Original Article

Dapsone-induced haemolysis among leprosy patients on MDT from an endemic area of central India

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Abstract

Background and Aim: Haemolysis due to dapsone as a part of MDT in leprosy patients has been long recognized. However, the frequency and severity of this side effect and factors associated with it have not been well documented. We planned to determine the frequency of dapsone-induced haemolysis in leprosy patients on MDT and various risk factors associated with it. **Materials and Methods:** This was a hospital-based retrospective analysis, conducted on 36 treatment completed or partially treated or on treatment leprosy patients in a tertiary care centre in Chhattisgarh. **Results:** Out of 36 patients, 83.3% showed a fall in haemoglobin from the baseline value (pre-treatment values). Dapsone was stopped in 33.3% of patients with a significant fall in haemoglobin. We found that the mean haemoglobin concentration for all patients fell from 13.05(+/−1.8) g/dl to 11.8(+/−1.9) g/dl ($P < 0.05$) which was statistically significant. A total of 25% of patients were labelled as confirmed cases of dapsone-induced haemolysis as per our definition. **Conclusion:** Our results underline the need to incorporate haematological investigations in leprosy management protocol, especially in primary care settings where the majority of leprosy patients are managed.

Keywords: Dapsone, haemolysis, leprosy

Introduction

Leprosy continues to be a major public health problem in India, despite an effective treatment regime. Chhattisgarh state has a prevalence rate of leprosy of 2.08 per 10,000 population, the highest in India.[1] Leprosy is curable with a combination of three drugs: dapsone, rifampicin, and clofazimine known as multidrug therapy (MDT), which was recommended by WHO in 1981.[2] The majority of leprosy patients are managed at the primary care level by primary care physicians.

Dapsone (4,4-diamino-diphenyl sulfone) inhibits bacterial synthesis of dihydrofolic acid.[3] Major adverse effects of dapsone are methaemoglobin formation, haemolysis and agranulocytosis.[4] Dapsone-induced haemolysis is common and individuals with a deficiency of erythrocytic glucose-6-phosphate dehydrogenase (G-6-PD) enzyme are more susceptible.[5] However, acute haemolysis can also occur in persons with normal G-6-PD activity. There are few studies on haemolysis in patients receiving dapsone as a part of MDT.

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Materials and Methods

This was a hospital-based retrospective analysis conducted at the Dermatology OPD of a tertiary care institute in Chhattisgarh from 1 July 2019 to 31 August 2019 after clearance from the Institutional Ethics Committee (AIIMSRPR/IEC/2019/279).

Inclusion criteria

Leprosy patients on MDT or who have completed MDT and whose medical records showed a baseline pre-treatment haemoglobin percentage and a repeated haemoglobin percentage done 1 month after starting MDT.

Exclusion criteria

1. Patients diagnosed with G-6-PD deficiency.
2. Patients on other drugs known to cause haemolysis.
3. Patients who did not take dapsone.
4. Patients on iron and folic acid.
5. Patients with eosinophilia.
6. Patients who have a diagnosed condition associated with haemolytic anaemia.

Demographic details, clinical details and treatment status of patients were noted down from the medical records. Laboratory parameters of pre-treatment haemoglobin, RBC indices, repeated value of haemoglobin percentage after 1 month of MDT, repeated RBC indices, reticulocyte count and lactate dehydrogenase levels, if available were noted down. The medical records were also checked for G-6-PD deficiency and sickle cell anaemia. Dapsone-induced haemolysis was defined as a decrease in haemoglobin with the presence of at least one laboratory marker of haemolysis (reticulocyte count/LDH) and an improvement in haemoglobin after discontinuation of dapsone.[6] All the patients with a fall in haemoglobin were started on oral iron supplements, and none of those patients needed a transfusion. The leprosy patients for whom dapsone was stopped, were continued on monthly Rifampicin and clofazimine and daily clofazimine. Dapsone was restarted, only if and when the haemoglobin recovered to pre-treatment values.

