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Multicentre Controlled Comparative Trial of Clofazimine and Dapsone in Low Dosages

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A multicentric, controlled double-blind trial was undertaken to compare the efficacy of low-dosage therapy with dapsone and clofazimine in lepromatous leprosy. The results, which were evaluated centrally allow the conclusion that lowering of the dosage, either of dapsone or of clofazimine, is not followed by a proportional loss of antibacterial activity. The incidence of lepra reactions, especially ENL, in the clofazimine group was significantly lower and skin discolouration no worse than in the dapsone group. The use of clofazimine in low doses would appear to serve a useful purpose and is recommended for periods of up to one year.

Introduction

The therapeutic activity of clofazimine in human lepromatous leprosy, which was first reported by Browne and Hogerzeil in 1962, has been assessed in a large number of clinical investigations. By the end of 1974, about 250 papers on this subject, dealing altogether with more than 2000 patients, had been published.

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The administration of clofazimine in daily doses of 300 mg was found to produce discolouration of the skin. This proved less troublesome at a dose of 100 mg twice weekly, and the results obtained in a few patients were otherwise comparable to those achieved in the initial phases of treatment with other anti-leprosy drugs (Waters, 1968). It remained to be seen whether this low dosage level would still exert an anti-inflammatory action, as had been suggested by Browne (1965) and others (Karat *et al.*, 1970; Tolentino *et al.*, 1971).

With dapsone, attempts to lower the dosage were originally prompted by the hope that this would decrease the incidence of erythema nodosum leprosum (E.N.L.). Short-term observations indicated that a dosage of 50 mg of dapsone twice weekly elicited a satisfactory antibacterial effect (Pettit and Rees, 1967; Pearson and Pettit, 1969).

Accordingly, it was decided to compare the results of low-dose therapy with dapsone and clofazimine as regards both antibacterial activity and the incidence of reactions. In view of the well-known difficulties in finding a sufficient number of suitable patients in any single institution, a double-blind trial was planned on a multicentric basis. The protocol for this trial was ready in 1968, but the drawbacks inherent in the multicentre method delayed its completion until the end of 1973.

Methods

The following investigators co-operated in the multicentric double-blind clinical trial:

Dr P. N. Behl and Dr Bhatia, Delhi (India)
Dr D. S. Chaudhury, Elmina (Ghana) and Liteta (Zambia)
Dr T. F. Davey and Dr A. Butt, Dichpalli (India)
Dr Z. A. Fazelbhoy and Dr Daud, Karachi (Pakistan)
Dr M. Flowers and Dr B. L. Whitty, Chandraghona (Bangladesh)
Dr M. Harahap, Medan (Indonesia)
Dr M. Hermes, Mwena-Ndanda (Tanzania)
Dr B. Pérez P., Trillo (Spain)
Dr Rajagopalan, Johore Bahru (Malaysia)
Dr C. Reyes C., Mérida (Mexico)
Dr K. Robson, Mount Hagen (Papua, New Guinea)
Dr E. Rodríguez C., Asunción (Paraguay)
Dr R. B. W. Smith, Honiara (Solomon Islands)
Dr T. Smith, Chiang Mai (Thailand)
Dr R. Thakolkaran, Kozhukully (India)
Dr. A. G. Warren, Hay Ling Chau (Hong Kong)

AIMS OF THE STUDY

The main purpose was to compare the antibacterial effects of low dosages of dapsone (50 mg) and clofazimine (100 mg), both administered twice weekly, for a period of 48 weeks. The incidence and severity of any lepra reactions or skin pigmentation occurring in either of the two treatment groups were to be noted.

CRITERIA FOR ADMISSION AND EVALUATION

The conditions of acceptance were that the patients should be male, over 12 years of age and suffering from active, purely lepromatous leprosy. They were also to be untreated cases or at least they were not supposed to have received any antileprosy treatment for the last 5 years. Patients suffering from other severe diseases in addition to leprosy in particular from tuberculosis or diseases requiring corticosteroid therapy, were excluded.

From the histological point of view, cases classified according to Ridley and Jopling (1962, 1970) as LL, including the sub-group LI (Ridley and Waters, 1969), were considered acceptable. All other classifications were excluded.

The histopathological index (HI), formerly known as LIB (Ridley, 1967; Ridley and Hilson, 1967) was determined, using the granuloma index (GI) as a factor, i.e. the fraction of the dermis accupied by granuloma in tenths. No cases showing a GI of less than 0.15 were considered for evaluation.

