JPDS Journal of the Philippine Dermatological Society

ORIGINAL ARTICLE

Dapsone-induced hemolytic anemia in non-G6PD deficient leprosy patients receiving multidrug therapy in Southern Philippines Medical Center: A retrospective study

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ABSTRACT

BACKGROUND Due to the high prevalence and incidence of leprosy in the Philippines, there is a continuing need to detect and document the occurrence of dapsone-induced hemolytic anemia.

OBJECTIVE The aim of this study is to determine the incidence of dapsone-induced hemolytic anemia in non-glucose-6-phosphate dehydrogenase deficient leprosy patients receiving multidrug therapy (MDT) in Southern Philippines Medical Center.

METHODOLOGY This is a retrospective study through chart review of leprosy patients treated with MDT regimen at Southern Philippines Medical Center from January 2016 to December 2018. The demographic profile, clinical characteristics, hemoglobin and hematocrit concentrations before and after initiation of MDT, the presence of symptoms of anemia, and the occurrence of dapsone-induced hemolytic anemia in leprosy patients were collected. The main outcome measure for this study was the incidence rate of dapsone- induced hemolytic anemia. Statistical-based analysis were used for continuous and categorical data which were summarized using means and standard deviations, and frequencies and percentages, respectively.

RESULTS There was a decrease in the mean hemoglobin and hematocrit levels noted in the majority of patients after initiation of MDT from baseline 143.46 g/dl and 0.44, respectively, to 94 g/dl and 0.28 on the third month of MDT. The incidence rate of dapsone-induced hemolytic anemia during the 3-year period was 20 cases per 100.

CONCLUISON The relatively high incidence rate of dapsone-induced hemolytic anemia highlights the importance of frequent monitoring of hemoglobin and hematocrit concentrations in leprosy patients being treated with multidrug therapy.

KEYWORDS Hansen's disease, leprosy, dapsone, hemolytic anemia

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Conflict of interest
None

Source of funding
None

INTRODUCTION

Leprosy, also known as Hansen's disease, is a chronic granulomatous infection caused by *Mycobacterium leprae*, and recognized as a neglected tropical disease. Despite efforts to eliminate this debilitating disease, it is far from being eradicated in the Philippines. The prevalence of leprosy in the Philippines is less than 0.4 cases per 10,000 and approximately 1,700 new cases are identified each year according to the Department of Health (DOH).[1] Likewise, Hansen's disease belongs in the top 10 most common reasons for consult in the Southern Philippines Medical Center (SPMC) Department of Dermatology. Based on the institution's census in 2018, there were 39 new cases of leprosy out of the 15,000 patients seen at the outpatient department with an average of 3 new patients per month. Therefore, the incidence rate and the prevalence rate of this disease in 2018 based on this data are 0.39, and 7.96 per 10,000, respectively.[2] Based on a study by Guinto et al., the average annual mortality rate for lepromatous leprosy patients was 5.1 times higher than that of the general population.[3] While leprosy is not often the immediate cause of death, sequelae from the disease and adverse events from medications can contribute to mortality.

The multidrug therapy (MDT) is an ef-

fective regimen for the treatment of leprosy. This regimen includes rifampcin 600 mg monthly, clofazimine 300 mg monthly and 50 mg daily, and dapsone 100 mg daily for adults. The duration of treatment depends on the type of leprosy: 6 months for paucibacillary and 12 months for multibacillary leprosy. Adverse effects to these drugs are uncommon and are mostly related to dapsone.[4]

Dapsone (4'4'-diaminodiphenylsulfone), one of the drugs included in the MDT, has a bacteriostatic effect on *Mycobacterium leprae* by the inhibition of dihydrofolate synthetase enzyme.[5] It has many adverse effects which include allergic reaction, exfoliative dermatitis, hemolytic anemia, jaundice, peripheral neuropathy, agranulocytosis, methemoglobinemia and dapsone hypersensitivity syndrome.[6,7,8] Based on the data from the Department of Dermatology of SPMC, there was one (1) case of dapsone hypersensitivity syndrome out of twenty-six (26) leprosy patients treated with MDT in 2018. Hence, the incidence rate of this adverse drug reaction is 3.84 cases per 100.[2] A study by Guragain et al. reported that four (4) patients died out of eighteen (18) cases secondary to dapsone adverse reaction.[6]

