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Intolerance to Leprosy Multi-Drug Therapy: More Common in Women?

KATHRYN MARGARET DUPNIK*,
FERNANDO JOSÉ RAMOS CARDOSO**,
ANA LUIZA BRAGA BRITO DE MACÊDO***,
IGOR LEONARDO CARDOSO DE SOUSA***,
RENATA CRISTINA BARROS LEITE***,
SELMA MARIA BEZERRA JERÔNIMO***,****,*****
& MAURICIO LISBOA NOBRE**,****,*****,******
**Division of Infectious Diseases and Center for Global Health, Weill Cornell Medical College, New York, NY, USA*
***Giselda Trigueiro Hospital, Natal, RN, Brazil*
****Department of Biochemistry, Federal University of Rio Grande do Norte, Natal, RN, Brazil*
*****National Institute of Science and Technology (INCT/DT), Natal, RN, Brazil*
******Institute of Tropical Medicine of Rio Grande do Norte, Federal University of Rio Grande do Norte, RN, Brazil*
*******Post-graduate Program in Tropical Medicine, Oswaldo Cruz Institute, Fiocruz, Rio de Janeiro, RJ, Brazil*

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Summary

Objectives: The objective was to characterise and identify potential risk factors for intolerance to multi-drug leprosy therapy (MDT) which prompted a medication change in a leprosy referral centre in northeastern Brazil.

Design: A retrospective chart review of leprosy patients treated at a state referral centre for leprosy in Natal, Rio Grande do Norte, Brazil was completed. Chart review focus was on adverse effects necessitating modification of MDT regimen.

Results: Six hundred and twelve records were reviewed with detection of 91 (14·8%) adverse effects with associated change in MDT regimen. The most common recorded causes of medication intolerance were anemia (8·7%), headache (4·2%), cyanosis (1·8%), and gastrointestinal symptoms (1·6%). Both female gender (OR = 2·63) and age less than 42 years old (OR = 2·7) remained risk factors for MDT intolerance in a multivariate model including gender, age, and WHO regimen

Correspondence to: Mauricio Lisboa Nobre, Hospital Giselda Trigueiro, Rua Cônego Monte, 110, Quintas, Natal, RN 59037-170, Brazil (Tel: +55-84-3615-5454; e-mail: nobreml@gmail.com)

type. With intolerance due to anemia as the outcome, female gender (OR = 2·36) and age less than 42 years (OR = 1·86) were associated.
Conclusions: In this study, female gender and younger age were associated with greater risk of medication intolerance and medication intolerance related to anemia. These findings have important operational implications for drug intolerance monitoring during therapy for leprosy.

Introduction

Leprosy remains a neglected tropical disease of significant public health importance. There were 219,075 new cases diagnosed worldwide in 2011 with 33 955 of these cases occurring in Brazil.[1] Leprosy is curable with antibiotic therapy and medications are available at no cost from the World Health Organization (WHO). Treatment for leprosy is administered as multi-drug therapy (MDT) using a modified directly observed therapy approach. Individuals with the less extensive paucibacillary form of leprosy (PB, one to five skin lesions) receive 6 months of daily dapsone with monthly rifampicin. Individuals with more extensive multibacillary leprosy (MB, more than five skin lesions) receive 12 months of daily dapsone and daily clofazimine with monthly rifampicin. Alternative regimens may include ofloxacin or minocycline.[2] Since 2009, the Brazilian Ministry of Health has recommended that MB patients with intolerance to dapsone receive ofloxacin or minocycline instead of dapsone. For PB or MB patients with intolerance to rifampicin, rifampicin is replaced with ofloxacin and minocycline.[3] Prior to 2009, MB patients with intolerance to dapsone stopped the drug without substituting a new medication, management which is still in the WHO guidelines.[2] PB patients with intolerance to dapsone receive clofazimine as a substitution.[3]

The foundation of leprosy therapy is dapsone, which causes the majority of side effects seen during MDT.[4–7] Side effects of dapsone include anemia, both hemolytic and non-hemolytic. Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are at risk for an acute, severe hemolytic anemia, but anemia can occur regardless of G6PD phenotype.[8] Other hematologic risks associated with dapsone include methemoglobinemia,[9] agranulocytosis,[10] and aplastic anemia.[11] In addition, dapsone can cause alterations in liver function tests,[12] generalised cutaneous rash, photosensitivity,[13] and a severe hypersensitivity reaction called dapsone syndrome.[14,15]

