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CHEMOTHERAPY OF HUMAN INTESTINAL PARASITIC DISEASES

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Human intestinal parasitic diseases are a major medical and public health problem in all tropical countries of the world, where poor sanitation, environmental factors, and low living standards facilitate the dissemination of these infections. Settlement in temperate countries by people from tropical areas and the rapid travel in and out of tropical countries by people from temperate zones make it necessary that pharmacologists, public health authorities, and physicians become acquainted with the current status of the treatment of the common intestinal parasites. It is with this aim that this publication is written, based on the author's experience in clinical trials with antiparasitic drugs and on the extensive use of chemotherapeutic agents in a tropical country. The first part of this chapter deals with the chemotherapy of the three common intestinal protozoan diseases (amebiasis, giardiasis, and balantidiasis) as well as of the six most frequent intestinal helminthiases (ascariasis, trichuriasis, ancylostomiasis, enterobiasis, strongyloidiasis, and tapeworm infections). The second part of this review is devoted to pharmacological comments on the antiparasitic drugs dealt with in this chapter.

CHEMOTHERAPY

Amebiasis

The colonization of the large intestine by *Entamoeba histolytica* is very frequent in tropical countries and not rare in temperate zones. The majority of patients harboring the parasite do not manifest symptoms and are considered carriers or asymptomatic cases. In these cases the amebae live in the lumen of the intestine and reproduce there with no invasion of the tissues. There is a large group of amebiasis cases in which the parasites invade the superficial part of the intestinal wall and produce lesions of the mucosa which are manifested by colic pain, irregular bowel function, and diarrhea. These cases are considered chronic and frequently alternate

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between periods of intense symptomatology and remission. A third clinical category of intestinal amebiasis involves definite ulcerations and sometimes necrosis of the large intestinal wall, leading to the classical dysenteric syndrome characterized by intense diarrhea, with mucus and blood, colic spasmodic pain, and rectal tenesmus. In a few cases, a fibrotic tumor-like lesion, called *ameboma,* may develop.

All antiamebic drugs act against the trophozoites of *E. histolytica,* but they cannot penetrate the cyst wall of this parasite. The disappearance of cysts after treatment in asymptomatic or chronic cases depends on the action against their predecessors, the trophozoite form. Infection by the other human nonpathogenic amebae, different from *E. histolytica,* do not require treatment. The antiamebic drugs can be divided into three groups, depending on the mode of action and the route of administration as follows:

ORAL LUMINAL AMEBICIDES In this group are included the old pentavalent arsenicals that are no longer used, the halogenated hydroxyquinolines, and the nonabsorbable amides that act by direct contact with the parasites in the intestinal lumen.

TISSUE AMEBICIDES ADMINISTERED ORALLY These drugs are actively absorbed from the small intestine. They are partially effective as luminal amebicides as a result of the effect of the nonabsorbed part of the compound and the action of metabolites eliminated through the bile. This group of drugs includes imidazole derivatives, metronidazole, ornidazole, and tinidazole.

TISSUE AMEBICIDES GIVEN PARENTERALLY These compounds do not act against the parasites in the bowel lumen. This group includes emetine hydrochloride and dehydroemetine. Oral preparations of these drugs are poorly tolerated and have low effectivity.

A few antibiotics are amebicides by themselves, such as paromomycin and erythromycin. Others, like the tetracyclines, act indirectly by modifying the intestinal flora. Neither group is effective in the treatment of intestinal amebiasis and cannot be recommended as the only treatment for amebic infections. Chloroquine is effective in the liver amebic abscess only but exerts no action on intestinal amebiasis. Depending on the clinical form of intestinal amebiasis, the following schemes of treatment are recommended:

ASYMPTOMATIC AMEBIASIS Only drugs acting in the bowel lumen should be used.

Amides In this group there are several preparations, such as etofamide (200 mg tablets), teclozan (100 mg tablets), clefamide (250 mg tablets), and diloxanide furoate (500 mg tablets). The usual dose is three tablets per day for five days, although a higher dose can be given as these compounds are nonabsorbable (1, 2).

