

Electrocardiographic alterations during treatment of mucocutaneous leishmaniasis with meglumine antimoniate and allopurinol

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Abstract

The electrocardiographic (ECG) changes in Bolivian patients with mucocutaneous leishmaniasis, treated with meglumine antimoniate and allopurinol, were evaluated. Electric changes due to the antimonial compound appeared in 45% of the patients, and consisted of repolarization alteration, principally affecting the T wave and the S-T segment. The changes disappeared within 2 months following the end of the antimonial treatment. In patients with associated Chagas disease and leishmaniasis, antimonial therapy did not aggravate the ECG changes characteristic of Chagasic cardiopathy.

Introduction

Pentavalent antimonial compounds still represent the first line drugs for treatment of all forms of leishmaniasis. Their cardiotoxicity is commonly acknowledged and should require electrocardiographic follow-up of treated patients. Moreover, the co-existence of Chagas disease with leishmaniasis in several South American endemic areas needs careful attention in the treatment of infected patients.

The electrical changes due to pentavalent antimonials are variable, and dose- and time-dependent (LACERDA *et al.*, 1965; CHULAY *et al.*, 1985). The electrical alterations due to chronic Chagasic cardiopathy are well documented (ROSEBAUM, 1964; ANTEZANA, 1984). However, the possible interaction between Chagas heart disease and antimonial side effects has not yet been investigated.

The present study evaluated the electrocardiographic changes in patients with mucocutaneous leishmaniasis, treated with meglumine antimoniate (Glucantime[®]) alone or in association with allopurinol. Several patients were also infected with Chagas disease.

Patients and Methods

The study was conducted between December 1988 and May 1990.

Forty patients infected with active mucous lesions of mucocutaneous leishmaniasis, due to *Leishmania braziliensis braziliensis*, were included in a clinical trial conducted under the auspices of the World Health Organization.

The sample consisted of 37 males and 3 females, aged 15-60 years, 39 of whom were native to Bolivia and one to Peru. Twenty-two patients received intramuscular meglumine antimoniate alone (20 mg Sb/kg/d for 30 d) and 18 received meglumine antimoniate (same dose) plus oral allopurinol (20 mg/kg/d for 30 d).

Before, during and after treatment, all patients were submitted to a clinical and otorhinolaryngological examination, thoracic radiology, electrocardiography, parasitological examination, biopsy, serology of leishmaniasis and Chagas disease, and haematological, hepatic and renal function tests.

The patients were followed up during one year after the end of treatment.

The electrocardiographic examinations were carried out by generally accepted procedures using Hewlett-Packard, Mingograph 34 and Hellige single channel EKG recorders.

The electrocardiographic interpretation was carried out following the international standards of the Minnesota code (ROSE & BLACKBURN, 1969). The corrected electric systole QT (QTc) was measured following the formula of BAZET (1920) as modified by TONAM & SZILAGYI (1947). The diagnosis of left anterior hemiblock was based on the criteria of ROSEBAUM *et al.* (1967). Statistical methods included one-way analysis of variance and χ^2 analysis of variables. Cardiac frequency and QTc

were statistically analysed by linear regression using the IBM Ecosoft[®] program (1984).

Results

Due to the high prevalence of positive serology for *Trypanosoma cruzi* (27 of 40 patients), the patients were divided into 3 groups. Group 1 consisted of 13 (32.5%) with negative Chagasic serology. Group 2 included 19 patients (47.5%) with positive Chagasic serology (by both indirect fluorescent antibody tests and enzyme-linked immunosorbent assays). In groups 1 and 2, the patients had no evidence of any electrocardiographic signs compatible with Chagasic cardiopathy. Group 3 included 8 patients (20%) who presented positive Chagasic serology and electrocardiographic changes of the Chagasic group II type as classified by the World Health Organization (OMS, 1971). None of these patients showed clinical signs of altered physical conditions or cardiomegaly (cardiothoracic index=0.49). In one patient it was impossible to differentiate accurately between vagotonomism and sub-endocardic ischaemia.

In group 1 (Table), a slight, non-significant decrease ($P<0.006$) of cardiac frequency was observed. No change was observed in the morphology of the QRS complex; specifically, deflection time was not increased and no significant change was observed in QTc ($P<0.64$). The most important alteration seen in this group (in 8 of 13 patients) concerned the T wave and the S-T segment, which roughly correspond to the 5-2 and 12-2 classes of the Minnesota code (ROSE & BLACKBURN, 1969) (Figure). None of the patients in this group presented precordial pain (neither typical nor atypical) and their functional capacity was unchanged (class I, following FRIEDBERG, 1971) by the end of the treatment period.

As in group 1, the second group of patients showed similar non-significant changes in cardiac frequency ($P<0.2$) and QTc ($P<0.2$); their QRS morphology was slightly altered.

Alterations of ventricular repolarization were seen in 52% of the subjects, including sub-epicardic ischaemia in 3 patients and late recuperation of repolarization in another 3 patients. These changes are not known to occur during Chagas disease.

Five cases of left anterior hemiblock of the His branch (BCRDHH) were observed in group 3. This conduction abnormality is highly suggestive of class II Chagas disease (OMS, 1971). Patients of this group did not present associated alterations related to the use of pentavalent antimonial drugs.

During antimonial treatment, the electrocardiographic patterns typical of Chagasic cardiopathy were not modified; in particular, conduction abnormalities, the QRS complex and QTc remained unchanged, and premature ectopic beats did not appear.

