Combined Chemotherapy of Multibacillary Leprosy Patients

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Abstract

380 multibacillary leprosy patients were treated with combined chemotherapy at Anandaban leprosy hospital in Nepal. The drugs used were Rifampicin, Dapsone, Clofazamine and Isoniazid. This treatment is modelled on the short course chemotherapy of tuberculosis. A remarkable clinical and bacteriological improvement was observed in all patients. Group A patients were bacteriologically negative after 24-32 months of treatment and Group B patients were skin smear positive even after 36 months of treatment. However, patients in Group C, who received five drugs, showed marked clinical and bacteriological improvement. Discoloration caused by Clofazamine did not lead to interruption of treatment. We found the drug regimens safe, effective and economical.

Introduction

The widespread emergence of dapsone resistance⁽¹⁾ has emphasised the necessity of using combinations of at least three antileprosy drugs for the treatment of lepromatous leprosy. Of the drugs available for use in combination with dapsone, rifampicin with its rapid bactericidal activity is the first choice⁽²⁾. Clofazamine is less costly than rifampicin, and its antileprosy activity is of the same order as that of dapsone⁽³⁾. Thioamides are another group of drugs with antileprosy activity⁽⁴⁾. It has been suggested⁽⁵⁾ that combination of drugs for a short period in the field conditions will be the best approach for leprosy control and for the interruption of the transmission of *M. leprae* in the community. Since 1981 combined drug regimens have been used in treating leprosy patients under our care at Anandaban leprosy hospital in Nepal⁽⁶⁾. This paper focuses mainly on the 380 multibacillary leprosy patients treatment with combined therapy, their follow up evaluated clinically and bacteriologically.

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Materials and Methods

For each patient under treatment, a case history was taken and clinical and bacteriological examinations were performed and recorded on standard clinical multidrug treatment⁽⁷⁾ files. Patients were classified on the Ridley-Jopling scale⁽⁸⁾: in a majority a lepromin test was performed and a skin biopsy was taken to confirm the diagnosis. The 380 patients were distributed as shown in Table 1.

Laboratory investigations:

1. Skin smears were taken by the slit and scrape method from both ear lobes and from two other sites for bacteriological and morphological indices⁽⁹⁾. These were performed on the day of the initial clinical examinations and at six months intervals.

2. Skin biopsies were taken from the active lesions prior to therapy and at intervals of six months during the treatment period. These were processed in the routine manner for histopathology⁽¹⁰⁾.

3. Lepromin A (Armadillo derived) 0.1ml of 2×10^6 cobalt irradiated bacilli per ml, was injected intradermally into the upper outer aspect of right arm. Reading was in mm of induration and was performed at 21 or 28 days. Two mm or less in diameter of induration was considered to be a negative reaction.

4. Mouse foot pad tests were performed in locally bred Swiss Albino and nude mice⁽¹⁵⁾. They were inoculated in both hind foot pads with *M. leprae* isolated from skin biopsies of several patients for drug sensitivity studies. Preparation of the inoculum, inoculation of mice and harvesting of *M. leprae* from the footpad tissues were accomplished by the method of Rees⁽¹¹⁾.

Table 1 Distribution of patients the drug regimen

Group	Number	Treatment
A Old patients with history of past, partial treatment.	82(22%)	1. Dapsone-100 mg daily 2. Clofazimine-100 mg daily 3. Rifampicin 600 on two successive days each month.
B New patients	245(64%)	" " "
C New patients	26(7%)	1. Isoprodian-2 tablets (Each tablet consisted Dapsone 50 mg, Prothionamide 175mg, Isoniazid 175 mg). 2. Clofazimine 100 mg daily 3. Rifampicin 600 mg on two successive days each month.
D Absconders	27(7%)	1. Dapsone-100 mg daily 2. Clofazimine-100 mg daily 3. Rifampicin 600 mg on two successive days each month.

Results

The distribution of patients according to sex and classification of disease is shown in Table 2. All patients were skin tested with lepromin and the test was negative in all the study subjects. The analysis of the histopathological changes will be reported in another communication.

Clinical and bacteriological evaluation

A marked clinical improvement was observed in all patients. The nasal congestion and the swelling of the feet and hands was remarkably diminished. The changes in the leprous lesions were characteristic: a flattening of the lesions was observed and the initial erythema and oedema which accompanied the lesions was noticeably absent.

