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Short Report: Short Course Combination Therapy for Giardiasis after Nitroimidazole Failure

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Abstract. Recommended first line treatments for giardiasis include the nitroimidazoles and, recently, nitazoxanide. For refractory cases, a combination of two or more drugs may be a viable approach. A review of 10 patients with giardiasis refractory to nitroimidazoles with response to a short course (< 2 weeks), combined treatment is presented.

INTRODUCTION

Giardia, a protozoon transmitted by the fecal-oral route, has a worldwide distribution but occurs mainly in developing countries.[1] This parasite impairs growth and development in children and it is also a cause of prolonged diarrhea in travelers.[2]

Guidelines recommend metronidazole or tinidazole and more recently nitazoxanide as first line treatments. Paromomycin, furazolidone, quinacrine, and albendazole are considered alternative drugs.[3] Efficacy rates of monotherapy with single treatment courses vary from 60% to 100%, with an average rate of over 80%.[2,4] A meta-analysis of randomized clinical trials showed that metronidazole for more than 3 days achieves a better parasitological cure rate than other longer treatment courses and that tinidazole was the drug with the highest cure rates within the single-dose regimens.[5] Treatment failure has been attributed to a number of causes, including parasite resistance to nitroimidazoles. Traditionally, refractory giardiasis has been treated with longer repeated courses and/or higher doses of the original agent, or using drugs from a different class to avoid potential cross-resistance, but a higher rate of adverse side effects may limit this approach.[6,7] Another approach in cases refractory to nitroimidazoles could be the use of combination regimens, but reports documenting such practice are scarce.[6–11] Ten patients with giardiasis refractory to nitroimidazoles who were successfully treated with combined short course therapies are presented.

MATERIAL AND METHODS

All documented cases of giardiasis treated at a Tropical Medicine referral Unit in Madrid, Spain, between 1989 and 2004 were retrospectively reviewed.

Patients with treatment failure following nitroimidazoles and who later received combination treatment were selected. Treatment failure was defined as presence of *Giardia* in at least one of three stool samples after concentration techniques and persistance of symptoms (diarrhea, bloating, abdominal pain, weight loss) after one or more courses of standard treatment. Treatment success was defined as symptom resolution and absence of *Giardia* in stools (three stool samples for ova and parasites after concentration techniques were performed). Data recorded were age, sex, country of origin or of recent travel, year of initial diagnosis, previous treatment courses prescribed (drugs, total dose, duration, and period of time during which these drugs were administered), and combination treatment prescribed (drugs, duration). Refractory patients had immunoglobulin levels, human immunodeficiency virus (HIV) serology, immunoglobulin A (IgA) and IgG antigliadin, and IgA anti-transglutaminase antibodies measured.

RESULTS

Between 1989 and 2004, 170 patients with giardiasis were treated. Only 10 patients failed to respond to conventional therapy (5.8%) and complete data were available for 8 patients. All but one was male, 7 adults, and 3 infants, with a mean age of 29 years (range 3–60 years). Eight cases were probably imported (3 immigrants, 3 travelers, and 2 recent adoptions).

All patients had received one or more courses of conventional treatment and the mean was three courses per patient. Two patients had received five or more courses. In 9 cases, metronidazole was used: in 6 this was at a dose of 500 mg tid for a minimum of 5 days, with total accumulated doses of 7,500 to 21,000 mg, 2 patients were children and children's dosing was adjusted for body weight at 15 mg/kg/day. The exact dose of metronidazole used was unknown in one patient.

Combined regimens following initial treatment failure included: metronidazole or tinidazole + paromomycin + albendazole in 3 cases, metronidazole + paromomycin in 2, tinidazole + paromomycin in 2, tinidazole + quinacrine in 2, and metronidazole + quinacrine in 1. All drugs were administered for 7 or 10 days except for tinidazole, given for 1 to 7 days. All combinations were well tolerated, with no reports of serious adverse effects.

