Effectiveness and Tolerability of 3-Day Mebendazole Treatment of *Giardia duodenalis* Infection in Adults and Children: Two Prospective, Open-Label Phase IV Trials

Roberto Cañete Villafranca[1]
Katia Brito Pérez [2]
Inara Brito Pérez [3]
Abel Iván Semper González[4]

[1] Dirección de Salud Pública/Consejo de Sociedades Cientificas de la Salud, Matanzas, Cuba, roberto.villafranca@infomed.sld.cu
[2] Clinica Docente Estomatológica Cesar Escalante/Periodoncia, Matanzas, Cuba, katiabrito.mtz@infomed.sld.cu
[3] Universidad de Ciencias Médicas/ Cardiología, Matanzas, Cuba, inarab.mtz@infomed.sld.cu
[4] Universidad de Ciencias Médicas/ Decanato, Matanzas, Cuba, decano.mtz@infomed.sld.cu

Background: *Giardia duodenalis* is the most common intestinal pathogenic protozoan infection reported in humans. Both in vitro studies and 4 separate, sequential, comparative clinical trials conducted by our group in Cuba demonstrated mebendazole activity against *G. duodenalis* infection in both children and adults. ***Objective:*** The 2 additional, prospective, open-label, Phase IV follow-up studies reported here were performed to further assess the effectiveness and safety profile of mebendazole in the outpatient treatment of *G. duodenalis* infection. ***Methods:*** Assenting children (n=522) whose guardians gave permission and consenting adults (n=423) diagnosed with *G. duodenalis* infection were given mebendazole (200 mg 3 times daily for 3 days). Medical histories and stool samples were obtained and physical/laboratory examinations were performed pre- treatment then repeated on days 3, 5, and 7 after treatment completion. The evaluation of efficacy (ie, cure) was based on parasitologic response to therapy. Participants were considered cured, if no *Giardia* trophozoites or cysts were found in any of the 3 posttreatment fecal specimens evaluated by direct wet mounts and/or after Ritchie concentration techniques. ***Results:*** No participant refused to be enrolled and all returned for follow-up examinations. At the end of the treatment, stool samples were negative in 450 out of 522 children (86.2%) and 392 of 423 adults (92.7%). Treatment was well tolerated. In adults, the only adverse effect reported was abdominal pain (6.2%). Side effects reported in children included abdominal pain (5.6%), nausea (2.9%), and vomiting (2.3%). Reported side effects were all mild, transient, and self-limited and did not require discontinuation of treatment or additional *medication.* ***Conclusions:*** Mebendazole may be an effective alternative treatment of *G. duodenalis* infections in both children and adults.

Key words: **clinical trial, drug therapy, *Giardia duodenalis*, mebendazole.**

HTTPS://DOI.ORG/10.1016/J.CURTHERES.2018.11.002

I. INTRODUCTION

Parasites are widely distributed throughout the world and represent an important cause of morbidity and mortality, especially in tropical and subtropical regions. Populations that experience the manifestations of socioeconomic inequality, including low in- come and consumption levels, poor housing, precarious employment, limited access to quality health services, fewer educational opportunities, inadequate access to clean water and sanitation services, and discrimination have the highest probability of being infected by parasites and suffer more because of them (1,2).

Giardia duodenalis is the most common intestinal pathogenic protozoan infection reported in humans. *Giardia* can cause severe gastrointestinal symptoms, including acute or chronic diarrhea with or without dehydration, abdominal pain, nausea, vomiting, bloating, or malabsorption, and in some cases has been associated with extra intestinal manifestations and long-term consequences such as chronic fatigue (1,2)

Because of the lack of a useful vaccine, prevention continues to be based on measures that interrupt the biological cycle of the parasite and treatment with antiparasitic drugs (3,4). Mebendazole (MBZ) has been used worldwide against soil-transmitted helminths because of its effectiveness even after single doses, limited absorption from the intestine, low incidence of adverse events, low cost, and broad spectrum of action against helminths but lack of effects on intestinal microbiota. The activity of MBZ demonstrated in vitro against protozoan and helminth organisms other than the common soil-transmitted helminths encouraged evaluation of its use for *G. duodenalis* infection (5-9).

A number of clinical trials performed in Cuba—3 in children and 1 in adults—that evaluated the efficacy and safety profile of MBZ in the treatment of *G. duodenalis* were used to propose an effective and well-tolerated MBZ dosage regimen to treat *G. duodenalis* infection (10-13).

