Journal of Infectious Diseases and Diagnosis

Escobedo et al., J Infect Dis Diagn 2017, 2:2
DOI: 10.4172/2576-389X.1000118

Review Open Access

Paediatric Giardiasis: Recent Advances in Therapeutic Management

Angel A. Escobedo[1,2,3*], Pedro Almirall[3,4], Maydel Alfonso[5], Jony Jones[5], Ivonne Avila[6], Yohana Salazar[7], Yaremis del Sol[8] and Nancy Duenas[5]

[1]*Academic Paediatric Hospital "Pedro Borras", Calle F No. 616 Esquina 27, Plaza, La Habana, CP, Cuba*

[2]*Working Group on Zoonoses, International Society for Chemotherapy, Aberdeen, United Kingdom*

[3]*Committee on Clinical Parasitology, Panamerican Association for Infectious Diseases (Asociación Panamericana de Infectología), Panamá*

[4]*Municipal Centre of Hygiene, Epidemiology and Microbiology "Plaza", Calle 8 No. 406 esquina a 19, Plaza, La Habana, CP, Cuba*

[5]*Faculty of Medicine 'Comandante Manuel Fajardo', Calle D Esquina a Zapata, Plaza, La Habana, CP, Cuba*

[6]*Academic Paediatric Hospital "Centro Habana", Benjumeda Y Morales, Cerro, La Habana, CP, Cuba*

[7]*National Institute of Hygiene, Epidemiology and Microbiology, Calle Infanta No. 1158 Centro Habana, La Habana, CP, Cuba*

[8]*Central Clinic Cira García, Calle 20 No. 4101 Esquina a Ave 41, Playa, La Habana, Cuba*

[*]**Corresponding author:** Angel A. Escobedo, Academic Paediatric Hospital "Pedro Borras", Calle F No. 616 Esquina 27, Plaza, La Habana, CP, Cuba, Tel: +53-7-8351752; E-mail: escobedo@infomed.sld.cu

Received date: January 20, 2016, **Accepted date:** September 4, 2017, **Published date:** September 5, 2017

Abstract

Giardiasis is one of the most common causes of diarrhoeal disease worldwide. *Giardia lamblia*, its etiological agent, is a protozoan parasite that infects the small intestine of humans and may be asymptomatic or cause acute or chronic diarrhoea, weight loss, malabsorption, and, in children, failure to thrive. Treatment is primarily with 5-nitroimidazole drugs, mainly metronidazole and tinidazole; however, treatment failures-which may occur in up to 20% of cases is a common cause of symptom persistence after a complete course of treatment. Development of alternative antigiardials for children is important. In this review, data are summarized providing information about current therapy against *G. lamblia* in paediatric use.

Keywords: *Giardia*; Giardiasis; Children; 5-nitroimidazole compound; Nitazoxanide

Introduction

Giardia lamblia, the aetiological agent of human giardiasis, is the most commonly detected pathogenic protozoan in the human intestine and is widespread throughout the world [1,2]. The global burden of *Giardia* infection is important, it is estimated that this protozoan infects approximately 5-10% of the world´s population [3]. *Giardia* is still responsible for significant morbidity in children in low- and middle-income countries, where it has been associated with poverty and low sanitary standards [4,5].

Previously considered a commensal protozoan infection, fortunately, the investigations on this parasite and the results of its presence in humans and animals have been growing throughout the years [6] and have evidenced that its previous categorization as simply a nuisance infection is erroneous.

Giardia infection may be asymptomatic or cause acute or chronic diarrhoea, weight loss, bloating, flatulence, malabsorption, and, is especially troublesome in children living in developing countries [7], where failure to thrive and poor cognitive function have been associated to this intestinal infection [8]. In fact, this infection has been reported in approximately 15% of children aged 0-24 months in the developing world [9].

In industrialized countries, giardiasis has been referred as a re-emerging disease because of its increasingly recognized role in numerous outbreaks of diarrhoeal diseases in day care centres and also due to water borne associated outbreaks [10]. Even in these countries there are deprived communities and some groups in the population exposed to suboptimal hygienic conditions and a high degree of faecal contamination, placing these persons at increased risk of diarrhoeal disease [11,12].

Although the risk of giardiasis may be reduced with attention to water quality, food hygiene, and sewage treatment, effective treatment of *Giardia* infection is needed when these measures fail.

Treatment of Paediatric Giardiasis

There are several effective drugs for the treatment of human giardiasis (Table 1). Some of these drugs may have adverse effects or be contraindicated under certain clinical situations. Before selecting a particular drug, it is important to consider whether the infection is in an asymptomatic individual, the likelihood of re-infection, etc. For instance, the requirement for treatment of asymptomatic cyst shedder remains controversial. Generally, they are not treated because the infection may be eradicated by host defense mechanism without the need for specific antiparasitic chemotherapy. However, in some important instances, treatment may be useful, such as outbreak control, food handlers, for prevention of household transmission by toddlers and in patients with different health conditions including cystic fibrosis, celiac disease and hypogammaglobulinaemia [7,13,14].