Hydroxyquinolines If one drug of this group is used, the one to be preferred is diiodohydroxyquin at the dose of 650 mg, three times daily for 21 days for adults

and 10 mg/kg three times a day for 21 days for children (3). The imidazole derivatives are not recommended in cases of asymptomatic carriers because of the low activity in the lumen of the large intestine (4).

CHRONIC AND DYSENTERIC AMEBIASIS In these cases it is necessary to use two different types of drugs, one acting against the amebae in the tissues and reaching the parasites through the blood and another attacking the parasites in the intestinal lumen by direct contact. In the former group are the imidazole derivatives, administered orally, and the emetines, given parenterally.

Metronidazole This is the oldest drug in the imidazole group. It is recommended at the dose of 1.0 to 2.0 g daily for eight to ten days for adults. In children, the dosage is 30 mg/kg day for the same time (5).

Ornidazole This newer drug is used in a dosage similar to metronidazole (6).

Tinidazole This is recommended for adults only, at the dose of 2.0 g per day for two days (7).

Emetine hydrochloride and dehydroemetine Both are good tissue amebicides and very effective in the control of diarrhea. The accepted dose is 1 mg/kg daily for four to six days (8).

Amides or diiodohydroxyquin One of these luminal amebicides should be used concomitantly or after the administration of the above-mentioned drugs. The dosage is the same mentioned already for asymptomatic amebiasis.

AMEBOMA This lesion of the colon should be treated with the imidazole derivatives or emetine, followed by the luminal amebicides at the same dosage mentioned for the symptomatic intestinal amebiasis.

Giardiasis

Giardiasis is produced by the protozoon *Giardia lamblia,* which lives in the upper part of the small intestine, where it causes irritation and inflammation. The disease is more frequent in children and the main symptoms are epigastric pain, diarrhea, flatulence, and bulky, bad-smelling stools. There are asymptomatic patients that occasionally may become symptomatic. All cases involving the parasite should be treated. Fortunately, the treatment is effective and simple but reinfections occur very easily.

IMIDAZOLES These are the drugs of choice, used as for amebiasis. Treatment for shorter periods than for amebiasis are usually equally effective (9, 10).

FURAZOLIDONE This is an alternative drug that is similarly effective at the dose of 100 mg, four times a day for seven days for adults. There are pediatric preparations in the form of emulsion and drops that are easily administered at the dose of 5 to 8 mg/kg per day (10, 11).

QUINACRINE HYDROCHLORIDE This antimalaric drug has been used for many years for the treatment of giardiasis and is still used in several countries, mainly in those where the imidazoles and furazolidone are not on the market. Cure rates of 80 to 95% are obtained with a dosage of 0.1 g three times a day, after meals, for five to seven days. In children the dosage is 7 mg/kg daily, divided into three doses during the same time (10, 39).

Balantidiasis

Balantidiasis is produced by the protozoon *Balantidium coli,* which inhabits the large intestine, where it may cause irritation and superficial ulcerations of the mucosa, manifested by diarrhea and sometimes by a dysenteric syndrome. The infection may also be asymptomatic. Actual treatment is based on the use of the imidazole derivatives at the dosage mentioned for amebiasis (12).

Ascariasis

This is one of the most common intestinal helminthiases. It must always be treated, even in cases of light infections, because even a single parasite can cause intestinal symptoms or produce important complications when migrating to abnormal sites, such as the bile ducts. The round worm *Ascaris lumbricoides* lives in the lumen of the small intestine and is sensitive to most of the known anthelmintics. The following drugs are recommended.

PYRANTEL PAMOATE Pyrantel pamoate is effective in a single dose of 10 mg/kg. Cure rates are close to 100% (13).

MEBENDAZOLE Treatment for three days is recommended at the dosage of 100 mg twice a day. This dosage is the same for children above two years of age and for adults. Cure rates are high, similar to those obtained with pyrantel pamoate (14).

LEVAMISOL OR TETRAMISOL Levamisol or tetramisol is very effective in a single dose of 150 mg in adults and in a single dose of 40 to 80 mg in children. Cure rates are near 100% (15, 16).

