Clinical Problems

Outbreak of Giardiasis: Effect of a New Antiflagellate Drug, Tinidazole

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British Medical Journal, 1972, 2, 449-451

Summary

We describe here an intensive outbreak of mostly symptomatic (90%) *Giardia lamblia* infestation in a Swedish student group visiting the U.S.S.R. A new antiflagellate drug, ethyl (2-(2-methyl-5-nitro-1-imidazolyl) ethyl) sulphone, tinidazole, Pfizer, was given in a dosage of 150 mg twice daily for seven days to 10 healthy volunteers and to 24 students infested with *G. lamblia*. The drug was found to be effective in curing giardiasis and in eradicating *G. lamblia* from the intestinal tract. All the students with symptomatic giardia infestation became free from gastrointestinal disturbance, usually soon after treatment was started. None of the 24 students had *G. lamblia* in their stools after tinidazole treatment was discontinued or at follow-up. No side effects of the drug were seen and all of the subjects tolerated it very well.

Introduction

Man is the natural reservoir for *Giardia lamblia*, a cosmopolitan protozoon which lives in the human duodenum and in the first part of the jejunum and can be found as trophozoites and cysts in diarrhoeic faeces or cysts in formed stools or trophozoites in duodenal contents.^{1,2} *Giardia* infestation can be spread by food¹ and water,^{3,4} and also direct from person to person in families,^{5,6,7} nurseries,^{8,9} and under unhygienic^{6,10} and overcrowded conditions.¹⁰

The incidence of infestation varies between countries and sometimes between different regions of a country.¹¹ With improved hygiene and standards of living this incidence will probably fall as, in fact, has been shown in Norway.¹² It is likely that the incidence has also fallen in Sweden since the 1930s, when it was about 7%.¹³ During the 1960s only one case of giardia infestation in Sweden was reported.¹⁴ However, the rising proportion of Swedish tourists travelling to the Far East, Africa, and South and Central America during the past five years has increased the number of patients with giardiasis observed in Sweden.^{5,7,15,16} Ever since tourists have been permitted to go to the U.S.S.R. outbreaks of *G. lamblia* infestation have been reported among tourists from Sweden^{5,7,17,18} as well as from other countries.^{19,20}

Most cases of *G. lamblia* infestation are said to be asymptomatic in countries where infestation is common.^{1,8} When giardia has been associated with disease the patients have had

gastrointestinal symptoms such as anorexia, nausea, abdominal pain, usually diarrhoea,^{1,21} and sometimes malabsorption.^{21,22,23}

We describe here an outbreak of *G. lamblia* infestation among a group of 38 Swedish students visiting Leningrad in April 1971. Surprisingly, 90% of the affected students had gastrointestinal symptoms. A new antiflagellate drug, tinidazole, was used to eradicate the parasite.

Materials and Methods

Epidemiological Background.—From 29 March to 4 April 1971 a group of 38 adults from different parts of Sweden, studying in Stockholm, visited Leningrad. They went by regular flight direct from Stockholm. During their stay in Leningrad they lived in a first-class hotel and took most of their meals in a good-class restaurant. They returned to Stockholm direct by air and then most of them left at once for their Easter vacation. While in Leningrad only a few of them had gastrointestinal symptoms, but from 8 to 12 April most of them fell ill with a gastrointestinal disorder. On 23 April one of them, a woman who still had diarrhoea, was examined at the outpatient department for infectious diseases, Danderyd Hospital. When informed of the above-mentioned epidemiological background to her disease we carried out an aetiological study in order to establish the agent responsible for the gastrointestinal symptoms in the group.

Clinical Studies.—All the 38 students were asked whether they had had any gastrointestinal symptoms, such as anorexia, nausea, vomiting, abdominal discomfort, diarrhoea, or loss of weight, before, during, or after their visit to Leningrad. Before their visit to the U.S.S.R. two of the students had had periods of slight diarrhoea and four had sometimes had symptoms often seen in patients with gastritis. The rest had been in good health. After treatment with tinidazole (see below) the students were asked whether they had become free from gastrointestinal symptoms or whether these had been aggravated during the treatment. Side effects other than those arising in the intestinal tract were also asked for. A group of 10 healthy volunteers were also given tinidazole to study any side effects. At the first examination of the students and volunteers and shortly after tinidazole was stopped routine blood counts and standard liver function tests were done. Urine from all the volunteers and from 23 of the 24 students who received tinidazole was studied for the presence of protein and sugar as well as microscopically. In the volunteer group the creatinine level was also estimated before and after tinidazole.

