Antiparasitic Drugs

(Antiprotozoal drugs, Nitazoxanide and Ivermectin)

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Antiprotozoal drugs are medicines used to treat infections caused by protozoa, single-cell parasitic organisms. Protozoal infections occur throughout the world and are major causes of morbidity and mortality in some regions such as Africa and South-East Asia. Commonly used oral antiprotozoal drugs can be generally classified into two main groups: antimalarial drugs and miscellaneous antiprotozoals. Commonly used miscellaneous antiprotozoals include metronidazole and tinidazole which are targeting intestinal protozoal infection. Drugs for intestinal protozoal infections can be divided into three groups which are imidazole, luminal and broad spectrum agents.

Imidazole group

Imidazole is an organic compound with the formula \((\text{CH})_2\text{N(NH)CH}\). It is a white or colourless solid that is water soluble, producing a mildly alkaline solution. In chemistry, it is an aromatic heterocycle, classified as a diazole, and having non-adjacent nitrogen atoms. Many natural products, especially alkaloids, contain the imidazole ring. These imidazoles, share the \(1,3-\text{C}_2\text{N}_2\) ring but feature varied substituents. This ring system is present in important biological building-blocks, such as histidine, and the related hormone histamine. Many drugs contain an imidazole ring, such as certain antiprotozoal drugs, the nitroimidazole series of antibiotics, and the sedative midazolam.\(^{[1-4]}\)
**Metronidazole**

Metronidazole (MNZ), 2-methyl-5-nitroimidazole-1-ethanol, is an antibiotic and antiprotozoal medication. It is effective for giardiasis, trichomoniasis, and amebiasis. Metronidazole is available as oral, tropical and intravenous forms. The drug induces generation of toxic oxygen species in parasite cells and damages DNA and may interfere CHO metabolism in protozoa. Metronidazole usually does not penetrate mammalian cells. Regarding pharmacokinetics, metronidazole can be almost completely absorbed via GI tract with bioavailability >95%; its T\(_\text{max}\) is about 1-3 hours and its t\(_\frac{1}{2}\) is 8 hours. Only 20% of the drug can be bound to plasma protein. Metronidazole is metabolized by the liver cells and excreted in urine (60-80%), in feces (6-15%). The drug is contraindicated in patients with known hypersensitivity to nitroimidazole derivative, chronic alcohol dependence and 1st trimester of pregnancy. Patients with hepatic impairment and encephalopathy, breast feeding or who have taken disulfiram in the last 2 weeks should avoid this drug. Common side effects are nausea, metallic taste, loss of appetite, and headache. Occasionally seizures or allergies to the medication may occur. Metronidazole began to be commercially used in 1960 in France.\(^5\) It is on the World Health Organization's List of Essential Medicines, the important medications needed in a basic health system.\(^6\) It is available in most areas of the world. Metronidazole is effective for giardiasis, trichomoniasis, amebiasis and also intestinal anaerobic bacterial infection (*Bacteroides, Fusobacterium, Peptostreptococci, Clostridium* spp. and *Helicobacter pylori*).

**Tinidazole**

Tinidazole is an anti-parasitic drug used against protozoal infections. It is widely known as a treatment for a variety of amoebic and other parasitic infections. It was developed in 1972. As a derivative of 2-methylimidazole, it is a prominent member of the 5-nitroimidazole derivative antibiotics.\(^7\) It can be completely absorbed via GI tract; its T\(_\text{max}\) is about 2 hours and its t\(_\frac{1}{2}\) is 13 hours. It is metabolized by the liver cells via cytochrome enzymes. For non metabolite form, it is excreted in urine (25%), in bile (12%). It is contraindicated in patients with known hypersensitivity to
nitroimidazole derivative, chronic alcohol dependence and 1st trimester of pregnancy. Moreover, the drug should be avoided in patients with hepatic impairment and encephalopathy, breast feeding or who have taken disulfiram in the last 2 weeks. Side effects are usually mild such as nausea and loss of appetite. It is available in most areas of Europe and the developed world. Tinidazole is effective for amoebic liver abscess, amoebic dysentery, giardiasis and other anaerobic bacterial infection (Bacteroides and Helicobacter pylori).

