Egyptian Dermatology Online Journal
Volume 9 Number 1

Electrocardiographic and Biochemical Adverse Effects of Meglumine Antimoniate During the Treatment of Syrian Cutaneous Leishmaniasis Patients

Siavash M. Shanehsaz and Silva Ishkhanian.

Department of Dermatology and Venereology, Aleppo University Hospital, Syria.

Egyptian Dermatology Online Journal 9 (1): 5

Correspondence: Dr. Siavash M. Shanehsaz
e-mail: mdsiavash@yahoo.com

Submitted: February 2, 2013
Accepted: May 5, 2013

Abstract

Background and aim:

Cutaneous leishmaniasis (CL) has been recognized as a major public health problem in several countries. It is highly endemic in the north and east Mediterranean regions in the Syrian Arab Republic with more than 75.9% of all CL cases recorded from these regions. Pentavalent antimonials have been considered as standard treatment for leishmaniasis. Use of pentavalent antimonials to treat leishmaniasis is associated with a range of cardiac, biochemical and hematological adverse effects. The most serious of these is the development of ventricular tachyarrhythmias associated with prolongation of the electrocardiographic (EKG) rate-corrected QT interval (QTc). Whereas some studies have reported that serious cardiac and biochemical adverse effects are common and often require treatment interruption or discontinuation, others have reported the drugs to be well tolerated. The aim of this study was to evaluate the effect of Meglumine Antimoniate (MA) on EKG and some liver, kidney, and pancreas function tests among Syrian CL patients.

Methods:

In this prospective study carried on 80 Syrian clinically suspected CL patients referred to the Aleppo University Hospital Clinic. Fifty patients were randomly selected and after the diagnosis of CL was made by tissue smear and skin biopsy, EKG and blood samples were taken to evaluate liver, kidney, and pancreas function tests before and after treatment with intramuscular injections of MA at a dose of 20 mg Sb+5/kg/day equivalent to 60 mg/kg/day for 21 days. Informed consent was obtained from all the cases. Data were analyzed by use of paired t- test and p-values < 0.05 were considered as significant.

Results:

There were 33 males and 17 females (34%) among Syrian CL patients with a mean age and SD of 28.3 ± 11 years. The mean + SEM QTc progressively increased from 382+2.8 msec to 402+ 2.5 msec during 21 days of treatment and the QTc reached the threshold for potential cardiac toxicity among 6 (12%) patients during the third week of treatment. ST depression occurred in 3% and inverted T was observed in 4% of the patients. The mean serum levels of blood urea nitrogen, creatinine, sodium, potassium, total and direct bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase significantly increased after treatment, although most of them were within normal ranges. There were no significant differences in serum levels of amylase and lipase before and after treatment, none developed clinical pancreatitis or hepatitis and treatment modification was not required.

Conclusions:

Our results showed that one course of treatment with 20 mg Sb+5/kg/day equivalent to 60 mg/kg/day MA for 21 days does not significantly alter the liver, kidney and pancreas function tests. Treatment with systemic MA can induce many ECG changes as QT prolongation and have a significant risk. Identification of the factors before and during treatment that may increase the risk of QTc prolongation and arrhythmias is important. Systemic MA can be used safely in this population with adequate monitoring and the need for treatment interruption is uncommon.

Introduction:

Leishmaniasis is prevalent in 88 countries, affecting an estimated 12 million people with approximately 2 million new cases per year, 500 000 of which are visceral leishmaniasis (VL) and l 500 000 CL (90% of them in Afghanistan, Algeria, Brazil, the Islamic Republic of Iran, Peru, Syria, Saudi Arabia and Sudan) [1]. Cutaneous leishmaniasis has been endemic in Syria for hundreds of years [2]. Common local names include 'Aleppo boil' and the 'one-year boil'. The annual number of reported CL cases is approximately 19 000. It has been documented that Leishmania tropica subtype Mon-76 [1], according to the Classification of Montpellier, is the causative parasite for the anthroponotic form of the disease (ACL) in the traditional focus of Aleppo city [3], while Phlebotomus sergenti is the vector [4]. After 1 to 12 weeks incubation period, the lesion appears as a red papule enlarging to a nodule or plaque with a purple infiltrative border and central crust. Spontaneous healing occurs after 6 to 12 months, with a remaining scar [5]. Although the adverse effects and inconveniences of pentavalent antimony derivatives used in the treatment of leishmaniasis for more than 7 decades are well known but these drugs remain the mainstay of systemic treatment [6]. The mechanism of action is that this drug inhibits the glucose uptake by promastigotes [7] and decreases DNA, RNA and protein synthesis [8]. 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 [9]. The reported efficacy of Meglumine antimoniate (MA) in the treatment of CL varies from 2-90% depending on dosage, duration of treatment definition of efficacy and the responsible Leishmania species

[10]. The main aim of the present study was to evaluate the safety of systemic use of MA on EKG, liver, kidney, and pancreas functions among Syrian CL patients.

Materials and Methods

This study was a prospective, before and after treatment comparison of blood urea nitrogen (BUN), creatinine, sodium (Na), potassium (K), total bilirubin (Bil T) and direct bilirubin (Bil D), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (Alk-Ph), amylase, lipase and EKG carried out in the department of Dermatology and Venereology, Aleppo University Hospital, Aleppo, Syria during the period from November 2009 to February 2010. Of 80 Syrian clinically suspected (CL) patients referred to the Aleppo University Hospital Clinic, 50 patients were randomly selected and after the diagnosis of (CL) was made by tissue smear and/ or skin biopsy, EKG and blood samples were taken to evaluate liver, kidney, and pancreas function tests before and after treatment with intramuscular injections of MA at a dose of 20 mg Sb+5/kg/day equivalent to 60 mg/kg/day for 21 days. Skin biopsies were taken from the active indurated margin of the lesion under aseptic conditions. A 4 mm tissue sample was taken using a sterile biopsy punch. Statistical before and after treatment comparison was performed to find out the effect of Meglumine Antimoniate (MA) on some liver, kidney, and pancreas function tests and EKG among Syrian CL patients, using of paired t-test and p-values < 0.05 were considered as significant. Parasitological confirmation, age 5 to 65 years, normal values of the aforementioned tests before treatment were inclusion criteria. Informed consent was obtained from all the cases. Contraindication to use MA, pregnant women, patients with cardiovascular problems, those under treatment with other drugs during the month prior to commencement of the study, acute or chronic medical conditions which might interfere with the results of the laboratory tests were considered as exclusion criteria. EKG was performed on the patients before starting the treatment, during the treatment (weekly) and 1 month after stopping the treatment. 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 [11]. The patients were treated with intra-gluteal injections of MA (Glucantime; Aventis, France) at a dose of 20 mg Sb+5/kg/day equivalent to 60 mg/kg/day of MA for 21 days. The drug was available in 5 ml vials.

Results

Fifty patients were enrolled in the study. There were 33 (66%) males and 17 (34%) females. The mean age ± SD of the patients was 28.3 ± 11 years and the mean duration of disease was 4.0 ± 1.2 months. The mean + SEM QTc progressively increased from 382 + 2.8 msec to 402 + 2.5 msec during 21 days of treatment and the QTc reached the threshold for potential cardiac toxicity among 6 (12%) patients during the third week of treatment. ST depression occurred in 3% of the patients and inverted T was observed in 4% of the patients. No case of tachycardia was seen. Atrial arrhythmia as single premature atrial contraction (PAC) occurred in 1 patient

(2%). All of these changes reversed after cessation of the treatment. Before and after treatment laboratory values are shown in **(table 1)**.