Serum IgA levels were low in 2 patients who required specific treatment with intravenous immunoglobulin before combination therapy. One patient was diagnosed with lung cancer, all were HIV-negative and no celiac disease was documented.

Clinical cure was achieved in all patients and parasitological cure in 8 of them (two did not bring stool samples after recovery). Five patients were followed up for at least 1 year, without recurrence. Patient characteristics and treatment regimes are summarized in Table 1.

DISCUSSION

This study assesses the use of combination treatment in the management of refractory giardiasis but has some limitations because of the number of cases and the long study period, which led to changes in treatment strategies over time, resulting in a heterogeneous group (choice of combination treatments was based on availability of drugs at the moment of diagnosis).

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TABLE 1
Giardiasis after nitroimidazole failure: patient characteristics, combination therapy schemes, and outcome

Patient	Age/sex Type of patient Origin	Underlying disease	Previous drugs*	Combination treatment scheme†	Outcome Follow-up‡ (duration)
1	28/M Immigrant Syria	None	MTZ: 5 (21 g) TDZ: 1 (2 g) PRM: 2 (15 g)	MTZ × 10 d + ABZ × 10 d + PRM × 10 d	Clinical improvement Negative stool test 2 months
2	38/M Immigrant Cuba	None	TDZ: 1 (2 g)	MTZ × 7d + PRM × 10d	Clinical improvement No stool test Lost to follow up
3	25/M Immigrant Nigeria	None	MTZ: 1 (10.5 g)	MTZ × 10 d + PRM × 10 d	Clinical improvement Negative stool test 1 year
4	6/M Adopted Colombia	None	MTZ: 2 (7.5 g)	TDZ × 3 d + PRM × 7 d	Clinical improvement No stool test 1 year
5	3/M Adopted Equatorial Guinea	None	MTZ: 4 (ND) ABZ: 1 (ND)	TDZ × 7 d + QNC × 7 d	Clinical improvement Negative stool test 2 years
6	36/F Traveler Latin American countries	Ig A deficiency	MTZ: 1 (10.5 g) ABZ: 1 (8 g) PRM: 1 (7.5 g)	TDZ × 7 d + ABZ × 10 d + PRM × 10d + iv IgA	Clinical improvement Negative stool test 2 years
7	40/M Traveler Sub-Saharan countries	None	MTZ: 3 (31.5 g) MBZ: 1 (1 g) PRM: 1 (7.5 g)	MTZ × 10 d + QNC × 10 d	Clinical improvement Negative stool test 6 months
8	3/M Traveler Cuba	IgA deficiency	MTZ: 2 (21 g)	TDZ × 1 d + ABZ × 7 d + PRM × 7 d + iv IgA	Clinical improvement Negative stool test 1 month
9	59/M Spain	None	MTZ: 2 (21 g) MBZ: 1 (1.4 g)	TDZ × 7d + QNC × 7 d	Clinical improvement Negative stool test 1 year
10	60/M Spain	Lung cancer	MTZ: 2 (20 g)	TDZ × 5 d + PRM × 7 d	Clinical improvement Negative stool test 1 month

* Previous anti-giardial drugs, number of full courses (total dose received).
† Drug doses: MTZ = metronidazole 500 mg every 8 hours (15 mg/kg/d in 3 doses in children); ABZ = albendazole 400 mg every 12 hours; PRM = paromomycin 500–750 mg every 8 hours (30 mg/kg/d in 3 doses in children); TDZ = tinidazole 2 g once (50 mg/kg/d once in children); QNC = quinacrine 100 mg every 8 hours for 7 days (6 mg/kg/d in 3 doses max 300 mg/d in children; iv IgA = intravenous immunoglobulin A.
‡ Three stool samples for ova and parasites after concentration techniques.
M = male; F = female; ND = no data; MBZ = mebendazole.

