

ELECTROCARDIOGRAPHIC CHANGES DURING TREATMENT WITH CUTANEOUS LEISHMANIASIS

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Date Received: December 01, 2012

Date Revised: February 05, 2013

Date Accepted: March 12, 2013

Contribution

All the authors contributed significantly to the research that resulted in the submitted manuscript.

All authors declare no conflict of interest.

ABSTRACT

Objective: To determine the frequency of Electrocardiographic changes during treatment with cutaneous Leishmaniasis.

Methodology: This was an observational study with convenience sampling. Baseline ECG was performed in all the consecutive patients prior to the treatment. Convenience sampling of all the patients reported from Jan 2011 to Dec 2011 confirmed as cutaneous Leishmaniasis and referred by consultant dermatologist because three of the patients died previously during treatment of cutaneous leishmaniasis during treatment with Inj. Glucantime. Mean and std. deviation will be computed for quantitative variables and frequencies of qualitative variables using SPSS version 16.

Results: Mean age was 35.67 ± 19.67 SD. Initially there were small Qwaves in 10 patients and with antimonial treatment these changes were found in 18 patients (30%). In 5 patients (8.33%) bradycardia was noticed and in 9 patients (15%) tachycardia. QTinterval was prolonged in 15% of the patients.

Conclusion: A team comprising of consultant cardiologist, consultant dermatologist and consultant physician with expertise in the management of cutaneous leishmaniasis because disease is not life threatening but treatment can life threatening. Treatment of cutaneous Leishmaniasis should be monitored strictly for Electrocardiographic changes and regular follow up by the team and if necessary hospitalization may be required.

Key Words: Electrocardiographic changes, Cutaneous Leishmaniasis

INTRODUCTION

Our study aimed at identifying base line ECG changes and during treatment ECG changes as our consultant dermatologist started sending patients diagnosed as cutaneous leishmaniasis with ECG changes during treatment with antimonial compounds and requested to involve monitoring, cardio vascular evaluation in the interest of the patients. Cutaneous Leishmaniasis is also found in Pakistan¹. This disease may involve single or multiple lesions, which are relatively heterogeneous and range from benign cutaneous ulcers to serious and mutilating forms².

Although CL has been classified as a zoonosis, remarkable epidemiological changes have occurred, transforming it into an important clinical and epidemiological disease in rural and urban centers³.

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Although other adverse effects have been seen with parenteral antimonial, we focused mainly on cardiac toxicity^{4,5}. Cutaneous Leishmaniasis (CL) is a major public health problem in Brazil, with an estimated incidence of 25 thousand cases a year⁶. Even out break of cutaneous Leishmaniasis have been found in Pakistan⁷. Cutaneous Leishmaniasis can present with different skin lesions. 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 and 1946 respectively. Currently, these 2 drugs are the most widely used in the treatment of leishmaniasis and both have an equal effect.

⁸Other alternatives which are safer for treatment of cutaneous leishmaniasis are being explored⁹. In one study Glucantime was found to be more effective than pentamidine¹⁰. Mechanism of cardiotoxicity of antimonial drugs is due to increased calcium currents rather than effect on potassium channels¹¹. During treatment of cutaneous Leishmaniasis ECG changes usually appear after 4th injection persist till last injection and are usually reversible after withdrawal of injection. Risk of sudden cardiac death is increased due to drug induced QTprolongation¹². After extensive literature review, this was found that very limited data was available for long term follow up of these patients. In our study long term follow up and mortality would be done even after completion of study. Our study is unique as compared to previous studies because team of Cardiologist, Dermatologist and Consultant Physicians were actively involved and had extensive counseling during treatment and even admissions of the patients receiving treatments in Cardiology Institute. Echocardiography was done when

required and treatment was discontinued when needed and started again accordingly. In most of the previous studies generally Dermatologist and Physicians were involved in contrast to this study which actively involved cardiac consultation throughout duration of the study.

METHODOLOGY

Inclusion criteria in our study were following:

All age groups and gender. Smear positive cases.

Female patients of childbearing age must have a negative serum pregnancy test at screening. LFT's, renal function test and blood complete picture should be normal at base line. Serum Electrolytes were also performed Patients or their guardians will give written informed consent Exclusion Criteria in our study were following: we excluded Smear negative cases. Patients should not use drugs other than antimonial History of mucocutaneous Leishmaniasis. Recent use of injectable or oral corticosteroids and This is an observational study with Convenience sampling method used to determine the frequency of ECG changes during treatment of cutaneous Leishmaniasis during one year treatment. Ethical approval was taken from ethical committee of the state teaching hospital.

Sixty consecutive patients were referred by consultant dermatologist confirmed as a case of cutaneous Leishmaniasis were analyzed by performing respective ECGs which included both base line ECG and with treatment ECG after one month. Most of the changes sub sided after dis continuation of the treatment.all the patients were analysed by doing baseline ECG and during treatment ECG at 4th week and after 12 weeks. i.e 12 lead ECGs of all the patients at very visit making 3 ECGs/patient.

