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BRIEF REPORT

Quinacrine Treatment of Nitroimidazole-Refractory Giardiasis

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Background. Limited evidence exists on efficacy and tolerability of quinacrine for nitroimidazole-refractory giardiasis.

Methods. Nitroimidazole-refractory giardiasis cases, defined as microbiologically (microscopy and/or PCR) confirmed treatment failure after 2 courses, during 2008–2020, were retrospectively identified.

Results. Of 87 patients, 54 (62%) had visited India. Quinacrine was used in 54 (62%); 51 received monotherapy and 3 combined with metronidazole. Only 3 had positive stool samples with persisting symptoms after quinacrine treatment (94% parasitological efficacy) and all were cured after a second treatment. One (1.9%) had mild adverse effects recorded.

Conclusions. Quinacrine is an effective treatment for nitroimidazole-refractory giardiasis with good tolerability.

Keywords. adverse effects; epidemiology; giardiasis; nitroimidazole refractory; nitroimidazole resistance; quinacrine; tolerability; treatment.

Giardia intestinalis, also known as *Giardia lamblia* or *Giardia duodenalis*, is one of the most common intestinal parasitic protozoa reported in humans worldwide. It can cause both acute and chronic diarrhea with malabsorption, abdominal pain, bloating, fatigue, and weight loss, but asymptomatic carriage is not uncommon [1, 2]. First-line treatment for giardiasis is the 5-nitroimidazoles (most commonly metronidazole and tinidazole) [1–3]. In recent years, giardiasis refractory to nitroimidazoles has, however, become a challenging problem worldwide [4–6]. Alternative agents that have been tried include nitazoxanide, paromomycin, albendazole, mebendazole, and chloroquine, sometimes in combination with a nitroimidazole, but with varying and often suboptimal cure rates [1–4, 7]. The old drug quinacrine is increasingly being used as an alternative treatment, although availability is limited in many countries [3–7].

Quinacrine was originally developed as an antimalarial drug but due to adverse effects it was replaced by chloroquine [2, 8]. Quinacrine was used to treat giardiasis already in the 1930s [9] and was reported to be 90% to 95% effective [2, 10]. In the 1960s it was largely replaced by the well tolerated 5-nitroimidazole derivatives after studies had shown their efficacy against giardiasis [2]. Only a few small studies exist that have evaluated quinacrine as a treatment alternative for nitroimidazole-refractory giardiasis [3–7].

The primary aim of this study was to assess the efficacy and tolerability of quinacrine in a larger patient cohort with well-defined nitroimidazole-refractory giardiasis. A secondary aim was to assess the infections' geographic origins.

METHODS

Patients with giardiasis at the Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden, during January 2008 through April 2020 were retrospectively identified by medical records' diagnostic codes. Data on patients' demographics, travel history, diagnostics, treatment, and outcome were collected from medical records. Patients were included if they had microbiologically proven giardiasis, either by positive stool microscopy (wet mount) or stool polymerase chain reaction (PCR; BD-MAX Enteric Parasite Panel). Microscopy was performed during the whole study period while PCR has routinely been performed since 2016. Nitroimidazole-refractory giardiasis was defined as having a positive stool microscopy and/or PCR for *G. intestinalis* after completing at least 2 treatment courses with nitroimidazoles. Patients who did not receive any medical treatment at our center were excluded from analyses of efficacy and tolerability. At our clinic, patients treated for nitroimidazole-refractory giardiasis are followed clinically and instructed to provide 3 separate stool samples, at least 7 days after completion of treatment and thereafter weekly [11]. Parasitological treatment failure was defined as a positive follow-up stool sample by microscopy and/or PCR for *G. intestinalis*.

Data are given as number of observations, medians, and ranges. Pearson χ^2 test, or Fisher exact test when needed, were used for comparing categorical data. The Mann-Whitney *U* test was used to compare continuous data between groups. For statistical analyses, JMP8.0.2 (SAS Institute) was used. The study was approved by the Regional Ethical Review Board in Stockholm and did not require informed consent from the patients due to its retrospective nature (2018/2309–31/1).

