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Tiberal (Ro 7-0207-Roche) in the Treatment of Intestinal Amoebiasis — Part II

by

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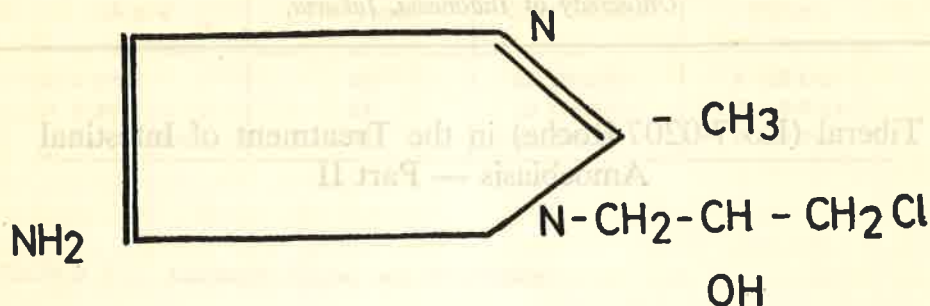
Abstract

Twenty-four intestinal amoebiasis patients have been treated with a new amoebicid tiberal (Roche) or metronidazole as a control in a dosage of 15 — 30 mg./kg. bodyweight per day for 5 consecutive days. The results show that both drugs achieve a 100% cure rate. No side effects or signs of drug toxicity as evaluated from the results of the safety tests were observed. No signs of clinical or parasitological relapses were seen after discharge. In comparison with the previous trial with a lower dosage (7½ — 15 mg.) and longer course (7 days) the results were even better, e.g. clinical improvement and parasitological disappearance were achieved in a shorter time.

Received 6 th. Dec. 1974.

Introduction

Tiberal (Ro 7-0207-Roche) has the following structure :



Chloromethyl 2-methyl-5-nitro-1-imidazoethanol

The above mentioned drug has been tried out in the Department of Child Health, Medical School, University of Indonesia, Jakarta, resulting in a 100% cure rate of intestinal amoebiasis by clinical as well as stool parasitology evaluation (Pudjiadi et al., 1972). The dosage was approximately $7\frac{1}{2}$ — 15 mg./kg. body weight per day, and the duration of treatment was 7 days. No side-effects, signs of drug-toxicity and relapses after a follow-up of 8 weeks have been observed. According to the data of information, the drug has been tested on rats as a dietary admix for 13 weeks. No direct signs of toxicity were noted in any rats receiving 100 mg./kg. body weight per day during the course of the experiment (Roche Ltd.). Due to the well-known fact that recurrence of amoebiasis is often encountered by improper treatment and due to our own experience (Pudjiadi and Harmanses, 1965) that a treatment of long duration in most cases could not be completed, the following

study was planned to evaluate the efficacy of the drug by shortening the course of treatment but doubling the dosage.

Material and methods

Twenty-four patients with either intestinal amoebiasis alone or intestinal amoebiasis plus other accompanying diseases were admitted to the Department of Child Health, Medical School, University of Indonesia Jakarta. Three patients were excluded from the trial due to the following reasons: 1 patient ran away from the hospital before the trial could be finished, and 2 other patients being in a bad nutritional condition died on the first and third day of admission because of a double-sided bronchopneumonia. Therefore only 21 patients could be included and evaluated in this trial.

They consisted of 12 male and 9 female children ranging in age from 1 to 7 years. The same methods of examination and evaluation, as also done in the pre-

vious trial (Pudjiadi et al., 1972), have been applied in this study so that a comparative result of both studies could be made. Metronidazole in the same dosage as tiberal has been used as a control.

* Stool examination

Fecal specimens were collected on the day of admission before treatment and on consecutive days during hospitalization. A weekly follow-up was continued after discharge. Macroscopic examinations of the stool specimen and number of defecations were noticed daily. Eosin (1%) and Lugol's solution (1%) staining of fecal material smears for detecting the *E. histolytica* parasites were used; the examinations were done in triplicates.

* Clinical investigations

A daily clinical check-up was carried out with special attention given to any possible complication and side-effect of the drug, i.e. abdominal discomfort, loss of appetite, skin rash, neurological signs, etc.

* Safety tests

Complete peripheral blood examinations, urine analysis, ECG, SGPT, and alkaline phosphatase level determination were done before, during, and after treatment.

* Administration of the drug

A double-blind set containing ten bottles of tiberal 125 mg. capsules

and 10 bottles of metronidazole 125 mg. capsules were supplied by the Roche Far East Foundation, Hongkong. The bottles were numbered 01 — 20 and contained either tiberal or metronidazole, unknown to the investigators. The first patient was treated with capsules from bottle 01, the second with capsules bottle 02, and so on. The last patient (no. 21) was treated with capsules from bottle 09, so there were 2 patients who were treated with capsules from bottle 09.

* Dosage application

Up to 2 years of age 125 mg., 2 to 6 years 250 mg., and 6 to 12 years 500 mg. daily divided into 3 doses for 5 consecutive days.

* Evaluation

Evaluation of the results was classified into 3 categories :

1. Excellent, if the patient shows very quick response, clinical symptoms disappear soon, and stool becomes negative for *E. histolytica* within 3 days.
2. Good, if clinical symptoms disappear and stool becomes negative for *E. histolytica* within 4 to 5 days.
3. Poor, if clinical symptoms and *E. histolytica* do not disappear after 5 days of medication.

Results

After the trial was entirely finished, the sealed envelope containing a list stating which bottles contained tiberol or metronidazole was opened. The following results were achieved.

