

ETIOLOGICAL DRUG TREATMENT OF HUMAN INFECTION BY *TRYPANOSOMA CRUZI*

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SUMMARY

Forty-nine American Trypanosomiasis (Chagas' disease) patients, with xenodiagnosis proven parasitemia were treated by the authors. Forty-one of these patients were given benznidazole, at dosages ranging from 5mg/kg/day to 8mg/kg/day, during a pre-established period of 60 days. In this group, 17 patients had an undetermined form of the disease, whereas 22 had cardiologic disease and 4 had digestive disease (two patients had a mixed form of the disease). Side effects were frequent, and led to the discontinuation of treatment in 17 patients. The follow-up period ranged from 1 to 20 years (mean follow-up period of 6 yrs. 7 mo). 26 (63.4%) of the patients became parasitemia-negative. The other eight patients were treated with nifurtimox, during 120 days, following a variable dose regime of 5mg/kg/day (initial dose) to 17 mg/kg/day (final dose). Six of them had severe side effects, and only one patient remained parasitemia-negative throughout the observation period (ranging from 1 to 18 years). Benznidazole proved to be better tolerated and more effective in the management of parasitemia when compared to nifurtimox, although more effective and less toxic drugs are still desirable.

KEYWORDS: Chronic Chagas' disease; Antiparasitic treatment; Benznidazole; Nifurtimox.

INTRODUCTION

Chagas' disease, a long lived infection caused by the hemoflagellate protozoan *Trypanosoma cruzi*, is an important cause of chronic disease in Latin America, affecting mainly the heart and the gastro-intestinal tract. Approximately 15 million people in Latin America are infected ⁸.

In the pathogenesis of the chronic complications of Chagas' disease, the parasite may play an important role, as previously demonstrated in experimental models ¹. Therefore, efforts to control the parasitemia are an attempt to change the natural history of Chagas' disease. A large number of different compounds have been assayed in a variety of ways, but still restricted the number of drugs available for clinical use ³. Nifurtimox (Bayer 2 502) and benznidazole (Roche 7

1051) are the only two nitroheterocyclic drugs currently available for treating infection with *T. cruzi*, effectively reducing the parasitemia.

We conducted an open trial for treatment of parasitemia in chronic Chagas' disease, using both benznidazole and nifurtimox, analyzing success of treatment using xenodiagnosis in the follow-up of the patients. One important aspect of this study is that none of the patients returned to regions with endemic Chagas' disease, therefore avoiding reexposition to *T. cruzi*.

CASES AND METHODS

Since 1972, patients with positive serology for Chagas' disease admitted to the Infectious Disease Service of the Hospital do Servidor Público Estadual "Fran-

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cisco Morato de Oliveira" de São Paulo were submitted to investigation which included clinical history, taking physical exam, chest roentgenogram, electrocardiogram and xenodiagnosis (using 40 to 60 third instar nymphs of *Triatoma infestans*). When digestive symptoms were present, an experienced gastroenterologist was consulted, and specific diagnostic procedures were performed as indicated. In the presence of any cardiovascular symptoms or abnormalities in the cardiological exams, all patients were also referred to a cardiologist. Patients with positive parasitemia observed by xenodiagnosis were eligible for treatment with nifurtimox or benznidazole. Exclusion criteria were: age under 18 years, pregnancy, return to an area endemic for Chagas' disease with the possibility of reinfection with *T. cruzi*, previous allergy history to the drugs, or serious debilitating illness.

Benznidazole was administered in the dose of 5 to 8 mg/kg/day, during 30 to 60 days. The drug was discontinued in presence of rash or evidence of peripheral neuropathy. Nifurtimox was administered in a dose of 5 - 7 up to 15 - 17 mg/kg/day, during 120 days of treatment.

After treatment, patients were submitted to regular xenodiagnosis, with the following frequency: a monthly exam in the first year, a quarterly exam in the second year, a semestral exam in the third and fourth year, and an annual exam thereafter. The result was considered positive when *T. cruzi* was visualized in the intestinal content of at least one parasite after 30 days.

Statistical analysis of data was considered significant when p was less than 0.05 using Fisher exact test.

RESULTS

Forty-nine patients fulfilled the entry criteria to

receive treatment. Forty-one received benznidazole (benznidazole group) and eight received nifurtimox (nifurtimox group). The imbalanced distribution of cases into the two groups was due to the high frequency of side effects and the initial poor results in the nifurtimox group.

Distribution of age, sex, and the clinical presentation form of Chagas' disease in both groups are shown in Table 1.

In the benznidazole group, side effects were often present, characterized by vesicular rash, peripheral neuropathy, and psychiatric manifestations, leading to discontinuation of treatment in 17 patients. The follow-up period ranged from 1 to 20 years (mean of 6 years and 7 months). Persistent xenodiagnosis negativation occurred in 26 (63.4%) cases (Table 2). Three patients were submitted to a second course of treatment due to a positive exam in the control xenodiagnosis, with subsequent negativation in two (data not included in statistical analysis). Another patient, who received three courses of treatment, persisted with parasitemia.

Except for the three patients submitted to retreatment, in all the other cases drug discontinuation due to side-effects was permanent. We included, in the analysis of the results, all the treated cases independently of the length of their treatment because there still is not a consensus on the minimum duration in order to obtain xenodiagnosis negativation.

Side effects in the nifurtimox group were more prominent, characterized by nausea, vomiting, anorexia, weight loss, peripheral neuropathy, and psychiatric disturbances, and were considered severe in six patients (75.0%), leading to discontinuation of treatment.

TABLE 1
Distribution of age, sex, and clinical presentation form of Chagas' disease in benznidazole and nifurtimox groups.