PIPERAZINE Several salts of piperazine are used, most commonly citrate, adipate, or phosphate. Single-dose treatments are recommended with good results (17), although our experience has shown that treatments lasting several days are preferable. The dosage is 50 mg/kg day divided into two or three doses for five days. The results obtained with this course of treatment are as effective as those obtained with the drugs mentioned above. When masses of worms are the cause of intestinal obstruction or other pathology, piperazine is the drug of choice.

Trichuriasis

General prevalence of *Trichuris trichiura* (whipworm) is high, similar to that of *Ascaris.* Most cases of trichuriasis are mild, especially in adults. Symptomatic cases exhibiting diarrhea or a dysenteric syndrome, involve massively infected children,

especially if they are undernourished. Fortunately, the drugs available are efficient and easy to administer for this parasitic infection, which not long ago was the most difficult one to treat.

MEBENDAZOLE This is the drug of choice at the dosage of 100 mg twice daily, for three days irrespective of the patient's age. This treatment produces cure rates of over 80% in heavy infections and near 100% in light infections (18–20).

OXANTEL PAMOATE This newer drug is effective in cases of *Trichuris* infections with dysenteric syndrome at the dosage of 10 mg/kg, twice daily for three days (21). When the drug was used in single dose from 10 to 25 mg/kg in light infections, the results favored the highest dose (22). In our experience a single dose of 10 mg/kg was effective only in light infections. A dosage of 15 mg/kg per day for two days was more effective for moderate and severe infections.

Ancylostomiasis and Necatoriasis

Ancylostomiasis and necatoriasis, due to *Ancylostoma duodenale* and *Necator americanus* (hookworms), prevail in the tropics, mainly in rural areas, where agricultural workers are more frequently affected. The most important clinical consequence is the production of anemia. Without exception, all cases should be treated because the parasites live for several years, sucking blood from the patient. Besides the anthelmintic treatment, iron therapy is necessary. The following anthelmintics are used.

PYRANTEL PAMOATE This drug is used at the dosage of 10 mg/kg per day for three days. Although cure rates are estimated at about 80%, reduction in the egg counts, which indicate decrease of the worm burden, reaches figures over 95% (23).

MEBENDAZOLE At the dosage of 100 mg twice a day, for three days, for children and adults, this drug produces cure rates similar to those observed with pyrantel (18, 19).

BEPHENIUM HYDROXYNAPHTHOATE This drug is more effective against *A. duodenale* than against *N. americanus.* The single dose for adults is 5 g of the drug containing 2.5 g of bephenium base. For children, the dose is half the one for adults. It is advisable to repeat this treatment once or twice in the following days. Our results in cases of *N. americanus* infections were inferior to those obtained with the previously mentioned drugs (23).

BITOSCANATE This is a newer drug effective for hookworms. In our studies we administered this drug every 12 hr at the dosage of 100 mg, three times for adults and two times for children between 10 and 14 years of age. In younger patients (5 to 9 years) this dose was reduced to one half. We obtained egg reductions ranging from 92 to 96% in cases of *N. americanus* infections, although cure rates were very low (24).

Enterobiasis

This cosmopolitan parasitic infection, due to *Enterobius vermicularis* (pinworm), is easily transmitted from person to person and usually affects children living in close contact with each other. Under this circumstance, it is frequently necessary to treat the whole group or family. Although anthelmintic therapy is very effective, reinfections or autoinfections are to be expected. Fortunately, the symptomatology is mild, and consists mainly in anal pruritus. The drugs mentioned below are effective for its treatment and usually should be repeated because reinfections are very frequent.

PYRANTEL PAMOATE A single dose of 10 mg/kg is very effective. Cure rates are as high as 96% (25, 26).

MEBENDAZOLE Mebendazole is also highly effective when administered as a single dose of 100 to 200 mg, irrespective of body weight (27). Treatment for three days is recommended if concomitantly there are other helmintic infections for which this drug is also effective.

