Increased incidence of nitroimidazole-refractory giardiasis at the Hospital for Tropical Diseases, London: 2008–2013

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Abstract

Giardia intestinalis is the commonest gastrointestinal protozoal pathogen worldwide, and causes acute and chronic diarrhoea with malabsorption. First-line treatment is with a nitroimidazole, with a reported efficacy rate of 89%. Failure of treatment can occur in patients with hypogammaglobulinaemia or human immunodeficiency virus (HIV), or be due to nitroimidazole-resistant organisms. There is little evidence to guide the clinical management of nitroimidazole-refractory disease. We performed a retrospective audit of nitroimidazole-refractory giardiasis in returned travellers at the Hospital for Tropical Diseases, London between 2011 and 2013. Seventy-three patients with microscopy-proven or PCR-proven giardiasis in whom nitroimidazole treatment had failed were identified, and their management was investigated. In 2008, nitroimidazole treatment failed in 15.1% of patients. This increased to 20.6% in 2011 and to 40.2% in 2013. Patient demographics remained stable during this period, as did routes of referral. Of patients with giardiasis, 39.0% had travelled to India; this rose to 69.9% in patients with nitroimidazole-refractory disease. Of the patients with refractory disease, 44.6% had HIV serological investigations performed and 36.5% had immunoglobulin levels determined. Patients with refractory disease were treated with various agents, including albendazole, nitazoxanide, and mepacrine, alone or in combination. All 20 patients who received a mepacrine-containing regimen were cured. This data shows a worrying increase in refractory disease, predominantly in travellers from India, which is likely to represent increasing nitroimidazole resistance. Improved tools for the diagnosis of resistant *G. intestinalis* are urgently needed to establish the true prevalence of nitroimidazole-resistant giardiasis, together with clinical trials to establish the most effective second-line agent for empirical treatment regimens.

Keywords: Albendazole, *Giardia intestinalis*, giardiasis, India, mepacrine, nitroimidazole, refractory, resistance, travellers

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Introduction

Giardia intestinalis is the commonest gastrointestinal protozoal pathogen worldwide. It causes a spectrum of clinical disease, ranging from asymptomatic carriage to acute or chronic diarrhoea with malabsorption. The commonest presentation in travellers is acute or chronic diarrhoea, which may be accompanied by flatulence and weight loss. Although giardiasis is rarely life-threatening, chronic tiredness and gastrointestinal symptoms may continue following eradication [1].

First-line treatment for giardiasis is using a nitroimidazole. Metronidazole, 500 mg three times daily for one week, is commonly used. The reported efficacy is 89% [2]. Single-dose tinidazole has similar efficacy but fewer side effects, and thus better compliance [2]. A study of 170 patients in Madrid between 1989 and 2004 found 5.8% failed a mean of 3 courses of metronidazole [3]. Between 2007 and 2009, a study of travellers returning to Barcelona found that nitroimidazole treatment failed in 22% [4].

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Risk factors for treatment failure include IgA deficiency [5], human immunodeficiency virus (HIV) [6], and coeliac disease. Patients may become re-infected from a contaminated water supply, an animal reservoir, or household or sexual contact. *G. intestinalis* can become resistant to nitroimidazole treatment and other antiprotozoal drugs [7].

The second-line treatment for patients in whom nitroimidazole treatment fails is unclear. Most drug efficacy studies have been conducted in treatment-naïve patients, and the results have been extrapolated to patients in whom nitroimidazole treatment has failed. A single randomized trial investigated 20 patients in whom metronidazole treatment had failed; of ten patients treated with albendazole, only two were cured, in comparison with nine patients cured when albendazole was combined with metronidazole [8]. Mørch evaluated a treatment ladder for refractory giardiasis during a waterborne outbreak in Norway [9]. Of 38 patients in whom metronidazole treatment failed, 79% (30/38) were cured with 7 days of combination metronidazole–albendazole. A further three of six patients were cured with 7 days of paromomycin. The remaining three were cured with combination quinacrine–metronidazole for 2–3 weeks. All patients experienced quinacrine-related side effects [9].

The Hospital for Tropical Diseases, London (HTD) is a tertiary referral centre for tropical disease, and is part of University College London Hospitals. An emergency self-referral clinic is run daily for travellers returning from the tropics with fever or diarrhoea. There are four general infectious disease clinics a week, in which referrals are received from general practitioners and hospitals around the UK. Diagnostic parasitological investigation is undertaken in the HTD Department of Clinical Parasitology, which is also the Public Health England National Parasitology Reference Laboratory.

Tinidazole is used as first-line treatment for giardiasis in our patients. Available second-line treatments include metronidazole, albendazole, paromomycin, nitazoxanide, and mepacrine (quinacrine). These are given at the discretion of individual clinicians.

In 2013, a number of clinicians at the HTD noticed an increase in the number of patients with nitroimidazole-refractory giardiasis. This audit aimed to establish whether the frequency of nitroimidazole-refractory giardiasis was increasing in our cohort, and the ways in which we were managing these patients.

Materials and methods

We performed a retrospective audit of patients diagnosed with giardiasis in 2008 and between the years 2011 and 2013 at the HTD. Patients with parasitologically proven giardiasis were identified from parasitology laboratory records of positive stool microscopy or PCR results. In 2008 and 2011, stool microscopy for cysts of *G. intestinalis* was the only available method for diagnosis. In 2012, a multiplex PCR, performed on stools, was introduced for the diagnosis of *G. intestinalis*, *Cryptosporidium* and *Entamoeba histolytica* infection. Thus, for 2012 and 2013, both stool microscopy and PCR were performed on stool specimens from patients with a queried diagnosis of giardiasis. Patients were excluded if they had a previous diagnosis of giardiasis at the HTD, or if they did not receive treatment for giardiasis at the HTD.

Cases were deemed to be nitroimidazole refractory if they fulfilled the following case definition: (a) patients referred to the HTD with previously documented positive stool samples for *G. intestinalis*, previous nitroimidazole treatment, and a positive stool sample at the HTD at least 2 weeks following treatment; or (b) patients reviewed at the HTD with a positive stool sample for *G. intestinalis* at least 2 weeks after documented nitroimidazole treatment.

Once refractory cases had been identified, further data were collected from laboratory records, electronic letters, and case notes. These included travel history and a complete history of antiprotozoal treatment. If performed, immunoglobulin levels, HIV status and coeliac status were recorded, together with re-infection history.

Data were analysed with MS Excel 2010. Research approval was not required, as this was an audit intended to document current practice and improve future outcomes.

Results

Between 2011 and 2013, 259 patients were diagnosed with giardiasis; 179 were seen in the emergency clinic, and 39 were referred from general practitioners. The source of referral was unclear for 41 cases.

In 2008, nitroimidazole therapy failed in eight (15.1%) patients diagnosed with giardiasis. This increased to 15 (20.6%) in 2011, 23 (23.2%) in 2012, and 35 (40.2%) in 2013 (n = 259 cases) (Fig. 1).

In 2011, all patients diagnosed with giardiasis, either sensitive or refractory to nitroimidazoles, were diagnosed by microscopy. In 2012, 16 (28.6%) patients diagnosed with giardiasis by microscopy had nitroimidazole-refractory giardiasis, as compared with 14 (22.2%) diagnosed by PCR. In 2013, 21 (38.9%) patients diagnosed by microscopy had refractory giardiasis, as compared with 26 (47.3%) diagnosed by PCR (Table 1).