

ASSESSING THE FREQUENCY OF ELECTROCARDIOGRAPHIC (ECG) CHANGES AMONG PATIENTS RECEIVING INTRAMUSCULAR MEGLUMINE ANTIMONIATE FOR THE TREATMENT OF CUTANEOUS LEISHMANIASIS

Original Research

Suhaib Ali Khan¹, Tanvir Ahmad Mujahid², Furqan Khan Warrach², Kashif Ali Khan^{3*}, Muhammad Imran Khan¹, Sana Hassan¹

¹Resident Dermatologist, Combined Military Hospital (CMH), Peshawar, Pakistan.

²Consultant Dermatologist, Combined Military Hospital (CMH), Peshawar, Pakistan.

³Consultant Cardiologist & Fellow Interventional Cardiology, Lady Reading Hospital, Peshawar, Pakistan.

Corresponding Author: Kashif Ali Khan, Consultant Cardiologist & Fellow Interventional Cardiology, Lady Reading Hospital, Peshawar, Pakistan, kashifali315587218@gmail.com

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ABSTRACT

Background: Cutaneous leishmaniasis (CL) is a neglected tropical disease endemic in Pakistan and several other low- and middle-income countries. Meglumine antimoniate, a pentavalent antimonial compound, remains the most widely used first-line treatment for CL. Despite its therapeutic efficacy, the drug is known to cause cardiotoxic effects, particularly electrocardiographic (ECG) abnormalities, which may remain subclinical but could progress to life-threatening arrhythmias. Monitoring ECG changes during therapy is essential to mitigate potential cardiac risks.

Objective: To evaluate the frequency and types of ECG changes in patients receiving intramuscular meglumine antimoniate for the treatment of cutaneous leishmaniasis and to assess associations with demographic and clinical variables.

Methods: This descriptive study was conducted over three months in the Dermatology Ward of Combined Military Hospital, Peshawar. A total of 78 patients, aged 18–75 years with confirmed CL, were enrolled using non-probability consecutive sampling. Patients with known cardiac disease, chronic systemic illness, or pregnancy were excluded. Baseline and 2-week post-treatment 12-lead ECGs were obtained and analyzed by a consultant cardiologist. Data were processed using SPSS version 23. ECG parameters including heart rate, PR interval, and QT interval were compared pre- and post-treatment. Chi-square and Mann-Whitney U tests were used for inferential analysis with $p \leq 0.05$ considered statistically significant.

Results: Out of 78 patients, 28 (35.8%) exhibited ECG changes following treatment. The most common abnormalities were QT interval prolongation in 10 patients (12.8%), tachycardia in 7 (8.9%), PR interval prolongation in 6 (7.7%), and ST-T wave abnormalities in 5 (6.4%). A significant association was observed between age above 50 years and ECG abnormalities ($p = 0.03$).

Conclusion: Intramuscular meglumine antimoniate is associated with subclinical but potentially serious ECG changes in a significant proportion of patients. Regular ECG monitoring is advised during therapy, particularly in older adults, to minimize cardiac risks.

Keywords: Cardiotoxicity, Cutaneous leishmaniasis, Electrocardiographic changes, Meglumine antimoniate, PR interval, QT interval prolongation, Tachycardia.

