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Safety of benznidazole use in the treatment of chronic Chagas' disease

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Objectives: To assess the safety of benznidazole use in adult patients with chronic Chagas' disease.

Methods: The Naranjo algorithm was applied to classify the causality of adverse drug reactions (ADRs).

Results: In total, 190 patients were treated with benznidazole over a period of 4–180 days (mean 58.90 ± 36.54 days) with a dose of 50–500 mg/day (221.33 ± 57.16 mg/day). Of the 190 patients treated, 93 had ADRs and 59 of these interrupted treatment. There was a higher incidence of ADRs among female and young adult patients. There was a higher incidence of ADRs during the first 30 days of treatment. Interruption of treatment was more frequent in women. Among the patients who interrupted treatment, 39 had mild ADRs, 19 had moderate ADRs and 1 had a severe ADR. There were no interruptions in treatment for 97 patients without ADRs. The survival curves indicated that the time until interruption of treatment in patients with moderate and severe ADRs was lower than in patients with mild or no ADRs. The most frequent disorders were in the skin (26.3%), gastrointestinal system (9.5%) and nervous system (5.3%).

Conclusions: The Naranjo algorithm was a useful tool to reduce the underreporting of ADRs. Events were common, but were associated with low morbidity and were reversible upon discontinuation of drug treatment. Moreover, there were no fatal events; therefore, benznidazole treatment was considered safe.

Keywords: *Trypanosoma cruzi*, adverse drug reactions, treatment interruption, Naranjo algorithm

Introduction

Chagas' disease is caused by *Trypanosoma cruzi*. In 1993, the World Bank considered Chagas' disease to be the parasitic disease with the greatest socio-economic impact in South America.[1] There are an estimated 7.5 million people infected in Latin America, with 28 million people at risk of contracting the disease in approximately 15 countries.[2] In Brazil, transmission by vector and blood transfusion has been interrupted; however, a large number of individuals remain infected. Due to the intense migration of individuals from endemic areas in Latin America to North America and Europe, Chagas' disease is now a global disease and represents a critical public health problem in several countries in the northern hemisphere.[3]

An individual who goes untreated in the acute phase will progress to the chronic phase. In an endemic area, 20%–30% of these patients progress to chronic Chagas' cardiomyopathy, a clinical form with higher morbidity and mortality, whereas 15%–20% progress to the digestive form. The remaining patients develop an indeterminate form of the disease.[4]

Only two drugs are available to treat Chagas' disease: nifurtimox and benznidazole (developed in the 1960s and 1970s, respectively).[5] These drugs work against the bloodstream forms of *T. cruzi* and are more effective in the acute phase of the illness. They are recommended for all cases of acute, congenital, reactivated and chronic Chagas' disease in children under 12 years of age.[6] Despite the controversy over the efficacy of treatment for adult patients in the chronic phase, when the parasite is primarily found in tissue but is scarce in blood, some centres advocate using these drugs in order to reduce the morbidity and mortality of the disease. There is an ongoing clinical trial comparing benznidazole with a placebo in patients with mild to moderate chronic cardiomyopathy [BENznidazole Evaluation For Interrupting Trypanosomiasis (BENEFIT)].[7] However, there is currently no clinical evidence for its use in this context.[8]

Most treatments are performed with benznidazole for 30 or 60 days.[8] In Brazil, the recommended dose of benznidazole for adults is 5 mg/kg/day orally two or three times a day for 60 days. Adjustment of the treatment duration is recommended if the patient's weight is >60 kg as long as it does not exceed 80 days.[9] Other changes in dosage have been recommended in patients with accidental infection, immunocompromised status and adverse drug reactions (ADRs).[10]

However, therapy with benznidazole does carry risks. The rate of ADRs has reached up to 50% in several clinical studies, leading to cessation of treatment in up to 18% of patients.[11] The most common ADR (20%–25% of treated patients) is dermatitis due to hypersensitivity, which is neither dose dependent nor related to the destruction of *T. cruzi*. This ADR occurs most frequently around the 9th or 10th day of treatment, and its intensity may be mild (90% of cases), moderate (5%–9.5% of cases) or severe (<1% of cases). Digestive intolerance is the second most common ADR (5% of treated patients). Moderate and severe dermatitis can lead to cessation of treatment. Other ADRs that can lead to cessation of treatment are bone marrow depression and peripheral polyneuropathy. The latter is uncommon and dose dependent, and regresses very slowly.[10] Children are less susceptible to ADRs than adults.[6,12,13]

Despite the high rate of ADRs associated with benznidazole use, they are not, in practice, an impediment to the treatment of chronic Chagas' disease. Treatment with benznidazole is safe if monitored by a qualified professional.

