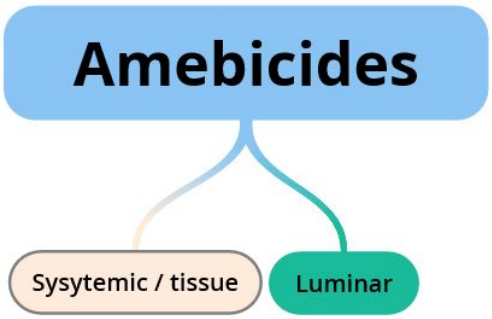
Objectives:

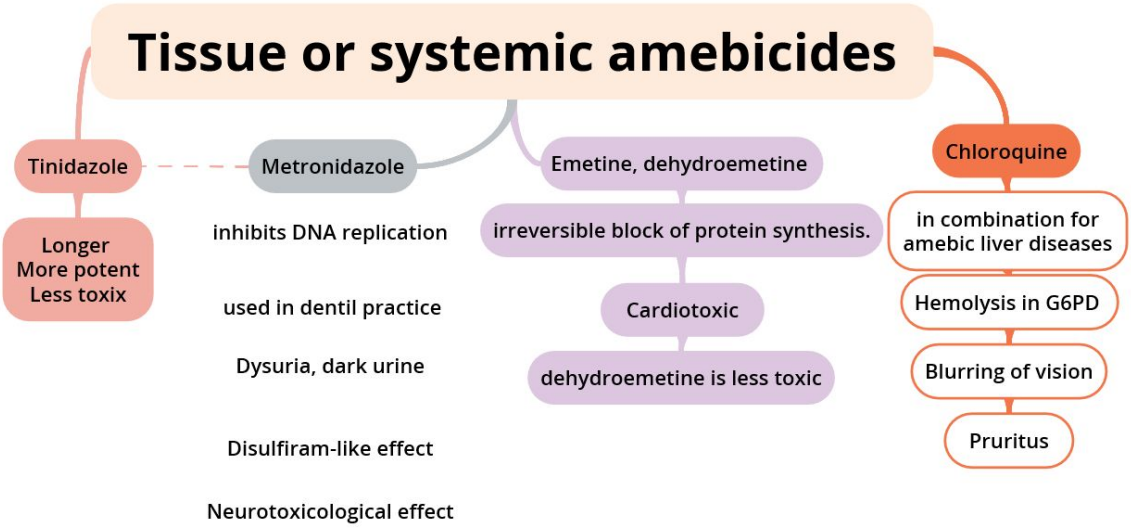
1. To understand different causes of dysentery.
2. To describe different classes of drugs used in treatment of both bacillary dysentery and amebic dysentery.
3. To be able to describe actions, side effects of drugs for treating bacillary dysentery.
4. To understand the pharmacokinetics, actions, clinical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

