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Treatment of Giardia lamblia infections in children: randomized open-labeled trial comparing rectal metronidazole with oral tinidazole

1. BACKGROUND

Epidemiology and clinical significance of Giardia lamblia infections

Giardia lamblia (G.lamblia) is a protozoan which infects small intestine of humans and other mammals. Ingestion of food or water contaminated with cysts represents the common route of transmission. The incubation period lasts from 7 to 28 days. In Nordic countries, including Finland, prevalence of giardiasis is 5.81 % in symptomatic population (Hörman, 2004). Infected persons can remain asymptomatic or present with a variety of symptoms, ranging from self-limited acute diarrhea to a chronic disease with abdominal pain, diarrhea, and failure to thrive.

Diagnostic tests

Giardiasis is commonly diagnosed by analyzing fecal samples and detecting G.lamblia cysts on microscopy. However, this method requires repeated stool samples to detect intermittent shedding of G.lamblia, e.g. when assessing the response to treatment. Whereas a single positive stool enzyme immunoassay (EIA) for G.lamblia antigen provides a sensitivity close to 100% and specificity of >90% for diagnosis of giardiasis (Jahan, 2014).

Treatment regimens

Nitroimidazoles (metronidazole, tinidazole and others) represent drugs of choice for giardiasis. Tinidazole given orally at a single dose of 50 mg/kg cures 72-100% of the patients (Escobedo, 2007). Trials examining oral metronidazole implicate different regimens of single and multiple daily doses for 1 to 10 days, resulting in variable cure rates. Metronidazole efficacy improves when prolonged (>1 day) treatment courses are administered, compared to single-dose therapy.
Rectal tinidazole preparation has been used for years in giardiasis treatment in Finland resulting in a satisfactory response rate, until the drug became unavailable. This treatment option has been particularly useful in children unable to tolerate oral tinidazole due to its unpleasant taste.
Rectally administered metronidazole reaches therapeutical concentrations in plasma and has been highly effective in treatmen of e.g. vaginal trichomoniasis (Panja, 1982). Rectal administration of metronidazol results in lower serum concentrations, necessitating higher dosage (Lau, 1992).
Side effects of nitroimidazoles are usually mild and self-limited. They include abdominal pain, nausea, diarrhea, metallic/bitter taste, headache and dizziness.

2. RATIONALE FOR THE PRESENT STUDY

While oral nitroimidazoles are the drugs of choice for lambliosis, the efficacy and safety of rectally delivered preparations remains unknown. Oral administration of nitroimidazoles in children often proves difficult due to the absence of palatable pediatric formulations. Some children refuse to swallow the medicine or vomit it out. Parents often fail to give oral tinidazole at home, which necessitates controlled drug administration in the hospital, and sometimes even nasogastrial tube placement. Thus, a rectally administered drug may represent a solution for the treatment of children who are unable to take oral preparations.

3. AIMS

This study investigates the efficacy and safety of rectally administered metronidazole, as well as the acceptance of this treatment regimen by patients/caregivers. We hypothesize that rectal metronidazole is non-inferior to single-dose of oral tinidazole and will cure at least 72% of patients. We also hypothesize that rectal metronidazole will be tolerated as good as tinidazole. This study will provide significant data on the new option for treatment of giardiasis. The results will be published as a single article in an international journal in the field of pediatrics/parasitology.

4. PATIENTS

We will recruit approximately 180 children (age 6 months to 10 years) whose clinical symptoms could be explained by giardiasis and whose fecal samples will test positive for the presence of G.lamblia in Uusimaa laboratory (HUSLAB). Exclusion criteria will be: 1) age <6 mo or >10 years, 2) weight <9.5 kg, 3) the absence of symptoms, 4) co-infection with another pathogen, which may cause giardiasis-like symptoms.

5. METHODS

1) The Epidemiologic operations unit of the City of Helsinki will issue information about our study to all its health stations. This note will contain information about the possibility to refer a child with diagnosed G.lamblia infection for ambulatory treatment to Children's Hospital, Helsinki University Central Hospital. Researchers will contact the referred patients/caregivers and invite them to participate in the study. If the family refuses the participation, this will not affect the availability and quality of treatment and standard care will be provided to the patient referred.

2) In case the primary diagnosis of G.lamblia infection is done by finding a positive G.lamblia antigen from fecal samples, we will perform additional microscopy examination of stool specimens to exclude other possible parasites/protozoa as a cause of patients symptoms.

3) Clinical data on the patient's symptoms will be collected during interviews at the clinical visits and by phone interviews after treatment. A structured questionnaire will assess clinical treatment response, acceptance and possible side effects.

