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Activity of CIBA 32644-Ba in Amoebic Liver Abscess in Man

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It is generally accepted that at present the principal drugs of value in the treatment of amoebic liver abscess are emetine and chloroquine. The great therapeutic value of emetine is well established. However, its local, cardiovascular, neuromuscular and gastrointestinal toxicity is equally well known. Chloroquine, which is widely used as an alternative to emetine and which is especially valuable in cases where the use of emetine is contra-indicated for some reason or other, may appear to be as potent as emetine, but it has the disadvantage of a high relapse rate and also exerts some toxic effects, although to a lesser extent than emetine. Thus, up to the present, no ideal systemic amoebicide has been found and the search for such a drug is still being continued.

CIBA 32644-Ba has been shown to be active in hepatic as well as intestinal amoebiasis in the experimental animal by KRADOLFER and JARUMILINTA (1). LAMBERT and CRUZ FERREIRA (2) have shown that this preparation has yielded promising results in human vesical bilharziasis without giving rise to any significant side effects. Clinical trials with the compound in amoebiasis were thus fully justified.

The main purpose of this preliminary trial was to ascertain whether the compound is effective in man as a systemic amoebicide and whether it is well tolerated in therapeutic doses.

Material and Method

The subjects of the study were 15 Siamese patients with amoebic liver abscess, admitted as in-patients to the Hospital of Tropical Diseases, Bangkok School of Tropical Medicine, during the 6-month period from July to December 1964. The patients were

* CIBA Laboratories, Basle.

all adult males, aged 24-70 years, with body-weights between 37 and 51 kg. The diagnosis was made on the basis of medical history, signs and symptoms, supplemented by blood count, erythrocyte sedimentation rate (E.S.R.), radiological findings and liver function tests. It was confirmed in all cases by aspiration of characteristic "anchovy-sauce" pus.

Routine physical examinations were made daily, particular attention being paid to subjective symptoms, signs of toxicity, body temperature, pulse rate, blood pressure, size of liver, physical well-being, body-weight and appetite. Other examinations included X-ray screening of the chest, estimation of the size of the abscess cavity by X-ray, electrocardiography, routine examination of blood, urine, stools and aspirated liver pus, and liver function tests. These were carried out prior to treatment, during the course of medication, on the first few days following completion of treatment, and later about once a week until the end of the hospital period. The size of the abscess cavity was estimated by injecting about 5 ml of an opaque medium and 50 ml of air into the abscess cavity after the pus had been removed, and immediately taking X-ray pictures (AP and lateral view). The size of the abscess cavity was subsequently checked by X-ray at the intervals stated above. 14 out of 15 cases presented with pain in the right costal region, 13 of them had fever, 13 leucocytosis, and all 15 cases a high E.S.R. Enlargement of the liver varied from 2 finger-breadths (F.B.) to 6 inches below the right costal margin (midclavicular line [M.C.L.]). In all patients appetite was poor. Nine cases had a previous history of dysentery. Characteristic pus was aspirated in all cases. In 6 cases *E. histolytica* was demonstrated in the pus. Further aspiration was done when clinically indicated.

Bed rest and normal hospital diet were prescribed for all patients, who were kept under observation in hospital for a period of 37-83 days and thereafter instructed to report for follow-up at intervals of about 4 weeks after discharge.

The general plan of treatment was to give CIBA 32644-Ba orally in daily doses of 25 mg/kg, administered in 2 equally divided doses morning and evening for 9 consecutive days.

Results

12 out of 15 cases received the full standard 9-day course of treatment. These patients were between 24 and 62 years of age and weighed between 37 and 49.3 kg at the outset of treatment. 7 of them were observed for a period of 110-191 days and 5 for

31-83 days. A satisfactory response was obtained in all cases. In assessing the response to treatment, the disappearance of signs, symptoms, and abnormal findings in the laboratory tests was regarded as a reliable indication, the major criteria being body temperature, pain in the liver region, liver size, size of abscess cavity, mobility of diaphragm, W.B.C., E.S.R., appetite and body-weight. The clinical findings in these cases are summarised as follows:

Body temperature, which was elevated between 37.9°C - 40°C at the outset of treatment in 10 cases, decreased significantly between the 1st and 4th day of treatment (o.t.) and became normal between the 2nd and 8th day of treatment in all cases. In 2 cases the temperature was normal throughout the period of observation.

Pain in the liver region, which was present in 11 cases, began to decrease significantly between the 2nd day of treatment and the 1st day after treatment (a.t.) and disappeared completely between the 4th day o.t. and the 33rd day a.t. In 1 case there was no pain throughout the period of observation.

Appetite and strength began to improve between the 2nd day o.t. and the 5th day a.t. The 12 patients had gained 2.5-14 kg *body-weight* by the end of the observation period.

Decrease in the *size of the liver* was progressive in all 12 cases; it was first observed between the 2nd day o.t. and the 33rd day a.t. The liver was no longer palpable 12-191 days a.t. in 8 cases. In the remaining 4 cases, a considerable reduction in the size of the liver was detected at the end of the observation period, 36-54 days after the completion of treatment.