INTRODUCTION

Cutaneous leishmaniasis (CL) is a neglected tropical disease caused by protozoan parasites of the *Leishmania* genus, transmitted through the bite of infected female sandflies (1). Endemic in regions of South America, the Middle East, North Africa, and South Asia, CL remains a significant public health challenge, particularly in resource-limited countries. In Pakistan, the disease is highly prevalent in southern districts of Khyber Pakhtunkhwa such as Tank, Karak, Lakki Marwat, Dera Ismail Khan, and border areas adjoining Afghanistan. The clinical spectrum of CL ranges from a solitary ulcerative lesion to multiple painful and disfiguring skin ulcers. These chronic lesions often result in secondary bacterial infections and lead to considerable psychological and social distress, particularly among affected women and children (2). The morbidity associated with CL underscores the need for timely diagnosis and effective treatment to prevent complications and reduce its long-term psychosocial burden. Pentavalent antimonial compounds have long been the cornerstone of CL treatment, with meglumine antimoniate being the most commonly used therapeutic agent in endemic settings, including Pakistan (3). Its antileishmanial effect stems from interference with parasite glycolysis and fatty acid metabolism, ultimately leading to cell death (4). Despite its therapeutic benefits, meglumine antimoniate is associated with significant systemic toxicity. Adverse effects such as hepatotoxicity, nephrotoxicity, and pancreatitis have been well-documented, but cardiotoxicity is increasingly recognized as the most worrisome, owing to its potential for fulminant and life-threatening arrhythmias (5). Cardiac involvement is believed to occur through interactions with myocardial ion channels, leading to alterations in cardiac repolarization and conduction. Electrocardiographic (ECG) abnormalities associated with antimonial therapy include QT interval prolongation, ST-segment and T-wave changes, bradycardia, and atrioventricular conduction delays. QT interval prolongation is particularly concerning due to its association with torsades de pointes—a potentially fatal form of polymorphic ventricular tachycardia (6,7).

While many ECG changes induced by antimonial therapy are reversible upon discontinuation of the drug, their occurrence necessitates careful cardiac monitoring, especially in patients with underlying cardiac disease or electrolyte imbalances. Notably, the route of administration significantly influences the drug's systemic absorption and toxicity profile (8). Intravenous administration is linked to higher plasma concentrations and a greater risk of cardiac events, whereas the intramuscular (IM) route is often favored in field settings for its ease of use and comparatively lower systemic impact (9). Nonetheless, the extent of cardiotoxicity associated with IM meglumine antimoniate remains poorly characterized. Most available studies focus on intravenous administration, leaving a knowledge gap regarding the safety of the IM route in relation to cardiac function (10). Preliminary findings suggest a lower incidence of ECG abnormalities with IM therapy, but comprehensive data on the nature, frequency, and severity of such changes are lacking. This research addresses an important clinical gap by investigating ECG alterations among patients receiving IM meglumine antimoniate for the treatment of CL (11). The study aims to determine the prevalence and pattern of ECG abnormalities—such as QT prolongation, ST/T-wave changes, PR interval deviations, and heart rate disturbances—associated with this commonly used therapy. Additionally, it evaluates the potential influence of demographic factors and comorbidities as risk modifiers. The findings are expected to inform clinical protocols and offer evidence-based recommendations regarding the need for routine ECG monitoring in patients undergoing IM antimonial therapy.

METHODS

This descriptive observational study was conducted over a period of three months in the Dermatology Ward of Combined Military Hospital (CMH), Peshawar, following approval from the Institutional Ethical Review Board and the College of Physicians and Surgeons Pakistan (CPSP). Written informed consent was obtained from all participants prior to their inclusion, and all study procedures were carried out in accordance with the ethical standards of the institutional research committee and the Declaration of Helsinki. The primary objective was to evaluate the frequency and pattern of electrocardiographic (ECG) changes in patients undergoing intramuscular meglumine antimoniate therapy for cutaneous leishmaniasis (CL). The study recruited 78 patients using a non-probability consecutive sampling technique. Sample size estimation was performed using the World Health Organization (WHO) sample size calculator, applying an estimated prevalence of ECG changes at 5.3%, with a 95% confidence level and a 5% margin of error. Adult patients between 18 and 75 years of age with a confirmed diagnosis of CL—based on either split skin smear or histopathological findings from skin biopsy—were eligible for inclusion. Exclusion criteria included known hypersensitivity to meglumine antimoniate, presence of

mucocutaneous or visceral forms of leishmaniasis, documented history of cardiovascular disease, and any chronic systemic condition such as diabetes mellitus, chronic kidney disease, or hepatic dysfunction. Pregnant and lactating women, as well as pediatric patients under the age of 17 years, were also excluded from the study (3,5).

