Original Article

Evaluation of Adverse Effects of Sodium Stibogluconate in the Treatment of Visceral Leishmaniasis

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Abstract:

This descriptive cross-sectional study was carried out in the Department of Medicine, Rajshahi Medical College Hospital to evaluate the adverse effects of sodium stibogluconate in the treatment of visceral leishmaniasis. Out of 30 patients, 19 patients (63.33%) developed abnormalities in ECG. Among them 14 patients (46.67%) developed prolonged QTc, 6 patients (20%) developed T-wave inversion and 1 patient (3.33%) developed transient first degree heart block. No patient developed symptomatic arrhythmia. Five patients (16.67%) developed transient raise of bilirubin, 11 patients (36.67%) developed raised SGPT. None of them developed clinical hepatitis. Twenty three patients (76.67%) developed raised serum amylase but none developed clinical pancreatitis. There was no change in renal function. No adverse effects were noted on complete blood count.

Introduction

Leishmaniases are parasitic diseases caused by protozoan flagellates of the genus Leishmania, parasites infecting numerous mammal species, including humans, and transmitted through the infective bite of an insect vector, the phlebotomine sand fly.[1]

Visceral leishmaniasis has a world-wide distribution, occurring in Mediterranean region, central Asia, the Middle East, Bangladesh, India, Africa and South and Central America. It is estimated that there are more than 12 million cases world-wide with 4000 cases reported each year, and 350 million people are at risk of acquiring the infection.

Transmission occurs mostly by the bite of sand fly, the species of which varies with geographical locations. In Bangladesh, India and Nepal, visceral leishmaniasis is transmitted by P. argentipes which feeds only on human. [2] There have been no significant changes in the treatment of leishmaniases for many years. Since the 1920s, treatment has been based on pentavalent antimonial compound. Two closely related pentavalent antimonial, are currently used: sodium stibogluconate available in English-speaking countries, and meglumine antimoniate available in France, Latin America and Francophone countries.

Antimonials have proven to be beneficial in Leishmaniasis treatment through a century of use. However, the mechanism of action as anti-Leishmanial agents remains unclear. They may involve inhibition of ATP synthesis. It might be possible that antimonial salts have to be concentrated within the macrophage or parasite and transformed into active trivalent metabolites to be efficient. Antimonials have poor oral absorption and therefore are administered by the parenteral route. They are rapidly excreted by kidneys.

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Inspite of numerous side effects attributed to antimonials, the scarcity of reported accidents allows their continued use, since no alternative efficient and non toxic drug is available. The side effects of pentavalent antimonials can be categorized into intolerance signs and toxic effects. The intolerance side effects include shivers, fever, arthralgias, myalgias, skin rashes, abdominal symptoms and headache. The stibo-intoxication signs occur at the end of treatment. They include reversible elevation of hepato-cellular enzymes, subclinical pancreatitis and decrease in haemoglobin levels and platelet count.

Cardiac side effects are the most worrisome. Several ECG changes occur, of which flattening and or inversions of T-waves are the most common. Patient can develop prolongation of the corrected QT interval, concave ST-abnormality and prolongation of PR interval. These ECG changes are transient; they gradually approach normal in a 1-3 week period after complete therapy.[2]

Severe cardio toxicity manifested by concave ST segment elevation, prolongation of QTc>0.5/msec, ventricular ectopics, runs of ventricular tachycardia, torsades de points, ventricular fibrillation and sudden death is not uncommon.[3]

Methods of Study :

This descriptive cross-sectional study was carried out on 30 cases of visceral leishmaniasis in the Department of Medicine, Rajshahi Medical College Hospital to evaluate the adverse effects of sodium stibogluconate in the treatment of visceral leishmaniasis.

Complete history was taken and physical examination was done and recorded in a case record form. At least 7 (seven) ECG tracings in each patient (one before, 5 during i.e. 1 ECG weekly and one after the completion of treatment) were recorded. Serial ECGs were analyzed by investigator himself and confirmed by supervisor. Any discrepancies in the interpretation varified by a 2nd reader. The rhythm, changes in the T wave amplitude, ST segment and the QT were determined. The corrected QT interval (QTc) was calculated using Bazett's formula.

QTc= ; RR interval = . QTc prolongation was considered to an increase of an absolute value >450 msce. Complete blood count was performed at the beginning, in the 15th day and last day of treatment. In the same manner Urine R/M/E, S.creatinine, S. bilirubin, SGPT and S.amylase were done.