Two additional open-label Phase IV studies were performed, 1 in children and the other in adults, to evaluate the effectiveness and safety profile of a 3-day MBZ dosing regimen for the treatment of *G. duodenalis* infections diagnosed in both pediatric and adult clinic outpatients in Matanzas, Cuba.

II. METHODS

I. STUDY SETTING

The trials were carried out in the outpatient clinics at the Centre of Hygiene, Epidemiology, and Microbiology, Matanzas City, Cuba.

II. ENROLLMENT AND PATIENT SELECTION

All medical doctors from the institution, as well as those from nearby hospitals and medical offices, were invited to refer children (aged 5–15 years) and adult patients (aged 18 years and older) who were seeking treatment for symptomatic acute *G. duodenalis* infections with or without diarrhea and positive stool samples for this intestinal parasite.

To be eligible for the study, patients had to have monoinfection with *G. duodenalis* (proven by microscopic examination of fecal wet mount samples and/or after Ritchie concentration carried out in the parasitology lab of the Centre of Hygiene, Epidemiology, and Microbiology, Matanzas City, Cuba. Patients were excluded from the study for any of the following: a history of sensitivity to any benzimidazole compound, having received any antiparasitic therapy in the preceding 4 weeks, diseases other than

giardiasis, participation in another clinical trial, pregnancy, or if judged by the study staff to be unlikely to attend all required follow-up examinations.

During 2010, the Cuban Public Health System accepted for the first time international standards that consider children patients who are up to age ≤17 years. However, when the Phase IV clinical trial in children began (in 2008), patients were considered to be children if they were between ages 5 and ≤15 years. This was the definition used for children used in our 3 previous comparative pediatric clinical trials. No patients aged 16 or 17 years were recruited into the pediatric study and only patients aged 18 years and older were recruited into the adult study. Therefore, no modification to the assent/consent process was needed after the change in definition of children.

The institutional review board of the Centre of Hygiene, Epidemiology, and Microbiology, Matanzas City, Cuba (internal referees code 2007-22) and the institutional review board of the University of Medical Sciences, Matanzas City, Cuba (external referees code 2007-56) both approved the protocols. Patients and/or parents were fully informed about the aims of the study and the drug under investigation and were told that their participation was optional. Written informed consent was obtained from adult patients or legal guardians before trial entry. Children gave their assent after being given some general information about parasitic infections, the implication of this parasite on human health, and treatments available.

III. EXPERIMENTAL DESIGN

Eligible patients who had none of the exclusion criteria and for whom written informed consent/permission/assent were obtained were enrolled in the study. All patients, both adults and children, were given MBZ (100 mg generic MBZ tablets; Reynaldo Gutierrez Pharmaceutical, Havana, Cuba) 200 mg 3 times daily for 3 days. 10 Patients made 3 follow-up visits (after 3, 5, and 7 days of treatment) during each of which a repeat stool sample collected. A standardized questionnaire in Spanish was used to record clinical signs and symptoms before and after treatment. Parents or legal guardians provided most questionnaire responses for pediatric patients. Physical examinations were performed before and after treatment end.

IV. COMPLIANCE

Comprehensive oral instructions were given to participants and/or parents/guardians by a trained professional from the Department of Parasitology in an attempt to increase compliance with drug administration, follow-up visit attendance, and performance of hygiene measures recommended to reduce the risk of reinfection. The presence of any of the following was considered evidence of treatment noncompliance: failure to attend a follow-up visit, reporting having not taken 1 or more prescribed dose, or discontinuing the drug without an instruction to do so from a study doctor.

V. EVALUATION OF EFFECTIVENESS

The effectiveness of the chemotherapy (ie cured or not) was evaluated based on the presence or absence of the parasite in stool specimens after therapy, as assessed by the same laboratory test done pretreatment, in all of their 3 fecal samples collected on days 3, 5, and 7 after treatment completing treatment. This was done to evaluate treatment failure, including the possibility of reinfection, which is common in developing countries like Cuba (14). They were advised to return to the clinic at any time if they or their child felt ill. A participant was considered cured only if no *Giardia* trophozoites or cysts were detected in any of the 3 posttreatment fecal specimens.