Children with diarrhoea, malabsorption, failure-to-thrive syndrome or lack of weight gain in which *Giardia* infections are identified should receive therapy. Occasionally, a patient may continue excreting *Giardia* cysts despite adequate treatment [15-17]. In these cases, re-infections due to poor hygienic conditions, inadequate drug levels, a compromised immune status or drug resistance, may be suspected [15]. Resistant *Giardia* strains have been isolated from patients with

refractory giardiasis [18-22]; however, it is necessary to take into account that resistance does not always be proven *in vitro* [23].

5-nitroimidazole drugs

Treatment with the 5-nitroimidazole class of drugs is the initial therapeutic recommendation. Historically, Metronidazole (MTZ) has been the first line drug of choice. MTZ may be considered as a prodrug because it is as such inactive; the nitro group is essential for the antimicrobial activity; once the drug enters the trophozoite through passive diffusion, electron transport ferredoxins from *Giardia* donate electrons to the nitro group of MTZ. The reduction of the nitro group makes the drug activated [24,25]. Reduced MTZ serves as a terminal electron acceptor which binds covalently to DNA and results in DNA damage [26]. Similar mechanisms are proposed for the rest of the 5-NIs-Tinidazole (TNZ), Ornidazole (ONZ) and Secnidazole (SNZ) which are used in giardiasis.

Curatives rates between 60 and 100% (measured by clearance of the protozoan) have been reported in paediatric patients when MTZ is given for 5 to 10 d courses, with a median efficacy of ~89% [27]. As longer duration of therapy reduces patient compliance and increases the possibility of side-effects, simpler schedules have been proposed by giving the drug in a higher dosage as a single dose for one, or less days than the conventional 5-10 d, but efficacy falls off considerably [28-30].

Other 5-NI compounds, TNZ, ONZ and SNZ, with the same mode of action as MTZ have been used fort *Giardia* infections. These compounds have the advantage of simpler dosing schedule, due to their longer half-lives. Other advantages are fewer side-effects. They are therefore better tolerated allowing for a greater likelihood of patient compliance [27].

A large body of clinical evidence with the use of TNZ in paediatric patients demonstrates its efficacy and safety for the treatment of giardiasis. Several different regimens have been evaluated; the commonest regimen is 50 mg/kg in paediatric patients, as a single dose. This drug is better tolerated than MTZ and its efficacy (measured by clearance of the protozoan) ranges between 72-100% with a median efficacy of ~89% [31-41].

TNZ may be used in some cases where previous MTZ treatment has failed. Symptoms like diarrhoea have been reported to ameliorate earlier when treating with TNZ in comparison with MTZ [42].

ONZ is other 5 NI compound which is also an alternative in the treatment of giardiasis. In paediatric patients, 40 or 50 mg/kg as a single dose have been assessed with excellent results [31,43].

SNZ has also been observed as a choice for the treatment of giardiasis. Clinical trials in children have employed single dose and its efficacy rates (measured by clearance of the protozoan) have ranged between 79.4-98% [44-46]. The most common regimen is 30 mg/kg in paediatric patients, as a single dose [27].

Furazolidone

Furazolidone is less effective than MTZ and Quinacrine (QC) in the treatment of giardiasis. However, it has the advantage of being available as a liquid formulation. This makes the drug useful for infants and young children. Dosing is usually 6 mg/kg/d in four divided doses over 10 d for children [27].

Common side effects include nausea, vomiting and diarrhoea, which sometimes cause problems with compliance [47]. In patients with glucose-6-phosphate dehydrogenase deficiency, a mild-to-moderate haemolysis may occur. Additionally, this drug should not be given to mothers who are breastfeeding or to neonates because they could develop haemolytic anaemia due to their normally unstable glutathione [27].

Paromomycin

Studies on *in vitro* susceptibility have shown that paromomycin has less activity against *G. lamblia* than that achieved with the nitroimidazoles, QC and furazolidone [48,49]. After oral administration, little of the drug is absorbed into the systemic circulation. Therefore, high concentrations in the gut are achieved.

The recommended dosage is 25 mg/kg/d (orally in three divided doses) in children. The side-effects are relatively uncommon and mainly limited to occasional abdominal distress, nausea and diarrhoea during the course of treatment. Additionally, intestinal flora may be modified by its action [27].

Benzimidazoles

Benzimidazoles were regarded only as anthelmintic agents, but investigations into the activity of this group have resulted in novel uses. Now, it is known that their wide spectrum include also an important activity against some protozoa, including *Giardia* [50,51]. These drugs bind β-tubulin, leading to the inhibition of cytoskeleton polymerization and to severe structural defects [52]. Treatment of giardiasis with this group of drugs has been based in two main drugs: Mebendazole (MBZ) and Albendazole (ABZ).

Mebendazole (MBZ): This drug has been used in clinical practice in different settings, schedules, and doses. Divergent results have been published such as the one reported by di Martino who did not find resolution of the symptoms and/or the disappearance of parasites from faecal specimens of adult patients [53]. However, others have reported curatives rates between 14.2-95% with 200 mg thrice a day, for 1 d [38,54,55]. When 200 mg thrice a day is given for longer period (5 d), the cure rates were 78.7% [56] and 86% [57], in two different studies. Other schedules have been proposed including 100 mg thrice a day, for 7 d, 100 mg twice a day, for 3 d and 200 mg thrice a day, for 3 d the cure rates achieved were 58.3, 80.4, and 78.1%, respectively [46,58,59].

