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**ELECTROCARDIOGRAPHIC FINDINGS IN ETHIOPIANS ON PENTAVALENT ANTIMONY THERAPY FOR VISCERAL LEISHMANIASIS**

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**ABSTRACT**

**Background:** The old short course regimens of pentavalent antimonial ( $sb^V$ ) therapy of visceral leishmaniasis (VL) have largely been abandoned worldwide as they are associated with increasing problems of relapse and unresponsiveness. In Ethiopia, some hospitals still use the old interrupted and short course regimen partly because of fear of drug toxicity.

**Objective:** To evaluate the safety of the WHO recommended uninterrupted therapy at a dose of 20 mg  $sb^V/kg$  for up to thirty days.

**Design:** A prospective study.

**Setting:** Patients were recruited from Addis Ababa hospitals and from Konso VL endemic area in southern Ethiopia.

**Subjects:** Forty nine patients who included, ten HIV-positive and 39 HIV-negative, were enrolled for the study.

**Results:** Twenty three HIV-negative patients got treatment for 20 days and the rest, 16 HIV-negative and 10 HIV-positive, were treated for 28 to 30 days. Among HIV-seronegatives, the mean QT interval corrected for heart rate (QTc) at the end of therapy in patients treated for 20 days and 28 - 30 days was comparable ( $0.419 \pm 0.031$  seconds versus  $0.424 \pm 0.027$  seconds, respectively). Among patients treated for 28 - 30 days, the mean QTc in HIV co-infected patients was comparable to that of HIV-negatives ( $0.416 \pm 0.018$  seconds versus  $0.424 \pm 0.027$ ). Comparable rates of new ECG changes involving the T waves were observed in two HIV-positive (20%) and two HIV-negative (12.5%) patients treated for 28 - 30 days, and in seven (30.4%) HIV-negative patients treated for 20 days. Overall, only two (4.1%) patients (all HIV-negative males) had QTc interval  $\geq 0.50$  seconds at the end of therapy. In one patient, the prolonged QTc was noted on the twentieth day with bradycardia of 44/minute.

**Conclusions:** In Ethiopian VL patients with normal renal function,  $sb^V$  therapy at a daily dose of 20 mg /kg for up to 30 days is safe and only rarely associated with clinically significant bradycardia which resolves after temporary cessation of therapy. Furthermore, in areas with limited facilities, monitoring the pulse rate during antimonial therapy may help detect impending cardiotoxicity.

**INTRODUCTION**

Until early eighties, pentavalent antimonial therapy of VL was based on repeated and interrupted, short course regimens of 10 mg  $sb^V/kg$  body weight. This practice, however, was associated with increasing problems of relapse and unresponsiveness particularly in East Africa and, to some extent, India(1).

The reports from Kenya on renal clearance studies(2) and on the safety and tolerance of prolonged treatment with higher doses of sodium stibogluconate(3), were landmarks in VL therapy which, by and large, have led to the current changes in treatment regimens(4,5). Although much of the safety and renal clearance studies of pentavalent antimonials were carried using sodium stibogluconate, these studies are also considered to be applicable to meglumine antimonate as both drugs have similar

pharmacokinetics, characterised by rapid absorption and excretion when administered at equivalent  $sb^V$ (6). Furthermore, at equivalent dose and duration of  $sb^V$  therapy, both drugs have comparable initial cure and subsequent relapse rate(7). However, the duration of therapy needed to effect cure of VL, seem to vary in different nosogeographical endemic areas(1,4,5,8,9) and some studies even suggest regional variation in the tolerance of patients to higher doses of pentavalent antimonial therapy. For example in Kenya, sodium stibogluconate administered at a dose of 10mg  $sb^V/kg$  eight hourly was found to be well tolerated and safe(10). However, this same regimen resulted in death of three out of four Indian VL patients due to cardiotoxicity(11).

Currently, the WHO recommends treating VL patients at 20 mg  $sb^V/kg$ , with 850 mg total daily dose, for at least four weeks(5). In Ethiopia, pentavalent antimonial therapy

of VL has, by and large, been changing along with changes in WHO's recommended treatment regimens. However, some hospitals still use the old regimen of two 10 day courses of antimonial therapy at 10 mg sb<sup>v</sup> /kg, with a maximum daily dose of 600 mg sb<sup>v</sup>, administered with a two weeks break in between. This, although unjustified, is partly due to the fear of drug toxicity. The aim of the present study is to evaluate the safety of uninterrupted pentavalent antimonial therapy, at a dose of 20 mg sb<sup>v</sup> /kg for up to 30 days, in Ethiopian VL patients treated hospitalised or on ambulatory basis.