Data were analyzed by using SPSS version-16 on computer. Descriptive statistics: mean and standard deviation computed for quantitative output response and frequency percentage for qualitative output response.

RESULT

Also only baseline Liver function tests, blood complete and Renal function tests could be performed and were found to be almost normal with exception of one person with raised liver Enzymes and raised creatinine and one case of Anaemia. Thrombocytopenia was not seen in our patients. Serum electrolytes were normal, due to financial constraints, serum calcium phosphate could not be done.

Total number of patients were (60) male were (26) and female were (34). (18) out of (60) patients developed ECG changes about (30%). Standard deviation was (19.673); Base line ECG changes generally minor were found in (20) patients. Ten out of these patients were admitted with interruption of treatment if QTC was longer than .5 seconds and if QTC longer than .45 seconds monitoring/ dose

Table 1: ECG Changes with treatment

T Inversion	25%
QT Prolongation	15%
Sinus Bradycardia	15%
Sinus Tachycardia	8.3%
Small q waves	30%
Nonspecific intraventricular conduction defects	6%

reduction was done.

Mean age was (35.67 +1967), Baseline ECG had changes in almost (21) patients. T wave inversion was found in (15) patients in baseline ECG. Which accounted for (25 %). Small q waves were present in (6) patients. In treated patients small q waves were present in (30%) patients. (8.3%) patients had tachy arrhythmias and (15%) had brady arrhythmias. QT interval was prolonged in (15%) of the patients. (18%) were hospitalized to give them treatment. Overall (30%) of the patients developed ECG abnormalities most of which were reversible with treatment. No Patient was found to have torsades de pointes 17 in our study. Almost (6%) Patients had non specific intraventricular conduction defects.

With Treatment ECG Changes on 4th week.

In almost all the patients with exception of patients with base line ECG changes. ECG changes resolved at 12 weeks serial ECG.

DISCUSSION

Cutaneous Leishmaniasis has been rated as category one disease by WHO which means emerging and uncontrolled disease¹⁸. Our study also showed that almost all age groups had this disease. Another interesting feature of our study was prevalence of disease even in high and middle classes socioeconomic classes contrary to popular belief that disease is confined mainly to lower socioeconomic groups. (30%) of the patients developed ECG abnormality, most of which were reversible after withdrawal of treatment. QT interval was prolonged in (15%) of the patients. In our study no patient was found to have torsades de pointes. Another study performed to see the frequency of ECG changes in treatment of cutaneous Leishmaniasis (19%) of the patients developed QT interval prolongation.¹⁹ What was unique to our study was minor baseline abnormalities in these patients

even without treatment and these patients were strictly monitored and even admitted. Most of our patients did not have traditional risk factors for coronary heart disease. Although echocardiography done of most of the patients was found to be normal and no significant cardiac symptoms were reported apart from fatigue. One should not forget that cutaneous Leishmaniasis itself is not a life threatening disease but treatment of this disease can be life-threatening. All of our patients were smear positive and confirmed cases of cutaneous Leishmaniasis. Fortunately life threatening arrhythmias were not documented in our study¹³⁻¹⁶. Base line ECG was done in all the patients including blood complete, liver function test and renal function test. Limitation of our study was all the patients could not be admitted. We were unable to get data about baseline ECG changes despite extensive literature review making it one of probably first study to show that even without treatment. These patients are prone to develop cardiac events, must be area of research in Future. Two Patients previously were reported dead during therapy, these patients were using cheap brand which was later on Withdrawn from market. The two patients were actually not enrolled in our studies. Unfortunately case reports were not published as the patients died at home.

Currently there are no guidelines available for initial cardiovascular evaluation and close monitoring. Also there is no convincing data about long term outcomes and mortality after Initial enrollment in studies conducted worldwide

Unfortunately stibogluconate injections are not available in Pakistan and we are left with choice of meglumine antimoniate (glucantime) we need more focus on local Intralesional injections and more safe alternatives. Still unanswered questions are long term follow up of the patients and long term mortality with treatment. Another unanswered question is there any genetic predisposition that some

patients developed ECG changes and some don't. Also worth mentioning is that no age group is immune, similarly detailed guidelines are not available for long term management of these patients. "The broad availability of polymerase chain reaction (PCR) allows a rapid determination of species. A species-specific treatment approach has been evaluated for many species and is widely applied in many centers."²⁰⁻²⁵

Recent data focusing on genetic differences of individual species between regions are integrated and region-specific treatment recommendations for *Leishmania braziliensis* and *Leishmania guyanensis* CL are given."²⁶⁻²⁸

"This manuscript focuses on new aspects of established compounds and on new drugs such as miltefosine. "Miltefosine (hexadecylphosphocholine, HePC), an alkyl phospholipids compound, was originally intended for breast cancer and other solid tumors. A current hypothesis is that phospholipids and phosphocholine derivatives such as edelfosine and presumably miltefosine move across membranes (from the outer to the inner layer) via inward translocation (also termed inward transbilayer movement, or flip), an energy-dependent, protein-mediated process.