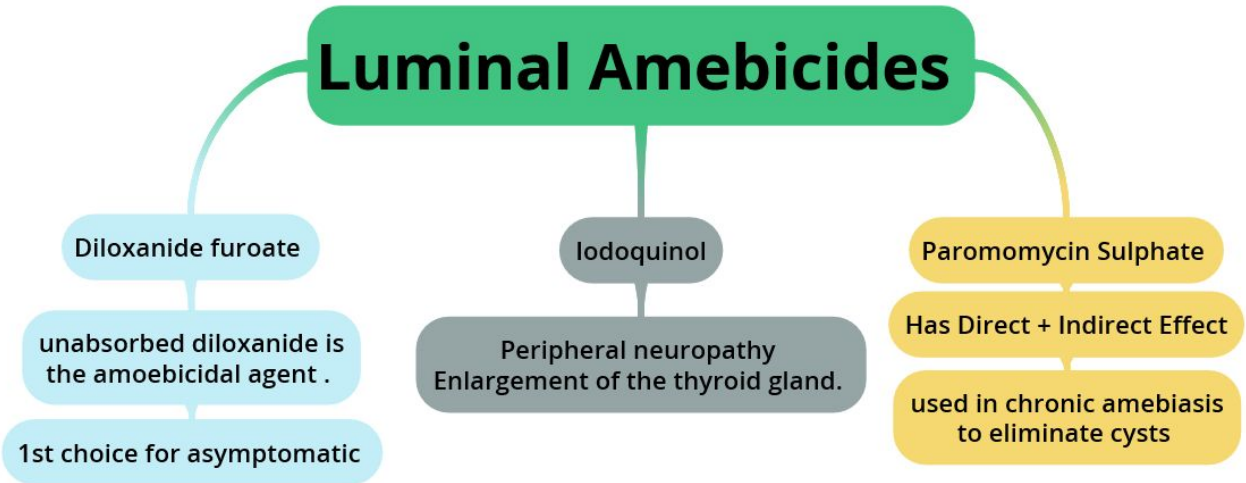
Editing File

Color index: Important Note Extra

Mind Maps


Amebicides
Sysytemic / tissue
Luminar


Tissue or systemic amebicides
Tinidazole
Longer
More potent
Less toxix
Metronidazole
inhibits DNA replication
used in dentil practice
Dysuria, dark urine
Disulfiram-like effect
Neurotoxicological effect
Emetine, dehydroemetine
irreversible block of protein synthesis.
Cardiotoxic
dehydroemetine is less toxic
Chloroquine
in combination for amebic liver diseases
Hemolysis in G6PD
Blurring of vision
Pruritus


Luminal Amebicides
Diloxanide furoate
unabsorbed diloxanide is the amoebicidal agent .
1st choice for asymptomatic
Iodoquinol
Peripheral neuropathy
Enlargement of the thyroid gland.
Paromomycin Sulphate
Has Direct + Indirect Effect
used in chronic amebiasis to eliminate cysts

Mnemonics

Metronidazole

- Metro → **systemic amoebicides(trophozoites)** الميتو يمشي لاماكن بعيده فيصير نستخدم هذا الدرق في
- Nida → ندى قرييب من DNA فهو يسوي انهبت لدي ان اي ريبليكيشن

- **Clinical uses : Gia tri pu pseudo!** جايه احاول اصير طبيبة اسنان بس قالوا لي بوو يا كذابه
- Gia (جايه) → giardiasis.
- Tri (احاول) → trichomoniasis.
- يستخدم في الدينتال براكتس- → طبيبة أسنان
- Pu (بو) → peptic ulcer.
- Pseudo(كذابه) → pseudomembranous colitis

-**ADRs :** ؟ ندى طبيبة اسنان طيب
حطت السيكشن وصار الفم جاااف (dry mouth) ثم حطت البنج وصار طعمه مو حلو **(metallic taste)** عاد ندى كثرت بنج وكان يحبه الفنقل لين سوى **oral thrush**لي
وبعد من كثرة البنج داخت البيشنت وصار عندها **neurotoxicological effect**
وللاسف البيشت بلعت نص البنج وطلع مع اليورن **(dysuria)** ولانها اخذت كحول قبل تروح للدكتوره ندى صار فيه تعارض مع البنج اللي بلعته **(disulfiram like effect)** .

Emetine

وحده موصيه اختها تجيب لها بروتين بار ، طولت اختها ودقت عليها قالت **امتا تجين** طولتي ؟ (**emetine**) قالت اختها مااااح اجي ومافيه بروتين بار ، فايشيسوي هذا الدرق ؟
اول شيء لانها طوولت معناته دارت ولفت فيكون systemic ولان البروتين بار ماجاها يصير يسوي block of protein synthesis

طيب متى نستخدم هذا الدرق ؟ الاخت طولت لانها سوت حادث بجدار المحل (intestinal wall infection) وتأثرت عندها الكبد لان كانت بنفس الجهه**(amoebic liver abscess)**
والاخت اللي بالبيت زعلت من اختها واكلت حاجة وكان فيها **cyst** وصار عندها **acute amoebic dysentery**

ADRs:
ام هالبنتين كانت (حامل) وعندها مشاكل ب(الكلى) وسمعت بخبر بناتها وجاها صدمة وبغى يوقف قلبها **(cardio toxicity)**

Chloroquine

الجزء الاخير من الدرق زي **الكوين** ، فهذي **الملكه** اكيد انها ترأس شيء كبير فيكون هذا الدرق systemic ، ولانها **كوين** ما تبي تشتغل لحالها تتعب فعادة يستخدم هذا الدواء مع الانواع الثانيه
الشيء المهم! انهم يبغون ينتقمون من هذي الملكه فحطوا لها **كلور "بداية اسم الدواء"** وصار عندها **hemolysis in G6PD**
وغير كذا ما كفاهم راحوا نقطة بعينها وسوى لها **blurring of vision**

Special thank for Ebtesam Almutairi ❤

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 (indicates invasion) and abdominal pain caused by any kind of infection.

