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Progress report

New developments in the therapy of amoebiasis

Although frequently overlooked in practice, it has long been taught that for the adequate therapy of invasive amoebiasis treatment should be directed at all the sites where *Entamoeba histolytica* may be present. Hence the ideal amoebicide should be active within the bowel lumen, in the bowel wall, and systemically, particularly in the liver.

Until quite recently all available amoebicides were selective in their sites of action. They consisted of a small number of reliable tissue amoebicides (chiefly emetine preparations and chloroquine), indirect-acting broad-spectrum antibiotics, and a great many predominantly luminal amoebicides. Inadequate assessment of the latter on inappropriate clinical material often led to misleading claims of their efficacy in invasive amoebiasis. However, almost all forms of amoebiasis could be treated effectively provided the correct combinations of drugs were used, although therapy was often a little complicated and prolonged, and occasionally associated with toxicity.

In 1964 a preliminary report of the effect of niridazole in amoebic liver abscess led to the introduction of a new series of compounds in therapy[1]. It was found that niridazole alone was capable of curing both intestinal and hepatic amoebiasis but it was soon evident that this drug possessed an undesirable degree of toxicity[2].

It was not, however, long before another nitroheterocyclic compound was shown to yield even better results. This was the nitro-imidazole derivative, metronidazole. At a dosage of 200 mg three times daily for seven days the drug had been widely and safely used since 1959 for the treatment of trichomoniasis, but this regimen in amoebic dysentery had been disappointing. It was only in 1966, after considerably higher dosage regimens were used, that successful clinical trials in amoebic dysentery and amoebic liver abscess were reported[3]. Further studies showed that extremely small amounts of the drug were effective in liver abscess[4,5] but at such low doses eradication of amoebae in the bowel is uncertain.

During the past four years metronidazole has been extensively investigated, particularly in invasive amoebiasis, and has been the subject of numerous favourable reports although the dosages used have varied widely[6,7,8,9]. The drug has proved effective at a dosage of 40-50 mg/kg daily for amoebiasis in childhood[10,11,12]. Good results have also been reported with relatively small doses in symptomless cyst-passers and in chronic intestinal amoebiasis[13,14]. However, in this respect it should be borne in mind that the drug is highly absorbed and is more active in the tissues than in the gut lumen. It follows that a higher dosage is needed to cure luminal than systemic infections. Whilst there is little doubt of the direct amoebicidal effect of metronidazole in the tissues the precise mode of action within the bowel is uncertain. Only very small amounts of the drug are excreted in the faeces although a metabolite with reduced activity against *E. histolytica* has been isolated[15]. Since the drug has activity against certain bacteria, notably *Bacteroides* and *Clos-*

tridia, it may be that it also acts indirectly by changing the bowel flora in a similar manner to that of some antibiotics[16]. It is also noteworthy that some organisms, including most strains of *Escherichia coli*, are capable of inactivating metronidazole[17]. Inadequate dosage in amoebic dysentery may result in apparent cure but patients are liable to be converted to a symptomless cyst-passing state with the danger of subsequent relapse. For this reason, whilst a regimen of 400 mg three times a day for five days suffices for the treatment of hepatic amoebiasis, 800 mg thrice daily is required for amoebic dysentery. In Durban such treatment schedules have consistently yielded cure rates of over 90% in several thousand patients.

Much of the most recent work on metronidazole has been related to duration of therapy. Amoebiasis has achieved some reputation as a chronic, relapsing condition and this has led to the belief that prolonged and often repeated therapy is necessary to obtain complete cure. However, this viewpoint may merely be a reflection of failure to grasp the principles of therapy with the drugs which were then available. The advent of a single drug with activity in all forms of amoebiasis should go far to achieving more effective treatment and it is possible that provided a sufficient concentration can be obtained duration of therapy may be very short. It has been found that a single large dose of 2·0-2·4 g of metronidazole is capable of curing the majority of patients with amoebic dysentery or liver abscess. If this dose is repeated on a second day the cure rate is increased while three such doses yield results which are similar to those obtained by our previously recommended optimal five-day courses[18]. Such short-term regimens provide alternative schedules in regions where there is much invasive amoebiasis although it is doubtful if they will prove as effective in predominantly luminal infections where the main objective of therapy is to achieve a 'contact' effect by high concentrations of the drug within the bowel lumen.

Many of the older amoebicides still remain of value and their use should not be entirely abandoned. Indeed, when oral therapy is impractical, as in peritonitis, parenteral emetine preparations remain life-saving. Nevertheless, metronidazole is at present the only single, safe, direct-acting amoebicide with activity at all the required sites. It is singularly lacking in toxicity and can be given in conjunction with any of the other amoebicides although this is not often necessary. In dysentery metronidazole produces a prompt cessation of symptoms with, in most instances, disappearance of the parasite from the stools and rectal ulcers in less than 24 hours. In liver abscess response is equally satisfactory but it is important to note that the indications for aspiration are unchanged. As with all other tissue amoebicides small abscesses will resolve without aspiration but if the indications are present[19,20] a liver abscess should always be promptly and thoroughly aspirated. If this rule is neglected response to therapy is slower and less certain. Inadequate drainage remains the commonest reason for treatment failure and relapse.

The advent of metronidazole has stimulated interest in other nitroimidazole compounds. Some of these have shown promise in experimental infections but laboratory evidence of increased activity against *E. histolytica* tends to be offset by increased absorption. In such instances higher blood and tissue levels will result but the concentration in the gut may remain inadequate. Whether or not any of these preparations will prove to be a significant advance on metronidazole depends on the outcome of current clinical trials.

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