Discussion

The therapeutic protocol used in the present study

Table. Summary of the characteristics distinguishing the groups of patients and the electrocardiographic (ECG) alterations observed

Group	No. of patients	<i>T. cruzi</i> serology	ECG alterations	
			Before treatment	During treatment
1	13	Negative	None	Diffuse repolarization alterations Negative T wave S-T segment elevation Late recuperation of repolarization
2	19	Positive	None	
3	8	Positive	Left anterior hemiblock and right bundle branch block ^a	

^aThe association of left anterior hemiblock and right bundle branch block is remarkably characteristic of Chagasic cardiopathy in endemic areas.

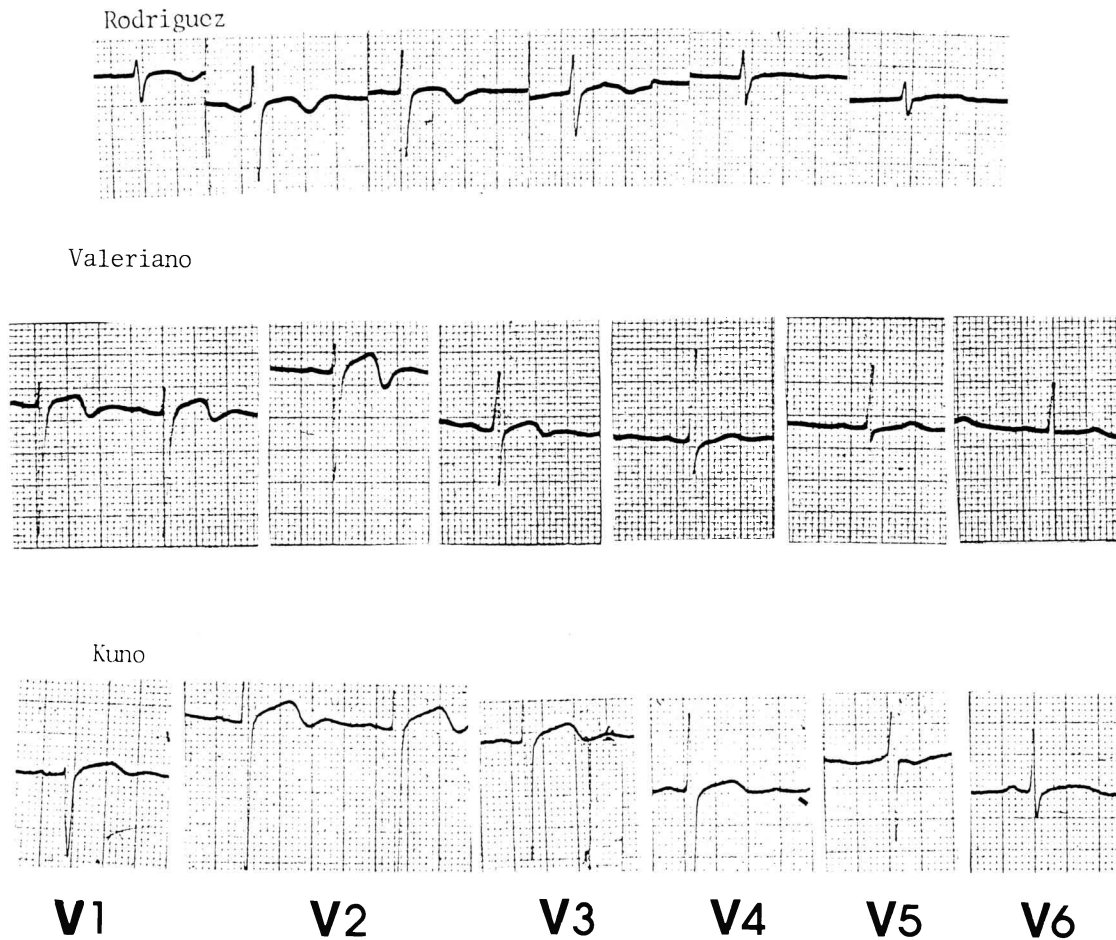


Figure. Electrocardiograms of three patients with mucocutaneous leishmaniasis, illustrating some of the atypical alterations of the T wave and of the S-T segment observed in precordial leads V1 to V6, during antimonial treatment. In all cases, the electrocardiogram before treatment commenced was normal.

followed the World Health Organization's requirements, especially concerning antimonial dosage, and was accompanied by regular electrocardiographic controls.

We did not observe any case of sudden death, a complication occasionally reported as a result of Chagasic cardiopathy (LOPES, 1981; PRATA *et al.*, 1986) and during pentavalent antimonial therapy of leishmaniasis (CHULAY *et al.*, 1985; SAMPAIO *et al.*, 1988).

The electrical changes observed in groups 1 and 2 of our patients principally affected the T wave and the S-T segment. They occurred during antimonial therapy using a generally accepted schedule and disappeared within 2 months following the end of antimonial treatment. The changes were totally independent of the absence or presence of allopurinol in the therapeutic schedule and were not related to coronary heart disease. These changes

were undoubtedly related to a cardiotoxic effect of antimonial compounds, similar to those previously described during treatment with trivalent (MAINZER & KRAUSE, 1940; HONEY, 1960) and pentavalent antimony (CHULAY *et al.*, 1985).

Contrary to the observation reported by MULLER *et al.* (1982), the present study indicates that electrocardiographic changes do occur during treatment with meglumine antimoniate, as previously described during treatment with sodium stibogluconate (CHULAY *et al.*, 1985).

In addition, our observations demonstrate that antimonial therapy does not result in additional pathological effects to those which are already present in chronic Chagasic cardiopathy, an important indication for countries where leishmaniasis and Chagas disease co-exist.

The general recuperation observed in our cases after

the treatment was completed favours a metabolic origin of the electrical alterations, and this lead us to propose the use of polarising medication, including potassium, magnesium and zinc, during treatment with pentavalent antimonial compounds. This precaution would not dispense, however, with the need for regular electrocardiographic follow-up during antimonial therapy.

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