Antiprotozoal drugs
Drugs for amebiasis, giardiasis, trichomoniasis & leishmaniasis

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Amebiasis, giardiasis and trichomoniasis

Amebiasis affects ~10% of the world's population, causing invasive disease in ~50 million people and death in ~100,000 of these annually. The outcome of *E. histolytica* infection is variable. Many individuals remain asymptomatic but excrete the infectious cyst form, making them a source for further infections. In other individuals, *E. histolytica* trophozoites invade into the colonic mucosa with resulting colitis and bloody diarrhea (amebic dysentery). In a smaller proportion of patients, *E. histolytica* trophozoites invade through the colonic mucosa, reach the portal circulation, and travel to the liver, where they establish an amebic liver abscess. Metronidazole and tinidazole are the drugs of choice for the treatment of amebic colitis, amebic liver abscess, and any other extraintestinal form of amebiasis. Because metronidazole is so well absorbed in the gut, levels may not be therapeutic in the colonic lumen, and the drug is less effective against cysts. Hence patients with amebiasis (amebic colitis or amebic liver abscess) also should receive a luminal agent to eradicate any *E. histolytica* trophozoites residing within the gut lumen. Luminal agents are also used to treat asymptomatic individuals found to be infected with *E. histolytica*. The nonabsorbed aminoglycoside paromomycin and the 8-hydroxyquinoline compound iodoquinol are effective luminal amebicides. Treatment of different forms of amebiasis is summarized in Table 1.

Giardiasis, caused by *Giardia intestinalis*, is prevalent worldwide and is the most commonly reported intestinal protozoal infection in the U.S. Infection with *Giardia* results in one of three syndromes: an asymptomatic carrier state, acute self-limited diarrhea, or chronic diarrhea. Chemotherapy with a 5-day course of metronidazole usually is successful, although therapy may have to be repeated or prolonged in some instances. A single dose of tinidazole probably is superior to metronidazole for the treatment of giardiasis. Paromomycin has been used to treat pregnant women to avoid any possible mutagenic effects of the other drugs. Treatment of giardiasis is depicted in Table 1.

Trichomoniasis is caused by the flagellated protozoan *Trichomonas vaginalis*. This organism inhabits the genitourinary tract of the human host, where it causes vaginitis in women and, uncommonly, urethritis in men. Trichomoniasis is a sexually transmitted disease, with >200 million people infected worldwide and at least 3 million women infected in the U.S. annually. Metronidazole remains the drug of choice for the treatment of trichomoniasis. However, treatment failures owing to metronidazole-resistant organisms are becoming more frequent. Tinidazole, appears to be better tolerated than metronidazole and has been used successfully at higher doses to treat metronidazole-resistant *T. vaginalis*. Treatment of trichomoniasis is depicted in Table 1.

Metronidazole

Metronidazole is the main stay of the treatment of amebiais, giardiasis and trichmoniasis (Table 1). It has been discussed elsewhere (see *"Antibiotics 3-Drugs affecting bacterial DNA"*).

Iodoquinol

Iodoquinol (diiodohydroxyquin) has been used as luminal agent to eliminate intestinal colonization with *E. histolytica*. When used at appropriate doses (never to exceed 2 g/day and duration of therapy not greater than 20 days in adults), adverse effects are unusual. However, the use of this drug, especially at doses exceeding 2 g/day, for long periods is associated with significant risk. The most important toxic reaction, which has been ascribed primarily to clioquinol, is subacute myelo-optic neuropathy. This disease is a myelitis-like illness that was first described in epidemic form (thousands of afflicted patients) in Japan. Peripheral neuropathy is a less severe manifestation of neurotoxicity owing to these drugs. Administration of iodoquinol in high doses to children with chronic diarrhea has been associated with optic atrophy and permanent loss of vision. Because of

its superior adverse-event profile, paromomycin is preferred by many authorities as the luminal agent used to treat amebiasis; however, iodoquinol is a reasonable alternative. Iodoquinol is used in combination with metronidazole to treat individuals with amebic colitis or amebic liver abscess but may be used as a single agent for asymptomatic individuals found to be infected with *E. histolytica*. For adults, the recommended dose of iodoquinol is 650 mg orally three times daily for 20 days, whereas children receive 10 mg/kg of body weight orally three times a day (not to exceed 2 g/day) for 20 days.

Table 1. Treatment of amebiasis, giardiasis & trichomoniasis.

Clinical Setting	Drugs of Choice and Adult Dosage
Asymptomatic intestinal amebiasis	Iodoquinol, 650 mg 3 times daily for 21 days *or–* Paromomycin, 10 mg/kg 3 times daily for 7 days
Intestinal amebiasis, Hepatic abscess, ameboma, and other extraintestinal amebic disease	Metronidazole, 750 mg 3 times daily (or 500 mg IV every 6 hours) for 10 days *or–* Tinidazole, 2 g daily for 5 days *plus–* Luminal agent (see above)
Giardiasis	Metronidazole, 250 mg 3 times or 500 mg twice daily for 5 days Or Tinidazole, 2 g once Or Paromomycin
Trichomoniasis	Metronidazole, 2 g once or 250 mg 3 times or 500 mg twice daily for 7 days *or–* Tinidazole, 2 g once

Paromomycin

Paromomycin is an aminoglycoside that is used as an oral agent to treat *E. histolytica* infection. The drug is not absorbed from the GI tract and thus the actions of an oral dose are confined to the GI tract. Paromomycin also has been used orally to treat giardiasis. It has been used to treat leishmaniasis.

