Antiamoebic Drugs

- BY:

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AMEBIASIS

Amebiasis (also called amebic dysentry) is an infection of intestinal tract caused by *Entamoeba histolytica*. The disease can be acute or chronic, with the patients showing varying degrees of illness, from no symptoms to mild diarrhea to fulminating dysentery.

The diagnosis is established by isolating E. histolytica from fresh feces.

Therapy is aimed not only at the acutely ill patients but also at those who are asymptomatic carriers, because dormant E. histolytica may cause future infections in the carrier and be a potential source of infections for others.

EPID:

Protozoal infections are common among the people in underdeveloped countries, where sanitary conditions, hygienic practices and control of vectors of transmission are inadequate.

Life cycle of Entamoeba histolytica

Entamoeba histolytica exists in two forms:

1. **Cysts form**

2. **Trophozoites form**

Life cycle

Life cycle consists of following steps:

1. **Ingestion of cysts**

   Cysts are ingested through feces, contaminated food or water.

2. **Formation of trophozoites**

   Cysts are passed into the lumen of intestine, where the trophozoites are liberated (excystation).

3. **Penetration and multiplication of trophozoites**

   Trophozoites are penetrated in intestinal wall and multiply within colon wall. They either invade and ulcerate the mucosa of intestine or simply feed on intestinal bacteria.

4. Systemic invasion

Large numbers of trophozoites within the colon wall can also lead to systemic invasion and caused liver abscess.

Once the trophozites have breached the intestinal walls, they can enter the bloodstream and travel to various internal organs. They can end up in your liver, heart, lungs, brain, or other organs. If trophozites invade an

5. Cysts excretion

The trophozoites within the intestine are slowly carried toward the rectum, where they return to cyst form and are excreted in feces.

