CLINICAL TRIAL OF RO7-0207, A NITROIMIDAZOLE DERIVATIVE IN AMOEBIC DYSENTERY

S. ALISAH NAOEMAR and BINTARI RUKMONO

Department of Parasitology and General Pathology, Faculty of Medicine, University of Indonesia, Jakarta, Indonesia.

INTRODUCTION

Since emetine was isolated from the dried root of *Cephalis ipecacuanhae* and introduced by Rogers (1912), this drug was considered to be the drug of choice for amoebiasis and remained so in the following 40 years. The main disadvantage, however, was its potential toxicity to skeletal muscle, heart muscle and the gastrointestinal tract. Many drugs such as 4-aminoquinoline compounds (Hoekenga and Maximo, 1950) and antibiotics (Elsdon-Dew *et al.*, 1952) were tried in amoebic dysentery, but none could be considered as effective as emetine.

In 1959, dehydroemetine, a pure synthetic compound was described to be as effective as natural emetine but with less toxicity (Brossi, 1959). It was released in the market in injection form and as late-release oral tablets in, respectively, 1963 (Sardesai *et al.*) and 1965 (Sardesai and Patil). In our experience this drug gave a slower remission of the clinical symptoms, although it gave a high clinical cure (Rukmono and Naoemar, 1971).

The clinical demonstration of the anti-amoebic activity of metronidazole opened a new area in the treatment of amoebiasis. The drug had been widely used since 1959 for the treatment of trichomoniasis, but only after higher dosage regimens were used successful clinical trials in amoebic dysentery and amoebic liver abscess were reported (Powell *et al.*, 1966). Metronidazole was regarded as a single, direct-acting amoebicide with activity at all sites. In amoebic dysentery it caused rapid disappearance of the clinical symptoms and gave a high parasitological cure rate (Powell *et al.*, 1966; Tjay *et al.*, 1972). Because of the successful use of metronidazole many investigators were searching for other nitroimidazole derivatives for the treatment of amoebiasis.

This paper reports the results of a double blind clinical study of metronidazole against another nitroimidazole derivative: Ro7-0207.

The objectives of this study were to assess: The antiamoebic properties of Ro7-0207 as compared with that of metronidazole; the toxicity and side effects of the new compound.

MATERIALS AND METHODS

Twenty patients with amoebic dysentery were selected for this study. Those with anaemia or other diseases were excluded. All of them had diarrhoea with blood and mucus, and actively motile haematophagous *E. histolytica* in their stools. All were given ambulatory treatment with either Ro7-0207 or metronidazole according to a randomized numbering system.

The patients consisted of 13 adults and 7 children, ranging in age from 2-52 years.

The drugs that were given were in identical physical forms (light yellow capsules), kept in bottles and were numbered. Children received the drug for 7 consecutive days. Those between 2-6 years were given 125 mg daily, those between 7-12 years received 250 mg daily. Adults were given 1,500 mg daily

for 5 days. The patients were asked to take the drug thrice daily after meals and to take soft and bland food. Direct stool examinations using eosin and iodine smears were carried out before and daily during treatment, and thereafter once weekly for 4 consecutive weeks.

Complete blood examinations, SGPT, serum alkaline phosphatase, BUN, urinalysis and ECG analyses were done before and after the end of treatment to evaluate the toxicity of the drugs. During treatment all patients were aksed to come daily for clinical assessment and special attention was paid to any side effects such as abdominal discomfort, nausea, anorexia, or dizziness which might occur during treatment.

Blood pressure and pulse rate were recorded daily. The list stating which bottle contained Ro7-0207 or metronidazole was opened after the trial was finished.

RESULTS

The group treated with Ro7-0207 consisted of 10 patients, 3 children and 7 adults. Clinical and parasitological cure rates were 100%. Clinical symptoms and *E. histolytica* in stools disappeared on the second and third day of treatment in 8 cases, while in 2 cases clinical symptoms and *E. histolytica* in stools disappeared on the fourth and the fifth day of treatment.

Ten cases were treated with metronidazole, 4 children and 6 adults. A 100% cure rate, clinically and parasitologically was also observed in this group. Clinical improvement and disappearance of *E. histolytica* from the stools were observed on the second and the third day of treatment in 7 cases, while in 3 cases clinical improvement and disappearance of *E. histolytica* from the stools were observed on the fourth and the fifth day of treatment.

In the follow-up one month after the end of treatment, no relapses or positive findings of *E. histolytica* were recorded in either group. No abnormal ECG, urinary and haematological findings were observed after treatment with either Ro7-0207 or metronidazole.

