



SCIENTIFIC GROUP ON INTESTINAL PROTOZOAN
AND HELMINTHIC INFECTIONS

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REVIEW OF RECENT ADVANCES IN KNOWLEDGE OF THERAPY OF HUMAN
INTESTINAL PARASITIC INFECTIONS

by

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The drugs for the treatment of intestinal parasites are presented here in 3 different categories:

(1) Recently produced therapeutic agents, widely used or having good potential for future use, well-described in the literature, such as: dichloroacetamide derivatives, metronidazole, tinidazole, mebendazole, pyrantel pamoate, and praziquantel.

For these drugs the following aspects will be considered: their chemical composition and mode of action, their toxicity, side-effects and contraindications, their individual therapy indications and dosages, and uses in mass treatment.

(2) New drugs that are incompletely described and well-known old drugs, of limited use. This group consists of the following drugs: emetine and dehydroemetine, ornidazole, nimorazole, flubendazole, tetramisole-levamisole, oxantel pamoate, tiabendazole and niclosamide.

(3) Long-standing antiparasitic drugs still found in the market and occasionally prescribed which are only mentioned but are not described in the text: hydroxyquinolines, furazolidone, mepacrine, paromomycin, piperazine, bphenium hydroxynaphthoate, pyrvinium pamoate.

The protozoan diseases considered are amoebiasis, giardiasis and balantidiasis. The helminthic diseases are ascariasis, trichuriasis, ancylostomiasis and necatoriasis, strongyloidiasis, enterobiasis, and cestodiasis.

ANTIPROTOZOAN DRUGS

Oral luminal amoebicides

Dichloroacetamide derivatives. These compounds are very little absorbed from the intestine and are presented as white or yellowish powders, tasteless and almost insoluble in water. Four compounds are currently in use:

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- teclozan dichloroacetyl-ethyl-aminoethyl-benzene,
(100 mg tablets)
- diloxanide furoate 4-(N-methyldichloroacetamide) phenyl
-2-furoate, (500 mg tablets)
- etofamide a derivative of clefamide, closely related
in chemical structure, (200 mg tablets)
- clefamide N-(B-oxyethyl)-N-(p-phenoxy-)4-nitro)-benzyl)
dichloroacetamide, (250 mg tablets).

These compounds are amoebicides by contact in the intestinal lumen. As all antiamoebic drugs, they act against the trophozoites, since the cysts are not affected by these chemicals. The amides are effective in high dilutions, over 1:80 000. The mode of action against the parasites is not completely known.

Experimental toxicity is low, the LD₅₀ by oral route being over 5000 mg/kg. At therapeutical dosages no toxic side-effects have been reported. No contraindications are known. A frequent side-effect is flatulence, which disappears after completion of treatment.

Indications for these drugs are treatment of asymptomatic cyst passers and of symptomatic intestinal amoebiasis, in the latter case combined with an amoebicide that acts in the tissues. The dosage for adults is 3-6 tablets per day for 5-10 days. For children, lower dosages of a suspension can be used.

Mass treatment for amoebiasis is not commonly used. Chemoprophylaxis is effective with these drugs; it can be used in highly endemic areas - mainly for visitors - in mental institutions and in communities with very poor hygienic conditions. One tablet, 2 or 3 times per week, is sufficient for prevention.

Oral tissue amoebicides

Nitroimidazole derivatives. These drugs are administered by mouth only; they are absorbed from the small intestine and act against amoeba trophozoites in the intestinal wall and other body tissues. They have very little activity against the parasites in the intestinal lumen. For this reason it is necessary to associate them with luminal amoebicides. There are a good number of compounds pertaining to the 5-nitroimidazole group, all with antiprotozoan activity. The ones more commonly used are mentioned below.

(i) Metronidazole. This was the first of the nitroimidazole derivatives used clinically in protozoan diseases. Since 1959, it has been used for Trichomonas vaginalis infections with excellent results. Several years later, its use was expanded to the treatment of amoebiasis and giardiasis. Metronidazole, (1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole) is a crystalline powder, soluble in water and readily absorbed from the small intestine. The plasma levels rise rapidly, reach effective concentrations in 2-3 h, and maintain these levels for 12 h after a single oral dose. It is excreted mainly through the urine, which sometimes presents a reddish colour; it is also eliminated through the bile in the form of a metabolite that, added to the small amount of the non-absorbed drug, is responsible for some activity against the luminal amoebic trophozoites. Other secretions in which the metabolite may be found are the saliva, semen, vaginal secretions and milk; the drug crosses the placenta, a fact that restricts its use in pregnant women.