**Secnidazole**

Secnidazole is a synthetic derivative of 5-nitroimidazole group. Its antiparasitic activity includes *Entamoeba histolytica*, *Giardia lamblia*, *Trichomonas vaginalis* and *Gardnerella vaginalis*. Regarding pharmacokinetics, secnidazole can be rapidly and completely absorbed via GI tract, with its \( T_{\text{max}} \) about 1-3 hours and its \( t\frac{1}{2} \) 17-29 hours. Only 15% of the drugs are bound to plasma protein. Secnidazole is oxidized by liver cells and excreted in urine. The drug is contraindicated in patients with known hypersensitivity to nitroimidazole derivative, alcohol dependence and 1st trimester of pregnancy patients must not be prescribed. Mild side effects are nausea, loss of appetite, and headache (2-10%). Secnidazole is effective for intestinal amoebiasis/giardiasis, hepatic amoebiasis and trichomoniasis.

**Luminal agents**

Since most of the intestinal protozoa remain in the lumen of intestine when tissue invasion occurs, it is important to get rid of these intraluminal protozoa or the patient will be at risk of developing recurrent invasive disease. Luminal agents are poorly absorbed from the intestine, and therefore, stay in the lumen of the intestine. Luminal agents are used for the eradication of immature protozoa or cysts inside the bowel, so helpful in elimination of carrier state. Effective luminal agents include paromomycin, iodoquinol and diloxanide. One of the following luminal agents should be prescribed as an adjunctive treatment to destroy *E. histolytica* in the colon.
Diloxanide

Diloxanide is a luminal amebicide used in the treatment of amebiasis.\textsuperscript{[8]} It is formulated as the furoate ester diloxanide furoate. It is considered the luminal agent of choice for mild intestinal amoebiasis or asymptomatic cyst carriers. It can also be added to metronidazole in acute amebic dysentery as well as hepatic abscess. Its mechanism of action, in protozoa, is still not well understood. However, it is believed that the unabsorbed diloxanide is the active anti-amoebic substance. For pharmacokinetics, diloxanide is poorly absorbed and is hydrolyzed within intestinal mucosa. Remaining diloxanide is subsequently excreted in feces (10%). The drug should be avoided in patients providing breast feeding and patients with 1\textsuperscript{st} trimester of pregnancy. Side effects are rare and relatively mild such as flatulence, nausea, diarrhea and urticaria. The drug was discovered by The Boots Company Plc in 1956. Diloxanide furoate is on the World Health Organization's List of Essential Medicines, a list of the important medications needed in a basic health system.\textsuperscript{[6]} Diloxanide is effective for acute and chronic intestinal amoebiasis.

Paromomycin

Paromomycin is an aminoglycoside antibiotic, first isolated from \textit{Streptomyces krestomuceticus} in the 1950s.\textsuperscript{[9]} Paromomycin is available as a capsule and as a cream. It is an antibiotic used to treat intestinal infections such as cryptosporidiosis,\textsuperscript{[10]} amoebiasis and other diseases such as leishmaniasis.\textsuperscript{[11]} Paromomycin inhibits protein synthesis in non resistant cells by binding to 16S ribosomal RNA.\textsuperscript{[12]} It is not absorbed from gut, therefore can be used in pregnancy. Side effects are nausea, abdominal discomfort and diarrhea. It was discovered by Parke Davis introduced as Humatin in 1960.\textsuperscript{[13]} It is on the World Health Organization's List of Essential Medicines, a list of the important medications needed in a basic health system.\textsuperscript{[6]} Paromomycin is effective luminal agent with some value in amoebiasis, cryptosporidiosis in AIDS patients and topical form for cutaneous leishmaniasis.
**Iodoquinol**

Iodoquinol is a quinoline derivative used in the treatment of amoebiasis.[14] It is poorly absorbed from the gastrointestinal tract and is used as a luminal amebicide. Regarding mechanism of action, it acts by chelation of ferrous ions essential for protozoal metabolism. It is contraindicated in patients with impair kidney/liver function and hyperthyroidism. Side effects are abdominal discomfort, skin eruptions, pruritus ani and thyroid gland enlargement. Rare reported adverse effects are severe neurotoxicity (in 1960’s), loss of vision after high dose oral administration. Iodoquinol is an amoebicide used against *Entamoeba histolytica*, and it is active against both cysts and trophozoites that are localized in the lumen of the intestine. It is considered the drug of choice for treating asymptomatic or moderate forms of amebiasis.