Dysentery results from:

1- Viral infection. (common in children)

2- Bacterial infection.

3- Parasitic infection.

Most common causes

Amebic dysentery (Protozoal infection Mainly by Entamoeba Histolytica).
Treat by anti-protozoan drugs

Bacillary dysentery (bacterial infection mainly by shigella)
treat by antibiotics

Treatment:

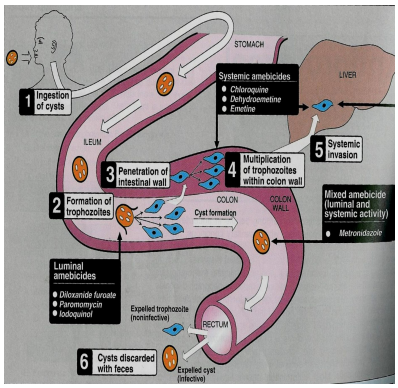
1- Maintain fluid intake using oral rehydration therapy or intravenous fluid therapy. (Compensate for fluid + electrolyte loss oral if they can tolerate and intravenous if they are vomiting it might be enough if the diarrhea is mild)
2- Antimicrobial agents should not be given until stool analysis is done to **specify** the etiological agent. bacterial , viral or protozoal
3- Antidiarrheal drugs are **contraindicated** because they delay fecal excretion that can prolong fever (diphenoxylate or loperamide)*. When you decreasing GI motility retaining the organism (not excreted from the body)
*Morphine derivatives so it has addiction liability

Amebiasis

Is a protozoal infection of the intestinal tract that occurs due to ingestion of foods or water contaminated with cysts (infective state) of Entameba Histolytica.
* trophozoite is an invasive stage

Life cycle of Amebiasis

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



Entamoeba histolytica exists in two form:

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

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.

Antiamebic drugs

Types	Luminal amebicides	Tissue or systemic amebicides
Site of action	Acts on the parasites in the lumen of the bowel (active against cyst). -most not absorbed	Act on amoeba in tissues e.g. the intestinal wall and/or other extra-intestinal tissues as liver, brain, and lung. -needs to be absorbed
Uses	Used for treatment of asymptomatic amebiasis (carriers). Used to eradicate cysts of E.histolytica after treatment of invasive disease.	Used for treatment of systemic form of the disease (invasive amebiasis) e.g. intestinal wall infection or liver abscesses.
Drugs	1- Diloxanide furoate. 2- Iodoquinol. 3- Paromomycin. 4- Tetracycline (not commonly used) DIP = inside the lumen	1- Metronidazole/ tinidazole 2- Emetine / dehydroemetine (not commonly used now). 3- Chloroquine (**liver only**).

Clinical presentations

1- The patients show varying degree of illness from no symptoms to mild diarrhea to severe dysentery.
2- **Asymptomatic amebiasis** = Carriers (passing cysts in stool)
3- **Mild to moderate** (in tissue) intestinal disease (colitis)
4- **Severe** intestinal infection (amoebic dysentery)
5- **Ameboma** (localized granulomatous lesion of colon).
6- **Hepatic abscess,** and other extra-intestinal diseases.

Tissue or systemic amebicides

Metronidazole

M.O.A

It is a Tissue amoebicide that acts on trophozoites by:

- Inhibiting DNA replication: It has a nitro group that receives electrons from ferredoxin (present in anaerobic parasites) in a redox reaction. The resultant compound binds both to proteins & DNA and is cytotoxic. (free radicals that damage the trophozoite's DNA).
- Does not eradicate cysts from intestine. so it should be followed by luminal amebicide

P.K

1. Given orally (PO) or IV "absorption is rapid and complete by PO (gives a systemic effect)"
2. Wide distribution to all tissues and body fluids (CSF, saliva, milk).
3. Plasma half life is (8 h).
4. Metabolized in liver (by CYP-450) by mixed function oxidase followed by glucuronidation (consider drug interactions).
5. Clearance is decreased in liver impairment.
6. Excreted in urine. should be used with precaution w/ kidney & liver diseases.