PYRVINIUM PAMOATE Pyrvinium pamoate is effective in a single dose of 5 mg/kg body weight. Cure rates are over 90% (28, 30).

PIPERAZINE The percentages of cure with this drug are similar to those obtained with the three drugs mentioned above, with the difference that piperazine should be used for five to eight consecutive days. The dosage is 50 mg/kg per day (29, 30).

Strongyloidiasis

This is a less common parasitic infection in comparison with those already mentioned; it is produced by a small roundworm, *Strongyloides stercoralis,* that lives within the tissues of the small intestine. There are no characteristic symptoms, and the diagnosis should always be based on the identification of the larvae in feces or duodenal fluid. High eosinophilia is frequent and dissemination of the infection may occur during immunosuppressive therapy or prolonged use of adrenal steroids. Treatment is always necessary. The common anthelmintics already mentioned are noneffective for this parasitic disease. The drugs effective against *Strongyloides* should be well absorbed in order to act within the tissues, where these helminths are lodged. Only one drug is considered effective.

THIABENDAZOLE This is the drug of choice at the dosage of 25 mg/kg/body weight, daily for three days. The daily dose should be subdivided into two or three subdoses, to be taken after meals, in order to diminish the frequently observed side effects. With this treatment, cure rates are over 90% (31, 32).

Tapeworm Infections

The two cosmopolitan and most frequently diagnosed tapeworms are the beef tapeworm, *Taenia saginata,* and the pork tapeworm, *Taenia solium.* A third large tapeworm is acquired from fish, *Diphyllobothrium latum,* but it has a limited geographical distribution. The dwarf tapeworm, *Hymenolepis nana,* and the less

frequent *Hymenolepis diminuta* are found in the tropics and subtropics. Occasional findings of human infection with the dog tapeworm *Dipyllidium caninum* have been reported. The symptomatology of the taenia infections is usually mild or absent. Only intestinal disturbances are occasionally reported. In a few cases of infections with the fish tapeworm, macrocytic anemia may be noticed. The ingestion of *T. solium* eggs can cause human cysticercosis, a disease that may involve production of varied and important symptoms by the central nervous system. Three drugs are recommended for the treatment of the above-mentioned infections that are due to adult intestinal worms.

NICLOSAMIDE This is considered the drug of choice for all tapeworm infections (33, 34). It is advisable to ingest only liquids the evening before treatment and take the drug on an empty stomach at a single dose of 2 g, for all ages. The tablets should be thoroughly chewed and passed with a little water. This nonabsorbable and well-tolerated drug can be administered for two or three days if necessary. In cases of *H. nana* infections, the treatment should last for five days and should be repeated after three weeks. In general, no purgatives are necessary but in cases of *T. solium* infections the use of a purge after two hours of the treatment is advisable to eliminate the worm segments before they disintegrate and release ova that may cause cysticercosis.

PAROMOMYCIN In our experience this antibiotic cured 93% of cases of *T. solium* and *T. saginata* at the dosage of 40 mg/kg per day for five days or 75 mg/kg single dose, with a maximum of 4 g (35). In cases of *H. nana* infection, the treatment should be prolonged for seven days and be repeated after three weeks.

MEBENDAZOLE Mebendazole is effective for cestodes when used at a dosage three times larger than recommended in other helminthiases. The preferable dosage is 300 mg three times a day for three days. With this dosage schedule, cure of 100% was obtained in cases of *T. solium* and *T. saginata* (36).

PHARMACOLOGY, SECONDARY EFFECTS, TOXICITY, AND CONTRAINDICATIONS OF THE ANTIPARASITIC DRUGS CONSIDERED

We do not include in this review the older antiparasitic drugs that have been replaced by more effective and less toxic agents. Neither do we mention the very recent products, still under investigation for which carefully planned clinical trials are necessary (42). For these reasons the number of products dealt with is low, although their effectivity is high. In few diseases has there been achieved such a degree of effectivity as in this group of intestinal parasitic infections. Most drugs are effective in single doses or in short-term treatments (3, 29). Toxicity is usually low, side effects are not severe, and the cost of treatment is reasonable. The ideal antiparasitic drug that eliminates all types of parasites has not been found, but several wide-spectrum compounds are already available. Below is a discussion of antiparasitic drugs, in alphabetical order.