Upon enrollment, all patients underwent a detailed clinical assessment including medical history, physical examination, and baseline investigations. These included a complete blood count (CBC), liver and renal function tests, serum amylase levels, urine routine examination, and a 12-lead resting ECG. Patient demographics and clinical information—such as age, gender, body mass index (BMI), residential background, educational level, occupation, and socioeconomic status—were recorded using a structured data collection form. All patients received hospital-based intramuscular therapy with meglumine antimoniate (Glucantime®, Sanofi Aventis), administered in the gluteal region at a dose of 15 mg/kg of body weight daily. Treatment continued for 14 consecutive days. At the end of the second week, a follow-up ECG was performed for each participant. All ECGs were interpreted by a board-certified consultant cardiologist who was blinded to the baseline clinical profiles of the patients. Any changes in the ECG parameters—such as QT interval prolongation, PR interval variations, ST-T wave changes, or rhythm disturbances—were documented systematically using a pre-designed proforma. Data were analyzed using IBM SPSS version 23. Categorical variables including gender, residential status, educational level, and ECG findings were summarized as frequencies and percentages. Continuous variables such as age, BMI, heart rate, PR interval, and QT interval were evaluated for normality using the Shapiro-Wilk test. Normally distributed variables were expressed as mean \pm standard deviation (SD), while non-normally distributed variables were reported as median with interquartile range (IQR). Chi-square tests were employed to explore the association between ECG changes and selected demographic and clinical variables, with a *p*-value ≤ 0.05 considered statistically significant.

RESULTS

The study included a total of 78 patients diagnosed with cutaneous leishmaniasis and treated with intramuscular meglumine antimoniate. The cohort had a mean age of 36.8 years (± 12.2 SD), with males constituting 60.3% ($n = 47$) of the sample. The majority of patients (73.1%) were from rural backgrounds, while 57.7% belonged to the lower socioeconomic class. Regarding education, 42.3% had no formal schooling, and only 26.1% had completed secondary education or higher. Baseline electrocardiographic parameters showed a mean heart rate of 76.5 ± 9.8 bpm, a PR interval of 168.3 ± 15.4 ms, QT interval of 412.2 ± 31.7 ms, and QRS duration of 92.1 ± 9.8 ms. These values fell within clinically acceptable limits at the time of initial evaluation. Two weeks after initiating therapy, 35.8% of patients ($n = 28$) demonstrated new or altered ECG findings. The most common abnormality observed was QT interval prolongation in 12.8% ($n = 10$) of the patients, followed by tachycardia in 8.9% ($n = 7$), PR interval prolongation in 7.7% ($n = 6$), and ST-T wave abnormalities in 6.4% ($n = 5$). The Shapiro-Wilk test was applied to determine the distribution pattern of continuous variables. Age, heart rate, and PR interval were normally distributed ($p > 0.05$), while BMI and QT interval deviated from normal distribution ($p < 0.05$). Accordingly, non-parametric testing (Mann-Whitney U) was used for further analysis of these variables.

A statistically significant association was found between age and ECG abnormalities ($p = 0.03$). Patients aged 46–75 years demonstrated a notably higher prevalence of ECG changes (65%) compared to those aged 18–45 years (25%). Gender ($p = 0.12$) and socioeconomic status ($p = 0.06$) did not show significant associations with ECG alterations. The Mann-Whitney U test showed that individuals who developed ECG changes had a significantly higher median BMI (28.5; IQR: 24.1–32.4) compared to those who did not (23.1; IQR: 21.5–25.4), with a *p*-value of 0.04. Similarly, patients with ECG changes had a higher QT interval median (418 ms; IQR: 405–430) than those without changes (408 ms; IQR: 380–420), with statistical significance ($p = 0.02$). These findings suggest that increased age and higher BMI may predispose patients to ECG abnormalities during intramuscular meglumine antimoniate therapy. Prolonged QT interval was the most frequently observed cardiac effect. These results underline the importance of ECG monitoring during treatment, particularly in older or overweight patients receiving antimonial therapy. Subgroup analysis of specific electrocardiographic abnormalities—including PR interval prolongation, ST-T wave abnormalities, and tachycardia—revealed distinct distribution patterns across demographic and clinical characteristics. Among patients with prolonged PR intervals ($n = 6$), the majority were females and individuals aged 46 years or older. A higher prevalence was noted among rural residents and those belonging to the lower socioeconomic class. ST-T wave abnormalities ($n = 5$) also showed a predominance in older age groups and rural populations, with a slightly higher occurrence among males. In cases of tachycardia ($n = 7$), the distribution was more balanced across genders; however, most individuals were in the younger age group (18–45 years), and a notable number came from middle and upper-middle socioeconomic backgrounds. These findings suggest that both age and socioeconomic status may influence the susceptibility to specific ECG abnormalities following meglumine antimoniate treatment.

