International Journal of Research in Medical Sciences
Alom MS et al. Int J Res Med Sci. 2023 Mar;11(3):775-779
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: https://dx.doi.org/10.18203/2320-6012.ijrms20230335

Original Research Article

Electrocardiogram changes due to sodium stibogluconate treatment of kala-azar

M. Shamshul Alom[1], M. Liaquat Ali[2]*, Abdul Alim Shaikh[3], Jakaria Kabir[4]

[1]Department of Cardiology, North Bengal Medical College and Hospital, Sirajganj, Bangladesh
[2]Department of Pediatrics, North Bengal Medical College and Hospital, Sirajganj, Bangladesh
[3]Department of Surgery, North Bengal Medical College and Hospital, Sirajganj, Bangladesh
[4]Department of Anesthesiology, North Bengal Medical College and Hospital, Sirajganj, Bangladesh

Received: 17 December 2022
Revised: 08 February 2023
Accepted: 09 February 2023

***Correspondence:**
Dr. M. Liaquat Ali,
E-mail: aticaali2011@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Kala-azar [visceral leishmaniasis (VL)] is caused by the protozoon *Leishmania donovani* complex. Without adequate treatment, most patients with clinical VL die due to secondary infections. Pentavalent antimonial compounds are commercially available as sodium stibogluconate and meglumine antimoniate. Sodium stibogluconate remains the mainstay of treatment in most parts of the world. The aim of the study was to evaluate the serious adverse effects of sodium stibogluconate in the treatment of kala-azar (VL).
Methods: The study was carried out in the medicine department of North Bengal Medical College Hospital, Sirajganj during the period of June 2021 to December 2021. It was a descriptive cross-sectional study with a sample size of 30. Complete history taking and physical examination were done and recorded in a case record form. At least 7 ECGs were done (1 before treatment, 5 during treatment weekly intervals, and 1 after completion of treatment).
Results: In ECG, the following changes were noted (the rhythm, T wave amplitude, ST segment, and QTc interval). Out of 30 patients, 19 patients (63.33%) developed abnormalities in ECG. Among them, 14 patients (46.67%) developed prolongation of QTc interval, 6 patients developed T wave inversion, and 1 patient developed transient 1st-degree heart block. No patients developed symptomatic arrhythmia.
Conclusions: Kala-azar is prevalent among the poor in Bangladesh and can be fatal without treatment. Sodium stibogluconate has been associated with cardiological adverse effects, but it can be used safely with proper monitoring.

Keywords: Visceral leishmaniasis, Electrocardiogram, ST change, Arrhythmia

INTRODUCTION

Kala-azar [visceral leishmaniasis (VL)] is caused by the protozoan *Leishmania donovani* complex. Without adequate treatment, most patients with clinical VL die due to secondary infections. Pentavalent antimonial compounds are commercially available as sodium stibogluconate and meglumine antimoniate, with sodium stibogluconate remaining the mainstay of treatment in most parts of the world.[1]

Leishmaniasis is a parasitic disease caused by protozoan flagellates of the genus Leishmania and can infect many mammal species, including humans, transmitted by the infected bite of a phlebotomine sand fly, an insect vector.[2] VL has a worldwide distribution, occurring in the Mediterranean region, Central Asia, Middle East, India, Bangladesh, Africa, South and Central America. It is estimated that there are more than 12 million cases worldwide with 4,000 cases reported each year and 350 million people at risk of acquiring the infection.[3] Before the second world war, kala-azar was endemic in Assam,

Bengal, Bihar, and southern parts of the eastern Indian subcontinent and was prevalent as far north-west as Punjub.[3]

A resurgence of the disease occurred in Bangladesh, Nepal, and adjoining parts of the Indian union in the seventeenth last century. Transmission occurs mostly through the bite of the sand fly, with the species varying with geographical location. In Bangladesh and Nepal, VL is transmitted by *P. argentipes*, which feeds only on humans.[3] The incubation period is difficult to evaluate precisely, generally ranging from 2-6 months but can range from 10 days to many years.[3] The onset of the disease may be sudden or gradual.