The drug has a bitter taste and produces side-effects in 15-30% of the treated cases, usually of low intensity. The most common symptoms are of the gastrointestinal tract, such as nausea, vomiting, abdominal pain, a metallic taste and diarrhoea. Symptoms of the nervous system are seen less frequently, such as dizziness, joint and muscle pain, headache and numbness of extremities. The inhibition of several enzymes concerned with the metabolism of alcohol is responsible for the frequency of symptoms present when alcohol is ingested during or shortly after the treatment with metronidazole. This disulfiram-like effect is characterized by a confusional state, flushing, headache, nausea, vomiting, drowsiness and fall in blood pressure. Contraindications are pregnancy during the first trimester, blood discrasias and diseases of the central nervous system. The question of carcinogenicity of metronidazole has created some fear in the medical profession and in the patients, but so far no clinical evidence of cancer production in human beings has been reported, in spite of widespread use of this drug throughout the world for the past 20 years. It would be prudent to consider metronidazole as a potential carcinogenic drug, since it was found in 1971 that the incidence of naturally occurring tumours in rats and mice was increased significantly when large doses of this drug were administered to those animals over long periods of time. The drug was also shown to induce mutagenic changes in certain bacteria, a fact that has been associated with carcinogenicity.

For the treatment of symptomatic intestinal amoebiasis the dosage used is 30 mg/kg/day, divided into 3 doses after meals, for 8-10 days. For giardiasis, 15 mg/kg/day is given in divided doses for 5 days. The liquid preparations are recommended for children. For balantidiasis a treatment similar to that for amoebiasis can be used.

Mass treatment or mass chemoprophylaxis with this drug are not recommended for amoebiasis. For giardiasis, group treatment can be used in children's institutions in which the inmates show high prevalence rates.

(ii) Tinidazole. Chemically it is ethyl (2-(2-methyl 1-5-nitro-1-imidazolyl)-ethyl) sulfone. This drug has similar absorption and pharmacokinetic properties to metronidazole, but the blood concentration after 24 h of administering the 2 drugs is twice as high for tinidazole as for metronidazole. The medium life span of tinidazole is 10-14, longer than for metronidazole. As opposed to metronidazole that is eliminated as a metabolite, tinidazole is eliminated as the drug itself and in a lesser proportion through the urine.

Experimental acute toxicity in rodents showed that the oral and intraperitoneal LD₅₀ was higher than 2000 mg/kg. Studies on subacute toxicity revealed that dosages of 150 mg/kg twice daily for 30 days did not produce clinical or necropsy changes in rats and monkeys. Human toxic effects have not been observed in patients receiving therapeutical dosages. Side-effects are not frequently observed; when present they are mainly those of the gastrointestinal tract, such as nausea and vomiting, usually transient. Although no teratogenicity has been demonstrated, the drug crosses the placenta and is excreted in the milk; for these reasons it is a good precaution not to give this drug during the first trimester of pregnancy or to nursing mothers. Disulfiram-like reactions with alcohol are observed.

The most common regimens used for intestinal amoebiasis are 2 g daily, as a single dose after a meal, for 2 days for adults, and 60 mg/kg in a similar way for children, during 2-3 consecutive days. These short treatments have shown comparably as good results as the longer treatments with metronidazole. For both drugs the efficacy in eliminating the parasites in amoebic carriers is low, since the effect on the luminal trophozoites is very little or absent. This is the reason why a luminal amoebicide should be associated when treating intestinal symptomatic cases.

For giardiasis a single dose of 2 g for adults or 60 mg/kg for children is effective.

As with other nitroimidazole derivatives, mass therapy is not recommended.

(iii) Ornidazole. It is α -(chloromethyl)-2-methyl-5-nitroimidazole-1-ethanol. In most pharmacological aspects it is similar to the 2 compounds already mentioned. Some special characteristics of ornidazole mentioned by the producers are: high plasma concentration of the drug in 1-2 h after oral administration; 85% excretion of the ingested amount in the first 5 days; 63% elimination through the urine and 22% through the faeces; no incompatibility with alcohol; little neurotoxicity, no teratogenicity and no carcinogenicity.

Ornidazole is clinically recommended in intestinal amoebiasis and giardiasis at a dosage of 500 mg twice a day during 5-10 days for adults and proportionally lower dosages for children. The results in cases of symptomatic intestinal amoebiasis were similar for ornidazole and metronidazole, with clinical and parasitological cure rates of over 90%. Tolerance was also similar for both drugs: 15% had side-effects usually of low intensity, consisting of dizziness, muscle and joint pains, nausea and vomiting.