In the group treated ith Ro7-0207, only 2 cases complained of dizziness on the second day of treatment; one had slight dizziness and the second had severe vertigo. These symptoms disappeared after reducing the dose to 250 mg four times daily and after taking a rest. In the group treated with metronidazole 3 cases complained of side effects. One had slight dizziness which disappeared after rest. The second developed nausea which persisted even after rest but the symptoms disappeared when dosage was reduced to 250 mg four times daily. The third case complained of nausea, dizziness, hypersalivation and anorexia. In this patient reduced dosage, rest and additional vitamins resulted in the disappearance of the symptoms.

DISCUSSION

In this study 12 patients had acute or subacute amoebic dysentery and 8 had a dysenteric relapse of chronic intestinal amoebiasis.

Treatment with metronidazole and Ro7-0207 gave similar results: a 100% cure rate, clinically and parasitologically. Of the 10 cases in the Ro7-0207 group, 8 showed a rapid clinical and parasitological response on the second and third day of treatment. In the metronidazole group 7 cases showed a rapid clinical and parasitological response. The dysentery subsided within 24-48 hours. In the follow-up period for one month, no signs of clinical or parasitological relapses were observed in either group.

Side effects were seen in a few cases in both groups, giving however, no reason to discontinue the treatment. Dizziness was found in 2 cases in the Ro7-0207 group and in one case in the metronidazole group. Nausea was found in one case in the metronidazole group. Also in this group one case had rather severe complaint of dizziness hypersalivation, nausea and anorexia. With rest and reduction in dosage, the symptoms disappeared.

When the efficacy and the side effects in the two groups were compared no significant differences were observed. Similar results were obtained in a study of 20 Indonesian children (Pudjiadi *et al.*, 1972).

A previous study conducted by the authors on oral dehydroemetine (1-1½ mg/kg body weight daily for ten days) showed a lower cure rate (Rukmono and Naoemar, 1971).

The material used in our present study is too small to make any decisive conclusions, However the results suggested, that Ro7 -0207 oral tablets are effective in the treatment of amoebic dysentery.

SUMMARY

Twenty patients with acute or subacute amoebic dysentery were given ambulant treatment with Ro7-0207, a nitroimidazole derivative or with metronidazole on a double blind schedule. The patients consisted of 13 adults and 7 children. Those with anaemia or other diseases were excluded.

The results of this study showed that Ro7-0207 was as effective as metronidazole. A 100% cure rate both clinically and parasitologically was observed in the two groups. The dysentery subsided within 24-48 hours; *E. histolytica* disappeared from the stools between the second and the fifth day of treatment and remained absent in the follow-up period.

It was suggested that Ro7-0207 oral tablets were effective in the treatment of amoebic dysentery.

ACKNOWLEDGEMENTS

The authors wish to express their thanks to Dr. P.A. Buhr, Roche Far East Research Foundation for the supply of the drugs and support in this study.

REFERENCES

BROSSI, A., (1959). Syntheseversuche in der emetin-reihe. 4 mitteilung: Racemisches 2-dehydroemetine. *Helv. Chim. Acta, 42*: 772. (quoted by Roche clinical data sheet, dehydroemetine late-release tablets, Rol-9334/20).

ELSDON-DEW, R., ARMSTRONG, T.G. and WILMOT, A.J., (1952). Antibiotics and amoebic dysentery. *Lancet, 2*: 104.

HOEKENGA, M.T. and MAXIMO, Q.G., (1950). Trial of enteric-coated camoquine in intestinal amoebiasis. *Amer. J. Trop. Med., 30*: 625.

POWELL, S.J., MACLEOD, I., WILMOT, A.J. and ELSDON-DEW, R., (1966). Metronidazole in amoebic dysentery and amoebic liver abscess. *Lancet, 2*: 1329.

PUDJIADI, S.H., SUNOTO, SUHARJONO and KADRI, N., (1972). A new oral amoebicid (Ro7-0207) in the treatment of intestinal amoebiasis. *Asian J. Med., 8*: 528.

ROGERS, L., (1912). Quoted by Goodman and Gilman: The Pharmacological Basis of Therapeutics. 2nd. ed. The MacMillan Company, 1958, New York.

RUKMONO, B. and NAOEMAR, S.A., (1971). Oral dehydroemetine treatment in amoebic dysentery. *Proceedings Tenth SEAMEO-TROPMED Seminar on Chemotherapy in Tropical Medicine of Southeast Asia and Far East.* Bangkok 26-30 October 1971. Ed. T. Harinasuta, p. 149.

SARDESAI, H.V. and PATIL, S.R., (1965). Clinical trials of oral dehydroemetine (Rol-9334/9) in acute amoebiasis. *The Antiseptic, 62*: 1.

SARDESAI, H.V., SULE, C.R. and GAVANKAR, S.S., (1963). Clinical trials with dehydroemetine in acute amoebiasis. *Indian J. Med. Sci., 17*: 334.

TJAY, J.K., RAID, N. and SUTANTO, A.H., (9172). Flagyl (metronidazole) in the treatment of intestinal amoebiasis (Part three). *Paediat. Indon., 2*: 82.