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KEYWORDS: Amebicide agents; Luminal amebicides; Systemic amebicides; Mixed amebicides

# AMEBICIDE AGENTS: LUMINAL AMEBICIDES, SYSTEMIC AMEBICIDES AND MIXED AMEBICIDES

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## Abstract

Amebiasis can be considered as acute or chronic, which contrasts degrees of illness, from no sign and symptoms to mild diarrhea to fulminating dysentery. A pathogenic parasite called Entamoeba histolytica is present in the intestine of human beings and multiple other animals. Entamoeba histolytica inhabits in the mucous and sub-mucous layers of large intestine. Mixed amebicides are highly active against on both the luminal and systemic forms of the disease, however luminal accumulations are too less for single-medicine management. Metronidazole is one of the blueprinted medicines for the management of anaerobic bacterial infections, protozoal infections, and microaerophilic bacterial infections. Metronidazole has a cytotoxic activity on facultative anaerobic bacteria such as helicobacter pylori and gardnerella vaginalis, but how metronidazole acts on these pathogens is unknown; however it rupture of DNA secretion as well as nucleic acid secretions/metronidazole diffuses into the microorganism to suppresses protein secretions by interacting with DNA and causing injury of helical DNA structure and strand cascading. Tinidazole is a nitroimidazole identical to metronidazole and is initiated intracellularly by bacterial or parasitic enzymes to a radical anion, which detriments high protein molecules and deoxyribonucleic acid. Diloxanide furoate is considered as a safe and effective medicine for the management of asymptotic or symptomatic persons who are passing cysts of entameba histolytica.

## Introduction

Amoebae are found worldwide and are extremely ubiquitous in soil, fresh water, and other habitats. However ordinarily hurtles, certain of them are human pathogens. While autophagy has been all over extendedly considered in the social amoeba dictyostelium discoideum, where it plays a function in survival and spore formation, it has only been partly described in pathogenic amoebae. E. histolytica is the causal agent of amoebic dysentery and amoebic liver abscess. It is a global health challenge, causing up to 100,000 deaths per year [1, 2]. Entamoeba histolytica can cause an infection of the intestinal tract which is called amebiasis (also called amebic dysentery) [3]. Amebiasis may be acute or chronic, which contrasts degrees of illness, from no sign and symptoms to mild diarrhea to fulminating dysentery [4]. The diagnostic criterion to amebiasis is demonstrated by extracting E. histolytica from feces. A pathogenic parasite called Entamoeba histolytica is present in the intestine of human beings and multiple other animals. Entamoeba histolytica suppresses the mucous and sub-mucous layers of the host large intestine. It feeds predominantly on the tissues of the intestinal wall and frequently generates severe ulcers and abscesses [5].

**Life cycle:** The life cycle of monogenetic E. histolytica is completed on one host only; the man. (1) Encystment: In the formation of precystic entamoeba present only in the intestinal lumen. Before undergoing encystment, E. Histolytica can round up, debar food vacuoles and concentrate major amount of food substances in the form of glycogen and black rod-like chromatoid granules. Chromatoid body's availability is the characteristic of the cysts of E. histolytica. Each cyst can now become tetra nucleate after the nucleus of the cysts separates twice. At this phase, the cyst is infective to a fresh host. Formed encyst pass out with the faecal matter of the host [6]. (2)Transfer to new host: If the environmental condition is confortable the infective cysts remain attainable for a major length of time exterior the human intestine. After swallowing the infective cysts with contaminated food and drinks Infection of new human host takes place [7]. (3)Excystment: For the formation trophozites of the next generation the metacystic trophozites are feed on the contents of the intestine to cultivate in size. The life cycle of E. Histolytica started again when the trophozoites stay in the lumen of the intestine for a specific period and they attack the wall of the. Amoebic dysentery caused by Entamoeba histolytica in abscesses of liver, lungs and brain and non-dysenteric infections [8].