MBZ can be easily administered and has not been associated with serious adverse events. It has been associated with transient abdominal pain [38,46,56].

Albendazole (ABZ): ABZ has been shown to be an alternative treatment against giardial infections. Clinically, it has been demonstrated that ABZ 400 mg is efficacious when given as a single, 5 d course; with a parasitological cure which ranges between 34.6-96.4% [36,60-62]. In two studies ABZ was given 400 mg daily for 3 d, and the efficacy obtained ranged from 50 [63] to 81% [61]. Given in a single dose of ABZ (800 mg) treatment showed an efficacy of 50% [63]. Given 200 mg thrice a day or 10 mg/kg for both for 5 d, the efficacy rates achieved were 77.7% [64], and 90.4% [65], respectively. A recent meta-analysis indicates that ABZ is a useful drug against giardiasis, although it was outperformed by TNZ [66]. Further work is needed to determine the best dose and duration for this treatment. Concerning side effects, these are rarely observed, when reported they include nausea, vomiting, diarrhoea and epigastric pain.

Nitazoxanide (NTZ)

NTZ is a broad spectrum 5-nitrothiazolyl derivative with potentially useful activity against a range of biological agents. *In vitro* and clinical studies have confirmed the efficacy of NTZ in the treatment of giardiasis [67,68]. Clinically, in the treatment of giardiasis, NTZ has demonstrated an overall response rate (measured by clearance of the protozoan) 75%, ranging between 64-94% [39,59,69].

NTZ is usually well tolerated; it has few significant adverse effects (primarily gastrointestinal upset) which may arise after administration of ordinary doses. The more frequent side-effects reported include abdominal pain, diarrhoea, vomiting, headache and yellowish urine. All of them has been considered mild and transit in nature [39,70].

NTZ is recommended in a dose of 500 mg twice a day for three days in children 12 years old and older; in children aged between 4 to 11 y old 200 mg twice a day for three days and children between 1 to 3 y old 100 mg twice a day for three days. Other way to calculate the dose in children has been 7.5 mg/kg twice a day for 3 d [27].

Chloroquine (CQ)

Based on various reports on CQ in giardiasis [71,72], two randomized clinical trials have been carried out; the first one comparing this drug with ABZ and TNZ [60], and a second one comparing with MTZ [73]; in both studies, the dose of CQ was 10 mg/kg bodyweight twice a day for five days. The parasitological efficacy of CQ was similar to that found with TNZ and MTZ in both studies.

A recent narrative review has been carried out on the effect of CQ in giardiasis and it supports that this drug needs further considerations in this context [74].

QC

QC is not currently recommended for routine use in patients with giardiasis because of its side effects and the availability of other drugs. However, it has been recommended, as single drug or in combination with other antigiardial drug, when treatment failures occur. The recommended dosing is 6 mg/kg daily in three divided doses over 5 to 7 d in children [27].

	Antimicrobial agent	
	Drug	**Mechanism of action [27]**
Currently in use	Metronidazole	Reduction of MTZ nitro group to nitroso radical highly reactive with DNA, free and protein cysteines, interfering with several biological processes.
	Tinidazole	Reduction is mediated by Pyruvate: Ferredoxin Oxidoreductase (PFOR), thioredoxin reductase and NADPH oxidase.
	Ornidazole	
	Secnidazole	
	Furazolidone	Similar to 5-NIs. Drug activation associated to NADH oxidase activity.
	Paromomycin	Inhibition of protein synthesis.
	Albendazole	Binding to β-tubulin and inhibition of cytoskeleton polymerization.
	Nitazoxanide	Non-competitive inhibition of the PFOR and nitroreductases, alterations on the ventral disk and surface membrane.
Under study	Mebendazole	Similar to albendazole.
	Chloroquine	Not fully understood.

Table 1: Therapeutic approaches for treating giardiasis in children.

Treatment Failures

Treatment failures are a matter of concern due to the increasing occurrence. In these cases, a second course of the same initial drug: for the same time or extended period or in a higher dose, may be recommended. Switching to another antigiardial compound with a different mode of action or combination therapy regimens of MTZ and ABZ or QC may be also the strategy [75].

Conclusions

Giardiasis continues to exert a significant toll on paediatric patients, particularly in tropical areas. The fact that this should happen despite the availability of relatively cheap and effective therapies is disappointing. The mainstays of giardiasis are 5-NI drugs; however, treatment failures occur with relative frequency. Alternative treatments are available although making the appropriate choice can be complex, taking into account the efficacy rate, and the adverse events associated, there are several drugs for patients to consider. Future alternatives for treating *G. lamblia* infections are still needed and should be explored.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not for profit sectors.

Conflict of Interest Statement

The author declares no conflicts of interest in preparing this article.

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