A 19-Year Retrospective Study of Adverse Drug Reactions to Multidrug Therapy in Leprosy Requiring a Change in Regime

Abstract

Background and Aims: Multidrug therapy (MDT) in leprosy has brought the prevalence of leprosy to elimination levels. However, these drugs are not without toxicity. The primary aim of this study was to find the prevalence of adverse drug reactions (ADR) to MDT and the secondary aim to study the clinical features of these drug reactions. Materials and Methods: This is a 19-year retrospective descriptive study of all new leprosy cases with ADR to MDT, requiring a change in regime. Results: There were 901 new leprosy cases in the study period. There were 28 cases of documented ADR to MDT necessitating a change in regime, thus accounting for a prevalence of 3.11%. There were 24 males (85.71%) and 4 females (14.29%) with a male/female ratio 6:1. Mean age was 39.58 years. Borderline tuberculoid was the commonest type of leprosy in which ADR were seen (46.43%). Dapsone was the commonest drug to cause ADR seen in 17 cases (60.71%). Hepatic involvement in the form of drug-induced hepatitis was the commonest presentation of ADR in this study accounting for 13 cases (46.43%), followed by skin rash, 9 cases (32.14%). There were no ADR reported to clofazimine. No ADR was reported to the alternative regimes given. Conclusions: The prevalence of ADRs was low in this study, with dapsone being the commonest drug. There were no adverse reactions to clofazimine. No adverse reactions were reported with the alternative regimes of ofloxacin and minocycline.

Keywords: Adverse drug reactions, leprosy, multidrug therapy

Introduction

The World Health Organization (WHO) in 1981 implemented the multidrug therapy (MDT) for leprosy, which was subsequently followed in India in 1982. This robust and proven regime was instrumental in bringing the prevalence of leprosy to less than 1 in 10,000 in India, thus satisfying the WHO parameter for elimination. MDT has been implemented in all the countries where leprosy is prevalent. However, these drugs are not without toxicity. Serious adverse drug reactions (ADR) have been reported with MDT. It is of paramount importance to recognize between serious adverse reactions to MDT and transient non-life-threatening reactions, as the alternative drugs are few in leprosy, unlike tuberculosis. We do occasionally encounter adverse reactions due to MDT in our urban leprosy center of a tertiary care institute, requiring implementation of the alternative regime. The primary objective of this study was to elucidate the prevalence of ADR to MDT, necessitating a change in regime and the secondary objective is to study the clinical features of these drug reactions.

Materials and Methods

This is a 19-year retrospective descriptive study (1997–2015) done in a tertiary care institute. The data were collected from the National Leprosy Eradication Program (NLEP) formatted leprosy cards. The study population included all new leprosy cases with normal baseline investigations and started on MDT who later developed documented ADR, requiring to stop the offending drug or drugs and to implement an alternative regime. The baseline investigations were blood hemogram, liver function tests, renal function tests, chest X-ray, and ultrasound abdomen. Patients who developed mild cutaneous drug reactions such as transient rash and clofazimine-induced pigmentation and ichthyosis, which did not require a change in regime, were excluded from the study. The clinical and demographic details of the cohort were studied in detail. The clinical features of ADR and laboratory data were analyzed and tabulated.

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abnormalities were also studied in detail. Hemolytic anemia was defined as a reduction of hemoglobin and hematocrit values to <42% in males and <36% in females from the baseline. Hepatic abnormalities were defined as bilirubin more than 1.2 mg/100 ml, an increase in the serum levels of aminotransferases, gamaglutamyltranspepdidase and alkaline phosphatase to twice the baseline levels. Dapsone syndrome (DS), rifampicin shock, hemolytic anemia, and drug-induced hepatitis were absolute indications for stopping conventional regime and starting alternative regime (clofazimine, ofloxacin, and minocycline). Dapsone was stopped in cases which developed transient skin rash. After the rash resolved, dapsone was restarted. If there was no rash, dapsone was continued, but if rash reappeared, dapsone was stopped and alternative regime given.

The data collected were analyzed in terms of descriptive statistics. Permission to conduct this study was forwarded to the Institution Review Board, who stated that this is a case records-based retrospective study with no direct patient involvement and permission was not required.

Results
In this 19-year retrospective study, there were 901 new leprosy cases. There were 28 cases of documented ADR to MDT necessitating a change in regime, thus accounting for a prevalence of 3.11%. The salient demographic and clinical features of the cases are given in Table 1. There were 24 males (85.71%) and 4 females (14.29%) with a male/female ratio 6:1. Mean age was 39.58 years, the oldest 75 years and the youngest 9 years. Borderline tuberculoid (BT) was the commonest type of leprosy in which ADR were seen (46.43%). ADR were seen more with multibacillary (MB) therapy, 20 cases (71.43%). The salient clinical features and organ involvement due to ADR are given in Table 2. Dapsone was the commonest drug to cause ADR seen in 17 cases (60.71%). Hepatic involvement in the form of drug-induced hepatitis was the commonest presentation of ADR in this study accounting for 13 cases (46.43%), followed by skin rash, 9 cases (32.14%). There was one case (3.57%) of “flu-like” syndrome due to rifampicin. There were no ADR reported to clofazimine.

