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Electrocardiographic changes during low-dose, short-term therapy of cutaneous leishmaniasis with the pentavalent antimonial meglumine

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Abstract

The pentavalent antimonial (Sb^{5+}) meglumine is the drug of choice for the treatment of cutaneous leishmaniasis (CL) in Brazil. Although the cardiotoxicity of high-dose, long-term Sb^{5+} therapy is well known, the use of low-dose, short-term meglumine has been considered to be safe and relatively free from significant cardiac effects. In order to investigate the cardiotoxicity of low-dose, short-term therapy with meglumine in cutaneous leishmaniasis, 62 CL patients treated with meglumine were studied. A standard ECG was obtained before and immediately after the first cycle of treatment (15 mg Sb^{5+} kg^{-1} day^{-1}). The electrocardiographic interpretation was carried out blindly by two investigators using the Minnesota Code. There were no significant differences in qualitative ECG variables before and after meglumine treatment. However, the corrected QT interval was clearly prolonged after antimonial therapy (420.0 *vs* 429.3 ms, $P<10^{-6}$). QTc augmentation exceeded 40 ms in 12 patients, 7 of whom developed marked QTc interval enlargement (500 ms) after meglumine therapy. This previously unrecognized cardiac toxicity induced by short-term, low-dose antimonial therapy has potentially important clinical implications. Since sudden death has been related to QTc prolongation over 500 ms induced by high-dose antimonial therapy, routine electrocardiographic monitoring is probably indicated even in CL patients treated with short-term, low-dose meglumine schedules. Until further studies are conducted to establish the interactions between pentavalent antimonials and other drugs, special care is recommended when using meglumine in combination with other medications, in particular with drugs that also increase the QTc interval.

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- Cutaneous leishmaniasis
- Electrocardiography
- QT interval

Cutaneous leishmaniasis (CL) is a major public health problem in Brazil, with an estimated incidence of 25 thousand cases a year (1). This disease may involve single or multiple lesions, which are relatively heterogeneous and range from benign cutaneous ulcers to serious and mutilating forms (2,3). Although CL has been classified as a zoonosis, remarkable epidemiological changes have occurred, transforming it into an important clinical and epidemiological disease in rural and urban centers.

The pentavalent antimonial (Sb^{5+}) meglumine (Glucantime®) is the drug of choice for the treatment of CL in Brazil. It is available in 5-ml bottles, with 85 mg of antimony per ml, and is administered intramuscularly or intravenously. The pharmacokinetics of antimony is best described by a three-compartment model, with a short initial distribution phase followed by biexponential elimination, primarily by the kidney. The slow terminal elimination phase may be due to the conversion of pentavalent to trivalent antimony, and this may be responsible for the toxicity observed with long-term, high-dose therapy. For the treatment of CL, the drug is administered parenterally at a dosage of 15-20 mg Sb^{5+} kg^{-1} day^{-1}, in cycles of 10 days, with equivalent intervals, until the clinical cure of the lesions (3).

The cardiotoxicity of Sb^{5+} is well known, especially in high-dose, long-term therapy (3,4). Dose-related changes are observed in the electrocardiogram (ECG), the most common being ST-T wave changes and prolonged QTc interval (4) . Sudden death has been reported in association with the use of meglumine (5,6). However, significant cardiotoxicity caused by low-dose, short-term therapy has not been well established. Up to now, its use has been considered relatively safe and free of significant cardiac effects (7-9). It has been proposed that routine electrocardiographic monitoring would not be necessary for patients receiving 10 mg Sb^{5+} kg^{-1} day^{-1} for up to 30 days or 20 mg Sb^{5+} kg^{-1} day^{-1} for up to 20 days (6). The present study was conducted to further investigate the cardiotoxicity of low-dose, short-term therapy with Sb^{5+} and to ultimately aid in the elaboration of a definite electrocardiographic monitoring conduct in patients receiving meglumine therapy.

Sixty-two CL patients (age 19-74) were interviewed and examined by the same physician at a leishmaniasis outpatient clinic, René Rachou Research Center, from 1991 to 1994. CL was diagnosed by direct observation of the parasite in Giemsa-stained smears, indirect immunofluorescence for IgG against the promastigote form of the parasite, and/or the Montenegro skin test. Subjects with typical CL were treated with meglumine at the dosage of 15 mg Sb^{5+} kg^{-1} day^{-1} using at least two 10-day cycles. Inclusion in the study occurred only after written informed consent was obtained from the patient, parent or guardian. Treatment was offered to all patients independent of their participation in the study. The study was approved by the Ethics Committee of the Rene Rachou Research Center.

