EVALUATION OF TWO REGIMENS OF MULTIDRUG THERAPY IN MULTIBACILLARY LEPROSY
(A preliminary report)

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A comparative evaluation of 2 regimens of multidrug therapy (IAL modification and the original WHO regimen) in multibacillary leprosy is presented. Patients were given MDT till the point of clinical and bacteriological inactivity. It was found that the IAL regimen confers a statistically significant advantage in patients with a higher initial BI (more than 2), as far as bacteriological inactivity is concerned. In patients with a lower initial BI, both regimens were equally effective. Side effects and lepra reactions were within reasonable limits with both the regimens. We feel that the IAL modification of the WHO regimen should be used in multibacillary leprosy, especially in cases with a high initial BI. The slight increase in the cost is compensated by the higher proportion of cases rendered negative.

Key words : Multibacillary leprosy, Multidrug therapy, WHO regimen, IAL regimen.

With the emergence of dapsone resistant leprosy, a new approach to chemotherapy was urgently needed. A WHO study group[1] recommended introduction of multidrug therapy (MDT) consisting of daily unsupervised dapsone, and clofazimine, and monthly supervised doses of clofazimine and rifampicin. This regimen was based on theoretical considerations[2] and had to be validated through field based trials. The Indian Association of Leprologists has recommended a schedule which consists of initial supervised daily doses of rifampicin for the first 3 weeks of therapy.[3] Our organization started MDT in a systematic manner from 1983. After more than 4 years of experience, it was decided to analyse our results vis-a-vis the utility of MDT on a mass scale.

Materials and Methods

Our organization functions in the L and M wards of Greater Bombay with an estimated population of 1 million. Patients present voluntarily, while about 50% are detected through survey techniques by our trained paramedical workers. After clinico-bacterial confirmation, the cases are classified according to Ridley-Jopling criteria.[4] Suitability for multidrug therapy is assessed through detailed history and physical examination. Pregnant females, alcoholics, persons with known kidney and liver disorders, and malnourished individuals are excluded. Patients with co-existing tuberculosis are also excluded unless taking regular therapy. Biochemical, histopathological and roentgenological examinations are not carried out routinely.

Patients who appear to be highly motivated (usually voluntary attenders) are taken up for the IAL regimen (regimen A), while the others are taken up for the regular WHO schedule (regimen B). For obvious reasons, we had fewer patients in regimen A (55) compared to regimen B (102).

We have slightly broadened the scope of the term "Multibacillary leprosy" in that patients with more than 5 lesions have also been included even though the initial BI may be negative.

Patients are clinically assessed every month, while bacteriological examination is done every 6 months. MDT is continued for a minimum of 24 doses; at which stage, if skin smears are negative and the patient is clinically inactive,

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MDT is stopped; however, if there is evidence of bacteriological and/or clinical activity therapy is continued and smears are repeated at 6-monthly intervals. We do not stop MDT until a patient is clinically and bacteriologically inactive.

MDT is stopped prematurely only in the following circumstances : (i) pregnancy, (ii) hepatitis or renal damage, (iii) severe type I or type II reactions which do not improve even with very high doses of corticosteroids. In this case only rifampicin is generally stopped while the dose of clofazimine is usually increased.

For the present study, we are including patients who have completed at least 24 doses of MDT.

Results

In regimen A, there were 30 males and 25 females, while the corresponding figures in regimen B were 63 and 39.

Most of our patients were previously untreated, while some had taken dapsone for varying periods of time. None had been receiving MDT previously.

For the purpose of analysis, we divided our patients into two groups : (1) patients whose initial average BI (taken from atleast four sites including both ears) was less than or equal to 2.0, and (2) patients whose initial average BI exceeded this limit. This distinction was made since the former group has been classified by the WHO as "Paucibacillary".[1]

When patients with BI less than or equal to 2 were considered, there was no statistically significant difference between the two regimens (chi-square=0.146 with Yates' correction; df=1; $p > 0.5$). However, when patients with a higher BI were considered, regimen A, was superior to regimen B in achieving negativity, (Chi-square=4.66 with Yates' correction; df=1; $0.05 > p > 0.02$).

When both the regimens were compared irrespective of the initial BI, it was found that regimen A achieved negativity in 45 (81.8%) patients, while regimen B rendered 74 (72.5%) patients smear negative. This difference too was not significant statistically (Chi-square=1.21; df=1; $0.5 > p > 0.1$).

At the time of analysis, active skin lesions were present in 11(20.0%) patients in regimen A, while 27 (20.31%) on regimen B showed active lesions. In regimen A, 26 patients had severe neuritis at onset, 4 developed it during treatment, and at the present time 15 still had neuritis. Interestingly, 4 of these were smear —ve. Out of 102 patients on regimen B, 36 had neuritis at onset, 14 developed it during therapy while at the present time, 20 had persistent neuritis, of which 3 were smear —ve.