Results:

Thirty (30) patients (26 male, 4 female) fulfilled the inclusion criteria who admitted into Rajshahi Medical College Hospital were enrolled in this study. Out of 30 patients 40% (11 male and 01 female) were between 13-25 yrs of age, 20% (4 male and 2 female) were between 26-30 yrs of age and 40% were 31 yrs and above .

Serial ECGs from 30 patients (before during and after completion of treatment) were obtained for interpretation (analysis). In all patients, ECG, obtained before treatment were normal. Abnormalities developed in the ECGs of 19 patients (63.33%).
Total 14 patients (46.67%) developed QTc prolongation. 12 patients (40%) developed isolated prolonged QTc and 2 patients (6.51%) developed T-wave inversion along with prolonged QTc. No patient developed any symptomatic arrhythmia despite the continued treatment.

At base line, serum bilirubin was normal in all patients, at D15 bilirubin was raised in 3 (9.99%) patients and D30 it remain elevated in two patients(6.66%). So there was transient raise of serum bilirubin which was gradually came to normal despite on going treatment with Sbv.

At base line (D0) serum SGPT was normal in all patients and at D15 it was raised in 8 patients (30.77%) and at D30 it was remained elevated in 3 patient (11.54%). So there were transient raise of SGPT which was gradually returned to normal despite on going sodium stibugluconate treatment.

At DO serum amylase was normal in all patients; the mean value was 83.50 IU/L. At D15 it was raised in 21 (19 male and 2 female) patients (70%) and the mean value was 130.57 IU/L.

At D30 along with the previous 21 patient, another two patients also developed raised serum amylase (76.67%) and mean value was 164.78 IU/L. The raise of serum amylase ranges from 100-500 IU/L.
At baseline serum creatinine values were normal and no protein and sugar in urine and remained unchanged despite ongoing treatment with sodium stibogluconate.

At diagnosis (D0) mean Hb% were 63, mean total count of WBC 3750/cumm. Differential count (Neutrophils-50, Lymphocytes-42, Monocyte-6, Eosinophil-2, Basophil 0.00) and mean Platelet count 193,000/µL.At D15 mean Hb% 65.00, mean total WBC count 4660/cumm, Neutrophil-54, lymphocytes-40, Monocyte-5, Eosinophil-1 and Platelet count 202333/cumm of blood. At D30 mean Hb% 68.43, Total count 7943/cumm, Neutrophils-59, Lymphocytes-38, Monocytes-2, Eosinophil-1, Basophil-0.0 and platelets count 202066/cumm.

There were no adverse effects on complete blood count, rather Hb%, total count of WBC, Platelets count, Neutrophils count were gradually increased with on going treatment with sodium stibugluconate and lymphocytes count, Monocyte count gradually fall on continued treatment.

Discussion :

In this study we have documented the cardiac, key biochemical, and hematological adverse effects of sodium stibogluconate treatment among the patients of visceral leishmaniasis. Overall, treatment was well tolerated. There was no premature discontinuation of treatment due to drug toxicity. All reported data were both test-based and collected at the same institution i.e. RMCH (e.g. serum biochemistry, ECGs) or were collected from standard pathological laboratories.

Ventricular tachycardia, torsades de pointes and sudden death are the most serious adverse effect of pentavalent antimonials.[4,5, 8,15] Previous reports indicate that QTc prolongation and ST segment changes usually precede and are predictive of serious cardiotoxicity and that these occur with increasing frequency with greater cumulative total doses of Sbv. While studies in India and Africa have reported frequent adverse cardiac events among patients, treated for VL using Sbv. Cardiac toxicity was not observed among 96. American military personnel with predominantly CL who were treated with pentostanTM formulation of Sbv.[6]

Differences in drug preparations, the much greater systemic morbidity associated with VL and the different cardiovascular risk profiles of these populations may explain these marked differences in frequency of cardiac toxicity.

In this study, abnormalities developed in the ECGs 19 (63.33%) patients. These were asymptomatic in all patients. We also observed among the whole study group that there was prolongation of QTc interval in 14 patients (46.67%). No patient developed clinically any obvious arrhythmia. But we cannot exclude the possibility that any of these asymptomatic patients had silent arrhythmias; continuous 24 hour ECG monitoring would have been required to investigate this.

