

# Clinical trial with Secnidazole in a single dose in venezuelan children infected by *Giardia intestinalis*.

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**Key words:** *Giardia intestinalis*, secnidazole.

**Abstract.** The aim of this work was to evaluate in an open, non-comparative study the use of secnidazole in oral suspension given to Venezuelan children infected with *Giardia intestinalis*, from a community in Carapita, a slum area in Caracas. Seventy children from 2 to 11 years old (38 males and 32 females) were treated with a single oral dose of secnidazole (30 mg/Kg of body weight), after clinical and parasitological evaluation to make the diagnosis of active giardiasis. The effectiveness of treatment was determined by clinical examination and parasitological evaluation of feces samples 15 days after treatment. The results showed 95% of clinical cure with a significant decrease of the frequency of gastrointestinal symptoms. The parasitological cure was 98%, there were 4 failures at the end of treatment. Side effects observed after treatment were of mild intensity, lasting only few hours. These results show that a simple dose of secnidazole in an oral suspension is an effective, safe and well tolerated treatment for giardiasis in children and that this drug may be used as a mass treatment in risk populations.

## **Ensayo clínico utilizando una dosis única de Secnidazol en niños venezolanos infectados por *Giardia intestinalis***

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**Palabras clave:** *Giardia intestinalis*, secnidazol.

**Resumen.** El objetivo de este trabajo fue evaluar mediante un estudio abierto no comparativo el uso de secnidazol en suspensión oral, suministrado a niños venezolanos infectados por *Giardia intestinalis*, procedentes de Carapita, un barrio marginal de la ciudad de Caracas. Setenta niños (38 masculinos y 32 femeninos) con un rango de edad entre 2 y 11 años fueron tratados con una dosis única (30mg/Kg peso corporal) de secnidazol, después de haber hecho el diagnóstico de giardiasis mediante examen clínico y evaluación parasitológica en tres muestras de heces. La efectividad del tratamiento se determinó 15 días después del tratamiento utilizando la evaluación clínica y parasitológica. Los resultados mostraron 95% de cura clínica demostrado por una disminución significativa de la frecuencia de síntomas gastrointestinales. La cura parasitológica fue 98%, hubo cuatro fracasos al final del tratamiento. Los efectos secundarios observados después del tratamiento fueron de moderada intensidad y duraron solamente algunas horas. Estos resultados muestran que una dosis única de secnidazol en una suspensión oral es un tratamiento efectivo, seguro y bien tolerado para niños con giardiasis y que esta droga pudiera ser administrada como tratamiento a poblaciones en riesgo.

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### **INTRODUCTION**

Giardiasis, a worldwide parasitosis, that occurs most commonly in children from sub-tropical and tropical regions (1), is produced by a flagellated protozoan, *Giardia intestinalis* that is localized to the small bowel, where it produces damage to the mucosa and gastrointestinal symptoms. This parasite affects mainly preschool and school children and it is a public health problem in tropical countries such as Venezuela.

Various immunological and non-immunological mechanisms

may influence the eradication of this parasitosis from their hosts (2, 3).

Immune responses to *Giardia intestinalis* occur in the intestinal mucosa and a spectrum of local inflammatory changes may accompany this infection. A number of reports have described the existence of allergic symptoms in persons with giardiasis and the local inflammation may contribute to induce these symptoms (4).

This infection may cause symptoms such as diarrhoea, abdominal pain, flatulence, and can be associated with growth retardation (5). The

most common treatment in many countries is the use of nitroimidazoles such as metronidazole or tinidazole (6). However, drug resistance has been demonstrated by *in vitro* and *in vivo* studies (7). It has been reported that secnidazole in single dose treatment could be very effective in the eradication of giardiasis and amoebiasis (8, 9, 10). Secnidazole has also shown a high cure rate in the treatment of human trichomoniasis, amoebiasis and giardiasis (11, 12, 13).

Intestinal parasitic infections are among the most common infections in humans, particularly in tropical regions, such as Venezuela. The current critical socio-economic conditions of the majority of the Venezuelan population favor these infections, therefore we have found a very high prevalence in Venezuela (14).

In the present study we used a single oral dose of secnidazole to be administered to giardiasis children from a highly parasitized community from Carapita, a slum area, in Caracas. We describe the results of a clinical trial performed as an open non-comparative study, in order to verify the effectiveness, tolerance and safety of this drug given to a group of Venezuelan children infected by *Giardia intestinalis* with or without clinical gastrointestinal symptoms.

## MATERIALS AND METHODS

### Studied patients

We evaluated 70 children (38 males and 32 females) with an age

range from 2 to 11 years old (mean: males  $4 \pm 2$  and females  $5 \pm 2$  years old) who attended a program of primary medical attention in a local medical dispensary of the Venezuelan Ministry of Health and Social Development, in Barrio Carapita, Caracas. The children fulfilled the criteria for inclusion in the study: informed written consent by the parents or legal guardians of the children, and the expressed intention to participate in all aspects of the study protocol (pre-evaluation, treatment and post-evaluation). The children were clinically examined, and the accompanying adults were questioned for the existence of gastrointestinal symptoms suggestive of giardiasis. Parasitological studies were performed in feces samples from all the children studied.

