

## **Adverse Drug Reactions (ADR) necessitating modification of multi-drug therapy (MDT) in Hansen's disease: a retrospective study from Kerala, India**

BETSY AMBOOKEN\*, SANDHYA GEORGE\*\*,  
NEEMA AZEEZ\*, N ASOKAN\* & TD XAVIER\*\*\*

\**Department of Dermatology and Venereology,  
Government Medical College, Thrissur, Kerala, India*

\*\**Department of Dermatology and Venereology,  
Government Medical College, Kottayam, Kerala, India*

\*\*\**Department of Statistics, St. Thomas College, Thrissur,  
Kerala, India*

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### *Summary*

*Objective:* To assess the frequency and type of adverse drug reactions (ADR) that necessitated modification of multi-drug therapy (MDT) in Hansen's disease, with emphasis to find out the interval between initiation of MDT and the occurrence of ADR.

*Design:* A retrospective analysis of case records of patients diagnosed with Hansen's disease (HD) and registered for MDT in a tertiary care institution between 2010 and 2015. Clinical details and laboratory data were collected using a proforma.

*Results:* One hundred and ninety-six patients were registered for treatment during the study period. We analysed 150 records that met the inclusion criteria. Thirty-six among them (24%) had ADR that needed modification of MDT. The most common ADR was haemolytic anemia (19 patients; 12.7%) followed by hepatitis (14 patients; 9.3%). The most serious ADR was agranulocytosis (three patients; 2%). Adverse effects were more common (72%) during the initial 2 months of MDT compared to later months. ( $P = 0.004$ ).

*Conclusion:* Nearly a quarter of the patients started on MDT for Hansen's disease needed its stoppage and subsequent modification due to ADR. Haemolytic anemia and hepatitis were the most frequent adverse events. 72% of the ADR events occurred during the initial two months of MDT which points to the need for more frequent monitoring of the haemogram and liver function tests during the initial months of treatment.

## Introduction

The introduction of multidrug therapy (MDT) in 1981 by WHO revolutionised the treatment of Hansen's disease (HD).<sup>1</sup> According to WHO, the side effects of MDT are few and relatively mild.<sup>2</sup> However, several severe and fatal adverse drug reactions (ADR), especially to dapsone and rifampicin, have been reported.<sup>3</sup> The serious side effects of dapsone include hemolytic anemia, agranulocytosis, methemoglobinaemia, hepatitis and dapsone syndrome.<sup>1,2,4</sup> Serious ADR to rifampicin are thrombocytopenia, hepatitis, flu-like syndrome and acute renal failure.<sup>1,2</sup> Clofazimine induced side effects are generally mild and includes skin discoloration, ichthyosis and mild gastrointestinal discomfort, which rarely necessitate modification of MDT.

There are very few studies reporting the frequency of severe ADR necessitating modification of MDT. We have observed several life threatening ADR, particularly to dapsone among patients on MDT. Hence we decided to undertake a retrospective chart review of patients who were treated with MDT in our hospital. Our objective was to estimate the frequency and type of ADR that necessitated modification of MDT with emphasis on finding out the interval between initiation of MDT and occurrence of ADR.

## Materials and Methods

**STUDY DESIGN:** Retrospective analysis of case records.

Treatment records of all patients registered to receive MDT between 1st April 2010 and 31<sup>st</sup> March 2015 at the Government Medical College, Thrissur (situated in the central part of Kerala state in south India) were analysed. The study was approved by the Institutional Review Board.

### INCLUSION CRITERIA

Records of only those patients who were started on and completed MDT at our institution during the study period. Incomplete records and records of those who were transferred to other centres for treatment and of those lost to follow-up were excluded. Minor side effects like mild gastrointestinal upset and discoloration of skin which did not necessitate interruption of MDT were not included.