Clofazimine is an antimicrobial and anti-inflammatory medication which is part of the MB multi-drug therapy regimen. Its side effects include increase in skin pigmentation, gastrointestinal symptoms, and eosinophilia.[16] Rifampicin can cause gastrointestinal symptoms, alterations in liver function tests, and hematologic abnormalities. Intermittent use of rifampicin has been associated with a flu-like syndrome.[17]

Several recent studies on adverse events from MDT have reported adverse event rates of between 37% and 45%, with a smaller percentage requiring a change in MDT regimen related to medication side effects, from 5 to 24%.[4,5,7] This is a much higher event rate than in prior studies showing less than 5% rate of adverse events during MDT,[16,18] although this difference may be related to study design and different adverse event reporting systems. Few studies have looked at the association between the type of MDT treatment regimen and patient demographics with development of side effects from MDT. Therefore, we conducted a retrospective chart review of medication side effects requiring a change in the MDT regimen.

Based on anecdotal observations in our clinical setting, we hypothesised that women would have a greater occurrence of anemia requiring change in the MDT regimen.

Materials and Methods

A 10-year retrospective chart review was completed for individuals treated for leprosy between January 1999 and December 2008 at the leprosy (Hansen's disease) clinic of Giselda Trigueiro Hospital in Natal, Rio Grande do Norte, Brazil. This clinic serves as a state-wide referral centre for cases of diagnostic uncertainty and for the management of complex cases of leprosy. It is also the primary diagnostic and treatment centre for Natal, the city in which it is located, and also for other municipalities where treatment for leprosy may not be available. To be eligible for inclusion in the study, individuals had to have both started and completed standard MDT therapy at the referral centre during this time period, with the exception of one case who died due to a complication of leprosy treatment. PB therapy was daily dapsone with monthly rifampicin for 6 months; MB therapy was daily dapsone and clofazimine with monthly rifampicin. During the period 1999 to 2008, an individual with MB leprosy might have been treated with the MB regimen for between 12 and 24 months. Charts were reviewed for age, sex, World Health Organization operational classification for anti-leprosy treatment (PB or MB), and symptoms as recorded in the medical chart. The duration of MDT was recorded. For individuals with medication intolerance during MDT, the timing of adverse effects and decision to alter MDT were recorded. If laboratory studies were included in the chart notes, they were recorded. Information about G6PD status was not available.

During this time period, five dermatologists were involved in determining changes in MDT regimen. Each patient was seen by a nurse or nursing assistant monthly during MDT, with referral to a physician for evaluation if symptoms were reported. A person was considered to have anemia if anemia or hemolytic anemia was recorded in the chart. Generally, an individual reported symptoms that could be consistent with symptomatic anemia and/or had a decrease in hemoglobin. Cyanosis, jaundice, pallor, and methemoglobinemia were considered separately. These were clinical diagnoses based on physical exam. Headache was defined as a persistent headache present after 1 month of MDT that interfered with daily life. Gastrointestinal side effects included anorexia, nausea, vomiting, diarrhea, and gastric or epigastric pain. Hepatitis was considered as a separate side effect. Dermatologic side effects included rash and photodermatitis. A chart review considered the reason for change in MDT as documented in the medical chart. Factors related to this decision may have included perceived danger to the patient or the likelihood of an individual continuing to comply with MDT because of the side effect. Laboratory studies, when available, may or may not have been recorded by the treating clinician. In this region of Brazil, it is customary for patients to keep their laboratory results, so the results may or may not have been retained in the medical chart.

Frequency data were analysed using GraphPad Prism (v5.0f). Percentages were compared using the Fisher's exact test. Medians were compared using the Mann-Whitney test for non-normal data. Multiple logistic regression analyses including sex, age less than or greater than the median age, and operational class as covariates were performed using STATA (v12.0). *P*-values of 0·05 or less were considered to be statistically significant.

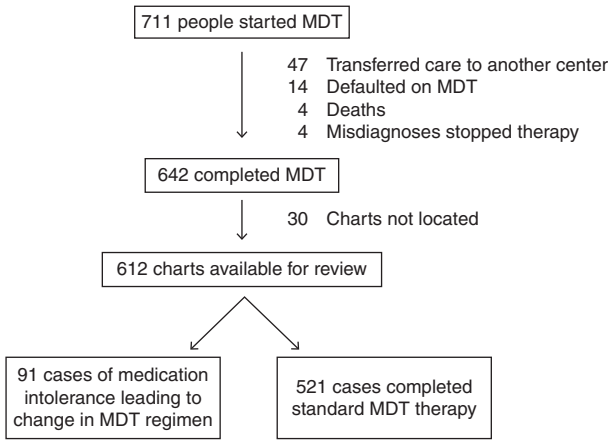

Figure 1. Outcomes for people starting MDT therapy for leprosy at the Giselda Trigueiro Hospital 1999 to 2008.

