# A Randomized, Controlled, Open-label Trial Evaluating the Efficacy and Safety of Chloroquine in the Treatment of Giardiasis in Children

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***ABSTRACT***

***Background:*** Giardia duodenalis *is among the commonest protozoan parasites in the intestinal tract of humans and may cause significant morbidity worldwide. Although there are several antigiardial agents, treatment failures have been commonly reported.*

***Objective:*** *To compare the efficacy and safety of chloroquine (CQ) versus metronidazole (MTZ) in the treatment of children with confirmed* G duodenalis *mono-infection.*

***Methods:*** *A randomized, controlled, open-label trial was carried out at the Cuban Institute of Gastroenterology. One hundred and twenty-two children were randomly assigned to receive either CQ (10 mg/Kg bodyweight twice a day for five days) or MTZ [15 mg/Kg bodyweight divided in three daily does for five days]. All children were asked to provide three faecal samples on days 3, 5 and 7 after treatment completion. Children were considered to be cured, if no* Giardia *trophozoites or cysts were found in any of the three post-treatment faecal specimens evaluated by direct wet mounts and/or after Ritchie concentration techniques.*

***Results:*** *The frequency of cure was a little higher for CQ than for MTZ but the difference was not statistically significant. Headache was more common in patients treated with CQ as was bitter taste. Yellowish colouration of the urine was more frequent in the MTZ treated group.*

***Conclusion:*** *Chloroquine, for five days, is as efficacious as the recommended treatment with MTZ in children infected with* G duodenalis.

**Keywords**: Children, chloroquine, *Giardia duodenalis* infection, metronidazole

# Estudio de Etiqueta Abierta, Randomizado y Controlado, para Evaluar la Eficacia y Seguridad de la Cloroquina en el Tratamiento de la Giardiasis en Niños

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***RESUMEN***

***Antecedentes:*** *La giardia lamblia (*giardia duodenalis*) se halla entre los parásitos protozoos más comunes del tracto intestinal de los seres humanos, y puede causar una morbilidad significativa a nivel mundial. Aunque existen varios agentes antigiardiales, se han reportado fracasos en el tratamiento*

***Objetivo:*** *Comparar la eficacia y seguridad de la cloroquina (CQ) con el metronidazol (MTZ) en el tratamiento de los niños con mono-infección de* G duodenalis.

***Métodos:*** *En el Instituto Cubano de Gastroenterología, se llevó a cabo un estudio de etiqueta abierta, randomizado y controlado. Ciento veintidós niños fueron aleatoriamente designados para recibir bien CQ (10 mg/Kg peso corporal dos veces por día durante cinco días) o MTZ (15 mg/Kg peso corporal dividido en tres dosis diarias por un período de cinco días). A todos los niños se les tomaron tres pruebas fecales los días 3, 5 y 7 después de terminado el tratamiento. Los niños se daban por curados, si no había presencia de tropozoítos o quistes de giardia en ninguno de los tres especimenes fecales post-tratamiento, evaluados directamente con portaobjetos húmedos y/o después de técnicas de concentración de Ritchie.*

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***Resultado:*** *La frecuencia de la cura fue un poco más alta para CQ que para MTZ, pero la diferencia no fue estadísticamente significativa. El dolor de cabeza fue más común en pacientes tratados con CQ que el sabor amargo. La coloración amarillenta de la orina fue más frecuente en el grupo tratado con MTZ.*

***Conclusión:*** *La cloroquina, administrada durante cinco días, es tan eficaz como el tratamiento recomendado con MTZ en niños infectados con giardias lamblias.*

**Palabras claves:** Niños, cloroquina, infección por *Giardia duodenalis*, metronidazol.

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## INTRODUCTION

*Giardia duodenalis* (*G duodenalis*) is a microbial eukaryotic parasite that represents a major cause of diarrhoea in children and in travellers worldwide (1, 2). Findings indicate that the infection causes diarrhoea *via* a combination of intestinal malabsorption and hypersecretion (2) and there is evidence that the majority of the world's population still lives in areas where contaminated drinking water with this parasite is common (3). Infection is spread by ingestion of contaminated food and water or by the fecal-oral route from person-to-person in settings with poor faecal hygiene *eg*, daycare centres, institutional settings or *via* sexual contact. There is a general consensus that the standard chlorination techniques used to control bacteria do not destroy *Giardia* cysts (4).

