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Short-term treatment of acute intestinal amoebiasis with ornidazole

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Introduction

Amoebiasis is a protozoal infection of world-wide distribution and is estimated to affect ten percent of the world's population, although its prevalence and severity differ from area to area (Wld Hlth Org. techn. Rep., 1969, No 421). Especially in the tropical and subtropical parts of Asia and of Africa amoebiasis belongs to the most frequent parasitoses.

So far, the most significant advance in the treatment of amoebiasis was the discovery of the potent amoebicidal effect of 5-nitroimidazole derivatives. These substances exert a powerful intestinal and systemic amoebicidal activity and are well tolerated. One of them, ornidazole, the active substance of 'Tiberal', proved to be even more active than metronidazole in experimental amoebic infection (hepatic amoebiasis of hamsters) (Richle et al., 1978).

A treatment course of 5 to 10 days duration (500 or 750 mg orally three times daily) is recommended for therapy of acute amoebic dysentery with metronidazole (Physicians' Desk Reference, 1979). With ornidazole too, in early clinical trials in amoebic dysentery daily doses of 1.0 to 1.5 g were applied for 5 to 10 days; a cure rate of more than 90% was obtained with this dosage regimen (Fernex et al., 1974). Nevertheless, a shortening of the treatment period was considered desirable by many physicians, especially for non-hospitalized cases of amoebic dysentery. This, because in many cases – due to economic reasons and ignorance – the prolonged course of treatment was not completed.

Already in 1969 Powell et al. reported on a trial of short-term treatment of acute amoebic dysentery with metronidazole. With 2.4 g in a single dose on each of 2 consecutive days and 2.4 g in each of 2 doses on the same day unsatisfactory cure rates of 86% and 80% respectively were obtained.

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E. and V. Heimgartner (1977) published a study on short-term treatment of symptomatic amoebiasis with ornidazole. 91 patients were treated for 1–5 days with a daily dose of 2.0 g (adult dose). In those patients treated for 3–5 days the cure rate was 80–100%. A 2-day treatment resulted in a cure rate of 64% and with a one-day treatment 72% of the patients were cured.

Further results on a 3-day treatment of intestinal amoebiasis were presented by Lasserre (1977) in a review paper comprising 107 cases. With a drug regimen of 2 g of ornidazole a day in one or two doses given for three consecutive days a clinical and parasitological cure was obtained in 97% of the cases.

Recent clinical trials on short-term treatment of amoebic dysentery with ornidazole

With the aim to elucidate whether a further reduction of the daily dose is possible without impairing efficacy a clinical trial with a 3-day treatment course of 1.5 mg per day, given as a single dose, was started in 1978.

Method

The trial was run as an open label multicenter study involving 4 trial centers (one each in Brazil and Chile and two in Mexico) (Table 1). The same trial plan and questionnaires were used by all investigators.

A total of 190 patients with symptomatic intestinal amoebiasis (mainly amoebic dysentery) confirmed by the presence of *E. histolytica* cysts and/or trophozoites in the stool were included into the study. Women in early pregnancy (first trimester) and patients with neurological diseases or known hypersensitivity to the drug were excluded.

The daily dose of 3 tablets 'Tiberal' (corresponding to 1.5 g of ornidazole) had to be taken in a single dose after the evening meal for 3 consecutive days.

The results of the treatment were assessed by clinical examinations performed before treatment and on days 1 to 5, 14 and 28 after start of treatment and by stool examinations with a concentration method which had to be performed before treatment and on days 5, 14, 21, and 28 after initiation of treatment.

Results

Influence of therapy on signs and symptoms of symptomatic intestinal amoebiasis

Diarrhea, assessed by average number of stools per day, improved rapidly under the treatment with ornidazole (Table 2). The other signs and symptoms of symptomatic intestinal amoebiasis, especially stools containing blood and/or pus as well as vomiting, usually abated already within 5 days after the beginning of therapy with ornidazole (Table 3).

Influence of therapy on the presence of E. histolytica

A rapid disappearance of *E. histolytica* from stools was obtained with the 3-day treatment course. Already 5 days after onset of therapy the stools of 76.1% of the patients were negative. At the end of the 4-week follow-up period the

Table 1. Trial centers

Country	No. of center (No. of patients)	Investigator
Brazil	20.5626 (50)	Prof. Geraldo José Marques Pereira, Departemento de Medicina Tropical, Faculdade de Medicina, – U.F.P.E., Hospital das Clinicas, Rua dos Coelhos 5/n, Recife – PE 50 000
Chile	21.1715 (50)	Dr. Hugo Schenone, Dpto de Microbiologia y Parasitologia, Universidad de Chile, Santiago
Mexico	35.1935 (40)	Dr. Florencio Fernandez, Sanatorio de la Cruz, Mexico D.F.
Mexico	35.1922 (50)	Dr. Boris Rubio Lotvin, Hospital American British Cowdray, Mexico D.F.

