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A DOUBLEBLIND CONTROLLED CLINICAL TRIAL TO ASSESS THE ROLE OF ANTI-HISTAMINES IN THE TREATMENT OF MULTI-BACILLARY LEPROSY

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ABSTRACT : *A double blind controlled clinical trial to assess the role of anti-histamines as a supplement in the treatment of leprosy was conducted in multi-bacillary cases of leprosy. In all, 120 patients with lepromatous or borderline leprosy were randomly allocated to a regimen of clofazimine and dapsone for* 12 *months with or without a supplement of pheniramine maleate for the first 3 months. During the 12-month period, 92% of the patients who received the supplement and 86% of the patients who had not received it had moderate or marked clinical improvement. The BI values decreased from* 4.1 *to* 3.4 *and* 4.2 *to* 3.3, *respectively. The results over the 12-month period showed that the addition of the antihistamine had not enhanced the efficacy of the regimen as evidenced by clinical and bacteriological findings.*

INTRODUCTION

Lepromatous leprosy represents the florid form of leprosy with a well-defined immunological defect which appears to lie either in the macrophages or in the T-lymphocytes. Increased levels of immunoglobulins, including IgE, are found in lepromatous patients (Jopling, 1984). It is known that IgE releases histamine from mast cells and basophils on contact with an antigen.

On the basis of experimental work *in vitro,* Veeraraghavan (1985) suggested that release of histamine at the sites of immediate hypersensiti-

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vity reaction could possibly generate histamine-induced suppressor activity by lymphocytes, which may play a regulatory role in the subsequent development of cellular immune response. Furthermore, it has been suggested by Veeraraghavan (1983) that histamine and heparin are growth-stimulants for *M. leprae* and that histamine H-1 and H-2 receptor antagonists have a marked inhibitory effect on the growth of the organisms *in vitro.*

It was reported that anti-histamines, particularly pheniramine maleate, produced marked clinical and bacteriological improvement in lepromatous leprosy patients (Gangadhara Sharma, 1982). Therefore, a controlled clinical trial was conducted to evaluate the potential beneficial effect of pheniramine maleate in the treatment of lepromatous or borderline lepromatous leprosy patients. The results up to 12 months are reported here.

Aims and Objectives : To assess the effect of a supplement of pheniramine maleate (anti-histamine) on the therapeutic efficacy of a regimen of clofazimine and dapsone in the treatment of multibacillary leprosy.

MATERIALS AND METHODS

The study was conducted concurrently at two places, namely the Leprosy Unit of the Tuberculosis Research Centre at the Govt. Royapettah Hospital, Madras, and the Rural Field Operational Area of the Central Leprosy Teaching and Research Institute, Thirumani, Chengalpattu, comprising 54 villages in Sriperumbudur Taluk of Chengalpattu District, Tamil Nadu.

Eligibility Criteria : Multibacillary leprosy patients aged 15 years and above, who were classified clinically and histopathologically as BL or LL type with a bacteriological index of 2.5 or more on Ridley's scale (1964) were included in the trial. Pregnant women and those suffering from diseases such as tuberculosis, severe protein energy malnutrition, diabetes or hypertension and those with hepatic damage were not included in the trial.

Chemotherapeutic regimens : The patients were allocated at random to receive one of the following two regimens:

AHCD : Clofazimine (C) and Diamino-diphenyl-sulphone (D) daily for 12 months, with the addition of pheniramine maleate (AH) daily for the first 3 months.

CD : Clofazimine and Diamino-diphenyl-sulphone daily for 12 months, with the addition of a calcium lactate tablet daily for the first 3 months.

The study was conducted double-blind to avoid any possibility of bias. Thus neither the doctors, clinic staff and para-medical workers nor the patients knew whether an individual patient was receiving the anti-histamine or the calcium lactate tablet. Each day's drugs for the first 3 months for each patient were pre-packed at the Tuberculosis Research Centre, Madras.

Clofazimine and DDS were given in a dose of 100 mg daily, anti-histamine 50 mg daily and a matching tablet of calcium lactate.

All the drugs were given daily in a single dose. The drugs were administered under supervision during the first 3 months. During 4-12 months, patients being treated at the Govt. Royapettah Hospital attended twice a week, received that day's drugs under supervision, and collected drugs for the rest of the days for self-administration. For patients in the villages, a paramedical worker visited the house of each patient daily in the first 3 months to administer the drugs under supervision, and weekly during the following 9 months to supply drugs for self-administration.

Allocation of treatment regimens : The patients were randomly allocated to the above two treatment regimens at the Tuberculosis Research Centre, Madras, after stratification according to the history of previous anti-leprosy chemotherapy as (a) less than one year, (b) 1 to 5 years, and (c) more than 5 years.

Assessments and examinations

(a) *On admission :* All the patients underwent (i) a general medical checkup to exclude other health problems, (ii) clinical assessment of leprosy, (iii) examination of skin smears from six active sites for lepra bacilli to determine the bacteriological index (BI) and morphological index (MI), (iv) estimation of haemoglobin and total and differential white blood cells counts, (v) urine tests for albumin and sugar, (vi) Mitsuda lepromin test, (vii) skin biopsy for histopathological examination, and (viii) colour transparencies of lesions.