Results

There were 711 people who started multi-drug therapy (MDT) for leprosy at the Giselda Trigueiro Hospital between 1999 and 2008 (Figure 1).

Approximately half (53%) were from outside the city of Natal in which the treatment centre is located. Of the 711 people, 47 (6·6%) were transferred to other treatment centres, 14 (2%) abandoned treatment, four (0·6%) died from other causes before concluding treatment, and four (0·6%) were considered misdiagnoses. There were 642 (90·3%) individuals who met inclusion criteria. Out of the eligible patients, 612 (95·3%) charts were available for review. Of these, 307 (50·2%) were female and 305 (49·8%) were male. Median age was 42 years, varying from 3 to 93 years. There were 280 (45·8%) multibacillary (MB) and 332 (54·2%) paucibacillary (PB) cases (Table 1).

One hundred and twenty two MB patients received 12 months of MDT, 34 MB patients received between 12 and 24 months, and 124 MB patients received 24 months of MDT. MB cases were on average older compared with PB cases (median 47 vs 38 years, $P < 0{\cdot}0001$). The gender distribution was not equal in the two WHO operational classifications. Women were approximately twice as likely to have PB as MB leprosy (66% vs 34%). Conversely, men were more likely to have MB than PB leprosy (58% vs 42%). This difference in WHO classification by gender was statistically significant ($P < 0{\cdot}0001$).

Medication side effects requiring change in MDT (referred to as 'intolerance') were recorded for 91 (14·9%) patients during the course of MDT (Table 1). The majority of MDT intolerance events were reported during the first 3 months of therapy: 35·1% in the first month, 33% in the second month, and 13·2% in the third month. No person had medication intolerance recorded after 12 months of initiation of MDT. People with PB and medication intolerance were most likely to develop the intolerance during the first month (41%), whereas the MB group was more likely to have the intolerance after 3 months of therapy (41%). Of the people with MB who received more than 12 months of MDT, 62% developed the intolerance within the first 3 months of MDT. All PB patients with medication intolerance stopped dapsone. For the MB patients, all stopped dapsone and one also stopped rifampicin.

Table 1. Characteristics of leprosy patients taking MB or PB regimens and the rates of intolerance reported in this study

	MB ($n = 280$)	PB ($n = 332$)	*P*-value
Median age (range)	47 (5–93)	38 (3–87)	<0·0001
Sex (% male)	62·9%	38·9%	<0·0001
MDT Intolerance			
In females	15·4%	23·6%	<0·0001
In males	6·3%	12·4%	0·0687
MDT Intolerance due to Anemia			
In females	8·6%	13·8%	0·2660
In males	4·5%	6·2%	0·6063

In univariate analysis, within the PB group, 19% (64/332) had MDT intolerance, whereas within the MB group 9·6% (27/280) had this outcome ($P = 0·0009$). Women were more likely than men to have MDT intolerance (20·8% vs 8·9%, $P < 0·0001$). Within the PB subgroup, 48/203 (23·6%) women and 16/129 (12·4%) men had MDT intolerance ($P = 0·0148$). Within the MB subgroup, 16/104 (15·4%) women and 11/176 (6·3%) men had MDT intolerance ($P = 0·0197$).

The most frequent recorded cause of medication intolerance was anemia; 58·2% of people who changed their MDT regimen had anemia or hemolytic anemia recorded as the reason for change (Table 1). This represented 8·7% of the overall study population. Anemia was more than twice as frequent in women as in men (12·1% vs 5·2%, $P = 0·0037$). Forty-one people with anemia (77·3%) had anemia listed as the only reason for change in regimen, while the remainder had anemia in addition to other symptoms or findings listed as the reason for MDT modification. The most common anemia-associated symptom was headache in six individuals. Women with PB leprosy were more likely to have intolerance due to anemia than women with MB leprosy, but this difference was not statistically significant (13·8% vs 8·6%, $P = 0·2660$). Of the 53 individuals with anemia, there were 46 (86·7%) with hemoglobin measurements. The mean hemoglobin for those who stopped PQT due to anemia was 10·6 g/dL, slightly higher in women (median 10·6 g/dL, range 2·4 to 12·7) than men (median 10·3 g/dL, range 8·8 to 12).

The most common documented causes of medication intolerance were anemia (8·7%), headache (4·2%), cyanosis (1·8%), gastrointestinal symptoms (1·6%), rash (0·8%), and fever (0·8%) (Table 2).

