Controlled Drug Trial of B.663 Compared with DDS. Preliminary (48 week) Report[1]

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B.663, a rimino compound of the phenazine series has been used in treatment of leprosy since 1962 ([2, 3, 4, 5, 6, 7, 8, 11]). The drug is generally regarded as having a specific anti-leprosy effect. Several observers ([1, 5, 6, 11]) have noted that patients receiving B.663 have fewer and milder *erythema nodosum leprosum* (ENL) complications. It has also been noted that some patients who have not improved on DDS show improvement on B.663 ([5, 6, 7]). One advanced lepromatous patient in Cebu who had become worse under DDS and streptomycin therapy showed very marked improvement when he was placed on B.663. This striking effect of the drug prompted the staff of the Philippine Division, Leonard Wood Memorial, to plan a controlled drug trial, comparing B.663 with DDS in lepromatous patients. In the clinical reports on B.663 there have been no series of cases in which this drug had been compared with DDS.

MATERIALS AND METHODS

Only patients clinically diagnosed as lepromatous leprosy, heavily positive for *Mycobacterium leprae*, and negative for lepromin reaction were first admitted to this study. Later, however, also patients with borderline-lepromatous leprosy (which are, strictly speaking, lepromatous in the Madrid classification ([10])) were also admitted provided that they were heavily positive for *M. leprae* and negative for lepromin reaction. Patients suffering from ENL were excluded.

The patients were examined by Dr. F.P. Diaz, an internist, to rule out the presence of other significant diseases. Chest x-ray, stool examination, complete hematologic studies, liver funotion tests, renal function tests, and urinalysis were done before the patient was admitted to the study. Certain of these tests were repeated bimonthly or trimonthly.

None of the enrolled patients had received previous specific treatment for leprosy. As new lepromatous patients who met the criteria for the study were admitted to the Eversley Childs Sanitarium, those willing to join the study were alternately put on either B663 or DDS.

At the beginning of the study it was planned to use the morphologic index (MI) as a basis for evaluation of the antileprotic activity of B.663, and only patients who had solid bacilli of four per cent or more were selected in accordance with the minimum requirement of the U.S.-Japan Panel on Leprosy.[3]

Due to difficulty in getting cases with a high index of solid bacilli, as recommended by the U.S.-Japan Panel, for admission, this requirement was finally abandoned and even cases without solid forms of bacilli were later admitted to the study. Nevertheless, the solid ratios of bacilli in the skin smears were routinely recorded throughout the study. The MI in cases originally with solid bacilli usually ranged from one to five per cent, except in two cases, one with seven per cent in the B.663 group and another with 13% in the DDS group. Of the 43 patients originally selected only 32 completed the 48 weeks therapy.

Clinical examinations. The Principal Investigator, in a manner that had been used in previous drug trials, made very careful examinations of all new patients, charting lesions, areas of anesthesia, etc. The dermatologic findings were recorded on black and

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3 U.S.-Japan Cooperative Medical Science Program. Protocol for Chemotherapy Trials in Lepromatous Leprosy, December 1967, pp 15 (mimeographed).

white photographs and color transparencies.

Another leprologist (J.N.R.) independently made complete pretreatment examinations of the patients, recording dermatologic and neurologic findings.

The Principal Investigator examined the patients carefully, observing any change that may have occurred in their clinical progress. Special attention was paid to patients who developed lesions of ENL. Observations on these patients were made and recorded weekly.

At the end of six months and of twelve months the Principal Investigator and the collaborating leprologist independently examined and assessed the changes that were observed in each patient.

Laboratory examinations. Smears were taken from four predetermined sites for the estimation of the number of organisms (BI), and for the measurement of the solid ratio (MI). The bacteriologic index devised by Ridley (9) was used. Smears were repeated at three month intervals during the study.

Biopsies were taken at the beginning of the study to confirm histopathologically the clinical classification of leprosy. Another biopsy, adjacent to the first one, was taken at the end of the study to determine changes after therapy. The post-treatment slides compared with the pretreatment slides are now under study by the pathologist (R.M.A.), and the findings will be reported later.

Treatment. All medicines were administered and recorded personally by a registered nurse. Daily temperature and pulse were recorded six days a week on all patients and their weights were determined once a month.

B.663 was given in a dose of 200 mg a day, six times a week; while DDS, the control drug, was given initially in 50 mg doses twice a week and increased in eight weeks to a maximum of 2.5 mg/kg body weight (approximately 100 mg) a day, six times a week.

Steroid hormones were given as little as possible, just enough to make the cases in reaction comfortable but not with the intention of completely suppressing this condition.

The following are the results noted after 48 weeks of treatment.

RESULTS

Clinical findings. Of the 43 patients admitted to the study, only 32 completed 48 weeks of therapy—16 cases on B.663 and 16 on DDS. Table 1 shows that 14 cases (87.5%) on B.663 and 12 cases (75%) on DDS were clinically improved. Although B.663 had a higher improvement rate, the difference in the two therapy groups is not statistically significant.

