Treatment of Amebiasis*

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The Dauphin de France was the first known patient with amebiasis treated by an extract of the root of the ipecacuanha plant, and little progress was made during the next 200 years. Emetine, the active alkaloid of ipecacuanha was introduced for the treatment of amebiasis in 1912 and was the standard drug used in this disease for about 50 years. Unfortunately, toxicity hampers its usefulness, a fact that justified the search for other drugs.

Because of the various aspects of amebiasis, one has to face several therapeutic problems in drug treatment: a) Reach the amebae in the colonic lumen; b) destroy the parasite in the tissues, both locally in the wall of the colon and in other organs where the parasite may have migrated; c) prevent the formation of cysts, in order to avoid the spread of the disease; d) reduce as much as possible the duration of treatment, bearing in mind that the disease occurs mainly in rural areas, where people are not inclined to take drugs for more than a few days; e) administer drugs with as few side effects as possible; f) administer inexpensive treatment. If we could fulfill all these conditions, then we would have the ideal drug to treat the various forms of amebiasis.

Reviewing the progress made during the past 50 years we shall see how near we are to the ideal amebicide.

Halogenated hydroxyquinolines, such as entero-vioforme, were improvements over emetine in that they have a better luminal amebicide action, are better tolerated and are easily administered. On the other hand, they have no action against tissue amebae and therefore their use is limited. They could be an adjuvant to treatment but should never be used alone. Moreover, the excessive use of drugs of this type can lead to serious toxic effects, as seen in Japan with the SMON disease.

Arsenicals, such as milibis, have been extensively used in intestinal amebiasis. They are well-tolerated and good amebicides. But they do not reach the parasites in the tissues and therefore can only be used as an adjuvant treatment. Apparently these compounds can prevent the formation of cysts by destroying the trophozoites. Arsenicals require a treatment of 10 days and the drugs are eliminated very slowly from the body. Therefore one needs a rest period of 10 days before giving a further course, if indicated.

Diloxanide furoate (Furamide) is another good luminal amebicide, devoid of toxic effects and able to eliminate trophozoites and cysts from the colon. But, again, it has no action on the tissue parasites and cannot be used alone. Among the antibiotics, paromomycin (Humatin) is the only one, which is directly amebicidal, both in vitro and in vivo. It was considered as a valuable luminal amebicide, but it has no tissue amebicidal action at all and severe side effects were reported so that it cannot be recommended in the management of average intestinal amebiasis. Being also bactericidal, it may be useful in severe amebic dysentery with marked bacterial over infection. Though it is true that luminal amebicides are sufficient to cure most cases of amebic dysentery, the risk of invasion of the liver by the parasite remains present and therefore this type of amebicide is far from ideal.

To eliminate the amebae from the colon requires a treatment lasting from one to three weeks which is far too long. One can say nowadays that luminal amebicides have a very minor role in the management of amebiasis.

The development of an emetine derivative, 2-dehydroemetine achieved a major breakthrough in the treatment of the disease. Within five years of the first report by Blanc in 1961, about one hundred publications confirmed the efficacy of this drug, with an overall success rate of 80% (Lasserre). The main advantage of this compound over emetine is its lower toxicity with much less accumulation in the tissues. A seven-day treatment with 2-dehydroemetine of 1 mg/kg body-weight destroys the parasite both in the colonic lumen and in the tissues. This compound is still frequently used.

In extra-intestinal amebiasis chloroquine, usually in association with emetine, has a good amebicidal action and has been used with success not in amebic liver abscess. But it has no action on luminal amebae.

So far, the most significant advance in the treatment of amebiasis is the discovery of amebicidal properties of nitroimidazole derivatives. In 1966 Powell et al reported the success of metronidazole (Flagyl) in both amebic dysentery and liver abscess. The drug is extremely active against *E. histolytica*. In culture, the morphology of the organism is altered markedly within 6 to 20 hours by concentrations of 1 to 2 ug/ml of metronidazole. Within 24 hours all organisms are for killed.

Clinically, a large number of reports confirm the efficacy of metronidazole given orally for 5 to 10 days at 2.25 g daily in amebic dysentery and 1.5 g to 2.25 g daily for 5-10 days in amebic liver abscess.

More recently, Bunnag et al in Bangkok successfully treated amebic liver abscess with 2.4 g of metronidazole given orally for a single day. This opened the door to most promising studies with new nitroimidazole derivatives.

Drugs in this chemical group are fairly well tolerated but some concern arose from studies showing a mutagenic activity of the urine from patients on metronidazole against *S. typhimurium* in vitro (Legator et al). In addition, metronidazole has shown evidence of tumorogenic activity in a number of studies involving long-term oral administration in mice and rats. It remains to determine whether or these findings have any bearing humans. So far, there are no documented cases of cancer related the use of nitroimidazole derivatives. Nevertheless, one has to aware of these facts and they justify the search and the development of new nitroimidazole derivatives which achieve a cure of amebiasis with a shorter treatment. Amongst them tinidazole (Fasigyn) and ornidazole (Tiberal) are most promising.