#### MATERIALS AND METHODS

From August 1994 to December 1997, a total of 49 parasitologically confirmed VL patients (38 males, 11 females; ten HIV-positive and 39 HIV-negative) with normal renal function tests were recruited for ECG assessment of cardiotoxicity of pentavalent antimonial therapy. Twenty two patients originated from Aba-Roba VL endemic area in south west Ethiopia, and the rest had acquired VL in different endemic areas of the country. Among the total 49 patients, 25 were treated on out-patient basis and the rest were hospitalised. Patients were treated with either sodium stibogluconate (eight patients) or meglumine antimonate (41 patients), depending on availability, at equivalent pentavalent antimony (sb<sup>v</sup>) content calculated at a daily dose of 20 mg sb<sup>v</sup> /kg with a maximum daily dose of 850 mg sb<sup>v</sup>. HIV-VL patients were put on 28 day treatment regimen while HIV-negative VL patients were treated for either 20 or 30 days. The later group was among study subjects of an ongoing research project aimed at determining the optimum duration of pentavalent antimonial therapy needed to effect cure in Ethiopian VL patients. In this protocol, patients were evaluated every tenth day and treatment was continued for another ten days after the first splenic aspirate reading of zero parasites in a smear preparation. Besides clinical evaluation, response to treatment was monitored parasitologically by grading the spleen/bone-marrow aspirate smear using the procedures described by Chulay and Bryceson(12). ECG recordings were taken before the start and just after completion of therapy and, when indicated, repeat ECG recordings were made during the course of therapy. QT interval corrected for heart rate (QTc) was calculated using Bazett's formula by dividing the measured QT by the square root of R-R interval. Using EPI-Info version- 6 statistical package (WHO-CTI), analysis of variance (one way ANOVA) was used to check for significant difference in mean age, weight and QTc interval

within and between groups, and Chi-square test was used to compare rates and proportions between groups.

The project had institutional ethical clearance, and all diagnostic and therapeutic interventions were carried out after obtaining informed consent from each patient.

#### RESULTS

Table 1 shows age and sex of 49 VL patients monitored for cardiotoxicity of pentavalent antimonial therapy. A total of 23 patients (nineteen males, four females) were treated for 20 days and 26 patients (nineteen males, seven females) were treated for 28 - 30 days.

**Table 1**

*Age and sex distribution of 49 VL patients treated with pentavalent antimonials at 20 mg sb<sup>v</sup> /kg b.wt./day for twenty to thirty days*

Age group (yrs)	Duration of therapy						Total (%)
	20 days		28 - 30 days				
	Male	Female	HIV-negative		HIV-positive		
<10	3	2	2	3	0	0	10 (20.4)
11- 20	4	1	6	2	0	0	13 (26.5)
21 - 30	10	0	7	0	5	1	8 (36.7)
>30	2	1	4	0	3	1	8 (16.3)
Total	19	4	19	5	8	2	49 (100)

Table 2 shows comparisons of clinical data by duration of pentavalent antimonial therapy. New ECG changes, mostly in the form of flattening or inversion of T waves, were observed in seven (30.4%) HIV-negative patients treated for 20 days, and in two (20.0%) HIV-positive and two (12.5%) HIV-negative patients treated for 28 - 30 days. Among HIV-seronegatives, the mean QTc interval at the end of therapy in patients treated for twenty days, and twenty eight to thirty days was comparable ( $0.419 \pm 0.031$  seconds versus  $0.424 \pm 0.027$  seconds, respectively). Among patients treated for 28 - 30 days, the mean QTc interval in HIV co-infected patients was comparable to that of HIV-negatives ( $0.416 \pm 0.018$  seconds versus  $0.424 \pm 0.027$ ).