Results

After the application of inclusion and exclusion criteria, 36 leprosy patients were included in the study. The gender distribution showed a male preponderance with 64% (n = 23) males and 36% (n = 13) females. Most 89% (n = 32) of our patients were below 50 years of age. According to NLEP modified WHO classification, all of our patients had multibacillary (MB) type of leprosy. The proportion of borderline tuberculoid patients (44.4%) was highest, followed by lepromatous leprosy (33.3%), borderline lepromatous (19.4%) and mid-borderline (2.8%). We found 47.2% of our leprosy patients in reaction at the time of data collection (22.2% type 1 + 25% type 2).

Out of 36 patients, 83.3% (n = 30/36) showed a fall in haemoglobin from baseline value (pre-treatment values), Dapsone was stopped in 33.3% (n = 12/36) patients because of either a significant fall in haemoglobin (≥2 g/dl) or a low absolute haemoglobin [Figures 1 and 2]. The average fall in haemoglobin concentration for our patients was from 13.05 (±1.8) g/dl to 11.8 (±1.9) g/dl ($P < 0.05$) [Table 1] and 70% had a fall in haemoglobin concentration of 1 g/dl or more. Of those, 46.6% (n = 14/30) had a haemoglobin fall between 1.0 g/dl and 1.9 g/dl, 3.3% (n = 1/30) between 2.0 g/dl and 2.9 g/dl and in 20% (n = 6/30) haemoglobin concentration fell more than/equal to 3 g/dl [Figure 3].

Out of the 12 patients in whom dapsone was stopped, 75% (n = 9 out of 12) patients were labelled as confirmed cases of dapsone-induced haemolysis as per our definition [Figure 2]. In 25% (n = 3/12) patients, laboratory markers of haemolysis (raised LDH levels/reticulocyte count) were unavailable and hence they were labelled as suspected cases of haemolysis [Figure 2]. Out of the remaining 18 patients in whom dapsone was not stopped, 11% (n = 2/18) patients had raised laboratory markers of haemolysis (raised LDH levels/reticulocyte count) and hence they were also labelled as suspected cases of haemolysis [Figure 2]. In males, the mean fall in haemoglobin was found to be 0.8 g/dl. Females, who had a lower level of mean baseline haemoglobin showed a fall of 1.8 g/dl in their mean haemoglobin levels. The screening revealed that 11% (n = 4 out of 36 patients) of patients had a positive sickling test but there was no co-relation with fall in haemoglobin.

Overall, patients with LL type of leprosy had the lowest mean baseline haemoglobin levels and their mean fall in haemoglobin concentration was found to be 0.8 g/dl. Patients with BT and BL type of leprosy had a fall of 1.4 g/dl and 1.5 g/dl, respectively

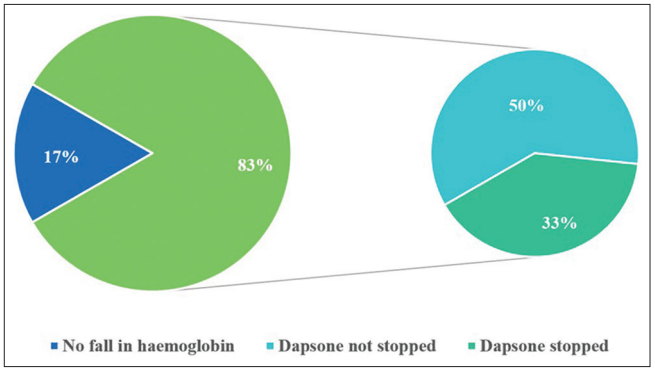

Figure 1: Proportion of patients regarding fall in haemoglobin

Table 1: Assessment of mean fall in haemoglobin and stoppage of dapsone

Parameter	Before treatment (Mean +/−SD)	After treatment (Mean +/−SD)	N	*P*-value (by paired-*t*-test)
Mean haemoglobin (g%)	13.05 (+/−1.8)	11.8 (+/−1.9)	36	0.00002