For drug binding, the phospholipid composition of cell membranes seems critical: miltefosine resistant *L. donovani* have altered fatty acid elongation and unsaturation, and the C-24-alkylation of sterols. For transport across the membrane, a putative transporter was recently identified; a *Leishmania* P-type ATPase gene, belonging to the aminophospholipid translocase (APT) subfamily termed LdMT (*L. donovani* Miltefosine Transporter) has been cloned. LdMT is expressed in the plasma membrane where it mediates the translocation of phospholipids across the plasma membrane in *Leishmania* parasites.

As *Leishmania* amastigotes reside inside macrophages, membrane binding and flip-flopping will have to occur multiple times across the various membranes until equilibrium is reached. *Leishmania* parasites do not seem to have the ability to metabolize miltefosine, but can extrude via either exocytosis or protein-dependent flop across the plasma membrane (possibly by proteins of the ABC transporters family, such as P-glycoprotein (mdr1)

However, it could not be developed as an oral agent because of dose-limiting gastro-intestinal toxicity, and only a topical formulation is approved for skin metastases a study conducted in Brazil explains that miltefosine therapy is more effective than standard Sb^v and safe for the treatment of CL caused by *Leishmania braziliensis* in Bahia, Brazil²⁹. and the combination of traditional compounds with immunomodulators. "Studies in experimental models of VL confirmed that the efficacy of pentavalent antimony (Sb^v) was T-cell dependent [14]. This observation initiated a slew of studies aimed at either bypassing the T-cell requirement

by direct provision of T-cell-derived effector cytokines (cytokine therapy), or by augmenting endogenous T-cell activation through enhanced antigen presentation (Toll-like receptor [TLR]-based and costimulation-based therapy). In immunodeficient mice, the T-cell-derived cytokines IL-2 and IFN-g restore the activity of Sb^v [14]. Treatment with recombinant (r)IFN-g reduced the amount taken to produce an effective dose in 50% of the participants of Sb^v tenfold. Sb^v is believed to be a prodrug requiring intracellular conversion to SbIII for leishmanicidal activity, therefore, the increased uptake of the drug by IFN-g-activated macrophages has been proposed as a mechanism underlying this treatment response [15]. There has been some success in clinical trials with combined therapy of IFN-g and Sb^v. IFN-g treatment accelerated responses and enhanced Sb^v efficacy; additionally, Sb^v-refractory patients retreated with Sb^v plus IFN-g also showed long-term responses to treatment"³⁰.

STUDY LIMITATIONS:

Due to financial constraints advanced cardiac investigations like thallium scan or coronary angiography could not be done.

CONCLUSIONS

Cutaneous leishmaniasis is a common problem and during treatment arrhythmias are common. These ECG changes can be easily mis interpreted either as ischemic heart disease with unnecessary treatment and unnecessary investigations which can have social, legal and even insurance complications. In this study in 10 patients the treatment was interrupted due to prolonged QT interval as we should not forget that torsade de pointes a life threatening ventricular arrhythmia can lead to sudden cardiac death and usually occurs in setting of prolonged QT interval. Serial monitoring of ECG changes at base line, after 4 weeks and if possible after 12 weeks shall be mandatory in management of patients. Our study results clearly show that treatment of cutaneous Leishmaniasis can be associated with morbidity and mortality as life threatening arrhythmias can develop if intense monitoring of patients is not done.

RECOMMENDATIONS

Spread of the disease is alarming like an epidemic and needs aggressive measures to control the disease in order to avoid the complications of the disease as well as complications of treatment. There is demand for new prevention strategies in treatment of cutaneous Leishmaniasis should include both vector Control and development of vaccine which is still investigational. Alternative less toxic drugs are needed. As this is first ever study conducted in Azad Kashmir with special focus on treatment of cutaneous Leishmaniasis and possible adverse effects on the cardiovascular system. Therefore strict ECG and cardio vascular monitoring is

recommended including baseline ECG. A team comprising of consultant cardiologist, consultant dermatologist and consultant physician with expertise in the management of cutaneous leishmaniasis because disease is not life threatening but treatment can be life threatening. Treatment of cutaneous Leishmaniasis should be monitored strictly for Electrocardiographic changes and regular follow up by the team and if necessary hospitalization may be required.

All the patients of Cutaneous Leishmaniasis should be managed by team of doctors with strict base line ECG and other modalities if required with strict follow up monitoring and cardiology consultation should be mandatory as disease itself is not life threatening but treatment can be fatal.

ACKNOWLEDGEMENTS

We are specially thankful to Mr. Muhammad Farman and Dr. Masood Jawaid for his kind support.

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30. Dalton JE, Kaye PM. Immunomodulators: use in combined therapy against leishmaniasis. *Expert Rev Anti Infect Ther* 2010;8:739-42. BaseLine ECG Changes Total Patients (60) T wave inversions 15 patients (25%) Small q waves 6 patients (10%) Normal ECG 39 patients (65%).