"B 663" IN THE TREATMENT OF LEPROSY

Preliminary Report of a Pilot Trial

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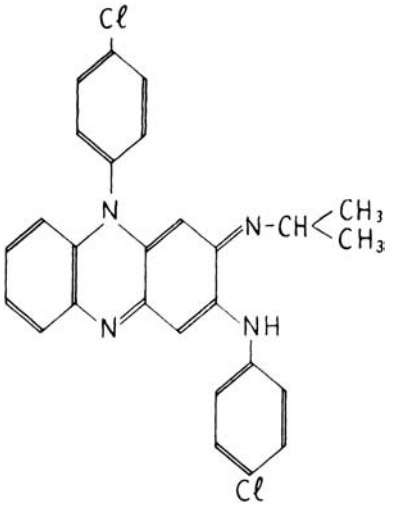
The very high anti-tuberculosis activity of many recently-synthesized phenazine dyes indicated that they might be of value in the treatment of leprosy. Dr. R. G. Cochrane (Leprosy Research Unit, London) and Dr. Vincent C. Barry (Medical Research Council, Dublin) suggested a clinical trial of "B 663" (Geigy S.A.), in many ways the most promising of the series, in a group of patients with lepromatous leprosy in Eastern Nigeria.

B 663 is a Rimino-compound with the structural formula:



The Rimino-compounds are derived by progressive chemical alteration of the anilino*apo*safranine molecule (BARRY *et al.*, 1957; DOULL, 1961). The forerunner of these compounds (B 283) has very high anti-tuberculosis activity *in vitro*, and some anti-tuberculosis and anti-leprosy activity *in vivo* (ALLDAY and BARNES, 1952; DOULL 1952).

In a series of papers, Barry and his co-workers have shown that, weight for weight, B 663 is more active in experimental tuberculosis in laboratory animals than any other substance hitherto investigated; it is the only substance known to exert a true chemoprophylactic action in animal tuberculosis. Other workers (e.g., CHANG, 1959;

ACHARYA *et al.*, 1959; STEENKEN *et al.*, 1960) have confirmed their main findings. The drug administered orally or parenterally appears to be taken up unchanged by living mycobacteria. When given in large doses, it is deposited in crystalline form in the principal organs, particularly in cells of the reticulo-endothelial system, but the slight toxicity observed seems to be limited to some foreign-body reaction provoked by the presence of these microcrystals. Adequate toxicological investigations have been carried out.

For the purposes of this investigation, the drug was supplied (by Messrs. J. R. Geigy, S.A.) in the form of orange-red micronized crystals (particles not exceeding 5μ in diameter), presented in capsules for oral administration containing 0.1g. As suggested by evidence obtained in experimental animals, a small amount of vegetable oil (1 teaspoonful of groundnut oil) was given to each patient with the daily dose of drug prescribed, to facilitate absorption from the intestine.

Choice of patients

All patients admitted to Uzuakoli Settlement just before the beginning of the trial, and suffering from lepromatous leprosy (14) or from borderline leprosy highly positive bacteriologically (2), were given recommended doses of B 663. These patients, unselected, had received no treatment before admission, but six of them, while awaiting the arrival of the drug, had received minimal doses of dapsone (0.05 to 0.1g. twice weekly) for two to eight weeks before the beginning of the trial.

Treatment

All 16 patients received a daily dose of 1, 2 or 3 capsules of B 663, each containing 0.1g. of active substance, for six days a week for six months. The amount of drug given was according to body-weight; thus,

1 patient weighing 50 lbs. received 1 capsule daily;

5 patients weighing on the average 94 lbs. received 2 capsules daily;

10 patients weighing on the average 116 lbs. received 3 capsules daily.

The 16 patients were divided into three groups:

Group 1: 3 patients received, in addition to B 663, standard doses of dapsone;

Group 2: 8 patients received no additional drug treatment. Of these 8 patients, 3 began their course of treatment at the same time, and the remaining 5 began later, the point of entry depending on the date of admission to the Settlement;

Group 3: In addition to B 663, 5 patients received daily inunction with 5 ml. of Etisul liquid formula (ditophal), kindly supplied by Messrs. I.C.I. (Pharmaceuticals) Ltd. (BROWNE, 1961). Inunction was carried out for six days a week for the first three months of the trial period.