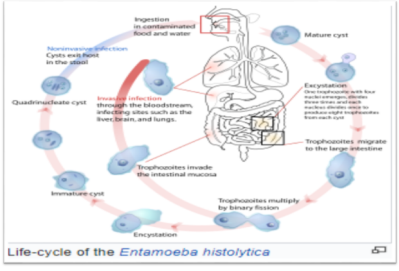


**Figure1 Schematic illustrations of E. Histolytica life cycles**

Management of E. Histolytica caused amebiasis in individuals who acutely ill and asymptomatic carriers, since dormant E. histolytica perhaps cause future infections in the carrier and be an implicit source of infection for other. Amebecide medications for management of amebiasis are grouped according to the site of action as follows: Luminal amebicides are active against on the parasite in the lumen of the bowel. For instances: Diloxanide furoate, paromomycin, etofamide, iodoquinol [10]. Systemic amebicides are active against a on the parasite in the intestinal wall and liver. For instances: chloroquine, emetine, dehydroemetine [11]. Mixed amebicides are active against on both the luminal and systemic parasite forms of the disease, however luminal accumulations are too less for single-medicine management. For instances: metronidazole, tinidazole, secnidazole [12].

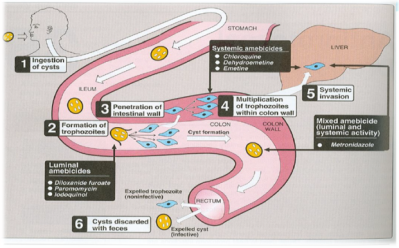


**Figure 2** Schematic illustration of site of antiamoebic medication works on E. Histolytica life cycles

**Metronidazole**

Metronidazole is chemically derived from a nitroimidazole and metronidazole (2-(2-methyl-5-nitro-1H-imidazol-1-yl) ethanol). Metronidazole is the cornerstone medicines used as the management of anaerobic bacterial infections, protozoal infections, and microaerophilic bacterial infections and also act as cytotoxic to facultative anaerobic microbes [13].

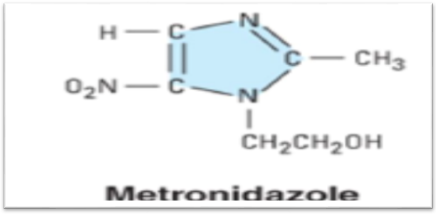


**Figure 3** chemical structure of metronidazole

Metronidazole has fast bactericidal outcomes against anaerobic bacteria by its killing rate proportional to the medicine concentration. The concentration-dependent bactericidal properties of metronidazole also act against entamoeba histolytica and trichomonas vaginalis [14].

Use: Metronidazole used for invasive amoebiasis and giardiasis; trichomoniasis; tissue nematode infections; Gram-negative anaerobes bacterial infections such as bacteroids fragilis, fusobacterium, clostridium perfringens/difficile etc; and gram-positive anaerobes bacterial infections such as clostridium species eubacterium species, peptococcus species, peptostreptococcus species dracunculosis, H. pylori eradication in peptic ulcers disease, it reserved for penicillin allergy patients instead of amoxacillin.

Mechanism of action: Metronidazole is act by rupturing of DNA secretion as well as nucleic acid secretion or it diffuses into the microorganism to suppress protein secretion by interacting with host cell DNA and causing damage of helical DNA structure and strand cascading. Thereupon, it causes cell death in vulnerable organisms. Metronidazole acts through the following four-steps. 1) Penetrate into the microorganism by diffusion via the cell membranes of anaerobic and aerobic pathogens but, antimicrobial consequence are limited to anaerobes. 2) Initiate bacterial cell wall decrement by intracellular transport proteins and altering the chemical structure of pyruvate-ferredoxin oxidoreductase. The minimization of metronidazole makes an accumulation gradient in the cell that drives uptake of further medicine and advances free radical formation that is cytotoxic. 3) Metronidazole interact with intracellular targets, to be achieved by cytotoxic particles interacting with host cell DNA resulting in DNA strand cascading and fatal destabilization of the DNA helix. 4) There is the breakage of cytotoxic products. Metronidazole has cytotoxic activity against facultative anaerobic bacteria such as helicobacter pylori and gardnerella vaginalis, and its activity against these pathogens is unknown [15, 16].

