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Original Article

Study of rifampicin resistance and comparison of dapsone resistance of *M.leprae* in pre-and post-MDT era

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The aim of this study to study the drug resistance patterns of dapsone (pre-and post-MDT) and rifampicin (post-MDT era). All the 84 patients from pre-MDT period (1985-1990) and 77 patients for post-MDT period (1990-2002) reporting to a tertiary care hospital-NJIL & OMD, Agra and referred for drug susceptibility testing were included in the study. Drug resistance was studied by mouse foot pad method. Dapsone resistance was high during pre-MDT era i.e. 8.3% (medium) and 19.1% (high) with an overall dapsone resistance of 27.4%. During the post-MDT era, the dapsone resistance was low i.e. 1.3% (medium) and 3.9% (high) respectively (overall dapsone resistance-5.2%). While no comparison with pre-MDT era is available, the rifampicin resistance in these selected self-reporting cases during the post-MDT era was comparatively rather high (9.1%). MDT appears to have been useful in reducing the prevalence of dapsone resistance in leprosy patients reporting to a tertiary care hospital.

Key words : Drug resistance, MDT, Leprosy

Introduction

Treatment of leprosy at individual patient and at public health level has been one of the most important success stories of the modern medicine. The clinical application of dapsone was a major event in the treatment of this disease. Subsequently, several other drugs like rifampicin (RFM), clofazamine (CLF), prothionamide (PTH), ethionamide (ETH), clarithromycin (CLA), minocycline (MINO) and ofloxacin (OFLO) have been found to effective against *M.leprae*. After the initial success of sulphone, dapsone resistance was first reported by Pettit and Rees (1964) and around that time, dapsone resistance had become a serious public health problem all over the world (WHO 1977) and was reported from the several countries (Matsuo et al 1982, Almeida et al 1983, Balakrishnan et al 1983, Sreevatsa et al 1985, dela Cruz et al 1996). By 1982, secondary dapsone resistance had been reported from more than 25 countries (WHO 1982). Most of the resistance strains were having intermediate to high degree of resistance (Ji 1985). Since 1970s, rifampicin has also been

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essential component of therapy of leprosy. Rifampicin is more bactericidal against *M. leprae* than other anti-leprotic drugs (Shepard et al 1974, Levy et al 1976). It has been found to be highly bactericidal, killing 99% of the bacilli within days by a single dose. It was used initially as monotherapy but subsequently became core drug of multidrug therapy (MDT) (WHO 1982). It kills *M. leprae* with exceptional speed in experimental animals as well as humans (Shepard et al 1974).

Pettit and Rees (1964) first reported dapsone resistance in 5 among 5000 patients in Malaysia. Subsequently in 1973, dapsone resistance among the same patients was estimated to be 25 per 10,000. Later, secondary dapsone resistance was reported from several countries ranging from 13 to 40 per 1000 treated cases. More disturbing fact was the detection of primary resistance in Ethiopia and subsequently in India and in other countries (WHO 1982). As the use of rifampicin began later reports of the rifampicin-resistance started appearing 1976 onwards (Jacobson and Hastings 1976, Hastings and Jacobson 1981, Guelpa - Lauras et al 1984, Grosset et al 1989). Sreevatsa et al (1984) also reported a case of parallel dapsone and rifampicin resistance.

After the introduction of MDT, DDS-and rifampicin resistant strains of *M. leprae* continue to be reported (Butlin et al 1996, dela Cruz et al 1996, Shetty et al 1996, Kai et al 1999, Matsuoka et al 2000, Maeda et al 2001, Cambau et al 2002, Shetty et al 2003). Since MDT was introduced in India in 1983, an effort has been made in this study to compare the drug resistance patterns of dapsone (pre-and post-MDT) and rifampicin (post-MDT era) so as to compare the drug resistance pattern in pre-and post-MDT era.

Materials and Methods

Patients attending the OPD of the institute were the subjects of the study. The patients were classified as in two groups-patients between 1985-1990 (84) who had undergone dapsone monotherapy and the patients from 1990 to 2002 (77) who had been on MDT. All the patients which were referred for drug susceptibility testing to the experimental leprosy lab have been included in this comparison. Bacilli for inoculation into mouse foot pads were obtained by biopsy specimens from active skin lesions. The bacillary suspensions were prepared as per the standard method of Desikan and Venkataramaniah (1976) and as used subsequently at this laboratory (Gupta et al 1997) and 10,000 bacilli were inoculated in a volume of 0.03 to 0.04 ml in both foot pads of mice. BALB/c strains of the mice were used for the experiments. As the purpose of the study to screen the resistance of the organisms to dapsone and rifampicin, the mice were divided into five groups of 6 mice each, one group served as control and other groups received normal commercial chow mixed with dapsone (0.0001 %, 0.001% and 0.01% - low, medium and high) in both pre-and post-MDT era or rifampicin (at concentration of 0.001%, 0.01% and 0. 3% - low, medium and high) respectively in biopsies after post-MDT era. Foot pad harvests were made after 8 and 10 months after inoculation and bacterial enumeration was done as per Desikan and Venkataramaniah (1976**).**

Results

The patterns of the dapsone and rifampicin during pre- and post- MDT era are presented in Table 1. It is apparent from the Table that the dapsone resistance was quite high during pre-MDT era i.e. 8.3% and 19.1% with a overall dapsone of 27.4%. On the other hand during the post-MDT era, the dapsone resistance was quite low i.e. 1.3% (medium) and 3.9% (high) respectively (overall Dapsone resistance 5.2%). Rifampicin resistance in 77 patients during the post-MDT era was comparatively high (9.1%).

Discussion

The high level of dapsone resistance in this study are in agreement with the results of other study (WHO 1982) while intermediate or high degree of resistance was as reported by Ji (1985). The high

Table 1: Drug resistance patterns during pre-and post-MDT era

Patients	Pre 1990 Dapsone		Patients	Post 1990 Dapsone		Patients	Post 1990 RFM
	Med Res	High Res		Med Res	High Res		High Res
84	7 (8.3%)	16 (19.1%)	77 (1.3%)	1 (3.9%)	3 (9.09%)	77	7
Total	**23 (27.4%)**		**Total**	**4 (5.2%)**		**Total**	**7 (9.09%)**

resistance of the dapsone in the pre-MDT era was observed due to the fact that dapsone during that era was being used as monotherapy and subsequently the low proportion of drug resistance to DDS in the post - MDT era in present study could be explained due to MDT which also includes rifampicin and clofazamine which control the emergence of DDS resistant strains. As the susceptibility patterns have been shown only in cases reported to a tertiary care hospital (NJIL&OMD, Agra), the findings of this study cannot be extrapolated epidemiologically. However, the trends are meaningful. DDS-resistant strains continue to be reported even in areas of the world after implementation of MDT (Butlin et al 1986, dela Cruz et al 1996, Kai et al 1999) which might have been due to improper coverage, irregular intake and earlier existing mutants.

As indicated in the Table 1, the rifampicin resistance in post-MDT era was on a higher side which could be biased because of self reporting cases at a tertiary care hospital (NJIL&OMD, Agra). As we do not have data of pre-MDT era, no comments about possible trends can be made. These could be backlog cases who might have been improperly treated. Situation seems to have further improved (no rifampicin resistance during the last 5 years, Gupta et al unpublished data). Based on this study, it is suggested that there is need to start proper drug resistance surveillance study(/ies) so as to monitor the impact of MDT at community level and identification of multidrug resistance (MDR) in relapsed cases in the new integrated setup.

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