Amides

The dichloroacetamide derivatives are absorbed very little from the intestine and are active against *E. histolytica* trophozoites by direct contact, even in very high dilutions (over 1:80,000). They are yellowish white powders with practically no taste and are almost insoluble in water. The tolerance to these drugs is very good, flatulence being the only known side effect (1). Toxicity is very low in animals. The LD_{50} dose is over 5000 mg/kg by oral route. In humans no toxicity has been reported. The most common amides used are clefamide, chemically N-(β-oxyethyl)-N-[*p*-phenoxy-(4'-nitro)-benzyl] dichloroacetamide and its derivative etofamide (2); teclozan or dichloroacetyl-ethyl-aminoethyl-benzene; and diloxanide furoate or 4-(N-methyldichloroacetamide) phenyl-2-furoate.

Bephenium Hydroxynaphthoate

This drug, synthetized in 1958, is used against *A. duodenale* and less frequently against *N. americanus*. It is also active for *A. lumbricoides*. The mode of action on the helminths is not well understood but it is known that the parasites suffer from irreversible paralysis. Chemically this drug is a quaternary ammonium compound, presented as a yellow crystalline substance of bitter taste and low solubility in water, poorly absorbed from the intestine. This last characteristic is responsible for the low toxicity at therapeutic doses. In contrast, there are frequent adverse reactions. These are mainly gastrointestinal symptoms such as nausea, vomiting, abdominal pain, diarrhea, and anorexia. Other general symptoms are dizziness and headache. In our experience, side effects occurred in 60% of the cases. This drug should not be used in patients with major gastrointestinal diseases. It should not be used also in hypertensive patients because, if absorbed in considerable amount, may cause a marked fall in blood pressure. This reason also makes caution necessary in using this drug during pregnancy. All the mentioned reasons may be responsible for the future decline in the use of this product, especially considering that there are other more effective and better-tolerated drugs for the treatment of hookworms (23).

Bitoscanate

This synthetic anthelmintic, chemically phenylene-1,4-diisothiocyanate, was initially studied in clinical trials in 1968 and proved to be effective for human hookworms. This compound has no special taste and is presented as a crystalline powder nearly insoluble in water and slowly absorbed and eliminated. The mode of action against the helminths is not clearly understood but it is known that the drug impregnates the cuticle of the worms and accumulates in their digestive tract. The drug is poorly tolerated. In our experience it produced side effects in 57% of the patients treated, the symptoms, being in order of frequency, diarrhea, nausea, vomiting, abdominal pain, and dizziness; no biochemical or hematological changes have been observed after the use of this compound (24).

Emetine and Dehydroemetine

Emetine hydrochloride has been in use longer than the other antiparasitic drugs dealt with in this chapter, more than 50 years. Its effectivity against *E. histolytica*

in the tissues has been known for a long time (8). It 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. The 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, diarrhea, 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 ECG (37). 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 diminished, and it is advisable not to use emetine in patients who are pregnant or who have cardiac, renal or neuromuscular diseases.

Dehydroemetine is a synthetic substance, racemic 2-dehydroemetine dihydrochloride, of recent appearance and is considered equally effective and less toxic (38). This drug is excreted more rapidly. The side effects and toxicity may be similar to those of emetine but probably occur with less frequency and severity.

Furazolidone

A synthetic 5-nitrofuran derivative, furazolidone [N-(5-nitro-2-furfurylidene)-3-amino-2-oxazolidinone], is a yellow crystalline compound that darkens when exposed to light. It is partially soluble in water and partially absorbed from the intestine. Besides its action on giardiasis, furazolidone has shown a wide spectrum of antimicrobial activity (10). Reported side effects have been mainly of the gastrointestinal tract. They are nausea, vomiting, anorexia, abdominal pain, and diarrhea (11). Also, it has been mentioned that in some cases the urine may appear brown. The possibility of producing mammary tumors in rats suggests the need for caution in its use (39).