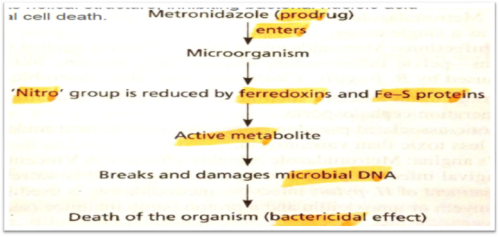


**Figure 4** Schematic illustration of metronidazole mechanism of action

Spectrum of activity: Metronidazole has bactericidal, amebicidal, trichomonacidal consequences and also acts as management of trichomoniasis, amebiasis, giardiasis, and antibiotic-associated pseudomembranous colitis and also has anthelmintic activity [17]

Adverse drug reactions: The initial adverse reactions of metronidazole involve confusion, peripheral neuropathy, metallic taste, nausea, vomiting, and diarrhea, headache, vaginitis, dizziness, genital pruritus, abdominal pain, xerostomia, dysmenorrhea, urine abnormality, urinary tract infection, bacterial infection, candidiasis, flu-like symptoms, upper respiratory tract infection, pharyngitis, and sinusitis. Rarely, metronidazole is cause transient leukopenia, encephalopathy, and neutropenia as well [18].

**Contraindications:** Metronidazole is not given in individuals with a past history of hypersensitivity to metronidazole or other nitroimidazole derivatives. In pregnant women's with trichomoniasis, metronidazole is not recommended during the 1st trimester of pregnancy. Concurrent use of oral metronidazole and alcohol not recommended because concomitant usage are cause psychotic reaction with disulfiram. Metronidazole is not given to individuals who received disulfiram within the last two weeks. If oral metronidazole given with alcohol they cause disulfiram-like reaction such as abdominal cramps, nausea, vomiting, headaches, and flushing. The patients should have to stop consumption alcohol and products containing propylene glycol at least three days after treatment with metronidazole [19, 20]

Drug interactions: Concurrent use of metronidazole with disulfiram cause psychotic reactions with disulfiram like reaction. In concomitant use metronidazole and warfarin and other oral anticoagulants; metronidazole potentiates the anticoagulant outcome of warfarin and other oral coumarin anticoagulants, sequencing in a prolongation of prothrombin time. In individuals who stabilized relatively on great doses of lithium and take metronidazole, the short-term metronidazole accelerates the serum level of lithium and, in a few cases; it aggravates the signs of lithium toxicity. In concomitant use metronidazole and busulfan; metronidazole accelerates plasma accumulations of busulfan, which can result in an escalated risk of severe busulfan toxicity. The coincidental administrations of medicines that reduce microsomal liver enzymes, such as cimetidine with metronidazole, they extend the half-life and reduce plasma clearance of metronidazole. The coincidental administration of medicines that induces microsomal liver enzymes, such as phenytoin or phenobarbital with metronidazole, perhaps enhances the elimination of metronidazole, and also sequencing in decreased plasma levels or lowered clearance of phenytoin. Concurrent administration of Drugs that prolong the QT interval with metronidazole may be cause potential extending the QT interval [21-23].

**Tinidazole**

Tinidazole is an orally avail, wide spectrum antimicrobial agent used in the management of bacterial, protozoal and parasitic infections. Tinidazole is a nitroimidazole identical to metronidazole and is probably to have a same spectrum and frequency of side effects, involving a less rate of serum enzyme elevations during treatment and rare examples of clinically visible acute liver impairment. Tinidazole is a nitroimidazole identical to metronidazole and is activated intracellularly by bacterial or parasitic enzymes to a radical anion, which harms great protein molecules and DNA [24].