4) The study will be performed as an open-label trial. We will randomize patients during primary visits alternately into two groups by random allocation to receive either of the two study drugs.

5) Patients from group 1 will be treated with a standard regimen of oral tinidazole (Fasigyn) at a single dose of 50 mg/kg, maximum 2 g/dose. Patients from group 2 will be given rectal metronidazole (Flagyl) 500 mg/dose for children weighing 10–14,9 kg, 1000 mg/dose for those weighing 15–29,9 kg and 1500 mg/dose for those weighing 30–44,9 kg. Suppositories will not be halved. Patients will be given 1 dose/day for 3 days. The first dose of metronidazole will be administered during the primary clinical visit and 2 additional doses will be provided to the parents for home administration.

6) Fecal samples will be collected from the study patients on day 7-10 post-treatment and will be analyzed in HUSLAB for the presence of G.lamblia antigen by EIA. Early collection of samples on day 7-10 will help to avoid the risk of tests being positive due to reinfection.

7) If any of the patients will not clear the infection by day 10, he/she will be invited to a second visit and re-treated. We will re-treat patients from group 1 by rectal metronidazole and patients from group 2 by oral tinidazole, thus performing a cross-over. Follow-up stool samples will be collected.

8) If the patient remains infected after two courses of treatment, mepacrine hydrochloride will be administered according to the clinical routine for imidazole-resistant G.lamblia infections.

9) Criteria for clinical cure will be resolution of symptoms by day 10 and microbiological cure will be defined as negative G.lamblia antigen test from fecal samples collected on day 7-10 post-treatment.

10) Clinical and microbiological data will be coded and analyzed using IBM SPSS Statistics software.

6. ETHICAL ASPECTS

The study will provide valuable information on the treatment of giardiasis. All of the study patients will be given treatment for G.lamblia infection and to those patients who will not respond to the regimen under evaluation a standard course of therapy will be given.
We will apply for the permissions to carry out the study from the Ethic's Board and Finnish Medicines Agency.
Informed consent will be obtained from the patients/caregivers, as well as from children aged ≥7 years.
Clinical and laboratory data will be collected into an electronic database. All the participants will be given codes and personal data will not be recorded. Only researchers listed on page 1 of this protocol will have access to the database.

7. RESEARCHERS

Eeva Salo, MD, PhD, associate professor, is a pediatrician and pediatric infectious disease specialist. She has a staff position at Hospital for Children and Adolescents, Helsinki University Hospital. She will be responsible for planning and organization of the study.

Svetlana Kostjukovits, MD, is a pediatrician and PhD student at the University of Helsinki. She will be responsible for recruiting the patients, carrying out clinical visits and collecting research data.

Tarja Saavalainen-Hakala is a nurse working in the Pediatric Infectious Diseases ambulatory services at the Hospital for Children and Adolescents, Helsinki University Hospital. She will be helping with patients recruitment and their clinical visits.

Susanna Bjorkbacka is a nurse working in the Pediatric Infectious Diseases ambulatory services at the Hospital for Children and Adolescents, Helsinki University Hospital. She will be helping with patients recruitment and their clinical visits together with Tarja Saavalainen-Hakala.

8. FUNDING

The primary diagnostic tests and follow-up fecal samples belong to the established clinical routine and are a part of standard management of patients with giardiasis. Drugs for the study will be covered by the Hospital for Children and Adolescents, Helsinki University Hospital as a part of routine patients care.

9. REFERENCES

Escobedo AA, Cimerman S. Giardiasis: a pharmacotherapy review. Expert Opin Pharmacother. 2007 Aug;8(12):1885-902. Review.

Hörman A, Korpela H, Sutinen J, Wedel H, Hänninen ML. Meta-analysis in assessment of the prevalence and annual incidence of Giardia spp. and Cryptosporidium spp. infections in humans in the Nordic countries. Int J Parasitol. 2004 Nov;34(12):1337-46.

Jahan N, Khatoon R, Ahmad S. A Comparison of Microscopy and Enzyme Linked Immunosorbent Assay for Diagnosis of Giardia lamblia in Human Faecal Specimens. J Clin Diagn Res. 2014 Nov;8(11):DC04-6. Epub 2014 Nov 20.

Lau AH, Lam NP, Piscitelli SC, Wilkes L, Danziger LH. Clinical pharmacokinetics of metronidazole and other nitroimidazole anti-infectives. Clinical Pharmacokinetics 1992;23(5):328-64.

Panja SK. Treatment of trichomoniasis with metronidazole rectal suppositories. Br J Vener Dis. 1982 Aug;58(4):257-8.