Original Article

To Determine the Frequency of Biochemical Adverse Effects in Patients on Meglumine Antimoniate Treatment for Cutaneous Leishmaniasis

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ABSTRACT

Objective: To determine frequency of biochemical adverse effects in patients on meglumineantimoniate treatment for cutaneous leishmaniasis.

Study Design: Cross sectional study.

Place and Duration of Study: This study was conducted at the Department of Dermatology, Bolan Medical College/ Sandeman Provincial Hospital, Quetta from January, 2017 to December, 2018.

Materials and Methods: A total of 241patients with the diagnosis of CL were included in this study. The patients were treated with intra-gluteal injections of MA (Glucantime; Aventis, France) at a dose of 20mg/kg/day for 21 days. Patients were interviewed regarding their basic demographics. Blood samples were taken at 2nd week after starting treatment. Blood was sent for complete blood count, liver functions tests, serum creatinine and serum amylase level. Data was analyzed using SPSS version 23.

Results: A total of 241 patients were included in the study. The mean age of the patients was found to be 26.04 ± 9.23 years. The gender distribution of patients showed that most of the participants were male in this study. Mean BMI was 29.25 ± 5.34 kg/m^2. Most of the patients were having their symptoms from 4-8 weeks. Regarding the abnormality in biochemical variables after start of treatment, it was observed that the most commonly deranged variable was serum amylase in 66 patients (27.3%), followed by alkaline phosphatase in 56 patients (23.23%), ALT levels in 47 patients (19.5%) and serum AST levels in 41 patients (17.01%). Stratification of all these variables was done for age, gender, BMI levels and duration since start of symptoms and was significant for very few of them.

Conclusion: It is concluded that biochemical changes in patients of cutaneous leishmaniasis taking meglumineantimoniate do occur. Therefore, we need to educate our patients and need to tell them about the expected changes before the start of treatment with meglumineantimoniate.

Key Words: Meglumine antimoniate; Leishmaniasis; Serum; Biochemical; Sandfly

Citation of articles: Ahmed SB, Jabeen S, Habibullah. To Determine the Frequency of Biochemical Adverse Effects in Patients on Meglumine Antimoniate Treatment for Cutaneous Leishmaniasis. Med Forum 2019;30(9):82-86.

INTRODUCTION

Leishmaniasis is caused by a protozoan parasite of the genus Leishmania. The main vector for it is the Sand fly that infects vertebrates, which act as reservoirs of the disease[(1)].

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Received: March, 2019
Accepted: July, 2019
Printed: September, 2019

The disease is transmitted through sand flies which must have fed any person previously having the disease. However, the outcomes depends upon many factors including species of sand fly, immune system of the recipient as well as on type of Leishmania[(2)]. The cutaneous type of Leishmanisais involves skin only and leaves a scar. However, it may evolve into diffuse cutaneous leishmaniasis, leishmanias is recidivans, or mucocutaneous leishmaniasis (MCL)[(3)]. Cutaneous leishmaniasis (CL) is the commonest variety of leishmaniasis, while visceral leishmaniasis (VL) is the most severe one.

Several agents had been being used since ages for its treatment including antimony.[(3)(4,5)]. Pentavalent antimonials are being used for treatment of leishmaniasis for more than six decades. However, their mechanisms of action are not yet well understood. It is not even clear whether the final active form is Sb(V) or Sb(III). It acts as a prodrug and undergoes biological reduction to its active ingredient, which acts against the

Leishmaniasis. It is now most commonly used agent against this particular disease[6].

One recent study has found serious hepatic biochemical changes in patients taking meglumineantimoniate. Serum AST, ALT and alkaline phosphatase were elevated in 20%, 20% and 7%. In the same study serum total bilirubin was elevated in 6% of patients[7]. Another study has reported serious biochemical changes in pancreatic and renal metabolism. Hyperamylasemia was noted in 40% and increases serum creatinine was reported in 8%. Leukocyte was elevated in 8%[8].