Hydroxyquinolines

The halogenated hydroxyquinolines are older synthetic amebicides that are still in use. The one most commonly used at present is diiodohydroxyquin (8-hydroxy-5,7-diiodoquinoline). This is a yellow-brown substance, containing about 64% iodine, tasteless and almost insoluble in water. It is partially absorbed and fairly well tolerated. Some gastrointestinal symptoms have been reported, and enlargement of the thyroid gland has been noticed in a few cases (3). Another hydroxyquinoline, iodochlorhydroxyquin, when given for long periods of time or in larger doses, can produce neurotoxicity, mainly optic atrophy and peripheral neuropathy. Recently a syndrome called subacute myelooptic neuropathy (SMON) has been described, consisting of polyneuritis and optic atrophy. This syndrome has been associated with the use of iodochlorhydroxyquin or with a new virus. Because of the severity of this syndrome, great caution should be exerted in the use of this drug, which has been widely prescribed as prophylactic or as treatment of nonspecific diarrhea and or amebiasis (40). Diiodohydroxyquin has not been implicated as a cause of neuro-

toxicity when used at the standard therapeutic dosage, but because of the possibility of causing optic atrophy when the drug is taken for long time or indiscriminately, its use is restricted. The halogenated hydroxyquinolines should no longer be used as a prophylactic or treatment of traveler's or nonspecific diarrhea. These drugs are contraindicated in cases of intolerance to iodine and where thyroid, renal, or hepatic diseases are present.

Levamisole or Tetramisole

Tetramisol is an anthelmintic that has been widely used in veterinary medicine; levamisole, its isomer, has been effectively used in human patients harboring *A. lumbricoides* (15, 16), although it also has an effect on hookworms and *S. stercoralis.* This white, crystalline substance, soluble in water, is readily absorbed. It produces paralysis of the worms by inhibiting several enzymes. The drug is well tolerated. A few cases of intestinal symptoms and dizziness have been reported as the only side effects. This drug is, at the moment, under clinical trials for diseases due to immunodeficiencies and for some malignancies (41), based on the findings that it enhances the immunological defense of the patients, probably by stimulating the production of T lymphocytes. In these cases, levamisole has been administered at the dose of 300 mg daily for three days weekly and for several months, with good tolerance.

Mebendazole

Chemically this drug is methyl-5-benzoylbenzimidazole-2-carbamate, a yellowish powder insoluble in water, with no special taste. It is very slightly absorbed from the intestinal tract. This anthelmintic shows the widest spectrum of activity (14, 19, 20, 27); it is effective against *T. trichiura,* hookworm, *A. lumbricoides,* and *E. vermicularis* (18). In doses larger than those usually established, it is also active against cestodes (36). The mechanism of action is by inhibition of the rate of glucose uptake by the helminths (43). The inability to utilize exogenous glucose followed by a decrease in the glycogen content results in a significant decrease in the adenosine triphosphate content. There is general agreement on the lack of toxic effects and on the absence of side effects. In a small number of cases, *Ascaris* has been seen to migrate to the mouth in children heavily infected by this parasite and who were under treatment with mebendazole; however, this finding must be observed more widely before it can be established that it is produced by the drug itself. In regard to teratogenicity, it was found that mebendazole, when given during the period of organogenesis in rodents, induces abnormalities in the fetuses, consisting mainly of some skeletal abnormalities in the ribs and tail. Neither teratogenic or embryotoxic effects were observed in dogs, sheep, or horses. As a precaution, this drug should not be used during the first months of pregnancy.

