Letter to the editor

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Nifurtimox chemotherapy: collateral effects in treated *Trypanosoma cruzi* infected patients

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Sir,

Chagas disease: is caused by the parasite *Trypanosoma cruzi* and is endemic in 21 countries of Latin America. Nevertheless, this infection is not only a health problem in the American continent, but also in those non-disease-endemic countries that receive immigrants, where it is an emerging disease[1-2]. Nifurtimox and benznidazol, whose anti-*T. cruzi* activity was discovered empirically more than 3 decades ago, are the only two available drugs for the etiological treatment of Chagas disease[3]. Both compounds are active in the acute phase, helping to control the disease and diminishing the probability of it passing to the chronic phase. The treatment of patients who are in the indeterminate or symptomatic chronic stages of Chagas disease has been debated for years, and the effectiveness of drugs in patient in this situation remains uncertain. The current consensus of Latin-American authors is to treat every person infected with *T. cruzi* with benznidazol or nifurtimox up to 18 years of age. Benznidazol is considered to be the most suitable medication in Latin America, and is the only one authorized in Spain. It is not available in pharmacies and it must be requested through the Ministry of Health. Nifurtimox, can be used as an alternative treatment to benznidazole through compassionate use programmes. However, both drugs may have numerous side effects in adults.

The most frequent side effects described in the case of nifurtimox are abdominal pain, anorexia, weight loss, nausea and vomiting. The possible neurological reactions are restlessness, disorientation, forgetfulness, insomnia, spasms, paresthesias, polyneuritis and convulsive seizure, which disappear through dose reduction or after suspending the treatment[4]. The daily dose is 8-10 mg/kg of body weight in adults, 12.5-15 mg/kg in adolescents and 15-20 mg/kg in children from 1 to 10 years. The treatment is administered orally, in 3 daily doses for 90 to 120 days[5].

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Nifurtimox, is a nitrofuran compound with a trypanocidal effect against both trypomastigote and amastigote forms of *T. cruzi*. Its antiparasitic activity is due to the formation of toxic derivatives of oxygen when nifurtimox is reduced. *T. cruzi* presents low levels of reduced glutathione and lacks catalase and glutathione peroxidase, which makes the parasite very sensitive to hydrogen peroxide and to the free radicals. The superoxide anion O_2-, hydrogen peroxide (H_2O_2) and the hydroperoxyl radical (HO_2), among other cytotoxic molecules, bind to cellular macromolecules, leading to lipid peroxidation and membrane alterations, enzyme inactivation, DNA degradation and mutagenesis[6].

In the present communication, we describe the side effect of nifurtimox treatment in 26 adults patients with chronic Chagas disease diagnosed in the Unit of Tropical Medicine of the Virgen the la Arrixaca Hospital in Murcia (Spain) between January 2007 and December 2009.

Patients were treated with nifurtimox (8-10 mg/kg in 3 daily doses for 90-120 days)[5] when benznidazol was not available (11 patients), when the patients presented adverse reactions to benznidazol that forced the interruption of treatment (12 patients)[7] or in the face of therapeutic failure, that is, when the parasitemia in blood was still detected by PCR (polymerase chain reaction) after benznidazol treatment (3 patients)[8].

All 26 patients completed the treatment with nifurtimox. Of these, 16 (61.5 %) presented adverse reactions, of whom 12 (12 of 26, 46.1 %) showed more that one collateral effect. Table 1 shows the side effects in the patients treated with nifurtimox. The most frequent side effect was digestive intolerance (nausea, vomiting, epigastralgy and dysphagia), followed by anorexia and forgetfulness. Nevertheless, none of the patients had to discontinue the treatment due to the adverse reactions.

Not many studies describing side effects of nifurtimox chemotherapy have been reported. Since the reactions are usually well controlled by dose reduction or by symptomatic treatment, knowledge of the side effects of nifurtimox in an area where Chagas disease is not endemic will facilitate its therapeutic management and consequently, the proper observance of treatment. Nevertheless, due to the low effectiveness of the pharmacological treatment and its high toxicity new drugs are urgently neded for the treatment of Chagas disease.

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

	n/Total	%
Patient with side effects/ number of treated patients	**16/26**	**61.5**
Adverse reactions recorder, separately or in association	**n/Total**	**%**
Digestive intolerance		
Nausea	6/26	23.1
Vomiting	1/26	3.8
Epigastralgy	1/26	3.8
Dysphagia	1/26	3.8
Anorexia	5/26	19.2
Weight lost	2/26	7.7
Taste alteration	1/26	3.8
Forgetfulness	5/26	19.2
Polyneuritis	1/26	3.8
Tremor	1/26	3.8
Headache	1/26	3.8
Asthenia	2/26	7.7
Insomnia	1/26	3.8
Palpitations	1/26	3.8
Polyarthralgias	2/26	7.7
Dermatological		
Erythema	2/26	7.7
Pruritus	1/26	3.8

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TRANSPARENCY DECLARATIONS

None to declare

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