Table 1: Demographic Characteristics of Study Participants

Demographic Variable	N = 78	Percentage (%)
Gender		
Male	47	60.3
Female	31	39.7
Age Group		
18-45 years	37	47.4
46-60 years	14	18.4
61-75 years	27	34.2
Residential Background		
Urban	21	26.9
Rural	57	73.1
Socioeconomic Status		
Lower	45	57.7
Middle	20	25.6
Upper-Middle	13	16.7
Educational Level		
No formal education	33	42.3
Primary education	25	31.6
Secondary or higher	20	26.1

Table 2: Baseline ECG Parameters

Parameter	Mean \pm SD	Median (IQR)	Range
Heart Rate (bpm)	76.5 \pm 9.8	76 (69-85)	55 - 110
PR Interval (ms)	168.3 \pm 15.4	170 (160-180)	120 - 200
QT Interval (ms)	412.2 \pm 31.7	408 (385-440)	360 - 480
QRS Duration (ms)	92.1 \pm 9.8	90 (85-100)	80 - 120

Table 3: Post-Treatment ECG Changes

ECG Change	N = 78	Percentage (%)
Prolonged QT Interval	10	12.8
Tachycardia (HR > 100 bpm)	7	8.9
Prolonged PR Interval (>200 ms)	6	7.7
ST-T Wave Abnormalities	5	6.4

Table 4: Results of Shapiro-Wilk Test for Normality

Variable	p-value	Conclusion
Age	0.28	Normally distributed
BMI	0.03	Not normally distributed
Heart Rate (bpm)	0.21	Normally distributed
PR Interval (ms)	0.08	Normally distributed
QT Interval (ms)	0.02	Not normally distributed

Table 5: Chi-Square Test for Association Between Demographic Factors and ECG Changes

Variable	ECG-Changes (%)	No-ECG-Changes (%)	p-value
Gender			0.12
Male	25.5	74.5	
Female	35.5	64.5	
Age Group			0.03
18-45 years	25.0	75.0	
46-75 years	65.0	35.0	
Socioeconomic Status			0.06
Lower	34.2	65.8	
Middle/Upper-Middle	25.0	75.0	

Table 6: Mann-Whitney U Test for BMI and QT Interval Between Groups

Variable	ECG Changes (Median, IQR)	No ECG Changes (Median, IQR)	p-value
BMI	28.5 (24.1 - 32.4)	23.1 (21.5 - 25.4)	0.04
QT Interval (ms)	418 (405 - 430)	408 (380 - 420)	0.02

Table 7: Subgroup Analysis of ECG Abnormalities

Gender	Femal e	Femal e	Femal e	Femal e	Femal e	Femal e	Male	Male	Male	Male	Male	Total
Age Group	18-45	18-45	46-60	46-60	61-75	61-75	18-45	18-45	18-45	46-60	61-75	
Socioeconomics Status	Lower	Upper- Middle	Lower	Upper- Middle	Lower	Middle	Lower	Middle	Upper- Middle	Lower	Middle	
ECG Abnormality												
Prolonged PR Interval	1	0	1	0	1	0	0	1	0	1	1	6
ST-T Wave Abnormalities	0	1	0	0	1	0	1	1	0	1	0	5
Tachycardia	1	0	1	1	0	1	0	0	1	1	1	7
Total	2	1	2	1	2	1	1	2	1	3	2	18