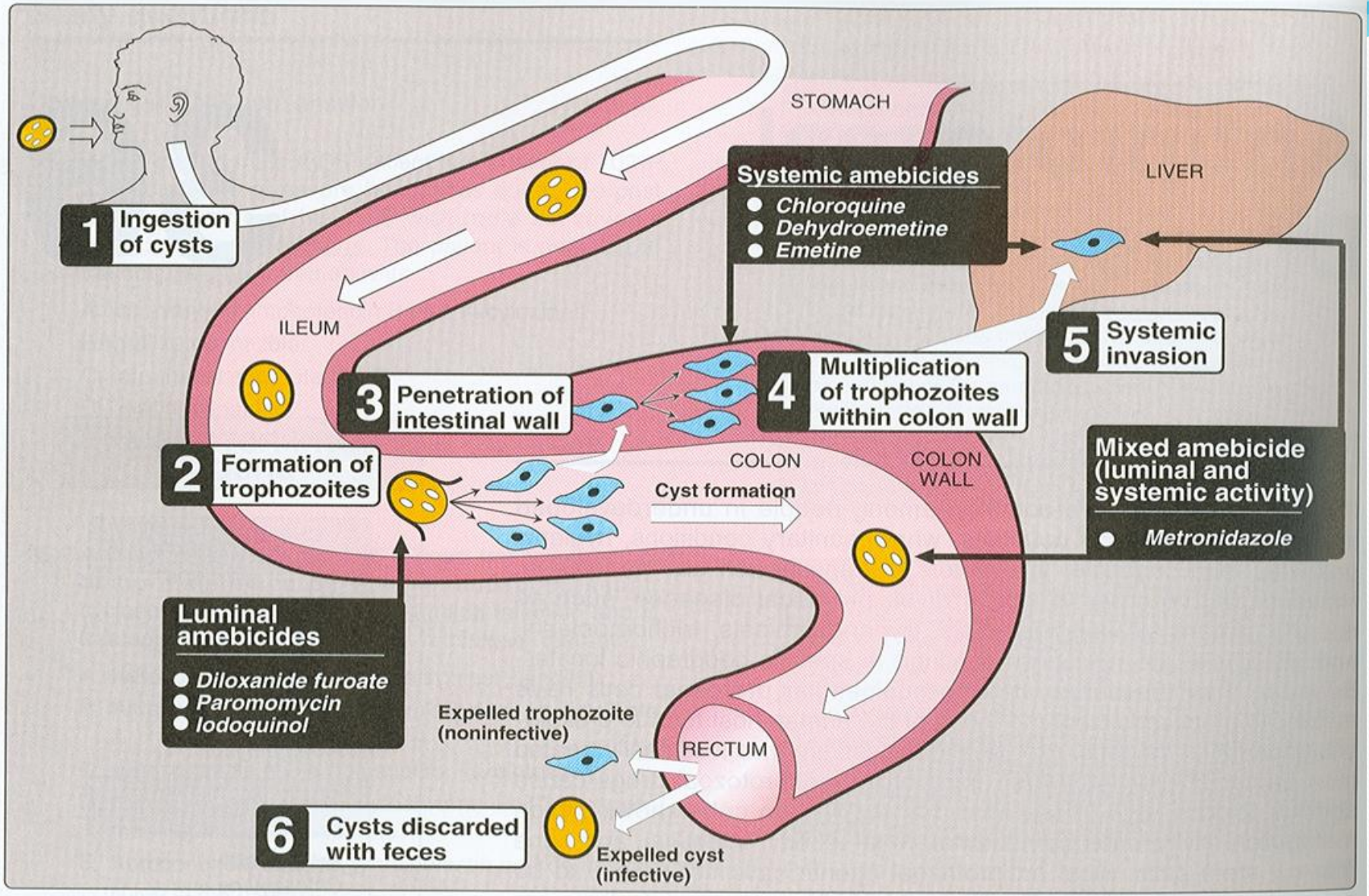


Figure 36.2
Life cycle of Entamoeba histolytica showing the sites of action of amebicidic drugs.

Classification of amebicidal drugs

According to the site where the drug is effective, the amebicidal drugs are classified as:

Luminal amebicides (Act on parasite in the lumen of bowel).

1.Dichloroacetamides:

These include

1.Diloxanide furoate

2.Etofamide

3.Teclozan

4.Clefamide

2. Halogenated hydroxyquinolines:

These include

1. Diiodohydroxyquin (Iodoquinol)
2. Iodochlorohydroxyquin (Clioquinol)

3.Antibiotics:

These include

Paromomycin

Erythromycin

Tetracycline

- **Systemic amebicides** (Against amebas in intestinal wall & liver plus other)

•1.Emetine,

•2.Dehydroemetine

•3.Chloroquine

- **Mixed amebicides** (Against both the luminal and systemic form of diseases).

1.Nitroimidazoles:

Metronidazole

Ornidazole

Secnidazole

Satranidazole

these tautomers readily interconvert. Drugs of the 5-nitro variety include metronidazole, tinidazole, nimorazole, dimetridazole, pretomanid, ornidazole, megazol, and azanidazole. Drugs based on 2-nitromidazoles include benznidazole.

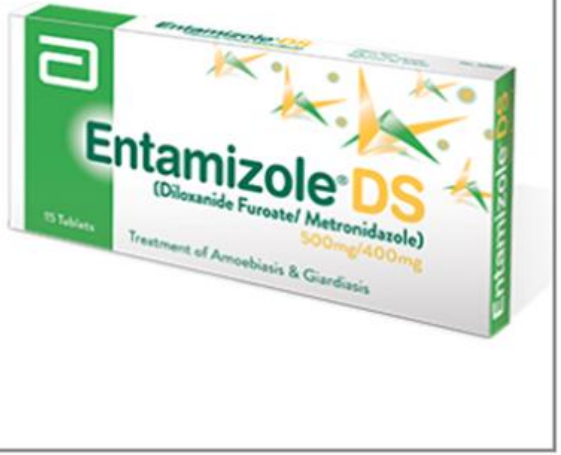
Metronidazole (Flagyl)

- is the drug of choice in the treatment of amebiasis. It kills trophozoites but not cysts of *E histolytica* and effectively eradicates intestinal and extraintestinal tissue infections.

Metronidazole 500 mg/100 ml Intravenous Infusion

Dosage forms: Strengths

Forms and strengths
– 200, 250 mg and 500 mg tablets
– 200 mg/5 ml oral suspension



ENTAMIZOLE®
(Diloxanide furoate/Metronidazole Benzoate)

ENTAMIZOLE DS

Ingredient(s): Each tab contains:
Diloxanide furoate 500mg
Metronidazole 400mg

Indications: Acute amoebiasis, Chronic amoebiasis, Hepatic amoebiasis and other systemic diseases due to E. histolytica, Giardiasis.