Hemolysis is the process of premature destruction or removal of erythrocytes from the circulation, which manifests as jaundice, cholelithiasis, anemia or isolated reticulocytosis.[9,10] This can either be inherited or acquired. In drug-induced hemolytic anemia, certain medications may cause an immune response that eventually destroys the erythrocytes. The clinical and laboratory findings of this type of hemolytic anemia are identical to autoimmune hemolytic anemia but with the remission of the disease attributed to the discontinuation of the causative drug.[11] Several laboratory tests are used to confirm the diagnosis of hemolytic anemia. Complete blood count is the first test requested to diagnose anemia. The most direct indicator of severity of hemolysis is the hemoglobin level.[12] Another test is the reticulocyte count, which is usually elevated in individuals with hemolytic anemia secondary to the response of the bone marrow to compensate for the loss of red blood cells.[9] Hemolytic anemia is suspected if there is anemia and reticulocytosis. Peripheral blood smear may reveal the presence of schistocytes or fragmented RBCs, which suggests intravascular hemolysis. Other laboratory findings suggestive of hemolysis include increased serum lactate dehydrogenase (LDH) and bilirubin, decreased haptoglobin, normal alanine aminotransferase (ALT) and hemosiderinuria. Direct and indirect Coombs tests may also reveal the presence of antibodies against red blood cells leading to its premature removal.[13]

Dapsone is primarily metabolized in the liver through N-acetylation and N-hydroxylation. Within the erythrocytes, the metabolite hydroxylamine, generates reactive oxygen species which are responsible for oxidation of oxyhemoglobin into methemoglobin. This process renders the erythrocytes senescent and these are removed prematurely by the spleen. Individuals with normal glucose-6-phosphat e dehydrogenase (G6PD) levels have the ability to reverse this oxidative damage by synthesis of glutathione within the erythrocytes. G6PD deficient patients are at increased risk of developing hemolytic anemia.[8,14] However, the hemolytic process may also occur in patients without G6PD deficiency and occurs in a dose-dependent fashion.14 This adverse drug reaction can lead to morbidity and mortality if not diagnosed and treated early.

A study conducted by Deps et al revealed that the dapsone used in the treatment of leprosy causes significant hemolytic anemia. The symptoms of hemolytic anemia were noted to appear within the first three (3) months of MDT regimen in the majority of patients (51%). In the study, the diagnosis of hemolytic anemia was made if the hemoglobin level was 12.7 g/dl or less for men and 11.5 g/dl or less for women, and/or the hematocrit level was less than 42% for men and 36% for women. At the end of the study, there was noted significant decrease in the mean hemoglobin and hematocrit concentrations.[7]

Another retrospective study by Guragain et al revealed that hemolytic anemia, along with jaundice and exfoliative dermatitis, were common adverse drug reactions in leprosy patients taking dapsone accounting for 22.22%.[6] A study conducted in Indonesia reported that the incidence of hemolytic anemia after 3 months of MDT was 66.7% with a significant decreased in hemoglobin level and an increased reticulocyte count.[5]

In leprosy patients undergoing treatment with MDT, 83% were reported to have a decrease in hemoglobin concentration of more than or equal to 1 g/dl, and 16% of patients had a decrease in hemoglobin concentration more than or equal to 3 g/dl. In addition, decreasing the daily dose of dapsone led to an increase in the hemoglobin level. These findings suggest that dapsone-induced hemolytic anemia is dose-related.[15]

Due to the high incidence and prevalence of leprosy in the Philippines, there is a need for the clinicians to familiarize themselves with the occurrence of adverse drug reactions after initiation of MDT. To this date, there has been no published study in the Philippines on dapsone-related adverse events.

This study aims to determine the incidence of dapsone-induced hemolytic anemia in non-G6PD deficient leprosy patients receiving multidrug therapy in SPMC.

Furthermore, we also aim to describe the dermatographic profile of leprosy patients seen at our center and determine their hemoglobin levels before and after initiation of MDT therapy.