A standard 12-lead ECG was obtained for 62 patients before and immediately after the first cycle of treatment. All electrocardiograms were obtained with a one-channel analogic FUNBEC 5 equipment. The electrocardiographic interpretation was carried out blindly by two authors in 1995 using the Minnesota Code. Additional standardized measurements were made to determine the duration of the P wave, QRS complex, RR interval, PR interval and Bazett's corrected QT interval. The QT measurements were performed in lead II using a sinus rhythm beat, avoiding atrial and ventricular premature beats. All patients were in sinus rhythm; atrial fibrillation, advanced AV blocks or pacemaker rhythm were not found. The ECG analyses were conducted at the Hospital das Clínicas of the Federal University of Minas Gerais.

Qualitative variables were analyzed by

matched chi-square analysis. Quantitative measurements were also paired; normally distributed data were analyzed by the Student *t*-test and non-normal variables by the non-parametric Wilcoxon test. Data are reported as means ± SD or medians and ranges. All analyses were two tailed. P values of less than 0.05 were considered to indicate statistical significance.

Electrocardiographic variables are presented in Table 1. There were no significant differences in qualitative ECG variables before and after meglumine treatment, including pathologic Q or T waves, ST depression or elevation, atrial or ventricular enlargement, intraventricular and atrioventricular conduction disturbances, and arrhythmias. The duration of the QRS complex, the PR interval and the heart rate were also not significantly different between the two groups. P wave duration was slightly reduced after meglumine treatment (102.4 *vs* 94.8 ms, P = 0.02). Moreover, the corrected QT interval was clearly prolonged after antimonial therapy (420.0 *vs* 429.3 ms, $P<10^{-6}$; Figure 1). QTc prolongation exceeded 40 ms in 12 patients; seven of these patients developed marked QTc interval prolongation (500 ms) after meglumine therapy. None of these patients were using other drugs that cause QTc prolongation.

In the present study, no major ECG alteration was caused by antimonial therapy. The slight reduction of P wave duration, although statistically significant, is of doubtful clinical meaning. In agreement with previous studies, electrocardiographic alterations induced by low-dose meglumine were mainly related to alterations in ventricular repolarization (6,9-12). Nonetheless, in all of these previous studies, patients were treated with doses larger than 20 mg Sb^{5+} kg^{-1} day^{-1}, for 20 or more days. Chulay and associates (6) reported that only four of 65 treated patients developed marked QTc prolongation (>500 ms): two of them had been receiving 60 mg Sb^{5+} kg^{-1} day^{-1} and the other two had been

Table 1 - Electrocardiographic features before and after 10-day low-dose meglumine therapy in 62 cutaneous leishmaniasis patients.

The patients received 15 mg meglumine kg^{-1} day^{-1}. Data are reported as means (SD) or medians (ranges).

Variables	Before meglumine	After meglumine	P
Heart rate (bpm)	66.5 (14.2)	66.8 (13.8)	0.87
P wave (ms)	102.4 (21.5)	94.8 (22.1)	0.02
PR interval (ms)	162.9 (30.6)	166.7 (30.1)	0.18
QRS complex (ms)	81.6 (24.9)	81.1 (22.1)	0.77
QTc interval (ms)	420.0 (334.0-558.6)	429.3 (377.3-611.3)	0.00
Pathologic Q waves	3/62	4/62	1.00
Pathologic ST depression	3/62	1/62	0.47
Pathologic ST elevation	3/62	2/62	0.64
Pathologic T waves	5/62	6/62	1.00
Atrial/ventricular enlargement	4/62	2/62	0.47
AV block (1st degree)	8/62	9/62	1.00
Intraventricular block	15/62	14/62	0.67
Ventricular arrhythmias	0/62	0/62	1.00
Supraventricular arrhythmias	1/62	4/62	0.24

