EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES

http://www.ejbps.com

ISSN 2349-8870
Volume: 10
Issue: 4
255-260
Year: 2023

ANTI-AMOEBIC DRUG: A FRIEND OF TUMMY AFTER EATING THE YUMMY & SPICY FOOD ENDS TOWARDS GUMMY EXCRETION

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Article Received on 21/02/2023 **Article Revised on 11/03/2023** **Article Accepted on 01/04/2023**

ABSTRACT

Infection with the protozoan *Entamoeba histolytica* is common in low- and middle-income countries, and up to 100,000 people with severe disease die every year. Adequate therapy for amoebic colitis is necessary to reduce illness, prevent development of complicated disease and extraintestinal spread, and decrease transmission. Amebiasis is an intestinal (bowel) illness caused by a microscopic (tiny) parasite called *Entamoeba histolytica*, which is spread through human feces (poop). Often there are no symptoms, but, sometimes it causes diarrhea (loose stool/poop), nausea (a feeling of sickness in the stomach), and weight loss. The parasite lives only in humans and is passed in the feces (poop) of an infected person. A person gets amebiasis by putting anything in their mouth that has touched infected feces or by eating or drinking food or water contaminated with the parasite. It can also be spread sexually by oral-anal contact. Some people with amebiasis may carry the parasite for weeks to years, often without symptoms, continually passing it in their feces. The majority of people who are infected with this parasite will experience no symptoms. Those who do become sick may experience mild or severe symptoms. The mild form of amebiasis includes nausea (a feeling of sickness in the stomach), diarrhea (loose stool/poop), weight loss, stomach tenderness, and occasional fever. Rarely, the parasite will spread the body beyond the intestines and cause a more serious infection, such as a liver abscess (a collection of pus). The symptoms may develop a few days to a few months after exposure but usually within two to four weeks.

KEYWORDS: Amoebiosis, Metronidazole, Tinidazole, Anti Amoebiosis.

INTRODUCTION

Antiamoebic drugs vary in efficacy at the three sites where parasites commonly exist and generally are divided into two classes based on their main site of activity. Luminal amoebicides act principally in the bowel lumen, and tissue amoebicides act principally in the bowel wall and in the liver.[1]

- Metronidazole, or a related drug such as Tinidazole, Secnidazole or Ornidazole, is used to destroy amoebae that have invaded tissue.
- Several drugs are available for treating intestinal infections, the most effective of which has been shown to be Paromomycin (also known as Humatin).

E. histolytica infections occur in both the intestine and (in people with symptoms) in tissue of the intestine and/or liver. As a result, both tissue and luminal drugs are needed to treat the infection, one for each location. Metronidazole is usually given first, followed by Paromomycin [CAS: 1263-89-4; IUPAC: 2R,3S,4R,5R,6S)-5-amino-6-[(1R,2S,3S,4R,6S)-4,6-diamino-2-[(2S,3R,4R,5R)-4-[(2R,3R,4R,5R,6S)-3-amino-6-(aminomethyl)-4,5-dihydroxy-oxan-2-yl]oxy-3-hydroxy-5-(hydroxymethyl)oxolan-2-yl]oxy-3-hydroxy-cyclohexyl]oxy-2-(hydroxymethyl)oxane-3,4-diol] or Diloxanide [CAS: 3736-81-0; IUPAC: 4-[(Dichloroacetyl) (methyl)amino]phenyl furan-2-carboxylate].[2]

E. dispar does not require treatment, but many laboratories (even in the developed world) do not have the facilities to distinguish this from *E. histolytica*.