Mobility of diaphragm: before treatment, fluoroscopy revealed reduction of mobility of the right dome of the diaphragm in all 12 cases, ranging from complete fixation to 50% reduction. The first signs of improvement were observed between the 4th day o.t. and the 1st day a.t. in 10 cases. Improvement was progressive in all 12 cases and at the end of the observation period 2 patients were completely normal in this respect and the others showed marked improvement.

The size of the abscess cavity at the outset of treatment ranged from approximately $5 \times 4 \times 4$ cm to $10.5 \times 16.5 \times 12.5$ cm, measured by horizontal, vertical and anteroposterior diameters, respectively. A reduction in cavity size was first observed between the 3rd day o.t. and the 6th day a.t. in most cases. All 12 cases showed a further progressive reduction, and by the end of the observation period there was evidence of complete healing of the abscess in 8 cases. In the 4 other cases a considerable reduction in the size of the abscess cavity was evident at the end of the observation

period. (Some X-ray pictures were presented to demonstrate these features.)

Laboratory Findings

The haemoglobin concentration prior to treatment was between 8 and 12.2 gm% in 11 cases. In all 12 cases a progressive increase in the concentration was noted; a significant increase began between the 4th day o.t. and the 2nd day a.t. in most cases. At the end of the observation period the concentration was between 14 and 16 gm% in 8 cases and between 11.8 and 13 gm% in the other 4 cases.

The leucocyte count at the outset of treatment showed a leucocytosis of between 10,500 and 17,100 cells per cu.mm in 10 cases. The count returned to normal between the 2nd day o.t. and the 14th day a.t. In the 2 remaining cases the W.B.C. was normal throughout. Neutrophilia of 71-92% was noted at the beginning of treatment in all 12 cases. The neutrophil count returned to normal between the 4th day o.t. and the 14th day a.t. No leucopenia was observed.

Erythrocyte sedimentation rate (at one hour) was in all cases high at the start, i.e. between 20 and 75 mm. An appreciable decrease in the E.S.R. was evident between the 4th day o.t. and the 1st day a.t. in most cases. A further reduction of the E.S.R. was observed in all cases, with fluctuation in some cases. At the end of the observation period most cases showed normal or nearly normal values.

Serum transaminase levels were normal throughout the period of observation in all but one patient. In this case the SGOT and SGPT were 130 and 111 units, respectively, at the outset of treatment; a significant decrease in the levels had already begun by the 4th day o.t. Thereafter they decreased progressively and were within the normal range from the 29th day a.t. onwards.

The cephalin cholesterol flocculation test (Hanger's), *thymol turbidity test* (McLagan's), *zinc turbidity test* (Kunkel's), *Iodine test* (Mallen's), the *serum alkaline phosphatase* (Bodansky's), *bilirubin*, *creatinine*, *cholesterol* and *NPN* levels, and the *albumin/globulin ratio* exhibited irregular variations of no particular significance. In all cases the urine remained normal throughout.

Trophozoites of *E. histolytica* were found in the pus obtained by liver aspiration in 5 cases. Amoebae could no longer be found on the 6th day o.t. in 2 of these cases; in one of them liver punctures were again attempted on the 2nd and 8th day a.t., but no pus was obtained; no second liver puncture was performed in the other 2 cases.

In another 3 out of the 15 cases, treatment with CIBA 32644-Ba had to be discontinued before the 9-day course was completed. All 3 cases were in fact already in a very serious state with a very poor general condition at the outset of treatment. The treatment was discontinued after 3 days in one case (a 70-year-old male) because the patient developed paralytic ileus marked by painful abdominal distension, absence of peristaltic sounds, nausea and vomiting. All symptoms and signs, however, disappeared a few days later, after gastric suction and administration of fluid, prednisolone, Prostigmine, and antibiotics. Another patient aged 40, presented with a very tender liver enlarged to 1 hand-breadth with moderate abdominal distension, moderate jaundice, a leucocytosis of 28,500, elevated transaminase levels of 150/60 (SGOT/SGPT), high blood bilirubin (direct 11.2 mg%, total 16.8 mg%), high NPN (50 mg%) bile (4⁺) and albumin (4⁺) in urine, associated with acute amoebic dysentery; treatment was discontinued after 4 days owing to worsening of the existing abdominal distension and development of generalised abdominal pain. The last patient, aged 60, was in an exceptionally serious state before treatment with an extremely tender liver enlarged to 1 hand-breadth and elevated transaminase levels of 126/109 (SGOT/SGPT). He also showed chronic, moderately advanced, bilateral tuberculosis. Treatment with INH and PAS in a daily dosage of 400 mg and 9 gm respectively had been started 9 days before commencement of treatment with CIBA 32644-Ba and continued simultaneously. The latter treatment had to be discontinued after 6 days, since the patient developed a psychotic state marked by hallucination, disorientation and delirium, together with moderate abdominal distension. The psychotic state began to improve on the 2nd day after discontinuation of the drug and had almost disappeared by the 5th day.