The aim of my study was to find the biochemical changes in patients on meglumineantimoniate treatment for cutaneous leishmaniasis. At the international level, a significant body of research has been done on this issue but the situation is very different in Pakistan, where not such any research of significance has been conducted on this subject. The present study is an endeavor in this direction, generating data, which could be utilized in early identification of adverse biochemical changes and developing treatment services for patients on meglumineantimoniate treatment for cutaneous leishmaniasis in our population.

MATERIALS AND METHODS

This Cross sectional was conducted at Department of Dermatology, Bolan Medical College/ Sandeman Provincial Hospital, Quetta. The Study duration was 2 years from January, 2017 to December, 2018. The sampling technique used was Non-probability consecutive sampling. Sample size was calculated using WHO calculator taking the prevalence of raised bilirubin (least proportion) in patients on antimoniatetherapy i.e. 6%, margin of error d=3% and 95% level of confidence. Sample size came out to be n=241. We included all patients between the ages18-60, diagnosed as leishmaniasis as per operational definition and on treatment for > 2 weeks. We Excluded all patients having CRF documented as serum Cr > 2.5 at presentation; Hepatitis A, B and C positive patients(determined by positive Elisa test for hepatitis A, B and C); and patients of chronic pancreatitis. The data collection was started after an approval from the CPSP. After taking ethical committee approval and explaining the procedure informed constant was taken. A total of 241 patients were recruited from Out Patient Department and wards of Department of Dermatology, Bolan Medical College/ Sandeman Provincial Hospital, Quetta onthe basis of inclusion criteria. The patients were treated with intra-gluteal injections of MA (Glucantime; Aventis, France) at a dose of 20 mg/kg/day for 21 days. Patients were interviewed regarding their basic demographics. Blood samples were taken at 2nd week after starting treatment. Blood was sent for complete blood count, liver functions tests, serum creatinine and serum amylase level. The diagnosis of biochemical adverse effects were made as per operational definitions and were noted in proforma by researcher. The patients having CRF documented as serum Cr > 2.5 at presentation or Hepatitis A, B and C positive patients determined by positive Elisa test for hepatitis A, B and C or patients of chronic pancreatitis documented on U/S abdomen were excluded from the sample to control effect modifiers so that bias in the study results can be overcome. The patients were assured for recovery and socioeconomic cultural values were considered while examining the female patients. Data was analyzed using software of Statistical Package of Social Sciences (SPSS version 23). Mean + SD were calculated for continuous variable of age, height, weight, BMI, daily dose and duration of treatment. Results on categorical variables of gender and patient outcome variable biochemical adverse effects i.e. Raised AST, raised ALT, raised Alkaline Phosphatase, raised total bilirubin, hyperamylasemia, raised creatinine and raised leukocyte count were expressed in frequencies and proportions. Stratification of age, gender, BMI and duration of treatmentwas done to see their effect on outcome variable. Assuming the P value of <0.05 as significant, Chi-Square was used to detect the difference between the categories.

RESULTS

A total of 241 patients were included in the study. The mean age of the patients was found to be 26.04 ± 9.23 years. Patients were further categorized according to age groups into 4 groups. The gender distribution of patients showed that most of the participants were male in this study. The mean BMI was calculated as 29.25 ± 5.34 kg/m^2.

