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Temporal Adverse Effects in Leprosy Saudi Patients Receiving Multi Drug Therapy

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Abstract

Background/Purpose: Leprosy or Hansen's disease is an infectious disease that yet represents major socio-economic burden to humanity. It results in permanent physical disabilities besides disgraceful social perception to patients. Multi Drug Therapy (MDT) treatment protocol is a combinatorial anti microbial treatments which has been approved by the WHO as the best treatment option for Hansen's disease. Side effects to MDT protocol are the main limiting obstacle for the treatment course completion that might differ from population to another.

Methods: Herein, we are assessing the temporal hematological and biochemical markers of side effects in Saudi leprosy patients treated with MDT protocol for one year.

Results: Hematological assessment revealed progressive temporal but mild decline in all the examined parameters (RBC, PCV, Hb, MCH and MCHC) in males and females patients treated with MDT compared to control group. Biochemical assessment for MDT treated leprosy Saudi patients presented mild progressive temporal hepato-renal complications. Patients were fully recovered from all hemato-biochemical adverse effects after 6 months of the MDT treatment completion.

Conclusion: MDT was well tolerated in Saudi leprosy patients with mild to moderate temporal hematological and biochemical adverse reactions.

Keywords: Leprosy; Multi drug therapy; Adverse effects; Saudi population

Introduction

Leprosy or Hansen's disease is an ancient infectious disease (in China since 400 B.C.) that yet represents major socio-economic burden to humanity with approximate one million cases in Africa, Asia, South America and Pacific [1,2]. Despite the permanent physical disabilities caused by leprosy, disgraceful social perception to these patients results in about 2.5 million undiagnosed cases [3]. The causative organism for leprosy is the acid fast carbole-fuchsine positive rod bacilli *Mycobacterium leprae* [4]. Leprosy is transferred via droplet infection and mainly affects skin and mucous membranes with preferentiality to cooler cosmetic spots such as face and limbs. Incubation period of leprosy is usually 2-4 years with major manifestations of skin lesions, numbness, muscle atrophy, algesia, photophobia, blurred vision and nasal stuffiness [5].

Multi Drug Therapy (MDT) treatment protocol has been approved by the WHO as the best treatment option for Hansen's disease [6]. The sporadic spread of Hansen's disease in multinational areas with different demographic characteristics and different response to MDT therapeutic effects and adverse side effects urged conservative regional studies to evaluate the disease and its therapeutic alternatives [7]. In low national income countries leprosy might be endemic [8-10]; however in high national income areas leprosy is transmittable with immigrants [11,12]. Saudi Arabia accommodates huge number of immigrants from several nationalities relative to its native population which might be risk factor for spreading leprosy among Saudi native population [13,14].

MDT protocol is based on combinatorial antibacterial effect of three chemotherapeutic agents, dapsone, clofazimine, and rifampicin [15]. This combination treatment is administered for 6-24 months under partial medical supervision (Table 1). Side effects to MDT protocol are the main limiting hurdle for the treatment course completion; these side effects are mainly attributed to dapsone and to lesser extend to the rest of medications [16]. Methemoglubinemia, hemolytic anemia, agranulocytosis and other hematological traits have been reported for MDT protocol or to dapsone *per se* [17]. Hepatitis, pancreatitis, and renal impairments have been reported for MDT patients which warrants close biochemical assessment to follow up these side effects [18,19]. Erythema nodosum hypersensitivity reaction is another major side effect for MDT that might lead to mortality [20,21]. Herein, we are assessing the temporal hematological and biochemical markers in leprosy Saudi patients treated with MDT protocol for one year.

Patients and Methods

Subjects

A total of 100 adult leprosy patients (50 males and 50 females) received MDT protocol for 12 month in Ibn Sena Hospital, Jeddah, KSA. Another group of 100 adult healthy volunteers (50 males and 50 females) were taken as control group. All healthy participants were clinically investigated and found free from clinical diseases such as, diabetic, hypertension, liver or kidney disorders CHD and major ECG abnormalities. Leprosy patients were free from glucose-6-phosphate deficiency syndrome. No elderly patients (more than 65 years old) were included in the study. The informed consent as well as statement of approval was obtained from the ethical committee of Ibn Sena Hospital and in accordance to Helsinki Declaration, 1975.