The data collected included demographic details, spectrum of the disease, type of treatment, time of the occurrence and type of ADR that necessitated modification of MDT. Laboratory investigations such as hemogram, urine analysis, liver function tests (LFT), renal function tests (RFT) and chest X ray were also analysed.

Collected data included those at the time of diagnosis, starting of MDT as well as during follow-up (once in 2 weeks during the first 2 months and monthly thereafter till completion of MDT). During each follow-up visit, a detailed clinical evaluation was done by the consultant and any untoward symptoms or signs were recorded in the chart. Investigations such as haemogram and LFT were repeated fortnightly in the first 2 months. Other special investigations such as reticulocyte count, absolute eosinophil count, RFT were done if clinically indicated.

ADR attributed to MDT were defined as undesirable side effects that necessitated modification of MDT. The definitions of serious adverse effects and indications to stop or modify MDT were as follows:

Haemolytic anemia that necessitated modification of MDT was defined as a reduction of blood haemoglobin by  $\geq 2$  gm/dl from the baseline level, accompanied by symptoms such as fatigue, weakness, shortness of breath or jaundice. Leucopenia was defined as a reduction in the total leucocyte count less than 4000 cells/mm<sup>3</sup>. Methaemoglobinaemia was defined as the presence of more than 1% of methaemoglobin in the blood accompanied by sudden onset of shortness of breath, central and or peripheral cyanosis, mental status changes, headache, fatigue, dizziness, loss of consciousness, dysrhythmias or seizures. Such patients were evaluated with a pulse oximeter to look for any decrease in oxygen saturation. A screening test for methaemoglobinaemia was done using filter paper. A drop of blood from the suspected person was placed on the filter paper and compared with a normal control.

Liver dysfunction was defined as any alteration in LFT with or without clinical evidence of jaundice. Elevation of serum aminotransferases to more than twice the upper limit of normal was taken as an indication to stop MDT. In such instances, both dapsone and rifampicin were temporarily stopped. Once the LFT returned to normal, rifampicin was re-introduced first and LFT were repeated three days later. If LFT derangement recurred, rifampicin was discontinued permanently and patient was started on an alternative regimen. If the LFT remained normal, dapsone was also restarted initially at a lower dose with weekly monitoring of LFT, increasing gradually to the full dose.

Flu-like syndrome was defined as fever and malaise within 1–2 hours lasting up to 12 hours after administration of rifampicin. Skin reactions were classified as one of the following types: maculopapular rash or exanthematous eruption, exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, bullous fixed drug eruption and urticaria. Dapsone syndrome was defined as an exfoliative dermatitis and/or other skin rashes, generalised lymphadenopathy, fever, hepatosplenomegaly, blood eosinophilia and hepatitis occurring within 6 to 8 weeks of starting therapy.

Data were entered using MS Excel 2007 and analysed using SPSS 17 (IBM.com). Normal test for difference of proportions (Z test) was used for statistical analysis. A *P* value of 0.05 or less was taken as statistically significant.

## Results

One hundred and ninety-six patients were registered for MDT during the study period. Twenty five (12.7%) patients were transferred to other treatment centers, 12 (6.1%) had incomplete treatment records and nine (4.6%) were lost to follow up. Finally, 150 treatment records that met the inclusion and exclusion criteria were taken up for analysis.

Of these 150 patients, 110 (73.3%) were males (male to female ratio = 2.75:1). The age of the patients varied from 6–72 years. The majority of patients were in the age group of 31–60 years (Table 1).

Treatment with two drugs, monthly rifampicin (R) and daily dapsone (D) for 6 months was given to 52 patients (34.7%) and the three drug regimen (rifampicin, clofazimine (C) and dapsone) for 12 months to 98 patients (65.3%).