There were no documented cases of dapsone syndrome. There was one case of agranulocytosis, which occurred in a 37 year old man during the second month of MDT for MB leprosy and was fatal, despite intensive care and use of granulocyte stimulating factor. After anemia, the most common reported side effect was headache. Twenty six people reported headache; six of them had concurrent anemia noted in the chart.

To assess for confounding between gender and age with WHO classification in the outcome of medication intolerance, multiple logistic regression analyses were completed. Female sex (OR = 2·63, CI: 1·59–4·36, $P < 0·001$) and age less than 42 years (OR = 2·7, CI: 1·66–4·5, $P < 0·001$) were associated with medication intolerance. There was a trend towards association of PB regimen with intolerance (OR = 1·57, CI: 0·945–2·61), but it did

Table 2. Six most common causes of medication intolerance leading to change in leprosy MDT regimen. A person may have had more than one reason for change in regimen

	Male ($n = 305$)	Female ($n = 307$)	Total ($n = 612$)
Median age (range)	41 (3–93)	44 (8–82)	42 (3–93)
Any cause of Medication Intolerance	27 (8·9%)	64 (20·8%)	91 (14·9%)
Anemia	16 (5·2%)	37 (12·1%)	53 (8·7%)
Headache	7 (2·3%)	19 (6·2%)	26 (4·2%)
Cyanosis	2 (0·6%)	9 (2·9%)	11 (1·8%)
Gastrointestinal symptoms	1 (0·3%)	9 (2·9%)	10 (1·6%)
Dermatologic	0 (0%)	5 (1·6%)	5 (0·8%)
Fever	2 (0·7%)	3 (0·1%)	5 (0·8%)

not reach statistical significance ($P = 0{\cdot}081$). With intolerance due to anemia as the outcome, female gender (OR = 2·36, CI: 1·25–4·44, $P = 0{\cdot}007$), and age less than 42 years old (OR = 1·86, CI: 1·02–3·39, $P = 0{\cdot}041$) remained associated. Controlling for sex and age, WHO class was not associated with intolerance due to anemia ($P = 0{\cdot}289$).

Discussion

Between 1999 and 2008, half of the people treated for leprosy at this referral centre were women. There were more PB than MB cases (54% vs 46%, respectively). In Brazil between 2001 and 2008, women comprised 45·5% of new cases and 52·9% of new cases were MB.[19,20] Women in this study were more likely to have PB leprosy and men were more likely to have MB leprosy. Differences in leprosy type by gender have been documented in different parts of the world.[21,22]

In this study, we found a rate of adverse events requiring change in MDT of 14·9%, which is the same percentage reported by Goulart [6] in another study in Brazil. It is lower than the 24% reported by Deps,[4] but higher than the 5·1% reported by Singh.[5] Our observation that 81% of medication intolerance occurred within the first 3 months is important because it has operational implications and suggests that close monitoring is most important at the time of initiation of MDT. We observed more adverse events in individuals on the PB regimen of MDT, which is surprising as the PB regimen contains one fewer medication and is given for a shorter period of time. This is contrary to Brasil *et al.*[18] who reported a higher rate of adverse events in the MB than PB group. However, that study was based on reporting from regional health offices to a state reference centre during the first decade of use of MDT for leprosy therapy, whereas the current study was a chart review of a single health centre after more experience with MDT as the standard of care. A trend towards more medication intolerance in PB rather than MB was seen in a study from southern Brazil, but the difference was not

statistically significant.[23] Also, that study included only severe side effects in their definition of medication intolerance. In our chart review, the difference in medication intolerance between PB and MB could be related to the greater percentage of women in the PB group. This is supported by the multivariate analysis in which only gender and age remained associated with intolerance to MDT. Additionally, the MB regimen includes clofazimine, which has anti-inflammatory effects in addition to anti-microbial activity and could potentially impact development of medication intolerance. However, a recent study which compared the occurrence of side effects in individuals (not stratified for age or gender) with PB leprosy taking PB or MB MDT regimens found lower hemoglobin levels in the MB MDT group,[24] which would not be expected if the clofazimine were mediating intolerance to dapsone.

