

Effects of systemic meglumine antimoniate on ECG in patients with cutaneous leishmaniasis

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Abstract

Objective: To determine ECG changes in cutaneous leishmaniasis patients, treated with systemic meglumine antimoniate therapy in Khyber Teaching Hospital, Peshawar.

Methods All patients with cutaneous leishmaniasis who met the inclusion criteria and were using systemic meglumine antimoniate (IM) were evaluated after receiving ethical approval from the hospital ethical committee. All patients signed a written informed consent form, and a thorough general physical, systemic, and dermatological examination was performed. Before and after twenty-one days of treatment with systemic glucantime[®] at a dose of 20mg per kilogram body weight, all patients had their ECGs and related investigations such as liver and renal function tests. To exclude any bias from the study, strict exclusion criteria were used.

Results The majority of the 87 patients were men (55.2%). The prevalence of ECG abnormalities (effect) was 24%. Sinus bradycardia (33.3%) was the most common ECG changes, while ST segment elevation was the least common (4.8%). Gender (p=0.76), age (p=0.15), and CL duration (p <0.001) were used to stratify the frequency of ECG changes (effect).

Conclusion ECG alterations have been linked to the use of Glucantime[®] systemically. As a result, during the drug's systemic administration, careful monitoring is required.

Key words

Cutaneous leishmaniasis; Meglumine antimoniate; Sinus bradycardia.

Introduction

Leishmaniasis is a protozoal disease, transmitted by the bite of female sandfly.¹ The disease is endemic in tropical and subtropical countries, in the communities of low socioeconomic status and poor hygienic conditions. Leishmania has

different species which are distributed in different geographical zones of the world.² There are about 1.5-2 million cases of leishmaniasis worldwide.

There are three clinical forms of leishmaniasis; Cutaneous leishmaniasis (the most common), Mucocutaneous leishmaniasis and Visceral leishmaniasis.³ The incidence of cutaneous leishmaniasis is about 1-1.5 million cases per year.⁴ Approximately 90% of all cases of cutaneous leishmaniasis occur in Syria, Algeria, Brazil, Afghanistan and Saudi Arabia.⁵ In Pakistan, Cutaneous leishmaniasis is endemic in

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KPK, tribal areas, Baluchistan and Southern regions of Punjab. Majority of cases have been detected in Afghan refugees.²

Cutaneous leishmaniasis has two clinical variants i.e. Old World Cutaneous leishmaniasis which is found in Africa, Southern Europe, Middle East and Southwest Asia and New World Cutaneous leishmaniasis which is found in Central and South America.⁶ Cutaneous leishmaniasis causes mild to severe disfiguring skin lesions that progresses over the course of weeks to months and manifests in various ways including papules, plaques, ulcerative lesions and nodules. The spontaneous cure rate is low.⁷ The diagnosis is based on history, clinical examination and laboratory investigations. The lab investigations are PCR, slit skin smear and biopsy for histopathology.⁷

The treatment of leishmaniasis consist of topical therapy with antiprotozoal creams and ointments, cryotherapy, thermotherapy, Intralesional injection of antileishmanial drugs and systemic treatment with antiprotozoal therapy.⁸The treatment of choice is pentavalent antimonials compounds; meglumine antimoniate (glucantime) and sodium stibogluconate (pentostam).^{2,3} Meglumine antimoniate is administered daily by intramuscular injection and sodium stibogluconate via slow intravenous injection.⁹ The dose of glucantime is 20mg/kg of pentavalent antimony. Meglumine antimoniate acts by disrupting the production of ATP in the amastigotes forms.⁹

The common side effect resulted from systemic administration of these drugs are headache, myalgias, fever, fatigue, urticarial reactions and gastrointestinal disorders. It also causes renal, pancreatic, liver and cardiac toxicity.⁴

Arcos L *et al.* recorded weekly ECGs in 131 patients of cutaneous leishmaniasis for 1 month, after the end of antimonial treatment. The most

common abnormality was QT prolongation, found in 19% of patients followed by bradycardia in 10.6%, T wave inversion in 7.4% and ST segment depression in 6%.¹⁰ de Freitas PF *et al.* conducted a study in the effects of systemic glucantime on ECG and concluded that 33% of the patients develop ECG abnormalities. Among them, 33c/o of patients develop sinus bradycardia, followed by prolongation of QT interval in 15.5% of the patients.¹¹