Table No. 1: Demographic and clinical details of patients

	No. of patients
Age of patients	
18-30 Years	135 (56.01%)
30-40 Years	56 (23.23%)
40-50 Years	21 (8.7%)
51-60 Years	29 (12.03%)
Mean ± SD(years)	26.04 ± 9.23
Gender: Male	177 (73.44%)
Female	64 (26.55%)
BMI: <25kg/m^2	36 (15%)
25-30kg/m^2	176 (73.0%)
>30kg/m^2	29 (12.0%)
Mean ± SD(kg/m^2)	29.25 ± 5.34
Duration Since Start Of Symptoms	
<4 weeks	35 (14.5%)
4-8 weeks	115 (47.7%)
>8 weeks	91 (37.7%)
Mean ± SD	8.32 ± 4.88 weeks
Duration Since Start Of Treatment	
≤10 days	138 (57.26%)
>10 days	103 (42.73%)
Mean ± SD(Days)	10.8 ± 2.81

Table No. 2: Distribution of patients according to deranged Biochemical Variable

Biochemical Variables		No. of patients	%
Raised AST	Yes	41	17.0%
	No	200	83.0%
Raised ALT	Yes	47	19.5%
	No	194	80.5%
Raised Alkaline Phosphatase	Yes	56	23.2%
	No	185	76.8%
Raised Bilirubin	Yes	35	14.5%
	No	206	58.5%
Raised Amylase	Yes	66	27.3%
	No	175	72.7%
Raised Creatinine	Yes	19	7.9%
	No	222	92.1%
Raised Leukocyte Count	Yes	21	8.71%
	No	220	91.29%

Table No.3: Stratification of Biochemical variables with respect to age

Biochemical Variables	Age groups	Yes	No	P-Value
Raised AST	18-30 Years	23	112	0.754
	30-40 Years	8	48	
	40-50 Years	5	16	
	51-60 Years	5	24	
Raised ALT	18-30 Years	26	109	0.604
	30-40 Years	9	47	
	40-50 Years	6	15	
	51-60 Years	6	23	
Raised Alkaline Phosphatase	18-30 Years	31	104	<0.001
	30-40 Years	11	45	
	40-50 Years	6	15	
	51-60 Years	8	21	
Raised Bilirubin	18-30 Years	18	117	0.860
	30-40 Years	9	47	
	40-50 Years	4	17	
	51-60 Years	4	25	
Raised Amylase	18-30 Years	41	94	0.209
	30-40 Years	11	45	
	40-50 Years	8	13	
	51-60 Years	6	23	
Raised Creatinine	18-30 Years	7	128	0.297
	30-40 Years	5	51	
	40-50 Years	3	18	
	51-60 Years	4	25	
Raised Leukocyte Count	18-30 Years	8	127	0.028
	30-40 Years	4	52	
	40-50 Years	5	16	
	51-60 Years	4	25	

The mean duration since start of symptoms of patients in this study was found as 8.32 ± 4.88 weeks. Most of the patients were having their symptoms from 4-8 weeks. The mean duration since start of treatment of patients in this study was found as 10.8 ± 2.81 days. Most of the patients were having their treatment from ≤10 days.

Table No.4: Stratification of Biochemical variables with respect to gender

Biochemical Variables	Age groups	Yes	No	P-Value
Raised AST	Male	27	150	0.234
	Female	14	50	
Raised ALT	Male	29	148	0.044
	Female	18	46	
Raised Alkaline Phosphatase	Male	38	139	0.289
	Female	18	46	
Raised Bilirubin	Male	18	159	0.001
	Female	17	47	
Raised Amylase	Male	51	126	0.395
	Female	15	49	
Raised Creatinine	Male	12	165	0.295
	Female	7	57	
Raised Leukocyte Count	Male	15	162	0.836
	Female	6	58	

Table No.5: Stratification of Biochemical variables with respect to BMI

Biochemical Variables	BMI (kg/m^2)	Yes	No	P-Value
Raised AST	<25	5	31	0.754
	25-30	32	144	
	>30	4	25	
Raised ALT	<25	6	30	0.696
	25-30	34	142	
	>30	7	22	
Raised Alkaline Phosphatase	<25	8	28	0.966
	25-30	41	135	
	>30	7	22	
Raised Bilirubin	<25	5	31	0.249
	25-30	23	153	
	>30	7	22	
Raised Amylase	<25	11	25	0.041
	25-30	42	134	
	>30	13	16	
Raised Creatinine	<25	4	32	0.578
	25-30	12	164	
	>30	3	26	
Raised Leukocyte Count	<25	4	32	0.026
	25-30	11	165	
	>30	6	23	

