Drug Therapy of Amoebiasis

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Amoebiasis is a readily curable condition which responds promptly and completely to correct management. There is no evidence of natural or acquired resistance by *Entamoeba histolytica* to amoebicides. Many drugs are effective but none is ideal. In the past, however, combinations have been shown to yield high cure rates. In most instances therapeutic failure is due to incorrect diagnosis or to failure to observe the principles of treatment. Lack of appreciation of these principles is related to failure to follow the proper criteria for the diagnosis or classification of the disease. This is a common source of confusion and is responsible for misleading claims in drug trials.[a]

The principles of drug therapy in amoebiasis are simple. The aim is to eradicate *E. histolytica* which may be present in any or all of the following sites: in the bowel lumen; in the bowel wall; systemically, chiefly in the liver.

" Luminal " or " contact " amoebicides which are not, or only slightly, absorbed will not be effective against amoebae in the tissues. Conversely, amoebicides given parenterally do not possess sufficient activity against amoebae in the bowel lumen. Antibiotics, which are indirect-acting amoebicides exerting their action against bacterial associates of *E. histolytica*, are not effective against amoebae dwelling in the tissues without bacteria. When given parenterally, they have little activity against amoebae at any site although they are of use in combating secondary bacterial infection.

Since, with the exception of certain new drugs, amoebicides vary in their efficacy at the 3 sites where the parasite may exist, combinations are often necessary, depending on the form of amoebiasis which is present.

In considering the drugs available for the treatment of amoebiasis it is convenient to classify them according to their mode and site of action.

Direct-acting amoebicides mainly active in the bowel lumen

There are many such preparations. The following is a selection:

(*a*) Quinoline derivatives: diiodohydroxyquinoline, clioquinol, chlorhydroxyquin and chiniofon.

(*b*) Arsenical derivatives: acetarsol, carbarsone, thioarsenites, glycobiarsol and diphetarsone.

(*c*) Oral emetine and dehydroemetine preparations: emetine bismuth iodide and dehydroemetine bismuth iodide are the most widely used. A late-release form of oral dehydroemetine has also been prepared.

(*d*) Miscellaneous drugs: chlorbetamide, 5,6-quinone-4, 7-phenanthroline, glaucarubin, diloxanide furoate, clefamide, dichloracetylethyl-aminoethyl-benzene; the last three of these are relatively new and have proved to be of value in practice.

Diloxanide furoate. This is the 2-furoic acid ester of diloxanide (dichloracet-4-hydroxy-*N*-methylanilide). It is rapidly absorbed and is present in the serum largely as the glucuronide. The mode of action against *E. histolytica* is unknown. It is without activity in extra-intestinal amoebiasis and is unreliable in amoebic dysentery where there is significant tissue invasion.[b] In milder cases and in chronic intestinal amoebiasis, reports have been favourable.[c, d] The drug is well tolerated and no toxicity has been reported. The average adult dose is 0.5 g orally thrice daily for 10 days.

Diloxanide furoate should be regarded for practical purposes as a useful amoebicide with activity in the gut lumen.

Clefamide. This is the recommended International Non-Proprietary Name for 2,2-dichloro-*N*-(2-hydroxyethyl)-*N*-[*p*-(*p*-nitrophenoxy)benzyl]acetamide. It is a " luminal " amoebicide which is well tolerated and of low toxicity. It is inadequate in amoebic dysentery.[b] The dosage is 0.5 g orally thrice daily for 10 days.

Dichloracetylethyl-aminoethyl-benzene. In the dosage of 100 mg orally thrice daily for 10 days, this

[a] Powell, S. J. (1969) *Bull. Wld Hlth Org.*, **40**, 956.

[b] Wilmot, A. J., Powell, S. J., MacLeod, I. & Elsdon-Dew, R. (1962) *Trans. roy. Soc. trop. Med. Hyg.*, **56**, 85.

[c] Marsden, P. D. (1960) *Trans. roy. Soc. trop. Med. Hyg.*, **54**, 396.

[d] Woodruff, A. W. & Bell, S. (1960) *Trans. roy. Soc. trop. Med. Hyg.*, **54**, 389.