Few studies have been conducted on the safety of benznidazole use. This study aimed to estimate the incidence of ADRs associated with the use of benznidazole in adult patients with chronic Chagas' disease and describe the causes of treatment interruption.

Methods

Ethical issues

This work was submitted and approved under number 0016.0.009.000-07 by the Research Ethics Committee of the Evandro Chagas Clinical Research Institute (IPEC), Oswaldo Cruz Foundation (Fiocruz), Rio de Janeiro, Brazil.

Patients and procedures

This was an observational, retrospective follow-up study conducted by review of medical records of patients with chronic Chagas' disease who were treated at IPEC/Fiocruz.

Outpatients undergoing trypanosomicidal treatment with benznidazole, followed up from December 1986 to May 2008, were included. Patients previously treated with benznidazole at another institution were excluded. Of the 1053 registered charts, 190 met the inclusion criteria for this study. The Chagas' disease diagnosis was made through two simultaneously positive serological tests for Chagas' disease: an ELISA and an indirect immunofluorescence test.[14,15]

Clinical research forms were developed to collect patient data. The main variables collected were gender, age, daily dose of benznidazole, treatment duration, treatment interruption, presence or absence of ADR and causality and severity of ADRs. Causality was assessed by application of the Naranjo algorithm,[16] which considers the compatibility of the time between the reaction onset and drug use, the nature of the event and the pharmacological characteristics and the medical or pharmacological plausibility. This algorithm is composed of 10 questions for which the answer can be positive ('yes'), negative ('no') or unknown ('not sure'). Based on the scores yielded by the algorithm, ADR events were classified as absent or doubtful (score 0), possible (score 1–4), probable (score 5–8) or definite (score ≥9). The presence of ADRs was established when the score was >1. The WHO Adverse Reactions Terminology (WHO-ART)[17] was used to code and classify ADRs.

ADRs were classified into the following four categories of severity: mild, a minor reaction of short duration that may have required treatment but did not substantially affect the normal life of the patient; moderate, a chemical reaction that altered the normal activity of the patient and required hospitalization or emergency care services and absence from work; severe, a reaction that directly threatened the patient's life; and fatal, a reaction that led to the patient's death.[18]

Analysis plan

The EpiData[19] and Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA)[20] applications were used for data entry and analysis, respectively. A statistical analysis was performed by descriptive analysis with numerical variables expressed as the mean ± SD and the median. The Kolmogorov–Smirnov test was used to test the sample distribution. When there was a normal distribution, Student's *t*-test was used to compare means between pairs of groups. The Mann–Whitney *U*-test was used when the distribution was not normal. Pearson's χ^2 test or Fisher's exact test for categorical variables was used for simple analysis of each variable for ADRs and interruption of treatment. The odds ratio was used as the measure of association between the outcome variable (ADR or cessation of treatment) and the exposure variable (gender or age). Survival curves were constructed for time to treatment interruption (Kaplan–Meier method), stratified according to the severity of ADRs and compared using the log-rank test. *P* values <0.05 indicated a significant association in all of the statistical tests used.

Results

In total, 190 patients were included in the study, of whom 58.9% were male, with ages ranging from 13 to 65 years (mean 32.31 ± 9.81 years; median 30.00 years). The dose of benznidazole ranged from 50 to 500 mg/day (mean 221.33 ± 57.16 mg/day; median 200.00 mg/day) and the duration of treatment ranged from 4 to 180 days (mean 57.46 ± 35.65 days; median 60.00 days). As shown in Table 1, 49% of the patients had ADRs during the use of benznidazole. The frequency of ADRs was significantly higher among female patients. There was a 2.3-fold higher probability of ADRs in the 20- to 40-year age group than in the other groups. Most patients received a daily dose of 50–200 mg/day. In 22.1% of patients, it was not possible to determine the administered dose due to a lack of pertinent data, and the dose was classified as unknown. There were no significant differences in ADR rate between the different doses. The rate of ADRs was higher in the first 30 days of treatment. Regarding the development of ADRs among the 190 patients treated, 97 (51.1%) were classified as absent/questionable, 75 (39.5%) as probable, 15 (7.9%) as possible and 3 (1.6%) as definite. In terms of severity, 72 (37.9%) cases were classified as mild, 20 (10.5%) as moderate and 1 as severe (0.5%). ADRs were reported in 93 (48.9%) therapies; 59 (31.1%) required treatment interruption due to intolerance to benznidazole (Table 1). The associated disorders, in order of frequency, were of the skin (26.3%), gastrointestinal system (9.5%) and central and peripheral nervous systems (5.3%) (Table 2). As shown in Table 3, there was no significant difference between the treatment interruption rate and age group or the daily dose of benznidazole. The rate of treatment interruption was significantly higher in the first 30 days of treatment and decreased progressively as the treatment duration increased. The same pattern was observed for causation and severity, in which the reactions were classified with increasing evidence (definite or probable) or greater intensity (severe or