### Ethical considerations

Because giardiasis is a major public health problem in Venezuela, the tests performed in this study were offered as part of the routine program implemented in the medical dispensary by the paediatric clinic.

We obtained the approval of the Ethical Committee of the Institute of Biomedicine, Faculty of Medicine, Central University of Venezuela and the Medical Board of the dispensary in Carapita.

The principles of these studies were ratified by the Venezuelan National Council for Scientific and Technological Investigation (CONICIT).

The informed consent of the legal representatives of the children was obtained for both the service

and research components of this study, and antiparasite treatment was administered to all children found to be infected after the blood sample had been collected.

### **Clinical evaluation**

Clinical evaluation was performed by pediatricians who work routinely at the medical dispensary in Carapita, Caracas.

The clinical history emphasized reports of gastrointestinal symptoms and signs that could be associated with giardiasis, such as diarrhoea, stomach cramps/discomfort, flatulence and vomiting. This clinical evaluation was performed once before treatment, and twice after administration of the drug (15 days and 3 months). The results were expressed as percentage of children presenting each gastrointestinal symptom.

### **Feces examination**

Parasitological evaluation was performed by microscopic examination of three consecutive stool samples from each child. Samples were collected into preservative solution (40% tincture of merthiolate, 5% formalin, and 1% glycerol) and examined for the presence of eggs, cysts, or larvae of intestinal parasites. The presence of other intestinal parasites did not exclude the patient from participation, but specific treatment for them was given only after the final evaluation.

### **Treatment**

The children were treated with 30 mg/Kg of body weight used as a

single oral dose of secnidazole suspension, donated by laboratories Rhône-Poulenc Rorer, in Venezuela. The effectiveness of secnidazole was determined by feces and clinical examination 15 days after treatment. After the completion of our study, the rest of the children who were not included in the protocol and were found to be infected by any intestinal parasite were appropriately treated.

### **Statistical analysis**

The data collected were examined and statistically analysed by the Fisher's exact and Wilcoxon's tests. They were considered statistically significant when  $p < 0.05$ .

## **RESULTS**

We evaluated the effect of secnidazole in a simple oral dose given to a group of 70 children with an age range from 2 to 11 years old. Age distribution is shown in Table I. Children attending the paediatric clinic at this medical dispensary, usually show a high frequency of gastrointestinal symptoms. The group of children evaluated in our study showed abdominal pain 53%, diarrhoea 32%, flatulence 21%, and vomiting 10% all over the previous 4 weeks. From the whole group studied, one child was concomitantly infected with *Ascaris lumbricoides* and three children with *Blastocystis hominis*.

The children were treated with an oral single dose of secnidazole equivalent to 30 mg/Kg of body weight, and 15 days after treatment,

**TABLE I**

AGE DISTRIBUTION OF CHILDREN INFECTED BY *GIARDIA INTESTINALIS* AND TREATED WITH A SINGLE DOSE OF SECNIDAZOLE (30MG/WEIGHT KG)

Age (years)	Number of patients (n= 70)	
Age groups	Male	Female
2-3	12	11
4-5	20	12
6-7	5	4
8-9	0	3
10-11	1	2
Sub-total	38	32

they were clinically reevaluated. We found a statistically significant decrease of the gastrointestinal signs and symptoms. (Figure 1). Of the 70 children treated with secnidazol, 66 (95%) were clinically asymptomatic. Parasitological negativization was found in 68 children (98%). We detected 4 children with persistent gastrointestinal symptoms, only 2 of them showed a positive feces examination.

The whole group was re-evaluated three months later and we detected five cases of reinfection, but they were clinically asymptomatic.

The tolerance was considered good, since only 6 patients (8.5%) reported at least one side effect during the first week following the treatment.

## DISCUSSION

Giardiasis has come into prominence during the last decade because of an increasing awareness

of its importance and improvements in diagnostic procedures. In the United States and Great Britain, giardiasis is the most frequent human intestinal parasitosis (15). Two hundred million infections by *Giardia intestinalis* occur annually in Africa, Asia and Latin America (16). In a previous report (14) we found a prevalence of approximately 25%, studying a group of children of low socioeconomic level in Caracas (Barrio Los Erasos), which is similar to that found by Torres *et al*, (17) when these authors evaluated 52 nurseries in Sao Paulo, Brazil.

We have studied the prevalence of giardiasis in different human groups in Venezuela, and found a range of prevalence from 15 to 45%. These variations were clearly associated with the socio-economic level of the population studied.

The high prevalence of giardiasis in our country clearly justifies investigation concerning the best anti-giardial treatment to be administered to these populations.