Metronidazole

Since 1959 this drug has been used for the treatment of *Trichomonas vaginalis* infection and, few years later, for the treatment of tissue invasive amebiasis (4–6, 8) and giardiasis as well. Metronidazole [1-(2-hydroxyethyl)-2-methly-5-

nitroimidazole] is a crystalline powder slightly soluble in water and readily absorbed from the gastrointestinal tract. It is excreted through the bile and urine, which sometimes acquires a reddish color. In lesser amounts, it is also excreted through saliva, semen, vaginal secretion, etc. (44). Side effects are relatively frequent (45). In our experience, approximately 30% of the patients presented some signs and symptoms of intolerance, usually of low intensity. They are mainly of the gastrointestinal tract, such as nausea, vomiting, abdominal pain, metallic taste, and diarrhea. Other symptoms are dizziness, joint and muscle pain, headache, and numbness. Alcohol is contraindicated when taking metronidazole because it produces a disulfiram-like reaction characterized by confusional state, flushing, headache, nausea and vomiting, drowsiness, and fall in blood pressure. These symptoms appear as a consequence of the inhibition of enzymes concerned with the metabolism of alcohol. Because metronidazole is carcinogenic to rodents in high dosages and mutagenic to bacteria, caution has been taken toward its indiscriminate use. The drug is contraindicated during the first trimester of pregnancy and in patients with CNS disease.

Niclosamide

Introduced for the treatment of tapeworms in 1960, niclosamide is still the drug of choice for these parasites (33, 34). It is a yellowish powder, insoluble in water and nonabsorbable. Chemically it is N-(2-chloro-4'-nitrophenyl)-5-chlorosalicilamide. The mechanism of action is by direct contact with the parasites and inhibition of oxidative phosphorylation in the mitochondria. The scolex of the parasite is released from the intestine and the worm may be destroyed by the proteolytic enzymes. This may be why it is difficult to find the scolex after treatment. Since this drug is not ovicidal, the eggs when or if regurgitated to the stomach in cases of *T. solium* infection create the possibility of producing cysticercosis. Niclosamide is very well tolerated and no toxic effects are known. For these reasons higher doses than those usually recommended can be used, and repeated treatments can be recommended when necessary.

Oxantel

Oxantel pamoate is *trans*-1,4,5,6-tetrahydro-2-(3-hydroxystyryl)-1-methylpyrimidine hydrochloride. It is used for the treatment of *T. trichiura* infections (21, 22). Unlike its analogue, pyrantel, oxantel is not effective in cases of ascariasis. The combination of the two drugs widens the spectrum of activity. The possible effect on other helminthiases has not yet been defined. Oxantel is a crystalline salt of yellow color, practically insoluble in water (46). In our experience this drug is well tolerated and does not cause toxic effects.

Paromomycin

This antibiotic, derived from *Streptomyces rimosus* var *paromomycinus,* has a broad spectrum of activity and is very slightly absorbed from the intestine. Its main use has been against intestinal bacteria. It is also an amebicide, but there are not enough reasons to recommend its use in the treatment of amebiasis. Its use in the treatment of *Taenia* infection started in 1969 when it was observed that patients treated for

intestinal amebiasis, who simultaneously had tapeworms, were cured of this parasitic infection. Today it is known to be effective against *T. solium, T. saginata, D. latum,* and probably *H. nana* (35). The mode of action is not known but depends upon direct contact with the worms. Detection of the parasites after the treatment is difficult probably because of their destruction by digestive proteolytic enzymes. It is advisable to give a purge after two hours of the treatment, especially in cases of *T. solium.* There are no known systemic toxic effects of the drug but tolerability is poor. We found from 33% to 67% side effects in patients treated for teniasis. The symptoms, in order of frequency, were diarrhea, abdominal pain, nausea, dizziness, and vomiting. This last symptom is especially important because it theoretically may cause the regurgitation of *T. solium* eggs to the stomach with the possibility of producing cysticercosis.