	Age (mean/ range)	Sex		Clinical presentation (n)		
		M	F	Undetermined	Cardiological	Digestive
Benznidazole group (n=41)	37.0 (25 - 62)	19	22	17	22	4
Nifurtimox group (n=8)	33.4 (27 - 39)	5	3	2	6	0

M: male; F: female; n: number.

Mean follow-up time was five years and two months, ranging from 1 to 18 years. Only one patient sustained negative parasitemia in the observation period of nine years (Table 2).

TABLE 2
Discontinuation of treatment due to side effects, follow-up and parasitemia negativation in the two groups

	Discontinuation of treatment (n%)	Follow-up (mean / range)	Parasitemia negativation (n%)
Benznidazole group	17 / 41.5	6 years 7 months (1 to 20 years)	26 / 63.4
Nifurtimox group	6 / 75.0	5 years 2 months (1 to 18 years)	1 / 12.5
p	ns	ns	< 0.01

n%: number per cent; p: Fischer exact test; ns: not significant ($p > 0.05$)

DISCUSSION

Despite some efforts to develop and submit to clinical trials new anti *T. cruzi* drugs, currently there are few references in the medical literature. Few trials have been conducted with new drugs, especially in recent years.

The accumulated experience in the parasitological treatment of Chagas' disease has been concentrated on two drugs, benznidazole and nifurtimox. The use of these drugs is well documented in acute Chagas' disease, effectively reducing the severity of parasitemia and disease⁶. However, their use in chronic Chagas' disease remains a point of controversy⁵.

A recent open labeled study compared 131 patients treated with benznidazole with 70 controls, showing less electrocardiographic changes in the treated group after 8-year average follow up, but did not analyze parasitemia⁷.

Some previous clinical trials conducted in Brazil have used benznidazole, nifurtimox or both to reduce or try to eliminate the parasitemia in chronic Chagas' disease with variable results^{2,4,5}. Persistently negative xenodiagnosis during variable control periods in patients treated with benznidazole ranged from 70 to 93% and with nifurtimox from 44 to 56.25%. In our study, these results were 63.4% in the benznidazole group and 12.5% in the nifurtimox group. We believe that these lower results may be explained by the longer follow-up of patients.

Side effects were frequent in both groups but were

more problematic in patients receiving nifurtimox, as previously described², although we did not find a statistical difference in the rate of discontinuation of the treatment between the two groups.

Benznidazole seems to be more efficient than nifurtimox in reducing parasitemia in Chagas' disease. However, geographical variations in susceptibility may be found, probably due to strain variability.

RESUMO

Tratamento etiológico por droga da infecção humana pelo *Trypanosoma cruzi*

Por meio do benznidazol e do nifurtimox foram tratados 49 pacientes acometidos de doença de Chagas. Xenodiagnóstico prévio tinha sempre resultado positivo, evidenciando parasitemia pelo *Trypanosoma cruzi* e sendo as seguintes as formas clínicas: indeterminada-19; cardíaca-28; digestiva-4 (dois pacientes apresentavam formas mistas).

Quanto ao benznidazol, houve administração de 5 a 8 mg/kg/dia, durante dois meses, e a propósito do nifurtimox o esquema terapêutico começou com a dose de 5 a 7 mg/kg/dia, sucedendo aumento progressivo até 15 a 17 mg/kg/dia, no decurso de quatro meses.

O benznidazol, usado por 41 doentes, propiciou negatificação em 26 (63.4%) à avaliação realizada por meio do xenodiagnóstico, em etapas de um a 20 anos e, em média, de 6 a 7 anos. Por seu turno, com o nifurtimox verificou-se uma negatificação relativamente a somente um indivíduo, tendo o seguimento sido efetuado em etapas de um a 18 anos.

Pôde-se constatar que o benznidazol mostrou-se melhor tolerado e também mais eficiente no sentido de negativar a parasitemia. Todavia, é desejável a disponibilidade de fármacos dotados de maior eficácia e melhor tolerabilidade para coibir a infecção devida ao *Trypanosoma cruzi*.

REFERENCES

1. ANDRADE, S. G. & ANDRADE, Z. A. - Aspectos anatómopatológicos e resposta terapêutica na infecção chagásica crônica experimental. Rev. Inst. Med. trop. S. Paulo, 18: 268-275, 1976.

2. BOAINAIN, E. - Tratamento etiológico da doença de Chagas na fase crônica. **Rev. goiana Med.**, 25: 1-60, 1979.
3. CASTRO, S. I. - The challenge of Chagas' disease chemotherapy: an update of drugs assayed against *Trypanosoma cruzi*. **Acta trop.(Basel)**, 53: 83-98, 1993.
4. FERREIRA, H. O. - Tratamento da forma indeterminada da doença de Chagas com nifurtimox e benzonidazol. **Rev. Soc. bras. Med. trop.**, 23: 209-211, 1990.
5. PRATA, A.; MACÊDO, V.; PORTO, G. et al. - Tratamento da doença de Chagas pelo nifurtimox (Bayer 2502). **Rev. Soc. bras. Med. trop.**, 9: 297-307, 1975.
6. RASSI, A. & FERREIRA, H. O. - Tentativas de tratamento específico da fase aguda da doença de Chagas com nitrofuranos em esquemas de duração prolongada. **Rev. Soc. bras. Med. trop.**, 5: 235-262, 1971.
7. VIOTTI, R.; VIGLIANO, C.; ARMENTI, H. & SEGURA, E. - Treatment of chronic Chagas' disease with benznidazole: clinical and serologic evolution of patients with long-term follow-up. **Amer. Heart J.**, 127: 151-162, 1994.
8. WORLD HEALTH ORGANIZATION - Chagas disease frequency and geographical distribution. **Wkly. Epidem. Rec.**, 65: 257-264, 1990.

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