Classically, 5-nitro-imidazole compounds, quinacrine and furazolidone have been used for the treatment of patients with giardiasis. However, treatment failures and drug resistance have been commonly reported (5−8). Chloroquine, an inexpensive drug used as an antimalarial, has been found to have antigiardial activity *in-vitro* (9, 10) but its clinical efficacy against human giardiasis remains almost unknown. The aim of the present study was to compare the efficacy and safety of CQ *versus* MTZ in the treatment of children infected with *G duodenalis*.

## SUBJECTS AND METHODS

The study, a randomized controlled open-label trial, was carried out from September 2006 to July 2007 at the Institute of Gastroenterology, Havana City, Cuba.

The subjects were patients infected with *G duodenalis* (aged 5 to 15 years) who visited the centre (with or without clinical manifestations). A physical examination was carried out and a standardized questionnaire was applied before starting treatment and at the end of the study. The criteria for inclusion were: (a) mono-infection with *G duodenalis* (proven by microscopic examination of faecal samples, as direct wet mounts and/or after Ritchie concentration) [11], (b) able to take oral medication, (c) not known to have contraindications to CQ or MTZ, with no history of disease other than giardiasis and (d) who had not received any antiparasitic chemotherapy in the previous four weeks. Those cases that were not able to attend for follow-up examinations were excluded from the study.

Ethical clearance was granted by the Institutional Research and Ethics Committee (Institutional Review Board) and by the Research and Ethics Committee of the Centre for Hygiene, Epidemiology and Microbiology, Matanzas City, Cuba (Independent Review Board). Patients signed an informed consent after being fully informed about the aim of the study and the characteristics of the drugs under investigation. The doctors also signed the agreement as well as the patients and parents or legal guardians. The Protocol was kept with the code (IGE-02-2006) at the Research Department of the Cuban Institute of Gastroenterology. A full copy of that protocol was also kept at the specialized library of the Institution.

The sample size for each treatment group (*n*) needed to ensure sufficient statistical power (80%) to reject the null hypothesis that CQ and MTZ are not equally effective (in terms of a parasitological cure) with a significant level of 5%, was calculated using EpiInfo 6.0 software (Public Health Domain software, CDC, Atlanta, GA, USA).

One hundred and twenty-two patients were required. The patients enrolled were divided into two treatment arms using a computer-based randomization table to receive either: CQ [10 mg/ Kg bodyweight twice a day for five days] or MTZ [15 mg/Kg bodyweight divided into three doses daily for 5 days (n = 61)]. Both drugs were provided by Reynaldo Gutierrez Pharmaceutical, Havana City, Cuba.

Treatment allocations were kept in envelopes, which were opened only on admission to the study, after obtaining the signed agreement, availability for follow-up examinations and all inclusion and exclusion criteria were checked. Each envelope was labelled beforehand. Patients and those providing the treatments were not blinded to the treatment allocation; however, to overcome this weakness, the laboratory personnel who analysed the faecal samples were unaware of the treatment allocation.

Comprehensive oral instructions regarding the study were given to all patients. All of them were investigated for compliance to treatment, and one of the following requirements was considered to indicate treatment non-compliance: (1) failure to attend the follow-up visits, (2) not taking one or more dose at the instructed level and duration and (3) discontinuation of the drug without first asking the consent of the doctor.

Treatment efficacy was determined based on parasitological cure rate for the therapy assessed. To avoid apparent treatment failure due to re-infection, the patients were asked to provide three faecal samples on days 3, 5 and 10 after treatment completion. A patient was only considered to be cured if no *Giardia* trophozoites or cysts could be found in any of the three post-treatment faecal specimens.