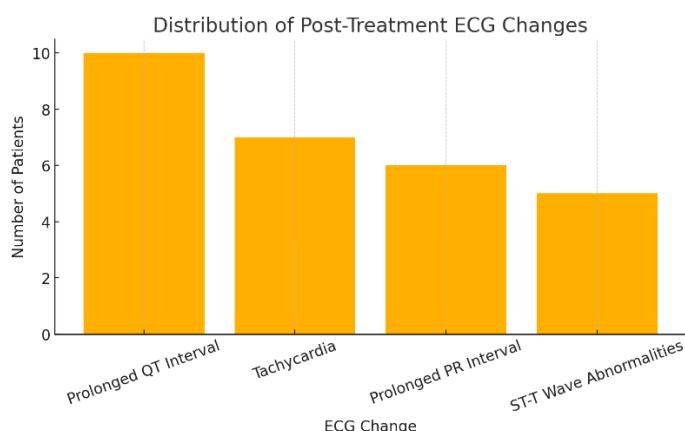


Figure 1 Distribution of Post-Treatment ECG Changes

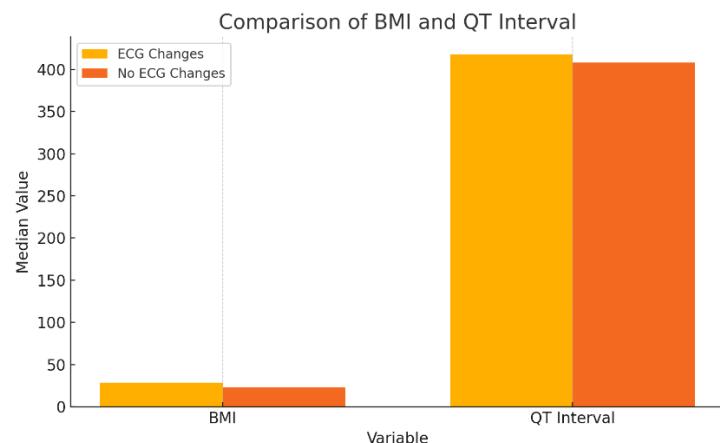


Figure 2 Comparison of BMI and QT Interval

DISCUSSION

The findings of this study reaffirm the cardiotoxic potential of meglumine antimoniate in the treatment of cutaneous leishmaniasis, particularly its capacity to induce electrocardiographic (ECG) alterations such as QT prolongation, tachycardia, and PR interval changes. These observations are consistent with previous evidence indicating that pentavalent antimonial compounds can significantly affect myocardial electrophysiology through mechanisms involving delayed repolarization, altered ion channel activity, and conduction disturbances (12,13). In the present cohort, ECG abnormalities were observed in 35.8% of patients two weeks after treatment initiation, with prolonged QT interval being the most common, followed by tachycardia and prolonged PR interval. The frequency and pattern of these findings are comparable, though somewhat higher, than those reported in earlier studies investigating sodium stibogluconate, another pentavalent antimonial, suggesting that meglumine antimoniate may carry a similar or potentially elevated risk for cardiac adverse effects (14,15). Prolonged QT interval has long been recognized as a marker of heightened risk for ventricular arrhythmias, particularly torsades de pointes, and this study reinforces its clinical importance in the context of antimonial therapy. Although the precise molecular mechanisms remain incompletely understood, meglumine antimoniate appears to exert direct modulatory effects on myocardial ion channels, particularly those responsible for potassium and sodium transport, which may explain its arrhythmogenic potential (16,17). This underlines the need for vigilant ECG monitoring during the course of therapy, especially in patients with predisposing factors such as electrolyte imbalances, comorbidities, or concurrent use of QT-prolonging medications.