The group treated with tiberol consisted of 11 children, 9 male and 2 female, varying in ages from 1 to 7 years (Table 1). The general condition was good in 4, fair in 2, and poor in 5 children. The range of illness before admission varied from 6 to 60 days, and consisted of watery, bloody stools stained with mucus. All stools became normal after the treatment was finished. Clinical improvement was achieved after a period of 1 to 3 days. *E. histolytica* disappeared from the stool after 2 to 3 days of treatment. According to the classification used in this trial, the results could be categorized as excellent in all of the patients.

The group treated with metronidazole comprised 10 children, 3 male and 7 female, with age varying from 2 to 6 years (Table 2). The general condition was good in 4, fair in 1, and poor in 5 children. The duration of illness before admission varied from 3 days to 2 years. All of them had frequent defecations varying from 6 to 15 times a day with watery, bloody stools stained with mucus. The stools became normal after the treatment was finished. Clinical improvement was achieved after a period of 2 to 5 days. Disappearance of the *E. histolytica* in the stool occurred after 2 to 4 days. The results of this treatment could

be categorized as excellent in 8 and good in 2 cases.

Ascaris ova were found in 11 out of 21 cases and disappeared in 2 cases at the end of the treatment. *Trichuris* ova were found in 5 out of 21 cases and still remained present in 4 cases after the treatment was finished. No ECG abnormality was observed in all patients treated with either tiberol or metronidazole. One patient (S., a 5-year-old boy) revealed Left Ventricular Hypertrophy before treatment, at the end of the treatment, and 1 week thereafter because of severe anemia and protein calorie malnutrition. No significant abnormalities were found on examination of hemoglobin, RBC, WBC, platelets, ESR, BUN, SGPT, and alkaline phosphatase. Another patient, a 4-year-old boy, showed a high SGPT value before treatment (580 IU) which at the end of the course decreased to 250 IU and 1 week thereafter to 120 IU. Jaundice was observed on this child but liver biopsy revealed a non-amoebic hepatitis.

Discussion

Amoebiasis is a disease well known for relapses when not treated properly. The cyst-form left after improper treatment will cause a recurrence of the symptoms (Pudjiadi, 1971). Several years before when efficient oral amoebiasis were not able, the Department of Child Health treated those patients with emetin hydrochloride intramuscularly for 5 — 7 consecutive days combined with

antibiotics followed by carbasone for 5 days to eliminate the cysts. Normally, they were not critically ill and the treatment was done in the out patient department so that during 5 — 7 days the patients had to come daily for the injections.

Due to economic reasons and ignorance of the parents, the course of treatment was mostly not completed resulting in a high incidence of relapses. A survey done on the results of treatment of vitamin A deficiency with 5 days daily injections of vitamin A showed that 52% of the patients could not get the complete treatment (Pudjiadi et al., 1958). Usually the parents did not bring back their children as soon as the clinical symptoms disappeared, or in the case of amoebiasis as soon as the frequency of the stools decreased and the blood and mucus disappeared. Relapses of the intestinal symptoms, the appearance of extra intestinal amoebiasis and cyst-passers will most probably be the results of such an improper treatment. A potent oral amoebicid which can be used to cure the disease within a short time without causing any side-effect and relapse would be ideal. The duration of treatment with oral amoebicids as also recommended by various authors is generally from 7 to 14 days (Shah et al., 1960; Pudjiadi, 1971).

Our previous trial with tiberol (chloromethyl - 2 - 5 - nitro - 1 - imidazoethanol-Roche) showed good results with 7½ — 15 mg./kg. body weight during 7 days. Doubling the dose with a shorter course

of treatment (5 days vs. 7 days) as also done in this study gives even better results of 50% versus 100% excellent (Table 3). This study shows that even in a higher dosage both drugs are not active against *ascaris* and *trichuris trichiura*.

No side-effects and signs of drug toxicity or relapses during treatment and up to 4 weeks thereafter have been observed in all the patients involved. A high level SGPT in one patient could not be caused by drug toxicity, as the patient was admitted with clinical signs of hepatitis, which were confirmed by liver biopsy. Notwithstanding the continuance of the amoebic treatment the SGPT level decreased with the disappearance of the jaundice. Signs of left ventricular hypertrophy as found in one of the patients could not be caused by the drug as this abnormality was already observed prior to treatment.

A comparison of the results of tiberol with metronidazole cannot be made as the dosage of tiberol and metronidazole was not the same, whereas the recommended dose for metronidazole is much higher, viz. 50 mg./kg. body weight per day. This study shows that a higher dosage in a shorter course of treatment with tiberol is effective against intestinal amoebiasis. A more extensive study and longer follow-up might be suggested to confirm the present results.

Acknowledgement

The authors wish to thank the Roche Far East Research Foundation, Hong-

TABLE 3: Results of treatment with different dosage of amoebicids

	Tiberal 7½ — 15 mg/ kg/bodyweight 7 days	Metronidasole 7½ — 15 mg/ kg/bodyweight 7 days	Tiberal 15 — 30 mg/ kg/bodyweight 5 days	Metronidasole 15 — 30 mg/ kg/bodyweight 5 days
Clinical Improvement	3 — 7 days	3 — 7 days	1 — 3 days	2 — 5 days
Disappearance of trophozoite	2 — 4 days	2 — 4 days	2 — 3 days	2 — 4 days
Results of evaluation:				
Excellent	50%	10%	100%	80%
Good	50%	80%	0%	20%
Poor	0%	0%	0%	0%
Side effects	none	none	none	none
Sign of drug toxicity	none	none	none	none
Recurrences after 4 weeks	none	none	none	none

kong, for the supply of the drugs and grant-in-aid in making this study possible; also to Professor R. Sutedjo, Head of the Department of Child Health, Medical School, University of Indonesia,

Jakarta, who stimulated the trial and kindly read the entire manuscript, and to Dr. Maemunah Affandi who did the ECG readings.

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