

Original Article

ECG Changes in Patients of Visceral Leishmaniasis (Kala-Azar) Receiving Sodium Stibogluconate Therapy

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Abstract:

Kala-Azar is a devastating parasitic disease caused by *Leishmania donovani*, increasing in our country and turning into serious public health problem in Bangladesh due to multiple problems. The standard drug for treatment of Kala-Azar is still Sodium Stibogluconate (SAG) in our country due to high cost of liposomal Amphotericin B. The aim of this study is to see the cardiac complication and electrographic alterations during SAG therapy in standard dose. One hundred and twenty five patients (62.4% male and 37.6% female) were included in this study. All had normal ECG prior to therapy. Various electrographic alterations were noted in 31 (24.8%) of the cases after starting antimony therapy. Most common changes seen in our study were T wave inversion (24.4%), reduced amplitude of T wave (7.3%) and ventricular ectopic (8%). These changes were observed during 2nd to 3rd weeks of therapy and disappeared within two weeks of stoppage of further antimony therapy. Alteration in ECG might be the prior evidence of cardiotoxicity and might explain sudden deaths encountered during antimony in Kala-Azar. Close clinical observations and ECG monitoring of the patients receiving antimony therapy for Kala-Azar is essential for early detection of cardiotoxicity and thereby to prevent further complications including sudden death.

Key words: Leishmaniasis (Kala-Azar), ECG, Stibogluconate.

Introduction:

Visceral Leishmaniasis is prevalent in more than 80 countries in Asia, Africa, Southern Europe and South America. *L. donovani* is the main causative parasite for Visceral Leishmaniasis. It is estimated that each year nearly 5,00,000 (Five Lac) new cases of Visceral Leishmaniasis occur in five countries of the world namely, India, Sudan, Bangladesh, Nepal and Brazil¹. There is a recent outbreak of Kala-azar in Bangladesh². Kala-Azar is nearly always fatal if untreated³. Even with treatment, case fatality rate often exceeds 10% in Visceral Leishmaniasis endemic areas of Asia and Africa. Treatment still relies largely on pentavalent antimony compounds such as Meglumine antimoniate and Sodium Stibogluconate (SAG)⁴. Although pentavalent antimony compounds have been proven to be very effective, drug use is often limited in patient because of toxic side effects such as nausea, abdominal pain, chemical pancreatitis, renal toxicity and electrographic abnormalities which are especially worrisome⁵.

The cardio toxicity of pentavalent antimony compounds, which may include inversion of ST segment on the electrocardiogram, QT prolongation, Torsades d pointes arrhythmias and sudden cardiac arrest. These ECG abnormalities develop in only approximately 10% of the patient, usually late during the course of the treatment. There are various number of ECG changes after starting of antimony therapy as described elsewhere of different international journal, but due to scarcity of relevant literature in Bangladesh we could not explore the actual frequency of ECG changes in Kala-Azar patient receiving SAG therapy⁶. So, the aim of this study was to find out the various ECG changes of Kala-Azar patient during treatment with standard dose of SAG in our populations.

Materials and Methods:

A total number of 125 patients with visceral leishmaniasis of both sexes and age over 5 years were included in this study. This cross sectional observational study was carried out in the department of medicine, Dhaka Medical College and Hospital, Trishal Health Complex and Fulbaria Health Complex of Mymensingh district from January 2008 to December 2008. Routine blood examination, urine analysis, bleeding coagulation parameters, hepatic and renal function tests, X-ray chest and ECG were done in each case before starting specific treatment. Patients

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with hepatic, renal, cardiac or any other systemic diseases and patients under 5 years of age were excluded. They were treated with SAG at a dose of 20 miligram per kg per day for 28 days.

Results:

The age of the 125 (78 male, 47 female) patients ranged from 5-70 years with mean (\pm SD) age of 21.09 (\pm 14.02 years). Out of all patients, fever (95.2%), splenomegaly (87.2%) and hepatomegaly (44%) were common presenting features. Complaints of weight loss were in 23.2%, 19.2% had anemia, 17.8% had malaise and 14.4% had anorexia. Pigmentation (4.8%), ascites (4.8%), jaundice (3.2%), abdominal distension (2.4%), and lymphadenopathy (0.08%) were less common presenting features.

Pretreatment ECG was normal in all cases. ECG changes were found in 24.8%, among them male were 26.9% and female were 21.3%. Most common changes were T wave inversion in 24.4%, reduced amplitude of T wave in 7.3% and ventricular ectopic in 0.8%. The ECG changes were observed during the 2nd and 3rd weeks of therapy but clinically all were asymptomatic. These ECG changes returned to normal within 2 weeks of stoppage of further SAG administration. Out of 125 patients 4 expired. All expired patients died suddenly without any obvious reasons. Significant ECG changes were found prior to sudden death except one who had ventricular ectopics. All dead patients were female.

Logistic regression analysis was done with ECG changes (Any type) as dependent variable and socio demographic variables (age, sex, occupation, and education) and anemia as independent variables. The change was not found to be associated with any of these variables.