Cutaneous leishmaniasis is endemic in parts of Khyber Pukhtunkhwa of Pakistan. Cases of CL are at the increase. Glucantime is being widely used as a first line treatment option in majority of the cases. Lesions at face and multiple lesions are preferably treated with systemic glucantime. Limited studies are available locally on the treatment monitoring and side effects of glucantime therapy in KPK. It was, therefore, necessary to conduct studies in this field. The results of this study will be shared with clinicians to update the monitoring of systemic therapy using pentavalent antimonials in cutaneous leishmaniasis

Methods

It is a descriptive case series conducted at Department of Dermatology, Khyber Teaching Hospital Peshawar. Minimum six months of duration, i.e; 25th March 2021 to 25th September 2021. Sample size of this study was 87 patients taking 6% prevalence of ECG abnormalities in patients with cutaneous leshmaniasis treated with meglumine antimoniate. This sample size was calculated using WHO calculator for sample size determination in health studies taking 95% confidence interval and 5% margin of error.¹⁰

Randomized non probability sampling technique. After taking ethical approval from the hospital ethical committee (reference no. 688/DME/KMC, dated 24-March-2021), all

patients with cutaneous leishmaniasis taking systemic meglumine antimoniate (IM) were assessed. A written informed consent was taken from all the patients and complete general physical, systemic and dermatological examination was carried out. ECG and relevant investigations like liver and renal functions test were carried out for all the patients having non healing nodular ulcerative skin lesion and history of travelling to the endemic area. Patients fulfilling the inclusion criteria for CL were subjected to slit skin smear.

In this particular technique of slit skin smear, under local anesthesia, the suspected lesion for CL was squeezed between the index finger and thumb. Fifteen size surgical blade was used and 5mm long and 3 mm deep incision was made. The lesion was scrapped several times by rotating the blade at right angle. The scrapped material was taken on the glass slide. The smear was stained with leishman or giemsa stain after fixing it.

The leishman stained slide was examined for areas having predominant mono nuclear inflammatory cells or large macrophages containing the protozoal antigen under light microscope.

Leishmania trophozoite (LT) bodies were seen on the basis of morphology under oil emersion lense. It was indentified on the basis of oval shape having nucleus or/ and kineoplast, intracellular or extra cellular.

According to the current recommended protocol for CL, each patient was given IM injection of glucantime® (meglumine antimoniate) with the dose of 20 mg per kg per day for twenty-one days. All the patients were strictly advised not to use any other therapy during this period in order to avoid any confounding factor or biased in the study.

ECG of all patients was monitored before and after the completion of treatment. During this period, other causes of abnormal ECG like acute MI, angina etc. were ruled out. Data was collected on purposefully designed Performa.

All the data was entered into and analyzed by SPSS version 22. Frequency and percentages were calculated for categorical variables like gender and effects of meglumine antimoniate of ECG while mean and standard deviation were calculated for numerical variables like age, duration of CL and number of lesions. Abnormal ECG findings (effect) were stratified on the basis of gender, age and duration of CL in order to see effect modification. Post stratification chi square test was applied keeping p value ≤ 0.05 as statistically significant. All data was presented in the form of tables and charts.

Results

In this study, a total of 87 patients were enrolled. Among these patients, 48 patients (55.2%) were males and 39 patients (44.8%) were females (**Table 1**).

The mean age was 37.82 with the standard deviation of 12.08 SD. On the basis of age, patients were divided into two groups. Majority of the patients i.e; 49 patients (56.3%) were having age 18 to 40 years (**Table 2**).

Table 1 Gender wise.

Gender	No. of patients	Percentages
Male	48	55.2%
Female	39	44.8%
Total	87	100%

Table 2 Age wise distribution of patients (n=87).

Age of patients	No of patients		Total patients
	Male	Female	
18-40 yrs.	23 (47)	26 (53)	49 (56.3)
41-60 yrs.	25 (65.7)	13 (34.3)	38 (43.7)
Total	48 (55.2)	39 (44.8)	87 (100)

Group A: In this groups, patients aged 18 to 40 years were included. In this groups, majority of the participants i.e; 26 patients (53%) were females.