"luminal" amoebicide has been claimed to be effective and well tolerated by several South American investigators. At this dosage it is without effect in amoebic dysentery and is only minimally effective at 500 mg thrice daily for 10 days (Powell et al., unpublished data).

Indirect-acting amoebicides active in the bowel lumen and wall but not in the liver

These comprise the antibiotics, many of which have some activity. By far the most effective are tetracycline, chlortetracycline and oxytetracycline. Erythromycin is also of value. Paromomycin, which is poorly absorbed, appears to have little activity in the bowel wall in conventional dosage but, when the dose is increased to the high level of 3 g daily, it is more effective.

Tissue amoebicides mainly active in the bowel wall and liver

Emetine hydrochloride; dehydroemetine. Given parenterally these drugs are excellent tissue amoebicides but, when used alone in amoebic dysentery, there is a high relapse rate owing to failure to eradicate amoebae in the bowel lumen.

Racemic 2-dehydroemetine was synthesized in 1959. The drug is excreted more rapidly and has been shown experimentally to be concentrated more in the liver and less in the heart than natural emetine although *in vitro* activity against *E. histolytica* is similar. It is less toxic than emetine but the same precautions should be observed. A dosage of 1 mg/kg–1.5 mg/kg of body-weight daily by intramuscular injection is recommended but this can be increased to 2 mg/kg daily. Oral preparations have been produced.

Dehydroemetine represents a definite advance on natural emetine but the same relative contra-indications prevail and it has similar limitations in activity against amoebae.

Tissue amoebicides mainly effective in the liver

Chloroquine; conessine. Conessine has undesirable toxicity and has not come into general use.

Amoebicides effective at all the required sites

Two new drugs are unique in that they are effective against *E. histolytica* at all sites.

Niridazole. This is 1-(5-nitro-2-thiazolyl)-2-imidazolidinone and was first used in the treatment of amoebic liver abscess by Jarumilinta and her associates in 1964.[e, f]

Powell et al.[g] in Durban carried out a trial of niridazole on 50 patients with amoebic dysentery and 50 with amoebic liver abscess. They concluded that a dose of 25 mg/kg gave better results than emetine in dysentery and equivalent results in amoebic liver abscess.

Powell[h] made a comparative electrocardiographic study of the toxicity of various systemic amoebicides. He concluded that niridazole and emetine showed similar changes, but that the combination of niridazole and dehydroemetine produced such severe abnormalities that these drugs should not be used together.

Doshi et al.[i] treated 14 patients with amoebic dysentery with a daily dose of 1.5 g and 12 were cured; 9 of 13 were cured with a daily dose of 1.0 g. Two out of 5 patients with hepatic amoebiasis had to be withdrawn from treatment; the other 3 were cured. Electrocardiographic changes were observed in 17 patients. It should be noted that although these patients were adult males, none weighed more than 50 kg.

Wolfensberger[j] found that niridazole was more toxic and gave no higher cure rate than oral dehydroemetine.

This drug is being extensively used in the treatment of schistosomiasis, but less toxic drugs are more effective against amoebiasis.

Metronidazole. This is 2-methyl-5-nitroimidazole-1-ethanol. It has been widely used since 1959 for the treatment of urogenital trichomoniasis and more recently against giardiasis and acute ulcerative gingivitis. The drug is given orally and is rapidly absorbed. In amoebiasis it is unique in combining powerful intestinal and systemic amoebicidal activity with good tolerance and lack of serious toxicity. Initial reports have shown that a higher dosage regimen is required for the cure of severe amoebic dysentery than for the treatment of liver abscess.[k, l]

[e] Kradolfer, F. & Jarumilinta, R. (1966) *Proc. 1st. Int. Cong. Parasit. (Rome), 1964*, p. 397.

[f] Jarumilinta, R. (1966) *Acta trop. (Basel)*, Suppl. 9 p. 102.

[g] Powell, S. J., MacLeod, I. N., Wilmot, A. J. & Elsdon-Dew, R. (1966) *Lancet*, **2**, 20.

[h] Powell, S. J. (1967) *Amer. J. trop. Med. Hyg.*, **16**, 447.