In sudden onset, there is a rapid rise of temperature which may be continuous or intermittent, persisting for several days.[3] The overall condition of patients is usually good in the early stage, while the gradual onset includes irregular fever that can sometimes fall to a sub-febrile level, potentially delaying diagnosis.[3] VL, if untreated, is associated with a high case fatality rate (up to 90%).[3] With therapy, the case fatality rate ranges from 3-15%.[3]

Despite numerous side effects attributed to antimonials, the scarcity of reported accidents allows for their continued use. The side effects of pentavalent antimony include shivers, fever, myalgia, arthralgia, skin rashes, abdominal symptoms, and headache.[3] Cardiac side effects are the most worrisome.

Several ECG changes occur, with flattening or inversions of T wave being the most common. Patients can develop prolongation of corrected QT interval, concave ST segment abnormality, and prolongation of PR interval.[3] The ECG changes are transient and gradually return to normal within 1-3 weeks after completion of treatment.[3] Severe cardio toxicity, manifested by concave ST elevation, prolongation of corrected QT>0.5/msec, ventricular ectopics, ventricular tachycardia, torsade de points, ventricular fibrillation, and sudden death, is not uncommon.[4]

METHODS

This descriptive cross-sectional observational study was conducted at the department of medicine, North Bengal Medical College Hospital, Sirajganj, Bangladesh. The study period was 6 months, from June 2021 to December 2021.

During this period, a total of 30 cases of kala-azar patients were selected for the study following a consecutive sampling method following the inclusion and exclusion criteria.

The inclusion criteria for the study included age between 18 and 65 years, confirmed diagnosis of kala-azar by parasite detection methods, and written informed consent. The exclusion criteria included other concurrent infectious or non-infectious diseases affecting ECG parameters, history of heart disease, pregnancy or lactation, and ECG abnormalities present at baseline. A baseline ECG was recorded for each patient before starting treatment, and follow-up ECGs were recorded each week for 4 weeks.

Ethical approval of the study was obtained from the ethical review committee of the study hospital, and informed consent was obtained from each participant. All collected data were analyzed using SPSS statistical software. Descriptive statistics were used to summarize the demographic and clinical characteristics of the participants.

RESULTS

Thirty patients (26 male and 4 female) were enrolled in a study conducted at North Bengal Medical College Hospital, Sirajganj. Of these 30 patients, 11 males and 1 female were between the ages of 13-25, 4 males and 2 females were between 26-30, and the remaining were 31 years or older.

Splenic aspiration was performed on 20 patients and all were found to be positive for *Leishmania donovani* body. An ICT for kala-azar was performed on 28 patients, with 27 resulting in a positive outcome and 1 resulting in a negative outcome. However, this one negative ICT patient was found to be positive for *Leishmania donovani* body in the splenic aspirate.

Each patient received sodium stibogluconate intravenously at a dose of 20 mg/kg body weight per day for 30 days. No treatment interruptions were necessary due to adverse effects. ECGs were obtained from all 30 patients before, during, and after treatment. Before treatment, all ECGs were normal, but abnormalities developed in 19 patients (63.33%) after treatment. 46.67% of these patients developed QTc prolongation, with 40% having isolated prolongation and 6.51% having both prolongation and T-wave inversion.

No symptomatic arrhythmias were observed. 20% of patients developed T-wave inversion, which appeared on the 7th day of treatment and persisted throughout the remainder of treatment. P-R interval prolongation was found in one patient (3.33%) and appeared transiently on the 14th day of treatment.

No changes in P-wave and ST-segment were observed before, during, or after treatment. Of the 30 patients, 28 were illiterate and 2 were literate, with 26 being directly involved in cultivation and 4 being involved in other activities. 83.3% of patients had a monthly income less than 3000 and 16.7% had a monthly income between 3000 and 5999. 93.93% lived in kacha houses and 6.7% lived in semi-pucca houses.

Table 1: Frequency distribution of kala-azar patients by age and sex.

Age group (years)	Frequency				Total	
	Male		Female			
	N	%	N	%	N	%
13-25	11	91.7	1	8.3	12	40.00
26-30	4	66.7	2	33.3	6	20.00
31 and above	11	91.7	1	8.3	12	40.00
Total	26	86.7	4	13.3	30	100

Table 2: Frequency distribution of kala-azar patients by occupation.

