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Adverse effects from Multi-drug therapy in leprosy: a Brazilian study

PATRICIA D. DEPS*, SOFIA NASSER*, PATRICIA GUERRA*, MARISA SIMON*, RITA DE CÁSSIA BIRSHNER** & LAURA C. RODRIGUES***
**Federal University of Espírito Santo*
***Leprosy Control Programme, Health Unit of Maruípe*
****London School of Hygiene & Tropical Medicine*

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Summary
Introduction The WHO MDT for leprosy treatment was officially introduced in Brazil in 1991 and comprises three drugs: dapsone, rifampicin and clofazimine. There are few good studies on the frequency of side-effects attributable to MDT in Brazil.
Methods A retrospective and descriptive study carried out in a LCP in Vitória, State of Espírito Santo, Brazil. A specific and detailed protocol about side-effects was prepared and filled in from the patient records.
Results One hundred ninety four patients' records were analysed looking for side-effects attributable to MDT. Side-effects were attributed to at least one MDT component in 88 (45%) patients and 85 had side-effects due to dapsone, 24 due to rifampicin and 18 due to clofazimine. 185 episodes were identified. The suspected drug was stopped in 47 out of 88 episodes (24% patients); 46 had dapsone stopped, 5 had rifampicin stopped and no-one had clofazimine stopped.
Conclusion Side-effects attributed to MDT is more frequent than previously described, resulting in interruption of treatment in many patients.

Introduction

In 1981, The World Health Organization (WHO) recommended the use of multi-drug therapy (MDT) against leprosy, using dapsone, rifampicin and clofazimine. The introduction of this regimen aimed to control primary and secondary resistance to drug monotherapy, to prevent further resistance of *Mycobacterium leprae* developing to other antibiotics and to prevent relapses.[1,2] MDT introduction came with additional benefits such as an intense monitoring of patients, coverage of affected populations, improvement of the closeness between leprosy patients and medical care, and that leprosy changed into a curable disease.[1]

Correspondence to: Patrícia D. Deps. Departamento de Medicina Social. Centro de Ciências da Saúde. UFES. Av. Marechal Campos 1468, Maruípe. Vitória-ES, Brasil. CEP: 29040-090. (Tel: +55 27 3335 7226; e-mail: pdeps@uol.com.br)

Among those three drugs, rifampicin is the most important anti-leprosy drug and is included in regimens for both paucibacillary (PB) and multibacillary (MB) patients. Although, WHO has stated that no toxic effects have been reported in monthly administration,[3,4] many authors have reported rifampicin as the cause of cutaneous eruptions, thrombocytopenic purpura, hepatitis, a flu-like syndrome, hemolytic anemia, shock, respiratory insufficiency and acute renal failure.[5–10]

Clofazimine is most active when administered daily; it is well tolerated and virtually non-toxic in the usual dosage.[3]

Dapsone is very safe in the dosage used in MDT and according to WHO,[3] side-effects are rare. The main side-effect is skin allergic reaction, however hemolytic anemia, methaemoglobinemia, jaundice, agranulocitosis, psychotic reactions and 'dapsone syndrome' have also been reported.[7,8,11]

MDT introduction met with considerable resistance in Brazil because of a significant risk of side-effects.[11–14] Despite this, in 1991, MDT was adopted as the sole treatment for leprosy patients in Brazil.[13,15]

Fixed-duration treatment was adopted and smear examination was no longer a requirement for declaring patients cured.[13,16–19] In 1997, the WHO Expert Committee stated that '. . .it is possible that duration of the current MDT regimen for MB leprosy could be further shortened to 12 months without increasing the risk of developing rifampicin resistance',[4] the Brazilian Ministry of Health followed this recommendation 3 years later.[13,19]

A wide range of frequency of side-effects caused by MDT has been reported from Brazil. In a recent publication, Goulart *et al.*[8] in Minas Gerais, reported that 37·9% of patients taking MDT had side-effects, and 39·4% of them received an alternative regimen. However, elsewhere in Brazil the published frequencies of side-effects attributed to MDT were 0·61% and 0·63%, and in both reports most patients had received alternative regimens, so removing the drugs suspected of causing undesirable reactions.[7,11]

WHO has noted that the frequency of adverse reactions caused by MDT is very low, and when such reactions occur, the standard regimen should simply be adjusted, so that treatment can continue.[7,11,20,21] Treatment of leprosy with only one anti-leprosy drug may result in development of resistance to that drug; and treatment with dapsone or any other anti-leprosy drug used as monotherapy should be considered unethical.[1,3] In addition, it would be considerably more hazardous to use the compounds separately.[22]

Stopping of MDT is not routinely reported by the LCP Reports and depends on the judgment of the LCP team. Usually in Brazil, leprosy patients are removed from the leprosy register system only when they are cured or abandon treatment.

In 2005 in Brazil 38,410 new leprosy cases were diagnosed and the prevalence rate in 2006 was 1·5/10,000 inhabitants.[23]

This paper reports side-effects attributed to MDT, the frequency and stoppage of the MDT components in a Health Unit in Vitória, Brazil.