Indications

1. Drug of choice for treating invasive (tissue) amebic infections (intestinal & extraintestinal amebiasis) "should be followed by luminal amebicides ".
2. Giardiasis. Metronidazole + Diloxanide furoate
3. Trichomoniasis
4. Broad spectrum of anaerobic bacterial infections e.g:
   a. Peptic ulcer as a part of triple therapy (Helicobacter pylori).
   b. Pseudomembranous colitis (Clostridium difficile).

ADRs

GIT:

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

CNS: Neurotoxicological effect

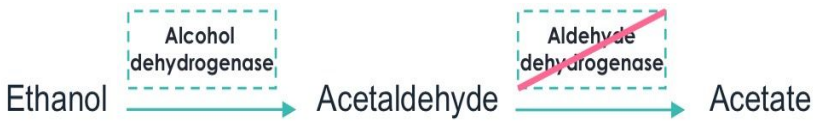
- Insomnia, dizziness
- Peripheral neuropathy, paresthesia.
- Encephalopathy, convulsion (IV infusion, rare).

Other ADRs:
Dysuria, dark urine, neutropenia.
Disulfiram-like effect if taken with alcohol.

Tissue or systemic amebicides

Metronidazole con.	
C.I	Pregnancy and breastfeeding women.(teratogenic effect) Alcohol intake. CNS diseases. Severe renal disease. Severe hepatic disease.

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.

Drug – Alcohol Interaction	• Combining metronidazole and alcohol causes nausea, vomiting, abdominal distress, flushing, headache, tachycardia, hyperventilation. "Disulfiram like-effect" 

Chloroquine	
M.O.A	Anti-malarial drug.
Uses	Used in combination with metronidazole or dehydroemetine for amebic liver diseases. NOT for colitis nor dysentery b/c it is Concentrated in liver
ADRs	• Pruritus is common • Nausea, vomiting, abdominal pain, anorexia (take it with food) • Blurring of vision cause deposits • Hemolysis in G6PD deficient patients rupture of RBCs membrane

Tissue or systemic amebicides

Emetine and dehydroemetine (not commonly used)

M.O.A

Both are effective against tissue trophozoites of *E. histolytica* causing irreversible block of protein synthesis.

P.K

- Emetine is an alkaloid derived from ipeca while dehydroemetine (used more bc less toxic than emetine) is a synthetic analog.
- Have erratic oral absorption.
- Given preferably subcutaneously but could be given IM, NEVER IV ➡ (b/c of CVS toxicity).
- Has long plasma half life about 5 days.
- Should not be used for more than 10 days (usually 3-5 days). B/c they will be accumulated due to slow excretion and long T1/2
- Metabolized & excreted slowly via kidney so they have a cumulative effect.

Uses

- Amoebic liver abscess. if azoles don't work as Chloroquine or dehydroemetine
- Intestinal wall infections no longer used use metronidazole or tinidazole
- Severe forms of amebiasis acute amoebic dysentery dehydroemetine is preferable due to less toxicity (3-5 days).

ADRs

- GIT: nausea, vomiting, diarrhea
- Serious toxicity: cardiotoxicity due to long half life
  (Hypotension, cardiac arrhythmias , heart failure)
- ❖ Dehydroemetine is less toxic than emetine.

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

C.I

This drug should not be used in:

- Patients with cardiac or renal disease bc it is excreted by kidney
- Young children
- Pregnancy

Tinidazole

M.O.A

Tinidazole has similar activity to metronidazole but better potency.

P.K

Advantages of tinidazole :

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

Luminal amebicides (DIP)