The bacteriological diagnosis was made on the basis of the bacterial index (BI) according to Ridley (1968), using a logarithmic scale from 0 to 6, and the morphological index (MI), indicating the percentage of evenly and deeply staining *Myco. leprae* in skin scrapings (Waters and Rees, 1962). No cases with a MI of less than 5, or a BI of less than 1.5 were included in the evaluation.

PROCEDURES

The 16 investigators listed above selected the patients according to a pre-established protocol. It was left to the investigator's discretion to withdraw a particular patient from the trial, if need be.

Clinical and bacteriological assessments were repeated at 6-weekly intervals throughout the period of treatment, and biopsies at 6-monthly intervals. The material for biopsies and smears was always taken from the same lesions. Biopsies were sent to London (D.S.R.), skin smears to Kuala Lumpur (J.H.S.P.) and clinical reports to Basle (T.F.A.). The appropriate examinations and evaluations of results were made at these centres.

The trial substances were supplied to the investigators in numbered bottles containing capsules of either 50 mg dapsone or 10 mg clofazimine, which were identical in appearance. Other material, including the fixative for the biopsies, was completely uniform. The allocation to treatment was randomized. Neither the investigators nor the present authors had knowledge about the key during the trial. There was, however, the possibility to have the code broken by an independent person in case of unwanted side effects. One of us (T.F.A.) took the responsibility for notifying the investigators of any unfavourable bacteriological or histological evolution that might make it necessary to stop the trial in the best interest of a particular patient.

Description of the Treatment Groups

Altogether 138 patients were selected in the 17 above-mentioned institutions for inclusion in the study. Of these, 44 proved primarily unsuitable, so that the population studied comprised in all 94 patients. Twenty-six of these were African, 51 Asian, 6 Melanesian, 4 Latin American and 7 European. The mean body weights ranged from 47.8 kg in Thai patients to 64.7 kg in Europeans. There was no significant difference between the two groups in respect of age.

Histologically, the dapsone-treated patients 48 in total, were classified as LL in 15, LI in 21 and BL in 12 cases. The distribution of the clofazimine-treated group ($n = 46$) was 12 for LL, 23 for LI and 11 for BL.

The nature and distribution of lesions were recorded in detail but, for lack of space, are not presented here. It may be stated that both groups were fully comparable as to their clinical features, with the one exception that diffuse infiltrations were more frequent among the LL/LI patients within the clofazimine group than among the corresponding cases of the dapsone-group. This difference was statistically significant.

As could be foreseen, the number of patients in both treatment groups diminished continuously during the trial. The rate of this process was about equal in both groups: the dapsone group initially comprised 48 patients; after 24 weeks there were 35, and by the end of the trial, after 48 weeks, 27. The respective numbers for the clofazimine-treated group were 46, 34 and 22 patients. Prolongation of the trial beyond the first year took place only in 4 patients, thus not allowing statistical analysis.

Results

In the following description of the bacterial and histopathological results, only the LL and LI patients are considered. BL patients, however, were taken into consideration together with the former for the evaluation of side effects and lepra reactions.

BACTERIAL FINDINGS

The bacteriological findings made at start of trial and during therapy with the two trial drugs are shown in Table 1. In both treatment groups, there was a significant decrease in the MI, which was practically zero by the 18th week. The decrease in the BI—as was to be expected—was slower.

TABLE 1

Bacteriological findings in evaluable LL/LI patients at the beginning of and during treatment

Week	Dapsone				Clofazimine			
	BI		MI		BI		MI	
	n	$\bar{x}$	n	$\bar{x}$	n	$\bar{x}$	n	$\bar{x}$
0	25	3.648	16	15.225	22	3.714	14	17.493
6	21	3.300	14	6.450	18	3.567	11	3.609
12	22	3.427	14	1.720	22	3.450	12	3.800
18	19	3.447	12	0.208	19	3.363	8	0.338
24	21	3.257	13	0.085	20	3.140	11	0.136
30	5	2.900	4	0.100	8	3.775	6	0.200
36	17	3.412	10	0.015	16	3.244	8	0.063
42	3	4.167	2	0.100	3	3.733	4	0.075
48	14	3.079	8	0.025	16	2.725	8	0.038
Initial ranges	1.7–4.7		5.5–28.0		1.5–4.8		5.3–49.0	
Regression coefficient for week 0-18, b_c =			−0.063				−0.055	
Regression coefficient for week 0-48, b_c =	−0.010				−0.02			

The decrease in the bacteriological indices was expressed by means of the linear regression coefficients, which were compared statistically for the two treatment groups. A method proposed by Bliss (1967) was used to combine the individual regression lines. In the regression analysis of the MI, only the obviously linear part of the semilogarithmic curve was taken into consideration, i.e. the section relating to the first 18 weeks of treatment. The analysis of both the MI and the BI does not show a statistically significant difference between the two treatment groups.