**Table 2**

*Comparison of clinical and ECG parameters among HIV sero-positive and sero-negative VL patients treated with pentavalent antimonials at 20 mg sb<sup>v</sup> /Kg b.wt./day for twenty to thirty days*

Variable	Duration of therapy			P. value
	Twenty days HIV negative	28 - 30 days HIV negative	28 - 30 days HIV positive	
Number of patients	23	16	10	
Clinical category	A	B	C	
Age in years, mean (SD)	20.9 (10.6)	16.5 (8.4)	29.3 (6.3) AB	0.003
Weight in kg, median (IR)	44.0 [21.0-50.0]	46.0 [43.0 - 48.0]	35.0 [26.7 - 47.5]	0.30
Old ECG changes (%)	34.8	50.0	30.0	0.50
New ECG changes(%)	30.4	12.5	20.0	0.40
QTc (seconds)	0.419 (0.031)	0.424 (0.027)	0.416 (0.018)	0.75
Patients with QTc $\geq$ 0.50 (%)	4.3	6.2	0.0	-

New ECG changes involving the T waves were observed in two HIV-positive (20%) and two HIV-negative (12.5%) patients treated for 28 - 30 days, and in seven (30.4%) HIV-negative VL patients treated for 20 days. These rates did not differ significantly at P values of 0.05. At the end of therapy, only two (4.1 %) patients (all HIV-negative hospitalised males) had QTc interval  $\geq 0.50$  seconds. In one of these patients, the prolonged QTc was observed with normal heart rate following successful completion of a 30-day course of antimonial therapy. In the other patient, the prolonged QTc was observed on day 20 of antimonial therapy and was associated with bradycardia of 44/minute. In the latter patient, a repeat renal function tests showed normal values and splenic aspirate smear showed no amastigotes. A repeat ECG a week after cessation of antimonial therapy showed normal heart rate with bi-phasic T waves in chest leads and the patient was discharged with a follow-up appointment. Six months after therapy, the patient was in good clinical condition with normal ECG recordings.

## DISCUSSION

Various researchers have addressed the cardiac side effects of pentavalent antimonial therapy (11,13-15). The cumulative toxicity of pentavalent antimonial therapy, manifested as the cardiac side effects, is related to total daily dose and duration of therapy rather than to the magnitude of individual dose (1,13,16). In Kenya, Chulay *et al* (13) noted ECG changes in more than 50% of patients treated with sodium stibogluconate at a daily dose of 20 mg sb<sup>v</sup>/kg b.wt. for 20-30 days. These changes, however, were transient and apparently inconsequential. De-Beer *et al* (17), after treating a large number of cases in the Sudan, noted no toxic side effects of sodium stibogluconate. Moreover, the latter group reported to have safely administered antimonial therapy in six VL patient with cardiac dysfunction due to pericarditis and anaemic heart failure.

Similar studies in South America have assessed the cardiotoxicity of pentavalent antimonials in cutaneous and mucosal leishmaniasis. Navin *et al* (15), monitored the side effects of sodium stibogluconate in cutaneous leishmaniasis patients treated at a daily dose of 20 mg sb<sup>v</sup>/kg bwt for 20 days, and noted marked reduction in the amplitude of T waves in 50% and inverted T waves in 20% of patients. The longest QTc interval was 0.46 seconds and all ECG changes normalised by six weeks after completion of therapy. Similarly, Franke *et al* (14) noted T wave inversions, which were of no clinical consequence, in 10% of mucosal leishmaniasis patients treated with sodium stibogluconate at a daily dose of 20 mg sb<sup>v</sup>/kg bwt for 28 days.

In our series, patients were treated with either sodium stibogluconate or meglumine antimonate, depending on availability, at equivalent sb<sup>v</sup>/kg body weight. New ECG changes, mostly in the form of flattening or inversion of T waves, were noted in eleven (22.2%) patients. The mean QTc interval at the end of therapy was  $0.42 \pm 0.03$  seconds. Only one patient (2%) developed sinus bradycardia (44/minute) with prolonged QTc interval, which normalised a

week after cessation of therapy. Although the rates vary, our ECG findings are similar to the earlier reports by Chulay *et al* (13); Franke *et al* (14); and Navin *et al* (15). We conclude that in Ethiopian VL patients with normal renal function, pentavalent antimonial therapy at a daily dose of 20 mg sb<sup>v</sup>/kg for up to 30 days is safe and only rarely associated with clinically significant bradycardia which resolves after temporary cessation of antimonial therapy. Furthermore, in a rural clinic setting with limited diagnostic facilities, monitoring the pulse rate may help detect impending cardiotoxicity and further studies are warranted to evaluate the sensitivity and specificity of this clinical sign in monitoring antimonial therapy.

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