DIP: 1-Diloxanide furoate. 2-iodoquinol. 3-paromomycin

Drug	Diloxanide furoate (First choice+ safer)	Iodoquinol
M.O.A	• M.O.A is unknown. • Direct amoebicidal action against luminal forms (Cyst). • Not effective against trophozoites in intestinal wall or extra-intestinal tissues.	• M.O.A is unknown. • Effective against the luminal forms of amebiasis it has iodine which gives ADRs.
P.K	• Ester of diloxanide +Furoic acid. • Given orally. ester broken up in stomach • It split in the intestine liberating diloxanide. • The little unabsorbed diloxanide is the amoebicidal agent. • The absorbed portion(furoic acid) is excreted in urine. • Good absorption.	• Is given orally. • Poorly absorbed, excreted in feces. biliary excretion
Uses	• Drug of choice for asymptomatic intestinal infection(cyst passers). • To eradicate cysts of E.histolytica after treatment of invasive disease with systemic amebicides.	• Luminal amoebicide for asymptomatic amebiasis. Carriers
ADRs	• all in GIT bc it's NOT absorbed • Flatulence. (Accumulation of gas in the alimentary canal). • Nausea, vomiting, abdominal cramps. (Because it is absorbed only in the GIT the ADRs will be related only for GIT.)	• GIT: Nausea,vomiting, diarrhea. • Peripheral neuropathy including optic neuritis. • Enlargement of the thyroid gland.(because the presence of iodine). • Iodine sensitivity. • interference with thyroid function tests (increase protein-bound serum iodine,decrease in measured (131I uptake).
C.I	• Pregnancy. • Children (less than 2 years).	• 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).

Luminal amebicides (DIP)

Drug	Paromomycin sulphate
M.O.A	• 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	• Given orally. • Not significantly absorbed from GIT. • Effective only against luminal forms of ameba. • Small amount absorbed is excreted unchanged in urine (may accumulate with renal insufficiency).
Indications	• Use in chronic amebiasis (carrier) to eliminate cysts (in cysts passers).
ADRs	• Gastrointestinal distress and diarrhea. • Remember that aminoglycosides may cause nephrotoxicity and ototoxicity.
C.I	• 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 **1st choice**
Hepatic abscess	Metronidazole or tinidazole or chloroquine 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) commonly used in traveler's diarrhea.
- 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.

Ciprofloxacin	
M.O.A	• Fluoroquinolones 3rd Generation are first-line treatment for shigellosis • Active against a variety of gram-positive and gram-negative bacteria • Block bacterial DNA synthesis and growth (DNA gyrase and topoisomerase) bactericidal
Indications	• Bacterial diarrhea caused by shigella, salmonella and E coli • Urinary tract infections • Respiratory tract infections • Soft tissues, bones, and joint infections
ADRs	• **Arthropathy (damage of growing cartilage)** (we should use cephalosporins here) • Phototoxicity • GIT disorder (nausea, vomiting, diarrhea) • CNS disorders (headache, dizziness) • CVS disorders (prolong QT interval) • Liver toxicity
C.I	• Children, pregnancy, nursing mother. use cephalosporins instead • Epilepsy • Arrhythmias. • Should not be combined with antacids, divalent cations it will decrease the effect of the drug. Yellow staining of teeth + bone

Cephalosporins (cefixime, ceftriaxone)	
M.O.A	• They are 3rd generation cephalosporins are Second line therapy • 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
Indications	• **In case of pregnancy ,children or patient allergic to sulfonamides, cephalosporins or azithromycin can be used.**

Summary

Tissue or systemic amebicides			
Drug	**Metronidazole And Tinidazole**	**Emetine and dehydroemetine**	**Chloroquine**
M.O.A	It is a Tissue amoebicide Acts on trophozoites by Inhibiting DNA replication **Tinidazole** has similar activity to metronidazole but better potency.	Both are effective against tissue trophozoites of *E. histolytica* irreversible block of protein synthesis.	Anti-malarial drug.
P.K	1. Given orally (PO) or IV "Absorption is rapid and complete by PO (give a systemic effect)" 2. Metabolized in liver (by CYP-450)	Emetine is an alkaloid derived from ipeca while dehydroemetine is a synthetic analog. Given preferably subcutaneously but could be given by IM,	-
Uses	1. Drug of choice for treating invasive (tissue) amebic infections (intestinal & extraintestinal amebiasis) 2. Broad spectrum of anaerobic bacterial infections	Amoebic liver abscess, Intestinal wall infections, severe forms of amebiasis acute amoebic dysentery dehydroemetine is preferable due to less toxicity (3-5 days).	Amebic liver diseases.
ADRs	GIT • Dry mouth, metallic taste. • Nausea, vomiting, diarrhea. • Oral Thrush (yeast infection). CNS (Neurotoxicological effects)	Serious cardiotoxicity Because of major toxicity concerns they have been almost completely replaced by metronidazole.	Pruritus is common, Nausea , Vomiting , abdominal pain , anorexia (take it with food).Blurring of vision.,Hemolysis in G6PD deficient patients.
C.I	Pregnancy and breast feeding women. Alcohol intake. CNS diseases. Severe renal disease. Severe hepatic disease.	the drug should not be used in : patients with cardiac or renal disease, young children.,pregnancy.	-