Tissue amoebicides: Metronidazole, or a related drug such as tinidazole, secnidazole or ornidazole, is used to destroy amoebae that have invaded tissue. These are rapidly absorbed into the bloodstream and transported to

the site of infection. Because they are rapidly absorbed there is almost none remaining in the intestine.
For amebic dysentery a multi-prong approach must be used, starting with one of:

- Metronidazole 500–750 mg three times a day for 5–10 days
- Tinidazole 2g once a day for 3 days is an alternative to metronidazole

Doses for children are calculated by body weight and a pharmacist should be consulted for help.[3]

Luminal amebicides: Since most of the amoebae remain in the intestine when tissue invasion occurs, it is important to get rid of those also or the patient will be at risk of developing another case of invasive disease. Several drugs are available for treating intestinal infections, the most effective of which has been shown to be paromomycin (also known as Humatin); iodoquinol (also known as Yodoxin) is used in the US; and diloxanide furoate (also known as Furamide) is used in certain other countries.

In addition to the tissue amebicides above, one of the following lumenal amebicides should be prescribed as an adjunctive treatment, either concurrently or sequentially, to destroy *E. histolytica* in the colon:

- Paromomycin 500 mg three times a day for 10 days
- Iodoquinol 650 mg three times a day for 20 days

Doses for children are calculated by body weight and a pharmacist should be consulted for help.[4]

Amoebic liver abscess
For amoebic liver abscess

- Metronidazole 400 mg three times a day for 10 days
- Tinidazole 2g once a day for 6 days is an alternative to metronidazole
- Diloxanide furoate 500 mg three times a day for 10 days (or one of the other lumenal amebicides above) must always be given afterwards. Doses for children are calculated by body weight and a pharmacist should be consulted for help.[5]

Mechanism of action

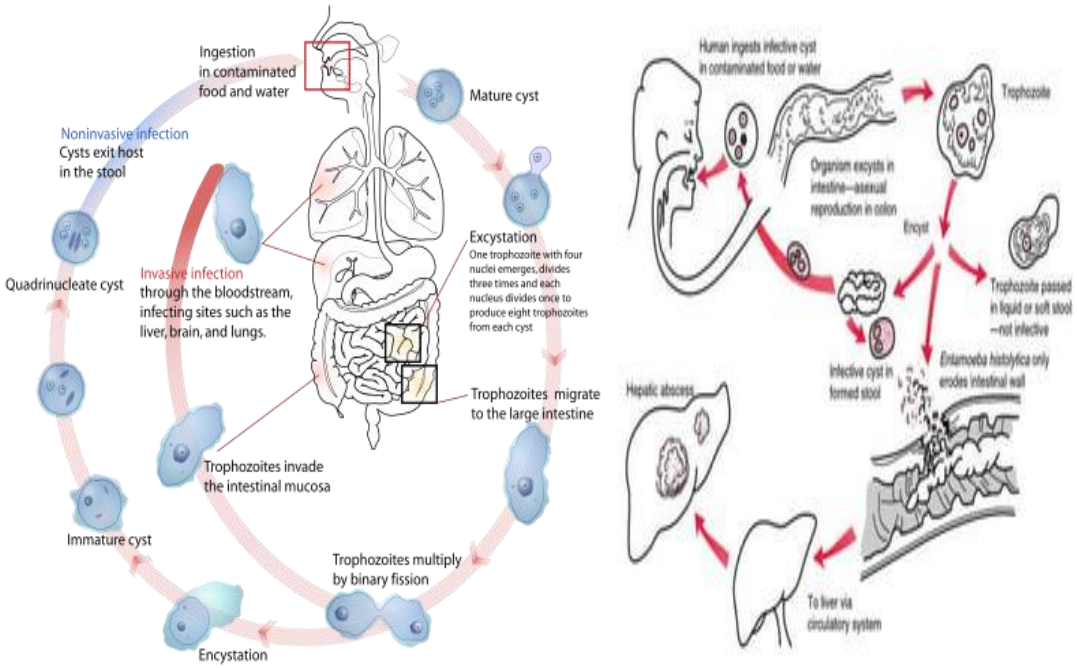


Figure-1: Mechanism of Action (Left side: Amoebiosis, Right Side: Anti Amoebic drugs in our body).

