Original Article

Electrocardiographic Changes in Patients with Cutaneous Leishmaniasis Treated with Systemic Glucantime

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Abstract

Introduction: Antimonial compounds are regarded as the treatment of choice for cutaneous leishmaniasis (CL). Systemic administration of these drugs has some side effects including cardio toxicity and electrocardiogram (EKG) changes. The objective of our study was to evaluate EKG changes in the patients with CL treated with systemic glucantime. Materials and Methods: One-hundred and thirty-one patients were enrolled in this prospective study. All of the selected patients had confirmed CL and were candidates for treatment with systemic glucantime. The patients were treated with systemic glucantime and EKG was performed before, during (weekly) and 1 month after cessation of the treatment. All of the collected data were analysed using SPSS software. Results: The most common change was prolonged QT interval that was seen in 19% of the patients. ST depression occurred in 6.1% of the patients. Minimal ST elevation occurred in 3% and inverted T was observed in 7.4% of the patients. Single premature atrial contraction (PAC) and single premature ventricular contraction (PVC) occurred in 0.7% and 2.29% of patients, respectively. Bradycardia was observed in 10.6% and left bundle branch block in 0.7% of the patients. All of these changes reversed after stopping the treatment except 1 case with left bundle branch block that lasted for 1 month after the treatment. Conclusions: Our results showed that treatment with glucantime can induce many ECG changes as QT prolongation have significant risk. We suggest that ECG monitoring should be performed in high-risk patients undergoing glucantime treatment with special attention to ECG changes mostly prolonged QT interval.

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Key words: Antimonial compound, Cardiac monitoring, Toxicity

Introduction

Antimonial compounds are regarded as the treatment of choice for cutaneous leishmaniasis (CL). The efficacy of sodium stibogluconate (pentostam) and the other compound of antimoniate meglumine antimoniate (glucantime) were reported in 1937[1] and 1946,[2] respectively. Currently, these 2 drugs are the most widely used in the treatment of leishmaniasis and both have an equal effect. Regarding pentavalent antimonial content, sodium stibogluconate solution contains about 10% antimony (100 mgsb^{+5}/mL) whereas meglumine antimonite solution (5 mL) contains about 8.5% antimony (85 mg sb^{+5}/mL). For the treatment of CL, the drug is administered parentally at a dosage of 15 to 20 mgsb^{+5}/kg/day, in cycles of 10 days, with equivalent intervals, until the clinical cure of the lesions.[3]

The mechanism of the drug inhibits the glucose uptake by promastigotes[4] and decreases DNA, RNA and protein synthesis.[5] In addition, both aerobic and anaerobic glucose oxidation are inhibited, resulting in a reduction in adenosine triphosphate (ATP) and guanosine triphosphate (GTP) production in the amastigotes.[6]

Antimonial toxicities are known and the first symptoms of toxicity are myalgia, joint stiffness, anorexia, bradycardia and other changes in electrocardiogram including prolonged QT, inverted T wave. Hepatotoxicity, haemolytic anaemia, nephrotoxicity, pancreatits and anaphylaxis are the rare side effects.[7]

It is recommended that in patients under treatment with this drug, electrocardiogram (EKG) monitoring should be performed before treatment and weekly during the treatment, and therapy should be discontinued if the patients develop concave ST segment, prolongation of QT interval to more than 500 millisecond, or significant arrhythmias. Death has been reported in a few patients receiving very high daily

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doses of drug (30 to 60 mg/kg/day). However, other patients have received high and even toxic doses of antimony without unwanted effects.[8] In this study, electrocardiographic changes were evaluated in the patients with CL under treatment with systemic glucantime.

Materials and Methods

This was a prospective study that was performed in the Skin Disease and Leishmaniasis Research Center, Isfahan, Iran. All of the patients had confirmed CL and were candidates for systemic glucantime treatment. Pregnant women, children under 5 years, patients who had diseases other than CL, those who had cardiovascular problems and those under treatment with other drugs were excluded from the study. The patients were treated with glucantime (Aventis, France) dosage of 20 mgsb^{+5}/ kg/day for 20 days.

Before starting the treatment, during the treatment (weekly) and 1 month after stopping the treatment, EKG (Hellige ECG) was performed on the patients, and electrocardiographic changes in P, PR, QT and QRS interval, heart rate (HR), ST depression, ST elevation, atrial and ventricular arrhythmia were recorded in the patient's file.

Normal QT interval was defined as QT interval less than 0.44 msec. Normal PR was defined as PR interval between 120 and 200 msec. Bradycardia was defined as heart rate less than 60 and tachycardia was defined as heart rate more than 100.[9] Patients with any baseline EKG abnormality were excluded from the study. Data were recorded in the patients' files and analysed using SPSS software version 12 (SPSS Inc, Chicago, USA).