In general, the increased risk of ventricular arrhythmias in related to the magnitude of QTc prolongation and especially when it exceeds a threshold of approximately 450 msec.[10] Based on our findings and previous reports of cardiac toxicity associated with antimonials, routine ECG monitoring during treatment should be advocated in all settings where this is possible with specific attention being paid to the QTC interval. Particular care should be taken with patients with pre-existing cardiac morbidity or cardiac risk factors.

Asymptomatic T-wave inversion was seen in the ECGs of approximately 20% of the patients in this study and in half of the patients as previously reported.[5] 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.[10] Although follow up investigations were not performed in this study after completion of treatment, there are no previous reports in the literature of post-treatment adverse events and none were reported during outpatient follow-up. P-R prolongation found in 1 patient (3.33%). Beside these, no other ECG abnormalities were observed in this study. Acute pancreatitis during treatment with pentavalent antimonials has been reported among patients with immunosuppression due to HIV-1 infection or post-renal transplant immunosuppresive therapy.[11] Hyperamylasaemia was reported among 16 of 17 patients treated in a prospective series of patients with CL treated with Sbv in USA, leading to treatment interruptions or discontinuation among 10 patients for presumed pancreatitis.[12]

VL-patient treated with sodium stibogluconate at a dose of 20 mg/kg/d for 28 days 97% developed pancreatitis.[6] Other case series have not reported clinical pancreatitis.[9,13,14]

In our study, asymtomatic hyper amylasaemia was observed in a majority (76.67%) of patients, peaking most frequently during the 4th week of treatment. All patients were clinically evaluated on a daily basis and none developed clinical evidence of pancreatitis.

A similar rise and fall in serum hepatic transaminase (SGPT) was also seen in 30.77% of the patients, without clinical evidence of hepatitis as has previously been described.[13] Our data indicate that althrough hyperamylasaemia and increased serum hepatic transaminase (SGPT) concentrations are observed in a remarkable number of patients treated with Sbv, these findings are usually not of any clinical significance and should not prompt treatment change per se in the absence of other evidence of pancreatitis or hepatitis. There was transient mild raise of serum bilirubin which gradually became normal despite the continued treatment.

26.3% patients of VL treated with Sbv developed acute renal failure.[16] But in our study no patient developed ARF.

Aronsen showed haematological suppression in 44% patients of VL treated with Sbv[6]. Sumita sharma showed acute erythroid toxicity in visceral leishmaniasis, a rare complication of antimonial therapy[7]. But in our study no haemotological suppression or erythroid toxicity were found.

In this study it has been shown that no patient developed VT, sudden death or increased bleeding tendencies or renal failure. It may be explained by that (a) we enrolled only those patients who had normal LFT, normal renal function, and normal cardiac function as evidenced by pretreatment normal ECG, normal BP and absence of symptoms of IHD and non-diabetic. (b) Small sample size (c) Differences in the formulation of drugs may present from batch to batch.
In the light of our data, we suggest that a risk assessment should be made of Kala-azar patients (VL) who require treatment with Sbv. Those who do not have pre-existing cardiac, hepatic, pancreatic or renal disease or other significant co-morbidity could be treated with Sbv as outpatients where as those with such conditions or other risk factors such as advanced age might be best managed as inpatients. Baseline ECGs, serum creatinine, electrolytes, transaminases, amylase and full blood count should be performed in all patients to detect pre-existing abnormalities. Performing twice weekly ECGs in all patients is a helpful strategy to identify QTc prolongation, Serum biochemical parameters should also be measured serially in patients with identified risk factors for toxicity. However, the value of regular monitoring of these parameters during treatment in healthy low-risk individuals with normal baseline parameters, a normal QTc and no symptoms is of debateable value.

Conclusion:

The use of this drug to treat Kala-azar is said to be associated with a range of cardiac, biochemical and hematologic adverse effects. But in our study, though there was rise of serum amylase and hepatic transaminases in a good number of cases, none of them developed clinical pancreatitis or hepatitis and treatment modification was not required. Some patient showed asymptomatic QTC prolongation and T-wave inversion. So, sodium stibogluconate can be used safely in Kala-azar patients with adequate monitoring. Identification of factors before and during treatment that may increase the risk of QTc prolongation and arrhythmia is important for prevention of deadly complications.

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