Some Anti Amoebic Drugs & Their Function
Metronidazole: Metronidazole [CAS: 443-48-1; IUPAC: 2-(2-Methyl-5-nitro-1H-imidazol-1-yl)ethanol], sold under the brand name Flagyl among others, is an antibiotic and antiprotozoal medication. It is used either alone or with other antibiotics to treat pelvic inflammatory disease, endocarditis, and bacterial vaginosis. It is effective for dracunculiasis, giardiasis, trichomoniasis, and amebiasis. It is an option for a first episode of mild-to-moderate *Clostridium difficile* colitis if vancomycin or fidaxomicin is unavailable.

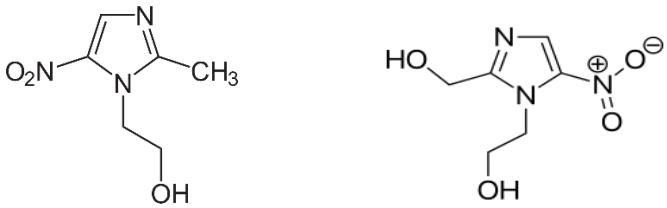
Metronidazole is available by mouth, as a cream, and by injection into a vein.[6]
Metronidazole is primarily used to treat: bacterial vaginosis, pelvic inflammatory disease (along with other antibacterials like ceftriaxone), pseudomembranous colitis, aspiration pneumonia, rosacea (topical), fungating wounds (topical), intra-abdominal infections, lung abscess, periodontitis, amoebiasis, oral infections, giardiasis, trichomoniasis, and infections caused by susceptible anaerobic organisms such as *Bacteroides*, *Fusobacterium*, *Clostridium*, *Peptostreptococcus*, and *Prevotella* species.[7]

Figure-2: Marketed Metronidazole Medication.

Pharmacology

Mechanism of action: Metronidazole is of the nitroimidazole class. It inhibits nucleic acid synthesis by forming nitroso radicals, which disrupt the DNA of microbial cells. This function only occurs when metronidazole is partially reduced, and because this reduction usually happens only in anaerobic bacteria and protozoans, it has relatively little effect upon human cells or aerobic bacteria.[8]

Pharmacokinetics



Figvure-3: Metronidazole and Hydroxymetronidazole, the main metabolite.

Oral metronidazole is approximately 80% bioavailable via the gut and peak blood plasma concentrations occur after one to two hours. Food may slow down absorption but does not diminish it. Of the circulating substance, about 20% is bound to plasma proteins. It penetrates well into tissues, the cerebrospinal fluid, the amniotic fluid and breast milk, as well as into abscess cavities.[9]

About 60% of the metronidazole is metabolized by oxidation to the main metabolite hydroxymetronidazole and a carboxylic acid derivative, and by glucuronidation. The metabolites show antibiotic and antiprotozoal activity *in vitro*. Metronidazole and its metabolites are mainly excreted via the kidneys (77%) and to a lesser extent via the faeces (14%). The biological half-life of metronidazole in healthy adults is eight hours, in infants during the first two months of their lives about 23 hours, and in premature babies up to 100 hours. The biological activity of hydroxymetronidazole is 30% to 65%, and the elimination half-life is longer than that of the parent compound. The serum half-life of hydroxymetronidazole after suppository was 10 hours, 19 hours after intravenous infusion, and 11 hours after a tablet.[10]

Synthesis: 2-Methylimidazole (**1**) may be prepared via the Debus-Radziszewski imidazole synthesis, or from ethylenediamine and acetic acid, followed by treatment with lime, then Raney nickel. 2-Methylimidazole is nitrated to give 2-methyl-4(5)-nitroimidazole (**2**), which is in turn alkylated with ethylene oxide or 2-chloroethanol to give metronidazole (**3**)