TABLE 1. *Clinical status of 32 cases after 48 weeks of therapy.*

Therapy groups	No. cases	Improved	%
B.663	16	14	87.5
DDS	16	12	75.0
TOTAL	32	26	81.3

Table 2 shows that six of 16 B.663 cases (37.5%) and 11 of 16 DDS cases (68.8%) developed ENL during the course of therapy. The difference is significant.

TABLE 2. *Frequency of ENL in the 32 cases in the study.*

Therapy groups	No. cases	ENL	%
B.663	16	6	37.5
DDS	16	11	68.8
TOTAL	32	17	53.1

As noted in Table 3, of the six ENL cases taking B.663, five were mild and one was moderately severe, while of the 11 that developed this reaction among the DDS patients, two were mild, three were moderately severe and six were severe. The difference in the severity of reaction was very marked between the two therapy groups. ENL is decidedly milder in patients taking B.663 than those taking DDS.

TABLE 3. *Severity of reaction in the 17 cases of ENL.*

Therapy groups	Mild	Mod.	Severe	Total
B.663	5	1	0	6
DDS	2	3	6	11
TOTAL	7	4	6	17

Acute neuritis developed in three of 16 cases taking B.663 (10.8%) and in eight of the 16 cases taking DDS (50%) (Table 4). In the B.663 cases (Table 5) one was mild and two were moderately severe, while in the DDS cases four were mild, three moderately severe and one severe. There is evidence that acute neuritis is much more frequent, although only slightly more severe in patients taking DDS than those taking B.663.

TABLE 4. *Frequency of acute neuritis in the 32 cases in the study.*

Therapy groups	No. cases	Acute neuritis	%
B.663	16	3	18.8
DDS	16	8	50.0
TOTAL	32	11	34.4

TABLE 5. *Severity of acute neuritis in the 11 cases affected.*

Therapy groups	Mild	Mod.	Severe	Total
B.663	1	2	0	3
DDS	4	3	1	8
TOTAL	5	5	1	11

Bacteriologic findings. The average preliminary bacterial index of the B.663 group (Table 6) was 4.5, and after 48 weeks of therapy it was 3.6, a reduction of 0.9. In the DDS group the preliminary BI was 4.6, and after 48 weeks of therapy it was 4.2 a reduction of 0.4. While the reduction in the bacterial index was greater under B.663, the difference was very small.

TABLE 6. *Bacteriologic (BI) status of 32 cases after 48 weeks of therapy.*

Therapy groups	No. cases	Bacteriologic index		
		Prelim.	48 wk.	Reduction
B.663	16	4.5	3.6	0.9
DDS	16	4.6	4.2	0.4
TOTAL	32	4.5	3.9	0.6

In cases with solid bacilli at the initial examination the MI was reduced to zero, or almost zero, in three months of therapy in both B.663 and DDS groups.

In order to determine the long range effect of B.663, a decision was made to continue the B.663–DDS trial for a period of 96 weeks. The result of the continuation of this trial will be reported later.

SUMMARY

In a controlled drug trial, 16 patients under B.663 and 16 under DDS completed 48 weeks of therapy. The differences in the rates of clinical improvement and in the reduction of bacterial index between the two therapy groups are not significant. The occurrence of ENL and acute neuritis were less frequent and less severe in patients taking B.663 than in those taking DDS. In both groups, cases that had solid bacilli at the beginning of the study reduced their morphologic index to zero, or almost zero, in three months of therapy.

RESUMEN

En una investigación controlada sobre drogas, se administró B.663 a 16 pacientes y DDS a 16 pacientes, durante 48 semanas. Las diferencias en las tasas de mejoría clínica y de reducción del índice bacteriológico entre los dos grupos con distinta terapéutica no son significativas. La aparición de ENL y de neuritis aguda fué menos frecuente y menos severa en los pacientes que tomaron B.663 que en aquellos que tomaron

DDS. En ambos grupos los casos que tenían bacilos sólidos al comienzo del estudio redujeron su índice morfológico a cero, o casi cero, en tres meses de tratamiento.

RÉSUMÉ

Dans un essai thérapeutique contrôlé, 16 malades recevant du B. 663 et 16 autres malades recevant de la DDS, ont poursuivi une cure avec ces médicaments pendant 48 semaines. On n'a observé aucune différence significative dans les taux d'amélioration clinique et dans la réduction de l'index bactériologique entre les deux groupes ainsi soumis à des régimes thérapeutiques différents. L'apparition d'ENL et d'une névrite aigue était moins fréquente et moins grave chez les malades qui recevaient du B. 663 que chez ceux qui prenaient de la DDS. Dans les deux groupes, les malades qui présentaient des bacilles solides au commencement de l'étude, ont vu leur index morphologique réduit à zéro ou presque à zéro, après trois mois de traitement.

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