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The Effect of CIBA 32644-Ba in Amoebic Dysentery and Amoebic Liver Abscess

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Following the encouraging preliminary report by JARUMILINTA and collaborators (1964) of the use of CIBA 32644-Ba in amoebic liver abscess this unit has undertaken a trial of the preparation in acute amoebic dysentery and in amoebic liver abscess.

Acute Amoebic Dysentery

Materials and Methods

CIBA 32644-Ba, in a dosage of 500 mg twice or thrice daily depending on the patient's weight, was given orally for 10 days to 22 African males complaining of diarrhoea with blood and mucus. All showed ulceration on sigmoidoscopy and had actively motile, haematophagous *Entamoeba histolytica* in their stools and ulcer scrapings. Severely ill patients, and those with complications or co-existing disease, were excluded.

All patients were hospitalised, and sigmoidoscopy was done on admission and on the 5th, 10th, 15th, 20th and 27th days after starting treatment. Daily stool examinations were performed.

Special Investigations

Electrocardiograms were taken in all cases on admission and on the 10th and 20th days after starting treatment.

In the initial 10 patients the following investigations were done on admission and repeated on the 10th day: haemoglobin, white cell and differential counts; chemical and microscopic examination of the urine; blood urea estimations; serum glutamic-oxalacetic transaminase, serum glutamic-pyruvic transaminase and serum

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lactic dehydrogenase; prothrombin index, serum bilirubin, alkaline phosphatase, zinc sulphate turbidity, thymol turbidity, serum albumin, and globulin and bromsulphthalein excretion.

Results

Results were classified as follows:

1. Success—symptom-free, ulcers healed and no parasites demonstrated.
2. Probable failure—persistent open ulceration but no parasites demonstrable in stools or scrapings.
3. Parasitic failure—*E. histolytica* still present, with or without open ulceration.

Cases which remained or became parasitic failures on or after completing their 10-day course of CIBA 32644-Ba were removed from the series at this point. Those classified as "successes" or "probable failures" were discharged without further treatment on the 27th day and requested to reattend for follow-up examination 1 month later, or sooner if their symptoms recurred.

After 27 days, 17 of the 22 patients (77%) appeared to be cured and were regarded as "successes". In 3 more patients, no amoebae were demonstrable although ulcers were still present; these cases were classified as "probable failures" (14%). Two patients were parasitic failures (9%), although one of these had become asymptomatic and was passing cysts.

Fifteen of the 20 patients requested to reattend after 1 month for follow-up did so. Of these, 13 were "successes", 1 still had open ulceration, and 1 had relapsed and was passing trophozoites of *E. histolytica* again.

Tolerance and Side-Effects

Three patients complained of anorexia, nausea, and slight abdominal discomfort towards the end of their course of treatment. In all instances this was mild and disappeared as soon as treatment was completed. One patient who was, on admission, malnourished and slightly oedematous, developed an episode of abdominal pain and distension with some increase in peripheral oedema from the 3rd to the 6th days of treatment. Treatment was not discontinued and he rapidly became symptom-free. Another patient appeared to develop a psychosis, which disappeared as soon as treatment was completed. However, at one month follow-up he was again mentally abnormal, and it is possible that this was quite unrelated to CIBA 32644-Ba.

The special investigations failed to show any significant effect attributable to the drug on the haemopoietic system or on liver or renal function.

Interpretation of the electrocardiograms is rendered difficult by the frequency of unexplained changes, particularly of the T wave, in Africans (POWELL, 1959). Moreover, such changes are influenced by the presence of severe dysentery. Nevertheless, 17 of the 22 patients showed changes in the T-wave pattern which were maximal on the 10th day on completion of their course of treatment and which tended to improve by the 20th day. Apart from a mild degree of tachycardia in a small number of patients, there was no clinical suggestion of cardiac toxicity.

Amoebic Liver Abscess

Material and Methods

Five African male patients with proved amoebic liver abscess were given CIBA 32644-Ba, 500 mg twice or thrice daily according to the patient's weight, for 10 days. The diagnosis was established in all cases by the aspiration of liver pus before commencement of treatment. The pus removed was bacteriologically sterile and characteristic in appearance. Three of the patients had concomitant proved amoebic dysentery.

Results

All 5 patients appeared to be cured at the end of periods of hospitalisation ranging from 24 to 38 days. Four attended for follow-up 1 month after discharge and remained cured.

Special Investigations and Side Effects

Electrocardiograms were done in all cases on admission and on the 10th and 20th days after starting treatment. Four of the patients showed T-wave changes tending to be maximal on the 10th day and similar to those seen in the group with amoebic dysentery.

Two patients developed marked sinus arrhythmia and another had bouts of clinical paroxysmal tachycardia which ceased on completion of treatment. Unfortunately, electrocardiographic confirmation could not be obtained in the latter instance. One patient also developed a transient maculo-papular rash which cleared spontaneously.

