

WHAT IS THE MOST APPROPRIATE TREATMENT FOR GIARDIASIS?

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The World Health Organization has produced guidelines for the management of common illnesses in hospitals with limited resources. This series reviews the scientific evidence behind WHO's recommendations. The WHO guidelines, and more reviews are available at: http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/PB.htm

This review addresses the question: *what is the most appropriate treatment for giardiasis?*

The **WHO Pocketbook of Hospital Care for Children** recommends for giardiasis metronidazole 5 mg/kg 3 times a day for 5 days. (Pocketbook chapter 5.3.1, page 123).

Introduction:

Giardia Lamblia is the most commonly detected pathogenic protozoan in the human intestine.² Found in about 20% in patients with diarrhoea, its incidence may be as high as a billion cases, contributing to the 2.5 million annual deaths worldwide from diarrhoeal disease.³ The most prominent symptoms, generally appearing 6-15 days after infection, are steatorrhoea, weakness, weight loss and abdominal pain. Mostly these are self-limiting, though it is estimated that 30-50% of patients develop chronic disease. Steatorrhoea, iron deficiency anaemia, micronutrient deficiencies and malnutrition are among the long-term sequelae and can cause failure to thrive and psychomotor retardation in children.⁵

Methodology

Search terms [Giardia\$] AND [treatment OR therapeutics] AND [child\$ OR paediat\$ OR pediat\$] were entered into MEDLINE, EMBASE and GLOBAL HEALTH with results limited to English language and 1990-2007. Only

randomised controlled trials (RCTs) performed in low or middle income countries (according to the World Bank) were eligible for inclusion. Recent literature reviews^{6,7} were also searched to ensure that no pertinent RCTs had been overlooked. Aside from two exceptional cases^{8,9}, only studies that featured both children with mono-infection and those who had presented symptomatically to health services, were included. The exceptions were included due to their high quality. 15 trials met the inclusion criteria and depending on the number of SIGN 50 criteria²⁷ they met, were sub-classified '1-', '1+' or '1++'.

Results

The literature on giardiasis since 1990 has concentrated on a relatively consistent set of pharmacological agents. In the RCTs included in this review metronidazole, currently the first line treatment, was shown to completely clear the protozoa on parasitological analysis with an efficacy ranging from 75-100% of patients^{8, 10, 11, 12, 16, 18, 20, 21, 22}. However, other nitroimidazoles (tinidazole, ornidazole and secnidazole), which have the advantage of requiring only a single dose, have demonstrated at least equivalent efficacy (100%, 79-100% and 82-93% respectively)^{9, 11, 13, 14, 19, 20}. The benzimidazoles, albendazole and mebendazole, were shown to be slightly less effective; results range from 50-100% and 58.3%-100% respectively⁸⁻¹⁹.

No drug was reported to be unsafe, causing only mild to moderate and transient side effects (SEs). Whilst metronidazole was reported to produce SEs in up to approximately a quarter of patients (0-27%)^{9, 17, 18}; tinidazole caused similar effects in nearly to two thirds of children in one study (28-59%). Most common SEs included nausea and vomiting, metallic taste, headache and vertigo^{8, 10, 11, 12, 16, 18, 20, 21, 22}. Various studies

confirm the lower incidence of reported SEs with albendazole (0-8%)^{8, 12-15, 17}.

Albendazole, mebendazole, metronidazole are on the WHO essential paediatric drug list.²³ Of the other drugs reviewed, only tinidazole is available cheaply in generic form from large international pharmaceutical suppliers. Tinidazole is the cheapest of these at \$40 per 1000 children treated compared to \$45 for metronidazole. Albendazole and Mebendazole are more expensive at \$52 and \$86 respectively.²⁴

Discussion

The nitroimidazoles appear to remain the most effective drugs available for treating giardiasis. The results of this review suggest that a single dose of tinidazole (50mg/kg) has a similar efficacy to that of metronidazole, though the former has particular advantages in a resource poor setting. It is generally well tolerated and, because it requires only a single dose, has the potential to improve compliance. It is also slightly cheaper than metronidazole per treatment.

