

# Albendazole versus metronidazole in the treatment of patients with giardiasis in the Islamic Republic of Iran

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مقارنة بين الألبيندازول والميترونيدازول في معالجة المصابين بداء الجيارديات في جمهورية إيران الإسلامية

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**الخلاصة:** قام الباحثون في إطار هذه الدراسة بتقييم التأثيرات العلاجية للألبيندازول بالمقارنة مع الميترونيدازول لدى 120 من المرضى بداء الجيارديات في مدينة همدان. وقُسم المرض عشوائياً لتلقي الألبيندازول (بمعدل 400 مغ مرة واحدة لمدة 5 أيام)، أو لتلقي الميترونيدازول (بمعدل 250 مغ، ثلاث مرات يومياً لمدة 5 أيام). وتم تسجيل المعطيات الديموغرافية للمرضى، ونتائج فحص البراز لتحريّ الدور النشط من دورة حياة طفيلي الجيارديات، قبل المعالجة وبعدها، وكذلك التأثيرات الجانبية للأدوية. وتبيّن بعد المعالجة أن ستة من فئة المرضى الذين تلقوا الألبيندازول (نسبة 10٪) كان لديهم الطور النشط للطفيلي، بالمقارنة مع 14 مريضاً (نسبة 23.3٪) من الفئة التي أُعطيت الميترونيدازول ( $P < 0.05$ ). ولوحظت تأثيرات جانبية أقل لدى فئة الألبيندازول، في حين عانى 43.3٪ من فئة المعالجين بالميترونيدازول من مذاق معدني، وعانى 35٪ منهم من نقص الشهية للطعام. واستنتجت الدراسة أن الألبيندازول علاج سهل وآمن وفعال للجيارديات.

**ABSTRACT** We examined the therapeutic effects of albendazole compared to metronidazole in 120 patients with giardiasis in Hamdan. Patients were randomized to receive albendazole (400 mg, once daily for 5 days) or metronidazole (250 mg, 3 times a day for 5 days). Demographic data of the patients, results of stool examination for Giardia trophozoites before and after treatment, and drug side-effects were recorded. After treatment 6 (10.0%) of the albendazole group had trophozoites compared with 14 (23.3%) of metronidazole group ( $P < 0.05$ ). Patients in the albendazole group had fewer side-effects while 43.3% of the metronidazole group experienced a metallic taste and 35.0% experienced loss of appetite. Albendazole is an easy, safe and effective treatment for giardiasis.

Comparaison entre albendazole et métronidazole dans le traitement des patients atteints de giardiase en République islamique d'Iran

**RÉSUMÉ** Nous avons examiné les effets thérapeutiques de l'albendazole par rapport au métronidazole chez 120 patients atteints de giardiase à Hamdan. Les patients ont été randomisés pour recevoir de l'albendazole (400 mg une fois par jour pendant 5 jours) ou du métronidazole (250 mg 3 fois par jour pendant 5 jours). Les données démographiques des patients, les résultats de l'examen coprologique à la recherche de trophozoïtes de Giardia avant et après le traitement, et les effets secondaires des médicaments ont été notés. Après le traitement, 6 patients (10,0 %) du groupe albendazole avaient des trophozoïtes contre 14 (23,3 %) dans le groupe métronidazole ( $p < 0,05$ ). Les patients du groupe albendazole avaient moins d'effets secondaires tandis que 43,3 % des patients du groupe métronidazole ressentaient un goût métallique et 35,0 % présentaient une perte d'appétit. L'albendazole constitue un traitement facile, sûr et efficace pour la giardiase.

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## Introduction

*Giardia lamblia*, also known as *Giardia duodenalis* or *Giardia intestinalis*, is one of the most common intestinal parasites worldwide and is a frequent cause of diarrhoeal illness [1–4]. It is estimated that about 300 million people annually are affected with the parasite all around the world [3] and it is an important cause of morbidity in the developing world [5]. *G. lamblia* causes both epidemic and sporadic disease and is an important cause of waterborne and foodborne diarrhoea, day-care centre outbreaks, and diarrhoea in international travellers [1]. Waterborne, foodborne and direct contact are 3 important patterns of potential transmission of the pathogen [5]. The infection may be asymptomatic or present with a variety of symptoms such as diarrhoea, weight loss, abdominal cramps and failure to thrive [1]. The incubation period is 1 to 2 weeks following ingestion and the acute stage of the disease lasts from 3 to 4 days but can go on for much longer [6]. Severe symptoms of diarrhoea and sickness can be persistent and even life-threatening in immunocompromized individuals, infants and in the aged, although the disease is self-limiting in the majority of patients [3]. Diagnosis of infection is by stool examination, which may also eliminate other possible infectious agents [2].