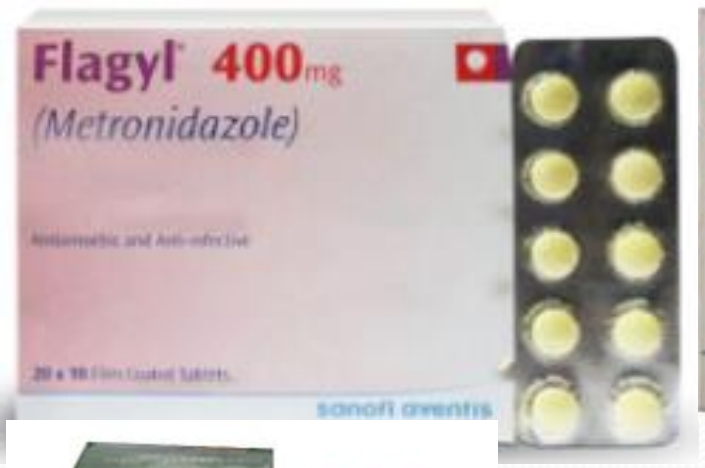
Pack Size: 5x3s in carton

ENTAMIZOLE TABLET

Ingredient(s): Each tab contains:
Diloxanide furoate 250mg
Metronidazole 200mg

Indications: Acute amoebiasis, Chronic amoebiasis, Hepatic amoebiasis and other systemic diseases due to E. histolytica, Giardiasis.

Pack Size: 3x10s in carton


Flagyl 400mg
(Metronidazole)
sanofi aventis


PRESCRIPTION ONLY MEDICINE
KEEP OUT OF REACH OF CHILDREN
Flagyl 200 mg
metronidazole
Metronidazole tablets BP
Each tablet contains metronidazole 200 mg
AUST R 160171
NEW
21 Tablets
FORMULATION


Flagyl
500mg
pessaries
metronidazole
vaginal use
10 pessaries
sanofi aventis

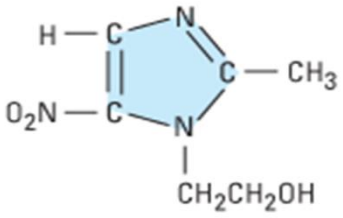

Entamizole
Entamizole


Flagyl
Suspensie
Metronidasool
200 mg/5 ml
100 ml
Suspensie
babypharmacy


Flagyl
Flagyl Injection
injection
SANOFI

Chemistry:
Metronidazole,chemically a nitroimidazole

metronidazole [2-(2-methyl-5-nitro-1H-imidazol-1-yl)ethanol]



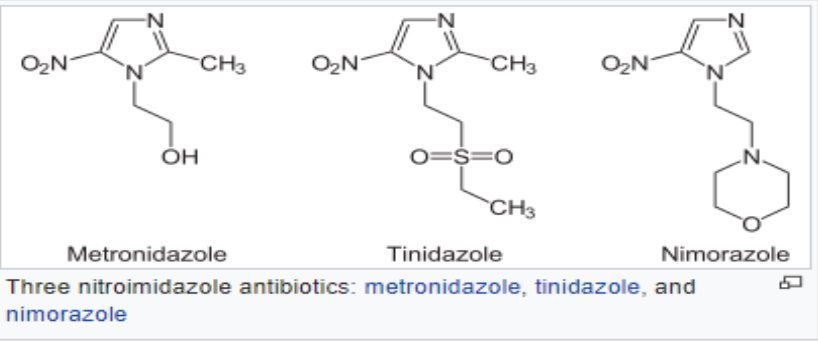
Metronidazole

Nitroimidazole antibiotics [edit]

Position numbers on the ring

From the chemistry perspective, nitroimidazole antibiotics can be classified according to the location of the nitro functional group. Structures with names 4- and 5-nitroimidazole are equivalent from the perspective of drugs since these tautomers readily interconvert. Drugs of the 5-nitro variety include metronidazole, tinidazole, nimorazole, dimetridazole, pretomanid, ornidazole, megazol, and azanidazole. Drugs based on 2-nitromidazoles include benznidazole.

Nitroimidazole antibiotics have been used to combat anaerobic bacterial and parasitic infections.[3] Perhaps the most common example is metronidazole. Other heterocycles such as nitrothiazoles (thiazole) are also used for this purpose. Nitroheterocycles may be reductively activated in hypoxic cells, and then undergo redox recycling or decompose to toxic products.[4]