Piperazine

Piperazine has been in use for a longer time than the other anthelmintics referred to in this review, almost 30 years. It is still one of the most used anthelmintics and one of the few that are practical for mass treatments. Its effectiveness is limited to *A. lumbricoides* and *E. vermicularis* (17, 29). Piperazine is chemically diethylenediamine. Several salts are used such as hexahydrate, citrate, phosphate, adipate, tartrate, all in the form of white crystals easily soluble in water and readily absorbable from the intestine. Its mechanism of action is clearly known, as a blocking agent of acetylcholine in the myoneural junctions of the helminths, producing a flaccid paralysis which facilitates the elimination of the living worms by the normal intestinal peristalsis. Because there is a wide range between the therapeutic and the toxic doses, drug reactions are uncommon. In few cases piperazine produces nausea, vomiting, and diarrhea. When a large amount of the drug is swallowed, such as when a child drinks a whole bottle, or when the drug accumulates in the organism, mainly in cases of renal insufficiency, toxic effects are seen with dramatic symptoms, which fortunately are transient and do not leave sequelae. These symptoms are due to the effect of piperazine on the myoneural mammalian junctions causing a blocking effect. The symptomatology is varied. We have observed muscular incoordination, ataxia, vertigo, speech difficulty, confused mental state, muscular weakness, and myoclonic contractions. It may produce or exacerbate epileptic seizures in predisposed patients. For these reasons, piperazine is contraindicated in patients with renal or hepatic insufficiency and in epileptic patients.

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. Although this action is somewhat similar to the action of piperazine, this drug produces flaccid paralysis of the parasites. Pyrantel is effective against ascariasis (13) and enterobiasis (25, 26) in a single dose

and against hookworms (23) in a three-day treatment. At present we consider pyrantel as the drug of choice for the treatment of these three helminthic infections. The drug is well tolerated and no toxic effects have been reported. In our experience only 20% of the treated patients described light side effects consisting of dizziness, drowsiness, and intestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain.

Pyrvinium Pamoate

This is a red cyanine dye with the formula bis-6-dimethylamino-2-[2-(2,5-dimethyl-1-phenyl-3 pyrvolyl)ninyl]-1-methylquinolinium salt of pamoic acid. It is a stable powder, insoluble in water and tasteless, not appreciably absorbed from the intestinal tract. Its only use is in the treatment of *E. vermicularis* infection (28,-30). The action on this helminth seems to be by depletion of available carbohydrates. Tolerability to this drug is good but gastrointestinal symptoms and dizziness have been reported. The suspension stains clothes and stools red. We believe that pyrvinium has been displaced by the newer anthelmintics in the treatment of pinworms and we do not recommend it in cases of strongyloidiasis, based on the negative results we have obtained and on the assumption that for *Strongyloides,* the drug must be absorbable to act in the tissues where the parasites live.

Quinacrine

Quinacrine hydrochloride is an antimalarial drug extensively used before the introduction of chloroquine. At the present time it is seldom used as an antimalarial, but is recommended for the treatment of giardiasis (10, 39) when no other drugs are available; it is rarely used for the treatment of teniasis, because better products for this parasitic infection are available. The most common side effects produced by quinacrine are nausea and vomiting. Other symptoms are headache, dizziness, and CNS stimulations. Psychotic reactions and the bluish or yellow staining of the skin and mucous membranes, although not frequent, are important adverse reactions.

Thiabendazole

Although this drug is a broad spectrum anthelmintic, its use is limited mainly to the treatment of strongyloidiasis for which it is considered the drug of choice (31, 32). When this parasitic infection is associated with ascariasis or enterobiasis, thiabendazole is also effective for these helminthiases. An absorbable drug effective against larval forms of nematodes, thiabendazole has also been used in the treatment of cutaneous larva migrans. Experimentally, it has been useful in trichinosis and visceral larva migrans. Thiabendazole is a white tasteless crystalline compound, chemically 2-(4-thiazolyl) benzimidazole. After oral administration it is rapidly absorbed and excreted via the urine. It is also absorbed from the skin (47). Its mechanism of action against adult and larval forms of nematodes is not well understood (48). The claims that this drug is an effective ovicidal drug have not been substantiated in our experience. Side effects are common. In our patients, 50% of the cases have shown symptoms of intolerance, the most common being dizziness. Other side effects observed are gastrointestinal symptoms such as nausea, vomiting,

abdominal pain, diarrhea, and anorexia. Headache, drowsiness, and lethargy have been also reported. Side effects are lowered when the daily dose is fractioned and administered after meals. A few cases of erythema multiforme and Stevens-Johnson syndrome, with two fatalities, have been reported as important toxic effects.

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