	Normal values (Range)	Before treatment value (mean ± SD)	After treatment value (mean ± SD)	P-value	Patients with abnormal value after therapy (%)
Na (mEq/L)	135-148	141 ± 2.8	143.6 ± 3.1	0.02	3(6)
K (mEq/L)	3.5-5	4.0 ± 0.2	4.4 ± 0.6	0.03	0(0)
AST (IU/L)	5 - 40	24 + 11	35 + 24	0.002	10(20)
ALT (IU/L)	5 - 40	21 ± 10	25 ± 20	0.007	10(20)
Alk-Ph (IU/L)	180-1200	194.1 ± 61	280 ± 90	0.002	7(14)
Bil T (mg/dL)	0.1-1.2	0.80 ± 0.2	0.93 ± 0.2	0.03	3(6)
Bil D (mg/dL)	0.0-0.5	0.3 ± 0.1	0.5 ± 0.2	0.02	7(14)
BUN (mg/dL)	14-50	22 ± 4.8	26.2 ± 6.0	0.03	0(0)
Creatinin (mg/dL)	0.6-1.3	0.71 ± 0.5	0.87 ± 0.3	0.02	0(0)
Amylase (IU/L)	70-340	168.3 ± 47	152 ± 51	0.08	0(0)
Lipase (U/mL)	Up to 90	36.4 ± 21	38.8 ± 21.4	0.6	0(0)

BUN = Blood urea nitrogen. Na = Serum Sodium. K = Serum potassium. Bil T = Total bilirubin. Bil D = Direct bilirubin. AST = Aspartate aminotranferase. ALT = Alanine aminotransferase. Alk-Ph = Alkaline phosphatase.

* significant P-value < 0.05.

Table 1. Laboratory values before and after treatment with 60 mg/kg/day of intramuscular injection of Meglumine Antimoniate (MA) for 21 days in Syrian (CL) patients

There were no significant differences in serum levels of amylase and lipase before and after treatment with MA 20 mg Sb5+/kg/day equivalent to 60 mg/kg/day for 21 days. Serum levels of BUN, creatinine, Na, K, Bil T and Bil D, AST, ALT, and Alk-Ph were significantly increased (table 1). The majority of these changes were not clinically significant and treatment modification was not required. ALT levels

increased two-folds in four men and two women and the AST level increased three-folds in three male patients. All of these abnormal values returned to normal in 2-4 weeks after completion of treatment.

Discussion and Conclusions

Cutaneous leishmaniasis (CL) has been endemic in Syria for hundreds of years [2]. Common local names include 'Aleppo boil' and the 'one-year boil'. It has been documented that Leishmania tropica is the causative parasite for the anthroponotic form of the disease (ACL) in the traditional focus of Aleppo city [3], while Phlebotomus sergenti is the vector [4]. The increasing incidence of ACL in this traditional focus, and the spread to other new foci in Syria, has led the Syrian Ministry of Health to address ACL control as a priority in the Aleppo Governorate [12]. Systemic pentavalent antimonies have been used in the treatment of leishmaniasis since 1929 [13]. Urea Stibamate was the first antimonial drug, later being replaced by Sodium Stibogluconate (SSG), Pentostam. Today, SSG and Meglumine Antimonies (MA) are considered to be standard treatments for (CL) [14]. Adverse drug effects are unfavorable events associated in time with the use of a medication and may have a causal relationship [15]. The safety of a drug is related to morbidity and mortality resulting from the incidence and severity of adverse effects [16]. Pentavalent antimonies are considered to be of low toxicity, depending on the cumulative doses used, and are rapidly excreted by the kidneys [17]. Although side effects and complications are known, few studies have been specifically designed to investigate changes in laboratory values after treatment with pentavalent antimonies. The adverse effects of pentavalent antimonials and pentamidine needed to be considered jointly, irrespective of formulation, daily dose, duration of treatment and route of administration. Mild to moderate clinical, laboratory and electrocardiographic adverse effects were frequent. In some cases, these effects were severe, resulting in temporary or definitive treatment discontinuation, or even in death [18,19,20]. The study was performed in 2002 to compare the efficacy of a 10 or 20 day course of SSG in the treatment of CL in US military personnel, and reported increases in amylase, lipase, AST and ALT levels and decreases in white blood cell count, hematocrit and platelets, which were more prominent in the group who received the drug for 20 days [21]. The investigation was carried out in 2004 to compare the efficacy and adverse effects of the generic and branded pentavalent antimonies in the treatment of new world (CL) in patients from Bolivia and Colombia. They administered the drug at a dose of 20 mg Sb5+/kg/day for 20 consecutive days and reported pancreatic enzyme abnormalities in (48-88%) and liver enzyme abnormalities in (48-87%) of their patients, respectively. The lowest frequencies of pancreatic enzyme abnormalities were observed in the generic stibogluconate group ($p < 0.01$) . The longer duration of drug administration in this investigation may explain the observed higher frequency of liver and pancreatic enzyme increases in comparison with the findings of our study [22]. The study was performed in 2005 to compare the efficacy and adverse effects of (MA) to pentamidine and reported no significant difference in mean values of creatinine among the two groups, but a significant increase in AST mean values in MA treated patients, although it exceeded 174 IU/L in none of the patients and the ALT level was not statistically significantly increased. In the Glucantime-treated group, pancreatic lipase values increased to a mean of 61 IU/L on day 4, to 73 IU/L on day 8, and were then maintained at 71 IU/L until the end of therapy. All these values were significantly greater than those in the Pentamidine-treated group, which