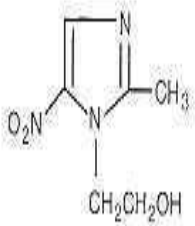


Metronidazole Tinidazole Nimorazole

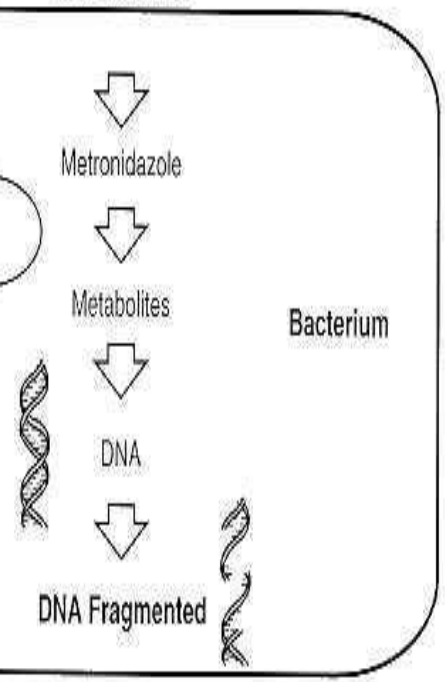
Three nitroimidazole antibiotics: metronidazole, tinidazole, and nimorazole

Mechanism of action

tronidazole is selective for anaerobic bacteria due to their ability to intracellularly uce**metronidazole** to its active form. This reduced **metronidazole** then alently binds to DNA, disrupt its helical structure, inhibiting bacterial nucleic acid thesis and resulting in bacterial cell death.



Metronidazole



Metronidazole (prodrug)

↓ enters

Microorganism

↓

'Nitro' group is reduced by ferredoxins and Fe–S proteins

↓

Active metabolite

↓

Breaks and damages microbial DNA

↓

Death of the organism (bactericidal effect)

Mechanism of action of Metronidazole

Metronidazole is a prodrug. It requires reductive activation of nitro group by susceptible organism. Its selective toxicity towards anaerobic and microaerophilic pathogens such as E. histolytica, G. lamblia, etc. These organisms contain electron transport components such as ferridoxin, small Fe-S proteins that have sufficiently negative redox potential to donate electrons to metronidazole.

The single electron transfer forms a highly reactive nitro radical anion that kills susceptible organisms by radical-mediated mechanisms that target DNA, resulting in cell death.

Pharmacokinetics

Tab.200,400;susp.200/5;iv inf.500/100

Absorption

Metronidazole is usually given orally and it is rapidly and completely absorbed achieving peak plasma concentration in 1-3 hours, with half life of about 7.5 hours.

Distribution It is distributed rapidly throughout the tissuesLLB,PB,BM,reaching high concentration in the body fluids, including cerebrospinal fluid.

Metabolism

Metabolism of metronidazole occurs in liver, oxidation, glucoronidation..

Excretion

The parent drug and its metabolites are excreted in the urine.

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CLINICAL USES AND SPECTRUM:

1.Amoebiasis: Metronidazole is the drug of choice in the treatment of E.histolytica.

It is not reliably effective against luminal parasites and so must be used with a luminal amebicide to ensure eradication of the infection.

2. Giardiasis:

Metronidazole is the treatment of choice for giardiasis.The dosage for giardiasis is much lower and the drug thus better tolerated than that for amebiasis.

3. Trichomoniasis: Metronidazole is the treatment of choice. 2G,single dose is effective.

4. Anaerobic Bacterial infections:

Metronidazole also useful in infections caused by anaerobic bacteria for e.g. bacteroids fragilis, fusobacterium, clostridium perfringens/difficile.

5. Dracunculosis: infection caused by guinea worm.

Adverse effects:

- Dry mouth, metallic taste and headache occurs commonly.
- Infrequent adverse effects include: paraesthesias, neutropenia, pancreatitis, ataxia, encephalopathy,
- I.V. infusion rarely caused seizures or peripheral neuropathy.
- Urine:-dark/reddish-brown.

DRUG INTERACTION:

Metronidazole has a disulfiram like effect, so that nausea and vomiting can occur if alcohol ingested during therapy.

It potentiate the anticoagulant effect of coumarin type of anticoagulants.

Phenytoin & phenobarbitone may increase elimination of the drug,

Cimetidine decrease plasma clearance

CAUTION:

THE DRUG SHOULD BE USED WITH CAUTION IN PATIENTS WITH CNS DISEASE. IT SHOULD BE AVOIDED IN PREGNANT WOMEN DUE TO RISK OF TERATOGENICITY(NOT PROVED IN HUMANS, PROVED IN BACTRERIA, MICE)

Tinidazole, a related nitroimidazole, having similar activity and a better toxicity profile than metronidazole, and it offers simpler dosing regimens.