



Original Article

5-Nitroimidazole refractory giardiasis is common in Matanzas, Cuba and effectively treated by secnidazole plus high-dose mebendazole or quinacrine: a prospective observational cohort study

R. Cañete¹, A.L. Noda², M. Rodríguez³, K. Brito⁴, E. Herrera⁴, P.-E. Kofoed^{5,6}, J. Ursing^{7,8}

¹ Council of Scientific Societies of Health, University of Medical Sciences, and Centre for Hygiene, Epidemiology and Microbiology, Matanzas City, Cuba
² Paediatric Hospital 'Eliero Noel Gamalo', Matanzas City, Cuba
³ Haematology and Immunology Institute, Havana, Cuba
⁴ University of Medical Sciences, Matanzas, Cuba
⁵ Rindim Health Project, INDEPTH Network, Bissau, Guinea-Bissau
⁶ Department of Paediatrics, Lillhögskolan Hospital, Stockholm, Denmark
⁷ Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden
⁸ Department of Infectious Diseases, Danderyd Hospital, Stockholm, Sweden

G. intestinalis... the most common intestinal pathogenic protozoan infection reported in humans.

Worldwide distribution

280 million infected each year.

Mainly in tropical and subtropical areas

In Cuba, the prevalence varies between 25% and 55%.

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.**

5-nitroimidazole compounds / first-line treatment worldwide.

Therapeutic failures are common / 5-nitroimidazole refractory giardiasis is increasing.

Re-treatment options include **taking 5-nitroimidazoles for longer periods** or at **higher doses**; treating with **alternative drugs** such as nitazoxanide, quinacrine, mebendazole, albendazole, furazolidone and paromomycin; or **combining drugs with different modes of action.**

In Cuba, giardiasis is typically treated with 5-nitroimidazoles.

Failure rates with metronidazole and secnidazole were approximately 15% and 10%, respectively, in studies conducted in 2009 and 2010.

5-Nitroimidazole refractory giardiasis appears to have increased in Matanzas during the last few years, though this has not been studied.

There is **no recommended treatment ladder for 5-nitroimidazole refractory giardiasis** but repeated treatment with different 5-nitroimidazoles is common.

Both mebendazole and quinacrine have been shown to effectively cure approximately 85% of individuals when used as first-line treatment in Cuba.

The aim of this study was to evaluate the effectiveness and tolerability of repeated 5-nitroimidazole treatment and standard-dose secnidazole combined with high-dose mebendazole for the treatment of 5-nitroimidazole refractory giardiasis.

Methods

Study design, participants, and setting

From January 2017 to October 2018 a prospective, observational cohort study was carried out at the hospital Faustino Perez Hernandez, Matanzas, Cuba.

Hospital characteristics / Patient reference

Patients with **signs and/or symptoms suggestive of gastrointestinal infection** referred to the parasitology outpatient clinic had stools examined for *G. intestinalis*.

Stool examination was part of the routine hospital services and consisted of microscopic examination of faecal wet-mount samples and examination after Ritchie concentration.

Microscopy was performed at the parasitology laboratory of the Centre of Hygiene, Epidemiology and Microbiology.

Routine PCRs for detection of *G. intestinalis* were not available.

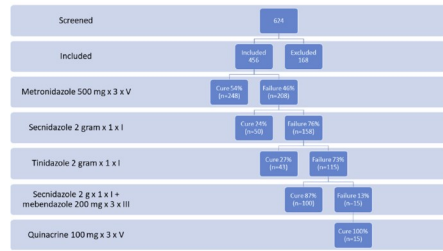


Fig. 1. Flow diagram. Cases for exclusion were as follows: not deemed likely to complete follow up (n = 95), age > 70 years (n = 24), pregnancy (n = 22), hypersensitivity (n = 8), unwilling to give informed consent (n = 5). The overall 5-nitroimidazole treatment success rate was 75% (341/456).