In our study the highest rate of MDT intolerance was observed in women taking the PB regimen (23·6%). Singh reported an association between any type of MDT-related adverse event, not necessarily leading to change in MDT regimen, and body mass index less than 18·5, but did not include gender, sex, or age in the reported analysis with BMI.[5] In a Sri Lanka study with a 2·4% rate of adverse reactions, those with adverse events were more likely to be women than men, but gender differences in occurrence of anemia was not reported.[6]

The association of dapsone with anemia has been well-documented. Anemia can develop during dapsone therapy even in people without G6PD deficiency[25] and with normal acetylation phenotype.[26] One study on the hematologic impact of 6 or more months of dapsone treatment for leprosy found that more than half of people had hypochromia and anisocytosis while all had an increase in osmotic fragility while taking dapsone as mono or combination therapy.[8] Those taking dapsone had significantly lower hemoglobin levels than those on an alternative regimen.[8] Byrd *et al.* found that hemoglobin level decreased an average of 2 g/dL after 1 month of dapsone therapy for leprosy, and that 87% of women and 83% of men had a decrease in hemoglobin of 1 g/dL or more, while 3% of women and 21% of men had a hemoglobin decrease of 3 g/dL or more.[27]

Goulart *et al.* reported a slightly higher percentage of hemolytic anemia related to dapsone in women (9·4%) compared with men (7·3%).[7] We observed that the occurrence of anemia requiring change in MDT was more than twice as high in women as in men. In multivariate analysis, female gender was associated with medication intolerance due to any effect, and to anemia specifically. Women treated with the PB regimen had the greatest chance of change in MDT regimen overall (23·6%) and related to anemia (13·8%). The association of MDT intolerance from anemia with female gender and in those less than 42 years of age may be a reflection of blood loss during menstruation in pre-menopausal women.[28] However, younger age was associated with all-cause and anemia-related MDT intolerance even when controlling for gender, so there may be other factors involved. It has been suggested that drug allergy in general occurs more frequently in young and middle-aged rather than older adults, and that it is more common in women than men,[29,30] but allergy may or may not be related to MDT-related side effects.

After anemia, the most frequent side effect recorded as a reason for change in MDT was headache in 4·2% of people treated. Headache is a common side effect of dapsone therapy. In a study in India, 20% of leprosy patients and 27% of non-leprosy patients receiving dapsone reported 'nervous side effects' which included insomnia, headache, and vertigo.[31] In a study investigating dapsone for treatment of seizures, 31·8% of people receiving dapsone 100 mg daily reported headache.[32] In our study population, headache was a reason for stopping MDT when it was persistent after 1 month of treatment, especially if it was felt that the headache

would impact a patient's compliance with MDT. Dapsone may also have been stopped considering that headache can also be a sign for methemoglobinemia[9] and the clinic did not have real-time access to testing for methylated hemoglobin which could have assisted in decisions regarding change in MDT.

The one case of agranulocytosis identified in this chart review corresponds to 0·16% of patients treated between 1999 and 2008, an incidence rate that is consistent with that reported in the literature for agranulocytosis during MDT for leprosy.[10] It is one of the most severe adverse effects of anti-leprosy MDT and one for which vigilance needs to be maintained to initiate prompt treatment.

Our study addresses MDT intolerance as determined by physicians working in a resource-limited setting. The patients treated in this clinic may travel hours to be evaluated by a clinician, and it is often not possible to obtain laboratory results to confirm clinical suspicion for MDT complications such as methemoglobinemia or hemolytic anemia. As such, this study has several limitations. The observations of side effects are limited to what was documented in the patient chart by the treating physician. Laboratory results were not consistently available in the chart, so laboratory abnormalities were not used to determine medication intolerance during chart review. Specifically, the clinicians did not have real-time access to G6PD or methylated hemoglobin levels to direct decisions on changing MDT regimen. The rate of G6PD deficiency in male blood donors in Natal, Brazil was 2·6% in a study published in 1986.[33]

During a portion of the time period included in this chart review, the recommended duration of treatment for MB leprosy was 24 months, so there was variation in duration of MDT in the MB therapy group. However, no one included in the chart review had onset of medication intolerance after 12 months of treatment, including the 158 people who received more than 12 months of MDT. It is important to consider that our study did not take into account minor side effects of MDT, such as skin pigmentation due to clofazimine, which did not lead to change in MDT regimen. Our study also did not include people who finished their MDT course outside of our center (6·6%) or who defaulted during the MDT course (2%). For these people, we do not know if there was medication intolerance. This chart review did not include information on reaction status, so we are unable to determine if co-administration of corticosteroids for leprosy immune reactions (reversal reaction or erythema nodosum leprosum) impacted the occurrence of intolerance to MDT.

In this study, women and the younger half of the cohort had greater risk of medication intolerance and medication intolerance related to anemia. There was a trend towards association of the PB type of regimen and MDT intolerance, although in multivariate analysis only female gender and age less than 42 remained significantly associated with MDT intolerance. The majority of MDT intolerance occurred during the first 3 months of therapy. These findings have operational implications for monitoring for drug intolerance during therapy for leprosy.

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