Tolerability and side effects

Most of the patients tolerated the drug very well. Of the 12 patients who received a full 9-day course of treatment, 7 did not complain of any gastro-intestinal disturbances, or cardiac or other symptoms that might have been attributable to the drug. Three patients experienced very mild gastro-intestinal symptoms during the first few days of treatment, in the form of slight nausea in 2 cases and slight flatulence in one. Two other patients developed moderate gastro-intestinal disturbance during treatment, consisting of anorexia and painful abdominal distension with diminution of

bowel sound in 1 case and moderate flatulence with giddiness and anorexia in the other. The history of these 2 patients, however, suggests that treatment with CIBA 32644-Ba was not solely responsible for the side effects observed; before treatment the first case showed SGOT/SGPT levels of 130/111 units and the other myocardial damage; in both cases the gastro-intestinal syndrome disappeared after the withdrawal of pus from the abscess cavity and discontinuation of the drug was not necessary in either case. The latter case also displayed, two days after the end of the treatment, a muscular twitching of the left arm lasting about 5 minutes; this was followed by a period of unconsciousness lasting about 10 minutes. The cerebrospinal fluid was, however, normal. In all these 12 cases there was no evidence that the compound exerted any toxic effect on the liver, blood, or kidneys.

The other 3 patients, whose condition necessitated cessation of therapy, should in fact not have been included in a trial of this nature, since they were already in a very serious state with a very poor general condition before treatment; this applied particularly to the last patient, who was also suffering from moderately advanced bilateral tuberculosis and required simultaneous treatment with INH and PAS. Hence, it is not impossible that the psychotic effect may have been due to the combination of INH and CIBA 32644-Ba.

Adequate *electrocardiography* was performed in all the 12 patients who received the full course of treatment. The electrocardiogram was normal before treatment in 11 cases and showed diffuse myocardial damage (particularly right ventricular) in 1 case. Appreciable changes in ECG tracings were observed in 9 of the cases; these became evident for the first time between the 4th day o.t. and the 1st day a.t. The principal changes were depression of T waves in all 9 cases, varying from slight lowering of amplitude to inversion. Inversion of T waves was recorded in 4 cases only; in some leads in 3 of these cases and in all leads in the other. Other changes included diphasic T waves in some leads in 2 cases, depressed ST segments in some leads in 1 case and QT prolongation in 1 case. Improvement was, however, noted in all cases between the 1st and 16th day a.t. and the tracings resumed their initial pattern between the 1st and 26th day a.t. in 7 cases and between the 37th and 50th day in 2 cases. In 3 other cases, including the case showing myocardial damage before treatment, no appreciable change was observed during or after treatment. It should be noted that these changes in the ECG pattern were not associated with signs or symptoms, such as arrhythmia, alteration in blood pressure or pulse rate, abnormal heart sounds, precordial

pain or dyspnoea. ECG tracings were not made regularly in the 3 patients who were treated for less than 9 days; it is thus impossible to assess the effect of the drug on the ECG pattern in these patients.

Summary and Conclusion

It is clear from the results obtained that all 12 patients, with amoebic liver abscess, who received a full standard course of treatment, i.e., 25 mg/kg of CIBA 32644-Ba daily for 9 days, showed an excellent response and made a rapid clinical recovery. All patients tolerated the drug very well, except 2 in whom the case history suggested that treatment with CIBA 32644-Ba may not have been solely responsible for the side effects observed.

The fact that all 3 patients with elevated transaminase levels developed side effects suggests that enzymatic insufficiency of the liver may result in inadequate metabolism. This would result in an abnormally high blood level of non-metabolised free substance. If this were the case, a therapeutic effect would be obtained at a lower daily dose and side effects should be avoided or reduced.

This trial shows that CIBA 32644-Ba is an effective systemic amoebicide and provides a satisfactory alternative to emetine. Nevertheless, further investigations, including a comparative study of this compound and emetine in the treatment of hepatic amoebiasis, should be carried out. Its efficacy in intestinal amoebiasis should also be studied.

Résumé et conclusion

Il apparaît clairement que les 12 malades, atteints d'abcès amibien du foie et qui reçurent un plein traitement de 25 mg/kg/jour pendant 9 jours de CIBA 32644-Ba, ont montré une excellente réponse thérapeutique et une guérison clinique rapide. Tous les malades supportèrent très bien le traitement, sauf 2 cas où l'histoire clinique suggère que le CIBA 32644-Ba pourrait n'avoir pas été seul en cause pour expliquer les effets secondaires observés.

3 malades, dont le taux de transaminases était élevé, ont présenté des effets secondaires qui pourraient s'expliquer par l'insuffisance enzymatique du foie qui produisait une métabolisation inadéquate du produit. Ce phénomène pourrait être à l'origine d'une concentration sanguine anormalement élevée de substance non dégradée ; si c'était le cas, l'effet thérapeutique pourrait être atteint avec des doses plus faibles et les effets secondaires évités ou réduits.

L'essai clinique présenté montre que le CIBA 32644-Ba est un amibicide tissulaire efficace et qu'il présente une alternative satisfaisante de l'émétine. Néanmoins, d'autres essais sont encore nécessaires pour une conclusion définitive, en particulier une étude comparative de l'émétine et du CIBA 32644-Ba dans les mêmes conditions de traitement de l'abcès amibien du foie.

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