had not changed from the pre-therapy values [23]. The investigation was carried out in 2006 to report both cardiac and biochemical adverse effects of pentavalent antimonial treatment in CL patients, but described the treatment as well tolerated overall. They reported normal baseline liver function tests in all of their patients. According to their findings, serum concentrations of ALT or AST increased above the upper limit of the normal range in 85% of patients and increased more than three times above the upper limit of the normal range in 33% of patients. The median transaminase concentration peaked on day 12 of treatment and decreased thereafter, despite ongoing treatment with pentavalent antimonial derivatives. QTc interval prolongation is a condition that, if not detected early, may cause sudden and fatal arrhythmia and was the most frequent electrocardiographic adverse effect. This study believed that weekly ECG monitoring should be sufficient to prevent this condition and treatment should be discontinued if the QTc interval prolongation exceeds 450msec [24]. The study was performed in 2007 to report mean serum levels of blood urea nitrogen, creatinine, sodium, total and direct bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase significantly increased after treatment, although most of them were within normal ranges. According to their findings, there were no significant differences in serum levels of potassium, amylase, lipase, and γ-glutamyl transpeptidase before and after treatment [25]. Our results was similar to this study, but EKG changes weren,t evaluated in this study. The investigation was performed in 2008 to evaluate EKG changes in the patients with (CL) treated with systemic Glucantime. Their results showed that the most common change in the Glucantime-treated patients was prolongation of QT interval in 25 patients (19%). The second most common change was bradycardia in 14 patients (10.6%) and the third change was inverted T wave in 10 cases (7.4%). 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 [26]. The study was performed in 1999, 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. 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 mgsb5+/kg/day up to 30 days or 20 mgsb5+/kg/day up to 20 days [27]. In another study that was carried out 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 wave [28], but in our study the problem in T wave was only inverted T in 4% of cases. The investigation was performed in 1992, patients with mucocutaneous leshmaniasis treated with systemic Glucantime, EKG changes occurred in (45%) that predominantly occurred in T wave and ST segment and which reversed 2 months after stopping the treatment [29].

In conclusion, there was no significant alteration in laboratory values of liver, kidney, or pancreas indices before and after treatment with MA at a dose of 60 mg/kg/day for 21 days in Syrian CL patients. According to past studies and results of the current study, EKG abnormality due to antimonial therapy in patients with normal EKG is minimal. However, we recommend the monitoring of laboratory and electrocardiographic adverse effects at a minimum interval of 7 days during treatment and on day 30 after the end of treatment. Monitoring should include a complete blood

count and the measurement of BUN, creatinine, electrolytes and liver and pancreatic enzymes, in addition to an electrocardiogram.