Thirty-six patients (24%) developed ADR to MDT necessitating stoppage or modification of the drug regimen. Forty-four events occurred in all, as more than one adverse event

**Table 1.** Age distribution of patients with Hansen's disease

| Age group          | Number of patients ( <i>n</i> = 150) | %      |
|--------------------|--------------------------------------|--------|
| ≤ 30 years         | 55                                   | (36.7) |
| 31–60 years        | 78                                   | (52)   |
| More than 60 years | 17                                   | (11.3) |

occurred in eight patients. In five patients, (three patients with temporary elevation of liver enzymes and two with mild haemolytic anemia) MDT was interrupted only temporarily for a period of 3 to 6 weeks after which we could re-introduce it without any modification and without encountering further serious adverse effects. Of the remaining 31 patients, five developed ADR to rifampicin and 26 to dapson. Five patients who were allergic to rifampicin were given an alternative regimen with clofazimine, ofloxacin and minocycline (COM) for 6 months followed by clofazimine and ofloxacin for 18 months. In the 26 patients who developed ADR to dapson, 16 patients on the three drug regimen (RCD) continued treatment with rifampicin and clofazimine for the remaining 1 year, while dapson was replaced by clofazimine in the 10 patients who were on the two drug regimen (RD) for 6 months.

The majority of ADR occurred in the 31–60 age group (52.8%) (Table 2).

ADR were observed in 26 of 110 males (23.6%) and in 10 of 40 females (25%). Twelve of 52 patients (23%) on the two drug regimen and 24 of 98 patients (24.5%) on the three drug regimen developed ADR. (Table 2). There were no statistically significant differences in the overall frequency of ADR with respect to age, gender or treatment regime using the Z test in our study. ( $P = > 0.05$ )

The most common ADR encountered was haemolytic anemia (19 patients; 12.7%) followed by hepatitis (14; 9.3%). Haemolytic anemia was more frequent among females (22.5%) compared to males (9%). On the contrary, hepatitis was seen more commonly in males (11.8%) compared to females (2.5%). However, no statistically significance difference was observed on analysing the incidence of hepatitis and haemolytic anemia with respect to gender (Table 3) and type of drug schedule (Table 4).

The other observed side effects were maculopapular rash in four (2.7%), agranulocytosis in three (2%), flu-like syndrome in two (1.3%), acute renal failure and methaemoglobinaemia in one patient each (0.7%) (Table 2). The adverse events observed due to rifampicin included hepatitis in two patients, flu-like syndrome in two patients and acute renal failure in one patient.

Methaemoglobinaemia was diagnosed in one female patient (0.7%) who developed a bluish discoloration of her finger tips three months after starting MDT with three drugs (RCD). Dapson was stopped in this patient and Vitamin C 500 mg was given twice daily for 1 month.

Maculopapular rash was observed in four patients. They had severe itching and the rash subsided with severe exfoliation. The rash developed between 10 and 26 days after starting MDT. Dapson was stopped in these patients. None of them had features to suggest Dapson syndrome.

Agranulocytosis observed in three of our patients was perhaps the most serious complication noted in our study. Two patients had to be hospitalised due to severe bone