All these details are summarized in table 1Regarding the abnormality in biochemical variables after start of treatment, it was observed that the most commonly deranged variable was serum amylase in 66 patients (27.3%), followed by alkaline phosphatase in 56 patients (23.23%), ALT levels in 47 patients (19.5%) and serum AST levels in 41 patients (17.01%). All details are given in table 2. Stratification of all these variables was done for age, gender, BMI levels and

duration since start of symptoms. All details are summarized in tables 3,4,5 and 6.

Table No.6: Stratification of Biochemical variables with respect to duration since start of treatment

Biochemical Variables	Durations since start of symptoms	Yes	No	P-Value
Raised AST	≤10 days	21	117	0.371
	>10 days	20	83	
Raised ALT	≤10 days	26	112	0.735
	>10 days	21	82	
Raised Alkaline Phosphatase	≤10 days	25	113	0.026
	>10 days	31	72	
Raised Bilirubin	≤10 days	18	120	0.431
	>10 days	17	86	
Raised Amylase	≤10 days	37	101	0.781
	>10 days	29	74	
Raised Creatinine	≤10 days	11	127	0.971
	>10 days	8	95	
Raised Leukocyte Count	≤10 days	14	124	0.373
	>10 days	7	96	

DISCUSSION

The main objective of the study was to determine the frequency of the biochemical changes in patients on meglumineantimoniate (MA) for CL.The dosing regimen of MA which is being used for VL in the Mediterranean area has been found having a raised frequency of side effects, particularly in patients having Human Immunodeficiency Virus (HIV). The most frequent side effects was acute pancreatitis in these patients.Also, these adverse events led to stoppage and poor compliance for its usage and Leishmaniasis remained endemic worldwide, spreading across almost 88 countries [(9)].[(10)]. In many of previously conducted trials, adverse events of MA had been studied mostly in adults and only small number of children had been part of these trials [(11)]. In a study by Masmoudi et al, joint and muscle pains were found as the most common complications among 87 patients who received MA. They reported an adverse event rate of 21%[(12)]. In our study, the concentrations of direct and total bilirubin, creatinine, and hematologic parameters demonstrated rise after starting the treatment. The most common derangement was found in Serum Amylase level in this study. In a study by Shahian et al, who used MA among children with VL, no rise in serum Amylase levels was observed and they negated the routine monitoring of biochemical markers[(13)]. This is contradictory to our data, however, we included only adult patients in our study. In another study, hyperlipasemia was found in 54.8% and raised amylase levels in 19.4% of patients receiving MA[(14)], which is similar to our results. Although mixed results are available in the literature, however, continued monitoring of renal, hepatic, and pancreatic function during and immediately after antimonial treatment is prudent and has never been negated [(15)].

My study also had some limitations. It was a single center study, so I recommend a multicenter study on the topic. Also it was a single group study, therefore more trials having more study limbs and with proper randomization is needed to reveal all the aspects.It is concluded that biochemical changes in patients of Leishmaniasis taking meglumineantimoniate do occur. Therefore, these patients need to be educated pre-handedly about the expected complicationsand these biochemical changes.

CONCLUSION

It is concluded that biochemical changes in patients of cutaneous leishmaniasis taking meglumineantimoniate do occur. Therefore, we need to educate our patients and need to tell them about the expected changes before the start of treatment with meglumineantimoniate.

Author's Contribution:

Concept & Design of Study:	Syed Bilal Ahmed
Drafting:	Sajida Jabeen
Data Analysis:	Habibullah
Revisiting Critically:	Syed Bilal Ahmed
Final Approval of version:	Syed Bilal Ahmed

Conflict of Interest: The study has no conflict of interest to declare by any author.

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