VI. EVALUATION OF SAFETY PROFILE

Regardless of their suspected causal relationship to study treatment, details of all reported adverse clinical events were considered potential adverse events (AEs), defined as any sign or symptom that did not exist before or became more pronounced following the start of MBZ. Serious AEs were defined as death; any life-threatening, disabling, or incapacitating event; or those requiring hospitalization.

VII. IN CASE OF TREATMENT FAILURE

All patients in whom MBZ failed to clear the infection were provided with rescue treatment consisting of secnidazole (500 mg generic secnidazole tablets; Reynaldo Gutierrez Pharmaceutical, Havana, Cuba); 30 mg/kg bodyweight given twice in 1 day for children or 500 mg secnidazole as a single dose for adults.

VIII. DATA MANAGEMENT AND STATISTICAL ANALYSIS

Data regarding the parasitologic response and AEs were recorded on predesigned case record forms by a professional from the Department of Parasitology and checked by the parasitologist responsible for the outpatient clinic before being subsequently analyzed to determine the frequency of therapeutic response and ad- verse effects using EpiInfo version 6.04 software (Centers for Dis- ease Control and Prevention, Atlanta, Georgia).

III. RESULTS

G. duodenalis is the most common human gastrointestinal protozoan parasite, has a worldwide distribution, affects people of all ages, and contributes significantly to the global burden of both diarrheal disease and post infectious chronic disorders (1). The global interest in *Giardia* increased in 2004, after its inclusion in the World Health Organization Neglected Diseases Initiative and the demonstration of its negative role in children's growth and development as well as its effects on quality of life in other age groups.

There are multiple techniques used to diagnose *Giardia* infection; however, direct fecal microscopy in combination with ether concentration technique—Ritchie technique—has been widely accepted largely as the most cost-effective alternative when is repeated 3 or 6 times on different days over a 10-day period. Other serologic or molecular methods used to diagnose *Giardia* are not always available for routine use, are costly, require highly trained personnel, and have no demonstrated superiority when they have been compared with the diagnostic methods used in these trials (2,5).

From the beginning of 2008 to the end of 2015, 522 children of both sexes (239 girls and 283 boys), aged 5 to 15 years with a weight range of 19 to 47 kg, were enrolled and treated for 3 days with MBZ, 200 mg 3 times a day, and 450 (86.2%) were assessed by microscopic examination (of direct wet mounts and/or after formol ether concentration of fecal samples collected 3, 5, and 7 days after treatment completion) to be cured of their infection (Table 1).

The children tolerated the regimen well. Only mild, transient, and self-limited side effects were reported. Abdominal pain (29 out of 522 patients [5.6%]), nausea (15 out of 522 patients [2.9%]), and vomiting (12 out of 522 patients [2.3%]) were the only side effects reported. No unexpected AEs occurred, and none of the children needed to discontinue treatment or receive additional drugs as a result of an AE (Table 2).

From 2010 to the end of 2015, an additional 423 adults of both sexes (208 women and 215 men), with a weight range of 50 to 86 kg, monoinfected by *G. duodenalis* were also enrolled and treated using the same MBZ regimen (ie, 200 mg 3 times daily for 3 days) (Table 1). Of these 423 enrolled patients, 392

(92.7%) were assessed as being cured. The only AE reported in these adults was abdominal pain in 26 out of 423 patients (6.2%) (Table 2).

MBZ (methyl 5-benzoyl-2-benzimidazole-carbamate) is a broad-spectrum anthelminthic drug introduced to the market in 1972 that is widely used for the treatment of different parasitic infections, mainly helminths (5,15–17). During its more than 40 years of use, the safety of MBZ has repeatedly been demonstrated. Even at the dose used in these trials, AEs were generally moderate, transient, and self-limiting similar to what was also observed in previous MBZ trials conducted in Cuba.

Table 1 Demographic characteristics of patients at admission as reported on data collection forms.

Variable	Mebendazole-treated group	
	Children (n = 522)	Adults (n = 423)
Sex*		
Male	283 (54.2)	215 (50.7)
Female	239 (45.8)	208 (49.3)
Age† (y)	8.4 (5-15)	30.8 (19-38)
Weight† (kg)	28.3 (19-47)	67.1 (50-86)

* Values are presented as n (%).
† Values are presented as mean (range).

Table 2 Parasitologic responses and drug-related adverse events after treatment, admission as reported on data collection forms. A patient under investigation could show more than 1 adverse event.

