

# Treatment of refractory paediatric giardiasis using secnidazole plus albendazole: a case series

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## SUMMARY

*Giardia lamblia*, the aetiological agent of human giardiasis, is a frequently identified protozoan infection of the upper small intestine. It mainly affects children and has a wide range of clinical manifestations, from asymptomatic carriage to acute or chronic diarrhoea with dehydration, abdominal pain, nausea, vomiting, excessive flatulence and weight loss. Standard treatment for giardiasis is commonly with 5-nitroimidazole (5-NI) compounds, or nitazoxanide; however, some individuals experience treatment failure. For such patients, a combination of two or more drugs may be a viable approach. We report our experience with 11 paediatric patients with drug-refractory giardiasis, for whom therapy with a combination of secnidazole (SNZ) (30 mg/

kg/day, divided into 2 doses, for 3 days) and albendazole (ABZ) (400 mg daily for 5 days) resulted in cure for 9 of the 11 (82%) patients. This combination of drugs was well tolerated; only mild, transient, and self-limited side effects were reported and these did not require discontinuation of treatment. These results support the use of SNZ plus ABZ as an alternative treatment for paediatric patients with giardiasis who have failed conventional treatments. Further research is needed to establish the safety of this combination and how it compares to other combination strategies.

*Keywords:* *Giardia*, giardiasis, secnidazole, ornidazole, combination therapy.

## INTRODUCTION

*Giardia lamblia*, the aetiological agent of human giardiasis, is a frequently identified protozoan infection of the upper small intestine. It affects mainly children and has a wide range of clinical manifestations, from asymptomatic carriage to acute or chronic diarrhoea with dehydration, abdominal pain, nausea, vomiting, excessive flatulence, and weight loss [1]. Standard treatment for giardiasis is commonly with 5-nitroimidazole

(5-NI) compounds and, recently, nitazoxanide. Other drugs including furazolidone, paromomycin, quinacrine (QC), and albendazole (ABZ) are considered as alternative drugs. Additionally, mebendazole and chloroquine have been also used to treat giardiasis with some success [2, 3].

Unfortunately, around 20% of individuals experience treatment failure despite standard therapy for desired duration, and a recent report from the Hospital for Tropical Diseases, in London, found that the failure rate for nitroimidazole therapy in giardiasis was 40.2% [4, 5].

For patients with giardiasis who do not initially respond to standard treatments with monotherapy, current therapeutic options include prolonged re-treatment courses and/or higher doses of the

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original anti-giardial agent, or from a different class to avoid potential cross-resistance. Combination therapy, based on the mechanisms of action of the anti-giardial drugs, is another approach that may also be useful in patients with giardiasis refractory to first line drugs [6]. Our aim is to present our experience with a combination drugs [secnidazole (SNZ) plus ABZ] in paediatric patients with *Giardia* infection who previously failed to respond to standard anti-giardial drugs.

### ■ CASES PRESENTATION

We retrospectively discuss 11 paediatric patients who had clinical manifestations of *Giardia* infection, and *Giardia* cysts or trophozoites demon-

strated in faecal smears. Six were boys and 5 girls. Mean age was 10.9 years (range 5-16). Details regarding patient demographics, previous courses of treatment and patients' clinical data are presented in Table 1.

For each patient described here, the decision to start with this combination therapy was based on clinical and parasitological data at the time, and failure to respond to at least a prior course of treatment with a 5-NI given as a single dose, in the first week before inclusion in this open label study. All were started at SNZ (30 mg/kg/day), broken into twice daily dosing for 3 days and ABZ (400 mg daily) for 5 days. The children enrolled were also followed prospectively, during their regular visits to the outpatients' clinic. They were followed up