Table 1. Demographic characteristics, treatment, causality and severity associated with the onset of ADR in patients using benznidazole ($N=190$)

		ADRs				
Variable	Category	yes, *n* (%)	no, *n* (%)	*P* value	Total, *n* (%)	Percentage of 190 patients
Sex	male	44 (39.3)	68 (60.7)	0.001	112 (100.0)	58.9
	female	49 (62.8)	29 (37.2)		78 (100.0)	41.1
Age	>20 and ≤40 years	79 (53.4)	69 (46.6)	0.022	148 (100.0)	77.9
	other ages	14 (33.3)	28 (67.7)		42 (100.0)	22.1
Daily dose of benznidazole	50–200 mg	62 (49.2)	64 (50.8)	0.680	126 (100.0)	66.3
	250–500 mg	9 (40.9)	13 (59.1)		22 (100.0)	11.6
	unknown[a]	22 (52.4)	20 (47.6)		42 (100.0)	22.1
Duration of treatment	≤30 days	32 (86.5)	5 (13.5)	<0.001	37 (100.0)	19.5
	>30 and <60 days	21 (42.0)	29 (58.0)		50 (100.0)	26.3
	≥60 days	40 (38.8)	63 (61.2)		103 (100.0)	54.2
Interruption of treatment	yes	59 (100.0)	0 (0.0)	<0.001	59 (100.0)	31.1
	no	34 (26.0)	97 (74.0)		131 (100.0)	68.9
Causality	definite	3 (100.0)	—		3 (100.0)	1.6
	probable	75 (100.0)	—		75 (100.0)	39.5
	possible	15 (100.0)	—		15 (100.0)	7.9
	doubtful ADRs	—	97 (100.0)		97 (100.0)	51.1
Severity	mild	72 (100.0)	—		72 (100.0)	37.9
	moderate	20 (100.0)	—		20 (100.0)	10.5
	severe	1 (100.0)	—		1 (100.0)	0.5
Total		93 (48.9)	97 (51.1)		190 (100.0)	100

[a]The dose of benznidazole could not be determined.

Table 2. ADR rates according to system organ class during treatment and relationship with treatment interruption in patients using benznidazole ($n=190$)

		Interruption of treatment			
Code	WHO–ART class	yes	no	*n*	%
100	skin and appendage disorders	33	17	50	26.3
600	gastrointestinal system disorders	10	8	18	9.5
410	central and peripheral nervous system disorders	7	3	10	5.3
1810	body as a whole—general disorders	2	4	6	3.2
433	special senses other, disorders	3	0	3	1.6
1220	white cell and reticuloendothelial system	2	0	2	1.1
431	vision disorders	0	1	1	0.5
200	musculoskeletal system disorders	0	1	1	0.5
420	autonomic nervous system disorders	1	0	1	0.5
1830	resistance mechanism disorders	1	0	1	0.5
Does not apply	ADRs doubtful/improbable	0	97	97	51.1
Total		59	131	190	100

moderate) and presented higher rates of treatment interruption (Table 3). The log-rank and Breslow tests showed that ADR severity classification significantly ($P=0.001$) affected the time to treatment interruption among ADR severity classifications. The Kaplan–Meier curves stratified by the severity of ADRs are shown in Figure 1 and indicate that the median time to interruption was lower in patients with moderate and severe ADRs than in patients with mild ADRs.

Table 3. Relationship between the interruption of treatment due to ADRs and the remaining variables in patients using benznidazole ($N=93$)