Patients and methods

This is a retrospective, descriptive study done in Vitória, Espírito Santo, Brazil. Data were collected from April to November 2004, by three medical students trained by one of the authors (PDD).

The LCP in Health Unit of Maruipe comprises one physician general practitioner, one nurse, one social assistant and one nurse technician. Currently, this team trains other LCP groups.

During that period, 194 leprosy patients were registered and treated in that Health Unit and all their records were analysed. During their treatment they were seen monthly by the same LCP team, therefore every side-effect, diagnosis and the therapeutic decision belongs to that physician. Hemolytic anemia, leucopenia, methahemoglobinemia and liver abnormalities were confirmed by laboratory examination. All other diagnoses were based on clinical signs and symptoms.

A specific questionnaire was prepared to collect data from the patient records, and detailing occurrence of side-effects and stoppage of the drug because of side-effects. The operational classification of patients (MB or PB) was collected from the LCP records.

Laboratory assessments were done before the start of MDT and between 30–90 days of the treatment. Tests included hemogram and liver function tests. Level of methemoglobin was only requested when there was clinical suspicion of methemoglobinemia.

Side-effects attributed to MDT were defined as the presence of undesirable secondary effects of onset after the start of MDT. Hemolytic anemia was defined as a reduction of hemoglobin from baseline to the end of 30–90 days (less than 12·7 g/dL for men and 11·5 for women), and reduction of hematocrit (less than 42% for men and 36% for women). Symptoms like fatigue, weakness, shortness of breath, jaundice, enlarge of spleen, or/and abdominal discomfort may be present. Leucopenia was definined as a reduction in the number of circulating leucocytes in the blood less than 4,500/ml. Methemoglobinemia was defined as raised of level of methemoglobin in the blood more than 1%; shortness of breath, cyanosis, mental status changes, headache, fatigue, dizziness, loss of consciousness, dysrhythmias, seizures, coma and death may occur. Psychiatric disorders was defined as mood, psychotic and anxiety disorders. All patients with suspected psychiatric disorders were reviewed by a psychiatrist. Gastrointestinal manifestation was defined as the presence of dyphagia, or dyspepsia, nausea, diarrhea, vomiting and bleeding (hematemesis, melena or hematochezia). Hepatic abnormalities were defined as any alterations at liver function tests with or without clinical evidence of jaundice, malaise and other symptoms. One or more of these had to be present: Serum aminotransferases, gamaglutamyl transpeptidase and alkaline phosphatase were defined as abnormal when they were twice the upper limit of normal. Total bilirubin more than 1·2 mg/dL. Dizziness was defined as one or more of these: Faintness, light-headedness, loss of balance, sense of spinning, and vague spaced-out feeling.

Hypersensitivity reaction was defined as one or more of these: Watery, itchy eyes, runny nose, rashes, itchy skin, sneezing, swelling in small areas of the skin and angioedema. Anaphylactic reaction was defined as a recent onset (1 minute to 1 hour after taking MDT) of the most of these: palpitations, low blood pressure, fainting, tingling sensations, itchy and flushed skin, throbbing in the ears, coughing, sneezing, hives, angioedema, and wheezing. Flu-like syndrome was defined as the most of these: Fever, runny nose, sore throat, cough, nausea, vomiting, poor appetite, headache, muscle/joint aches, and malaise.

Skin reactions were defined as the following: Skin rashes or exanthematous eruption which may be localised or generalised; exfoliative dermatitis (exfoliation extending to over 90% of the body surface area including the scalp and fever); toxic epidermal necrolysis causing several large flaccid blisters extending over the entire skin surface except the scalp, malaise and fever may be present. Stevens-Johnson syndrome or erythema multiforme

bullosum in which the skin and oral mucosa are always involved and eyes may be sometimes involved, fever and prostation.

Sulfone syndrome was defined as an exfoliative dermatitis and/or other skin rashes, generalised lymphadenopathy, fever, hepatosplenomegaly and hepatitis occurring within 6 weeks of starting therapy. Data on skin discolouration and icthyosis attributed to clofazimine were not collected here.

All patients completed leprosy treatment and were considered 'cured'. All of them lived in the Metropolitan Region of Vitória.

Ethical approval was granted by the local Ethics Committee from the Federal University of Espirito Santo, Vitória, Brazil. The statistical analysis was performed using the SPSS version 9.0 for Windows.

Results

194 patients were included in this study, 78 (40%) male and 116 (60%) female. 40% were MB and 60% were PB; 34% of the patients were under 30 years old, 51% 31-60 year old and 15% over 60 year old.

Side-effects were attributed to at least one MDT component in 88 (45%) patients; 85 had side-effects due to dapsone, 24 due to rifampicin and 18 due to clofazimine. Considering the three drugs, a total of 185 episodes were found, in 89 (48%), the onset occurred during the first 3 months of treatment. Fifty-one (58%) out of 88 patients had more than one side-effect and 35 (40%) had side-effects attributed to more than one drug. Eighty-five patients had adverse effects from dapsone such as hemolytic anemia, gastrointestinal manifestations, hepatic abnormalities, dizziness, headache, psychiatric disorders, skin reactions, methahemoglobinemia, muscles weakness and severe leucopenia (Table 1). Both patients with severe leucopenia had died: one patient was hospitalised and died after 3 weeks because of systemic infection, and no detailed information was available from the other one. Also, two other patients had died during MDT, however no relationship with adverse effects attributed to MDT were found.