Occupation	Frequency				Total	
	Male		Female			
	N	%	N	%	N	%
Farmers	24	92.31	2	7.69	26	100.0
Others	2	50.00	2	50.00	4	100.0

Table 3: Educational status of kala-azar patients.

Educational status	Frequency			
	Male		Female	
	N	%	N	%
Literate	1	3.85	1	25
Illiterate	25	96.15	3	75
Total	26	100.0	4	100.0

Table 4: Frequency distribution of kala-azar patients by ICT and splenic aspirate.

ICT	Frequency				Total	
	Male		Female			
	N	%	N	%	N	%
Positive	23	85.00	4	14.81	27	96.43
Negative	1	4.17	0	0	1	3.57
Total	24		4		28	100
Splenic aspirate						
Positive	17	85.00	3	15.00	20	100
Negative	0	0	0	0	0	0

Table 5: ECG changes among kala-azar treated with SAG.

ECG components	1st day		7th day		14th day		21st day		28th day		After SAG treatment	
	M	F	M	F	M	F	M	F	M	F	M	F
P wave	0	0	0	0	0	0	0	0	0	0	0	0
PR interval	0	0	0	0	1	0	0	0	1	0	0	0
ST segment	0	0	0	0	0	0	0	0	0	0	0	0
T wave	0	0	4	0	5	0	4	0	6	0	6	0
QTc	0	0	5	1	9	1	13	1	13	1	13	1
Ventricular ectopic	0	0	0	0	0	0	0	0	0	0	0	0
VT	0	0	0	0	0	0	0	0	0	0	0	0
Torsades de pointes	0	0	0	0	0	0	0	0	0	0	0	0
VF	0	0	0	0	0	0	0	0	0	0	0	0

DISCUSSION

In this study, we have documented the cardiac adverse effects of sodium stibogluconate treatment among patients of kala-azar (VL).[5-7] Overall, the treatment was well-tolerated, and there was no premature discontinuation of treatment due to drug toxicities. A retrospective study has known limitations, but these limitations should not affect the parameters measured in this study. Ventricular tachycardia, torsades de pointes, and sudden death are the most serious adverse effects of pentavalent antimony.[4,8,10,12] The previous report indicates that QTc prolongation and ST segment changes usually precede and predict serious cardiac toxicities, and these occur with increasing frequency with the cumulative effects of the total dose of sodium stibogluconate.[4,8,10,12] A study in India and Africa has reported frequent adverse cardiac effects among patients treated for VL with sodium stibogluconate.[4,8,10,12] However, cardiac toxicities were not observed among 96 American military personnel with predominantly CL who were treated with the pentosan formulation of sodium stibogluconate.[9]

In this study, ECG abnormalities developed in 19 (63.33%) patients, but all of these patients were asymptomatic. The QTc interval was prolonged in 14 (46.67%) patients. No patients developed any clinically obvious arrhythmia, but the possibility of asymptomatic patients having silent arrhythmias cannot be excluded by using Holter ECG monitoring, which can detect it. The increased risk of ventricular arrhythmia is related to the magnitude of QTc interval prolongation, especially when it exceeds approximately 450 msec.[11] Based on our findings and previous reports of cardiac toxicity associated with antimonials, routine ECG monitoring should be advocated in all settings, with special attention given to the QTc interval. Approximately 20% of patients in this study had asymptomatic T wave inversion in their ECGs, as previously reported in half of these patients.[8] Using 24-hour ECG monitoring and echocardiography in a small group of patients with CL, such T wave changes were not associated with arrhythmias or cardiac dysfunction and were found to be reversible.[11] In this study, it has been shown that no patients developed VT or sudden death. We enrolled only patients who had normal cardiac function as evidenced by a pretreatment normal ECG, normal BP, and absence of symptoms of IHD.