Variable	Mebendazole-treated group*	
	Children	Adults
Treated	522	423
Cured	450 (86.2)	392 (92.7)
Adverse event		
Abdominal pain	29 (5.6)	26 (6.2)
Nausea	15 (2.9)	–
Vomiting	12 (2.3)	–

* Values are presented as n or n (%).

Pharmacologic therapy remains an important component of *G. duodenalis* control in both industrialized and resource poor countries. Treatment failures have been observed with all of the common antigiardial agents, and drug resistance has been demonstrated in the laboratory. For decades, 5-nitroimidazole compounds have been the treatment of choice for giardiasis and are still widely used. However, reports of infections refractory to treatment with these compounds are becoming more common and have stimulated the search for alternative treatment options (5,18). Other clinical situations, such as postinfection lactose intolerance or reinfections, explain why treatment of *G. duodenalis* continues to be challenging and why not all patients treated with the standard, recommended therapies are cured (5).

While investigating the activity of MBZ against intestinal nematodes, Hutchison et al (19) noticed that the drug could cure some *G. duodenalis* infections. Results of subsequent in vitro and in vivo stud-

ies confirmed that MBZ had considerable anti- *Giardia* activity (6-13). Although not yet completely understood, it has been proposed that MBZ acts primarily through binding to *Giardia β*-tubulin, inhibiting microtubule polymerization and impairing glucose uptake. Additionally, MBZ at low concentration has been shown to inhibit *Giardia* attachment (5-9).

Both previously reported, comparative, variable treatment duration Phase III clinical trials (10-13) and extensive clinical use in Cuba have suggested that MBZ (200 mg 3 times daily for 3 days) (10) can be an effective and well-tolerated treatment for both children (aged 5–15 years) and adults monoinfected with *G. duodenalis*. Based on these and other published trials, MBZ, a drug already commonly used in human medical practice, may have additional usefulness.

There are at least 6 different classes of drugs in use for the treatment of *G. duodenalis* (20); however, none of them are universally effective in meeting all clinical needs. The effectiveness of MBZ, demonstrated on these Phase IV trials carried out in Cuba, provides evidence of the utility of the drug for this novel indication as an alternative treatment of infected individuals in a population.

The absence of other Phase IV clinical trials around the world evaluating the effective- ness of MBZ against *Giardia* in other populations prohibits the authors from comparing these results to those in other environments and population. However, the percent of children and adults cured with the administered dose, comparable to what was found in previous Phase III trials in Cuba, support the use of MBZ in other clinical settings. [10–13]

Study patients who were not cleared of infection after treatment with MBZ were treated with secnidazole; a drug with a different mode of action. Secnidazole affects electron transport of the parasite, whereas MBZ probably exerts its antigiardial effects by interaction with tubulin in the *Giardia* cytoskeleton. The difference in the mode of action, inclusion of secnidazole as a first-line drug against *Giardia*, approval of this drug by the Cuban Ministry of Public Health for this use, as well as the opportunity to use it in a single dose were the reasons secnidazole was selected as the rescue treatment in these Phase IV trials. All study patients who were not cured with MBZ were cured after treatment with secnidazole and bitter taste was the only side effect noted by 4 adults.

Another important consideration is the cost of the drug. In Cuba, a full treatment course with MBZ as used in these trials will cost 3 times less if metronidazole were used instead.

Effective management of *G. duodenalis* infections has been considered problematic, especially in resource-poor tropical and sub- tropical countries. Although additional studies in other populations are needed, the availability of low-cost MBZ in almost all countries, its long history of effective use against helminthic infections, its low frequency of AEs, and its demonstrated effectiveness to treat *Giardia* infection increases the potential importance of this drug for national public health systems around the world.

IV. CONCLUSIONS

The results of these trials are in agreement with previous studies carried out in Cuba suggesting that MBZ can be used effectively as an alternative treatment of *G. duodenalis* infections, both in children and in adult patients.