Stoppage of dapsone occurred in out of 46 (54%) patients out of 85. Out of the 46 who had dapsone stopped, 34 (74%) were female and 12 (26%) were male, 50% of the patients were PB and 50% were MB.

Twenty-four (27%) of 88 patients had side-effects due to rifampicin. All those patients who had general manifestations of hypersensitivity had the rifampicin stopped, and in 30% hepatic abnormalities were confirmed by laboratory testing.

Stoppage of the suspected drug was done in 47 out of 88 who had side-effects, corresponding to 24% of all 194 patients. Five (3%) had the rifampicin interrupted and none of them had the clofazimine interrupted. Once a drug was stopped it was not reintroduced.

Table 1 shows the proportion of side-effects and stoppage of each MDT components.

Discussion

Eighty-eight - almost half - of the 194 studied patients had at least one side-effect attributed to at least one MDT component. Dapsone caused most of the side-effects. However 40% had side-effects due to more than one of the studied drugs. Half of the patients, who had

Table 1. Proportion of side effects and interruption of MDT components

Side effect caused to dapsone in 85 patients	N (%)	Stoppage of dapsone N (%)
Hemolytic anemia	48–56·5	25–52·1
Methahemoglobinemia	05–05·9	05 – 100
Leucopenia	02–02·4	02 – 100
Gastrointestinal manifestation	23–27·1	03 – 13
Psychiatric disorders	08–09·5	02 –25
Skin reaction	06 – 07	04–66·7
Hepatic abnormalities	20–23·5	15 – 75
Headache	11 – 13	0
Dizzness	14–16·5	0
Muscles weakness	04–04·7	0
Side effects caused to rifampicin in 24 patients		Stoppage of rifampicin
Hepatic abnormalities	10–41·7	03 – 30
Hemolytic anemia	08 – 33·3	0
Gastrointestinal manifestation	05–20·8	0
Hypersensitivity manifestation	02 – 08·3	02 – 100
Flu-like syndrome	01 – 04·16	0
Side effects caused to clofazimine 18 patients		Stoppage of clofazimine
Gastrointestinal manifestation	17 – 94	0
Lower limbs oedema	01 – 05·5	0

side-effects, had more than one side-effect. Over half of the patients who had a side-effect – and a quarter of all studied patients – had their treatment stopped.

The main limitation of this study is its retrospective nature: it was restricted to the information in patient's records.

Although discolouration and icthyosis caused by clofazimine are the most common side-effects caused by MDT,[3] they were underestimated and were not cited by the LCP team in the patient's records as side-effect or/and as cause of the MDT stoppage in this study. Some side-effects could be attributed to two or even three drugs. To resolve this, the physician used to stop the drug most likely to cause the side-effect and see the patient again in a short time. If the side-effect did not resolve, the second most common drug was stopped. Sometimes both drugs were stopped.

With similar methodology, in a retrospective study of 187 patients, Goulart *et al.*[8] found side-effects attributed to MDT in 71 (37·9%) and 28 (14·9%) received an alternative regimen, however those authors did not explain what kind of regimen was established. The present study shows side-effects in 88 (45%) patients and an alternative treatment regimen was needed in 47 out of 88 (24%). All patients completed the alternative scheme. The drug that was stopped was not reintroduced and in MB cases, no other drugs were introduced to replace dapsone.[8,10,22]

Otherwise, WHO stated alternative treatments can be given to patients who do not tolerate MDT due to adverse reactions or contra-indications, but first of all it is very important to establish conclusively that the adverse reactions noticed are due to the anti-leprosy drugs. Once this is established, other new anti-leprosy drugs can be tried.

Alternative regimens should be administered under direct supervision in a referral centre: Daily administration of 50 mg of clofazimine, together with 400 mg of ofloxacin and 100 mg of minocycline for 6 months; followed by daily administration of 50 mg of clofazimine,

together with 100 mg of minocycline or 400 mg of ofloxacin for at least an additional 18 months could be used to replace rifampicin in adult MB patients. For PB patients, dapsone may be substituted by clofazimine in the same dosage as that used for MB patients during 6 months. For MB patients, dapsone should be stopped and treatment continued with rifampicin and clofazimine in the standard dosage. Patients who do not accept clofazimine can be treated with a monthly administration of a combination consisting of 600 mg of rifampicin, 400 mg of ofloxacin and 100 mg of minocycline (ROM) for 24 months.[3]

Surprisingly, despite the importance of this subject, no other similar studies have been published and the current literature describes the frequency of MDT interruption as a very scarce event. The difference in rate of side-effects attributed to MDT may be due to ethnic, genetic differences in the Brazilian population.

In conclusion, side-effects necessitating treatment stoppage may be more frequent than previously described. There are important issues to discuss such as when to stop drugs. Alternative drugs active against *M. leprae* should be available to the Leprosy Control Programme.

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