An important finding of this study was the significant association between patient age and the likelihood of developing ECG abnormalities. Older patients, particularly those aged 46 to 75 years, were more likely to exhibit prolonged QT intervals and other conduction disturbances. These observations align with previous literature showing that aging is associated with structural and functional changes in the cardiac conduction system, diminished ion channel reserve, and impaired ability to compensate for pharmacologic stressors (18). Consequently, the elderly population is particularly vulnerable to drug-induced cardiac toxicity, and the findings of this study underscore the need for enhanced caution in prescribing meglumine antimoniate to this demographic group. Tachycardia observed in a subset of patients may be related to systemic inflammatory responses triggered by both cutaneous leishmaniasis and its treatment. This finding is supported by prior research highlighting the influence of inflammatory mediators on sympathetic activation and heart rate elevation during infectious disease states (19). While the exact mechanism remains speculative, it reflects a possible indirect cardiovascular response to treatment-related stress. Similarly, PR interval prolongation, detected in 7.7% of patients, suggests an effect on atrioventricular nodal conduction. Though often clinically silent, PR prolongation may indicate early myocardial conduction system involvement and warrants monitoring, particularly in individuals receiving cumulative dosing or those with borderline baseline conduction metrics (20).

The strength of this study lies in its focused assessment of ECG changes following intramuscular administration of meglumine antimoniate, a route commonly used in resource-limited endemic settings. The prospective evaluation and structured cardiological interpretation of serial ECGs lend clinical robustness to the findings. Additionally, the inclusion of demographic stratification and subgroup analyses has highlighted critical risk factors such as age and BMI, which may inform future risk mitigation strategies. However,

the study has several limitations. Being a single-center study, the results may not be generalizable to broader populations, especially considering regional variability in health infrastructure, baseline comorbidities, and access to cardiac care. The relatively modest sample size of 78 patients may have limited the power to detect less common ECG changes and to perform more nuanced multivariate analyses. Furthermore, the study only evaluated short-term ECG effects and did not capture any potential delayed or cumulative cardiotoxic effects of meglumine antimoniate. This limitation precludes definitive conclusions regarding the long-term cardiovascular safety profile of the drug. The absence of follow-up beyond the two-week window restricts insight into the reversibility or progression of ECG changes. In addition, objective biomarkers of cardiotoxicity, such as serum troponin or B-type natriuretic peptide (BNP), were not evaluated, which could have added a biochemical dimension to the observed electrophysiological alterations. Future research should focus on elucidating the mechanistic underpinnings of antimonial-induced cardiotoxicity, particularly through ion channel studies and cardiac electrophysiological modeling. Comparative trials between meglumine antimoniate and other antileishmanial agents, including amphotericin B or miltefosine, could clarify relative cardiac safety profiles. Large-scale, multicenter longitudinal studies with extended follow-up are necessary to determine the persistence and clinical outcomes of ECG changes (21). Additionally, integrating cardiac biomarkers and echocardiographic parameters would offer a more comprehensive assessment of myocardial impact. There is also a need to develop or identify alternative therapeutic agents for cutaneous leishmaniasis that retain efficacy but minimize cardiovascular risk. Until such data become available, clinicians should adopt a cautious and individualized approach to meglumine antimoniate therapy, ensuring routine ECG monitoring across all patient subgroups, with particular vigilance in older adults and those with elevated BMI or other modifiable risk factors.

CONCLUSION

This study concludes that intramuscular meglumine antimoniate, while effective for the treatment of cutaneous leishmaniasis, carries a tangible risk of electrocardiographic alterations, notably QT interval prolongation and other rhythm disturbances indicative of cardiotoxicity. These findings reinforce the importance of routine ECG monitoring during therapy, particularly in older adults and patients with pre-existing cardiac vulnerabilities. The study contributes to the growing body of evidence advocating for more cautious and individualized treatment approaches, highlighting the need to balance therapeutic benefits with potential cardiac risks. These insights are crucial for optimizing patient safety in clinical settings where antimonial therapies remain a mainstay.

AUTHOR CONTRIBUTION

Author	Contribution
Suhail Ali Khan	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Tanvir Ahmad Mujahid	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Furqan Khan Warraich	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Kashif Ali Khan*	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Imran Khan	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Sana Hassan	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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