The use of steroids to prevent cutaneous reactions to benznidazole in patients with Chagas disease

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The treatment of Chagas disease is limited by the frequent cutaneous side effects of benznidazole. We tested the use of steroids plus escalating doses of benznidazole to prevent this complication in 17 adult patients with chronic *Trypanosoma cruzi* infection and found extremely good tolerance. A randomized trial is warranted.

Keywords: Chagas disease, Benznidazole, Steroids, *Trypanosoma cruzi*

To the Editor

Chagas disease has become a frequent emerging infection in Europe, particularly in Spain where a large number of migrants from endemic Central and South American countries have settled during the last decade.¹ Benznidazole is the preferred drug for the treatment of acute *Trypanosoma cruzi* infections and is also widely used to treat chronic infections.¹ Adverse reactions to benznidazole are common (31–56%).^{2–7} Dermatological problems are the most frequent side effects, occurring in approximately 18–50% of patients and leading to discontinuation of the drug in 5.6–31% of cases.^{2–8} In a recent systematic review including a meta-analysis, up to 18% of patients discontinued treatment due to toxicity.⁸

Dermatological side effects including allergic dermatitis can occur in a variety of forms including urticarial, petechial or palmar-plantar rashes, itching without rash, and Steven-Johnson syndrome.⁴ These problems appear approximately 10 days after the start of treatment. The cause is believed to be an idiosyncratic reaction⁶ and a T-cell mediated mechanism, involving CD4+ and CD8+ lymphocytes, is thought to be the pathophysiological basis of delayed adverse reactions.⁹ The drug should be discontinued in cases of severe allergic dermatitis, exfoliative forms, or if a reaction is associated with high fever.¹ One of the main

limitations in treating Chagas disease with benznidazole or nifurtimox in non-endemic countries is the lack of experience in managing adverse reactions to these specific drugs.⁴ There is also a lack of experience in strategies to prevent these reactions.

To the best of our knowledge, there are no data in the literature describing the use of steroids concomitantly with benznidazole to prevent toxic cutaneous reactions in the treatment of Chagas disease. Steroids are currently used as premedication to prevent severe allergic and hypersensitive reactions, particularly those classified as non-immediate reactions by the European Network for Drug Allergy, working under the aegis of the European Academy of Allergy and Clinical Immunology,¹⁰ to other drugs, such as cancer therapy,¹¹ antimicrobials such as amphotericin B,¹² or to contrast materials.¹³ They are also used in the treatment of parasitic diseases such as neurocysticercosis to prevent acute inflammation due to massive destruction of parasites when albendazole or praziquantel is administered.¹⁴ The biochemical basis for its use is to target the inflammatory response of the host and its efficacy has been clearly demonstrated in clinical trials, particularly those designed for the prevention of hypersensitive reactions to contrast materials.¹³

The purpose of this study is to present our experience of using steroids to prevent drug side effects, especially rash, in a cohort of patients with chronic Chagas disease diagnosed at the Division of

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From January 2009 until December 2011, a total of 39 patients with chronic Chagas disease received benznidazole. The diagnosis of *T. cruzi* infection was made following international recommendations using two serological tests with different antigens, an indirect immunofluorescence test and an ELISA test, according to the manufacturer's instructions. The mean $\pm$ SD age of patients in the study was 29.9 ± 12.2 years. Most were female (77.3%; female: male ratio = 3.3:1). The most frequent country of origin was Bolivia (34 patients) followed by Paraguay (four patients) and one was from Ecuador (Table 1). To study the side effects of benznidazole, patients were monitored at 15, 30, and 60 days of treatment with clinical follow-up, hematological tests, and biochemical tests (including hepatic and renal function).

The first 22 patients were treated with a total dose of 5 mg/kg/day of benznidazole in three divided doses for 60 days. One patient of this initial group developed a severe hypersensitive reaction with extensive generalized rash and fever (Fig. 1). The drug was discontinued and after scaling of the skin the patient improved with complete recovery after a few weeks. No other severe side effects were recorded in this initial group of patients.