REFERENCES

1. Ortega-Pierres MG, Jex AR, Ansell BRE, Svärd SG. Recent advances in the genomic and molecular biology of *Giardia*. Acta Trop. 2017 Sep 6. pii: S0001-706X(17)30857-4.
2. Humbert P, Guichard A, Bennani I, Chiheb S. *Giardia duodenalis* and its involvement in skin diseases. Ann Dermatol Venereol. 2017 Nov; 144(11):676- 84.
3. Cañete R, Díaz MM, Avalos García R, Laud Martinez PM, Ponce FM. Intestinal parasites in children from a day care centre in Matanzas City, Cuba. PLoS One. 2012; 7:e51394.
4. Ansell BR, McConville MJ, Ma'ayeh SY, Dagley MJ, Gasser RB, Svärd SG, et al. Drug resistance in *Giardia duodenalis*. Biotechnol Adv. 2015 Nov 1; 33(6 Pt 1):888- 901.
5. Cañete R, Escobedo AA, Almirall P, González ME, Brito K, Cimerman S. Mebendazole in parasitic infections other than those caused by soil-transmitted helminths. Trans R Soc Trop Med Hyg. 2009; 103:437- 42.
6. Cedillo-Rivera R, Munoz O. In vitro susceptibility of *Giardia lamblia* to albendazole, mebendazole and other chemotherapeutic agents. J Med Microbiol. 1992; 37:221- 4.
7. Morgan UM, Reynoldson JA, Thompson RC. Activities of several benzimidazoles and tubulinin hibitors against *Giardia* spp. In vitro. Antimicrob Agents Chemother. 1993; 37:328- 31.
8. Chávez B, Cedillo-Rivera R, Martínez-Palomo A. *Giardia lamblia*: ultrastructural study of the in-vitro efecto of benzimidazoles. J Parasitol. 1992; 39:510- 5.
9. Katiyar SK, Gordon VR, McLaughlin GL, Edlind TD. Antiprotozoal activities of benzimidazoles and correlations with beta-tubulin sequence. Antimicrob Agents Chemother. 1994; 38:2086- 90.
10. Escobedo AA, Cañete R, González ME, Pareja A, Cimerman S, Almirall P. A randomized trial comparing mebendazole and secnidazole for the treatment of giardiasis. Ann Trop Med Parasitol. 2003; 97:499- 504.
11. Cañete R, Escobedo AA, González ME, Almirall P, Cantelar N. A randomised, controlled, open- label trial of a single day of mebendazole versus a single dose of tinidazole in the treatment of giadiasis in children. Curr Med Res Opin. 2006; 22:2131- 6.
12. Cañete R, Escobedo AA, González ME, Almirall P. Randomized clinical study of five days therapy with mebendazole compared to quinacrine in the treatment of symptomatic giardiasis in children. World J Gastroenterol. 2006; 12:6366- 70.
13. Almirall P, Escobedo AA, Ayala I, Alfonso M, Salazar Y, Cañete R, et al. Mebendazole compared with secnidazole in the treatment of adult giardiasis: a randomised, no-inferiority, open clinical trial. J Parasitol Res. 2011; 2011: 636857.
14. Cañete R, Campos Y, Valdes R, Rodriguez P. Prevalence and factors associated with intestinal parasitic infection among schoolchildren from Jagüey Grande Municipality in Matanzas Province, Cuba. West Indian Med J. 2017; 66 (2):361- 6.

15. Torp-Pedersen A, Jimenez-Solem E, Cejvanovic V, Poulsen HE, Andersen JT. Birth outcomes after exposure to mebendazole and pyrvinium during pregnancy – A Danish nationwide cohort study. J Obstet Gynaecol. 2016 Nov; 36(8):1020- 5.

16. Joseph SA, Montresor A, Casapía M, Pezo L, Gyorkos TW. Adverse Events from a Randomized, Multi-Arm, Placebo-Controlled Trial of Mebendazole in Children 12-24 Months of Age. Am J Trop Med Hyg. 2016 Jul 6; 95(1):83- 7.

17. Silber SA, Diro E, Workneh N, Mekonnen Z, Levecke B, Steinmann P, et al. Efficacy and Safety of a Single-Dose Mebendazole 500 mg Chewable, Rapidly-Disintegrating Tablet for *Ascaris lumbricoides* and *Trichuris trichiura* Infection Treatment in Pediatric Patients: A Double-Blind, Randomized, Placebo-Controlled, Phase 3 Study. Am J Trop Med Hyg. 2017 Dec; 97(6):1851-1856.

18. Cañete R. Mebendazole is a potential alternative in the treatment of *Giardia duodenalis* Infection. Curr Ther Res Clin Exp. 2016 May 31; 80:1- 2.

19. Hutchison JG, Johnston NM, Plevey MV, Thangkhiew I, Aidney C. Clinical trial of mebendazole, a broad-spectrum anthelminthic. Br Med J. 1975; 2:309- 10.