[i] Doshi, J. C., Doshi, M. J., Vaidya, A. B., Mehta, J. M. & Sheth, U. K. (1968) *Amer. J. trop. Med. Hyg.*, **17**, 702.

[j] Wolfensberger, H. R. (1968) *Trans. roy. Soc. trop. Med. Hyg.*, **62**, 831.

[k] Powell, S. J., MacLeod, I. N., Wilmot, A. J. & Elsdon-Dew, R. (1966) *Lancet*, **2**, 1329.

[l] Powell, S. J., Wilmot, A. J. & Elsdon-Dew, R. (1967) *Ann. trop. Med. Parasit.*, **61**, 511.

Several other workers have reported equally favourably on the use of metronidazole,[m, n, o, p] and it seems likely to become the drug of choice for the treatment of all forms of amoebiasis.

Therapeutic regimens

Therapy will be considered according to the clinical form of amoebiasis to be treated.

Asymptomatic intestinal amoebiasis. In this condition *E. histolytica* is usually confined to the bowel lumen and cure may then be achieved by "luminal or contact" amoebicides. There are many such drugs but none is completely reliable in eradicating amoebae. This is confirmed by the constant addition of new preparations. With many there is a tendency for relapse on completion of the course. Few have been thoroughly evaluated, and, as there is probably little to choose among them, there is room for individual preference. Satisfactory tolerance, lack of toxicity and expense should be guiding factors in choice. Diloxanide furoate for 10 days seems to fulfil these criteria better than any others in general current use [q]. Of the older drugs glycobiarsol given for 10 days or diiodohydroxyquinoline (diodoquin) for 21 days are satisfactory.

More potent amoebicides are also effective in asymptomatic amoebiasis. The tetracyclines and oral emetine preparations are of value. Metronidazole holds great promise.

It is noteworthy that, although of value as adjuvant therapy, no "luminal or contact" amoebicide is adequate treatment for invasive amoebiasis. Claims of efficacy based on poorly assessed clinical material are misleading.

Chronic, non-dysenteric intestinal amoebiasis. Misleading claims readily arise in this condition as the border-lines between asymptomatic amoebiasis on the one hand and amoebic dysentery on the other are obscure. Because the amoebae are predominantly in the bowel lumen, tissue amoebicides alone are unsatisfactory but mild cases, with minimal or no tissue invasion, respond to "luminal" amoebicides. However, as a general rule, all cases should be treated as for amoebic dysentery.

Amoebic dysentery. In addition to eradicating amoebae in the bowel lumen and bowel wall, treatment should be designed to protect the liver from possible hepatic invasion. There are several combinations of drugs which yield cure rates of over 95%. The following have proved reliable in a wide experience:

(*a*) Mild to moderate cases: tetracycline + "luminal" amoebicide + chloroquine. This provides a safe, non-toxic, well-tolerated and effective treatment for ambulant patients. The tetracyclines tend to promote rapid healing of rectal ulcers and have the useful advantage, where the etiology is in doubt, of efficacy against bacillary dysentery.

(*b*) For severe cases with much tissue invasion: dehydroemetine + tetracycline + a "luminal" amoebicide. In such patients the rapid and potent tissue amoebicidal properties of emetine preparations may be life-saving. Moreover, at times oral therapy is not possible and these drugs remain the best form of parenteral therapy. When they are used for the treatment of amoebic dysentery, chloroquine is superfluous.

(*c*) Emetine hydrochloride followed by emetine bismuth iodide is a long-established form of treatment in amoebic dysentery. This is effective but, unless carefully administered, it is liable to cause nausea and vomiting. Furthermore, it regularly causes diarrhoea or exacerbates dysentery.

(*d*) Metronidazole is a recently introduced, safe, well-tolerated and highly effective form of treatment. It is the only single, non-toxic drug which is effective at all sites and is the treatment of choice in most instances. The optimum dose regimen appears to be 800 mg thrice daily for 5 days.