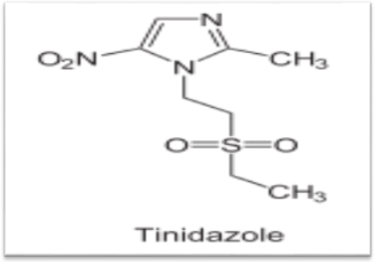


**Figure 5** chemical structure of tinidazole

Mechanism of action: After diffusing into the organism, it causes cytotoxicity by damaging DNA and preventing farther DNA production

**Use:** For bacterial vaginosis, mixed amebiasis, giardiasis, and trichomoniasis Adverse drug reaction: Potentially severe adverse events involve allergic reactions, metallic taste, stomach pain, nausea, headache, dizziness, rash, seizures, anaphylaxis and toxic megacolon.

**Contraindications:** For those who have hypersensitivity to 5-nitroimidazoles derivatives, in 1st trimester pregnancy, blood dyscrasias, breastfeeding mother.

Drug interactions: If tinidazole administered coincidentally with bile acid sequestrants such as cholestyramine, colestipol etc its absorption perhaps decreased. If take with anticoagulant medications such as warfarin, it accelerates anticoagulant effects of the medicine.

### Aminosidine (Paromomycin)

Paromomycin is an antimicrobial used to manage a number of parasitic infections involving amebiasis, giardiasis, leishmaniasis, and tapeworm infection. Paromomycin is act as 1st line management for amebiasis or giardiasis during pregnancy and also acts as 2nd line treatment alternative. Paromomycin is administered via mouth, applied to the skin, or by injection into a muscle route [25]

**Mechanism of action:** Paromomycin is a family of aminoglycoside medications that causes microorganism death by ceasing the formation of bacterial proteins. It inhibits a protein secretion in nonresistant cells by attaching to 16S ribosomal RNA. Like neomycin wide-spectrum antibiotic are is extremely soluble in water. Paromomycin has antimicrobial activity against escherichia coli and staphylococcus aureus. Paromomycin facts as enhancing the fault rate in ribosomal translation as an antibiotic. After paromomycin binds to a RNA loop the debris A1492 and A1493 are ordinarily stacked, and ejects this dual debris. This dual debris is included in determination of veracious Watson-Crick pairing between the codon and anti-codon. The binding provides energy to eject the dual debris as veracious interactions are reached. Paromomycin binding provides an adequate energy for debris ejection and hence sequences in the ribosome integrating the mistaken amino acid into the budding peptide chain [26]

**Use:** Paromomycin is act as antimicrobial for management of intestinal parasitic infections such as cryptosporidiosis and amoebiasis, and other disease such as leishmaniasis. Treatment of acute and chronic intestinal amebiasis and management of hepatic coma as auxiliary therapy (i.e., used to constrain intestinal bacteria that can generate ammonia and deteriorate encephalopathy related to liver failure) [27].

**Adverse drug reaction:** Paromomycin routine side effects are associated with abdominal cramps, diarrhea, heartburn, nausea, and vomiting. Long-term usage of paromomycin accelerates the risk for bacterial or fungal infection. Signs of outgrow involve white mends in the oral cavities. Other least frequent adverse events involve myasthenia gravis, kidney damage, enterocolitis, malabsorption syndrome, eosinophilia, headache, hearing mislay, ringing in the ear, itching, severe dizziness, and pancreatitis [28].

**Drug interactions:** Concurrent administration paromomycin and other medications cause kidney impairment have additive risk kidney damage. If paromomycin concurrently used with foscarnet; foscarnet accelerates the risk of renal impairment. Coincident usage of colistimethate and paromomycin can cause a hazardous sluggishing of breathing demonsterated as respiratory depression, and should be done with very great gingerliness if needed. Paromomycin usage with strong diuretics may be cause ototoxicity. Paromomycin perhaps have hazardous reactions when used with the paralytic succinylcholine by enhancing its neuromuscular outcomes. Paromomycin accelerate potential respiratory paralysis after inhalation anesthetics or neuromuscular blockers and enhance occurrence of ototoxicity with loop diuretics and enhance the anticoagulant effects of warfarin, and also decrease the absorption of digoxin and methotrexate [2].

