ORIGINAL CONTRIBUTIONS

EFFECT OF PROTHIONAMIDE ON THE INFECTIVITY OF LEPROMATOUS LEPROSY

A Girdhar, B K Girdhar, Sreevatsa, G Ramu, R K Lavania and K V Desikan

To study the effect of prothionamide on the infectivity of untreated lepromatous patients, 20 cases were randomly given either 250 mg or 500 mg prothionamide monotherapy daily for 2 months. All patients tolerated the drug well. Clinical improvement with healing of mucosal ulcers was seen in 13 of the 16 cases. Nasal smears became negative in all the cases within 2 months. Mouse foot-pad inoculation done from biopsy specimens/skin scrape suspensions became non-infective to mice in all the cases within the trial period. There was a substantial reduction in the MI, and histopathology showed complete fragmentation of the bacilli with a significant increase in the lymphocyte content. The findings suggest a rapid bactericidal effect and a similar usefulness of both the doses of the drug for the treatment of multibacillary leprosy.

Key words : Leprosy, Prothionamide, Treatment.

Thiomides, ethionamide and prothionamides, have been shown to have a potent bactericidal effect against *M. leprae* in the mouse footpad.[1] Earlier, several workers had used the drug in lepromatous patients and shown good clinical effect.[2-4] However no work seems to have been undertaken to study the effect of either of the drugs on the infectivity of lepromatous patients. The present investigation was undertaken to compare the effect of 2 dosage schedules of prothionamide on the infectivity of untreated lepromatous leprosy patients.

Material and Methods

Twenty, fresh, active lepromatous cases were admitted to the hospital for the study. After the investigations such as haemogram, urine, sputum, LFT and blood urea had been found to be normal, the cases were randomly allocated to one of the two regimens, (a) 250 mg prothionamide daily for 2 months, (b) 500 mg prothionamide daily for 2 months. During this period the drugs were given under direct supervision. At the end of 2 months, all the patients were put on multi-drug therapy giving rifampicin, clofazimine and DDS.

In each case, initially and at the end of 1,2, 4 and 8 weeks, clinical assessment and smears for BI and MI were done. Skin scraps/biopsies for mouse foot-pad inoculation were taken at the above time intervals. Biopsy for histopathology was taken initially and at the end of 8 weeks. Particular care was taken to look for occurrence of any adverse effects. For this, haemogram, urine, LFT and blood urea were repeated every 2 weeks to detect any functional abnormality.

Results

Ten patients received 250 mg prothionamide daily and the rest were given 500 mg prothionamide per day. Four of the 20 cases (3 belonging to 250 mg group and 1 to 500 mg group) could not stay in the hospital continuously for the stipulated 2 months. These 4 cases have not been included in the analysis as for some time their drug intake could not be supervised.

From the Central Jalma Institute for Leprosy, Tajganj, Agra-282001, India.

Address correspondence to : Dr. B. K. Girdhar.

The clinical response in the two treatment groups (table I), was similar. In both the groups a fairly uniform regression of infiltration was observed. An almost equal number of patients showed healing of mucosal ulcers in the observation period of 2 months. The fall in BI was also practically the same in the two groups (table II). In contrast, the fall in MI was slightly slower in the 500 mg group (statistically not significant). There was a gradual decrease in the positivity of nasal smears in both the groups with all the patients becoming nasal smear negative in 4 to 8 weeks. Nasal smear negativity was achieved a little earlier in the 500 mg group vis-a-vis those given 250 mg prothionamide.

Two patients in each of the groups showed BL/LL picture, while all the others were histo-

Table I. Comparison of the clinical responses to the two dosage schedules of prothionamide.

Weeks after treatment	Mean clinical score with prothionamide		Nasal/oral ulcer positivity with prothionamide	
	250 mg	500 mg	250 mg	500 mg
0	11.55	11.94	7/7	8/9
1	8.92	11.66	7/7	7/9
2	9.4	10.4	3/7	4/9
4	8.0	8.92	4/7	3/9
8	7.72	8.1	2/7	1/9

Table II. Comparison of the bacteriological improvement with the two dosage schedules of prothionamide.