Variable	Category	Interruption of treatment due to ADRs		*P* value	Total, *n* (%)	Percentage of 93 patients
		yes, *n* (%)	no, *n* (%)			
Sex	male	27 (61.4)	17 (38.6)	0.693	44 (100.0)	47.3
	female	32 (65.3)	17 (34.7)		49 (100.0)	52.7
Age	>20 and ≤40 years	50 (63.3)	29 (36.7)	0.943	79 (100.0)	84.9
	other ages	9 (64.3)	5 (35.7)		14 (100.0)	15.1
Daily dose of benznidazole	50–200 mg	37 (59.7)	25 (40.3)	0.271	62 (100.0)	66.7
	250–500 mg	6 (66.7)	3 (33.3)		9 (100.0)	9.7
	unknown[a]	16 (72.7)	6 (27.3)		22 (100.0)	23.7
Duration of treatment	≤30 days	28 (87.5)	4 (12.5)	0.001	32 (100.0)	34.4
	>30 and <60 days	13 (61.9)	8 (38.1)		21 (100.0)	22.6
	≥60 days	18 (45.0)	22 (55.0)		40 (100.0)	43.0
Causality	definite	3 (100.0)	0 (0.0)		3 (100.0)	3.2
	probable	48 (64.0)	27 (36.0)		75 (100.0)	80.6
	possible	8 (53.3)	7 (46.7)		15 (100.0)	16.1
Severity	mild	39 (54.2)	33 (45.8)		72 (100.0)	77.4
	moderate	19 (95.0)	1 (5.0)		20 (100.0)	21.5
	severe	1 (100.0)	0 (0.0)		1 (100.0)	1.1
Total		59 (63.4)	34 (36.6)		93 (100.0)	100

[a]The dose of benznidazole could not be determined.

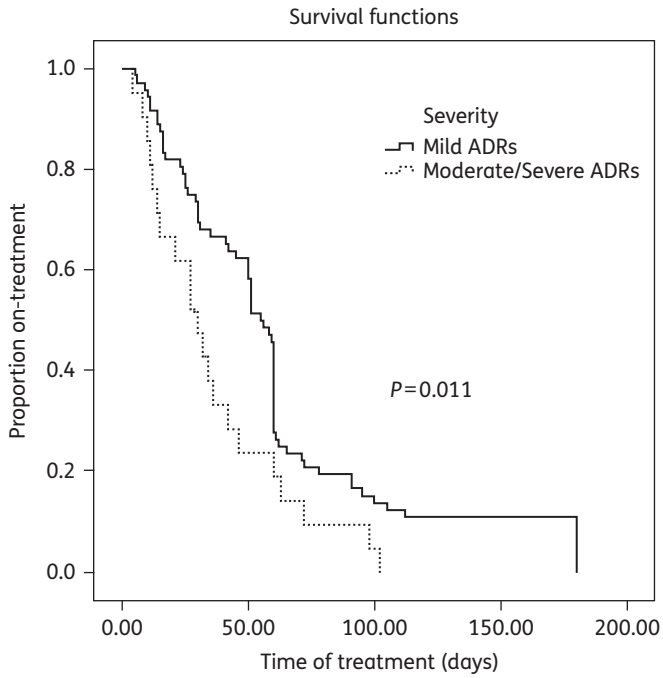

Figure 1. Kaplan–Meier curves showing the interruption of treatment stratified by mild ADRs (continuous line) and moderate/severe ADRs (broken line).

Discussion

Currently, benznidazole and nifurtimox are the only therapeutic alternatives for the treatment of Chagas' disease anywhere in the world.[21] However, benznidazole is the only therapeutic available for the specific treatment of Chagas' disease in Brazil, and its use may depend on circumstances such as disease stage, patient age and associated conditions.[10] This paper describes one of the few studies conducted in Brazil that focused mainly on the safety of benznidazole use.

The Naranjo algorithm[16] is a useful method for monitoring suspected ADRs and classifying them by relating them directly to the clinical outcomes in patients. Using the classification criteria of causality proposed by Naranjo, 48.9% of the 190 patients presented events that were classified as ADRs related to benznidazole.

According to Viotti *et al.*,[11] most of the treatment regimens in clinical studies of benznidazole in patients with chronic Chagas' disease last for 30 or 60 days. In this study, the mean treatment duration was 58.9 days and the median was 60 days, with no significant difference between the groups with and without ADRs. Benznidazole was well tolerated in treatment regimens that continued for longer periods (60–180 days).

The average age of our cohort was similar to that in the Viotti *et al.*[11] study. In our study, young adults showed a greater incidence of ADRs. After application of the Naranjo algorithm, we observed a higher rate of ADRs in females. A similar result was

observed by Viotti *et al*.,[11] who reported 54.2% of the ADRs were identified in women.