All cases in which recommended medication failed were provided with rescue treatment using secnidazole 30 mg/kg bodyweight given three times daily for five days.

An adverse drug reaction was defined as noxious and unintended responses that did not exist beforehand, or those signs and symptoms that were present at the inclusion but became more serious following the commencement of the treatment. Unexpected adverse drug reaction was defined as an adverse drug reaction which was not consistent with the product information in terms of nature or severity. Serious adverse drug reaction was defined as those resulting in death or life-threatening events. All adverse drug reactions were graded as mild, moderate or severe.

The data regarding the parasitological response and adverse events were noted on pre-designed record forms and subsequently analysed to determine the frequency of each response/effect using EpiInfo 6.0 software (Public Health Domain software, CDC, Atlanta, GA, USA). The statistical significance of differences between mean values was determined using the Student's *t*-test. Where appropriate, Fisher exact test was used to establish the significance of differences in proportions.

## RESULTS

One hundred and twenty-two children of both genders, aged from 5 to 15 years, were included on the study, 61 in each treatment group. Both treatment groups were similar with respect to gender, race and mean age. The frequency of parasitological cure after CQ was a little higher 52 out of 61 (85.25%) than for MTZ 45 out of 61 (73.77%), but the difference was not statistically significant ($p = 0.1163$) [odds ratio; 2.05 (confidence interval, CI): 0.76−5.63] (Table 1).

Both treatments were well tolerated with only mild, transient and self-limited adverse events notified. Adverse events recorded are listed in Table 1. Of the children included, fifty-five (45.08%) had no adverse events, but sixty-seven (54.92%) − thirty-eight in the CQ group (62.29%) and twenty-nine (47.54%) in the MTZ group − reported at least one of such events, none of them unexpected ($p = 0.1015$) [odds ratio; 1.82 (CI): 0.83, 4.01]. Headaches were more common in patients treated with CQ ($p = 0.0435$) [odds ratio; 2.56 (CI): 0.93, 7.21] bitter taste ($p = 0.0000025$) [odds ratio; 0.03 (CI): 0.00, 0.24] and yellowish colouration of the urine ($p = 0.0001$) [odds ratio; 0.09 (CI): 0.01, 0.43] were more frequent in MTZ treated group.

Table.1: Cure rates and drug-related adverse events notified by treatment groups

| **Treated** | **Chloroquine group (n = 61)** | | **Metronidazole group (n = 61)** | |
|---|---|---|---|---|
| | **n** | **(%)** | **n** | **(%)** |
| Cure rate | 52 | (85.25) | 45 | (73.77) |
| Any adverse event | 38 | (62.29) | 29 | (47.54) |
| Abdominal pain | 8 | (13.11) | 3 | (4.92) |
| Nausea | 3 | (4.92) | 2 | (3.29) |
| Bitter taste | 1 | (1.64) | 21 | (34.43)† |
| Yellowish colouration of the urine | 2 | (3.29) | 17 | (27.87)† |
| Headache | 17 | (27.87)† | 8 | (13.11) |
| Sickness | 11 | (18.03) | 4 | (6.56) |

* One patient could have had more than one adverse event.
† Statistically significant ($p < 0.05$).

## DISCUSSION

*Giardia duodenalis* is a common gastrointestinal protozoan and a well-recognized cause of abdominal discomfort, diarrhoea and abdominal pain worldwide (1, 2, 12, 13). In developing countries, the prevalence of human giardiasis is around 20% (4−43%), compared with 5% (3−7%) in developed countries, where it is associated mainly with travelling and waterborne outbreaks (12, 14, 15).