Results

One-hundred and thirty-one patients were enrolled in the study. There were 85 (65%) male and 46 (35%) female. The mean age was 33.41 ± 15 years and the mean duration of disease was 150 ± 37 days. Prolongation of QT interval was seen in 25 patients (19%). This problem was severe in 1 case (increased from 440 to 520 ms) (Fig. 1). This change occurred in the last week of treatment. Bradycardia occurred in 14 patients (10.6%). No case of tachycardia was seen. ST depression was observed in 8 patients (6.1%) but was severe only in 1 case and led to a stopping of the treatment. Minimal ST elevation occurred in 4 patients (3%), and inverted T wave was observed in 10 cases (7.4%). Atrial arrhythmia as single premature atrial contraction (PAC) and ventricular arrhythmia as single premature ventricular contraction (PVC) occurred in 1 patient (0.7%) and 3 patients (2.99%), respectively. Left bundle branch block was observed in 1 patient (0.7%). First-degree block and second-degree block did not occur. All of these changes reversed after cessation of the treatment except 1 case with left bundle branch block that lasted for 1 month after stopping the treatment.

Discussion

In this study, EKG changes were evaluated in patients under treatment with systemic glucantime. Our results showed that the most common change in the glucantime-treated patients was prolongation of QT interval. The second most common change was bradycardia and the third change was inverted T wave. Other changes included ST depression, ST elevation, PAC, PVC and left bundle branch block. The electrocardiographic abnormality which was only left after 1 month was the left bundle branch block. A study performed in Kenya showed that in patients treated with sodium stibogloconate, (18 to 20 mg/kg/day for 30 days), heart problems and EKG changes were minimal.[10] Another study showed that treatment with low dose glucantime (15 mg/kg/day) did not induce significant EKG changes. However, prolongation of QT interval occurred in the patients.[3] Significant cardio toxicity caused by low-dose, short-term therapy has not been well established and its use has been considered relatively safe and free of significant cardiac effects. It has been proposed that routine monitoring would not be necessary for patients receiving 10 mgsb^{5+}/kg/day up to 30 days or 20 mgsb^{5+}/kg/day up to 20 days.[3] However, some authors recommend EKG to be performed at weekly intervals for patients treated for more than 20 days.[8] Also in a study of patients treated with glucantime, the most EKG changes were in the ST segment, T wave and QT interval.[3] However, in our study the most significant changes were increased QT interval (19%) followed by bradycardia (10.6%).

In another study that was performed in 80 patients with visceral leishmaniasis under treatment with sodium stibogluconate, 40% of cases showed a flattening of T wave and 9% showed inverted T,[11] but in our study the

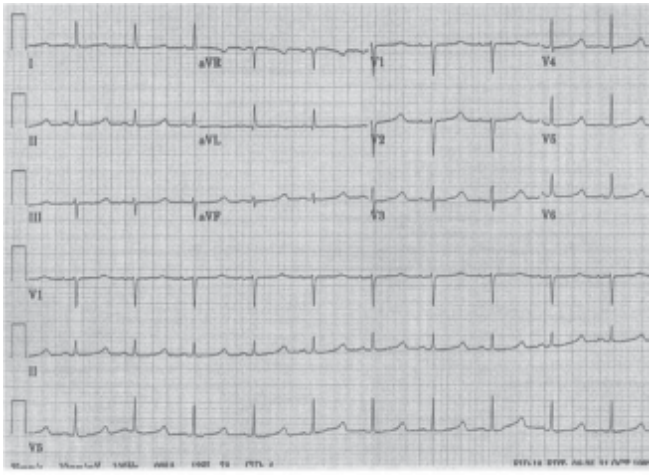

Fig. 1. QT prolonged (520 ms in long DII).

problem in T wave was only inverted T in 7.4% of cases. In a study of patients with mucoCL treated with systemic glucantime, electrocardiographic changes occurred in 45% that predominantly occurred in T wave and ST segment and which reversed 2 months after stopping the treatment.[12]

In visceral leishmaniasis, treatment with glucantime 20 mg/kg/day for 30 days was reported to be safe and was only rarely associated with clinically significant bradycardia which was resolved after cessation of therapy. Furthermore it was said that in areas with limited facilities, monitoring the pulse rate during antimonial therapy may help detect impending cardiotoxicity.[13] In the literature review, we did not find any report of bundle branch block in the patients under treatment with glucantime. Regarding the continuation of this complication for 1 month after cessation of treatment, it should be more cautiously evaluated in the EKG of glucantime-treated patients.

According to past studies and results of the current study, electrocardiographic abnormality due to antimonial therapy in patients with normal EKG is minimal. This drug is almost safe in young patients except in those with cardiovascular diseases and, of course, a significant risk is QT prolongation and special attention to ECG changes mostly prolonged QT interval is necessary. However, EKG monitoring is recommended before starting the treatment with this drug in patients with CL.

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