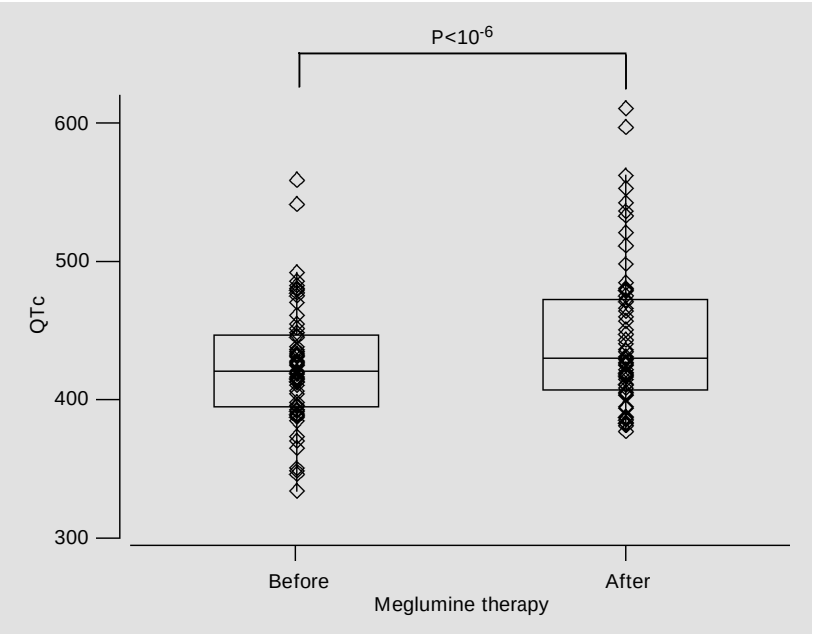

Figure 1 - Corrected QT interval (in milliseconds) before and after the first 10-day cycle of meglumine therapy in 62 cutaneous leishmaniasis patients. The Wilcoxon statistical test was used.

receiving 20 Sb^{5+} kg^{-1} day^{-1} for more than 30 days. In another study, Navin et al. (12) did not find QTc prolongation exceeding 460 ms in patients treated with 20 mg Sb^{5+} kg^{-1} day^{-1} for 20 days. Within this context, short-term, low-dose antimonial therapy has been considered to be safe (12).

At variance with these data, we found that the QTc interval was significantly prolonged by a short ten-day course of 15 mg Sb^{5+} kg^{-1} day^{-1}. QTc prolongation of more than 40 ms occurred in a relatively high percentage of treated patients (12/62, 19%) and seven patients (11%) developed marked QTc interval prolongation (500 ms) after meglumine therapy. The reasons for this difference are not clear, but indicate a previously unrecognized cardiac toxicity induced by short-term, low-dose antimonial therapy.

The present study has some limitations, mainly due to the unknown prevalence of concomitant cardiovascular diseases, especially those due to the possible presence of Chagas' disease in the study population. In a study comparing different Chagas' disease serological reaction in CL, conducted at the same leishmaniasis outpatient clinic, Passos et al. (13) found that 8.4 to 46.4% of CL patients also have positive serology for Chagas' disease. However, many of these individuals have false-positive conventional serological tests for Chagas' disease due to cross-reactions between antibodies for *Trypanosoma cruzi* and *Leishmania sp*. Moreover, Antezana et al. (11) did not find a significant interaction of Chagas' disease and antimonial therapy in leishmaniasis patients.

The present study did not include a control group and each patient served as his own control. Furthermore, the authors did not study the evolutionary changes in the ECG, so that the possible reversibility of the QT prolongation could not be determined. Since the two serial electrocardiograms were done less than 20 days apart, there is only a remote possibility that other factors influenced the QTc interval in these patients. The statistical analyses were conducted in a paired way, also reducing the interference of the interpatient variation of QTc duration. Although we did not calculate agreement between the two observers, the ECG analyzers were blind to patient identification and the therapy status, avoiding bias related to the observer.

Low-dose meglumine has been widely used in the treatment of CL in Brazil in the last decades, although Brazilian studies about the cardiotoxicity of pentavalent antimonial drugs are scarce (5,10). Thus, our findings may have potentially relevant medical implications. Since sudden death has been related to QTc prolongation of more than 500 ms induced by antimonial therapy (6), routine electrocardiographic monitoring is probably indicated even in CL patients treated with short-term, low-dose meglumine schedules. Moreover, there are many other drugs that prolong the QTc interval, including quinidine, procainamide, disopyramide, sotalol, amiodarone, probucol, chloral hydrate, tricyclic antidepressants, anthracyclines, trimethoprim/sulfamethoxazole, tetracycline, erythromycin, pentamidine, ketoconazole, and the antihistamine terfenadine (14). Some of these drugs had been considered selective and safe, although subsequently it was shown that, under certain clinical circumstances, they may induce pro-arrhythmia, "torsade de pointes" and ventricular fibrillation. Indeed, when terfenadine was approved by the FDA in the United States in 1985, it was considered free of cardiotoxicity. Afterwards, many cases of malignant ventricular arrhythmias and "torsade de pointes" were reported, mainly involving patients with hepatic insufficiency or receiving concomitant medications such as erythromycin or ketoconazole (15). Since interactions between pentavalent antimonials and other drugs are largely unknown, special care is recommended when using meglumine in combination with other medications, in particular with drugs that also increase the QTc interval. Furthermore, se-

rial QTc measurements are recommended as a valuable tool for the early detection of the unwanted cardiac effects of these drugs (14).

In conclusion, low-dose, short-term meglumine treatment of CL was significantly related to prolongation of the QTc interval, with potentially important clinical implications.

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