Bacteriological and Parasitological Studies.—Stool specimens were obtained from all the 38 students. One part of the first specimen sampled was submitted for culture of salmonella and shigella bacteria. Enteropathogenic coli were not regularly looked for. The other part was concentrated according to a method described by Ridley and Hawgood.²⁴ The stools were then examined microscopically for the presence of cysts (and

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trophozoites) of *G. lamblia*. If the first specimen did not contain *G. lamblia* a second specimen was asked for. If this second specimen was also free from cysts (or trophozoites), a third specimen was studied. A subject with three negative stool examinations was considered to be free from *G. lamblia* infestation. The duodenal contents were not examined. A few days after tinidazole treatment was discontinued and after one and two months stool specimens from all the treated students were examined for the presence of *G. lamblia* cysts with the same method as described above.²⁴

Therapeutic Trial.—Tinidazole, ethyl (2-(2-methyl-5-nitro-1-imidazolyl) ethyl) sulphone (Fig. 1), is a new antitrichomonal

TINIDAZOLE: Ethyl (2-(2-methyl-5-nitro-1-imidazolyl) ethyl) sulphone

METRONIDAZOLE: 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole

FIG. 1—Structural formulae of tinidazole and metronidazole.

drug produced by Pfizer Research Laboratories, Sandwich, England.^{25 26 27} This drug was kindly placed at our disposal to study its effect on *G. lamblia* infestation, which had not been done before. It was planned to give tinidazole to all the students affected with giardia. Four of the giardia-positive patients, however, were given metronidazole (Fig. 1) by their own doctors when they received the results of our examinations of their stool specimens. Two female students were pregnant and they were not given any antitrichomonal drug, either tinidazole or metronidazole. The remaining students with *G. lamblia* infestation and the healthy volunteers received oral tinidazole 150 mg twice daily for seven days.

Results

Altogether 30 (79%) of the 38 students had cysts of *G. lamblia* in their stools—27 (90%) were found to have cysts in the first stool specimen, two (6.7%) in the second, and one (3.3%) in the third specimen. In eight of them three stool specimens were free from giardia. Besides *G. lamblia*, *Endolimax nana* was found in four stool specimens, *Entamoeba coli* in one, and *Iodamoeba butschlii* in one. None of the students had salmonella or shigella bacteria in their stools.

Eight students were healthy and free from *G. lamblia* in three stools. Of the remaining 30 students who were affected with *G. lamblia* 27 (90%) had gastrointestinal symptoms and only

FIG. 2—Incidence of various symptoms from the gastrointestinal tract in 30 students with *G. lamblia* infestation.

three were symptomless carriers. When the study started 19 days after the students had returned to Sweden 26 (87%) still had abdominal discomfort of various types and most of them were distressed by their disease. Three patients had more than five loose stools daily and eight (30%) lost up to 3 kg in weight. The stools were sometimes mucoid but never bloody. Twelve patients had four or more of the symptoms shown in Fig. 2, six had three, and nine had only one or two. All the students were afebrile.

Effect and Side Effects of Tinidazole.—The 24 students and 10 volunteers who received tinidazole tolerated the drug very well. No side effects involving the skin, mucous membranes, abdominal tract, peripheral blood, liver, or kidney were noted. None of the giardia-positive students showed parasites in the first stool specimen investigated a few days after treatment was stopped and also in stools examined after one and two months. Most of the 21 students treated with tinidazole for symptomatic *G. lamblia* infestation recovered early during the therapy. When the treatment was completed only two of them still had some slight gastrointestinal discomfort. One of them had also had such symptoms immediately before visiting the U.S.S.R. At follow-up these two students were in good health.

Discussion

The surprisingly high incidence (79%) of *G. lamblia* infestation in this group of students after visiting Leningrad in April 1971 supports the incidence of 73% found by us in another group of Swedish students visiting the same city in October 1970.¹⁷ Neither salmonella nor shigella infections were found in any members of these two groups of students. The incidence of enteropathogenic coli infection could not be established because such infections were not consistently looked for. Parasites other than *G. lamblia* are not thought to cause gastrointestinal disturbances. The mode of transmission of *G. lamblia* among tourists visiting the U.S.S.R. is not known but is probably by contaminated food.