HISTOPATHOLOGICAL FINDINGS

Only those patients were assessed histologically whose lesions showed sufficient activity at the beginning. Subsequently, the activity of the lesions was classified as "regressing", "quiescent" or "healed". No statistical analysis was made of the distribution of cases among these purely qualitative categories, but steadily progressive healing took place in response to both treatments. It is particularly noteworthy that none of the lesions revealed any signs of activity after 24 weeks' treatment, either with dapsone or with clofazimine.

TABLE 2

Histopathological findings in evaluable LL/LI patients at the beginning of and during treatment

Week	Dapsone				Clofazimine			
	GI		HI		GI		HI	
	n	$\bar{x}$	*n*	$\bar{x}$	*n*	$\bar{x}$	*n*	$\bar{x}$
0	18	0.46	18	5.2	20	0.53	20	5.3
24	17	0.24	18	4.5	20	0.33	20	4.8
48	13	0.16	13	3.6	12	0.27	12	4.3
Initial ranges	0.2–0.7		4.6–5.9		0.15–0.9		4.75–5.9	
Regression coefficient, b_c =	−0.012		−0.034		−0.008		−0.020	

Quantitative data on the improvement observed are listed in Table 2, which shows the mean values of the Granuloma Index (GI) and the Histopathological Index (HI), the latter being the product of the individual GI and the BI at a given time. In both treatment groups, the extension of the granuloma within the dermis diminished linearly. Analysis of variance proved that the reduction was statistically significant. The same was the case with the HI.

As is evident from the gradient of the regression lines, determined by the three points of measurement, the thickness of granuloma diminished slightly more rapidly in response to dapsone than in response to clofazimine. This difference is statistically not significant.

CLINICAL FINDINGS

In 69 patients, the investigators came to a general conclusion about the clinical progress. On dapsone 27 patients improved, 6 were unchanged and 3 became worse (i.e. new lesions appeared during therapy). On clofazimine, 31 improved and 2 remained unchanged. As the improvement could not be quantified it was not amenable to statistical analysis.

A comparison of the body-weight before and during treatment of the LL/LI

patients in both treatment groups revealed an average increase of 2.0 kg (from 50.4 to 52.4 kg) after 24 weeks in the dapsone group and 4.0 kg (47.4 to 51.4 kg) after 18 weeks in the clofazimine group. Although the average body-weight of the patients in the clofazimine group was slightly lower than that of the dapsone-treated patients, it was never significantly different.

SIDE EFFECTS

Discolouration of the skin is regarded as a common side effect of clofazimine. Hypermelanosis of lesions has been observed as well as an extensive red discolouration. Although dapsone can also give rise to cutaneous pigmentation, especially of the lesions, there was nevertheless occasion to fear that it might occur more frequently in the patients treated with clofazimine and thus jeopardize the double-blind design of the trial.

TABLE 3

Frequency and localization of skin discolouration

Localization	Dapsone		Clofazimine		Total	
	abs.	%	abs.	%	abs.	%
Lesions only	2	(4.2)	3	(6.5)	5	(5.3)
Generalized	8	(16.6)	7	(15.2)	15	(16.0)
Lesions and generalized	3	(6.3)	2	(4.3)	5	(5.3)
Total	13	(27.1)	12	(26.0)	25	(26.6)
Size of treated group	48	(100.0)	46	(100.0)	94	(100.0)

In the total of 94 patients, altogether 25 instances of discolouration were recorded, the distribution of which is shown in Table 3. The times when this phenomenon was first reported were almost evenly spread over the entire duration of the trial in both treatment groups. Patients of darker hue (African) and of lighter hue (Chinese, European) were also equally represented in both treatment groups.

One may conclude that at least at this dose level, there is no significant difference between the two drugs in this respect. Since there was no clear-cut predominance of generalized discolouration in the group treated with clofazimine it may be inferred that this side effect was less pronounced than would have been expected at a daily dosage of, say, 100 mg.

