Tinidazole in treatment of amoebic liver abscess in children

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SUMMARY Tinidazole as a single drug therapy given in a single dose daily for 5 or 3 days was put to rigorous test in malnourished children. Of 25 children with amoebic liver abscess, 23 were cured. The 2 remaining cases required surgical drainage followed by other amoebicides, one subsequently dying from complicating bronchopneumonia.

In amoebic liver abscess age alone is a most important factor in prognosis and can readily affect evaluation of treatment. A liver abscess of medium size in an adult is relatively enormous in an infant and causes extensive liver destruction. Regardless of the nature of therapy, the mortality is higher in infants than in older children and adults.

Because of the severity of the condition in the very young we were, in the past, reluctant to abandon parenteral emetine preparations entirely and felt it prudent to use these in combination with other amoebicides (Scragg and Powell, 1966, 1968, 1970). However, modern amoebicides, prompt diagnosis, adequate aspiration, and surgical drainage in selected instances have done much to improve the prognosis and we have shown a steadily falling mortality rate during the past 15 years.

With the advent of nitroimidazole it was shown that in adults this drug was extremely effective in curing amoebic liver abscess (Powell *et al.*, 1967; Powell and Elsdon-Dew, 1972), a fact which prompted a trial of single drug therapy with metronidazole in children (Scragg and Powell, 1973). Though this showed that in the absence of any other drug therapy metronidazole is effective in curing the majority of children with amoebic liver abscess, the seriousness of the condition in children has led us not to employ metronidazole as a single drug given in one or two doses, as has been effective in most adult patients (Powell *et al.*, 1969). Tinidazole, the most recent derivative of the nitroimidazole group of compounds, has given excellent results in the treatment of amoebic liver abscess in adults (Nava *et al.*, 1974; Hatchuel, 1975). The drug has been well tolerated and is

free from toxic effects. Having established safety in children, the present trial was designed to determine the efficacy of tinidazole in the treatment of children in Durban with amoebic liver abscess.

Material and methods

Studies were made on 25 African children, their ages ranging from 3 months to 6 years, with a median age of 15 months. 8 were undernourished, 6 were severely malnourished (weight <3rd centile), 6 had frank kwashiorkor, and only 5 were well nourished. Liver abscess was confirmed by the aspiration of characteristic pus from the liver; in 14 of the 25 aspirates trophozoites of *Entamoeba histolytica* were identified. In 23 the amoebic gel diffusion precipitation test was positive; in the 2 in whom this test was negative trophozoites of *E. histolytica* were identified in the pus. 3 had concomitant amoebic dysentery with haemato-phagous *E. histolytica* in their stools. Full blood count, liver function tests, blood urea estimation, and urine examination were done in all patients before treatment, and were repeated on days 7, 14, 21, and 28 after treatment.

Since metronidazole had been used previously in a 5-day course (Scragg and Powell, 1973), it was deemed wise at the start of this trial to use tinidazole for the same duration. The adult dose of 2 g daily was adjusted for these children according to the percentage method of Catzel (1974) and was given in a single daily dose for 5 days. On a weight basis, in the first 10 cases observed, the mean dose was 57 mg/kg per day, and the effectiveness of tinidazole was obvious; therefore the next 15 children received tinidazole in a dose of 50 mg/kg per day, but only for 3 days. In 22

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children repeated aspirations of the liver were required and in 2 surgical drainage of the abscess was necessary.

Results

Response to treatment was rapid and cure was obtained in 23 patients (Table). One female infant

Table Results of treatment with tinidazole

Dose/duration	No. of patients	No. of cures	Surgical drainage
% of adult dose proportional to surface area 5 single daily doses (mean 57.0 mg/kg)	10	8	2*
50 mg/kg 3 single daily doses (mean 53.0 mg/kg)	15	15	0

*1 subsequent death.

with bronchopneumonia, aged 11 months, remained ill and febrile after a 5-day course of tinidazole. Needle aspiration of the liver was inadequate and the liver continued to enlarge. Laparotomy was carried out. A huge abscess containing 300 ml pus occupying almost the entire right lobe of the liver was found. The left lobe of the liver was adherent to the diaphragm and pericardium but no actual abscess was shown. Postoperatively she received emetine and appeared to be doing well. However, 2 weeks later the signs of pneumonia increased and x-ray confirmed extension of the consolidation. There were no signs of pericardial involvement. She failed to respond to antibiotic therapy and died on the 23rd day. Permission for necropsy was refused.

Another 11-month-old infant with bronchopneumonia remained ill and febrile in spite of 2 aspirations and the completion of a 5-day course of tinidazole. Multiple liver abscesses were suspected since the liver had not decreased in size. Laparotomy showed a very large abscess in the right lobe and multiple smaller abscesses in the left lobe of the liver. After surgical drainage emetine hydrochloride and metronidazole were given during the post-operative period. He made a complete recovery.

No relapses were observed during a 3- to 6-month follow-up. One child, however, who had concurrent amoebic dysentery, had shown a satisfactory response of both liver and intestinal lesions to a 5-day course of tinidazole (49 mg/kg per day). At follow-up 5 months later haematophagous *E. histolytica* were found in the stools. Retreatment with tinidazole in 3 single daily doses of approximately 60 mg/kg per day resulted in cure.

Tolerance was excellent, with no toxic effects shown by the blood counts, liver function tests, blood ureas, and urines.

Discussion

Tinidazole was highly effective in the treatment of amoebic liver abscess and cured 23 (92%) of 25 children. The single daily dose was a simple form of treatment. These results compare very favourably with previous studies in which metronidazole combined with dehydroemetine in a 10-day course resulted in cure in 73% (Scragg and Powell, 1970), and later when metronidazole as single drug therapy in divided doses for 5 days cured 72% (Scragg and Powell, 1973).

It has been shown that tinidazole is well absorbed and achieves significantly higher peak serum concentrations than metronidazole (Taylor *et al.*, 1969; Howes *et al.*, 1969; Welling and Monro, 1972). High serum concentrations of an amoebicide are important in terms of efficacy in dealing with amoebae located outside the gastrointestinal tract but higher blood and tissue levels may mean that the concentration of a drug in the intestine is inadequate. However, in a trial of amoebic dysentery, tinidazole in a dose based on the percentage method and given as three single daily doses (mean dose 63 mg/kg per day) cured 28 (93%) of 30 children (Scragg *et al.*, 1976). When this dose was lowered to approximately 50 mg/kg per day the cure rate fell to 76%. On further study the dose was increased to approximately 60 mg/kg per day and the cure rate was again 93% (Scragg and Proctor, 1976). Thus tinidazole has been shown to be most effective in the treatment of intestinal amoebiasis and its hepatic complication.

In this trial of treatment of amoebic liver abscess the mean dose of tinidazole in 25 cases was 55 mg/kg per day. In intestinal amoebiasis the high cure rate obtained with tinidazole appears to depend on a dose of at least 60 mg/kg per day; therefore it is advisable to use this dose in all cases of amoebiasis since a certain number of patients with liver abscess do have concomitant bowel lesions.

We would stress that the use of a single direct-acting amoebicide has in no way reduced the need for liver aspiration, which should be thorough, viewed as part of treatment, and repeated when indicated. If this aspect of management is neglected relapse may occur whatever drugs are used. While premature surgical intervention is undesirable, in selected instances open drainage plays a greater role in management in children than in adults because of the frequency of multiple abscesses that are inaccessible to needle aspiration. In such

instances it is wise to give emetine in the post-operative period.

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