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Comparative study of aminosidine, etophamide and nimorazole, alone or in combination, in the treatment of intestinal amoebiasis in Kenya

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Summary. 417 patients suffering from intestinal amoebiasis were randomly allocated to 6 different treatment groups in a controlled study in 3 District Hospitals in Kenya. The patients received either aminosidine (A), etophamide (E), nimorazole (N), or the combinations NA, NE, EA. Treatment in all cases was given twice daily for 5 days. Before and after treatment, rectosigmoidoscopy was done in each patient, and stool examination with characterization of invasive (IF) and non invasive (NIF) forms of amoeba was done daily throughout treatment, and on Days 15, 30 and 60 of follow-up.

Clinical cure was good after all the treatments, varying from 90 to 100%; parasitological cure at the end of treatment was 100% in the NA and EA treatments groups, and 98% in A group. The incidence of relapses was nil in the EA group, followed by 3% in NA and 6% in A groups. Anatomical cure (healing of ulcers) was 97.8% in the NA group, 95.5% in the N group and 88.5% in the A group. Drug tolerance was excellent or good after all the treatments, except that the EA combination produced diarrhoea in 76.5% of patients.

Overall analysis of the findings, including tolerance of the various treatments, showed that aminosidine either alone or in combination with nimorazole gave the best results.

Ulcers seen on rectosigmoidoscopy were more common in patients excreting invasive forms of amoebae in their stools.

Key words: Intestinal Amoebiasis, Aminosidine, Etophamide, Nimorazole; Drug combinations, adverse effects

Amoebiasis, especially in the invasive form, constitutes a major health and social problem in many tropical countries [1]. In Kenya the disease is common in all parts of the country, with an incidence varying from 10 to 30% of the general population [2]. Intestinal amoebiasis is the most widespread form; in highly endemic areas, approximately 90% of the affected subjects are asymptomatic carriers, while the remaining 10% show definite clinical evidence of the disease [3].

Drugs used for treating amoebiasis in general, and its intestinal form in particular, are numerous and chemically diverse [4, 5]. Several of them, however, are not widely used, at least as first choice therapy, partly because of their limited efficacy, and partly because of the adverse effects they produce [6, 7]. Some, such as nitroimidazole and dichloracetamide derivatives, and one aminoglycoside antibiotic (paromomycin, or aminosidine), are still widely used for the treatment of intestinal amoebiasis, but the literature remains vague about their particular indications in the various pathological manifestations of amoebiasis. Very little is known of the activity of such drugs when used in combination.

The aim of the present study was to assess the efficacy of three different antiamoebic drugs administered individually, or variously combined two at a time, in invasive and non invasive intestinal amoebiasis. At the same time, possible correlations were sought between the various test parameters measured before the start of treatment.

Patients and methods

The study was conducted at the District Hospitals of Kiambu, Machakos and Kilifi, in a total of 417 patients (183 m and 234 f), between the ages of 6 and 80 y, who were suffering from *E. histolytica* intestinal infection. Pregnant women, patients with known allergy to the drugs, those with coexisting extra-intestinal amoebiasis or other major diseases, and those treated with antiamoebic drugs in the 30 days prior to recruitment, were excluded from the study.

The patients selected were informed of the purpose and nature of the study and were entered after giving their consent in writing. They were hospitalized for the duration of treatment. Before treatment (Day 0), each patient were examined: clinical history and general physical examination; gross stool examination for mucus and/or blood; microscopical stool examination (three direct examinations and a concentration test) to detect invasive (IF) or non invasive (NIF) amoebic forms [8]; rectosigmoidoscopy to detect amoebic ulcers (classified as mild or severe according to their number and/or size). The same tests were repeated daily throughout the treatment period and again at follow up examinations after 15, 30 and 60 days,

Table 1. Details of the main patient characteristics and diagnostic features in the six treatment groups (Day 0)

Treatment	Number of patients	Mean Age (years)	Mean BW (kg)	Stool examinations NIF (No.)	IF (No.)	Rectosigmoidoscopy Patients with ulcers no. positive/no. examined
A	100	28.3	51.0	65	35	54/ 88
E	102	28.9	50.1	67	35	50/ 80
N	100	31.2	49.4	73	27	68/ 93
NA	49	22.2	49.2	37	12	32/ 48
NE	49	30.5	49.8	33	16	35/ 44
EA	17	27.3	54.2	11	6	11/ 16
Mean or Total	417	28.6	50.2	286	131	250/369

A = aminosidine; E = etophamide; N = nimorazole

Table 2. Patient distribution by invasive (IF) and noninvasive (NIF) amoebic forms in the stools according to the features observed at rectosigmoidoscopy (RSS)