It is therefore suggested that the current WHO guidelines may no longer be the most appropriate; though this is mitigated by awareness that long term safety data for tinidazole is not available in either adults or children. As cases of resistance to all anti-giardial agents have been reported, it is important that physicians have access to a range of medications and, in regions where the disease is prevalent, it is imperative to periodically audit local drug sensitivity patterns.

Summary

Decades of evidence confirm that giardiasis responds well to antimicrobial treatment, decreasing the length of the illness and reducing the possibility of long term complications^{25, 26}. Nitroimidazoles are the most effective drugs available, and considering compliance, side-effects and cost, a single dose of tinidazole is the most appropriate treatment for children in resource poor settings.

References

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Table 1 Summary of 15 included trials.

Name, Year & Country	Age of children	Clinical Question	Patient Numbers	SIGN 50 Grade	Outcomes or Results (% of patients cured*)	P Value / 95% CI	Reviewers Comments & Assessment of Methodology
Hall et al. 1993 Bangladesh ¹	5-10 years	Albendazole (ABZ) vs Metronidazole (MTZ)	Phase I: Albendazole 600mg:n= 103; Albendazole 400mgx3d:n= 116; Metronidazole: 375 mgx5d): n= 115 Phase II: Albendazole 800mg:n= 114; Alb 400mgx 5 days: n= 115; Met: 375mg x 5d 115 Total of 768 children, with 678 cases of infection among 426 children.	1++	Phase 1 ABZ 600mg: 62.1%; ABZ 400mg x 3d: 81.0%; MTZ 375mg x5d: 97.4% Phase 2 ABZ 800mg: 74.6; ABZ 400mg x5d: 94.8; MTZ 375 x 5d: 97.4%	All treatments sig. different from each other: p<0.05 except ABZ 400mg x 5 which p>0.05 than MTZ	Excellent randomisation and parasitology descriptions in methods. Very large study. 2 phase study, retested with different doses. Not necessarily symptomatic children or mono-infection. Followed up for 15 months.
Dutta et al India, 1994 ²	2-10 years	400mg of ABZ daily as a single dose for 5d. or MTZ 7.5 mg/kg/dose x TDS x 5 day	N=150 75:75	1++	97% cure rate for both ABZ and MTZ	None given	Patients described as attending hospital, not clear if they are attending for GI symptoms or just enrolled opportunistically. Excluded if acutely febrile. Multicenter Study Well designed trial let down by its poor description of its parasitological methodology.
Misra et al. India 1995 ³	2-12 yrs	ABZ vs. MTZ	N=64 32 in each arm	1-	All were clear (100%) within 7 days. But ABZ was (mean) 3.7 days (+/-1.4) and MTZ was 4.5 +/- 1.1 days).	Not given	Performed on children who were not acutely unwell. Funded by SmithKline Beecham
Yereli et al. 2004 Turkey ⁴	3-15 yrs	ABZ vs. MTZ	N=107 52 ABZ, 55 MTZ	1+	By day 14 90.4% of ABZ and 89.1% with MTZ cured No SEs reported.	P= 0.92	No SEs reported but methodology to record them is not given.

¹ Hall A. and Nahar Q. Albendazole as a treatment for infections with Giardia duodenalis in children in Bangladesh Transactions of the Royal Society of Tropical Medicine and Hygiene (1993) 87, 84-86

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Pengsaa et al. Thailand, 2002 ⁵	7-15 yrs	Comparison of ABZ/ Praziquantel (PZ); ABZ and Tinidazole (TDZ)	N=84 I: ABZ/PZ:31 II: ABZ:26 III: TDZ: 27	RCT 1+	I: 74.2%; II: 50%; III: 92.6% SEs- two cases of "severe" (i.e. needing treatment) were recorded with combined treatment (abdominal pain).	P=0.01 between all three. But P>0.05 between combined treatment and either of the other two	Directly observed therapy. School children not hospital patients.
Escobedo 2003 (B) Cuba ⁶	2-15 yrs	Chloroquine (CQ) vs. ABZ vs. TDZ	N=165, ABZ:60; TNZ: 55 and CQ: 50	RCT 1+	TDZ cure: 91%, CQ: 86% ABZ: 62%. ABZ significantly less effective than other two, which were not significantly different from each other.	TDZ vs. CQ p>0.05. ABZ vs both others p=<0.01	
Canete et al. (A) Cuba 2006 ⁷	5-15 years	1 day with 600mg of MBZ (200mg TDS) vs 50mg/kg of TDZ in a single dose	N=122 61 in each arm	RCT 1+	MBZ 39 (64%) vs TNZ 50 (82%)	None given	
Cañete et al. (B) 2006, Cuba ⁸	5-15 yrs	Mebendazole vs. Quinacrine	N=122 61 children in each arm	RCT 1+	MBZ: 78.7% QC: 83.6%.	p> 0.05	

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⁵ Pengsaa et al. Single-dose therapy for giardiasis in school-age children. Southeast Asian J Trop Med Public Health. 2002 Dec;33(4):711-7.

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Sadjjadi, 2001, Iran ⁹	7-12 yrs	Comparison of MBZ and MTZ	50: 50	RCT 1-	MBZ cure rate: 43/50 (86%); MTZ: 45/50 (90%). Using chi sq. no stat. difference found. Only MTZ had SEs.	Not given	School children recruited rather than patients acutely presenting to health care services. Concept of blinding never addressed.
Al-Waili et al. 1992, Iraq ¹⁰	3-13 yrs	MBZ: 200mg TDS for 5 days vs. MTZ 200mg TDS for 5 days	44 patients: 23 in MBZ and 21 with MTZ	RCT 1-	100% parasitological cure in both arms. Some mild SEs in MTZ	None given	Very brief report many details not given. Can't read how many SEs and where took place and how recruited not explained
Bulut et al. Turkey, 1996 ¹¹	6- 13 yrs	Comparison of 1d mebendazole; 7d mebendazole, MTZ 7 days, single dose ODZ	Total 60: 17, 17, 15, 11	RCT 1-	Group I: 41.7% (CI 6.2-77.2); II: 58.3% (CI 22.8-93.8); III: 92.6% (CI 74.4-100.0); IV: 100% (CI: 100)	See left	School children recruited rather than patients acutely presenting to health care services.
Escobedo et al. 2003 (A) Cuba ¹²	5- 15yrs	MBZ vs Secnidazole (SCZ)	N=146; 73 x 2	RCT 1+	MBZ 78.1%; SCZ 79.4%.	P> 0.05	
Rastegar-Lari et al Iran, 1996 ¹³	3- 14 yrs	SCZ vs. MTZ	N=52 27 SCZ: 27 and MTZ: 25	RCT 1+	SCZ: 100% cure, MTZ: 96%	P = 0.41	Some asymptomatic carriers included.
Ortiz et al, Peru 2001 ¹⁴	6- 11 yrs	Nitazoxanide (NZN) vs. MTZ	N=110: 55 in each arm.	RCT 1+	NZN: 71% and MTZ: 75%.	P>0.83 95% CI: - 20.1%-	Intention to treat analysis included. Funded by Romark Laboratories, (inventors of Nitazoxanide).

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Talari et al., 2006, Iran ¹⁵	5-12 yrs	MTZ vs. Furazolidone (FLD)	62 MTZ, 60 FLD (120 total)	RCT 1-	MTZ 87% , FLD 81.7% parasite free at 4 weeks	12.6% Not given	Concept of blinding never addressed.

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