Other side effects were observed in 10 of the 48 patients on dapsone and in 12 of the 46 on clofazimine. The nature and the distribution of these are shown in Table 4. The side effects were usually mild and not always clearly related to the drug administered. Treatment had to be withdrawn on account of side effects in two cases receiving dapsone (1 rash, 1 anaemia) and two receiving clofazimine (1 rash, 1 gastric complaints).

LEPRA REACTIONS

During the 48-week trial, 47 of the 94 patients, i.e. exactly half of the whole series, suffered at least one reactional episode. There were about twice as many dapsone- as clofazimine-treated patients amongst those showing reaction. Table 5 illustrates these relations. The difference between the two treatment groups is statistically significant at the 95% probability level (χ^2 6.252, d.f. 2). The

TABLE 4

Kind and frequency of other supposed side effects

Nature of side effect	Dapsone	Clofazimine	Total
General (weakness, dizziness, headache)	4	3	7
Gastro-intestinal (abdominal pain, nausea)	3	2	5
Anaemia	1	1	2
Vascular (Oedema, Epistaxis, Phlebitis)	4	3	7
Pain (bone and joint pain, myalgia)	2	2	4
Epidermal (rash, pruritus)	2	6	8
Total of occurrences	16	17	33
Patients concerned	10	12	22

TABLE 5

Patient population according to presence or absence of lepra reaction

Patients showing	Dapsone	Clofazimine	Total
ENL	14	7	21
Other reactions only	16	10	26
No reaction	18	29	47
Total	48	46	94

frequency and severity of ENL and all types of reaction including iritis, orchitis, stasis syndrome, panniculitis, acute exacerbation of lesions, or neural reactions, were higher in the dapsone-treated group than in the clofazimine-treated group. The frequency of reactive phases can vary enormously from one patient to the other and combinations are manifold. Because of this great complexity it is difficult to describe the events adequately. For example, the cumulative frequency of bouts of ENL while on dapsone (24 times in 14 patients) and on clofazimine (8 times in 7 patients) is depicted in Fig. 1.

The nature of the curve in this cumulative presentation, whether rising or horizontal, may be regarded as an indication of the stress imposed upon the treating and nursing personnel.

Seven patients (4 on dapsone, 3 on clofazimine) were withdrawn from the trial on account of lepra reactions. As a rule, however, the concomitant treatment given for the reactions (antimonials, chloroquine and in some cases steroids) sufficed to suppress the inflammatory processes.

Discussion and Conclusions

THE RESULTS OF THE TRIAL

The results presented here were obtained on a multicentric basis. Although the patients treated originated from very different countries and circumstances, they were nevertheless homogeneous in respect of their histological classification. Evaluation of the bacteriological and histopathological progress was strictly limited to LL/LI patients, whereas the assessment of side effects and lepra reactions included also the BL patients.

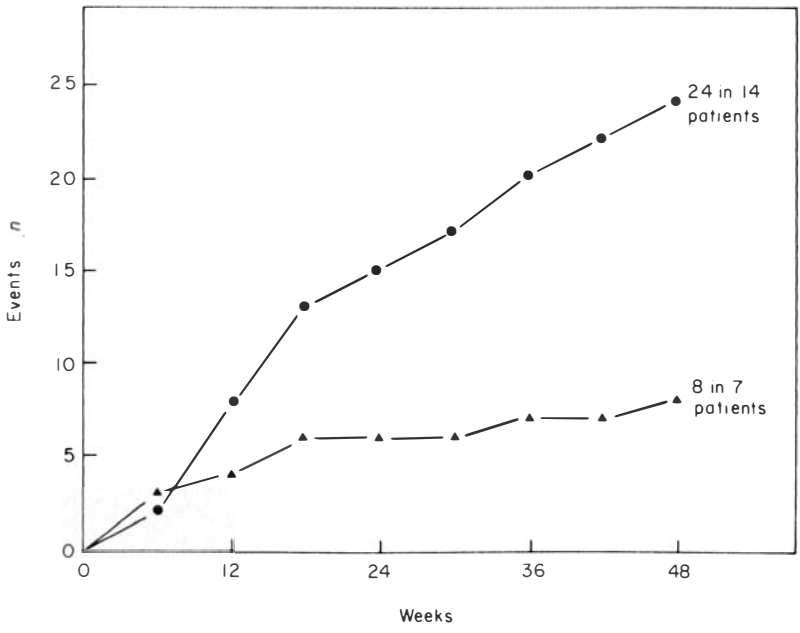

Fig. 1. Cumulative frequency of bouts of ENL while on dapsone (●–●) (14/48 patients) or clofazimine (▲–▲) (7/46 patients).