In addition, a clinical examination for leprosy was undertaken on admission by an independent assessor, who was unaware of the treatment regimen and the bacteriological findings.

(b) *During treatment :* The clinical, bacteriological, blood and urine examinations were undertaken every three months. All the patients were clinically examined by the independent assessor and clinical photographs were taken at 3, 6 and 12 months.

RESULTS

Study population : In all, 120 patients were admitted to the trial. Of these, 17 patients were excluded; 2 patients died of causes unrelated to leprosy (one with burns and the other of cardio-pulmonary failure) and 15 patients (7 AHCD, 8 CD) became unto-operative and discharged themselves against medical advice (10 patients stopped attending during the first 3 months, 3 during 4-6 months and 2 in 9-12 months). Thus there remained 103 patients (52 AHCD, 51 CD) for analysis.

Of the 103 patients, 89 were males; 38 patients were under 30 years of age, 29 were aged 30-39 years, and the reamining 36 were aged 40 years or more. The mean age was 34 years (range 15-65 years) and the mean weight 44.5 kg (range 29.2-83.3 kg). All the 103 patients gave a history of previous dapsone monotherapy for periods of less than one year (40), 1 to 5 years (29), and more than 5 years (34).

In all, 88 patients had histopathology findings; 62 (32 AHCD, 30 CD) (70 %) were classified as lepromatous, 13 (4 AHCD, 9 CD) (15 %) as borderline lepromatous and 13 (7 AHCD, 6 CD) (15 %) as indeterminate.

Drug regularity : A total of 27 (52%) patients in the AHCD regimen and 23 (45%) patients in the CD regimen did not miss a single dose during the first 3 months; the remaining 25 (48%) patients in the AHCD and 28 (55%) patients in the CD regimen received 80-99% of the scheduled chemotherapy. Over the period of 12 months, 13 (25%) patients in the AHCD and 12 (24%) patients in CD regimen did not miss a single dose 38 (73%) patients in the AHCD and 38 (75%) patients in the CD regimen received 80-99% and 1 patient in each regimen had less than 80% (78% and 77%) of their scheduled chemotherapy. Thus the regularity in the 2 regimens was similar.

Clinical progress : The independent assessor classified as having moderate or marked clinical improvement 36 (69%) AHCD and 33 (65%) CD patients at 3 months, 81% and 88% at 6 months, and 92% and 86% at 12 months, respectively. Thus the clinical improvement was similar in the 2 regimens.

Bacterial indices : The mean BI was high and similar at the time of admission, viz., 4.1 for AHCD and 4.2 for CD patients. There was a steady fall in the BI values, the fall being 0.2 by 3 months, 0.3 by 6 months and 0.7 by 12 months for the AHCD regimen; the corresponding figures for the CD regimen were 0.2, 0.4 and 0.9. Thus the reduction was similar in the 2 regimens.

Morphological indices : The morphological indices (Ml) were determined for 54 patients; a high proportion of the patients had low MI.

ENL reactions during treatment : Of the 103 patients, 42 (19 AHCD, 23 CD) had ENL reactions. The incidence of reactions was similar in the two regimens. The reactions were controlled with chloroquine, anti-histamines, analgesics, prednisolone and/or thalidomide, the chemotherapy being continued.

DISCUSSION

The study presented in this report was conducted to elucidate the role of anti-histamines in the treatment of bacilliferous lepromatous leprosy cases, having been designed to avoid bias at any stage. Gangadhara Sharma (1982) had reported marked clinical and bacteriological improvement on concurrent administration of pheniramine maleate with anti-leprotic drugs in lepromatous leprosy patients. However, there were no controls who had not received the anti-histamine supplement. The findings of the present study do not confirm the findings of the above study.

Several workers have investigated the role of histamine and anti-histamines in mycobacterial infection. Increased levels of histamine and histaminases in tuberculosis and lepromatous leprosy cases were reported by Rai *et al.* (1977). Kato (1957) reported immunosuppression with anti-histamines in guinea-pigs infected with *M. lepraemurium.* However, the findings were not corroborated by Kirchheimer (1964). Veeraraghavan (1983) had reported growth-promoting effect with the addition of histamine to culture media used for *in vitro* cultivation of *M. leprae* which was not substantiated by Prabhakar *et al.* (1983) and Katoch and Desikan (1983). Furthermore, though histamine could induce suppressor T-cells *in vitro* as observed by Nanda and Nath (1982), it probably does not alter the delayed type of hypersensitivity response to *M. leprae* (Guimaraes, 1961). Converse *et al.* (1987) have recently reported that administration of Cimetidine abolished the suppressive effect of mediators released by mononuclear cells from lepromatous leprosy patients. However, the therapeutic implication of this observation needs to be established. Thus it may be seen that several observations regarding the possible beneficial effect with anti-histamines in the treatment of leprosy have been reported which were not substantiated subsequently by other workers, and many hypotheses purported need to be confirmed by conducting meticulously designed studies.

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