In persistent diarrhea caused by giardiasis, symptom persistence after treatment may reflect conditions other than drug failure, such as secondary lactose intolerance. Re-infection should be considered in patients responding to the original agent. Therefore, to consider treatment failure, documentation of persistent infection in stool samples is mandatory when patients present with recurrent symptoms. Resistance to metronidazole, quinacrine, albendazole, and furazolidone has been induced *in vitro*; however, correlation between *in vitro* sensitivity and clinical outcomes is not consistent.[2] Immunosupression, both humoral and cellular, is a well-known cause of treatment failure and should be detected and specific treatment strategies adopted.

In our series (Table 1), treatment failure was documented by parasitological methods in all patients. No sensitivity/resistance *in vitro* tests were performed. Study of close contacts in this cohort was not considered strictly necessary because of the low prevalence of this infection in Spain. Nevertheless, giardiasis is endemic in Spain where it is not a reportable illness, and then re-infection would be a rare cause of treatment failure in our environment. Two patients had selective IgA deficiency and were subsequently treated with immunoglobulin A. In case of recurrent giardiasis, it is important to evaluate for IgA immunodeficiency and consider IgA replacement together with combined antigiardial-drugs to clear the parasites, but serious and potentially fatal side effects of intravenous immunoglobulin include anaphylactic reactions, aseptic meningitis, acute renal failure, and thrombotic complications. Clinicians should pay close attention to patient selection and consider the potential risk/benefit ratio versus anti-giardial-drugs alone.

Nitroimidazoles are the mainstay of therapy and the low failure rates of these drugs in our cohort (5.8%) reflect the efficacy of this class of drugs. Historically, failures have been treated with longer courses/higher doses of the original agent with the risk of increased toxicity or with other drugs. One of the newest drugs, nitazoxanide, has showed efficacy in the treatment of intestinal giardiasis in immunocompetent children and adults, and is generally well tolerated and can be used in cases refractory to metronidazole treatment. *In vitro*, the active metabolite, tizoxanide, is eight times more active than metronidazole against susceptible strains and twice as active against resistant isolates. These conditions have resulted in the inclusion of the drug by the Food and Drug Administration as one of the first line treatments for giardiasis.

Unfortunately, in many countries like Spain it is only available through compassionate drug use protocols. However, older drugs in combination may have a role in the manage-

ment of treatment failures, but reports on this treatment approach are scarce. In 2001, Nash and others[8] reported a series of 6 patients, including both immunocompetent and immnunocompromised individuals, with giardiasis refractory to multiple courses of standard drugs. A combination regimen of metronidazole/tinidazole and quinacrine for a minimum of 2 weeks resulted in clinical and parasitological cure in 5 patients and temporal eradication in the sixth patient. The latter was finally cured with another combination regimen, consisting of bacitracin and paromomycin. Important side effects such as hepatotoxicity, seizures, and transient psychoses were observed in 2 patients and were probably related to quinacrine toxicity. Two previous case reports[9,10] documented cases of refractory giardiasis, which were cured after a well tolerated combined approach including metronidazole and quinacrine administered during at least 2 weeks. Another series published in 1995[11] reported on the outcome of 20 patients with giardiasis in whom metronidazole treatment had failed. The patients were randomized into two groups and were treated either with oral albendazole or with albendazole plus metronidazole for 7 days. The patients receiving dual therapy had a better outcome than those treated with albendazole alone. A recent observational study during an outbreak of giardiasis in Norway[12] included 38 adult patients with metronidazole-refractory giardiasis who were treated with sequential treatments. All patients received albendazole plus metronidazole and this combination was effective in 30 cases. Those who failed were then treated with paromomycin alone, which was effective in 3 patients, and those who failed following paromomycin received quinacrine in combination with metronidazole, which was effective in another 3 patients.

CONCLUSION

This study identifies a role for combination treatment based on a nitroimidazole with one or two second-line drugs, in a 7–10 day short course, in persistent giardiasis after conventional treatment. This approach would be especially interesting when first-line drugs have failed, in settings where nitazoxanide is not available, or in areas where co-infection with other sensitive parasites is prevalent. The use of combination treatment in the management of refractory giardiasis warrants further study with prospective randomized trials.

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