Group B: In this group, patients aged 41 to 60 years were included. Among these patients, majority of them i.e; 25 patients (65.7%) were males.

Among these 87 patients, 21 patients (24%) were found to have changes in ECG after 21 days of treatment with intramuscular meglumine antimoniate (20 mg per Kg body weight daily) (**Table 3**).

The ECG changes were further divided into types of ECG changes (**Table 4**). The most common ECG abnormality was sinus bradycardia which was noted in 07 patients (33.3%) while the least common ECG abnormality was ST segment elevation which was noted in a single patient (4.8%).

Frequency of ECG changes (effect) was stratified on the basis of gender (**Table 5**). Among these patients, 11 males (23%) and 10 females (25.6%) were found to have ECG changes. Post stratification, the chi square test was applied and the p-value was 0.76 which was not significant statistically

Table 3 ECG changes (effect) in patients taking IM Glucantime® (n=87).

ECG changes (Effect)	No of patients	%age
Yes	21	24%
No	66	76%
Total	87	100%

Table 4 Types of ECG changes in patients taking IM Glucantime®.

Type of ECG changes	No of patients	%age
Bradycardia	07	33.3%
ST segment depression	06	28.6%
T wave inversion	05	23.8%
QT prolongation	02	9.5%
ST segment elevation	01	4.8%
Total	21	100%

Table 5 Stratification of ECG changes on the basis of gender (n=87).

Gender	ECG changes (Effect)		Total
	Yes	No	
Male	11 (23%)	37 (77%)	48 (100%)
Female	10 (25.6%)	29 (74.4%)	39 (100%)
Total	21 (24%)	66 (76%)	87 (100%)

P value: 0.76.

Table 6 Stratification of ECG changes on the basis of age (n=87).

Age of pts.	ECG changes (Effect)		Total
	Yes	No	
18-40 yrs.	09 (18.3%)	40 (81.7%)	49 (100%)
41-60 yrs.	12 (31.5%)	26 (68.5%)	38 (100%)
Total	21 (24%)	66 (76%)	87 (100%)

P value: 0.15.

Table 7 stratification of ECG changes on the basis of duration of CL (n=87).

Duration of Cutaneous leishmaniasis	ECG changes (Effect)		Total
	Yes	No	
< 6 months	08 (14%)	50 (86%)	58 (100%)
> 6 months	13 (45%)	16 (55%)	29 (100%)
Total	21 (24%)	66 (76%)	87 (100%)

P value: 0.001.

ECG changes were also stratified on the basis of age (**Table 6**). Among patients aged 18 to 40 years, 09 patients (18.3%) experienced changes in their ECG after treatment with intramuscular glucantime® while in patients aged 41 to 60 years, 12 patients (31.5%) experienced changes in their ECG. By applying the chi-square test, the p-value was 0.15 which was statistically not significant.

The mean duration of cutaneous leishmaniasis (CL) in this disease was 5.89 months with a standard deviation of 2.51. Among patients with CL duration of less than six months, 8 patients (14%) experienced ECG changes while in patients with CL duration of more than six months, 13 patients (45%) were reported with ECG changes. The difference was statistically significant (p<0.001) (**Table 7**).

Discussion

Cutaneous leishmaniasis is a protozoal illness

caused by various protozoan species from the genus *Leishmania*, as well as organisms from the subgenus *Leishmania*. It exhibits viscerotropism and dermatotropism in the Old World (the Middle East, Africa, southern Europe, Asia) and dermatotropism in the New World (Latin America), particularly species belongs to the subgenus *Viannia* (in the New World) that exhibits only dermatotropism.^{12,13} According to WHO 2007, dermatographic *Leishmania* is endemic in roughly 82 countries of the World, Pakistan is among one of them. More than 90% of cutaneous leishmaniasis cases are found in Brazil and six other developing nations around the world.¹⁴ Pentavalent antimonials, such as meglumine antimoniate, are the first-line treatment for cutaneous leishmaniasis and are given at a dose of 10 to 20 mg per kilogram of body weight for a minimum of twenty days.¹⁵ Meglumine antimoniate was administered in our study at a dose of 20 mg per kilogram of body weight for 21 days, which is in accordance with the guidelines.¹⁵ Adverse effects of drugs are unfavourable occurrences that occur over time as a result of the use of medications, whereas drug safety refers to morbidity and mortality as a result of the incidence and severity of adverse effects.¹⁶ Apart from diarrhoea, pain in the abdomen, fever, erythema, urticaria, herpes zoster, and changes in liver and pancreatic functions, glucantime is linked to changes in electrocardiographic in its normal dose of 20 mg/kg/day.¹⁶ Arrhythmia has also been documented in some cases. The ECG abnormalities associated with intramuscular use of meglumine antimoniate were the focus of this study.