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Clinical diagnosis	*Drugs*	*Dose*	*Mode of administration*	*Duration*
Paucibacillary	Rifambicin	600 mg	Once a month/supervised	1-2 years and could be extended
	Dapsone	50 mg	Once a month/supervised	
		50 mg	Daily/self administered	
Multibacillary	Rifambicin	600 mg	Once a month/supervised	
	Clofazimine	300 mg	Once a month/supervised	
		50 mg	Daily/self administered	
	Dapsone	100 mg	Once a month/supervised	
		100 mg	Daily/self administered	

Table 1: WHO recommendation for MDT leprosy treatment protocol.

Clinical examination

Body Mass Index (BMI) was calculated as body weight (in kg) divided by squared height (in meters). The procedure for the measurements of weight, height, waist circumference and hip circumference, systolic and diastolic blood pressure was according to the standard procedures within Saudi health care institutes.

Collection of blood samples

Venous blood samples (two samples per patient) were withdrawn from peripheral vein while the patient is sitting. Blood samples were allowed to clot, centrifuged and the sera were kept frozen at −20°C for biochemical assessment. Another blood samples were sent for hematological assessment in the same day sampling.

Hematological assessment

Whole blood was injected immediately after sampling into the automatic coulter counter, Sysmex™, K800 (Block Scientific Inc., Bohemia, NY, USA). Red Blood Cell Count (RBC), Packed Cell Volume (PCV), Hemoglobin (Hb), Mean Cellular Hemoglobin (MCH), and Mean Cellular Hemoglobin Concentration (MCHC) were determined using azide free reagent mix and according the manufacturer procedures [22].

Biochemical assessments

Biochemical assessments were assessed in isolated sera using specific kits purchased from Dade Behring, Marburg, Germany. Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT) were assessed as previously described [23]. Bilirubin (direct, indirect and total) was determined using end point technique with blank solution correction analysis [24]. Creatinine was determined via picric acid chromophore interaction assay [25]. Gamma Glutamyl Transferase (GGT), Alkaline Phosphatase (ALP), α-Amylase (Amyl), urea and potassium ion (K^+) were determined in sera using the manufacturer standard operating protocol of the kit.

Statistical analysis

Data is expressed as mean ± SD. Analysis Of Variance (ANOVA) with Tukey's post hoc test was used for testing the significance of parametric data using SPSS® for windows, version 10.0.1. $P<0.05$ was taken as the cut off value for significance.

Results and Discussion

Despite all the advancement in the treatment of infectious diseases, leprosy represents serious socio-economic burden to humanity [26]. Yet, MDT protocol has been the regimen of choice for Hansen's disease [27]. However, several hematological and biochemical adverse effects have been reported for medications of MDT [17]. Dapsone is the only sulfone derivative drug in clinical use these days due to the serious adverse reaction of this group of drugs such as elevated oxidative stress and hemato-biochemical traits [28]. In the current work, we evaluated the hematological and biochemical parameters of MDT toxicity in Saudi leprosy patients every three months for one year.

BMI was not significantly different between treated and control groups in the current study; it lies within the normal range of Saudi population (Table 2). The different BMI of Saudi population from other populations, due to food habits and life style, affects to some extend the pharmacokinetics and drug distribution of several drugs in Saudi population [29]. Yet, no need in the current study to recalculate drug dosing regimen due to the relatively homogenous BMI in study group.