Table 2. Influence of treatment on number of stools per day in 188 patients with diarrhea

No. of stools (mean values and standard deviation)			
Before treatment	day 5	day 14	day 28
5.5 SD: 2.36	1.7 SD: 1.46	1.1 SD: 0.89	1.1 SD: 0.76

Table 3. Influence of treatment on other signs and symptoms of symptomatic intestinal amoebiasis

Symptom	No. of patients with symptoms			
	before treatment	day 5	day 14	day 28
Vomiting	48 (100%)	1 (2.1%)	0	0
Stool with blood	55 (100%)	3 (5.5%)	3 (5.5%)	1 (1.8%)
Stool with pus	77 (100%)	11 (14.3%)	4 (5.2%)	0
Abdominal pain	188 (100%)	66 (35.1%)	16 (8.5%)	8 (4.3%)

parasitological cure rate amounted to 93.1%. At this time only 3 out of 188 evaluable cases continued to show trophozoites in their stools and 10 patients remained cyst passers (Table 4).

Overall therapeutic response

The rapid onset and the reliability of action of the 3-day treatment course is also evident as far as the overall therapeutic result is concerned (Table 5). Al-

Table 4. Results of the parasitological examination of stool of 190 patients for *E. histolytica* before treatment and on days 5, 14, 21, and 28 after start of therapy

	Before	Day 5	Day 14	Day 21	Day 28
Number of patients					
with trophozoites	27	16	1	1	1
with cysts	26	22	5	8	10
with trophozoites plus cysts	136	7	4	2	2
without given data	1	2	3	3	2
negative for *E. histolytica*	0	143	177	176	175
Total number of evaluable cases	189	188	187	187	188
Percentage of negative cases (parasitological cure rate)		76.1	94.7	94.1	93.1

Table 5. Overall therapeutic results

	Day 5	Day 16	Day 28
Cure (disappearance of symptoms and of *E. histolytica)*	131 (71.6%)	162 (92.6%)	161 (91.5%)
Probable cure (persistent symptoms but disappearance of *E. histolytica)*	7 (3.8%)	3 (1.7%)	2 (1.1%)
Failure (persistence or recurrence of *E. histolytica)*	45 (24.6%)	10 (5.7%)	13 (7.4%)
Total evaluable cases	183 (100%)	175 (100%)	176 (100%)
No data given	7	15	14

ready 5 days after the start of therapy almost three quarters of the patients were cured, i.e. there was complete disappearance of signs and symptoms as well as of *E. histolytica* in stools. The overall therapeutic result of approx. 92% of cured cases at the end of the follow-up period corresponds to that obtained in earlier clinical trials with a 7 to 10-day treatment course.

Tolerance

The 3-day treatment course with a daily dose of 1.5 g ornidazole was well tolerated but not devoid of side effects.

36 (18.9%) out of the 190 patients involved into the study reported on one or more side effects. The most frequently encountered side effect is dizziness, alone or in combination with other adverse reactions.

Table 6. Type, frequency and distribution of side effects

Type of side effect	No. of patients
Nausea	3 (8.3%)
Nausea + dizziness	5 (11.1%)
Nausea + pyrosis + intestinal spasms	1 (2.8%)
Dizziness	19 (52.8%)
Dizziness + vomiting	1 (2.8%)
Dizziness + vomiting + metallic taste	1 (2.8%)
Dizziness + pyrosis + metallic taste	1 (2.8%)
Dizziness + intestinal spasms	4 (11.1%)
Dizziness + vomiting + headache + pyrosis	1 (2.8%)
Intestinal spasms	1 (2.8%)
Total	36 (100%)

Conclusion

The conclusion to be drawn from these results is that for the therapy of acute amoebic dysentery with ornidazole a shortened treatment schedule of 3 days duration can be considered an alternative to the prolonged treatment of 5 to 10 days duration. This especially for such non-hospitalized patients who, due to ignorance or other (e.g. economic) reasons, frequently do not seem to complete the prolonged course of treatment. The daily dose of 1.5 g (corresponding to about 25 mg per kg bodyweight) is preferably administered as a single dose in the evening.

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