RSS / DRUG	Not done		Normal		Mild		Severe	
	NIF (No.)	IF (No.)	NIF (No.)	IF (No.)	NIF (No.)	IF (No.)	NIF (No.)	IF (No.)
A	6	6	29	5	27	14	3	10
E	14	8	24	6	22	15	7	6
N	4	3	24	1	37	13	8	10
NA	1	0	14	2	20	4	2	6
NE	4	1	8	1	16	6	5	8
EA	0	1	5	0	6	1	0	4
Total	29	19	104	15	128	53	25	44

with the exception of rectosigmoidoscopy, which was repeated only at the end of treatment for logistic reasons. IF and NIF forms of *E. histolytica* were distinguished in accordance with WHO recommendations [9].

The patients were randomly allocated to 6 different treatment groups (Table 1), each of which was treated orally for 5 consecutive days. The doses of drugs given on their own and in combination were: aminosidine (A) 500 mg b. d. for adults, 15 mg · kg^{-1} body wt. b. d. for children; etophamide (E) 600 mg b. d. for adults, 15 mg · kg^{-1} body wt. b. d. for children; nimorazole (N) 1 g b. d. for adults, 20 mg · kg^{-1} body wt. b. d. for children. All drugs were administered under direct medical supervision. The persons in charge of stool examination and rectosigmoidoscopy were not informed of the drug being taken. All patients were monitored daily from the start of the trial for possible adverse events attributable to the test drugs.

The criteria adopted for assessing results at the end of the study were as follows [10]: *Clinical cure*, defined as the disappearance of all symptoms present on entry. *Parasitological cure* – disappearance of all parasitic forms from stools or ulcer scrapings. *Anatomical cure* – healing of previous ulceration. The persistence of any form of *E. histolytica* at the end of treatment was rated as a failure, and the reappearance of any form during the follow up period, after initial disappearance, was rated as a recurrence.

Drug tolerance was rated as excellent in the absence of any side effects, good in the presence of mild side effects, and poor if there were severe manifestations attributable to treatment.

Results

The distribution of the 417 patients into the six treatment groups is shown in Table 1. There was homogeneity for age, body weight, presence of invasive or non-invasive forms of *E. histolytica* in the stools, and ulcers at rectosigmoidoscopy. Overall, the prevalence of NIF (68.6%) was greater than that of IF (31.4%). Rectosigmoidoscopy before treatment revealed parietal ulcers in 67.8% of the 369 patients examined.

Rectosigmoidoscopy findings on Day 0 have been correlated with the amoebic forms found in the stools in Table 2. When the rectosigmoidoscopy was normal, there was a definite prevalence of NIF over IF, ratio approximately 7:1. When ulcers were present, the ratio dropped to 2.4 in the case of mild ulcers, and to as low as 0.6 with severe ulcers. Overall, IFs in patients subjected to rectosigmoidoscopy occurred most commonly in patients (86.6%) with amoebic ulcers.

The pattern of amoebic forms found in the stools over time is displayed in Table 3. During treatment, IFs disappeared more rapidly and more often than NIFs, regardless of the drug being administered. At the end of treatment the total prevalence of IFs in the faeces was 0.7% and that of NIFs was 7.7% relative to the initial findings. The incidence of failures, essentially reflecting the persistence of non-invasive forms, was nil in patients treated with the NA or EA combinations, as compared to 2% in patients treated with A alone, 6.1% in those treated with NE, 8% in those treated with N alone, and 9.8% in those treated with E alone.

The incidence of recurrence in the various treatment groups was judged from follow up data. With the proviso that the percentage of patients reporting for recheck was 88.5% at 15 days, 67.6% at 30 days and 51.3% at 60 days, the overall distribution of recurrences was fairly uniform over time, namely 8.4% after 15 days, 9.2% at 30 days, and 7.5% at 60 days of follow up. At all rechecks, however, the incidence of recurrence was nil in the EA group, 3% in the NA group, 6% in the A group, 6.8% in the E group, 14.6% in the N group, and 17.3% in the NE group. Only the reappearance of parasites on Days 15 and 30 should be considered as true recurrences, as reappearance at Day 60 could represent reinfection [4, 10].

Rectosigmoidoscopy was done in 88.5% of all patients before treatment and it was repeated in 83.2% at the end of treatment (Table 4). At the time of recruitment, rectosigmoid ulcers were present in 67.8% of patients, with a larger number of mild than of severe forms. In general, treatment seemed to promote the healing of such lesions, which were present at termination in only 9.2% of cases, and then with an even greater predominance of mild forms. The best results in terms of ulcer healing were obtained with the NA combination (97.8% cured), followed by N (95.5%), A (88.5%), NE (87.8%), E (87.5%), and EA (77.0%).