Hematological assessment revealed progressive temporal but mild decline in most of the examined parameters in males and females patients treated with MDT compared to control group (Table 3). About 10-20% of RBC count and 4-11% in PCV% was decreased since the first three month of MDT treatment in both males and females Saudi patients. Hemoglobin concentration decreased by 10-30% in both genders since the first 3 months of MDT treatment. Mean Corpuscular Hemoglobin (MCH) and Mean Corpuscular Hemoglobin Concentration (MCHC) was decreased by 3-10% in males and females equivalently. Hemolytic anemia in normal glucose-6-phosphate dehydrogenase persons is common adverse effect for MDT and might explain the 20% drop in RBC count in MDT treatment group compared to normal group. The drop in Hb concentration (30%) might be partly attributed to hemolytic reaction and partly to methemoglobenemia. This is supported by the decrease by 10% in MCHC which might not be related to change in RBC count. Hemolytic anemia and methemoglobinemia are commonly reported in MDT treated leprosy patients and might be to greater extent than reported in the current study. Other hematologic adverse reaction such as agranulocytosis and immunosuppression mainly attributed to dapsone in MDT are commonly reported in several demographic studies [18,30,31]. None of the patients in the current study manifested agranulocytosis or any other immunologic deficiency syndrome; and most of hematological adverse effect were mild to moderate in severity and well tolerable by all ages in the study. In contrary, two cases of complete agranulocytosis were reported in the local anti-leprosy campaign in Sri Lanka [32]. Sample of patients in the study (n=48) were fully recovered from all hematological adverse effects after 6 months of the MDT treatment completion. Similar to Saudi population, Chinese population showed reversible hematological adverse effect after treatment with MDT [33].

Biochemical assessment for MDT treated leprosy Saudi patients presented mild progressive temporal hepato-renal complications (Table 4). Transaminases, AST and ALT increased progressively in both genders since the first 3 months of treatment with 5-35% relative to control group. The elevated level of AST and ALT were significantly high. However, these levels do not represent clinical value warrants treatment termination. Dapsone induced hepatitis has been clinically reported previously in leprosy patients with elevated AST and ALT levels. Bilirubin level increased temporally after 3 and 6 months in

	Control		*MDT*	
	Male	Female	Male	Female
Number	50	50	50	50
Age category	25-58	28-60	26-60	25-59
Age	42.6 ± 5.2	45.1 ± 7.6	46 ± 8.1	46.9 ± 6.3
BMI	26.1 ± 1.6	24 ± 1.3	25.7 ± 1.4	23.1 ± 2.1
Treatment duration (month)	6-12	6-12	6-12	6-12

Table 2: Sociodemographic characteristics of Saudi cases under investigation.

		Control				*MDT*			
		Zero	3-month	6-month	12-month	Zero	3-month	6-month	12-month
RBC (×10^6/ml)	M	5.5 ± 0.6	5.2 ± 0.6	5.5 ± 0.7	5.4 ± 0.7	5.5 ± 0.7	4.5 ± 0.6*	4.8 ± 0.7*	4.3 ± 0.6*
	F	4.7 ± 0.5	4.6 ± 0.5	4.9 ± 0.5	4.8 ± 0.5	4.9 ± 0.5	4.3 ± 0.5*	3.9 ± 0.4*	3.8 ± 0.5*
PCV (%)	M	45.8 ± 3.5	43.6 ± 5.2	45.3 ± 4.8	46.1 ± 4.7	45.8 ± 3.7	39.8 ± 4.1*	37.4 ± 3.8*	35.3 ± 4.1*
	F	42.5 ± 3.6	39.7 ± 4.3	41.8 ± 3.7	42.3 ± 4.6	41.8 ± 3.4	36.9 ± 4.1*	34.5 ± 3.5*	32.3 ± 3.5*
Hb (g%)	M	15.5 ± 1.1	14.7 ± 1.5	15.5 ± 1.7	15.5 ± 1.7	15.5 ± 1.2	13.1 ± 1.4*	11.5 ± 1.3*	10.9 ± 1.1*
	F	13.7 ± 1.1	12.4 ± 1.2	13.5 ± 1.4	13.3 ± 1.4	13.4 ± 1.13	11.3 ± 1.2*	10.2 ± 1.1*	9.5 ± 1.0*
MCH (pg)	M	30.6 ± 1.9	30.2 ± 2.8	30.7 ± 2.5	31.0 ± 3	30.6 ± 2.0	29.6 ± 2.5*	28.2 ± 2.4*	28.1 ± 2.6*
	F	30.6 ± 2.3	29.9 ± 2.5	30.3 ± 2.9	30.2 ± 2.6	30.3 ± 2.0	28.5 ± 2.8*	27.4 ± 2.7*	27.6 ± 2.8*
MCHC (g%)	M	32.7 ± 1.5	32.1 ± 2.1	32.0 ± 2.4	32.4 ± 2.2	32.6 ± 1.3	30.8 ± 2.1*	30.0 ± 1.9*	30.5 ± 2.4*
	F	32.5 ± 1.4	31.9 ± 2.7	32.6 ± 2.3	32.4 ± 2.4	32.7 ± 1.5	31.6 ± 2.2*	29.9 ± 2.0*	30.3 ± 2.3*

*Significantly different from corresponding control group ($p<0.05$)

Table 3: Temporal hematological findings in Saudi patients under MDT protocol for one year.

