INTRODUCTION

Cutaneous Leishmaniasis (CL) is endemic in Pakistan. Upto 2 million cases are reported annually worldwide. It has not only increased at a significant rate but also involved a wider geographic distribution. In Balochistan areas affected are Uthal, Quetta and Ormara1. CL is found in metropolitan Multan city and outbreaks of CL were reported in 14 of the 68 Union Councils of Multan2. Disease is considered as major health burden. CL is a vector-borne infection caused by flagellated parasitic protozoans in the genus Leishmania. Female sand flies of the genera Phlebotomus or Lutzomyia transmit infective promastigotes. Clinical spectrum varies from classical oriental sore to unusual presentations3,4. The unusual presentations included acute paronychial, chancreform, annular, palmoplantar, zosteriform and erysipeloid forms. The reason for clinical pleomorphism of CL is not clear but immunosuppression may have a role.

The predominant parasite in lowland areas of Pakistan was L. major (97.9%), while high land areas L. tropica (76.2%) was more common. Systemic treatments are not equally effective against all species of Leishmania, and healing rates differ among the same species geographically. Host cell-mediated immunity is important to control infection. Therefore, CL treatment needs to be individualized to the patient, Leishmania species, and the geographic region where infection was acquired5.

Pentavalent antimonial compounds are considered as effective treatment for CL as first line agents6. Miltefosine is the only oral anti-leishmanial drug widely practiced but decrease in its susceptibility has been documented. Manzamines are new unique group of β-carboline alkaloids isolated from marine sponges and showed potent anti-leishmanial activity7. Indications for systemic treatment of cutaneous leishmaniasis are lesion size >4 cm, number of active lesion >3, lesion location on body areas potentially disfiguring or disabling from scar formation (e.g., face, fingers, toes, ears, large joints), lesion duration >6 months, associated medical conditions e.g. diabetes mellitus, pregnancy, immunosuppression (including HIV), and chronic comorbidities (e.g., congestive heart failure, moderate to severe liver disease, renal dysfunction), age >55 years and local spread or disseminated infection8. Meglumine antimonite (5mL) contains about 8.5% antimon (85mg 5/mL). This drug is administered paren-
tally at a dosage of 15-20mg/kg/day, until clinical cure of the lesions\(^6\).

Cardiotoxicity of high-dose pentavalent antimony is well known, though low-dose short-term meglumine has been considered to be safe and relatively free from significant cardiac effects. Cardiotoxic effects of pentavalent antimony compounds include ST segment depression, QT interval prolongation, torsadepointes arrhythmias and sudden cardiac death. These changes are estimated in 10% of population in late stages of treatment\(^9\). There are other changes described in published literature but frequency of these changes in population of Pakistan has not been described earlier with standard dose of meglumine antimoniate. The aim of present study was to identify ECG changes associated with IM meglumine antimoniate (15mg/kg/day) recommended for the treatment of the CL and to estimate the frequency of these changes. The study would ensure safe practice.

**METHODOLOGY**

This study was conducted at tertiary care hospital of Quetta and Multan after Institutional Ethical Review Board (IERB) approval from April 2018 to February 2019. Ejaz \textit{et al}, in their study of cutaneous Leishmaniasis in Balochistan described estimated prevalence of cutaneous Leishmaniasis as 2.7% in the northwestern population of the Pakistan\(^1\). Sample size of 41 or more with confidence interval of 95% and margin of error 5% was calculated with WHO sample size calculator. Total of 87 patients were enrolled by consecutive sampling technique after informed consent. All patients were confirmed cases of CL. Diagnosis was confirmed by positive LD smear or histopathology findings consistent with cutaneous Leishmaniasis. Patients with plaque >4 cm, lesion number >3, non-healing sore >4 months, lesion on face, large joints, hand and toes were included in the study. Patients with known hypersensitivity to meglumine antimoniate, cardiac disease, chronic medical illness, and children, pregnant and nursing mothers were excluded. Routine blood examination, urine analysis, hepatic and renal function tests, serum amylase and ECG were done in each case before starting treatment. All patients were hospitalized and treated with intramuscular intragluteal Meglumine antimoniate (Glucantime-sanofi Aventis) in a dose of 15 mg/kg/bwt per day. ECG was done before, during (weekly) and at follow up visit two weeks after hospital discharge. ECG analysis was done by dermatologists who were blinded to therapy status. Collected data was analysed using SPSS-20 software. Descriptive statistics were used for age, duration of treatment, ECG changes. Frequency of ECG changes was recorded. Dose and day when ECG change appeared was analyzed by paired sample t-test and \(p\)-value of <0.05 was considered as significant.