In order to avoid similar severe skin reactions, we decided to change our treatment regimen and subsequently gave escalating doses of benznidazole for the first 9 days together with reducing doses of

oral methylprednisolone for the same period. Methylprednisolone in conjunction with slowly increasing dose of benznidazole is likely to reduce drug toxicity and any allergic reaction to antigen release, whilst maintaining treatment efficacy. Oral informed consent was obtained from all patients.

Seventeen patients were treated with benznidazole in escalating doses, starting with 100 mg daily (one tablet/day) for 3 days, then 100 mg twice daily (two tablets/day) for 3 days, then 100 mg three times daily (three tablets/day). After the first 9 days' treatment, patients were given the full dose of 5 mg/kg/day, or more according to weight, in three divided doses for 60 days. These patients were also given methylprednisolone for the first 9 days of treatment, initially at a dose of 16 mg once daily for 3 days, then 8 mg once daily for 3 days, and then 4 mg once daily for 3 days. Tolerance to the new scheme of treatment was extremely good in this second group of patients. No severe side effects (dermatological, gastrointestinal, biochemical, or neurological) or even any minor skin reactions were recorded. None of the patients in this group discontinued treatment.

The frequency of side effects reported in the literature is variable,²⁻⁸ and is less common in studies performed in endemic countries^{6,7} than in non-endemic countries.³⁻⁵ Side effects were less common in our study than in previous studies.²⁻⁷ The application of specific questionnaires to detect side effects at follow-up visits would probably have yielded higher rates of mild adverse reactions but not of severe ones.

The scheme of escalating benznidazole doses plus steroids was well tolerated and could open the door in terms of reducing severe side effects, especially dermatological ones. Recently some authors in non-endemic countries have introduced escalating doses of benznidazole but using schemes different from ours and without steroids.³ Other authors have used escalating doses of benznidazole plus dextchlorpheniramine, with no dermatological side effects.¹⁵

Several aspects regarding the possible deleterious impact of a short course of steroids on the efficacy of benznidazole are unknown, particularly whether there is an effect on the negativization of polymerase-chain reaction (PCR) assays or serological tests for *T. cruzi*, or on parasite dynamics in patients with immunosuppression due to long term steroid use.

A negative PCR result after treatment is not a guarantee of parasitological cure as parasitemia may fluctuate during the chronic phase of infection.¹⁶ Taking this into account, results in our study were negative in all six patients who had PCR done 6 months after completing the treatment. This surrogate efficacy test should be included in the outcome of future trials if steroids are included.

Table 1 Clinical characteristics of patients with Chagas disease who received benznidazole with and without steroids

	First group without steroids, N = 22	Second group with steroids, N = 17
Mean age (years)	33.25	37.46
Male gender (n/%)	3/13.6%	2/11.7%
Country of origin		
- Bolivia	21	16
- Paraguay	0	1
- Ecuador	1	0
Disease stage		
- Acute	0	0
- Indeterminate	21	17
- Chronic	1	0
Organic lesions		
- Cardiac	1	0
- Intestinal	0	0
Positive serology (%)	100	100
Positive blood <i>T. cruzi</i> PCR (%)	13.6	47
Severe adverse events (n)		
- Cutaneous	1	0
- Gastrointestinal	0	0
- Neurological	0	0
Treatment discontinuation (n)	1	0

Figure 1 (A) Extensive rash after benznidazole treatment in a patient with Chagas disease. (B) Magnified image of the skin lesions.

Currently the optimal treatment for Chagas disease^{1,6,8} is not well established. Until new, better drugs, such as posaconazole¹⁷ or combined therapies become available, we should try to improve the tolerability of benznidazole. Escalating benznidazole doses with steroids could be an adequate alternative. Due to the small number of patients in our study, the absence of a severe skin reaction in the group receiving steroids could have been a chance effect. Our results do not provide statistical proof of benefit. A randomized trial comparing different treatment strategies using benznidazole and studying the biochemical and immunological data of patients with and without cutaneous reactions is clearly needed.

Conflict of Interest

The authors declare no conflict of interest.

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