Comparison of the results obtained in this study demonstrates, in a statistically sound manner, that low-dose therapy with both these agents elicited an almost identical short-term antibacterial effect. This was manifested by a decline in the MI, which approached zero after about 18 weeks' treatment. As was to be expected, there was little change in the BI up to the first year of treatment, and during this time fluctuations were noted in both groups. This factor was less pronounced in the GI and the HI: here the decline was almost linear, and there was no significant difference between the two treatments. From the clinical point of view also, the two groups appear to have made equal progress.

It should be borne in mind that the reason for administering low doses of dapsone was the hope of diminishing the incidence of lepra reactions. However, though Karat *et al.* (1969), found that the severity of ENL was diminished when dapsone was given in doses of only 35 or 10 mg weekly, neither they, nor Leiker and Carling (1969) who administered 20 mg weekly noted any difference in the incidence of reactions. In the present trial the incidence, severity and duration of lepra reactions were not noticeably less than would have been expected on high doses of dapsone. This applies especially to ENL. Compared with the clofazimine-treated patients, about twice as many patients on dapsone displayed ENL and, individually, their bouts of reaction were about twice as frequent. Reversal reactions, resulting histologically in a shift towards the other pole were too rare (3 on dapsone, 2 on clofazimine) to allow statistical analysis.

In the case of clofazimine the object of trying low-dosage treatment was to

avoid, at least partly, the inconvenience of red discolouration. (The hypermelanosis which sometimes occurs with both sulphone and clofazimine therapy seems unavoidable.) The results clearly show that this complication, if present, was not a problem here, thus supporting the view that it is a dose-dependent phenomenon.

The conclusion therefore appears to be that clofazimine is superior to dapsone at the low dosage level, and for a limited period of time. It should be recommended in cases where treatment phases of this kind are indicated. No conclusions can be reached concerning the relative value of the two treatments over a period of more than one year. Although at the time when the present trial was initiated there were a number of reports favouring the use of low dose therapy the current view of many workers is that monotherapy at low dose over a long period invites the risk of bacterial resistance (Jacobson, 1973; Meade *et al.*, 1973; Gelber *et al.*, 1974). Although these reports all refer to sulphones, and although the minimal effective dose of clofazimine may be as low as about 7 mg a day (Shepard, 1969) this objection probably has general application.

The original intention was that any BL patients would be used only for a study of the effect of clofazimine on reversal reactions. In the event there were scarcely any BL patients except those of the "histiocytic" type (Ridley and Jopling, 1966) with few lymphocytes. It has since been observed that the response of these patients is similar to those of the LI group, and it has been proposed that with certain provisos they should now be graded as LI (Ridley, 1975). Consequently, there were few reversal reactions and the BL group could be disregarded for the bacteriological and histological evaluation. It is not recommended that true BL patients should be included in this sort of trial. The dearth of such patients in this series is to the credit of the clinicians in selecting lepromatous patients.

THE PROBLEMS OF THE MULTI-CENTRE METHOD

Difficulties are always likely to arise in clinical trials conducted on a multicentric basis, unless virtually unlimited funds and resources are available to ensure that all organizational requirements are met. This double-blind study proved no exception. Loss of information and the long duration posed major problems of the sort familiar enough in therapeutic trials in any chronic disease.

There was no independent clinical observer, whose task it would have been to assess the clinical progress in a consistent manner. In a trial covering such a vast area as this one did, it is, however, difficult to achieve this ideal, as Waters *et al.* (1967) have already pointed out. In the present study, each investigator was impartial in so far as he had no knowledge of the treatments administered, and his statements were based mainly on the presence or absence of any marked or persistent deterioration in a patient's condition. Regular contact with an independent observer interested in the trial would certainly have afforded more encouragement and incentive to the investigators. Better communications would probably have helped to increase the volume of evaluable data and reduce the number of drop-outs. Under the circumstances, histology is the only approach that affords opportunity for uniform evaluation and assessment. As to the value of the methods used in this trial, there appears to be no doubt that this type of investigation can supply answers to preformulated questions, as long as they relate to measurable parameters or to the presence or absence of particular phenomena.

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