(iv) Nimorazole. This drug, also called nitrimidazine, is 1-(N, B-ethyl-morpholine)-5-nitroimidazole. The *in vitro* activity against Entamoeba histolytica is similar to metronidazole but the blood and urine levels are higher. The recommended dosage for amoebiasis and giardiasis is 40 mg/kg/day for 5-10 days. In cases of balantidiasis, similar dosages have been effective. Results and side-effects seem to be similar to the other imidazoles mentioned, although less information on nimorazole was found.

(v) Emetine and dehydroemetine. Emetine has been in use for more than 50 years. Its action on E. histolytica in the tissues has been known for a long time. The active ingredient is the methyl ester of cephaline, derived from the plant ipecac, which also can be synthesized. Emetine is freely soluble in water and is given by injection. Oral presentations are poorly tolerated and not very effective. It is stored in the tissues and eliminated slowly. For this reason the toxic action is cumulative. At therapeutic doses, side-effects are not severe. They comprise pain in the area of injection, diarrhoea, and nausea. The more important toxic effects are cardiovascular and neuromuscular, when the drug is used for long periods or when there are predisposing factors. The symptoms are hypotension, tachycardia, changes in cardiac rhythm and in the electrocardiogram. Occasional deaths due to cardiac enlargement, congestive heart failure, or other complications have been reported. The neurological symptoms are mainly muscular weakness. Bed rest and medical supervision are recommended during treatment. In very old and debilitated patients the dose should be reduced, and it is advisable not to use emetine in patients who are pregnant or who have cardiac, renal or neuromuscular diseases.

Dehydroemetine is a recent synthetic substance, racemic 2-dehydroemetine dihydrochloride, considered equally effective and less toxic. This drug is excreted more rapidly. The side-effects and toxicity appear similar to those of emetine but probably occur with less frequency and severity. Both drugs are used at the dose of 1 mg/kg/day for 4-6 days.

ANTHELMINTIC DRUGS

(i) Mebendazole. This synthetic compound pertains to the benzimidazole group. Chemically it is methyl-5-benzoylbenzimidazole-2-carbamate. It is presented as a white to yellowish powder, very slightly soluble in water, and tasteless. Absorption from the intestine is minimal and 90% of the drug is excreted unchanged in the faeces, within 24 h after oral administration. Its mode of action is by inhibition of the glucose uptake by the helminths, which result in a depletion of glycogen and adenosine triphosphate contents, necessary for parasite survival, thus leading to the slow death of the worms.

It is generally accepted that this drug does not show toxic effects at therapeutical dosages. The LD₅₀ values in mice and rats is 1280 mg/kg and in dogs and guinea-pigs 640 mg/kg. It has been observed in children heavily parasitized by Ascaris, that some of these worms are expelled through the mouth and nose during the treatment with mebendazole. This side-effect may have to do with starvation of the parasites as a consequence of the inhibition to use exogenous glucose and the insubsequent slow death. When the drug is administered during the organogenesis period in rodents, abnormalities of the foetuses were observed, consisting of skeletal deformities in the ribs and tail. Neither teratogenic or embryotoxic effects were observed in dogs, sheep or horses. As a precaution, mebendazole should not be used during the first months of pregnancy.

Individual treatment with mebendazole is effective for trichuriasis, ascariasis, enterobiasis and hookworms. The usual dosage is 100 mg twice daily for 3 days irrespective of the patient's age. For ascariasis and enterobiasis even shorter treatments are effective. Other indications of this drug are in the treatment of Capillaria philippinensis infections, in which it is considered the drug of choice, at the dosage of 400 mg daily for 10-30 days. For Taenia sodium and T. saginata the recommended dose is 300 mg twice daily for 3 days, although the results are not always good.

Mass treatment with mebendazole aiming to reduce the prevalence rates of the 4 common nematodes for which it is effective, has been successful. Repeated mass treatment with a 1-3 months' interval have shown good effects and drastic reductions of prevalence rates. It is necessary to have in mind that the ideal for mass therapy is the single dose, which is effective only for Enterobius and Ascaris. For enterobiasis a single dose of 100 mg cures from 87% to 100%. The possible teratogenic effects and the occasional Ascaris migrations, are drawbacks for mass treatment with this anthelmintic.

(ii) Flubendazole. This is a parafluor analogue of mebendazole showing activity against animal and human nematodes. The LD₅₀ for flubendazole in acute toxicity tests is 2560 mg/kg for several animal species. No teratological effects were observed in rats and rabbits, which seems to be an advantage over mebendazole. Flubendazole is effective for enterobiasis in a single dose of 200 mg, and for ascariasis, trichuriasis and necatoriasis at the dose of 200 mg daily for 3 days or 300 mg twice a day. The results are similar, but not superior, to those found with mebendazole. Tolerance is equally good for both drugs.