Thereafter, patients in Group 1, and the first 3 patients in Group 2, received standard doses of dapsone alone. The remaining 5 patients in Group 2 are continuing to receive B 663 alone. The 5 patients in Group 3 are now receiving standard doses of dapsone alone.

Laboratory investigations

Smears were taken at fortnightly intervals from eight sites, and the Bacterial Index determined by the same experienced technician, who from the preparations estimated the proportions of *M. leprae* of degenerate morphology at each site. Smears were taken on at least two occasions before the beginning of treatment with B 663 to minimize errors due to the hazards of smearing and to fortuitous changes in concentration of bacilli in the dermis.

Full blood examination, including estimation of the Erythrocyte Sedimentation Rate, was performed at monthly intervals.

Full urine examination was made every fortnight.

Investigation of liver function was made every month, by means of Schlesinger's test (for urobilinogen), the Takata-Ara test, and the Thymol turbidity test.

Results

All patients supported well the drugs given, and none had to be withdrawn from the trial.

Within ten days of the start of the trial, all the patients began to develop a ruddiness of the skin, shown particularly in the less pigmented and thin skin of the face (e.g., peri-orbital), the palms and soles. Generally, it was the skin not affected by lepromatous infiltration that became ruddy. The lepromatous infiltrated skin and the lepromatous nodules became hyperpigmented, and remained so. In some patients, a progressive generalized hypermelanosis became apparent. These changes in cutaneous pigmentation were not accompanied by subjective symptoms, and appeared to have no deleterious significance. They indicated good absorption of the drug from the intestine.

The conjunctivae became slightly muddy in most patients.

A baby at the breast became ruddy like its mother, and then slightly hypermelanotic. Five months after the end of the trial, the pigmentation of the skin had returned to normal, but the baby (then aged 15 months) developed the typical hazy patches of early leprosy, bacteriologically negative.

Toxicity

No signs of toxicity have developed beyond slight transient nausea and giddiness in two patients in whom the drug/body-weight ratio was somewhat higher than the average.

Clinical results

Notwithstanding the small size of the groups, and the short period of observation, the progress made by these patients treated with B 663 appears to warrant publication of this preliminary report.

All the patients who received B 663 alone (8) or with dapsone (3), and 2 of the 5 patients who received ditophal in addition to B 663, showed considerable improvement: the size and elevation of the lepromata became markedly less, some of the smaller lenticulate nodules on cheeks and ears almost disappearing; lepromatous infiltration decreased; repigmentation of lepromatous macular areas took place, sometimes as part of a generalized hyperpigmentary process.

The greatest average clinical improvement was shown by the 3 patients who received dapsone in addition to B 663.

Of the remaining 3 patients, who had all received ditophal in addition to B 663, one was moderately improved, and two were unchanged.

Bacteriological results

Reduction in the Bacterial Index and degenerative changes in *M. leprae* ran *pari passu* with clinical improvement.

The reduction was most marked in the 3 patients treated with dapsone: viz. 49%. It was 28% in the 8 patients treated with B 663 alone. Of the ditophal group, the fall in B.I. was 65% in the 2 markedly improved patients, 19% in the patient moderately improved, and unchanged in the remaining 2 patients.

Histological studies of skin sections, which will be reported later, together with details of bacteriological findings, show progressive reduction in the concentration of bacilli and in the density of the lepromatous infiltrate.

Conclusions

Clinical improvement in such patients suffering from severe lepromatous leprosy, and consistent bacteriological improvement of the magnitude indicated, cannot be attributed to spontaneous regression. Even after this short trial period of six months, the following tentative conclusions may be drawn:

1. B 663 alone has a definite effect on lepromatous leprosy,

causing an improvement in the clinical state, a concurrent fall in the Bacterial Index, and degenerative changes in *M. leprae;*

2. This effect is enhanced by the addition of standard doses of dapsone;

3. The addition of ditophal to recommended doses of B 663 has apparently a capricious result both clinically and bacteriologically, augmenting the beneficial effect of B 663 in some patients.

4. These results indicate that the Rimino-compounds merit further trial in leprosy.

Acknowledgments

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