Adverse skin reactions and gastrointestinal disorders are the most frequent ADRs,[8] and they frequently appear after 10 days of treatment in 20%–25% of patients. Other ADRs are associated with the toxic action of benznidazole and its cumulative effects, which include bone marrow depression and polyneuritis. These effects can be enhanced in treatment lasting >30 days.[11] In this study, the most frequent ADRs were skin reactions, followed by gastrointestinal disorders and central and peripheral nervous system disorders. Among the 93 patients who experienced ADRs, 65.6% occurred after 30 days of treatment. However, even with a greater number of ADRs after 30 days of treatment, this effect was not accompanied by a higher probability of greater severity of ADRs because most of the ADRs consisted of mild dermatitis (28 patients) unrelated to cumulative effects but due to immunological processes. Mild ADRs were the most common, indicating that benznidazole therapy is safe for most patients, corroborating previous findings from Viotti *et al*.[11] and the study by Sosa-Estani and Segura.[13]

Of all patients, 37 were treated for only 30 days and 32 (86.5%) of these presented with ADRs. Of the 50 patients treated for 30–60 days, only 21 (42%) presented with ADRs. In contrast, in 103 patients treated for >60 days ADRs were observed in only 40 (38.8%). There was a significant decrease in the incidence of ADRs after the first 30 days of treatment and a reduction in the incidence of treatment interruption due to ADRs. Skin reactions were less common in treatment lasting >30 days. Similar data have been reported[6,11] that show a higher rate of skin reactions in the first 30 days of treatment. In contrast, digestive intolerance and especially peripheral nervous system impairment were more common in treatment that lasted >60 days. The latter is possibly due to a cumulative toxic effect of benznidazole.[11]

According to Pérez-Molina *et al*.,[8] the low incidence of ADRs can be attributed to the criteria used to define ADRs, leading to underreporting in medical records. In this work, we can infer that the adoption of the Naranjo algorithm could correct for the underreporting of cases because both this work and that of de Pontes *et al*.[22] adopted the criteria used in the Naranjo algorithm to classify adverse events and obtained very similar results. Both studies reported a higher number of ADRs associated with benznidazole use compared with other series.

Data from the literature[11,23–26] indicate that 12%–18% of patients treated with benznidazole stop treatment because of ADRs. Sosa-Estani *et al*.[24] treated 249 patients with benznidazole and had to discontinue treatment in 17.7% of cases due to ADRs. As in the results of our analysis, the main reasons for interrupting treatment were exanthema and pruritis. In our study, treatment was interrupted in 31% of patients. This difference from other studies can be attributed to the methodology used to classify ADRs. Using the same methodology (the Naranjo algorithm) as our study, in an analysis of 32 patients treated with benznidazole, de Pontes *et al*.[22] observed ADRs in 81.25% of patients, and 28.57% of these required treatment interruption. The differences in the methodology used to detect and manage ADRs may explain the lower rate of interruptions in other studies.

By examining the association between treatment interruption and gender, it was evident that the frequency of treatment interruption was higher in women, suggesting greater susceptibility to more severe ADRs. There were no significant relationships between age and the daily dose of benznidazole with treatment interruption. A significantly higher incidence of treatment interruptions occurred in cases where the presence of ADRs was evident, reaching 100% in ADRs classified as definite and 0% in ADRs classified as doubtful.

There was a significant correlation between the intensity of the event and the interruption of treatment. The more intense the event, the higher the probability of interruption. Similar to the finding of de Pontes *et al*.,[22] moderate or severe ADRs produced a higher probability of treatment interruption. Among the ADRs classified as mild, there was a 54.2% probability of treatment interruption, not because of its intensity but probably due to the uncertainty of physicians regarding the benefit of benznidazole in the treatment of chronic Chagas' disease.

The probability of treatment interruption was higher in the first 30 days, with 87.5% of ADRs associated with interruption during this period. ADRs were most often associated with skin disorders, followed by disorders of the gastrointestinal tract and central and peripheral nervous systems. Survival curves with time to treatment interruption (Kaplan–Meier method) were used to examine the temporal behaviour of benznidazole interruption, taking into account the severity of adverse events. It was evident that the time until interruption of treatment in patients with moderate and severe ADRs was significantly lower than that in patients with mild or absent ADRs. As the treatment duration increased there was a reduction in the severity of ADRs, and consequently a smaller proportion (45.0%) of patients required treatment interruption.

Conclusions

The adoption of the Naranjo algorithm was a useful tool to reduce the underreporting of ADRs associated with the use of benznidazole in Chagas' disease. Despite the high rate of ADRs, they were associated with low morbidity. Interruption of treatment was mainly due to the presence of moderate or severe ADRs. Treatment with benznidazole was considered safe because symptoms disappeared after interruption of benznidazole, only one patient had serious ADRs and none of the patients had fatal ADRs.

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Transparency declarations

None to declare.

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