**Table 1 - Patient characteristics in 5-NI- refractory giardiasis associated with treatment response**

Patient	Gender	Age (years)	Underlying disease	Duration of symptoms previous SNZ+ABZ	Previous unsuccessful treatments	Outcomes	Comments
1	Female	12	None	12 weeks	TNZ	Clinical improvement. Negative faecal test.	Abdominal pain and nausea during the days of treatment. These did not require discontinuation of treatment.
2	Male	15	Asthma	6 weeks	MTZ, TNZ	Negative faecal test.	No side effects reported.
3	Male	7	None	3 weeks	TNZ	Negative faecal test.	No side effects reported.
4	Female	8	None	8 weeks	TNZ	Positive faecal test for <i>Giardia</i> cysts.	Clinical improvement. She was then treated with MTZ+QC.
5	Male	13	None	8 weeks	MTZ, SNZ	Negative faecal test.	No side effects reported.
6	Male	10	None	3 weeks	SNZ	Negative faecal test.	No side effects reported.
7	Female	14	None	15 weeks	MTZ, Ozonized sunflower oil, TNZ	Negative faecal test.	Diarrhoea and abdominal pain. These did not require discontinuation of treatment.
8	Male	5	None	3 weeks	SNZ	Negative faecal test.	No side effects reported.
9	Female	11	None	4 weeks	SNZ	Positive faecal test for <i>Giardia</i> trophozoites and cysts.	No clinical improvement. She was then treated with MTZ+QC.
10	Female	9	None	2 weeks	SNZ	Negative faecal test.	No side effects reported.
11	Male	16	Malnutrition	8 weeks	Propolis, MTZ, SNZ	Negative faecal test.	Mild nausea and headache.

requesting faecal specimens on days 3, 5 and 7 of treatment. Faeces were examined as fresh direct preparations and formalin-ether concentrations. Parasitological cure was defined as the absence of *Giardia* cysts or trophozoites in these faecal tests. Any adverse effects were assessed and recorded by physician at each clinic visit.

Nine (82%) of the 11 patients treated were cured. The combination of SNZ and ABZ was well tolerated. No patient experienced any treatment limiting adverse effects while taking the medication. Only mild, transient, and self-limited side effects were reported and these did not require discontinuation of treatment. The two patients who failed to respond to SNZ and ABZ were treated with a combination of metronidazole (MTZ) and QC and responded clinically and parasitologically.

## ■ DISCUSSION

Giardiasis is an important problem world-wide [1]. Although it is mainly observed in developing countries, in industrialized countries is frequently found in some specific groups [7-9]. Treatment failure in giardiasis is an under-recognized issue that receives inadequate attention, although it affects a substantial percentage of patients [10]. Treatment failures are disappointing for the patients and their providers and may carry a significant economic burden, as well. For patients and the community, treatment failures may result in ongoing symptoms and potential transmission to family and household members [11, 12]. For doctors, this problem occasionally poses a therapeutic challenge, because without further specific guidance, clinicians are often uncertain how to proceed at the time of treatment failure. Treatment is given at the discretion of individual clinicians. Otherwise, most studies on drug efficacy have been conducted in treatment-naïve patients, and the results have been extrapolated to patients in whom nitroimidazole treatment has failed [13, 14].

Treatment failures in giardiasis have been attributed to a number of causes, including prolonged treatment periods, unpalatability and unpleasant side-effects, all of which reduce the probability that (the often unsupervised) therapy be completed [15]. This was ruled out in our cases because a single-dose rather than multiple-dose regimen was used as a previous treatment in all of them. Additionally, re-infections were ruled out as fol-

low up and the decision to offer a treatment combination were carried out during the first week after treatment; fairly soon after treatment -less than 12 days-, and before any new, post-treatment infection could have become patent [16]. It is necessary to take into account that in places where *Giardia* infection is endemic, recurrence of infection may be a common feature and occur within a short period [17, 18].

The management of treatment failures is challenging. In these cases, a second course with either the same drug or an alternative, generally a structurally unrelated anti-giardial agent, is usually effective. Combination of drugs has also been recommended when monotherapy fails in the treatment of giardiasis. There is evidence from other infectious diseases (*i.e.*, malaria, HIV/AIDS) that resistance is less likely to occur when two drugs acting on distinct targets are used simultaneously. However, reports documenting combination therapy in giardiasis are scarce and largely confined to case reports or series [5, 19-23]. Selecting drugs from a different class and with different profiles of mechanisms of action is an excellent way to improve the efficacy and avoid potential cross-resistance and dose-limiting toxicities. Previous studies have demonstrated the effectiveness of a combination MTZ-ABZ in refractory cases to MTZ [20, 24]. Additionally, one study demonstrated the superior efficacy of MTZ-ABZ combination therapy over ABZ alone [24]. On the basis of these reports, we initiated combination therapy in eleven patients using a combination of SNZ with ABZ which represents an interesting approach that includes a 5-NI with a benzimidazole carbamate. There is no published literature on these two drugs combination that were used in our patients. In most of our patients, this was parasitologically effective, offering a favorable *Giardia* clearance from the faeces; and it was also well tolerated.