Mechanism of Action

Paromomycin shares the same mechanism of action of aminoglycosides (binding to the 30S ribosomal subunit) and has the same spectrum of antibacterial activity. Following oral administration, 100% of the drug is recovered in the feces.

Antimicrobial effects; therapeutics uses

Paromomycin is the drug of choice for treating intestinal colonization with *E. histolytica*. It is used in combination with metronidazole to treat amebic colitis and amebic liver abscess and can be used as a single agent for asymptomatic individuals found to have *E. histolytica* intestinal colonization. Adverse effects are rare

with oral usage but include abdominal pain and cramping, epigastric pain, nausea and vomiting, steatorrhea, and diarrhea. Paromomycin has been advocated as a treatment for giardiasis in pregnant women, especially during the first trimester, when metronidazole is contraindicated and as an alternative agent for metronidazole-resistant isolates of *G. intestinalis*.

Paromomycin is also efficacious as a topical formulation containing 15% paromomycin in combination with 12% methylbenzonium chloride for the treatment of cutaneous leishmaniasis The drug has been administered parenterally alone or in combination with antimony to treat visceral leishmaniasis. Paromomycin (intramuscular injection, 11 mg/kg per day for 21 days) produced a cure rate for visceral leishmaniasis (94.6%) that was statistically equivalent to liposomal amphotericin B. However, adverse events (general side effects of aminoglycosides i. e. nephrotoxicity, ototoxicity) were more common with paromomycin than with liposomal amphotericin B.

Leishmaniasis

Leishmaniasis is a complex vector-borne zoonosis caused by ~20 different species of obligate intramacrophage protozoa of the genus *Leishmania*. The particular localized or systemic disease syndrome caused by *Leishmania* depends on the species or subspecies of infecting parasite, the distribution of infected macrophages, and especially the host's immune response. In increasing order of systemic involvement and potential clinical severity, major syndromes of human leishmaniasis have been classified into *cutaneous, mucocutaneous, diffuse cutaneous*, and *visceral* (*kala azar*) forms. Leishmaniasis increasingly is becoming recognized as an AIDS-associated opportunistic infection.

Cutaneous forms of leishmaniasis generally are self-limiting, with cures occurring in 3-18 months after infection. However, this form of the disease can leave disfiguring scars. The mucocutaneous, diffuse cutaneous, and visceral forms of the disease do not resolve without therapy. Visceral leishmaniasis caused by *L. donovani* is fatal unless treated. The geographical distribution of disease in Iran has been shown in Figure 1.

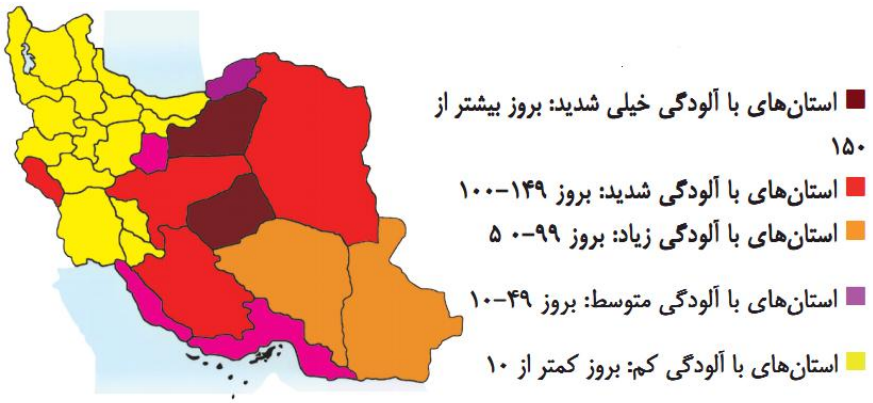

Figure 1. Geographical distribution (number of cases per 100,000 population) of leishmaniasis in Iran, 1383 (2004).

The classic therapy for all species of *Leishmania* is pentavalent antimony [Meglumine antimonite (glucantime ®); sodium stibogluconate (Pentostam®). Resistance to this compound has led to widespread failure of this drug in India, although it remains useful in other parts of the world. As an alternative, liposomal amphotericin B is a highly effective agent for visceral leishmaniasis, and it is currently the drug of choice for antimony-resistant disease. Importantly, treatment of leishmania has undergone major changes owing to the success of the first orally active agent, miltefosine, in clinical trials. Miltefosine was approved in India for the treatment of visceral leishmaniasis in 2002. The drug also appears to have promise for the treatment of the cutaneous disease.