ECG abnormalities were found in 24 percent of the 87 patients in our study. Bradycardia was the most prevalent anomaly, occurring in 33.3 percent of cases, followed by ST segment depression in 28.6 percent. While ST segment elevation was the least prevalent ECG abnormality, it was only seen in one patient. In

their study, Arcos L *et al.* found that ECG changes were observed in 30% of their patients, which is similar with our findings.¹⁰ ECG alterations with a standard dose of systemic glucantime[®] were studied by Tahir M *et al.* by including 87 patients in their study, which is similar to ours. They also observed ST segment elevation in a single patient, which is consistent with our findings as well.¹⁷

In our study, 9.5% of individuals had QT interval prolongation. QT interval prolongation was reported in 12% of patients by Shanehsaz SM *et al.*; which is similar with our findings.¹⁸ Males made up the majority of our participants (55.2%). Shanehsaz SM also reported that males made up the majority of their study (66%), which matches our findings. Another study conducted by Abid R in Azad Jammu and Kashmir found that 15% of their patients had QT interval prolongation.¹⁹ According to Duque *et al.*; QTc interval prolongation can cause torsade de pointes, a potentially deadly consequence. As a result, patients with systemic glucantime[®] had a longer QT interval. It needs to be closely watched QT interval prolongation was seen in 15.5% of CL patients by de Freitas PF *et al.*¹¹ In 19% of these CL patients, Arcos L *et al.* found QT interval prolongation.¹⁰

Sinus bradycardia was found in 33.3 of patients in our study, and it was the most common finding in our patients' ECGs. According to de Freitas PF *et al.*; sinus bradycardia was the most common alternation seen in 33% of their patients taking systemic glucantime[®] for CL, which is also consistent with our findings.¹¹ Serious electrocardiographic changes such as ST segment elevation and QT interval lengthening are found in less than 10% of patients, according to data. ST segment elevation was observed in 4.8 percent of patients in our study, while QT interval prolongation was observed in 9.5 percent of cases, which is consistent with the data mentioned by Daadaa N *et al.*²⁰

In our analysis, when ECG alterations were stratified by gender (23% in males vs. 25.6% in females, $p=0.76$), there was no statistically significant difference in ECG changes. However, there was a numerically significant difference in ECG effects, as it was noticed higher in patients over the age of 40 (31.6% versus 18.3%), although the difference was statistically insignificant ($p=1.5$). This could be related to the increase in their ages.

Conclusion

In Pakistan, cutaneous leishmaniasis is endemic. Systemic glucantime[®] is administered to patients with face involvement and multiple CL lesions. In its usual dose, systemic glucantime[®] can have unfavourable systemic consequences, such as an alteration in ECG. Patients taking systemic glucantime[®] should have their ECGs checked on a regular basis, and if any severe changes are seen, treatment should be stopped and alternative medications may be considered.

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Author's contribution

IAU: Contribution to the conception, design, data acquisition, analysis, has given final approval of the version to be published.

SB: Contribution to the interpretation of data, critically reviewed for intellectual content, has given final approval of the version to be published.

ZKS: Contribution to data acquisition and interpretation, drafting the article, has given final approval of the version to be published.

NU: Contribution to the design of the work, critically reviewed the manuscript, has given final approval of the version to be published.

WZK: Data acquisition and interpretation, drafting the article, has given final approval of the version to be published.

MK: Conception of the study, analysis of data, drafting the work, has given final approval of the version to be published.

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