**Table 2.** Distribution of ADR with respect to age, gender, time of onset and type of treatment

| ADR*                | ≤ 30 years<br>(n = 55) |   | 31–60 years<br>(n = 78) |    | > 60 years<br>(n = 17) |    | Male<br>(n = 110) |   | Female<br>(n = 40) |  | Onset<br>< 2 months |  | Onset<br>> 2 months |  | Two drug regime<br>(RD)<br>(n = 52) |  | Three drug regime<br>(RCD)<br>(n = 98) |  |
|---------------------|------------------------|---|-------------------------|----|------------------------|----|-------------------|---|--------------------|--|---------------------|--|---------------------|--|-------------------------------------|--|--|--|
|                     |                        |   |                         |    |                        |    |                   |   |                    |  |                     |  |                     |  |                                     |  |  |  |
| Hemolytic anemia    | 7                      | 9 | 3                       | 10 | 9                      | 13 | 6                 | 7 | 12                 |  |                     |  |                     |  |                                     |  |  |  |
| Hepatitis           | 5                      | 8 | 1                       | 13 | 1                      | 11 | 3                 | 3 | 11                 |  |                     |  |                     |  |                                     |  |  |  |
| Agranulocytosis     | 1                      | 2 | –                       | 3  | –                      | 3  | –                 | 1 | –                  |  |                     |  |                     |  |                                     |  |  |  |
| Maculopapular rash  | 1                      | 1 | 2                       | 4  | –                      | 4  | –                 | 2 | –                  |  |                     |  |                     |  |                                     |  |  |  |
| Flu like syndrome   | –                      | 2 | –                       | 2  | –                      | 1  | 1                 | – | –                  |  |                     |  |                     |  |                                     |  |  |  |
| Methemoglobinemia   | –                      | 1 | –                       | 1  | –                      | –  | –                 | – | –                  |  |                     |  |                     |  |                                     |  |  |  |
| Acute renal failure | –                      | 1 | –                       | –  | –                      | –  | –                 | – | –                  |  |                     |  |                     |  |                                     |  |  |  |

\*More than one side effect was observed in 8 patients. 44 adverse events in 36 patients.

**Table 3.** Relationship of haemolytic anemia and hepatitis with gender

| ADR              | Male<br>$n = 110$ | Female<br>$n = 40$ | Proportion $x/n$ |          | P1-P2     | Z value | 95 % CI interval        | P value | Fisher's exact<br>test P value |
|------------------|-------------------|--------------------|------------------|----------|-----------|---------|-------------------------|---------|--------------------------------|
|                  |                   |                    | P1               | P2       |           |         |                         |         |                                |
| Hemolytic anemia | X = 10            | X = 9              | 0.090909         | 0.225000 | -0.134091 | 1.88    | -0.274207 to 0.00602513 | 0.061   |                                |
| Hepatitis        | X = 13            | X = 1              | 0.118182         | 0.025000 | 0.0931818 | 2.36    | 0.158493 to 0.170414    | 0.018   | 0.114                          |

$n$  is the total number of patients analysed.

$x$  is the number of patients who developed ADR.

\* NOTE. The normal approximation may be inaccurate for small samples. Hence Fisher's exact test in case of hepatitis.

**Table 4.** Relationship of haemolytic anaemia and hepatitis with the type of treatment regime

| ADR              | Two drug regime<br><i>n</i> = 52 |                                | Three drug regime<br><i>n</i> = 98 |          | Proportion ( <i>x/n</i> ) |       | P1-P2                  | Z value | 95% CI interval | P value |
|------------------|----------------------------------|--------------------------------|------------------------------------|----------|---------------------------|-------|------------------------|---------|-----------------|---------|
|                  | <i>x</i> = 7<br><i>x</i> = 3     | <i>x</i> = 12<br><i>x</i> = 11 | P1                                 | P2       | P1                        | P2    |                        |         |                 |         |
| Hemolytic anemia |                                  |                                | 0.134615                           | 0.122449 | 0.0121664                 | 0.21  | -0.101050 to 0.125383  | 0.833   |                 |         |
| Hepatitis        |                                  |                                | 0.057692                           | 0.112245 | -0.0545526                | -1.20 | -0.143559 to 0.0344534 | 0.230   |                 |         |

*n* is the total number of patients analysed.

*x* is the number of patients who developed ADR.

**Table 5.** Relationship of time of onset of ADR with the duration of therapy

| ADR             | N   | X  | Proportion X/N            | P <sub>1</sub> -P <sub>2</sub> | Z value | 95% CI                | P value |
|-----------------|-----|----|---------------------------|--------------------------------|---------|-----------------------|---------|
| Within 2 months | 150 | 26 | P <sub>1</sub> = 0.173333 | 0.106667                       | 2.88    | 0.0341196 to 0.179214 | 0.004   |
| After 2 months  | 150 | 10 | P <sub>2</sub> = 0.066667 |                                |         |                       |         |

N is the total number of patients analysed.