Most of the students fell ill within 10 to 12 days after their arrival in the U.S.S.R., which means that they had returned to Sweden two to four days before the onset of illness. This incubation period is in line with findings in experimental infestations in volunteers.²⁸

Earlier studies^{17 18} of outbreaks of *G. lamblia* infestation in Swedish tourists visiting the U.S.S.R. have shown that symptomatic giardia infestation was very common among these subjects. This finding is confirmed by the present study. Thus in natives of a country where *G. lamblia* infestation is uncommon such infestation seems fairly often to give rise to gastrointestinal symptoms. On the other hand, in countries where *G. lamblia* is common infestation with this parasite seems to be mostly asymptomatic.^{1 8} Heavy infestation with *G. lamblia* in these tourists may also account for the high frequency of gastrointestinal symptoms.¹ This explanation may be supported by the fact that we found *G. lamblia* in 90% of the first stool specimens obtained from the patients in this series. The reliability of stool examination was studied by Petersen¹² in seven non-epidemic cases in which *G. lamblia* was known to be present in the duodenal contents. *G. lamblia* was found in the stools of six out of the seven patients, but in many of the stool specimens obtained from these patients no cysts were found even when a concentration technique of the faeces was used.²⁴ In a group of patients with unexplained non-organic diarrhoea investigated at a Norwegian medical department Petersen also found that as many as 15% harboured *G. lamblia* in the duodenal contents.¹² In the light of this finding and other reports from Scandinavia^{14 20} we recommend a search for *G. lamblia* in patients with diarrhoea and malabsorption of unknown origin, especially if they have visited foreign countries where such infestation is common. To exclude the presence of *G. lamblia* at least three negative stool examinations are necessary, and in suspected non-epidemic cases a negative duodenal content should also be obtained.

The main symptoms associated with *G. lamblia* infestation were changes in defecation habits, abdominal pain, diarrhoea, and a feeling of bloatedness. The diarrhoea was continuous or intermittent, sometimes frequent—up to five or more daily—and mucoid but not bloody. Three weeks after their disease started most of the patients still had these gastrointestinal disturbances, often combined with nausea, anorexia, and weight loss (Fig. 2).

Spontaneous cure of *G. lamblia* infestation may occur²⁸ but it is well known that many patients with such infestation may have symptoms for months or years.^{1 14 17 20} It is also known that spread of *G. lamblia* may occur in nurseries^{8 9} and in families.^{5 6 7 10} Hence we believe that all patients affected with *G. lamblia* living in a community where such infestation is uncommon should be given an antitrypanosomal drug. To date metronidazole has been the drug of choice.^{29 30 31} In the present study we used a new antitrypanosomal drug, tinidazole, which has been found to be eight times more effective than metronidazole in treating *Trichomonas foetus* infection in mice.^{25 27} Tinidazole has also been reported to be free from side effects involving the blood, kidney, and liver in animals and man.^{25 26 32 33}

Immediately after stopping the tinidazole therapy (150 mg twice daily for one week) 90% of the students with giardiasis were free from gastrointestinal symptoms, and at follow-up after one and two months all were fully recovered and none harboured *G. lamblia* in their stools. For comparison we¹⁷ found that metronidazole 200 mg three times daily for one week given to a similar group of students infested with *G. lamblia* (see above) could eradicate the parasites from the stools of only 71% of the cases. A cure rate of 67% was reported by Petersen¹² when he used the same dose of metronidazole in the treatment of patients with *G. lamblia* in the duodenal contents.

The effectiveness of tinidazole in eradicating *G. lamblia*, the absence of side effects, the low doses required, and administration only twice daily, seems to us to favour tinidazole over metronidazole in treating *G. lamblia* infestations. Further clinical trials with tinidazole and metronidazole may give a definitive answer to the question whether this opinion is well-founded. Finally, it should be mentioned that neither tinidazole nor metronidazole was given to pregnant women.

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Scientific Basis of Clinical Practice

Viral Epidemiology: The Hidden Universality of Infection

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British Medical Journal, 1972, 2, 451-456

A leading investigator of the epidemiology of viral diseases, the late Prof. J. R. Paul of Yale University, used the phrase "the hidden universality of infection" as a succinct description of the concept that clinically apparent infections are far outnumbered by those in which the viral infection produces no sign or symptom of disease. In *A History of Poliomyelitis*¹ he reminds us that in its origins this idea owed nothing to laboratory investigations, but derived from the close clinical and epidemio-

logical observations made by Wickman on the behaviour of the disease in small rural communities during the Swedish epidemic of 1905. Wickman had deduced that the mode of spread of the infection could be explained satisfactorily only if he included as cases of infection not only those suffering from paralytic poliomyelitis but also those with the non-paralytic and minor illnesses, and, by extension, those who remained well but who nevertheless were incriminated on epidemiological grounds.

That a virus so manifestly pathogenic for the central nervous system in reality infected most people without causing them to become ill was a notion over which controversy persisted for a generation until, with the accumulation of evidence from the field and the laboratory, its truth eventually came to be accepted. So intensively have the virology and epidemiology of

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