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## **A retrospective study of the effect of modified multi-drug therapy in Nepali leprosy patients following the development of adverse effects due to dapsone**

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### *Summary*

*Introduction* Dapsone Hypersensitivity Syndrome (DHS) occurs in approximately 2% of leprosy patients in Nepal. DHS and other adverse effects of dapsone lead to withdrawal of the drug.

*Methods* We reviewed the notes of patients who had dapsone withdrawn from their multi-drug therapy (MDT) following an adverse reaction to the drug between 1990 and 2007.

*Results* 105 patients were identified from the database and 67 had a documented completion of a modified course of MDT. The majority were treated with rifampicin and clofazimine. All 36 individuals who were slit-skin smear positive had a satisfactory fall in their mean bacterial index. There were no cases of relapse.

*Conclusions* Rifampicin and clofazimine appear to be satisfactory treatment for both paucibacillary and multibacillary patients who have to have dapsone stopped because of severe adverse effects.

Dapsone is associated with severe adverse effects such as dapsone hypersensitivity syndrome (DHS), dermatitis, hepatitis, agranulocytosis and severe haemolysis.

The TRIPOD 1 controlled trial of steroid prophylaxis for the prevention of nerve function impairment in 636 newly diagnosed multibacillary (MB) patients, conducted in Bangladesh and Nepal, reported a rate of 'dapsone allergy' of 3.1%.<sup>1</sup> We have previously reported a rate of DHS of 2% in individuals started on MDT at our centre and that it has a high mortality of 10%.<sup>2</sup> This is consistent with data from other settings in Asia.<sup>3,4</sup>

In Brazil dapsone is the most likely component of MDT to be associated with adverse effects.<sup>5,6</sup> Daps et al. have reported that 54% of individuals experiencing adverse effects attributed to dapsone had to have the drug withdrawn.<sup>5</sup>

In the event of severe dapsone toxicity the World Health Organization (WHO) recommends that no modification to MDT other than immediately stopping dapsone is required in the case of those receiving MB MDT. Individuals being treated for paucibacillary (PB) disease should have the dapsone stopped and clofazimine substituted in the dosage used in the MB regimen for a period of 6 months.<sup>7</sup> This is the practice at our centre. It has the advantages of the modified treatment being free and readily available.

The WHO Study Group on Chemotherapy of Leprosy for Control Programmes, which met in Geneva in 1981, recommended dapsone containing MB MDT for all cases of multibacillary leprosy including those suspected of having dapsone resistant disease.<sup>8</sup> It therefore seems reasonable to surmise that rifampicin and clofazimine are sufficient for individuals unable to tolerate dapsone. However, we could find no published data to support our practice apart from the study by Cellona and colleagues.<sup>9</sup> They compared three rifampicin and clofazimine combinations in the treatment of lepromatous leprosy patients who had relapsed following dapsone monotherapy. The doses of the two drugs used in these regimens were not entirely comparable with standard MDT. The regimens used rifampicin 600 mg daily for either 2 or 4 weeks or 1200 mg once every 4 weeks for 24 weeks (six doses). All three combinations included clofazimine 100 mg three times per week for 5 years. All three combinations were effective.

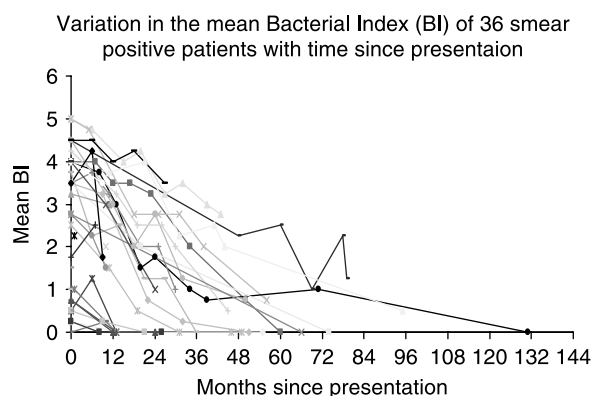
We decided to perform a retrospective review of our patients who required a modified MDT regimen because of an adverse event attributed to dapsone.

The electronic database of all the patients treated at Anandaban Hospital for leprosy (or its complications) between 1st January 1990 and 30th June 2007 was searched. Individuals labeled as 'dapsone allergic' were identified and their case notes retrieved. Ethical permission was granted by the Ethics committee of Anandaban Hospital.

The charts were reviewed by an experienced physician and the data were entered into an Excel spreadsheet. Patients in whom there was confirmation of completion of a modified course of MDT were included for further analysis. Individuals were excluded if there was no record of completion of a modified MDT regimen (including those who died before completion of MDT) or if the diagnosis of dapsone allergy was not supported by the clinical record.

One hundred and five patients were identified from the 6,019 in the database; 101 charts were available for review. Sixty-seven of these individuals (40 of whom were male) had completed a course of MDT. The age range was 16–67 years (mean 36). The classification of leprosy in this group was as follows: tuberculoid six, borderline tuberculoid 21, mid-borderline two, borderline lepromatous leprosy 18, lepromatous leprosy 12, indeterminate one and pure neural leprosy one. A Ridley-Jopling classification was not available for six cases. Fifty-two were initially treated with MB MDT and 15 with PB. The types of adverse reaction diagnosed were: 35 patients with dermatitis, 21 with DHS, two cases of photodermatitis, one case each of hepatitis, Stevens-Johnson syndrome and one of an enanthem. Six records did not state the nature of the adverse reaction to dapsone.

Following the withdrawal of dapsone 60 patients received rifampicin and clofazimine (RC). Three individuals received minocycline in addition to RC, two were treated with prothionamide and RC. One individual received rifampicin, ofloxacin and minocycline and another ofloxacin, minocycline and clofazimine. The mean duration of treatment with a modified MDT regime post-cessation of dapsone was 15 months (range 4–55 months).



**Figure 1.** The variation in mean bacterial index of individual smear positive patients ( $n = 36$ ) taking modified MDT with time since presentation.

Thirty-six individuals, all but one of whom had been initially treated with MB MDT, had positive slit-skin smears at their first presentation. Thirty of these patients received RC. Further slit-skin smears were performed in all 36 during treatment. The variation in mean bacterial index (BI) with time for each patient is shown in Figure 1 and shows a steady decline in mean BI for the majority of individuals similar to that expected with rifampicin, clofazimine and dapsone.

There were no cases of relapse documented in the 67 patients who completed a modified course of MDT.

The retrospective nature of this study means that firm conclusions can not be drawn but our findings suggest that there are a significant proportion of leprosy patients in Nepal who are intolerant of dapsone. The management of these patients with modified MDT using rifampicin and clofazimine appears to be satisfactory. Patients with positive slit-skin smears show a steady decline in their mean BI whilst on RC and there were no cases of relapse in this cohort. It is possible that patients who did relapse were treated elsewhere but as they were complicated cases (in that they had relapse and were also unable to take dapsone) we feel that it is probable they would have been referred back to our centre for specialist care.

Dapsone adverse reactions have been the subject of much discussion on the Leprosy Mailing List recently.<sup>10</sup> The use of dapsone as part of MDT in areas where DHS appears to be a significant problem has been questioned. We believe that prospective data of adverse reactions to the components of MDT would be extremely useful in providing good evidence on which to base any future policy decisions about MDT, particularly in those populations where potentially life-threatening DHS appears to be a frequent adverse event.

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