Antimonial agents

Antimonials were introduced in 1945 and have been used for therapy of leishmaniasis and other protozoal infections. Nowadays, sodium stibogluconate (PENTOSTAM) and meglumine antimonate (GLUCANTIME) are the mainstay of the treatment of leishmaniasis. However, increasing resistance to antimonials has reduced their efficacy and they are no longer useful in India where lipid-based amphotericin B and miltefosine are now recommended instead.

Mechanism of action and drug resistance

It seems that these compounds are reduced to the more toxic Sb^{3+} species that kill amastigotes within the phagolysosomes of macrophages. This reduction preferentially occurs in the intracellular amastigote stage.

Sb^{3+} induces a rapid efflux of trypanothione and glutathione from the cells, and also inhibits trypanothione reductase, thereby causing a significant loss of thiol reduction potential in the cells. Trypanothione is an unusual form of glutathione containing two molecules of glutathione joined by a spermidine. A major function of trypanothione is in the defence against oxidative stress.

Important pharmacokinetics characteristics

The pentavalent antimonials are not active orally and must be given intravenously (preferred) or intramuscularly. The agent is absorbed and distributed rapidly. Sequestration of antimony in macrophages may contribute to the prolonged antileishmanial effect after plasma antimony levels have dropped below the minimal inhibitory concentration observed *in vitro*.

Therapeutic uses

Antimonials are given parenterally, with the dosage regimen individualized depending on the local responsiveness of a particular form of leishmaniasis to this compound. The standard course is 20 mg/kg per day for 21 days for cutaneous disease and for 28 days for visceral disease. In Iran, shorter duration of treatment (10-14 days for cutaneous form, 20 days for visceral leishmaniasis) has been applied and showed acceptable results. Intralesional treatment has also been advocated as a safer, alternative method for treating cutaneous disease.

Children usually tolerate the drug well, and the dose per kilogram is the same as that given to adults. Patients who respond favorably show clinical improvement within 1-2 weeks of initiation of therapy. The drug may be given on alternate days or for longer intervals if unfavorable reactions occur in especially debilitated individuals. Patients infected with HIV present a challenge because they usually relapse after successful initial therapy with either pentavalent antimonials or amphotericin B.

Side effects

In general, high-dose regimens of sodium stibogluconate are fairly well tolerated; toxic reactions usually are reversible, and most subside despite continued therapy. Effects noted most commonly include pain at the injection site after intramuscular administration; chemical pancreatitis in nearly all patients; elevation of serum hepatic transaminase levels; bone marrow suppression manifested by decreased red cell, white cell, and platelet counts in the blood; muscle and joint pain; weakness and malaise; headache; nausea and abdominal pain; and skin rashes. Changes in the electrocardiogram that include T-wave flattening and inversion and prolongation of

the QT interval found in patients with systemic disease are uncommon in other forms of leishmaniasis. The electrocardiogram should be monitored during therapy in these patients.

Amphotericin B

Amphotericin B is a highly effective antileishmanial agent that cures >90% of the cases of visceral leishmaniasis in clinical studies, and it has become the drug of choice for antimonial-resistant cases. Numerous dosing schedules have been reported for the treatment of visceral leishmaniasis, with most achieving high cure rates and good safety. It is also considered a second-line drug for cutaneous or mucosal leishmaniasis, where it has been shown effective for the treatment of immunocompromised patients. However, because cutaneous leishmaniasis is typically self-limiting, the drug has not been evaluated for treatment of a broader range of patient populations.

Amphotericine B has been discussed in detail elsewhere (see *"Antibiotics 4-Antifungal drugs"*).

Miltefosin

Miltefosine is the first orally available therapy for visceral leishmaniasis. In 2002, it was approved in India for this indication. It is highly curative against visceral leishmaniasis in the trials conducted to date and also appears to be effective against the cutaneous forms of the disease[1].

The mechanism of action of miltefosine is not yet understood. Resistance to miltefosine develops readily in vitro. To prevent clinical resistance, various drug combinations, including miltefosine with antimonials, amphotericin, or paromomycin, are under study.

Vomiting and diarrhea have been reported as frequent side effects in up to 60% of the patients. Elevations in hepatic transaminases and serum creatinine also have been reported. These effects are typically mild and reversible, and they resolve quickly once the drug is withdrawn.

Other potentially useful drugs for treatment of leishmaniasis

Paromomycin is efficacious as a topical formulation for the treatment of cutaneous leishmaniasis. Since its application is easy, it is very useful in epidemics. The drug has been administered intravenously to treat visceral leishmaniasis and produced a cure rate for visceral leishmaniasis (94.6%) that was statistically equivalent to liposomal amphotericin B. However, general adverse effects of aminoglycosides (ototoxicity, nephrotoxicity) are the main barriers for its systemic use.

Ketoconazole and fluconazole (orally active azole antifugals) has been used successfully in the treatment of cutaneous leismaniasis with cure rates of 70-80 %[2,3].

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