### Diloxanide furoate

Diloxanide furoate is derived from furoate ester of 2, 3-dichloro-4-hydroxy-N-methyl acetanilide. Diloxanide furoate antiamoebic medicine was elaborated as a sequence of the discovery that different α, α-dichloroacetamides collected an amoebicidal activity. Diloxanide furoate is measured as a safe and effective medicine for the management of asymptotic or symptomatic persons who are passing cysts of E. histolytica. Also used predominantly in the bowel lumen, and is used in the management of the intestinal amoebiasis, but has little activity on amebic dysentery than in asymptotic infection, but the furoate gives great intestinal accumulations and is implicitly mostly active than metronidazole in the management of cyst passers [30].

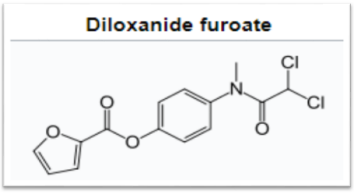


**Figure 6** chemical structure of diloxanide furoate

**Mechanism of action:** Diloxanide furoate has no well-known mechanism of action, but it diminishes the trophozoites of E. histolytica that ultimately figure into cysts. The cysts are then excreted by persons infected with asymptomatic amebiasis.
Use: Diloxanide furoate used for treatment of amoebiasis (asymptomatic carriers in non-endemic areas; eradication of residual luminal amoebae after management of invasive disease with other medicines)

Drug interactions: Diloxanide furoate and metronidazole have synergistic activity and their combination hastily generates great parasitological and clinical heal rates.

Indications: Acute amoebic dysentery, chronic intestinal amoebiasis and other systemic diseases owing to entamoeba histolytica and for extra-intestinal amoebiasis and giardiasis.

**Side effects:** Diloxanide furoate is usually well-tolerated, but flatulence and mild gastric upset perhaps happen in hypersensitive individuals. Metallic taste or darkening of urine perhaps also happens.

**Contra-indications:** There are no absolute contra-indications to the usage of diloxanide furoate; although, it is judicious to avoid its usage during pregnancy and lactation.

### Etofamide

Etofamide (INN, AKA eticlordifene) is an antiprotozoal medicine used in the treatment of amoebiasis. Its consequence against giardia lamblia has been delineated as intermediate [31].

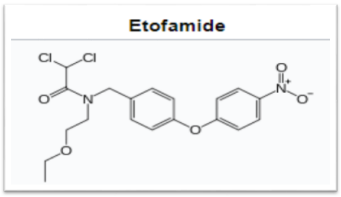


**Figure 7** chemical structure of etofamide
Adverse drug reaction: Abdominal discomfort, nausea, vomiting, dizziness

### Conclusion

Amoebae are found worldwide and are extremely ubiquitous in soil,

fresh water, and other habitats. However ordinary hurtles, certain of them are human pathogens. While autophagy has been entire extendedly considered in the social amoeba dictyostelium discoideum, where it plays a function in survival and spore formation, it has only been partly described in pathogenic amoebae. Metronidazole has the ability to diffuse into the organism to suppress protein secretion by interacting with DNA and causing rupture of helical DNA structure and strand cascade. Thereupon, it causes cell death vulnerable organisms. If tinidazole administered coincidentally with bile acid sequestrants such as cholestyramine, colestipol etc its absorption perhaps decreased. If take with anticoagulant medications such as warfarin, it accelerates anticoagulant effects of the medicine. Diloxanide furoate is usually well-tolerated, but flatulence and mild gastric upset perhaps happen in hypersensitive individuals. Metallic taste or darkening of urine perhaps also happens.

## Abbreviations

ADRs: Adverse drug reactions; CYP450: cytochrome P450; DDIs: drug-drug interactions, DI: Drug interaction; PH: Potenz Hydrogen; GERD: Gastroesophageal reflux disease; GIT: Gastrointestinal Tract; PD: Pharmacodynamic; PK: Pharmacokinetic; P-gp: Pglycoprotein

Funding
None

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