Chloroquine is an inexpensive drug used as antimalarial (8, 16), against *Entamoeba histolytica* (8) and in the control of some chronic inflammatory diseases like rheumatoid arthritis (17) but its usefulness in giardiasis is still under investigation. Gordts B *et al,* (9) in 1985 tested 25 *Giardia* isolates and found that more than a half of the isolates were very susceptible to CQ *in-vitro*. Similarly, Baveja *et al* (10) in 1998 demonstrated the usefulness of CQ *in-vitro* reducing the ability of *Giardia* to attach and colonize.

Clinical studies evaluating the efficacy and safety of CQ in *G duodenalis* infection are almost non-existent in medical databases but in the last century, three Cuban articles evidenced that CQ cleared more than 70% of the infection either in children or in adults (18−20). The first index article in a high impact scientific magazine evaluating the efficacy and safety of CQ in this relatively novel indication was published in 2003 (21). It was a comparative trial in which 165 Cuban children with confirmed giardiasis were randomized to receive albendazole, CQ or tinidazole. The article demonstrated that tinidazole and CQ appeared equally effective curing 91% and 86% of the children treated, respectively, and significantly better than albendazole, which only cured 62% of the children evaluated and concluded that CQ was a good alternative to tinidazole for the treatment of paediatric patients with giardiasis.

In the present study, the frequency of parasitological cure after CQ was a little higher than for MTZ but the difference was not statistically significant and corroborates

the usefulness of this alternative drug against *G duodenalis* infection in Cuban children. The efficacy of CQ was similar to that reported by Escobedo *et al* (21) in Cuban children.

On the other hand, the efficacy demonstrated with MTZ was less than those reported by other authors. A study published by Busatti *et al* (22) demonstrated that MTZ and its derivate were highly effective against *Giardia* trophozoites *in vitro* being additionally safe for human mononuclear cells presented on the culture. *In vivo* studies have been demonstrating the excellent efficacy of MTZ in *G duodenalis* (8).

Sadjjadi *et al* (23), in a trial evaluating the efficacy and safety of mebendazole and MTZ in the treatment of infected children, aged 7 to 15 years, showed an efficacy of 90% with MTZ similar to the 85.3% reported by Saffar *et al,* in 2005 (24) or the 89.1% reported by Yereli *et al* (25) in 2004.

Adverse events reported in both treatment groups were all mild, transient and self-limiting. No previously undescribed adverse events occurred and none of the children included needed to discontinue treatment or receive additional drugs as a result of an adverse event. The adverse events notified generally occurred at frequencies similar to those observed in previous trials using the same drugs.

In a phase I trial evaluating the pharmacokinetic and safety of CQ and another experimental anti-malarial in a healthy voluntary group, Mzayek *et al* (26) evidenced, like in the first Cuban trial (21), that headache, abdominal pain and sickness were the adverse events more frequently reported similar to Laufer *et al* (27) when treating African children infected by *Plasmodium falciparm*. Jong and Nothdurft (28), in a review article published in 2001, and Santaella and Fraunfelder (29) in an excellent work published in 2007 demonstrated that headache, abdominal pain and sickness were among the commonest adverse events in patients treated with CQ and were more serious and intense when the drug were taken for a long period or in high quantity. In the latter case ocular adverse effects, alopecia, neuromuscular disorders and blood disturbances could also occur.

Yellowish colouration of the urine and a bitter taste were the commonest adverse events notified in the MTZ treated group. Similar results were reported by Sadjjadi *et al* (23) in a trial evaluating the efficacy and safety of mebendazole and MTZ in children from Iran. Alizadeh *et al* (30) also reported similar results from Iran in adult patients. It's widely accepted that MTZ may produce yellowish colouration of the urine, bitter taste, anorexia, sickness and headache (31, 32).

The present study confirms that CQ is an excellent alternative treatment for children aged 5 to 15 years infected with *G duodenalis* because its efficacy is similar to those notified with MTZ one of the drugs considered until now, the gold standard in the treatment of these protozoa. Chloroquine could be highly important in cases refractory to conventional treatments or in cases co-infected with *Entamoeba histolytica* or *Plasmodium* spp.

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**DECLARATION OF INTEREST**

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