Acknowledgements

Financial Support: This project was funded by University of Aleppo, Aleppo, Syria. Conflict of interest: None.

References

1. Desjeux P. Leishmaniasis: current situation and new perspectives. Comp Immunol Microbiol Infect Dis 2004;27:305-18.

2. Douba M, Mowakeh A, Wali A. Current status of cutaneous leishmaniasis in Aleppo, Syrian Arab Republic. Bull World Health Organ. 1997;75(3):253-9.

3. Belazzoug S et al. Un nouveau zymogeme de Leishmania tropica, agent du Bouton d'Alep (Syrie). Archives de llnstitut Pasteur, Alg6rie, 1988, 56: 95-99.

4. Depaquit, J., Ferte, H., Leger, N., Lefranc, F., Alves-Pires, C., Hanafi, H., Maroli, M., Morillas-Marquez, F., Rioux, J.A., Svobodova, M., Volf, P.,. ITS 2 sequences heterogeneity in Phlebotomus sergenti and Phlebotomus similis (Diptera. Psychodidae): possible consequences in their ability to transmit Leishmania tropica. Int. J. Parasitol. 2002; 32, 1123-1131.

5. Hepburn NC. Cutaneous leishmaniasis. Clin Exp Dematol 2000, 25: 363- 370.

6. Herwalt BL. Leishmaniasis. Lancet 1999; 354: 1191-9.

7. Voller A, shaw JJ, Bryant C. The effects of two antimony drugs on the in vitro metabolitm of radioactive glucose forms of leishmania tropica. Ann Trop Med Parasitol 1963;57:404-8.

8. Berman JD, Waddell D, Hanson BC. Biochemical mechanisms of the antileishmanial activity of sodium stibogluconate. Antimicrob Agents Chemother 1985;27:916-20.

9. Berman JD, Wyler DJ. An in vitro model for investigation of chemotherapeutic agents in leishmaniasis. J Infect Dis 1980;142:83-6.

10. Khatami A, Firooz A, Gorouhi F, Dowlati Y. Treatment of acute Old World cutaneous leishmaniasis: A systematic review of the randomized controlled trials. J Am Acad Dermatol 2007; ;57(2):335.e1-29

11. Josephson ME, Zimetbaum P. The bradyarrhythmias: disorders of sinus node function and AV conduction disturbances. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editors. Harrison's Principles of Internal Medicine. 16th ed. New York: McGraw Hill, 2005:1333-42.

12. Curtis, C.F., Lines, J.D., Carnevale, P., Robert, V., Boudin, C., Hana, J.-M., Pazart, L., Gazin, P., Richard, A., Mouchet, J., Charwood, J.D., Graves, P.M., Hossain, M.I., Kurihara, P., Ichimori, T., Li Zuzi, Lu Baolin, Majori, G., Sabatinelli, G., Coluzzi, M., Njunwa, K.J., Wilkes, T.J., Snow, R.W., Lindsay, S.W., 1990. Impregnated bed nets and curtains against malaria mosquitoes, in: Curtis, C.F. (Ed.), Appropriate Technology for Vector Control. CRC Press, Florida, pp. 5-46.

13. Berman JD. Human leishmaniasis: clinical, diagnostic, and chemotherapeutic developments in the last 10 years. Clin Infect Dis 1997;24:684-703.

14. Olliaro PL, Guerin PJ, Gerstl S, Haaskjold AA, Rottingen JA, Sundar S. Treatment options for visceral leishmaniasis: a systematic review of clinical studies done in India, 1980- 2004. Lancet Infect Dis 2005;5:763-74.

15. Deeks, J.J., Higgins, J.P.T., Altman, D.G., 2006. Including Adverse effects. In: Higgins, J.P.T., Green, S. (Eds.), Cochrane Handbook for Systematic Reviews of Interventions. John Wiley & Sons, Ltd., Chichester, UK (4.2.6 [updated September 2006]; Appendix 6b. The Cochrane Library, Issue 4, 2006).