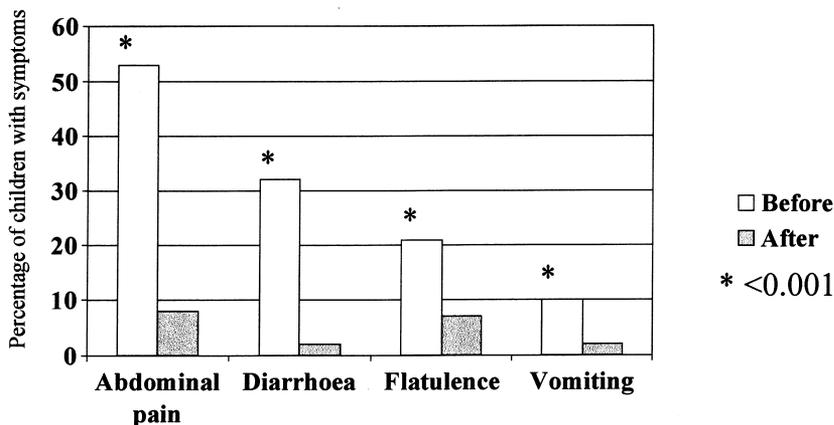


Fig. 1. Gastrointestinal symptoms of seventy giardiasic children clinically evaluated before and 15 days after treatment with 30 mg/weight Kg of secnidazol.

The present clinical study shows results of the effectiveness and low toxicity of a single dose of secnidazol used at 30mg/Kg of body weight, given to a group of children infected with *Giardia intestinalis* attending the paediatric clinic at the medical dispensary of the Venezuelan Ministry of Health and Social Development, in Barrio Carapita.

The classic treatment for giardiasis includes the use of drugs such as metronidazole, tinidazole, ornidazole and furazolidona, however, a good mass treatment for giardiasis for populations with high prevalence of the infection, would be conformed by the use of a drug that could be administrated in a single oral dose, with low toxicity and few side effects.

Secnidazole is a drug with pharmacological characteristics which make it a useful tool for single dose treatments of intestinal amebiasis, including amebic liver

abscess, and giardiasis. It has been found to be twice as active as metronidazole for amoebiasis. (13, 18).

Secnidazole is the nitroimidazole with the longest half-life *in vivo* (19). *In vitro* assays to test antigiardial activity of drugs showed that concentrations inhibiting 50% of growth of *Giardia intestinalis*, were significantly lower for secnidazole than for furazolidone or metronidazole (20). Moreover, toxicity studies showed that secnidazole was well tolerated, and side effects are seen less frequently than those observed with long term metronidazole therapy (21).

Our results demonstrate the clinical eradication of gastrointestinal signs and symptoms and the parasitological cure of the treated population. The results shown in the present study are similar to those obtained by Botero *et al*, (22) on the efficacy and safety of a single oral dose of secnidazole (30 mg/Kg)

given to children aged 2 years or more with intestinal amoebiasis; these authors obtained a clinical cure rate of 95%, which is similar to ours.

In previous clinical trials, Rastegar-Lari and Salek-Moghaddam (13), in a comparative study between secnidazole and metronidazole, found a cure rate of 100% with secnidazole and 96% with metronidazole. When metronidazole was used in a single dose, its cure rate was highly reduced to 36-54% (23, 24). On the contrary, a single dose of secnidazole reaches the response achieved with multiple dosage regimens of metronidazole or tinidazole.

With the aim of confirming the parasitological cure of the children, we collected feces samples 15 days after the end of the treatment, a relatively short period; however this period was considered long enough to detect the failure of treatment, because the prepatent period of giardiasis has been reported to be around 12 days (25, 26). Moreover, Rangel *et al.* (26) reported parasitological negativization after 15 days post-treatment in 68 adult patients with intestinal amebiasis, which supports the results of the present study.

Although the parasitological cure we obtained was high (98%), parasitological relapse occurred in five patients three months after the administration of treatment. The explanation of this finding could well be the existence of high contamination of the environment, rather than

the occurrence of resistant strains. Although, these patients showed negative feces examination fifteen days after treatment, they might have remained infected after treatment. The lack of a placebo-treated group makes it difficult to evaluate any side effects such as abdominal pain, diarrhoea and flatulence, the most common side effects observed after secnidazole treatment; these were of mild to moderate intensity and lasted only a few hours.

The convenient and easy administration associated with single-dose therapy, combined with good tolerance, make secnidazole a suitable option for anti-giardial treatments to be used in human populations in tropical countries such as Venezuela.

Possible disadvantages could be associated with the use of single dose antiprotozoal treatments in patients with impaired absorption because of diarrhoea, or that the ease of such treatments may lead to frequent self medication. However, single dose treatments have a number of important advantages that result in excellent compliance: administration is simple, possible in mass treatments, and the intake of the drug can be checked easily. Since side effects will last for a short period, patients will not interrupt treatment. Moreover, the rate of emergence of resistance organisms could be lowered by the short period of drug action.

Prevention of tropical infectious diarrhoea should be a high priority for international health authorities.

These parasitic diseases are frequently associated with poor socio-economic conditions and inadequate sanitation, which require education and improved availability and quality of water. Although the development of vaccines against enteric pathogens is an area of active research, it would require a long time until the use of these is acceptable for mass human groups. Therefore the selection of adequate antiprotozoal drugs is a priority in tropical countries.

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