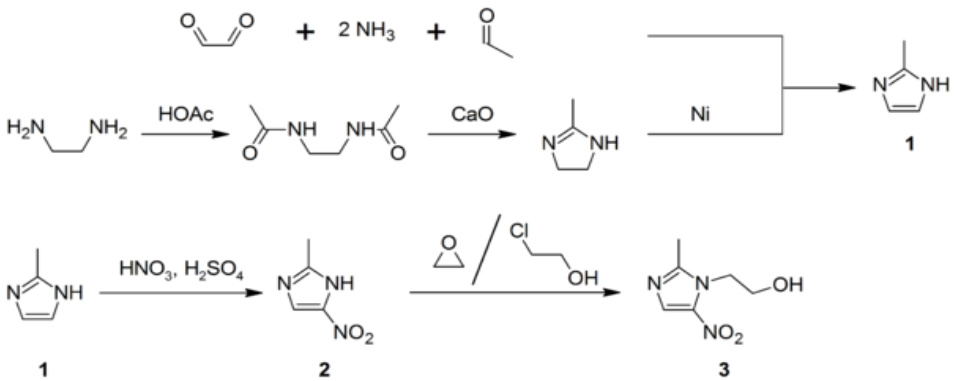


Figure-4: Synthesis of Metronidazole.

Tinidazole
Pharmacokinetics
Half-life: 12-14 hr
Metabolism: Mainly by CYP3A4
Vd: 50L
Protein binding: 12%
Peak plasma time: 1.6 hr
Metabolites: Undergoes oxidation, hydroxylation & conjugation
Excretion: Mainly in urine (20-25% as unchanged drug); feces: 12%

Tinidazole [CAS: 19387-91-8; IUPAC: 1-(2-ethylsulfonylethyl)-2-methyl-5-nitro-imidazole] is a drug used against protozoan infections. It is widely known throughout Europe and the developing world as a treatment for a variety of anaerobic amoebic and bacterial infections. It was developed in 1972 and is a prominent member of the nitroimidazole antibiotic class. It is on the World Health Organization's List of Essential Medicines.[11]

Tinidazole is marketed by Mission Pharmacal under the brand name **Tindamax**, by Pfizer under the names **Fasigyn** and **Simplotan**, and in some Asian countries as **Sporinex.**

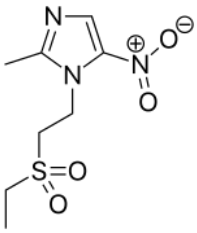


Figure-5: Tinidazole Structure.

Pharmacology
Indication: For the treatment of trichomoniasis caused by *T. vaginalis* in both female and male patients. Also for the treatment of giardiasis caused by *G. duodenalis* in both adults and pediatric patients older than three years of age and for the treatment of intestinal amebiasis and amebic liver abscess caused by *E. histolytica* in both adults and pediatric patients older than three years of age.

Associated Conditions
Amoebiasis
1. Bacterial Vaginosis (BV)
2. Giardiasis
3. Mixed Vaginal Infections
4. Nongonococcal urethritis
5. Sexually Transmitted Disease (STD)
6. Trichomonas Vaginalis Infection
7. Trichomonas Vaginitis
8. Vaginal Candidiasis

Pharmacodynamics: Tinidazole is a synthetic antiprotozoal agent. Tinidazole demonstrates activity both in vitro and in clinical infections against the following protozoa: *Trichomonas vaginalis*, *Giardia duodenalis* (also termed *G. lamblia*), and *Entamoeba histolytica*. Tinidazole does not appear to have activity against most strains of vaginal lactobacilli.

Figure-6: Tinidazole Marketed Medication.

Mechanism of action: Tinidazole is a prodrug and antiprotozoal agent. The nitro group of tinidazole is reduced in *Trichomonas* by a ferredoxin-mediated electron transport system. The free nitro radical generated as a result of this reduction is believed to be responsible for the antiprotozoal activity. It is suggested that the toxic free radicals covalently bind to DNA, causing DNA damage and leading to cell death. The mechanism by which tinidazole exhibits activity against *Giardia* and *Entamoeba* species is not known, though it is probably similar.

Absorption: Rapidly and completely absorbed under fasting conditions. Administration with food results in a delay in T_{max} of approximately 2 hours and a decline in C_{max} of approximately 10% and an AUC of 901.6 ± 126.5 mcg hr/mL.

Volume of distribution: 50 L.

Protein binding: Plasma protein binding of tinidazole is 12%.