**RESULTS**

A total of 87 male patients were enrolled in this study. Age ranged from 21-50 years with mean of 30.12 ± SD 2.1. Number of lesions range from 1-9; mean 3.03 ± SD 1.072. Pretreatment ECG of all patients was normal. Meglumine antimoniate was administered intramuscular (IM) intragluteal after test dose (ATD) as 15mg/kg/day. All patients received 28 days treatment with Meglumine antimoniate.

These changes were observed from 7-27 days, mean 16 ± SD 4.58. ECG change were unique to each patient, MA therapy was discontinued after ECG change for 5 ± SD 3 days. Treatment was restarted as ECG returned to normal. All patients remained clinically asymptomatic and completed 28 days of treatment. Follow up ECG two weeks after completion of treatment was normal. Dose of meglumine antimoniate was standardized to 15mg/kg for all patients. However 72 (82.7%) received 15mg/kg of meglumine antimoniate therapy whereas 15 (17.24%) patients were switched to meglumine antimoniate 10mg/kg due to systemic upsets as nausea, myalgia, fever. Five (5.74%) patients receiving 10 mg/kg of MA developed ECG changes. Dose of MA mean 13.05 ± SD 2.965 and day mean 16 ± SD 4.53 when ECG changes appeared. There was no significant difference \(p\)-value <0.153.

<table>
<thead>
<tr>
<th>Table-I: Frequency of electrocardiograph change.</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>T- wave inversion</td>
<td>41 (47.12)</td>
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<tr>
<td>ST Elevation</td>
<td>1 (1.14)</td>
</tr>
<tr>
<td>QT interval Prolongation</td>
<td>1 (1.14)</td>
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<tr>
<td>Total Patients with ECG Change</td>
<td>43 (49.4)</td>
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<tr>
<th>Table-II: Frequency of t-wave changes in leads.</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>III</td>
<td>8 (19.5)</td>
</tr>
<tr>
<td>III, aVF</td>
<td>16 (39.02)</td>
</tr>
<tr>
<td>II,III, aVF, V2-V6</td>
<td>3 (7.3)</td>
</tr>
<tr>
<td>V2-V6</td>
<td>2 (4.8)</td>
</tr>
<tr>
<td>II,III, aVF, V4-V6</td>
<td>7 (17.07)</td>
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**DISCUSSION**

Cutaneous leishmaniasis (CL) is a major public health problem. The WHO considers it a neglected and an emerging uncontrolled disease. The management of CL is based on regional evidence based experience\(^12\).
There are concerns about cost, availability, poor compliance, and systemic toxicity of pentavalent antimonial compounds. Males are more commonly affected, this finding is in accordance with a study conducted by Moein et al, in the city of Kehsan at Iran they reported 58% of males were affected due to disease. Disease is more frequent in males due to risks of exposure but also due to gender related difference in host response to infection.

T-wave changes in particular T-wave inversion were the commonest finding in our patients. Kevric et al, described reversible T-wave changes in ECG and cardio toxicity as common reported adverse effect of meglumine antimoniate therapy. ECG was recommended before initiating treatment and then biweekly during therapy. However in a study conducted in Syria, treatment with 60mg/kg/day (MA) for 21 days induced ECG changes such as prolong QT interval was observed. They emphasized identifying potential factors that may increase the risk of QTc prolongation and arrhythmias. However it was concluded that systemic (MA) can safely be used with adequate monitoring. It doesn’t need treatment interruption. Sadeghian in a prospective study of 131 patients at Iran found prolonged QT interval (19%) as commonest finding, and ECG changes reversed after discontinuation of therapy. Viguier MTC et al, reported that MA is well tolerated in Spain, nevertheless it frequently altered ventricular repolarization and lead to sudden cardiac death, possibly due to ventricular arrhythmias. They reported a case of torsade pointes during treatment with MA, with coexisting hypokalemia due to acute transitory tubulopathy.

ST segment deviations and T-wave inversions are considered as early repolarization ventricular defects. Although MA remains first line of drug by the WHO for the treatment of all types of Leishmaniasis. Its mechanisms of action and toxicity, including its genotoxic effects, remain unclear. Weekly ECG monitoring with standard dose of MA should be sufficient to safeguard cardiac adverse effects. The present study has limitations as all patients were healthy young males and each patient served as his own cont-rol. Other potential mechanisms leading to toxicity of pentavalent antimonial were not addressed.

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CONCLUSION
Early repolarization defects T-wave inversion followed by ST segment deviation were found with standard doses of meglumine antimoniate therapy.

CONFICT OF INTEREST
This study has no conflict of interest to be declared by any author.

REFERENCE:

