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# Pharmacotherapy of Giardiasais: Past, Present & Future

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**Review Article**

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## Abstract

**Objective:** In view of the scattered information about pharmacotherapy of the common protozoal infestation in the English medical literature, this update aims at providing a state-of-the-art review concerning the drug therapy of giardiasis.

**Resource and Design**: Systemic literature review augmented with authors' own first-hand experience in dealing with pediatric giardiasis spread over quite a few decades. Salient Features: Most subjects with giardiasis, a neglected disease, respond favorably to the available drugs though frequency of recurrences is high. However, immunocompromised persons pose the problem of less satisfactory response to routine pharmacotherapy, often necessitating a change in the drug regimen. In some cases, therapy needs to be complemented with other measures aimed at safeguarding against reinfection and passing infection to family members, peers and coworkers. Currently, albendazole, metronidazole, tinidazole and nitazoxanide stand out as the most acceptable amongst the plethora of drugs for giardiasis.

**Conclusion:** Choosing an appropriate agent with attention to rationality in therapy plus preventive measures is mandatory to meet the challenge of giardiasis.

**Keywords:** Alkbendazole; Giardiasis; Firazolidine; L. giardia; Mepacrine; Metronidazole; Nitazoxanide; Ornidazole; Secnidazole; Tinidazole

## Introduction

Infection with *L. giaredia* is a common cause of morbidity, especially in resource-limited communities **[**1-5].

Conventionally speaking, only symptomatic giardiasis needs drug therapy [6-10]. The view that even asymptomatic giardiasis (after all it is set to become symptomatic sooner or later), especially in immunocompromised hosts, should be treated is catching up fast [9,10].

In a nutshell, all symptomatic cases must be offered the benefit of effective pharmacotherapy. Additionally, all asymptomatic cases likely to spread infection to immunocompromised contacts, pregnant women and subject with cystic fibrosis should be treated. Family members and close contacts of asymptomastic but

positive for *L. giardia* need to be treated lest they reifect others. Some experts advocate treatment of symptopm-free cases on the plea that they are potentional risk to others and likely to become symptomatic at some point of time [9,10]. A multitude of antigiardial drugs are available [11].

## Conventional Antigiardial Drugs

### Mepacrine (Atabrine, Quinacrine)

Related to mefloquine, it is, in all probability, the oldest among the antigiardial drugs administered in a dose of 100 mg TID in adolescents and 5 to 8 mg/kg/day (3 divided doses) in children for 5 to 7 days. It gives excellent clinical as well as parasitological cure of the magnitude of 90-95%.

Its use has become obsolete on account of its bitter taste, poor tolerance (nausea, vomiting and abdominal cramps) and toxicity (transient yellow discoloration/ staining of the skin, sclera and urine). Moreover, it is no longer freely available. Presently, its use is restricted to symptomatic giardiasis refractory to modern drugs.

### Metronidazole

Over recent decades, metronidazole, a first generation nitroimidazole, has occupied a pride of the place as an antigiardial agent. It continues to be the most commonly employed antigiardial therapy.
Though quite a safe agent, an unpleasant metallic taste owing to its excretion in the saliva is often irritating to the patient.

The dose is 200-300 mg TID in adults and 15 to 20 mg/kg/day in children for 5 to 7 days. A cure rate of around 90% is expected [5]. Of late, resistance to metronidazole is being increasingly reported.

### Tinidazole

This 5-nitroimidazole, given in a dose of 2 g in adults and 50-60 mg/kg once only or 20 mg/kg/day for 5 days, yields a higher clinical and parasitological cure rate compared to metronidazole [2,5].

Usually, mild gastrointestinal disturbance is the only ADR.

### Secnidazole

This, a long-acting 5-nitroimidazole, given in a dose of 2 g for adults and 30 mg/kg for children as a single dose, once only, yields a cure rate of around 85%. lid and transient gastrointestinal ADRs may be encountered.

### Ornidazole

A relatively new 5-nitroimidazole, administered 2g in adults and 40 mg/kg in children as a single dose once only, ornidazole is very effective in giardiasis. It is better tolerated by children compared to the earlier 5-nitroimidazoles [2,5]. ADRs include unpleasant taste, decreased appetite and dark urine.

### Furazolidine

A nitrofuran, it has a potent antigiardial activity, acting by gradual inhibition of monoamine oxidase [2,5]
Dose is 100 mg 3 or 4 times a day in adults and 6-8 mg/kg/day (3-4 divided doses) over a period of 7-10 days.
Usual ADRs include gastrointestinal upset, staining of the urine and mild drug rash.

### Albendazole

A benzimidazole, structurally related to mebendazole, albendazole is effective against many infestations, including giardiasis [2,5]. Albendazole, given for 5 days, is as effective as metronidazole for the treatment of giardiasis with the advantage of fewer ADRs.Dose is 400 mg (200 mg for < 2 years) daily for 5 days. In view of the safety, effectiveness, and low cost, and anti-helmintic action albendazole, is now considered an acceptable alternative for metronidazole in the treatment of giardiasis.

### Paromomycin

A non-absorbable oral aminoglycoside, it is less effective than other antigiardial agents. Its plus point is that it is the only available antigiardial agent that can be safely given to a pregnant woman with symptomatic giardiasis [5]. Dose is 500 mg BID for 5-10 days. It acts by interfering with ribosomal subunits. Efficacy rate is around 60-70%. It has minimal absorption with minimal side effects

### Relatively New Antigiardial

**Nitazoxanide:** Nitazoxanide, a prodrug of niclosamide, is the latest entry as an alternative agent for treatment of giardiasis [12]. Given 500 mg twice daily in adolescents and adults and 7-10 mg/kg/dose twice daily in pediatric subjects for 3 days (Table 1), it yields excellent results. ADRs include abdominal pain, diarrhea, vomiting and headache.

| Age Group | Dose |
|---|---|
| Adults and adolescents | 500 mg BID |
| 1-3 yr | 100 mg BID |
| 4-11 yr | 200 mg BID |
| 12 yr and beyond | 500 mg BID |

Table 1: Dosage of nitazoxanide in terms of age groups.

Notably, nitazoxanide, is generally well tolerated and can be used in cases refractory to metronidazole treatment. Tizoxanide, its active metabolite, is eight times more active than metronidazole against susceptible strains. Even against against resistant isolates, its activity is double that of metronidazole. The Food and Drug Administration (FDA) has included it as one of the first line treatments for giardiasis. When giardiasis and cryptosporidiosis coexist in a immunocompetent person, nitazoxanide is strongly recommended as it is effective against both [13].

### Herbal Therapy for Giardiasis

In early 1971, a chance observation suggested that berberine—an alkaloid from the Indian medicinal plant *Berberis aristata*—may be an effective antigiardial drug. [14] A controlled study suggested that berberine, administered orally in a dose of 10 mg/kg/day for ten days, resulted in satisfactory parasitological cure, comparable to that obtained with other established antigiardial drugs (quinacrine hydrochloride [mepacrine], furazolidone, and metronidazole). Not much has been done in subsequent decades on the efficacvy of berbereine in giardiasis, except for an occasional investigation or two that provided encouraging outcome [15].

## Relative Efficacy of Antigiardial Drugs

Undoubtedly, mepacrine tops the list in case of clinical and parasitological cure. But, on account of its ADRs and difficult-to-obtain status, its use is limited to difficult and resistant cases.

Among the commonly employed drugs, in case of a single dose therapy, best outcome is with tinidazole followed by ornidazole . Secnidazole, though effective as a single dose therapy, gives a somewhat lower cure rate.

For multidose therapy, cure rate with metronidazole, tinidazole, albendazole and nitazoxanide is of a similar order. Furazolidine gives somewhat lower cure rate but is better tolerated. A nitazoxanide vs metronidazole trial shows comparable results [12]. However, nitazoxanide is also effective against *E. hitolytica* as well as some helminthes, its course spreads over just 3 days compared to 5-7 days in case of metronidazole and is better tolerated.

## Currently Recommended Drug Regimens

Table 1 presents a summary of the currently recommended drug regimens for giardiasis.

| Drug | Dosage in adults/adolescents | Dosage in children |
|---|---|---|
| **Metronidazole** | 200-400 mg TID x 7-10 days | 15 mg/kg/day x 7-10 days |
| **Tinidazole** | 2 g once only | 50-60 mg/kg once only |
| **Ornidazole** | 2 g once only | 40 mg/kg once only |
| **Nitazoxanide** | 500 mg BID x 3 days | 7-10 mg/kg/day in 2 divided doses x 3 days |
| | | 1-3 yr: 100 mg BID x 3 days |
| | | 4-11 yr: 200 mg/kg BID x 3 days |
| | | >12 yr: 500 mg BID x 3 days |
| **Albendazole** | 400 mg OD x 5 days | <2 yr: 200 mg OD x 5 days |
| | | >2 yr 400 mg OD x 5 days |
| **Furazolidine** | 100 mg QID x 10 days | 6-8 mg/kg/day in 4 divided doses x 5 - 7days |

Table 1: Dosage of recommended drug regimens for giardiasis [1-3,6,7].

## Drug Therapy in Refractory/Recurrent Giardiasis

The following options are available for refractory or recurrent giardiasis, problem common in immunocompromised states:-

- Simultaneous therapy of family members with improvement in water, food and personal hygiene
- Routine drugs with higher doses

- Repeated courses
- Relatively longer courses.
- Varied combination of standard drugs (say, metronidazole plus albendazole; metronidazole plus mepacrine; metronidazole plus furazolidine). At times, a combination of more than 2 drugs may be required.

There is evidence that cotherapy with vitamin A may be of help in resistant giardiasis [16].

When L.giadia and cryptosporidium are coexisting, nitazoxamide gives good results and should be the drug of choice.

## Ongoing & Future Research

Until recently, gateway to development of high potency antigiardial therapy effective in resistant cases has been in modification of existing drug leads in relation to nitrimidazole and benzamidazole. . Additionally, several new classes of antigiardial drug candidates have recently been identified by high-throughput screening of large compound libraries [17].

Consequent upon this, the pipeline of new antigiardial drug candidates has significantly expanded in the recent years. Nevertheless, the expansion has as not shown convincing efficacy in animal models or by a clear understanding of the mechanism, of action.

Molecules under investigation for this use include ivermectin, disulfuram, rifampin, bacitracin and bacitracin-zinc. Preliminary investigations employing bacitracin and bacitracin-zinc have demonstrated impressive efficacy. The mechanism of action of these compounds is interfering with a 10 dephosphorylation step. Both are given at a dose of 120,000 U twice daily for 10 days. ADRs include gastrontestinal symptoms and, with prolonged use, kidney injury

Even probiotics are being investigated for possible efficacy as such or in combination with established antigiardial agents.

## Conclusions

Pharmacotherapy of giardiasis, a neglected disease with potentials of causing considerable morbidity, especially in children, has continued to evolve from meparine through metroinidazole, furazoline, ornidazole and albendazxole to nitazoxanide over the past some decades. No doubt, an understanding of changing concepts and the application of the currently recommended drugs in a rationalized way is important for the clinical as well as parasitological cure of giardiasis.

Take Home Messages

- Included by the World Health Organization in the “neglected diseases”, giardiasis occurs on a massive scale in the low-income populations globally, constituting an important cause of morbidity, especially in children.
- Most infections are vulnerable to the available drugs though frequency of recurrences is high.
- Immunocompromised persons pose the problem of less satisfactory response to routine pharmacotherapy, often necessitating a change in the drug regimen.
- Since recurrences are common, therapy needs to be complemented with other measures aimed at safeguarding against reinfection and passing infection to family members, peers and coworkers.
- Albendazole, metronidazole, tinidazole and nitazoxanide stand out as the most acceptable amongst the plethora of drugs for giardiasis.
- Choosing an appropriate agent with attention to rationality in therapy plus preventive measures is mandatory to meet the challenge of giardiasis.

## References

1. Gupte S (2013) Giardiasis: Four decades of experience in pediatric practice. Proceedings, First Asian Congress of Neglected Diseases, Hong Kong, Abstract No. ACND/II/02.

2. Yoder JS, Gorgano JW, Wallace RM, et al. (2012) Giardiasis surveillance – United States 2009-2010. *MMR* Surveill Summ 6: 13-23.

3. Katz DE. Taylor DN (2001) Parasitic infections of the gastrointestinal tract. Gastroenterol Clin North Am 30(3): 797-815.

4. Gupte S (2009) Intestinal parasitic infestations. In: Gupte S, Horvath K (eds): Pediatric Gastroenterology, Hepatology and Nutrition New Delhi: Peepee: 265-273.

5. Ali SA, Hill DR (2003) Giardia intestinalis. Curr Opin Infect Dis 16(5): 453-460.

6. Escobedo AA, Cimerman S (2007) Giardiasis: A pharmacotherapy review. 8(12): 1885-1902.

7. Gaur A, Gupte S. Protozoal infections and infestations. In: Gupte S (Ed): The Short Textbook of Pediatrics, 12th ed. New Delhi: Jaypee 2016:379-394.

8. Wright JM, Dunn LA, Upcroft P, Upcroft JA (2003) Efficacy of antigiardial drugs. Expert Opin Drug Saf. 6: 529-541.

9. Gupte N. Rational pharmacotherapy of intestinal protozoan infections. J Rational Pharmacother Res In press.

10. Gupte N, Gupte S, Bhardwaj A (2013) Pharmacotherapy in pediatric gastroenterology. In: Gupte S (ed): Recent Advances in Pediatrics (Special Vol 23: Pediatric Gastroenterology, Hepatology and Nutrition). New Delhi: Jaypee 383-403.

11. Escobedo AA, Cimerman S (2007) Giardiasis: a pharmacotherapy review. Exp Opin Pharmacoth 12:1885-1902.

12. Ortiz H, Ayoub I, Gargia G (2001) Randomized clinical study of nitazoxanide compared to metronidazole in the treatment of symptomatic giardiasis in children from northern Peru. Alim Pharmacol Ther 15: 1409-1415.

13. Huang DB, White AC (2006) An updated review on Crypotosporidium and Giardia. Gastrenterol Clin North Am 35(2): 291-314.

14. Mathur AK, Moudgil S (2013) Berberine in pediatric giardiasis not responding to standard therapy. Proceedings, First Asian Congress of Neglected Diseases, Hong Kong, Abstract No. ACND/II/07.

15. Gupte S (1975) Use of berberine in treatment of giardiasis. Am J Dis Child 129: 866.

16. Lima AA, Soares AM, Lima NL, Mota RM, Maciel BL, et al. (2010) Effect of vitamin supplementation on intestinal barrier function, growth, total parasitic and specific Giardia spp infections in Brazilian children: A prospective randomized, double-blind, placebo-controlled trial. J Pediatr Gastroenterol Nutr 50(3): 309-315.

17. Tejman-Yarden N, Eckmann L (2011) New approaches to the treatment of giardiasis. Curr Opin Infect Dis 24(5): 451-456.