METHODOLOGY

A descriptive study design was utilized for this study. This retrospective study was conducted using a chart review. Leprosy patients treated with MDT regimen for a minimum of 6 months at the Department of Dermatology in SPMC from January 2016 to December 2018 were included in the study. Exclusion criteria were the following: Leprosy patients diagnosed with G6PD deficiency and were given a treatment regimen without dapsone, those who had pre-existing anemia prior to initiation of MDT, those who started with MDT prior to the first consult, and those with incomplete data on the chart.

Upon approval by the Ethics Board Committee, the names of the patients diagnosed with Hansen's disease were retrieved from the leprosy central registry logbook, dermatopathology logbook and outpatient logbook of the department. Chart retrieval was requested from the SPMC medical records section. Demographic data, leprosy disease spectrum, as well as hemoglobin and hematocrit concentrations before and after initiation of therapy were gathered. We defined dapsone-induced hemolytic anemia as a hemoglobin level of 12.7 g/dl or lower for men and 11.5 g/dl or lower for women after initiation of therapy. These were the independent variables of the study. The main outcome of the study was the incidence rate of dapsone-induced hemolytic anemia in leprosy patients treated with multidrug therapy. Continuous data were summarized as means + standard deviations. Categorical data were summarized using frequencies and percentages. All statistical tests were done using Epi Info 7.2.2.6.

RESULTS

A total of eighty (80) leprosy patients treated with multidrug therapy (MDT) in the Department of Dermatology of Southern Philippines Medical Center from January 2016 to December 2018 were included in the study.

A. DEMOGRAPHIC PROFILE

Table 1 shows the demographic and clinical profiles of patients included in the study. The mean age of patients with leprosy treated with MDT regimen was 34.29 ± 15.29 years old. There were sixty-three (63) male patients (78.75%) and seventeen (17) female patients (21.25%). The majority of patients had a lepromatous leprosy (LL) spectrum (52.50%), followed by borderline borderline leprosy (BB) (26.25%), and borderline lepromatous leprosy (BL) (11.25%).

B. COMPARISON OF HEMOGLOBIN AND HEMATOCRIT LEVELS

The hemoglobin and hematocrit levels of the patients before and after initiation of MDT is shown in Table 2. The baseline mean hemoglobin of patients was 143.46 ± 15.33 g/dL, and the baseline mean hematocrit was 0.44 ± 0.04. Based on the table shown, decreased hemoglobin and hematocrit were seen after 1 month of MDT. By the third month, the mean hemoglobin was 94.00 ± 28.40 g/dL, and the mean hematocrit was 0.28 ± 0.09.

C. INCIDENCE OF DAPSONE-INDUCED HEMOLYTIC ANEMIA

The incidence of dapsone-induced hemolytic anemia is shown in Table 3. The year with the highest incidence rate of dapsone-induced hemolytic anemia was during 2018. Nine (9) out of the twenty-six (26) total patients during that year had dapsone-induced hemolytic anemia comprising 34.62%. On the other hand, the incidence rate of hemolytic anemia for the year 2016 and 2017 were 9.38% and 18.18%, respectively. The average incidence rate of dapsone-induced hemolytic anemia for 2016-2018 was 20%.

DISCUSSION

Based on the results of the study, there was a decreasing trend

Table 1. Demographic and clinical profiles of Hansen's disease patients.

Characteristics	Values (n=80)
Mean age ± SD, years	34.29 ± 15.29
Sex, frequency (%)	
Male	63 (78.75)
Female	17 (21.25)
Spectrum of leprosy, frequency (%)	
TT	1 (1.25)
BT	6 (7.50)
BB	21 (26.25)
BL	9 (11.25)
LL	42 (52.50)
Histoid	1 (1.25)

Table 2. Hemoglobin and hematocrit levels of leprosy patients before and after starting MDT.

Characteristics	Hemoglobin (g/dL)				Hematocrit			
	Baseline (n=80)	Month 1 (n=80)	Month 2 (n=9)	Month 3 (n=5)	Baseline (n=80)	Month 1 (n=80)	Month 2 (n=9)	Month 3 (n=5)
Mean ± SD	143.46 ± 15.33	132.73 ± 18.38	113.44 ± 28.75	94.00 ± 28.40	0.44 ± 0.04	0.41 ± 0.06	0.34 ± 0.09	0.28 ± 0.09
Minimum	117.00	77.00	63.00	57.00	0.36	0.24	0.20	0.19
Maximum	178.00	164.00	144.00	119.00	0.51	0.50	0.44	0.36

Table 3. Incidence rate of dapsone-induced hemolytic anemia in leprosy patients treated with MDT at SPMC Dermatology from January 2016 to December 2018.