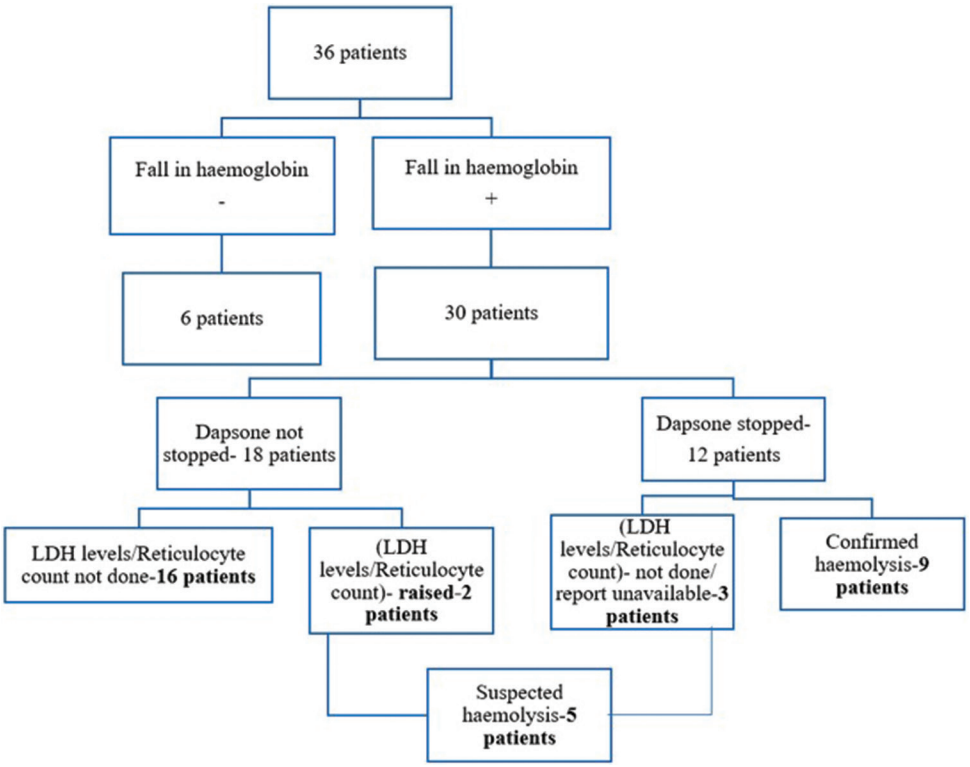

Figure 2: Flowchart showing outcomes for patients started on therapy with dapsone

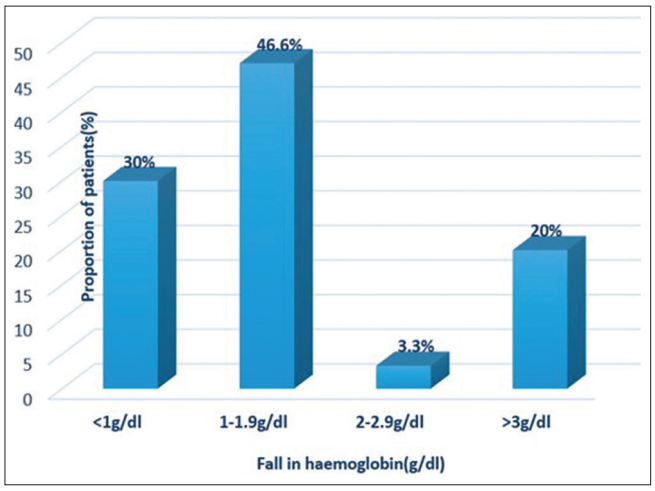

Figure 3: Distribution of patients with falls in haemoglobin

in their mean haemoglobin concentration. Patients with type 2 lepra reaction had lower mean baseline haemoglobin levels and their mean fall in haemoglobin concentration was found to be 0.7 g/dl. Patients with type 1 lepra reaction had a fall of 1.4 g/dl in their mean haemoglobin concentration.