Papers, published or presented at congresses, show that tinidazole given for three days at, dosage of 2 g a day for adults and about 60 mg/kg bodyweight a day children achieves a parasitic cure rate of 83% (Soh) to 96% (Scragg) and 98% (Islam). In cyst passers, tinidazole in a short two-day treatment course at 2 g per day gave poor results: only 33% of the cases were cleared (Spillman). In amebic liver abscess in children, Scragg et al reported a success rate of 93% with three days' treatment at a daily dose of 63 mg/kg bodyweight, in combination with regular aspiration of the abscess. Mathur et al obtained excellent results with a two-day treatment with 2 g per day. The compound is well absorbed and has a half-life of 12 hours. Reports of side-effects vary greatly from one author to another, ranging from intolerable, even at fairly low dosage (Chanco) to total absence of side-effects (Mistry). In 50 cases, Islam tabulated the following side effects observed: general malaise 20%, anorexia 10%, metallic taste 6% and nausea 4%. Toxic effects are usually mild and rarely lead to termination of the treatment.

A newly developed nitroimidazole derivate, ornidazole (Tiberal) also shows excellent anti-protozoal action at a low dose against *Trichomonas vaginalis*, *Giardia lamblia* and *Entamoeba histolytica*. It is a L-chloromethyl-2-methyl-5-nitroimidazole-l-ethanol, a light crystalline substance with bitter taste and a pH of 6.48 in a 1% aqueous solution. The substance is rapidly and almost completely absorbed and reaches its maximum blood level within two to four hours after ingestion and 40 to 60 minutes after intravenous injection. The mean peak value in human plasma is 10.8 ug/ml, which is well over the MIC for *E. histolytica.* The half-life is 14.4 hours and 15% is protein bound. The total radioactivity excreted in the urine and feces over a

period of five days, expressed as a percentage of the administered dose, amounts on average to 62.6% in the urine and 22.1% in the feces. The LD50 in mice is 1420 mg/kg. It is worth noting that ornidazole is compatible with alcohol as shown by Schweitzer.

In view of the good results obtained with ornidazole in amebic dysentery in seven, then five day therapy, trials were conducted with a higher dose of 2 g per day for three days only. The results were assessed by stool examination performed three to eight times after treatment with an interval of one to 35 days. Clinically, the symptoms subsided within two to five days. The analysis of 207 well-documented cases shows a success rate, both clinically and parasitically, of 98.5%.

The data on cyst passers is still insufficient to allow any scientific analysis, but it seems that ornidazole, like tinidazole, is not a drug of choice against amebic cysts.

In a series of 30 cases of amebic liver abscess, Jaroonvesama, in Bangkok, obtained a cure rate of 96.7% with a one-day treatment of 2 g ornidazole, together with regular aspiration of the abscess. The drug was given orally in eight cases and intravenously in 22. Fever, pain anorexia and malaise subsided within five to six days on average. All cases were followed up for six months.

Ornidazole is well tolerated but not devoid of side effects. In 207 cases of intestinal amebiasis, side effects were reported in 41 cases (20%) with the following distribution: dizziness 9.1%, nausea 8.6%, vomiting 1.4%, and malaise 1.4%. They were all mild and subsided at the end of the treatment.

There have been both open and double-blind studies in intestinal amebiasis, whilst in amebic liver abscess no study has been conducted with the one-day regimen on a double-blind basis: a multi-centre double-blind study therefore has just been initiated and one should wait for these results before a final assessment of the value of this short treatment can be made.

From comparative studies between metronidazole, tinidazole and ornidazole, the latter two compounds seem to be superior in terms of efficacy in the management of intestinal amebiasis. Moreover, with these drugs the treatment is of a shorter duration. Side-effects reported are comparable, when comparing tinidazole and ornidazole in double-blind studies and both compounds are equally potent without statistical differences in the side-effects reported.

Ornidazole, however, has a longer half-life, which is an advantage and its efficacy in a one-day treatment in amebic liver abscess is documented, which is not the case with tinidazole.

CONCLUSIONS

In conclusion, it appears that the nitroimidazole derivatives are the drugs of choice for treating intestinal amebiasis and amebic liver abscess. They are effective against *E. histolytica* at all locations bowel, lumen, wall and extra-intestinal, have few and mild side-effects, require a short one to three days course of treatment and are inexpensive.

The mutagenic activity and tumor-producing action in animals does not appear to be applicable to patients as yet.

The relative lack of effect of these drugs on the cyst is a minor drawback since transmission of the disease can only effectively be controlled by sanitation measures regarding deposition and disposal of human excreta and not by the administration of drugs.

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