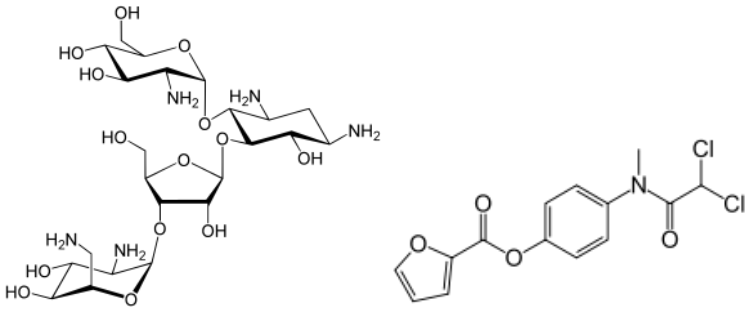


Figure-7: Paromomycin and Diloxanide furoate.

Metabolism: Hepatic, mainly via CYP3A4. Tinidazole, like metronidazole, is significantly metabolized in humans prior to excretion. Tinidazole is partly metabolized by oxidation, hydroxylation and conjugation. Tinidazole is the major drug-related constituent in plasma after human treatment, along with a small amount of the 2-hydroxymethyl metabolite.

Route of elimination: Tinidazole crosses the placental barrier and is secreted in breast milk. Tinidazole is excreted by the liver and the kidneys. Tinidazole is excreted in the urine mainly as unchanged drug (approximately 20-25% of the administered dose). Approximately 12% of the drug is excreted in the feces.

Half-life: The elimination half-life is 13.2±1.4 hours and the plasma half-life is 12 to 14 hours.

Adverse Effects

Toxicity: There are no reported overdoses with tinidazole in humans. In acute studies with mice and rats, the LD_{50} for mice was generally > 3,600 mg/kg for oral administration and was > 2,300 mg/kg for intraperitoneal administration. In rats, the LD_{50} was > 2,000 mg/kg for both oral and intraperitoneal administration.

Pharmacogenomics Effects/ADRs

Drug Interactions

Table-1: Approved drugs and interaction.

DRUG	INTERACTION
Abacavir	Tinidazole may decrease the excretion rate of Abacavir which could result in a higher serum level.
Abametapir	The serum concentration of Tinidazole can be increased when it is combined with Abametapir.
Aceclofenac	Aceclofenac may decrease the excretion rate of Tinidazole which could result in a higher serum level.
Acemetacin	Acemetacin may decrease the excretion rate of Tinidazole which could result in a higher serum level.
Acenocoumarol	The risk or severity of bleeding can be increased when Tinidazole is combined with Acenocoumarol.
Acetaminophen	Acetaminophen may decrease the excretion rate of Tinidazole which could result in a higher serum level.
Acetazolamide	Acetazolamide may increase the excretion rate of Tinidazole which could result in a lower serum level and potentially a reduction in efficacy.
Acetylsalicylic acid	Acetylsalicylic acid may decrease the excretion rate of Tinidazole which could result in a higher serum level.
Aclidinium	Tinidazole may decrease the excretion rate of Aclidinium which could result in a higher serum level.

Food Interactions: Avoid alcohol. Avoid concomitant use of alcohol with tinidazole as it may cause flushing, nausea, vomiting, and headaches. Take with food. Administering with food may reduce gastrointestinal upset and epigastric discomfort caused by tinidazole but does not affect bioavailability.[12]

Figure-8: Amoebic diarrhea and excretion pattern.

CONCLUSION

Consuming alcohol while taking metronidazole has been suspected in case reports to cause a disulfiram-like reaction with effects that can include nausea, vomiting, flushing of the skin, tachycardia, and shortness of breath. People are often advised not to drink alcohol during systemic metronidazole therapy and for at least 48 hours after completion of treatment. However, some studies call into question the mechanism of the interaction of alcohol and metronidazole, and a possible central toxic serotonin reaction for the alcohol intolerance is suggested. Metronidazole is also generally thought to inhibit the liver metabolism of propylene glycol (found in some foods, medicines, and in many electronic cigarette e-liquids), thus propylene glycol may potentially have similar interaction effects with metronidazole.

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