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RESULTS

Patients and Origin of Infection

During the study period, 201 patients with microbiologically verified intestinal giardiasis were identified. Among those with persistent disease after 1 nitroimidazole course, 24% (28/115) were cured with repeated courses. A total of 87 cases (43%) were nitroimidazole-refractory according to our definition. The patients' characteristics are shown in Table 1. Of 87 patients, 59 (68%) had acquired the infection in South-Asia (Indian subcontinent) compared to 32 of 114 (28%) with nonrefractory giardiasis ($P < .0001$). Among 91 patients who had been to the Indian subcontinent, 59 (65%) had nitroimidazole-refractory giardiasis, compared to 28 of 110 (25%) who had visited other regions ($P < .0001$).

Treatment Efficacy

A total of 85 patients with nitroimidazole-refractory giardiasis were treated (an additional 2 were regarded as asymptomatic carriers and were not treated), of which 54 (64%) received quinacrine (Mepacrine; BCM Specials), either directly (32 patients) or following other treatments (22 patients); 51 as monotherapy and 3 directly in combination with metronidazole. The administered adult quinacrine dose was 100 mg 3 times per day; 35 patients were treated for 5 days, 1 for 6 days, 17 for 7 days, and 1 for 10 days. Follow-up stool samples were provided by 49 of 54 (91%) quinacrine-treated patients at least 7 days after treatment (47 provided 2 or more stool samples, while 2 patients provided only 1), and 51 (94%) had a clinical follow-up at our clinic (2 of the 3 remaining patients had other medical contacts after quinacrine treatment, with medical records available for all). Three patients had positive stool samples for *G. intestinalis* after quinacrine treatment, 2 treated for 5 days and 1 for 7 days (94% parasitological efficacy), all with persisting symptoms (Table 2). All 3 were cured, verified with negative stool samples and resolution of symptoms, after a second course of quinacrine: 1 received a prolonged monotherapy (for 7 days), while 2 received quinacrine as a combination treatment with albendazole for 7 days or paromomycin for 10 days. An additional 4 patients had mild gastrointestinal symptoms after quinacrine treatment, of which 3 had repeated negative stool examinations (5, 3, and

Table 1. Characteristics and Geographic Origin of Infection in 201 Patients with Intestinal Giardiasis

Characteristics	Nitroimidazole-Refractory Giardiasis (n = 87)	Nonrefractory Giardiasis (n = 114)	*P* Value[a]
Median age, y, (range)	37 (3–78)	35 (1–85)	NS
Female sex	38 (44)	58 (51)	NS
Immunosuppression	2 (2)[b]	4 (4)[c]	NS
Type of travel			
Tourism	67 (76)	68 (60)	
Business or studies	10 (12)	10 (9)	
Visiting friends and relatives	2 (2)	16 (14)	
Migration	4 (5)	4 (4)	
Not travel related	4 (6)	16 (14)	
Origin of infection			
Asia	62 (71)	47 (41)	<.0001
India	54 (62)	28 (25)	<.0001
Other Asia	8 (9)[d]	20 (18)	
Africa	14 (16)[e]	30 (26)	NS
Europe	10 (11)	27 (24)	.03
Sweden	4 (5)	16 (14)	.03
Other Europe	6 (7)[f]	12 (11)	
Americas	1 (1)[g]	8 (7)	NS

Data are No. (%) of patients unless otherwise indicated.

Abbreviation: HIV, human immunodeficiency virus; n, number of patients; NS, not significant.

[a]Pearson χ^2 test (or Fisher exact test when needed), were used for comparing categorical data. Mann-Whitney *U* test was used to compare median age between the groups.

[b]One patient on rituximab + methotrexate + prednisolone, 1 patient on prednisolone only. None with HIV (of 29 patients tested) and none with IgA deficiency (of 15 patients tested).

[c]Four patients with HIV.

[d]Thailand (3), Bangladesh (2), Nepal (2), Pakistan (1).

[e]Tanzania (3), Benin (1), Central African Republic (1), Chad (1), Congo DR (1), Ghana (1), Madagascar (1), Somalia (1), South Africa (1), Sudan (1), Uganda (1), Zimbabwe (1).

[f]Spain (2), Belgium (1), France (1), Italy (1), Switzerland (1).

[g]Colombia (1).