In regimen A, 8 patients had ENL at onset of treatment, 3 developed it during treatment while 1 patient still had it at the time of analysis. In regimen B, 16 had ENL at the time of starting treatment, 7 developed it during MDT, and 7 still had it at the present time.

There was no statistically significant difference between the two regimens as far as clinical parameters were concerned ($p > 0.5$).

One patient on regimen A, and 4 on regimen B, became pregnant. As soon as this was detected, MDT (but not dapsone) was stopped. In all, pregnancy was uneventful and soon after delivery, MDT was restarted. Two patients (one on each regimen), developed hepatitis; though it was not definite that rifampicin was the aetiological agent, it was stopped while the other drop was continued.

In 2 patients on regimen A and 3 on regimen B, it was judged by the treating doctor that rifampicin was contributing to the severity of ENL reaction; it was stopped in these cases and not restarted.

In 4 cases on regimen A and 22 on regimen B, the dose of clofazimine was increased (usually 200 mg daily) in cases of severe neuritis and/or ENL.

Comments

Though the rationale of MDT is undoubtedly valid, many workers expressed serious reservations, mostly over the use of monthly rifampicin, which could cause rifampicin resistance.[5,6] Some workers have advocated the use of daily rifampicin, at least for the first 3 months.[7] The possibility of rifampicin resistance has, on the other hand, been discounted by others,[8] who advocate pulse doses of rifampicin, mainly on economic grounds. The IAL regimen, which recommends an initial 3 week supervised daily course of rifampicin, was probably a via media between these two extreme opinions. However, the scientific basis of this regimen has yet to be decided.[9] Multidrug therapy is undoubtedly efficacious. With the use of 3 drugs, there is greater chance of synergism with less chance of developing drug resistance,[10] while addition of clofazimine may prevent lepra reactions.[11] Pharmacokinetically, however, it is reported that clofazimine can reduce rifampicin absorption and serum levels.[12]

Kaur et al[13] reported smear negativity to occur in all their cases at the end of 2 years. Katoch[14] on the other hand, reported that no patient became smear negative at this time, while when the treatment was continued further, only 2 out of 56 patients with an initial average BI of >4, became negative. In our series, with the original WHO regimen, 75% of patients who had completed 24 doses were rendered negative. However, when patients with higher BI were considered, regimen B could achieve negativity in only 40% of the cases. With the IAL regimen, the corresponding figures were 80% and 58% respectively. At present, only a few studies comparing the WHO and IAL regimens have been conducted.[9,15] In both these studies, IAL regimen did not show significant advantage over WHO regimen. On the other hand, smear conversion at 24 doses was 67% with WHO regimen compared to 47% with IAL regimen. At 36 doses, the corresponding figures were 75% and 59%. In our analysis, the number of patients were appreciably fewer. Overall, we had a 72% conversion rate with WHO regimen compared to 81% with IAL regimen, the difference was not statistically significant. When patients with higher BI(>2) were considered, the superiority of the IAL regimen was definitely marked, since only 39% cases on WHO regimen became negative compared to 69% on IAL regimen. We cannot explain the discrepancy between our findings and those of Ganapati et al.[15] Further studies may clarify this issue.

In many cases, the bacteriological conversion may not correlate with the clinical or the histological findings.[16] We had a similar experience. Thus, with regimen A, 4 patients who were smear negative had active neuritis, while with regimen B 3 patients with neuritis were smear negative. Thus, smear negativity should not be the only criterion for stopping therapy. Other factors (skin lesions, neuritis, ENL) should also be taken into consideration.

Some workers[15,17] deem it unnecessary to continue MDT till the point of negativity, with the proviso that atleast 6 post-MDT follow up smears be taken every 3-6 months. With the ever present difficulty of following up the patients, we think it is prudent to give patients MDT till the point of clinical inactivity and bacteriological negativity.

MDT has generally been well tolerated. Kaur et al,[13] reported that 75% patients develop ichthyosis and hyperpigmentation with clofazamine, while 3% patients developed jaundice (Viral hepatitis). Birch[18] reported no major side effects, 15% patients developed reactions. In our series, around 12% patients developed

neuritis during MDT, while 7% developed ENL de novo. In 5 patients, rifampicin had to be stopped due to the severity of the reactions. Only 2 patients developed jaundice which may or may not have been drug related. Since almost every patient developed some degree of pigmentation and xerosis with clofazimine, we have not included this among the major side effects.

We feel that multidrug therapy is an efficacious, acceptable and safe modality of treatment. Wherever possible, and especially in patients with a high initial BI, the IAL modification be employed. After all the cost of the IAL regimen is only marginally higher than the WHO regimen (Rs. 825 vs Rs. 718)[9] and this small sum is well worth spending considering the advantage the IAL regimen can offer.

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