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Side effects of benznidazole treatment in a cohort of patients with Chagas disease in non-endemic country

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ABSTRACT

Chagas disease is a disease endemic in Latin America, caused by the parasite *Trypanosoma cruzi*. Benznidazole is the most commonly used drug for the etiological treatment of the disease although its effectiveness varies according to the phase of the same and toxic side effects are frequent. This prospective study describes the side effects of benznidazole treatment of a cohort of 373 chronic patients. Of these 40.2% presented adverse reactions. The most frequent side effect were dermatological reactions 32.4% (121 of 373) followed by digestive intolerance 9.1% (34 of 373). Surprisingly, three cases of migratory arthritis were observed. Patients treated with benznidazole must be followed up so that the long term incidence of side effects can be studied.

Efectos secundarios del tratamiento con benznidazol en una cohorte de pacientes con enfermedad de Chagas en un país no endémico

RESUMEN

La enfermedad de Chagas es endémica en América Latina y está causada por el parásito *T. cruzi*. El benznidazol es la droga usada con mayor frecuencia para el tratamiento etiológico de la enfermedad. Su eficacia varía según la fase de la misma y los efectos secundarios son frecuentes. Este es un estudio prospectivo que describe los efectos secundarios del tratamiento con benznidazol en una cohorte de 373 pacientes crónicos. De estos, el 40,2% presentó reacciones adversas siendo las de tipo dermatológico las más frecuentes (32,4% (121 de 373)) seguidas de la intolerancia digestiva (9,1% (34 de 373)). Sorprendentemente, se observaron tres casos de artritis migratoria. Los pacientes tratados con benznidazol deben ser seguidos para estudiar y tratar los efectos secundarios a largo plazo.

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INTRODUCTION

Chagas disease, or American trypanosomiasis, is a parasitic zoonosis endemic to 21 countries of Latin America. Produced by *T. cruzi*, it affects eight million people worldwide[1]. Benznidazole is commonly used to treat Chagas disease, and the results obtained vary according to the phase of infection, the period of treatment and the dose[2,3,4]. The side effects associated with benznidazole represent the main disadvantage, forcing treatment to be suspended in an average of 10% of patients, frequently due to cutaneous reactions[5]. The most important adverse reactions observed with benznidazole are dermatitis due hypersensitivity, digestive intolerance, polyneuritis, bone marrow depression and toxic hepatitis[6]. Nevertheless, the incidence of adverse reactions has been insufficiently reported, making it difficult to interpret the safety profile of benznidazole.

This article describes the most commonly observed side effects in 373 cases of Chagas disease treated at the Unit of Tropical Medicine (UTM) of the Virgen de la Arrixaca Hospital in Murcia (Spain), from January 2007 to December 2009. A better understanding of the side effects of the treatment of Chagas in non-endemic countries is essential since health services are not accustomed to managing it.

MATERIALS AND METHODS

Subjects, data collection and benznidazole treatment

This prospective study describes the side effects of benznidazole treatment in chagasic patients. A cohort of 373 chronic patients treated at the UTM were examined between January 2007 and December 2009. All the patients were from Bolivia. The mean (± SD) age was 34.7 ± 10.6 SD years and the median age was 34. According to the age, patients were stratified as

Table 1 **Side effects from benznidazole treatment.**

Side effects/ number of treated patients	n/Total	%
Side effects	150/373	40.2
Side effects severity/number of patients with side effects		
Mild intensity	99/150	66
Moderate intensity	39/150	26
Severe intensity	12/150	8
Adverse reactions recorder, separately or in association	**n/Total**	**%**
Dermatitis from hypersensitivity	121/373	32.4
Digestive intolerance	34/373	9.1
Neurological		
Polyneuritis	30/373	8
Headache	9/373	2.4
Vertigo	3/373	0.8
Insomnia	2/373	0.5
Astenia	1/373	0.3
Depression of bone marrow (neutropenia, plaquetopenia)	4/373	1.1
Migratory arthritis	3/373	0.8
Fever	4/373	1.1
Renal failure	1/373	0.3

follows: 18 patients were included in the young group (2-19 years), 243 patients were classified as adults (20-39 years) and 112 as seniors (≥ 40 years).

Diagnosis of *T. cruzi* infection and classification of the clinical groups was made as described in a previous publication[7]. A total of 224 patients underwent a complete clinical study: 124 (55.4%) were asymptomatic and 100 (44.6%) symptomatic. Of those, 46 (20.5%) were only cardiac, 21 (9.4%) had both cardiac and digestive disorders and 33 (14.7%) had only digestive disorders.

Patients were treated orally with benznidazole, 5-7 mg/kg of body weight per day in pediatrics and 100 mg three times a day in adults, for 60 days[8]. The daily dose was increased gradually over a period of three weeks (100 mg/day during the first week, 200 mg/day the second week and 300 mg/day thereafter). The accumulative dose did not exceed 18 g of benznidazole to prevent some side effects such as polyneuritis and bone marrow depression[9]. To avoid interruption of treatment others measures were taken into account. The medication was taken after meals and patients avoided fatty foods and alcoholic drinks. Information about the possible undesirable side effects must be clearly provided.

To study the side effects of benznidazole, patients were monitored 30, 90, 150, 240, and 420 days post-treatment (haemogram and biochemical analysis). During the follow-up period, patients had the possibility of daily consultation if needed and were instructed as to how they could manage any side effects. Patients were asked about previously well defined adverse reactions such us cutaneous hypersensitivity, gastrointestinal intolerance such as nausea, abdominal pain, vomiting and diarrhoea, neurological such as polyneuritis (inflammation of nerves, paresthesias in hand and foot (limb numbness, limb pain and limb tingling), headache, vertigo, insomnia and asthenia, articular involvement and fever. Side effects severity of benznidazol were classified into three categories: mild when symptoms did not interfere with the patient's daily activity or did not require treatment, moderate when clinical manifestations necessitated treatment and severe when they entailed vital risk or produced sequels.