More than 90% of cases of kala-azar occur in India, Bangladesh, Nepal, Sudan, and Brazil. Without prompt and appropriate treatment, up to 90% of kala-azar patients die, leading to at least 50,000 deaths per year worldwide. While nearly 25 compounds have been reported to have an anti-leishmanial effect, not all are in use, and pentavalent antimony compounds have remained the mainstay of treatment for nearly 75 years. The use of pentavalent antimony compounds to treat kala-azar is associated with a range of cardiological adverse effects, with the most serious being the development of ventricular tachyarrhythmia associated with prolongation of the electrographic rate corrected QT interval (QTc). In our study, 63.33% of patients developed ECG abnormalities, with 46.67% having QTc prolongation, 20% having T wave inversion, 33.33% having transient P-R prolongation, and no abnormalities revealed by P-wave and ST segment. While some studies have reported serious cardiological adverse effects that may require treatment interruption or discontinuation, others have reported the drugs to be well tolerated. Sodium stibogluconate can be used in kala-azar patients with adequate monitoring and treatment interruption is uncommon. Identifying factors before and during treatment that may increase the risk of QTc prolongation and arrhythmia is important.

CONCLUSION

Kala-azar is a disease of poor people and it is not uncommon in our country without treatment as many as 90% die. The use of this drug to treat kala-azar is said to be associated with a range of cardiological adverse effects. Some patients showed asymptomatic QTc prolongation and T wave inversion. So sodium stibogluconate can be used safely in kala-azar patients with adequate monitoring. It is required to identify factors before and during treatment that may increase the risk of QTc prolongation.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Raiston SH, Penman ID, Strachan MWJ, Hobson RP. Infectious disease in Davidson's Principle and Practice of Medicine. 23rd ed. Philadelphia: Elsevier; 2018: 281-282.
2. Dedet JP, Pratlong F. Leishmaniasis in Manson's Tropical Diseases. 21st ed. Philadelphia: Saunders Elsevier; 2003: 1339-1364.
3. Rashid KM, Rahman M, Hyder S. Special Health Problems and Programmes. Textbook of Community Medicine and Public Health. 4th ed. Dhaka: RHM; 2004: 325-330.
4. Todd WTA, Lockwood DNJ, Sunder S. Infectious disease in Davidson's Principle and Practice of Medicine. 20th ed. Philadelphia: Elsevier; 2006: 283-376.
5. Sunder S, Sinha PR, Agrawal NK, Shrivastar R, Rainey PM, Berman JD, et al. A cluster of cases of severe cardiotoxicity among Kala-azar patients treated with antimony gluconate. American J Trop Med Hygiene. 1998;59(1):139-43.
6. Rang HP, Dale MM, Ritter JM, Moore PK. Harmful effects of drugs. Pharmacology. 5th ed. London, UK: Churchill Livingstone; 2003: 724-737.
7. Kiri R, Sati ME. Observations on the use of sodium antimony gluconate in the treatment of Kala-azar. Anna Trop Med Parasitol. 1947;41:14-21.

8. Chulay JD, Spencer HC, Mugambi M. Electrocardiographic changes during treatment of leishmaniasis with pentavalent antimony (sodium stibogluconate). Am J Trop Med Hyg. 1985;34(4):702-9.
9. Aronson NE, Wortmann GW, Johnson SC, Jackson JE, Gasser RA, Magill AJ, et al. Safety and efficacy of intravenous sodium stibogluconate in the treatment of leishmaniasis: recent U.S. military experience. Clin Infect Dis. 1998;27(6):1457-64.
10. Chappuis F, Sundar S, Hailu A, Ghalib H, Rijal S, Peeling RW, et al. Visceral leishmaniasis: what are the needs for diagnosis, treatment and control? Nat Rev Microbiol. 2007;5(11):873-82.
11. Yap YG, Camm AJ. Drug induced QT prolongation and torsades de pointes. Heart. 2003;89(11):1363-72.
12. Lawn SD, Armstrong M, Chilton D, Whitty CJ. Electrocardiographic and biochemical adverse effects of sodium stibogluconate during treatment of cutaneous and mucosal leishmaniasis among returned travellers. Trans R Soc Trop Med Hyg. 2006;100(3):264-9.

Cite this article as: Alom MS, Ali ML, Shaikh AA, Kabir J. Electrocardiogram changes due to sodium stibogluconate treatment of kala-azar. Int J Res Med Sci 2023;11:775-9.