Discussion

Dapsone (4,4 -diamino-diphenyl sulfone) is an aniline derivative belonging to the group of synthetic sulfones.[3] Dapsone has been used extensively for the treatment of leprosy, and other dermatological disorders like dermatitis herpetiformis and vasculitis. Dapsone is metabolized mainly in the liver where it undergoes hydroxylation by cytochrome P-450 enzymes, resulting in the generation of dapsone hydroxylamine (DDS-NOH). This hydroxylamine metabolite is held responsible for some of the major adverse effects of dapsone including methaemoglobin formation, haemolysis and agranulocytosis.[4]

The age and gender distribution in our study was similar to the majority of previous studies,[7-11] although a study from Brazil showed female predominance and the majority of patients were older.[12] We found only multibacillary leprosy patients, similar to previous Indian studies done in Kerala and Chhattisgarh with more MB patients[7,8] but in contrast to a study from Brazil[12] with more paucibacillary (PB) leprosy patients. We found a higher percentage of leprosy patients in reaction, in contrast to a retrospective study of 531 leprosy patients in Delhi which showed the prevalence of reactions to be 12.8% (n = 68 out of 531) with a prevalence of 8.09% for the type 1 and 4.70% for the type 2 reactions.[13] Another cross-sectional study of 211 patients with leprosy reactions in Brazil showed type 1 reaction in 64.5% (n = 136 out of 211) of patients, followed by the type 2 reaction, with 30.8% (n = 65 out of 211) of patients.[14] Possibly, patients with leprosy reaction and more specifically chronic and recurrent type 2 reaction are in greater distress and more likely to visit a tertiary care centre in a high endemic region.

The retrospective study conducted in San Francisco shows results similar to us with the mean haemoglobin

Table 2: Comparison of different studies*(confirmed cases of haemolytic anaemia as per our definition)

	Brazil[12]	Kerala, India[8]	Bastar (Chhattisgarh, India)[7]	Present study (Chhattisgarh, India)
Study Duration	8 months	6 years	2 years	2 months
Sample size	194	150	176	36
Haemolysis due to dapsone	48 (24.7%)	19 (12.7%)	9 (5%)	9 (25%)*
Stoppage of Dapsone due to haemolysis	25 (12.8%)	19 (12.7%)	2 (1.09%)	12 (33.3%)

concentration for all patients falling from 14·25 (±1·27 g/dl) to 12·31 (±1·61) ($P < 0.001$) and 83% having a fall in haemoglobin concentration of 1 g/dl or more,[9] but it was significantly higher than data from an older study done in India.[15] Our 25% confirmed cases of haemolysis were similar to studies done in Brazil (24.7%)[12] but substantially higher than earlier studies done in India (5–13%) [Table 2].[7,8] This may be due to ethnic variations of population in different geographic areas. Also, the definition of haemolysis differed between different previous studies. Higher falls in haemoglobin in females, similar to our study have been reported in other studies.[8,9,16] However, dapsone-induced haemolysis showed no significant association with either type of leprosy or lepra reaction status of the patient. Lower mean baseline haemoglobin levels in patients with type 2 lepra reaction were probably due to the chronic nature of type 2 lepra reaction.

Our study was a time-bound, hospital-based, retrospective study with a small sample size and it emphasizes the need for larger community-based studies. We found out very high burden of dapsone-induced haemolysis which led to the stoppage of dapsone in many of these patients. Therefore, we should monitor all patients on MDT by recording at least a baseline and a repeat haemoglobin percentage for early detection of dapsone-induced haemolysis, especially in primary care settings where the majority of the leprosy patients are managed.

Take home message

1. Dapsone-mediated haemolysis is a significant problem among leprosy patients in Central India
2. We should monitor all leprosy patients on MDT by recording at least a baseline and a repeat haemoglobin percentage after 1 month of MDT for early detection of dapsone-induced haemolysis.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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