Our result showed that the most changes were reduced amplitude of T wave (7.3%) and least changes were ventricular ectopic (0.8%). The prominent ECG

Table I: Distribution of the patients by different types of ECG changes

ECG changes	7 th day No(%) (n=125)	14 th day No(%) (n=124)	21 st day No(%) (n=123)	28 th day No(%) (n=122)
T wave inversion	10 (8.0)	25(20.2)	30(24.4)	28 (23.1)
Reduced amplitude of T wave	2 (1.6)	9 (7.3)	9 (7.3)	7(5.8)
Ventricular ectopics	1 (0.8)	1(0.8)	0 (0)	0 (0)

Table II: Distribution of the patients by Sex.

ECG Changes	Male No (%)	Female No (%)	P value*
Yes	21(26.9)	10(21.3)	0.479
No	57(73.1)	37(78.7)	
Total	78(100.0)	47.100.0)	

*Chi-square test was done to measure the level of significance.

Logistic regression analysis is done to see predictions & outcome ie. to predict risk factor/cure which can independently influence the outcome it it applicable here ?

Table III: Logistic regression analysis taking ECG changes as dependent variable

Independent Variables	B	S.E	Wald	df	Sig	Odds ratio
Age	.030	.023	1.642	1	.200	1.030
Sex	.073	.527	.019	1	.890	1.076
Occupation	.199	.179	1.240	1	.265	1.220
Education	-.104	.449	.054	1	.816	.901
Anaemia	-.642	.513	1.564	1	.211	.526

Discussion:

Antimonial compounds are regarded as the treatment of choice for Leishmaniasis. The efficacy of sodium stibogluconate and the other compound of antimoniate meglumine antimoniate (glucantime) were reported in 1937 and 1946 respectively. Currently, these two drugs are the most widely used in the treatment of leishmaniasis and both have an equal effect⁷. Regarding pentavalent antimonial content, sodium stibogluconate solution contains about 10% antimony whereas meglumine antimoniate solution (5 mL) contains about 8.5% antimony. For the treatment of Kala-Azar, SAG is administered parenterally at a dosage of 20 mg/kg/day for 30 days. 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 wave⁸⁻¹⁰. Present study was conducted with an aim to evaluate the different type of ECG changes in Kala-Azar patient receiving SAG therapy in our population. One-hundred and twenty five patients were enrolled in this study. There were 62.4% male and 37.6% female. The mean age was 21.09 + 14.02 years and more than 60% of the patients were up to 20 years. Our result of age and sex distribution was almost comparable with that of Saldarha et al scenes⁹. In their series 65% were male and 35% were female with a mean age of 33.41 years. A total 81 consecutive cases of Kala-Azar admitted in all four medicine units of Mymensingh Medical College Hospital during the period from January 2002 to mid August 2002, reported the symptoms and signs of Kala-Azar as fever (100.0%), weight loss (79.01%), general weakness (72.84%), cough (25.92%), splenomegaly (100.0%), hepatomegaly (91.36%), pallor (69.13%), jaundice (17.28%), and ascites (4.94%)¹¹. Similar observations were also made in the present series as fever (95.2%), splenomegaly (87.2%), and hepatomegaly (44.0%) was found as the most common presenting features. Of all patients 23.2% had complaints of weight loss, 19.2% had anaemia, 17.8% had malaise, and 14.4% had anorexia. Pigmentation (4.8%), ascites (4.8%), jaundice (3.2%), abdominal distension (2.4%), lymphadenopathy (0.8%), consolidation (0.8%), and pleural effusion (0.8%) was less common presenting features.

In this study, ECG changes were evaluated in patients under treatment with SAG. Our results showed that the most common change in the SAG treated patients was T wave inversion. The second most common change was reduced amplitude of T wave and the third change was ventricular ectopics. A study performed in Kenya showed that in patients treated with sodium stibogluconate (18 to 20 mg/kg/day for 30 days), heart problems and ECG changes were minimal¹². Another study showed that treatment with low dose antimony did not induce significant ECG changes. However, prolongation of QT interval occurred in the patients¹³.

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. In another study conducted by Thakur et al¹³ 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, but in our study the problem in T wave was only inverted T in 24% of cases as observed in 28th day of treatment. In Henderson and Jolliffe study sodium stibogluconate did not appear to influence on PR interval, QRS duration or R wave height. In agreement with others however a fall in T wave amplitude was noted in every patient

although T wave inversion did not occur¹³. Mean T wave height fell significantly from 41.32 mm to 33.4 mm ($p < 0.01$) but became normal by day 10. This effect although clinically unimportant cannot be ignored as it confirms that even pentavalent antimonials are not entirely innocuous. In a study of patients with mucocutaneous leishmaniasis treated with systemic antimony, electro-cardiographic changes occurred in 45% that predominantly occurred in T wave and ST segment and which reversed 2 months after stopping the treatment¹⁴. According to past studies and results of the current study, electrocardiographic abnormality due to antimonial therapy in patients with normal ECG is minimal.

Conclusion:

One fourth of Kala-Azar patients treated with SAG developed ECG changes. Most of the ECG changes occurred between 14th to 21th day of treatment in patient of Kala-Azar treated with SAG. Alteration in ECG may warrant the sudden death which occurs during SAG therapy. So, close clinical observations and ECG monitoring of the patients receiving SAG therapy for Kala-Azar is essential for early detection of cardio toxicities and therapy to prevent further complication including sudden death.

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