The results of the morphological indices (MI) before initiation of therapy and at the time of evaluation is shown in Table 3. In group A patients who had previous therapy

the administration of combined therapy resulted by six months for morphological indices to be negative. In groups B and C by eight months the morphological indices were negative.

The bacteriological changes observed and the months of treatment are shown in Table 4. In group A, 32 (39%) patients initial BI was 2.8 and after 24 months of treatment it was negative. Similarly 50 patients (61%) with initial BI of 3.2 were negative after 32 months of treatment. This suggests that multibacillary patients who had previous treatment with monotherapy will do well with a course of combined chemotherapy for the elimination of bacilli from the skin.

In group B all 11 mid-borderline patients with BI negative after 22 months of combined therapy.

Three patients developed mild ulnar neuritis after 15 months of therapy. They were hospitalised and treated with steroids. The bacteriological changes observed in BL and LL patients is noteworthy. Among BL patients, 88 (62%) after 36 months of therapy were BI 1+; 48 (34%) after 40 months of chemotherapy the bacteriological indices dropped to 2+; and 5 (4%) patients remained BI 3+ even after 42 months of therapy. The BI changes seen in LL patients is as follows: in 26 patients (28%) the BI was 2+ after 42 months of therapy; in 6 patients (6%) the BI was 1+ after 36 months of treatment; and in 37 (40%) there were high bacterial counts in the skin of the patients even after treatment for 36 months. In 24 (26%) LL patients the BI was 4+. This suggests that chemotherapy alone may perhaps be inadequate

Table 2 Distribution of subjects according to type of leprosy and sex

Sex	BB	BL	LL	Total
Male	10	144	143	297(78%)
Female	1	36	46	83(22%)
Total	11(3 %)	180(47%)	189(50%)	380(100%)

Table 3 The results of average morphological indices (M. I) before and during therapy

Group		M.I.
A	Pretreatment	3.5
	After 6/12	Negative
B	Pretreatment	4.2
	After 6/12	0.82
	After 8/12	Negative
C	Pretreatment	5.2
	After 1/12	0.65
	After 8/12	Negative

Table 4 Showing the months of combined chemotherapy and the bacteriological status at the time of evaluation

Group and type	No. of patients	Pretreatment BI (average)	At the time of evaluation.		
			Number of months of combined therapy		Bacteriological Index (BI) (average)
A BL	32(39%)	2.8		24	0
LL	50(61%)	3.2		32	0
B BB	11	2.6	Pts %	22	0
BL	141	4.7	88(62%)	36	1+
			48(34%)	40	2+
			5(4%)	42	3+
LL	93	5.3	6(6%)	36	1+
			26(28%)	42	2+
			37(40%)	36	3+
			24(26%)	24	4+
C LL	26	4.3		26	1.6
D BL	7	3.6		3	
LL	20	3.8		7	Not recorded

in multibacillary leprosy to eliminate dead bacilli from the skin of these patients.

The bacteriological changes observed in group C patients were remarkable. These patients were treated with five anti-leprosy drugs. After 26 months of therapy the BI had dropped from a BI of 4.3 to 1.6.

The multibacillary patients in group D were irregular on treatment. All the 20 patients tested on the mouse footpad showed dapsone resistance i. e. 12 were primary and 8 were secondary. All efforts to follow up these patients failed.

Adverse effects

Clofazimine was tolerated by all patients in the study. It induced pigmentation in all patients. The pigmentation was variable between light grey initially to pronounced blackish pigmentation. Two patients of group B were diagnosed clinically to have infective hepatitis. In group C five patients complained of gastritis and two suffered hepatitis. No other side effects attributable to the drugs were observed.

Discussion

There have been several major landmarks in the chemotherapy of leprosy. The first was the introduction of dapsone and its anticipated impact on leprosy control. The second was the discovery of clofazimine⁽¹²⁾ and its use in leprosy treatment. The third was the introduction of the powerful bactericidal drug rifampicin. The fourth was the use of yet another group of antibacterial drugs, the thioamide group and the fifth was the introduction of supervised, intermittent, short duration chemotherapy with combinations of the above drugs. We consider this combined therapy beyond doubt the latest landmark⁽⁵⁾ which is modelled on the short course chemotherapy for tuberculosis⁽¹³⁾.