Relapse in intestinal amoebiasis. There is a well-known tendency for patients with intestinal amoebiasis to relapse owing to failure to eradicate the parasite. It has been shown in non-endemic areas, where the possibility of reinfection is slight, that relapse in asymptomatic and chronic intestinal amoebiasis most frequently occurs within one month of completion of treatment and that all but a small proportion will be revealed by competent stool examination by the end of the second month.[q] In areas of endemic amoebiasis distinction between relapse and reinfection may be impossible but recurrence 4–6 weeks after completing treatment is more likely to be due to relapse than to reinfection. Patients with amoebic dysentery who have been

[m] André, L. J., Bon, J. F., Zerdani, S. & Bandelier, J. (1967) *Méd. trop.*, **27**, 245.

[n] Cadena, E. N. & Biagi, F. F. (1967) *Bull. Soc. Path. exot.*, **60**, 503.

[o] Chhetri, M. K. & Chakravarty, N. C. (1968) *J. Indian med. Ass.*, **50**, 312.

[p] Huggins, D. (1967) *Hospital (Rio de J.)*, **72**, 621.

[q] Woodruff, A. W. & Bell, S. (1967) *Trans. roy. Soc. trop. Med. Hyg.*, **61**, 435.

treated either with antibiotics alone or by the older direct-acting amoebicides (emetine preparations and quinoline derivatives) have a significant but similar relapse rate. Combinations of these preparations are more effective.[r] It is noteworthy that, where metronidazole has been used in adequate dosage, the relapse rate by the end of the second month after completing treatment has been extremely low (Powell, unpublished data).

Where circumstances permit, search should be made for a source of reinfection in all adequately treated patients who relapse. The source is frequently a member of the same household with an asymptomatic infection.

Hepatic amoebiasis. There are relatively few drugs which are effective in this condition but cure rates approximating to 100% can be achieved. In all patients it must be assumed that intestinal infection is also present and treated accordingly. Adequate aspiration is an essential feature in the management of large abscesses.

Chloroquine is inferior to other drugs in hepatic amoebiasis but, by combining it with emetine preparations, a second course of the latter is unnecessary.[s] Initial loading doses of chloroquine should be given to attain an adequate concentration in the liver.

Metronidazole is highly effective in hepatic amoebiasis and, if given in sufficient dosage, will also eradicate the parasite from the bowel.

Any of the following treatment regimens are recommended:

(*a*) metronidazole 400 mg thrice daily for 5 days

or

(*b*) metronidazole in a single dose of 2.4 g

or

(*c*) dehydroemetine+chloroquine+a " luminal " amoebicide.

Should dysentery also be present, either the dosage of metronidazole should be increased to 800 mg thrice daily for 5 days or tetracycline may be added to the preceding regimens.

[r] Powell, S. J. (1967) *Trans. roy. Soc. trop. Med. Hyg.*, **61**, 765.

[s] Wilmot, A. J., Powell, S. J. & Adams, E. B. (1959) *Amer. J. trop. Med. Hyg.*, **8**, 623.

Drug Trials in Amoebiasis

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Clinical drug trials on amoebiasis are undertaken in many parts of the world and conflicting results are common, leading to claims of peculiar and resistant forms of the disease. More logical reasons are differences in diagnostic and clinical criteria and failure to accept a standardized classification of amoebiasis. It is significant that there is greater uniformity in results obtained in the two forms of invasive amoebiasis, amoebic dysentery and liver abscess, where diagnostic criteria are more firmly established. However, misleading claims arise when trials in " amoebic dysentery " are reported where only some of the subjects meet the true criteria, and absurd results are claimed when none at all have dysentery. In general, the most conflicting reports arise from trials in chronic intestinal amoebiasis and " amoebic hepatitis ", which are both conditions of doubtful validity.

It is evident that the morphological identification of *Entamoeba histolytica* is unreliable in the hands of many investigators. Serological tests would assist in defining the disease by excluding many patients who do not have amoebiasis. Such tests, however, do not provide proof of active infection and cannot be used as criteria of cure.

Certain ethical aspects and general principles are important in trials in any form of amoebiasis.

Ethical aspects

In many regions, informed consent to trials is not possible owing to ignorance and lack of insight into disease among the general population. Acceptance of treatment is an act of faith by the patient and a particularly high ethical standard is demanded of the physician who becomes the trustee of the patient's