X is the number of patients who developed ADR.

marrow suppression and agranulocytosis 4 weeks and 6 weeks after MDT which necessitated blood transfusion. In one patient, who was asymptomatic, the total leucocyte count fell to 3500 cells/mm<sup>3</sup> associated with a low neutrophil count (15%) in the second week after starting MDT with two drugs. Dapsone was discontinued immediately in this patient. The blood counts returned to normal within 10 days.

Acute renal failure was diagnosed in one patient who complained of severe reduction in urine output soon after the third pulse of rifampicin. Routine urine examination showed albuminuria, blood urea nitrogen was 76 mg/dl and serum creatinine was 2.3 mg/dl. MDT was discontinued. Once the RFT returned to normal, clofazimine, ofloxacin and minocycline (COM) was started, which the patient tolerated.

Twenty-six patients (72.2 %) developed ADR during the first 2 months of MDT whereas 10 patients (27.8%) developed ADR after 2 months ( $P = 0.004$ ) (Table 5).

Adverse effects observed during the first 2 months and later are given in (Table 2). Of the 36 patients with ADR in relation to MDT, six patients had Type I reaction and five had Type II lepra reaction. Eight of these patients had lepra reaction at the time of diagnosis and were treated with tapering doses of systemic corticosteroids from the beginning. Three patients developed lepra reactions later. From the cohort studied, lepra reactions or its management did not influence the onset or course of ADR.

## Discussion

Thirty-six (24%) of the 150 patients in the present series developed adverse events that necessitated modification of MDT. However in five patients MDT could be restarted after temporary cessation. Dapsone induced side effects were observed in 26 (17.3%) patients whereas five (3.3%) patients developed side effects to rifampicin. None of the patients required stoppage of clofazimine.

Deps *et al.* reported adverse effects in 45% of the patients treated with MDT and 24% of patients had to be given an alternative treatment regimen.<sup>5</sup> Goulart *et al.* reported side effects to MDT in 37.9% of patients and 14.9% required an alternative regimen.<sup>6</sup> Singh *et al.* reported that only 5% of patients in their series required alternative treatment.<sup>7</sup> Geographic and ethnic differences may contribute to such variations in the frequency of ADR. Meticulous follow-up also may be another contributing factor.

There was no difference in the overall incidence of ADR between the two and three drug regimens in our study. This is in contrast to several other studies.<sup>3,8</sup> This is probably because minor side effects like clofazimine-induced pigmentation which is observed exclusively in



the three drug regimen was not taken into consideration as it did not necessitate modification of MDT. Hence the introduction of Uniform MDT is unlikely to influence the incidence of drug-related side effects according to our study. Shortening the duration of MDT might not reduce the incidence of dapsone or rifampicin induced side effects as the majority occur in the initial months, but might result in a potential loss of opportunities to detect complications due to disease *per se*.

The majority of ADR were observed in the age group 31–60 years probably because the study population predominantly consisted of that age group. Drug allergy is known to occur more frequently among the young and middle aged rather than among the elderly population.<sup>9,10</sup> There was also no statistically significant difference in the overall incidence of ADR in male and female patients which is in contrast to a few other studies which noted a female preponderance.<sup>3,5</sup>