Table 1 Baseline characteristics and symptoms of patients before each round of treatment

Treatment given	Metronidazole	Secnidazole	Tinidazole	Secnidazole + mebendazole	Quinacrine
Number	456	248	208	115	15
Median age (range), years	32 (19–69)	36 (22–72)	39 (23–71)	42 (21–69)	29 (22–67)
Sex (male:female)	183:273	87:161	78:130	44:71	6:9
Median weight (range), kg	73 (65–82)	70 (63–79)	71 (65–80)	73 (65–78)	70 (64–74)
Abdominal pain, n (%)	218 (48%)	99 (40%)	71 (34%)	34 (30%)	5 (33%)
Diarrhoea, n (%)	160 (35%)	74 (30%)	60 (29%)	28 (24%)	4 (27%)
Bloating, n (%)	186 (41%)	95 (38%)	62 (30%)	25 (22%)	3 (20%)
Nausea, n (%)	96 (21%)	44 (18%)	19 (9%)	11 (10%)	3 (20%)
Fatigue, n (%)	80 (17%)	28 (11%)	17 (8%)	6 (5%)	1 (7%)
Weight loss, n (%)	79 (17%)	32 (13%)	16 (8%)	5 (4%)	1 (7%)

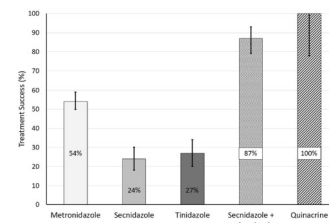


Fig. 2. Treatment outcomes after treatment with metronidazole, secnidazole, tinidazole, secnidazole plus mebendazole, and quinacrine. The error bars represent 95% CI.

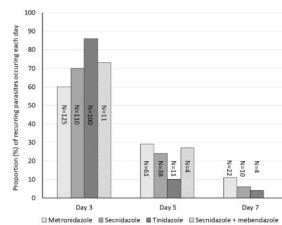


Fig. 3. Proportion of *Giardia* (shed/dstools) detected on days 3, 5 and 7 after end of treatment with metronidazole, secnidazole, tinidazole and secnidazole plus mebendazole. The number of treatment failures in each colour are shown as n = no.

Table 2 New or more severe symptoms since start of treatment elicited by active questioning on days 3, 5 and 7 after end of treatment

	Metronidazole	Secnidazole	Tinidazole	Secnidazole + mebendazole	Quinacrine
Number	456	248	158	115	15
Abdominal pain, n (%)	142 (31%)	40 (16%)	28 (18%)	25 (22%) ^a	4 (27%) ^b
95% CI	275–378	145–253	125–230	135–305	85–95
Nausea, n (%)	97 (21%)	33 (16%)	24 (15%)	19 (17%) ^a	4 (27%) ^b
95% CI	185–255	115–225	105–225	105–255	85–95
Vomiting, n (%)	81 (18%)	31 (15%)	22 (14%)	19 (16%) ^a	3 (20%) ^b
95% CI	145–225	105–205	95–205	105–255	45–85
Bitter taste, n (%)	37 (8%)	12 (6%)	8 (5%)	0	0
95% CI	85–115	35–105	25–105	0	0
Yellowish coloration of urine, n (%)	24 (5%)	8 (4%)	3 (2%)	0	0
95% CI	35–85	25–75	0/45–55	0	0

^a The frequency of reported symptoms did not differ significantly between patients taking secnidazole alone compared with secnidazole and mebendazole.
^b The frequency of reported symptoms did not differ significantly between patients taking quinacrine and any other drug nor when compared with the 5-nitroimidazoles, as a group.

To summarize, in a cohort of 456 adult Cuban patients the frequency of metronidazole refractory giardiasis was 48% and repeated treatment with tinidazole and secnidazole was suboptimal.

High-dose mebendazole plus secnidazole was well tolerated and cured 87% (100/115) and quinacrine was well tolerated and cured 100% (15/15) of patients with 5-nitroimidazole refractory giardiasis.

The clinical implications of the results are that repeat treatment with 5-nitroimidazoles should be avoided and that mebendazole plus secnidazole is an effective and well-tolerated treatment option for 5-nitroimidazole treatment failures.

The study also adds to previous data indicating that that quinacrine is safe and effective.