Many drugs, including metronidazole and albendazole, are used for the treatment of the disease. For the treatment of giardiasis, metronidazole is the drug of choice [7] but in cases of resistance, drugs such as albendazole have been said to be effective [1]. Review of the literature shows that there have been few clinical trials to compare albendazole with other effective anti-giardial drugs [2,4,8]. As albendazole is an available and safe antiprotozoal medicine in the Islamic Republic of Iran and perhaps in other

parts of the world, we conducted a clinical trial in order to assess the anti-giardial effects compared to metronidazole.

## Methods

The study was conducted in Hamadan, a city in the north-west of the Islamic Republic of Iran over a period of 1 year (2001). Cases were selected from among patients attending 4 pre-defined private outpatient clinics in 4 different parts of the city. Due to difficulty in coordination, patients of medical centres of the health administration network were not entered in the study. Based on biostatistical calculations (alpha level of 0.05 and beta level of 0.2), the sample size needed was calculated to be 120 documented cases of the disease. Before starting the study one number was assigned for each case. All the numbers were assigned in 2 groups (60 cases in each) at random and a physician was assigned to give the needed numbers to the clinics. The physician was also responsible for following up the cases. Referral with acute symptoms of giardiasis and a positive stool examination report for trophozoites of the pathogen were considered as the inclusion criteria. One parasitologist who was blinded to the treatment received was responsible for detecting the trophozoites in the samples and checked all iodine-stained wet stool preparations before and after treatment.

The first group received the standard treatment with albendazole (400 mg daily as a single dose for 5 days) and the second group received metronidazole (250 mg 3 times a day for 5 days). Patients received the specified dosages daily and they were asked whether they had taken the complete dose of the drugs. A week after starting the treatment, stool examination to detect trophozoites of *G. lamblia* was performed 3 times

in 3 consecutive days for all the patients. Response to treatment was determined as negative stool examination for trophozoites and cysts. Those who continued to be positive for trophozoites and/or cysts despite completing the course of treatment were considered non-responders. Demographic data, the results of stool examination for *Giardia* trophozoites before and after treatment, and any side-effects experienced were recorded.

All the cases signed an informed consent form before starting treatment. For cases under 16 years, one of the parents signed the consent form. The Ethics Committee of Hamadan University of Medical Sciences approved the study.

We used protocol-based analysis instead of intention-to-treat analysis because, according to the primary design of the trial, patients who refused to participate in the study were replaced by new patients to reach the desired number of cases in each

group. However, in the follow-up period we sought the reasons why the patients refused to participate. Although protocol-based analysis tends to bias the interpretation of the results, concerning the main cause of the patients' drop-out, it was possible to get similar results by using each kind of analysis. Descriptive statistics for both groups were reported. Using the chi-squared and independent Student *t*-tests, statistical analysis of the data was performed with SPSS, version 9.01. The level of significance was set at  $P < 0.05$ .

## Results

The mean and standard deviation (SD) of the patients' age was 22.3 (SD 11) years (range 2–53 years). Table 1 shows the characteristics of patients in the 2 groups. Male to female ratio was 61:59. Mean (SD) of duration of the symptoms in the first group

Table 1 Characteristics of patients in the groups receiving albendazole and metronidazole in the treatment of giardiasis

Characteristic	Albendazole group (n = 60)	Metronidazole group (n = 60)
Mean age (SD) (years)	21.3 (8.9)	22.9 (12.1)
Male/female	30/30	31/29
Mean duration of symptoms (SD) (days)	3.4 (0.6)	4.2 (0.7)
Education <sup>a</sup>		
Illiterate (No.)	4	5
Educated (No.)	44	32
Highly educated (No.)	12	13
Quit treatment	15	9
Response to treatment		
All patients, No. (%)	54/60 (90.0)	46/60 (76.7)
Male, No. (%)	26/30 (86.7)	22/31 (71.0)
Female, No. (%)	28/30 (93.3)	24/29 (82.8)

SD = standard deviation.

<sup>a</sup>Illiterate: no schooling/not able to read or write; educated: able to read or write up to high-school diploma; highly educated: attended university.

was 3.4 (0.6) days and in the second it was 4.2 (0.7) days. Independent Student *t*-test showed a significant difference between the 2 groups in terms of duration of the symptoms ( $P < 0.01$ ). None of patients in the 2 groups had a history of immune deficiency or disabling disease. As regards compliance, 15 patients from the albendazole group and 9 patients from the metronidazole group failed to complete the course of medication. In follow-up of these patients, we found it was due to difficulty in revisiting the clinic, not to continuation of symptoms or side-effects of the drugs.