**Broad spectrum agents**

Antiparasitics are a class of medications which are indicated for the treatment of parasitic diseases, such as those caused by helminths,[15] ectoparasites, parasitic fungi,[16] and protozoa,[15] among others. Antiparasitics target the parasite by destroying them or inhibiting their growth; they are usually effective against a limited number of parasites within a particular class. Broad-spectrum antiparasitics, analogous to broad-spectrum antibiotics for bacteria, are antiparasitic drugs with efficacy in treating a wide range of parasitic infections caused by parasites from different classes (helminths and protozoa).

**Nitazoxanide**

Nitazoxanide is a broad-spectrum antiparasitic and broad-spectrum antiviral drug that is used in medicine for the treatment of various helminthic and protozoal infections. It is indicated for the treatment of infection by *Cryptosporidium parvum* and *Giardia lamblia* in immunocompetent individuals,[17-24] Nitazoxanide has also been shown to have *in vitro* antiparasitic activity and clinical treatment efficacy for infections caused by other protozoa and helminths;[25][26] Chemically, 5-Nitrothiazole
benzamide compound of nitazoxanide is the prototype member of the thiazolides, a class of drugs which are synthetic nitrothiazolyl-salicylamide derivatives with antiparasitic activity. Tizoxanide, an active metabolite of nitazoxanide in humans, is also an antiparasitic drug of the thiazolide class. Regarding pharmacokinetics, nitazoxanide can be better absorbed with food; its $C_{\text{max}}$ is $10 \mu g/ml$ at 2-4 h after 500 mg nitazoxanide. Almost all of the drugs are bound to plasma protein (99%). It can be rapidly metabolized to active derivative, tizoxanide (diacetyl-nitazoxanide). It is conjugated by the hepatic cells and excreted in urine (32%), in bile, feces (66%). It is contraindicated in patients with known hypersensitivity to nitrothiazolyl-salicylamide derivative. Patients with renal or hepatic impairment and breast feeding should avoid this drug. Common side effects include abdominal pain, diarrhea, nausea and headaches. Nitazoxanide is an effective first-line treatment for infection with *Blastocystis* species\[25\] and is indicated as the treatment for infection caused by *Cryptosporidium parvum* or *Giardia lamblia* in immunocompetent adults and children.[17-18] It is also an effective treatment option for infections caused by other protozoa and helminths (e.g., *Entamoeba histolytica*, *Hymenolepis nana*, *Ascaris lumbricoides*, and *Cyclospora cayetanensis*).

### Ivermectin

Ivermectin is a medication that is effective against many types of parasites. It is used to treat head lice,[27] scabies,[28-29] river blindness,[30] strongyloidiasis,[31] and lymphatic filariasis, among others. Chemically, it is a semi-synthetic derivative of avermectins, a group of macrocyclic lactone produced by actinomycete *Streptomyces avermitilis* (renamed: *S. avermectinius*, 2002). It has same structure as macrolides but it has no bacterial activity. It is composed of 80:20 mixture of avermectin $\beta_1\alpha$ and avermectin $\beta_1\beta$. Ivermectin was discovered from soil sample at Japanese golf course (soil bacterium *Streptomyces avermitilis*) in 1975 and introduced into medical use in 1981.[32-35] Then it was registered in France in 1987.
and US-FDA approved the drug for strongyloidiasis, onchocerciasis in 1996. Regarding mechanism of action, in invertebrate, it can interact with glutamate-gated and g-aminobutyric acid (GABA)-gated chloride ion channels in nerve and muscle cells preventing their closure. Moreover, it can cause hyperpolarization of the neuronal and muscular membrane that resulting in paralysis of pharyngeal and somatic muscle. Regarding pharmacokinetics, ivermectin can be absorbed via GI tract with 50-60% bioavailability. Its C_{max} is 50 ng/ml within 4 hr after 12 mg oral administration. It can be bound to plasma protein (93%). It is metabolized by liver and excreted in urine (1%), in feces (98%). It is contraindicated in pregnancy, lactation, small children, asthma and CNS disorders patients. Common side effects include fever, itching and skin rash. Ivermectin is on the World Health Organization's List of Essential Medicines, the list of important medications needed in a basic health system. Ivermectin is a broad-spectrum antiparasitic agent, traditionally against parasitic worms. It is mainly used in humans for the treatment of onchocerciasis (river blindness), but is also effective against other worm infestations (such as strongyloidiasis, ascariasis, trichuriasis, filariasis and enterobiasis), and some epidermal parasitic skin diseases, including scabies.

REFERENCES