Weeks after treatment	Mean BI in skin smear after prothionamide		Mean MI in Skin smear after prothionamide		Nasal smear positivity after prothionamide	
	250 mg	500 mg	250 mg	500 mg	250 mg	500 mg
0	5.2	5.7	1.7	1.52	7/7	7/9
1	5.0	5.2	1.4	1.28	6/7	5/9
2	4.7	5.8	0.7	1.3	6/7	3/9
4	4.57	4.8	0.3	1.0	1/7	0/9
8	4.35	4.5	0.1	0.5	0/7	0/9

pathologically lepromatous (LL). At the end of eight weeks, in all cases irrespective of the dose of prothionamide, a significant increase in the lymphocyte content was found. There was no difference in the other constituents of the granuloma or granuloma fraction. Most significant observation was the complete lack of solid bacilli at the end of 2 months, in contrast to several solid staining bacilli seen in the initial biopsy specimens. In the latter biopsies, on the whole the bacilli were not as brightly and deeply stained as in the initial specimens.

The mouse foot-pad test for the loss of viability of *M. leprae* showed (table III) that in 2 cases from the 250 mg group, there was no multiplication of *M. leprae* in the mouse foot-pad from the beginning. Sequential inoculation of

Table III. Loss of viability of M. leprae with the two schedules of prothionamide treatment.

Weeks after treatment	The number of positive takes/total number of inoculation following prothionamide	
	250 mg	500 mg
0	5/7	8/9
1	4/7	6/9
2	4/7	4/9
4	1/7	2/9
8	0/7	0/9

M. leprae obtained from the patients by skin scrape method or biopsy, showed almost a similar rate of kill of the organisms in both the groups. All the patients in both the groups

appeared to have been rendered non-infectious to the mice by the end of 8 weeks.

Comments

Ethionamide and its analogue prothionamide have been shown to have similar anti *M. leprae* efficacy in the mouse foot-pad.[1] We selected prothionamide as it causes less gastric side effects and is thus better tolerated.[5] Using proportional bactericidal test, the MIC of prothionamide for *M. leprae* has been found to be 0.05 μg ml.[1] Further in the above study, the authors have shown a significant anti *M. leprae* effect when prothionamide was fed to mice at a dietary concentration of 0.1%. This dietary concentration was found to give serum levels of 0.5 μg/ml; a level only about 10 times higher than the MIC. In contrast, a dose of 500 mg prothionamide in man gives rise to a peak serum concentration of around 3.0 μg/ml. i.e. higher by 60 fold.[6] Therefore, it seemed reasonable to expect that a smaller dose of 250 mg prothionamide per day, would also be effective. The two doses of prothionamide taken for this investigation, were based on this.

The study has shown that both the doses give comparable clinical response. The regression of infiltration and healing of nasal ulcers occurred at the same pace. As expected, no significant change in the BI was noticed in either group in the two-month observation period. The MI on the other hand, showed a gradual fall in both the dosage groups. Nasal smear negativity was achieved in almost the same time. It was interesting to find that in all the cases, irrespective of prothionamide dosage, there was a significant increase in lymphocytes in the skin biopsy specimens taken at the end of 2 months. The entire bacillary population had become fragmented and still further, the bacilli took up less stain i.e. the post-treatment bacilli were not brightly stained with carbol fuchsin. This indicates that the organisms had been rendered non-viable and also the lipid coat of the organisms has been affected by the drug.

Mouse foot-pad inoculation results have shown complete kill of organisms in all the patients within 8 weeks of the start of treatment in both the groups, suggesting a potent bactericidal effect of prothionamide on *M. leprae*, indicating that the patients were rendered non-infectious within a matter of 8 weeks. Similar complete kill of *M. leprae* was obtained in mice with 8 weeks of administration of the drug.[1]

The good clinical response observed in the present study is in line with the observations of other workers who used ethionamide instead of prothionamide.[2-4] All these authors studied the clinical improvement only. Revankar et al[7] too found good clinical and bacteriological (BI and MI) improvement in 8 cases (6 LL and 2 BL) treated for 2 months with prothionamide.

Prothionamide has generally been considered to be a toxic drug.[8-12] Gastric intolerance and hepatotoxicity have been frequently observed in some countries. Deaths due to hepatotoxicity have also been reported.[13] In the present investigation, no such side effects were encountered. All the patients tolerated the drug well. Biweekly laboratory investigations did not reveal any biochemical and / or functional abnormality. These findings are in direct contrast to the above reports. In all the above studies, prothionamide had not been used alone but was one of the constituents of multi-drug regimens given for tuberculosis or leprosy. Therefore, it is possible that the liver damage was on account of the likely synergistic hepatotoxic effect of drugs. In our earlier study[14] using combinations involving rifampicin, prothionamide, INH and DDS, no case of liver damage was encountered, though one patient had persistent vomiting. Therefore, it appears that liver damage due to prothionamide may have something to do with other factors like diet, alcoholism, ethnic origin of the patients etc.

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