Table 2. Agents Used to Treat 85 Patients with Nitroimidazole-Refractory Giardiasis (124 Treatment Episodes)

Therapy	Treatment Episodes, n	Parasitological Treatment Failure, n (%)	Persisting Symptoms, n (%)
Quinacrine-containing therapies	57[a]	3 (6)[b]	7 (12)
Quinacrine monotherapy	52[c]	3 (6)[d]	6 (12)
Quinacrine + metronidazole	3	0 (0)[e]	1 (33)
Quinacrine + paromomycin	1[f]	0 (0)	0 (0)
Quinacrine + albendazole	1[f]	0 (0)	0 (0)
Albendazole + metronidazole	42[g]	18 (49)[h]	21 (50)
Albendazole + tinidazole	1	[i]	0 (0)
Albendazole monotherapy	10[c]	7 (88)[j]	7 (70)
Paromomycin	10[k]	8 (100)[j]	9 (90)
Nitazoxanide	4	2 (67)[l]	2 (50)

Abbreviation: n, number of treatment episodes.

[a]Fifty-four unique patients were treated with quinacrine (3 needed retreatment to improve), of which 22 had received at least 1 other alternative therapy for the refractory giardiasis prior to quinacrine (most commonly a combination of albendazole and metronidazole, 13 patients).

[b]Of 52 cases with follow-up stool samples.

[c]One patient received 2 treatment courses due to treatment failure.

[d]Of 46 cases with follow-up stool samples.

[e]Of 2 cases with follow-up stool samples.

[f]A patient with treatment failure after quinacrine monotherapy.

[g]Two patients received 2 treatment courses.

[h]Of 37 cases with follow-up stool samples.

[i]Follow-up stool sample not available.

[j]Of 8 cases with follow-up stool samples.

[k]Nine as monotherapy, 1 in combination with tinidazole. One patient received 2 treatment courses.

[l]Of 3 cases with follow-up stool samples.

3 examinations, respectively) while the fourth patient did not provide any follow-up stool samples.

Among the 85 patients treated for nitroimidazole-refractory giardiasis, 26 received multiple treatment courses, resulting in a total of 124 treatment episodes (Table 2). The proportion of patients treated with quinacrine was 29% (11/38) during the first half of the study period but increased to 91% (43/47) during the second half. Fifty-three were prescribed a therapy other than quinacrine. The second most common treatment after quinacrine was albendazole in combination with metronidazole, after which 18 of 37 with follow-up samples were positive for *G. intestinalis* (51% parasitological efficacy). The treatment failure rate was very high with other treatments (Table 2).

Quinacrine Tolerability

None of the 54 patients receiving quinacrine terminated their treatment prematurely, and possible mild adverse effects were recorded in only 1 (1.9%). This was a patient with a previous history of anxiety disorder who experienced reversible symptoms with mild headache, vomiting, diarrhea, and feeling distracted (received 2100 mg cumulative dose of quinacrine). An additional 6 patients with documented previous history of psychiatric disorders (eg, depression, anxiety disorder, bipolar disorder) received quinacrine without reporting any adverse effects.

DISCUSSION

In this retrospective observational study, quinacrine was used with good results and tolerability. Only 3 patients had a microbiologically verified treatment failure after 1 treatment course (94% parasitological efficacy) and all were cured after a second course.

Metronidazole and tinidazole have historically had about 90% (range, 60% to 100%) cure rate for intestinal giardiasis [1–3]. A second or more treatment courses with nitroimidazoles are sometimes tried for persistent cases but had a low efficacy in our cohort (24%), similar to other studies [4, 6, 7]. In this study we used microbiologically verified *Giardia* in stool samples after at least 2 full treatment courses to make sure we were evaluating true refractory disease, as opposed to compliance issues.