Discussion

E. histolytica is unable to survive in the bowel in the absence of certain bacteria or their metabolites, but should it spread to structures outside the bowel, such as the liver, it is able to multiply in these tissues without bacteria. It follows that in bowel amoebiasis, such as amoebic dysentery, drugs which have no direct amoebicidal action may be effective. Over the past 20 years, as a result of a great many trials of almost all the drugs used in therapy of this disease, and of many others which have not progressed beyond the trial stage, our highest cure rates have been obtained with the tetracyclines. These have no direct amoebicidal action but appear to act by altering the bacterial flora in such a way that the amoeba is unable to survive (ARMSTRONG et al., 1950, 1952; WILMOT, 1955). Not all antibiotics are effective. Both the antibacterial spectrum of the drug and the degree of absorption from the bowel are important. Antibiotics such as neomycin and paromomycin which are only very slightly absorbed from the bowel yield disappointing results because, despite a wide antibacterial spectrum, their concentration in the blood is too low to affect the bacteria and hence the amoebae in deep ulcers in the bowel wall (ELSDON-DEW et al., 1952; WILMOT, 1955). On the other hand, certain of the newer antibiotics which are very highly absorbed and reach high blood levels are also relatively ineffective because, we believe, the bowel flora in the lumen of the bowel is insufficiently altered, and some amoebae survive (ELSDON-DEW et al., 1959-60; POWELL et al., 1965a). Consequently, the need in amoebic dysentery is for a drug which reaches a desirable blood level but some of which remains in the lumen of the large bowel, and the older tetracyclines meet this requirement. However, they have a major disadvantage. They are not directly amoebicidal and have no effect on any amoebae which may have reached the liver. Not only are antibiotics useless in uncomplicated amoebic liver abscess but, when used in the treatment of aemobic dysentery, they fail to protect the liver from invasion. It is therefore necessary when using a tetracycline to give, in addition, a directly acting amoebicide effective in protecting the liver from infection or in curing any amoebic infection which may already be established (POWELL et al., 1960).

Up to the present there have only been 2 groups of amoebicidal drugs which have become generally accepted as effective against amoebic infection of the liver. These are the chloroquine preparations and emetine hydrochloride and, most recently, dehydroemetine. The chloroquine group are of little direct value in amoebic dysentery although there is some evidence that they potentiate the

action of tetracycline and di-iodohydroxyquinoline (POWELL et al., 1960). They are safe and protect the liver from invasion, so that we commonly give them for that purpose when using tetracycline in amoebic dysentery. Emetine hydrochloride and dehydroemetine are of value in amoebic dysentery but, when used alone, have unsatisfactory cure rates (POWELL et al., 1962, 1965b). In amoebic liver abscess we have shown that chloroquine is inferior to emetine hydrochloride and dehydroemetine (WILMOT et al., 1958; POWELL et al., 1962, 1965c). However it must be borne in mind that emetine hydrochloride is a drug of proved cardiotoxicity and even the synthetic preparation, dehydroemetine, is probably not entirely without danger in this respect. Consequently, due care must be taken when using these preparations and toxicity may occasionally be a limiting factor.

In the past, therefore, there has been no single drug which is fully effective in both amoebic dysentery and amoebic liver abscess. CIBA 32644-Ba is the only preparation we have tested that appears capable of doing this. Not only has it been effective in curing patients with amoebic dysentery and others with amoebic liver abscess, but it has also cured patients with both forms of amoebiasis concomitantly, suggesting that the drug has an effect in the lumen of the bowel, in the bowel wall and also systemically in the liver. The success rate of 17 (with removal of *E. histolytica* in a further 3) out of a total of 22 cases indicates that it is the most effective directly acting amoebicide that we have tested in amoebic dysentery. Nevertheless, this cure rate remains somewhat inferior to that obtained with the tetracyclines; but possibly with careful dosage adjustment results could be improved. In amoebic liver abscess, CIBA 32644-Ba has been shown to be effective, but a more extensive trial is necessary to compare its efficacy with that of emetine hydrochloride and dehydroemetine. Should the drug be shown to compare favourably with other forms of treatment, much will depend on the ultimate evaluation of toxicity, particularly of its cardiotoxicity. If it can be demonstrated that it is devoid of serious toxicity when used in an effective dosage it will establish for itself a place in the treatment of amoebiasis. Our own experience still suggests that caution should be exercised in the assessment of possible cardiotoxicity.

Summary

The results of a trial of CIBA 32644-Ba in a dosage of 1 to 1.5 g daily in divided doses for 10 days in amoebic dysentery and in

amoebic liver abscess are reported. Of 22 patients with amoebic dysentery, cure was obtained in 17 and disappearance of *E. histolytica* occurred in a further 3 patients. All 5 patients with amoebic liver abscess appeared to be cured.

The ideal amoebicide is a drug capable of being effective on *E. histolytica* in the lumen of the bowel, in the bowel wall, and systemically in the liver. Although satisfactory drugs exist for the treatment of amoebiasis, there has been no single preparation capable of exerting all the actions required. CIBA 32644-Ba shows promise of meeting these criteria. Further trials are necessary and caution is indicated before cardiotoxicity can be excluded.

Résumé

Les résultats d'un essai clinique sur le CIBA 32644-Ba, donné à raison de 1 à 1,5 g par jour pendant 10 jours dans la dysentérie amibienne et l'abcès amibien du foie, sont rapportés. De 22 malades traités pour dysentérie amibienne, la guérison fut obtenue chez 17 d'entre eux ; 3 autres malades furent parasitologiquement négatives. Les 5 malades traités pour abcès amibien du foie furent guéris.

Le médicament amibicide idéal devrait être efficace contre la forme histolytique de l'amibe dans la lumière intestinale, dans la paroi intestinale et dans le tissu hépatique. Bien que des médicaments satisfaisants existent pour traiter l'amibiase, il n'y en a aucun capable d'agir sur toutes les formes d'infestation. Le CIBA 32644-Ba montre un avenir prometteur pour répondre aux critères requis. Des essais cliniques sont encore nécessaires et une certaine prudence est encore indiquée avant de pouvoir exclure toute cardiotoxicité du traitement.

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