		Control				*MDT*			
		Zero	3-month	6-month	12-month	Zero	3-month	6-month	12-month
AST (IU/ml)	M	35.2 ± 10.3	37.1 ± 11.2	35.3 ± 10.6	35.1 ± 10.4	35.5 ± 10.7	40.1 ± 12.1*	41.9 ± 12.9*	44.0 ± 13.6*
	F	25.8 ± 7.4	25.0 ± 7.3	23.5 ± 7.4	23.8 ± 7.3	23.7 ± 7.1	26.7 ± 8.4*	28.2 ± 8.6*	29.3 ± 8.8*
ALT (IU/ml)	M	43.7 ± 16.4	51.4 ± 13.8	48.1 ± 12.0	47.9 ± 12.2	47.5 ± 12.0	55.6 ± 14.0*	61.2 ± 15.4*	63.5 ± 16.2*
	F	25.8 ± 7.4	24.9 ± 7.3	23.5 ± 7.4	23.8 ± 7.3	23.7 ± 7.1	26.7 ± 8.4*	28.2 ± 8.6*	29.3 ± 8.8*
Total billirubin (mg%)	M	0.81 ± 0.23	0.84 ± 0.22	0.8 ± 0.20	0.81 ± 0.22	0.81 ± 0.21	0.90 ± 0.23	0.96 ± 0.26*	1.00 ± 0.27*
	F	0.85 ± 0.21	0.93 ± 0.20	0.87 ± 0.19	0.88 ± 0.19	0.88 ± 0.18	0.99 ± 0.21*	1.05 ± 0.23*	1.09 ± 0.23*
Creatinine (mg%)	M	1.00 ± 0.18	1.07 ± 0.18	1.02 ± 0.18	1.02 ± 0.18	1.02 ± 0.17	1.19 ± 0.2*	1.29 ± 0.21*	1.07 ± 0.18*
	F	0.86 ± 0.13	0.91 ± 0.17	0.85 ± 0.16	0.87 ± 0.16	0.85 ± 0.15	0.99 ± 0.18*	1.08 ± 0.21*	1.13 ± 0.21*

*Significantly different from corresponding control group ($p<0.05$).

Table 4: Temporal biochemical parameters in Saudi patients under MDT protocol for one year.

females and males respectively. The higher level of Bil in females might be attributed to the cholestatic effect of female hormones [34]. Bil level remained high in both genders until the treatment completion however, its level does not present clinical jaundice at any time point. MDT-induced hepatitis was manifested with elevated transaminases and bilirubin as well [18]; in the current work MDT was well tolerated by Saudi patients with no aggravated hepatic affection. Serum creatinine showed progressive temporal elevation in MDT group compared with control group; however kidney function evaluated by creatinine clearance was not affected. Creatinine is a known biochemical marker for glumerular filtration rate of kidney [35]; however, creatinine clearance is much more accurate in assessing kidney filtration function [36]. Creatinine production is related to skeletal and cardiac muscle metabolism while its clearance is related to kidney function [37,38]. Negative effect of MDT on creatinine clearance while mild elevated creatinine level might be attributed to moderate muscle atrophy in response to MDT or Hansen's disease *per se* [17,39,40].

Other biochemical parameters assessed such as α-amylase, GGT, ALP, urea, and K^+ did not show any significant change between MDT treated group compared to control group over the whole year of the study. In contrary to Saudi population, other demographic populations presented pancreatitis, muscle atrophy, hepatitis and other complains attributed to MDT treatment.

Conclusion

In conclusion, MDT was well tolerated in Saudi leprosy patients with mild to moderate temporal hematological and biochemical adverse reactions.

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