In a study from Barcelona, all 14 patients with nitroimidazole-refractory giardiasis (defined as microbiologically confirmed persistence after 1 metronidazole course) had improved clinically 1 month after quinacrine treatment (100% clinical efficacy), but PCR was still positive in 3 (79% parasitological efficacy) [5] (Supplementary Table). In another Spanish study on nitroimidazole-refractory giardiasis, all 14 quinacrine-treated patients who had a follow-up were cured, verified with negative stool samples (12 patients had received at least 2 nitroimidazole courses and 2 only 1 course prior to quinacrine) [6]. In a study from the United Kingdom, quinacrine was considered effective because 20 patients with nitroimidazole-refractory giardiasis did not need any further treatment at their center (11 received quinacrine monotherapy, 7 in combination with albendazole, 2 with tinidazole). However, the number of nitroimidazole treatment courses needed to define refractory disease was not specified and patients were not routinely tested for microbiological cure following treatment [4]. In a recent Cuban study, 15 adult patients who had failed to respond to multiple nitroimidazole-containing courses were all cured with quinacrine (confirmed with negative posttreatment stool samples) [7]. These studies along with our experience indicate that quinacrine is an effective treatment alternative for nitroimidazole-refractory giardiasis. At our center, currently almost all patients with nitroimidazole-refractory giardiasis are treated with quinacrine.

Quinacrine was very well tolerated among our patients and none discontinued the treatment prematurely. Other recent studies have similarly reported a very low rate of treatment discontinuation due to adverse effects (Supplementary Table) [5–7]. Historically, quinacrine was replaced by chloroquine for malaria due to reported adverse effects, the most alarming being psychiatric ones [2, 8]. In a report from 1945, including 7604 soldiers treated with quinacrine for malaria (receiving a total of 2100 mg), 35 (0.4%) experienced what was called "toxic psychosis". The definition of toxic psychosis was, however, not specified and the effect was usually described as one of euphoria and expansiveness and only occasionally with disorientation. No cases of irreversible psychiatric disturbances were observed [12]. In a study from 1946, a total of 28 cases of toxic psychosis, most commonly being described as confusion, were detected among more than 14 000 soldiers (0.2% risk). Only 2 of 28 had received a total dose of 2100 mg while 26 had received higher doses. Rapid recovery was observed after cessation of therapy [13, 14]. When reevaluating these old studies, the possibility that the psychiatric mood disturbances could have been a result of malaria and the fact that the soldiers were at war under severe conditions must be taken into consideration. Furthermore, the patients received higher cumulative doses for malaria than we use for giardiasis (most frequently 2100 mg compared to 1500 mg in our cohort). In a later paper, it was reported that 1.5% of adults treated with quinacrine for giardiasis experienced "toxic psychosis of excitation or depression" but neither the number of treated patients, nor the details of psychiatric adverse effects were presented [10]. Due to our study size it was not possible to estimate the incidence and pattern of uncommon psychiatric adverse effects and thus further evaluations are needed. However, we believe that the incidence, when using a low dose for giardiasis treatment, is probably lower than the 0.2% to 1.5% stated in previous difficult to interpret, older reports.

The majority of our patients with nitroimidazole-refractory giardiasis acquired the infection in India. The proportion of giardiasis cases in India refractory to nitroimidazoles is not well known and is difficult to estimate in an endemic area with a

constant risk of reinfection. In a study from 2014, the ratio was reported to be 10% (8 of 82 cases) [15], while referral centers and units specializing in tropical diseases in Europe have reported higher proportions (up to 50%) [4–6]. The very high proportion of refractory cases from the Indian subcontinent noted in our cohort (65%) can probably to a certain extent be explained by selection bias, because the great majority of refractory giardiasis cases in Stockholm are referred to our hospital. The proportion of nitroimidazole-refractory cases acquired on the Indian subcontinent was, nevertheless, significantly higher than among the nonrefractory cases, underlining the importance of nitroimidazole-refractory giardiasis in that region.

The study has several limitations. It is retrospective and observational, and the treatment was not standardized for all patients. Adverse effects were not asked for systematically and may therefore have been underreported or not recorded. Even though this is, to our knowledge, the largest study on quinacrine treatment for nitroimidazole-refractory giardiasis so far, its size is nevertheless relatively small and not likely to capture uncommon adverse effects. Strengths of this study are the strict definition of nitroimidazole-refractory giardiasis, the high proportion of patients with clinical follow-up as well as posttreatment stool samples, and that it was carried out in a single center in a nonendemic setting with a low risk for reinfection.

In conclusion, nitroimidazole-refractory giardiasis is an emerging challenge in clinical practice worldwide, especially noted among cases from the Indian subcontinent. Quinacrine is an effective treatment for nitroimidazole-refractory giardiasis and seems to be well tolerated when given as a short-course therapy.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Potential conflicts of interest. All authors: No reported conflicts of interests. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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