Statistical analysis

The chi-squared test and t-student test were used to compare categorical and continuous variables. Relationships were considered significant if $p<0.05$. All statistic tests were performed with SPSS 15.0

Ethical considerations

The study was reviewed and approved by the Ethical Committee of the Hospital Virgen de la Arrixaca. Written informed consent was obtained from all patients enrolled in the study.

RESULTS

Of the 373 patients that have received treatment with benznidazole, 150 (40.2%) presented adverse reactions, of whom 43 (43 of 373, 11.5%) showed more than one reaction and some required symptomatic treatment. Side effects were less common in young than in adult and senior patients (33.3% in young, 39.5% in adults, 48% in seniors) although the difference it was not statistically significant ($p= 0.6940$). Moreover, no differences in side effect frequency were observed between chronic patients with cardiac (39.8%; $p= 0.4618$) or digestive (53.6%; $p= 0.2617$) disorders. The side effects of benznidazole treatment of the patients are shown in table 1.

Regarding the severity, mildly intense side effects occurred in the most of the patients who suffered adverse reactions (99 of 150 (66%)), followed by moderate adverse effects (39 of 150 (26%)), while severe side effects were found in 12 patients (8%). Of the patients with severe side effects, two patients needed hospital admission, one of them because of a pharmacological rash with eosinophilia accompanied by generalized systemic symptoms. The second patient required hospitalization because of a severe episode of migratory arthritis. Two other patients also presented migratory arthritis. In one of them, the reaction began at the end of the first month of treatment and continued producing symptoms until one month after treatment stopped. The other patient presented clinical

manifestations of migratory arthritis in the third week of treatment, and had to abandon the therapy. This patient's symptoms persisted for 2 months and required emergency consultation on two occasions. In the subjects with polyneuritis one patient presented paresthesias 2 years after treatment. She was examined by the neurologist without finding any other cause to justify her symptoms. In the one case of renal failure, the patient presented an alteration in the normal level of alanine amino-transferase and creatinine. As regards severe skin reactions, one patient showed a skin reaction with generalized pustules and bleeding lesions. In two young women, cutaneous reactions persisted for several months after stopping the treatment.

A total of 21 patients (21 of 373 (5.6%)) had to suspend the treatment due to the side effects and of these, 12 did so following a severe adverse reaction. All of the patients who had to discontinue the treatment presented dermatitis due to hypersensitivity separately or in association with other side effect (p= 0.0001).

DISCUSSION

Antitrypanosomal treatment is recommended for acute or congenital cases, and for all children with infection. Although the effectiveness of drugs in eradicating *T. cruzi* in chronic cases is not clear, treatment with benznidazol has been suggested due to the evidence of its beneficial effect during this phase of the disease[5].

Of the drugs with proven efficacy against Chagas disease, benznidazole has the best safety record and is better tolerated than most, making it the first choice for treatment[5,6] The incidence and tolerance of side effects seems to be related with the dose and the age of the patient. In our study, even though side effects were less common in young than in adults and senior patients, significant differences were not detected between the frequency of adverse reaction and age. In other reports, the better tolerance to benznidazole of this age group has been attributed to the low enzymatic activity of nitroreduction and generation of the free radicals in children, both of which are related with the most important side effect of benznidazole[9].

During treatment, the accumulative dose did not exceed 18 g of medication and the percentage of patients with side effect was not higher than that previously described (between 4 and 50% of the treated patients). Moreover the severity of side effects among most of the patients who suffered adverse reaction was mild and only 5.6% of the patients had to suspend the treatment due to the side effects. Polyneuritis was observed in 8% of patients in contrast with the result previously reported[6]. Nevertheless, Carpintero et al.[10] described paresthesias in 28% of patients treated with 5 mg/kg/day for 30 days. On the other hand, only 1.1% of patients presented bone marrow depression, and as in previous studies, it was an infrequent toxic side effect.

Renal failure is not a common side effect with benznidazole. However, any toxic effects can be assessed through renal function tests such us alanine amino-transferase and creatinine, which should be measured after the end of treatment[11]. We observed only one patient with renal failure who showed an alteration in the normal levels of these renal parameters.

The most frequent side effect of benznidazole treatment is dermatitis due to hypersensitivity although the extent varies[9]. This has been described as the most relevant adverse reaction to the drug because it is frequent and it makes treatment difficult. In our practice, 32.4% of the treated patients presented this side effect and all of the 21 patients who had to interrupt the treatment, presented dermatitis due to hypersensitivity separately or in association with another adverse reaction.

Digestive intolerance is another frequent adverse reaction to benznidazole. In our study, in accordance with the results of others authors[6], digestive intolerance was the second most common side effect presented in our patients.

Migratory arthritis was the most interesting side effect of benznidazole treatment observed in our patients. Articular involvement have been described previously[2,12], nevertheless, to the best of our knowledge, this is the first study to describe migratory arthritis as a side effect to benznidazole.

Lymphomas have been reported in experimental animals treated with benznidazole although there is no clinical evidence that benznidazole therapy is a risk factor for lymphoma in humans[6,9]. Our group of patients treated for Chagas disease is currently being followed up to study the long term incidence of side of benznidazole.

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TRANSPARENCY DECLARATIONS

None to declare

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