Summary

Luminal amoebicides (DIP)			
Drug	**Diloxanide furoate**	**Iodoquinol**	**Paromomycin sulphate**
M.O.A	Direct amoebicidal action against luminal forms Cyst.	Effective against the luminal forms of amebiasis it	Aminoglycoside antibiotic., direct amebicidal action (causes leakage by its action on cell membrane of parasite).
P.K	The little unabsorbed diloxanide is the amoebicidal agent.	Poorly absorbed	Given orally, May accumulate with renal insufficiency).
Uses	Drug of choice for asymptomatic intestinal infection(cyst passers).To eradicate cysts of E.histolytica	Luminal amoebicide for asymptomatic amebiasis.	Use in chronic amebiasis (carrier) to eliminate cysts(in cysts passers).
ADRs	Flatulence. .Nausea, vomiting, abdominal cramps.	optic neuritis, Enlargement of the thyroid gland, interference with thyroid function tests	Gastrointestinal distress and diarrhea. CI:Severe renal diseasePatients with GIT ulceration.

Ciprofloxacin	
M.O.A	Fluoroquinolones are first-line treatment for shigellosis, Block bacterial DNA synthesis and growth.
Indications	Bacterial diarrhea caused by shigella, salmonella and E coli, ,Urinary tract infections Respiratory tract infections.Soft tissues, bones, and joint infections
ADRs	**Arthropathy (damage of growing cartilage)**,Phototoxicity
C.I	Children, pregnancy, nursing mother., Epilepsy, Should not be combined with antacids, divalent cations

Cephalosporins(cefixime, ceftriaxone)	
M.O.A	Act by inhibit cell wall synthesis
P.K	• Oral cefixime or parenetral ceftriaxone are safe and effective
Indications	• In case of children or patient allergic to sulfonamides, cephalosporins can be used.

Summary from Hannan's slides:

- 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.

MCQs:

Q1. Which of the following can't be given orally ?
A- Iodoquinol
B- Metronidazole
C- Paromomycin
D- Tetracycline

Q2. Which of the following drugs have disulfiram like effect ?
A-Diloxanide furoate
B-Iodoquinol
C-Paromomycin Sulfate
D-Metronidazole

Q3. What is the Drug of choice for invasive amebic infection?
A- Emitine
B- Metronidazole
C- Chloroquine
D- Iodoquinol

Q4. Tinidazole is different from Metronidazole by which of the following?
A- Tinidazole does not increase lithium toxicity
B- Metronidazole have a better taste
C- Tinidazole has lower potency
D- Tinidazole has longer duration of action

Q5. The used drug should be used in combination with ?
A-Metronidazol or dehydroemetine
B- dehydroemetine or Cotrimoxazole
C- Iodiquinol or diloxanide furoate
D-Metronidazole or azithromycin

Q6. What is commonly used with traveler diarrhea?
A-Cotrimoxazole (TMP-SMX)
B-Ampicillin
C-Azithromycin
D- ciprofloxacin

Q8. You gave a drug to cure amebic liver disease in a 17 year old female patient
Which of the following is a side effect of that drug ?
A- Cardiac toxicity
B- Flatulence
C-Optic neuritis
D- Blurring of vision

Q8. A 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 ?
Hint : you can identify the drug based on the shared side effects

A- Arthropathy
B- Phototoxicity
C- CNS effects (insomnia, headache, anxiety)
D-Blurring of vision

Q9. Which of the following is considered a contraindication for this drug ?
A- Heart failure
B- Renal failure
C- G6PD
D- Arthritis

SAQ

A 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 ?
What drug did she take ? dehydroemetine
What the is the mechanism of action of the drug she is using? irreversible block of protein synthesis
What drug should we replace it
What other ADR of that drug nausea, vomiting, diarrhea

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

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Thanks for those who worked on this lecture:

Abdullah Almeaither
Maan Shukr
Abdullah Alzahrani
Mohammed Alomar
Mohammed Nouri
Sultan AlNasser
Fahad Alfaiz
Abdullah Alsergani
Rahaf Althnayan

References:

✓ Doctors' slides and notes

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