(iii) Tetramisole-levamisole. Tetramisole and its isomer levamisole have been used against a broad range of nematodal infections in animals. These 2 benzimidazoles are soluble in water and readily absorbed from the intestine. They act on the neuromuscular system of the worms producing paralysis. Due to the good tolerance and low single dosage, levamisole has successfully been used for mass treatment in ascariasis. At the present, it is under clinical investigation for immuno deficiency diseases and some malignancies. Several cases of agranulocytosis are known after prolonged use of this drug.

(iv) Tiabendazole. This is one of the oldest benzimidazoles, absorbed from the intestine, with good activity against adult and larval forms of some tissue nematodes. It is still the drug of choice for strongyloidiasis and cutaneous larva migrans. Side-effects are present in 50% or more of the treated patients, dizziness being the most common symptom. Other symptoms are nausea, vomiting, abdominal pain, anorexia and diarrhoea. Headache, drowsiness, lethargy, erythema multiforme and Stevens-Johnson syndrome, with 2 fatalities, have been reported. The recommended dosage is 25 mg/kg/day, divided into 3 doses, administered with meals, during 3 or more days.

Pyrantel Pamoate. This compound of the amidine group is a tetrahydropyrimidine with the chemical formula trans-1, 4, 5, 6-tetrahydro-1-methyl-2-(2-(2-thienyl)-vinyl) pyrimidine hydrogen pamoate. It is a crystalline powder insoluble in water and very slightly absorbed

from the intestine. It has no special taste and is stable to moisture, light, and temperature. Its mode of action is inhibiting neuromuscular transmission, thus producing spastic paralysis of the worms.

The oral LD₅₀ for mice, rats and dogs, ranges between 2-5 g/kg. No toxic effects at therapeutic dosages have been reported and the side-effects are light and transient; some reports have shown that from 4% to 20% of the patients treated, present gastrointestinal symptoms such as abdominal cramps, diarrhoea, nausea and vomiting. Less frequent are headache, dizziness and drowsiness. No teratogenicity has been found. There are no specific contraindications.

Pyrantel is effective for ascariasis and enterobiasis at the single dose of 10 mg/kg. For hookworm, the same daily dosage should be repeated for 3 consecutive days.

Mass treatment with pyrantel has been effective for reducing Ascaris infection to very low prevalence rates. Repeated treatments every 3 months have maintained large groups of populations under control for ascariasis, with the prevalence reduced from 80% to less than 1%.

These experiences are applicable also to groups of children infected with Enterobius. This drug has the advantage of being effective for these 2 parasites in a single dose. The good tolerance and the lack of teratogenicity are in favour of the use of this drug for mass therapy, especially on a large scale. For hookworms it is necessary to give the treatment for 3 days to achieve appropriate worm reductions.

(v) Oxantel pamoate. Oxantel pamoate is trans-1, 4, 5, 6-tetrahydro-2-(3-hydroxystyryl)-1-methylpyrimidine hydrochloride. It is used for the treatment of Trichuris trichiura infections. Unlike its analogue, pyrantel, oxantel is not effective in cases of ascariasis. The combination of the 2 drugs widens the spectrum of activity. The possible effect on other helminthiasis has not yet been defined. Oxantel is a crystalline salt of yellow colour, practically insoluble in water; this drug is well tolerated and does not cause toxic effects.

For trichuriasis the dosage of 10-15 mg/kg/day for 2-3 days is recommended. Single doses are effective only for light infections. The combination of pyrantel and oxantel has been successfully used as a wide spectrum anthelmintic, being effective for Ascaris, Enterobius, Trichuris and hookworm. This combination has promising efficacy for mass therapy.

(vi) Praziquantel. Chemically this drug is 2-cyclohexylcarbonyl-1, 3, 4, 6, 7, 11b-hexahydro-2 H pyrazino(2, 1-a)isoquinolin-4-one, a new type of acylated heterocyclic compound, an isochinolin-pyrazin-derivative. It is a colourless crystalline powder with a bitter taste and insoluble in water. After oral administration the drug is rapidly absorbed from the gastrointestinal tract; maximum serum concentrations appear after 2 h; it is metabolized in the liver and excretion is completed after 24 h, partially via the mucosal epithelia of the gastrointestinal tract, but mainly through the urine in the form of several metabolites. The detailed method of action of this drug is still under investigation, but initial studies have shown that the compound acts on the carbohydrate metabolism of the parasites.

Acute toxicity tests in rats and mice showed that LD₅₀ was over 2000 mg/kg/by mouth. Tolerance is good in experimental animals and in human beings. Very few, transient side-effects of the gastrointestinal tract, dizziness, headache and drowsiness, have been mentioned by some authors, while others refer to complete absence of side-effects. No embryotoxic, teratogenic or mutagenic effects were found experimentally.