Pharmacologically, it is possible to explain why this particular combination of agents should have been so successful. It has been proposed that SNZ has similar mechanism of action as MTZ and the rest of the 5-NIs. It is though this drug enters the cell through passive diffusion, is generally activated by oxidoreductase enzymes and appears to induce oxidative stress, leading to protein and DNA damage [25, 26]. SNZ has a longer terminal elimination half-life (approximately 17 to 29

hours) than commonly used drugs in this class (allowing once daily dosing), and reduced gastrointestinal side effects [27]. It has shown to be efficacious against giardiasis in various clinical trials [28-31]. Otherwise, ABZ may act by binding very efficiently to  $\beta$ -tubulin in *Giardia* trophozoites, leading to the inhibition of cytoskeleton polymerization and, consequently, to severe structural defects, thereby paralyzing the parasite and inducing its excretion [32]. In addition, it has been shown that this drug inhibits the growth of the trophozoites of this protozoan and their adhesion to intestinal epithelial cells *in vitro* [33].

Since the dose of SNZ that we used was higher than the dose reported in most studies in children and it was used in combination with ABZ, a broad spectrum benzimidazole carbamate with well-known *in vitro* and *in vivo* anti-giardial activity, one might postulate that the efficacy observed may be related to one of the agents alone and not to the combination of the two agents [34, 35]. In fact, according to two meta-analyses, the reported efficacy of ABZ to treat giardiasis is described to be similar to MTZ and lower than tinidazole [36, 37]. However, poor outcomes have been showed using ABZ as monotherapy in the treatment of refractory cases; *i.e.*, in one study 9 out of 10 cases responded to a combination of ABZ-MTZ, while only 2 out of 10 responded to monotherapy with ABZ [24]. Additionally, ABZ resistance in giardiasis has also been reported [38]. ABZ now appears to have emerged as a useful therapeutic adjunct in patients with refractory giardiasis. It offers several advantages, *i.e.* more tolerable side effect profiles and once dosing schedule.

Having taken into consideration that our patients had failed a prior course of therapy with a 5-NI, we thought that immediate re-treatment with a new regimen that included other 5-NI and ABZ could be necessary. This strategy seemed to be effective for preventing patients from dropping out of treatment because of side effects and had a sufficient anti-giardial effect. In agreement with a review of previous literature, the use of two drugs with different mechanisms of action is a good option for treating refractory giardiasis.

The two patients who failed to respond to the combination of SNZ and ABZ showed adequate clinical and parasitological response to QC and MTZ. QC is a highly effective anti-giardial drug, alone or in combination; however, its adverse ef-

fects and toxicity profile, particularly in children, have made that this drug was superseded for *Giardia* infection [13]. Nowadays, it is mainly used in combination with other drugs, in cases where other anti-giardial drugs have failed [6, 19, 20]. Unfortunately, QC is no longer manufactured in many parts of the world. However, according to the different reports in which this drug has had a role in the clinical management of treatment failures in giardiasis, it seems that QC might experience a revival [39, 40].

This case series suggest that for the subset of paediatric patients with giardiasis who do not respond to repeated courses of conventional therapy, treatment with SNZ plus ABZ can lead to a beneficial effect. Although the number of patients in this study was small, our results nevertheless appear clear-cut and the success rate (81.8%) was high.

While in our experience, the combination of these two drugs was effective and safe with minimal side effects observed, the small number of patients and the lack of a control group were limiting factors in our study and therefore we could not generalize our findings. For a more valid conclusion, additional comparative controlled trials in paediatric patients need to be conducted exclusively in those who experience treatment failures in giardiasis, to test for appropriate dosing, the optimal duration of treatment, response to treatment and safety of these treatment regimens.

## ■ CONCLUSIONS

Our case series reinforces the role of combination therapy in treating patients with giardiasis refractory to 5-NIs. SNZ in combination with ABZ seems to be a good alternative when treatment failures occur after treatment of children with standard drugs against *Giardia* infection. However, it is necessary to take into account that treatment with two drugs for this number of days might be long, burdensome, and reduce patient compliance. Further evaluation in prospective randomized studies is needed to establish the safety of this combination and how it compares to other combination strategies before it could be recommended as a treatment strategy, it may be an option worth considering in patients who have failed therapies with currently available drugs.

### Declaration of interests

The authors state they have no conflicts of interest to declare.

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