The alternative regimes given are were clofazimine (50 mg) + ofloxacin (400 mg) + minocycline (100 mg) for 6 months, followed by clofazimine (50 mg) + ofloxacin (400 mg) for 18 months. No ADR were reported to the alternative regimes given. There was no mortality due to ADR in this study.

Discussion
This retrospective study detected a prevalence of 3.11% of ADR to MDT requiring a change in regime. The low prevalence in this study points to the fact that MDT is very effective and safe. Another reason for the low prevalence in this study is that the study population included only the cases with ADR severe enough to start alternative regimes. Most of the similar studies conducted in India and elsewhere have included all the ADR to MDT, including even transient reactions to MDT. Majority of the patients who are on clofazimine develop pigmentation and ichthyosis, and if these patients are included in a study to detect ADR, a high prevalence will ensue. This will lead to bias and unscientific conclusions. Therefore, we have included only ADR to MDT in this study which necessitated an alternative regime. Moreover, in diseases such as leprosy and tuberculosis, it is imperative to draw the line between serious and transient non-life-threatening ADR as the alternative regimes are few and expensive, especially in a resource-poor country like India. A transient drug rash to dapsone will usually disappear on stopping the drug temporarily and on restarting will not appear.
However, reappearance of the rash is an indication for starting alternative regime as severe drug reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis may follow. A study done by Singh et al., in Chhattisgarh, India detected a high prevalence of 45% ADR to MDT. However, this study, as mentioned above, included all the ADR including transient rash and systemic symptoms such as headache and dizziness. A study in Brazil done by Deps et al. also showed a prevalence of 45% ADR to MDT. This study again included all the adverse reactions, including transient reactions and non-life-threatening adverse reactions. In the present study, ADR were more common in males. This is similar to other studies. This can be explained by the fact that leprosy affects males more than females in all geographic areas. The mean age of patients who had ADR was 39.58 years. This is similar to the study done by Singh et al. BT was the commonest type of leprosy in which ADR were encountered (46.43%). This can be explained by the fact that BT is the commonest type of leprosy seen in our center. Some of the BT cases had six or more lesions or more than two nerve trunks involved, and thus were given MB-MDT. Similar studies have not commented on the type of leprosy in which ADR occurred.

Dapsone was the only commonest single drug to cause ADR in this study, accounting for 60.71%, while ADR to multiple drugs together (dapsone and rifampicin) were seen in 35.71%. This finding is similar to the study by Singh et al. and Deps et al. Skin rash to dapsone was the commonest cutaneous ADR seen in this study accounting for 32.14%. The rash varied from maculo-papular, exfoliative dermatitis to fixed drug eruption [Figure 1]. Vesiculo-bullous rash as mentioned in the literature was not seen in this study. The rash was severe enough and recurrent to start alternative regimes. This prevalence of rash was much higher than other comparable studies. The general prevalence of skin rash was 8.22% in the study by Singh et al., and 7.01% in the study by Deps et al. The prevalence of DS in this study was 7.14%. The prevalence of DS in studies vary from 1.6 to 3.6%. DS is a serious ADR and an absolute contraindication for restarting dapsone, and has to be treated by systemic steroids. The clinical features of DS range from rash, exfoliative dermatitis, vesiculo-bullous lesions, hepatitis, hemolytic anemia to renal failure. Mortality has been reported to DS. In the present study, the rash seen was exfoliative dermatitis and no mortality occurred [Figure 2]. Hepatitis was the commonest systemic ADR seen in this study accounting for 46.43%. Out of this, both dapsone and rifampicin were responsible in 10 cases and dapsone alone in 3 cases. This prevalence is higher than in the study by Singh et al., where it was 30.14% and in the study by Deps et al., it was 35.29%. Before starting MDT, a history of alcoholism is to be carefully taken and baseline investigations should also include viral diseases such as hepatitis A, B, and C, so that any hepatic abnormality should not be erroneously attributed to MDT. The prevalence of hemolytic anemia to dapsone in this study was 10.71%. This compares with the Indian study done by Singh et al., which showed 12.33%. However, in the Brazilian study the prevalence was very
high, 56.5%. This could be due to racial factors. There was one case of “flu-like syndrome” to rifampicin. This is similar to other studies, which show a low prevalence of this ADR to rifampicin.[10] However, in our case it was severe enough to start alternative regime. Interestingly, this study did not show any serious ADR to clofazimine and to the alternate drugs like ofloxacin and minocycline.

In conclusion, this study has shown a low prevalence of ADR to MDT. Dapsone was the commonest drug to cause ADR. Skin rash and hepatitis were the commonest ADR seen. No serious ADR events were reported with clofazimine and the alternative drugs, ofloxacin and minocycline.

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Conflicts of interest
There are no conflicts of interest.

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