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dosage, the relapse rate by the end of the second month after completing treatment has been extremely low (Powell, unpublished data).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

by S. J. POWELL, *Head, Sub-department of Tropical Medicine, University of Natal, Durban, South Africa, and Visiting Professor of Tropical Medicine, Tulane University School of Medicine, New Orleans, La., USA*

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

welfare. In these circumstances the decision to undertake trials of preparations and their management should not be in the hands of a single investigator. He should be responsible to a local supervisory committee which must ensure that correct standards are maintained.

Since effective forms of treatment are already available, there must be reasonable evidence, before new drugs are accepted for trial, that they possess some advantage over preparations already in use. There must be proof of *in vitro* and of experimental *in vivo* activity against *E. histolytica.*

Distinction must be made between trials primarily undertaken to evaluate activity against amoebae and those where evaluation of toxicity is a feature. While it is usually possible to assess tolerance and side-effects, it is not the prime function of therapeutic trials to determine toxicity. Where informed consent is not obtainable, there must be sound evidence that the drug is safe and that toxicity studies have been adequately performed.

Criteria of cure and failure are objective in most forms of amoebiasis; hence double-blind studies are rarely necessary or practicable. It is, however, essential that the laboratory identification of *E. histolytica* should be divorced from clinical assessment and it is desirable that the clinician observing progress should be unaware of the form of treatment received by individual patients. Ideally one clinician should assess clinical response while another is concerned with drug administration and management.

It is unethical to maintain a control group of patients with invasive amoebiasis on placebos only. It is nevertheless desirable that 2 drugs or different regimens of the same drug should be assessed simultaneously, or, alternatively, that a group receive a standard form of treatment as a reference. In such instances patients should be randomly allocated to one or other form of treatment.

General principles

The type of amoebiasis studied must be clearly defined. Where studies include trials on 2 or more forms of the disease, the groups must be kept distinct. Diagnostic criteria should be fully described and, if possible, should include serological confirmation.

The dosage and method of administration of the drug should be stated and any other medication which may have affected the outcome should be described.

Patients should have uncomplicated amoebiasis without other concomitant disease. While a definite degree of severity is required in trials on symptomatic amoebiasis, it must not be so severe that the life of the patient is endangered by unknown therapy. There is really no substitute for clinical experience in this aspect. Furthermore, because of uncertainty over administration and dosage of drugs, out-patient or ambulant trials are, if possible, best avoided.

Irrelevant special investigations should be omitted.

Criteria of cure or failure must be defined. Adequate post-treatment and follow-up studies are essential. In assessing long-term results the possibilities of both reinfection and relapse should be considered. The number of patients necessary to provide significant results should be determined by sequential analysis.

Trials in specific forms of amoebiasis

The following additional points regarding trials in specific forms of amoebiasis may be made.

Asymptomatic and non-dysenteric amoebiasis

Since diagnosis is commonly based solely on the identification of cysts of *E. histolytica*, this must be made by skilled observers. Specimens preserved in formol–saline and slides fixed with PVA (polyvinyl alcohol) are of value in providing a permanent record of the accuracy of the diagnosis.

In addition to direct saline preparations of faeces, smears should be stained by the Gomori or Heidenhain methods and a concentration technique used.

Many amoebicides tend only to suppress the passage of cysts which reappear shortly after completion of treatment. Moreover, cysts are often passed intermittently. In most instances, however, these reappear within the first 2 months of ceasing treatment.[a] Ideally post-treatment specimens should be examined daily for 3 weeks after completing treatment and thereafter at 1-, 2- and 3-month follow-up.

Amoebic dysentery

Criteria for choice of subjects. Only patients in hospital with active dysentery should be studied. They should have had no previous amoebicides. Definite rectal ulceration should be present on sigmoidoscopy. Haematophagous trophozoites should be demonstrable in the pre-treatment stools and ulcer scrapings and culture of a stool should be free of bacterial pathogens.

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

Conduct of treatment. All treatment should be administered under the supervision of a clinician by a trained member of the nursing staff who must ensure that the drugs are taken by the patient. The patient must be visited daily by the clinician who, in addition to observing general progress, should note signs of intolerance or toxicity.

Daily stool examinations should be examined by direct saline smears and a concentration technique. If there is doubt, staining procedures should be used.

Sigmoidoscopy should be performed before treatment and at 5-day intervals. Healing of ulcers and mucosal changes should be noted. Where active open ulceration is present, scrapings should be taken and examined by direct and, if necessary, staining procedures.

Assessment of results and follow-up. Patients should remain in hospital for 15–25 days after completing treatment and an initial assessment of results should be made on discharge. These should be assessed as follows:

(*a*) Parasitic failure: persistence or recurrence of either trophozoites or cysts of *E. histolytica* after completion of therapy.

(*b*) Probable failure: persistent rectal ulceration despite disappearance of *E. histolytica.*

(*c*) Cure: disappearance of symptoms, and of *E. histolytica,* and healing of ulcers.

Patients who become parasitic failures should be given other, effective treatment. The remainder should be requested to return at once should symptoms recur and routinely at 1 month after discharge.

At 1-month follow-up sigmoidoscopic and stool examination should be repeated and the results of the trial reassessed. If possible, further follow-up examinations should be done at 2 and 3 months after discharge. However, in endemic areas it becomes progressively more difficult to distinguish between relapse and reinfection.[b]

Drug trials at regular intervals with a standard reference drug are advisable to ensure that neither the disease nor the criteria have changed. Emetine hydrochloride has been found useful for this purpose.

Hepatic amoebiasis

Since definitive evidence of " amoebic hepatitis " is not obtainable and as it appears curable by all the drug regimens which are effective in amoebic liver abscess, drugs are best assessed by trials in the latter condition where diagnostic proof is provided by the aspiration of characteristic pus. Failure to observe this recommendation may lead to false observations.

Criteria for choice of subjects. Patients must have uncomplicated amoebic liver abscess and should not have recently received amoebicides. No coexisting disease should be present.

The diagnosis must be proved by the aspiration of characteristic pus, which should be bacteriologically sterile. Ideally, *E. histolytica* should be isolated from the pus.

Conduct of treatment. There is no place for diagnostic aspiration. Aspiration should be thorough and viewed as part of treatment. It should be repeated when indicated.

Stool examination must be done.

Intestinal amoebiasis must be presumed to be present in all cases and, if the drug under trial is thought to be effective only against hepatic amoebiasis, appropriate additional treatment must be given.

Other special investigations are largely unnecessary but it is usual to obtain a leucocyte count, haemoglobin estimation, erythrocyte sedimentation rate and a radiograph of the chest and right hemidiaphragm. Serological tests for amoebiasis are of value.

Similar procedures regarding drug administration and management to those described under amoebic dysentery are advisable.

Assessment of results and follow-up. Criteria of failure or cure are as follows:

(*a*) Failure is persistence or recurrence of symptoms or signs after completion of therapy. Complete proof of failure is obtained by the aspiration of pus containing *E. histolytica.*

(*b*) Cure is disappearance of symptoms. Radiographic elevation of the diaphragm may persist for months after cure. Although the liver usually rapidly regresses in size in response to aspiration and therapy, it is not uncommon for a small, non-tender lump to persist for some weeks at the site of aspiration, particularly if the abscess was situated in the epigastrium.

Patients can be discharged on the twentieth day in most instances. Follow-up attendance should be at 1, 3 and 6 months after discharge. Most relapses occur within the first 3 months.

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