The major cause for modification of MDT in our series was dapsone-induced haemolytic anemia. A similar observation was also made by Dupnik *et al.* Although there were no statistically significant difference in the incidence of ADR among males and females, haemolytic anemia showed a female preponderance (22.5%) compared to 9% among males. Similar observations of anemia occurring more among women have been reported in other studies.<sup>3,6</sup> The exact cause of haemolytic anemia could not be ascertained. G6PD levels tested were found to be normal in four of the patients tested for it. Dapsone induced anemia tends to occur even in individuals with normal G6PD levels.<sup>3</sup> Baseline haemoglobin levels were low (10.5–11.5 gm/dl) in eight patients, which could have been one contributing factor to the severity of anemia. It also needs to be studied whether such patients would be benefitted by a lower dose of dapsone and correction of anemia. Two of our patients who were restarted with a lower daily dose (50 mg) of dapsone subsequently tolerated the full dose (100 mg). But three of our patients did not respond to these measures and we had to discontinue dapsone permanently. Detection and correction of all possible causes of anemia is essential as a 1–2 gm/dl fall in haemoglobin is inevitable in most patients.<sup>11</sup> Proper counseling of patients and periodic monitoring may decrease default from MDT due to anemia.

Hepatitis was the second most common ADR. In all these cases, other causes of hepatitis were sought and excluded. Since rifampicin and dapsone are both known to cause toxic hepatitis, it is usually difficult to ascertain the culprit drug in such cases. In our series both drugs were temporarily discontinued and expert opinion from a gastroenterologist was sought prior to modification of MDT. Rifampicin induced hepatitis was suspected in two patients and dapsone induced hepatitis in nine patients. In the remaining three patients liver enzymes returned to normal after temporary discontinuation of MDT. A higher incidence of drug induced hepatitis necessitating modification of MDT was observed in our study compared to other studies.<sup>7,8</sup> Hepatitis showed a male preponderance (11.8%) compared to 2.5% in females. It was also more frequent in those taking MB (11.2%) compared to PB treatment (5.7%). Further studies with a larger sample size are needed to analyse the contributory factors for drug induced hepatitis. Although previous studies have detected hepatic abnormalities due to rifampicin and dapsone, stringent monitoring of LFT has not been stressed.<sup>5,6,12</sup>

Severe flu-like syndrome was observed in two patients. Flu-like syndrome can herald the development of severe ADR associated with intravascular haemolysis and renal failure.<sup>13</sup> Rifampicin was discontinued in both patients and they were treated with the COM regime.

The main limitation of our study is its retrospective design. The exclusion of forty-six of the 196 patients (23.5%) who were registered initially but had incomplete data, may also

influence the results. It is also possible that being a tertiary care centre, a higher frequency of ADR might have been detected due to closer monitoring. A reasonably large sample size and proper evaluation of patients who met with systemic complications by specialists are the major strength of our study.

Contrary to the widely held view that side effects to MDT are few and relatively mild, a higher frequency of serious ADR including potentially fatal conditions such as agranulocytosis, haemolytic anemia and hepatitis were noted in our study; 72% of the adverse events occurred in the initial 2 months of MDT in our study. Similar observations of side effects to MDT and derangement of hepatic and other haematological parameters was observed by Dupnik *et al.* and Al-Sieni *et al.* during the first 3 months of MDT.<sup>3,12</sup> This has important operational implications and underlines the need for closer monitoring of patients started on MDT which may be done using simple blood tests such as haemogram and LFT once in 2 weeks, especially in the initial 2 months.

In our institution, we routinely counsel the patients regarding the commonly encountered symptoms of side-effects related to MDT. Counseling is done by both the Medical Officer in charge and the non-medical programme officer who dispenses the blister packets. Findings of this study prompt us to suggest the need to have standard and structured pre-treatment counseling to be incorporated in the national guidelines. This would enhance the safety of MDT thereby increasing its acceptability.

## Conclusion

Nearly one quarter of the patients started on MDT for Hansen's disease in a tertiary care hospital needed its stoppage and subsequent modification due to ADR. Haemolytic anemia and hepatitis were the most frequent adverse events; 72% of the adverse events occurred during the initial 2 months of MDT compared to later months. ( $P = 0.004$ ). Irrespective of age, gender and type of treatment we need to monitor all patients started on MDT by repeating the haemogram and LFT at least once in 2 weeks during the initial 2–3 months. This would help in the early detection of potentially fatal complications like agranulocytosis, haemolytic anemia and hepatitis.

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