Chemotherapy of leprosy has two purposes: first, the treatment of individual patient and, secondly, the control of leprosy in the community by interrupting the transmission of *M. leprae*. Most of the leprosy patients in Nepal have been treated with dapsone monotherapy⁽¹⁴⁾. Due to the lack of basic health infra-structures, the treatment with dapsone has not been successful. Both primary and secondary dapsone resistance has been detected by using the mouse footpad tests^(15,16). Previous reports have shown that the combined chemotherapy is acceptable by patients and lead to increase in patient compliance⁽¹⁷⁾. It is also anticipated that with combined chemotherapy there will be a higher proportion of cure among the multibacillary patients and that the risk of relapse will be reduced.

This paper has shown that 380 multibacillary leprosy patients have been successfully treated with the combination of drugs in Nepal and the clinical and bacteriological results observed are remarkable. The present results have shown that within 24 to 32 months of administration of combined therapy, group A patients obtained negative results in the skin smears. The 11 mid-borderline patients achieved negativity in 22 months of treatment. These patients are probably the most unstable from the immunological point of view. The bacteriological observations of patients in group B is that, 36 months of treatment, the skin smears recorded are 1+. To achieve skin smear negativity in multibacillary patients, it will probably require treatment for up to five years (or more). It is known that, due to the defective immune mechanisms among these patients, the bacilli tend to persist and may contribute to clinical relapse even after cessation of combined treatment. However, the likelihood of relapses occurring in patients who have successfully completed combined therapy is less than those who were given this treatment.

Patients in group C who received five anti-leprosy drugs showed a more remarkable clinical and bacteriological improvement than patients in group B. We are aware that the number of patients in this group is small but the results observed are promising. A "stronger" regimen might cure a greater proportion of the patients. Contrary to expectations, the incidence and severity of adverse reactions was not significant^(18,19). Perpetua *et al.*⁽²⁰⁾ suggested only a small proportion of leprosy patients would take combined chemotherapy for more than six months due to either the high cost of treatment or because of the discolouration caused by clofazimine. Twenty-two patients complained that they were recognised by others in the community as leprosy patients because of pigmentation. When information with respect to regression of the dark pigmentation was given, they proceeded to complete the treatment. Discolouration caused by clofazimine did not therefore lead to interruption of the treatment. We found the regimens adopted in this report very effective, safe and fairly economical for the treatment of multibacillary patients. We emphasize the importance of supervision of rifampicin to avert the serious epidemiological problem of rifampicin resistance in leprosy patients^(21,22,23). The prospect that we visualize is that at the end of five years or so it may perhaps be possible to remove multibacillary leprosy patients from control with advice to present again for diagnosis and treatment if new lesions occur. Despite the unremitting effects of the governments and non-governmental organizations, the incidence of leprosy has not been decreasing and it is

still a major public health problem in endemic countries⁽²⁴⁾.

In summary, although evidence is lacking, these regimens appear likely to be capable of curing a proportion of multibacillary patients but in a small core of patients they are only partially effective. To achieve cure in all, if not in a large proportion, of multibacillary patients effective immunotherapeutic agents may have to be combined with stronger chemotherapy regimens to restore the patients to normality.

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多菌らい患者の多剤併用療法

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キーワード：併用化学療法，薬剤耐性，再発，形態及び菌指数

ネパールのアナンダバンらい病院において、380名の多菌らい患者の多剤併用療法が行われた。併用療法に用いられた薬剤はリファンピシン、DDS、クロファジミン (B663) およびイソプロディアン (INH, プロチオナミド, DDS の合剤) である。この治療は結核の短期化学療法をモデルとしている。

全症例において臨床的にも細菌学的にも顕著な改善が見られた。A群患者は24～32カ月後にらい菌陰性となっ

た。一方、B群では36カ月治療後においても、なお皮膚塗抹標本で菌陽性であった。しかしながら、5薬剤を投与したC群患者は明らかな臨床的、細菌学的改善が示された。クロファジミンによる変色で治療を中断した例はなかった。

我々の薬剤投与法は安全であり、有効で、さらに経済的であることが確められた。