Year	Total number of new leprosy cases treated with MDT	Total number of Dapsone-induced hemolytic anemia	Incidence rate of hemolytic anemia
2016	32	3	9.38%
2017	22	4	18.18%
2018	26	9	34.62%
Total	**80**	**16**	**20.00%**

noted on the mean hemoglobin and hematocrit concentration of leprosy patients before and after initiation of MDT. The incidence rate of dapsone-induced hemolytic anemia among leprosy patients treated with MDT during 2016, 2017, and 2018 were 9.38%, 18.18%, and 34.62%, respectively. During the 3-year period, the incidence rate of this adverse drug reaction was 20%. All patients who developed hemolytic anemia manifested after 1 month of initiation of MDT with a mean difference of hemoglobin from baseline of 30.94 g/dl with the highest drop of 54 g/dl seen in one (1) patient. Eleven (11) out of sixteen (16) patients who developed dapsone-induced hemolytic anemia were male. The diagnosis of leprosy in many countries is more commonly seen in males than females with a ratio of 2:1.[16] Currently, no study has reported any association between male sex and occurrence of dapsone-induced hemolytic anemia. However, it is known that G6PD deficiency is an X-linked recessive disorder. Hence, clinically significant hemolysis occurs more commonly in males. Fourteen (14) out of sixteen (16) patients who developed dapsone-induced hemolytic anemia had lepromatous leprosy (LL) spectrum. Although most of the patients included in the present study had LL spectrum (52.50%), a study by Rea et al. reported a decreased in mean hemoglobin values in patients with erythema nodosum leprosum (ENL) reactions. This type of leprosy reaction occurs most often in lepromatous leprosy (LL) patients. However in the study, those who developed ENL before 6 months of antimicrobial treatment had passed were excluded to remove the possible influence of dapsone on hemoglobin values. ENL-associated anemia still has an unknown mechanism.[17]

Thirteen (13) out of sixteen (16) patients who developed hemolytic anemia were symptomatic. The most common symptoms were fever (62.50%), icteric sclera (43.75%), and weakness (25%). These symptoms manifested within a month of taking MDT which is compatible with the study conducted by Deps et al wherein majority of symptoms of hemolytic anemia were noted to appear within the first three months of therapy.[7] However, not all patients who developed symptoms had hemolytic anemia. There were five (5) patients who had symptoms, such as fever and weakness, but with normal hemoglobin and hematocrit levels after initiation of MDT. Hence, the presence of symptoms in these patients may point to another cause which may include, but are not limited to, leprosy reactions.

Although there are different causes of hemolytic anemia, a strong association was noted between dapsone and the development of hemolytic anemia in these patients considering the normal hemoglobin and hematocrit concentration before initiation of MDT and the onset of symptoms after MDT initiation. However, other laboratory tests, such as reticulocyte count, peripheral blood smear, bilirubin, haptoglobin, serum lactate dehydrogenase (LDH), ALT, urine hemosiderin, and Coomb's test, that could help confirm the diagnosis of this condition, were not included in this study. Another limitation was that the data used in this study is a secondary data. Hence, the results of this study depend on the completeness of the chart. Those with incomplete data were not included in this study which resulted to a smaller sample size especially in month 2 and month 3 of treatment.

Dapsone-induced hemolytic anemia is a life-threatening adverse drug reaction if not recognized and treated early. This study provides evidence on the incidence rate of dapsone-induced hemolytic anemia among non-G6PD deficient leprosy patients treated with MDT. Based on the results of the study, there is a high incidence rate of this adverse drug reaction that can often be overlooked.

CONCLUSION

In conclusion, the results of this study highlight the importance of more frequent evaluation and monitoring of the hemoglobin and hematocrit concentrations of leprosy patients being treated with multidrug therapy to detect the presence of dapsone-induced hemolytic anemia. Early diagnosis and management of this condition can prevent further morbidity and mortality.

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