16. Kane-Gill, S., Rea, R.S., Verrico, M.M., Weber, R.J., Adverse-drug- event rates for high-cost and high-use drugs in the intensive care unit. Am. J. Health Syst. Pharm. 2006; 63, 1876-1881.

17. Rees PH, Keating MI, Kager PA, Hockmeyer WT. Renal clearance of pentavalent antimony (sodium stibogluconate). Lancet 1980; 2: 226-9.

18. Kopke, L.F.F., Café, M.E.M., Neves, L.B., Scherrer, M.A.R., Machado-Pinto, J., Souza, M.S.L.A., et al., Morte após uso de antimonial pentavalente em leishmaniose tegumentar americana. An. Bras. Dermatol. 1993; 68, 259-261.

19. Rodrigues, M.L., Costa, R.S., Souza, C.S., Foss, N.T., Roselino, A.M., Nephrotoxicity attributed to meglumine antimoniate (Glucantime) in the treatment of generalized cutaneous leishmaniasis. Rev. Inst. Med. Trop. Sao Paulo 1999; 41, 33-37.

20. Costa, J.M., Garcia, A.M., Rêbelo, J.M., Guimarães, K.M., Guimarães, R.M., Nunes, P.M.,. Óbito durante tratamento da leishmaniose tegumentar americana com stibogluconato de sódio bp 88® (shandong xinhua). Rev. Soc. Bras. Med. Trop. 2003; 36, 295–298.

21. Wortmann G, Miller RS, Oster C, Jackson J, Aronson N. A randomized, double-blind study of the efficacy of a 10- or 20-day course of sodium stibogluconate for treatment of cutaneous leishmaniasis in United States military personnel. Clin Infect Dis 2002; 35: 261-7.

22. Soto J, Valda-Rodriquez L, Toledo J, Vera-Navarro L, Luz M, Monasterios-Torrico H, Vega J, Berman J. Comparison of generic to branded pentavalent antimony for treatment of new world cutaneous leishmaniasis. Am J Trop Med Hyg 2004; 71: 577-81.

23. Andersen EM, Saldarriaga MC, Cuentas AL, Cjuno ML, Echevarria J, Verastegui CM, Colina O, Berman JD. Comparison of meglumine antimoniate and pentamidine for peruvian cutaneous leishmaniasis. Am J Trop Med Hyg 2005; 72: 133-7.

24. 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: 264-9.

25. Nassiri Kashani M, Firooz A, et al., Evaluation of meglumine antimoniate effects on liver, kidney and pancreas function tests in patients with cutaneous leishmaniasis. Eur J Dermatol 2007; 17 (6): 513-5.

26. Sadeghian Giti et al., Evaluate EKG changes in the patients with CL treated with systemic glucantime. Ann Acad Med Singapore 2008;37:916-8.

27. Ribeiro ALP, Drummond JB, Volpini AC, Andrade AC, Passos VMA. Electrocardiographic changes during low-dose, short-term therapy of cutaneous leishmaniasis with pentavalent antimonial meglumine. Braz J Med Biol Res 1999;32:297-301.

28. Thakur CP, Sinha GP, Pandey AK, Kumar N, Hassan SM, Narain S, et al. Do the diminishing efficacy and increasing toxicity of sodium stibogluconate in the treatment of visceral leishmaniasis in BiharIndia, justify its continued use as a first-line drug? An observational study of 80 cases. Ann Trop Med Parasitol 1998;92:561-9.

29. Antezana Zeballos R, Mendoza C, Lyevre P, Valda L, Cardenas F, Noriega I, et al. Electrocardiographic alternations during treatment of mucocutaneous leishmaniasis with meglumine antimoniate and alloporinol. Trans R Soc Trop Med Hyg 1992;86:31-3.