After the whole course of treatment, 6 patients in the albendazole group were found still to have trophozoites in the stool while 14 (23.3%) in the metronidazole group still had the pathogen, giving a significant difference in non-responder rate between the 2 groups ( $P < 0.05$ ). The difference in response rate between the 2 groups was statistically significant (Yates corrected  $\chi^2$ ,  $P < 0.05$ ). There was no significant difference between males and females in response of treatment of each group. Table 2 shows the side-effects of the treatment with the 2 drugs. Metallic taste, vertigo and loss of appetite were significantly higher in the pa-

tients who had taken metronidazole. Transient abdominal pain was only observed in the albendazole group. Participants taking metronidazole reported more side-effects than those taking albendazole, metallic taste being the commonest side-effect (43.3%), followed by loss of appetite (35.0%).

## Discussion

In human giardiasis, therapeutic failure is occurring more and more frequently due to low compliance with drug therapy, re-infestation or parasite resistance to metronidazole and/or the nitroimidazole-related compounds like tinidazole [9]; hence examining alternative treatments is always valuable. In this study we found that albendazole was more effective than metronidazole in the treatment of acute giardial infection. As all the cases were followed for a fairly acceptable period (1 week) after the start of treatment and no significant side-effects of the drugs were documented, prescription of albendazole not only in cases of drug resistance but also as an alternative first-line therapy is advised. Nevertheless, it must be considered that it could increase the risk of

Table 2 Frequency of side-effects of metronidazole and albendazole in the treatment of patients with giardiasis

Side-effect	Metronidazole (n = 60)		Albendazole (n = 60)		P-value
	No.	%	No.	%	
Metallic taste	26	43.3	–	–	< 0.0001
Vertigo	14	23.3	4	6.6	0.01
Nausea/vomiting	11	18.3	12	2.0	NS
Loss of appetite	21	35.0	–	–	< 0.0001
Urticaria	2	3.3	–	–	NS
Transient abdominal pain	–	–	18.3	–	< 0.0001

NS = not significant.

developing resistance to albendazole. The lack of sensitivity in the diagnostic test applied in this study [10] cannot be considered a serious limitation as the probability of obtaining a false negative result was the same for both groups.

Review of the literature shows that some controversy exists about the efficacy of albendazole compared to metronidazole in the treatment of giardial infection. As metronidazole is a well-established anti-giardial medicine and has generally remained the first-line chemotherapeutic agent against this microorganism [7], we sought data indicating the therapeutic effects of albendazole rather than metronidazole on giardiasis. In most studies, albendazole was as good as metronidazole or better [8,11–19]: only a few studies reported that albendazole was inferior to metronidazole in treatment of giardiasis. Chan Del Pino et al. indicated that albendazole is as effective as furazolidone, tinidazole and secnidazole but faster at eradicating the *G. lamblia* in children and is better tolerated than metronidazole [11]. In a study performed in France, the researchers found that in some cases of metronidazole resistance, albendazole was an effective drug [12]. After performing a randomized clinical trial, Pengsaa et al. indicated that albendazole appeared to be safe and produced a moderate cure rate for *G. intestinalis* infection when a 3-day anti-helminthic regimen was given [13]. Reynoldson et al. examined the efficacy of albendazole at a dose rate of 400 mg daily for 5 days on eradicating giardial and hookworm infections and concluded that the drug was highly effective in reducing hookworm egg numbers and both *Giardia* antigen and cysts [16]. In a randomized trial Romero-Cabello et al. concluded that al-

bendazole and metronidazole were equally effective in a 5-day treatment period, but some undesirable side-effects may occur with metronidazole [17]. Albendazole has been proved to be effective in *in vitro* settings and asserted to be the most effective antihelminthic benzimidazole [18]. In a clinical trial in children in the Islamic Republic of Iran, Sadjjadi, Alborzi and Mostovfi showed that mebendazole was as effective as metronidazole with fewer side-effects [19].

In a systematic review done by Zaat Mank and Assendelft it was shown that most of the clinical trials on drug therapy for giardiasis had some methodological flaws; a single dose of tinidazole appeared to give the highest clinical cure rate for giardiasis with relatively few adverse side-effects [20]. It has been reported that albendazole was inferior to other known anti-giardial drugs [21]. However the study was conducted as an open pilot trial in travellers returning from the tropics, while we used a randomized clinical trial with precise monitoring of patients.

The results of the current study show that albendazole is a safe and effective drug in the treatment of giardiasis and provide further evidence of the usefulness of this drug. However, this will not put an end to the controversies surrounding the treatment of giardiasis. Hence, new evidence about the efficacy of anti-giardial medicines is needed. In the future, studies should be designed to better evaluate albendazole in comparison with other new medicines. In addition, we need studies with larger numbers of cases and clinical trials in children and immune-compromised patients, especially patients with humoral abnormalities.

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