Nifuratel-Containing Initial Anti-*Helicobacter pylori* Triple Therapy in Children

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Keywords
amoxicillin, bismuth, children, gastritis, *Helicobacter pylori*, nifuratel.

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Abstract

Background: Proton pump inhibitor-containing triple therapy with amoxicillin and metronidazole is recommended as initial treatment of *Helicobacter pylori* in childhood. However, eradication rate with this "classic" regimen is relatively low in Russia.

Aim: To evaluate empiric nifuratel, amoxicillin, and bismuth triple therapy for *H. pylori* gastritis in childhood.

Materials and Methods: Pediatric outpatients with *H. pylori*-associated chronic gastritis who underwent endoscopy for dyspeptic symptoms received the combination of bismuth subcitrate (8 mg/kg/day, q.d.s.), nifuratel (30 mg/kg/day, q.d.s.), and amoxicillin (50 mg/kg/day, q.d.s.) for 10 days. *H. pylori* status was determined before and after the treatment (in 4–6 weeks) by modified Giemsa staining.

Results: Seventy-three children (48 boys, 25 girls, age range 9–14) were entered. *H. pylori* was eradicated in 63 patients (86%; 95% confidence interval: 76.6–93.2; intention-to-treat and per protocol). There were no serious adverse reactions and were no withdrawals due to any side-effects. All of side-effects were self-limiting (dark stools, urine discoloration, blackening of the tongue, and others).

Conclusions: The combination of nifuratel, bismuth subcitrate, and amoxicillin was an effective and tolerable regimen for *H. pylori* eradication.

Helicobacter pylori infection is the main etiologic factor in chronic gastritis in childhood [1–3]. Eradication of *H. pylori* results in healing of *H. pylori* gastritis [3,4]. Randomized clinical trials have tested proton pump inhibitor (PPI)-containing triple-eradication regimens with two antibiotics and these are the usual treatments of choice for *H. pylori* infection [5,6]. The eradication rates with 7- or 10-day triple therapy in adults have fallen and are now typically 80% or less [7–9]. Primary resistance to metronidazole and clarithromycin is a key factor leading to treatment failure of *H. pylori* [10,11]. In addition, it is common in our area and other Eastern European countries [12,13].

Bismuth-containing triple therapies containing imidazoles, and either clarithromycin or amoxicillin have been reported to have favorable eradication rates (up to 95–100%) in pediatric patients [3,14,15]. Nitrofurans have been used as alternatives for imidazoles/clarithromycin and are now widely used to treat *H. pylori* infection in China, Iran, and South America [10,16–18]. Recent pediatric studies of nifuratel-containing eradication regimens have reported successful eradication rates of 80 and 89% [19,20]. Nifuratel is a furane-derivative agent that exhibits broad-spectrum activity against Gram-positive and Gram-negative bacteria, *Trichomonas*, *Giardia*, *Chlamydia*, and *Candida* spp. [19,21].

The aim of this study was to determine the efficacy of a triple bismuth-containing therapy with nifuratel and amoxicillin for the treatment of *H. pylori* infections in pediatric patients.

Methods

This was an open-label prospective study. During 2 years between January 2002 and December 2003, 90 consecutive pediatric outpatients with upper abdominal complaints, undergoing endoscopy in the Outpatient Department of the Children's Republican Hospital (Ufa, Russia), were investigated for *H. pylori* infection. Upper gastrointestinal endoscopy was carried out using an Olympus GIF XP 20 fiber-optic gastroscope (Olympus

optical Co. Ltd, Tokyo, Japan) after an overnight fast without any prior medication. During endoscopy, four biopsy specimens of gastric mucosa (antrum and body) were taken for histology. The gastroscope and biopsy forceps were disinfected in 2% glutaraldehyde after each use.

Biopsy samples were fixed in 10% buffered formalin, processed, embedded in paraffin, and cut into 5 μm sections. The slides were stained with standard haematoxylin and eosin (H&E) and modified Giemsa staining to estimate gastric inflammation score and *H. pylori* presence and density [4,19]. The score of gastritis severity and the density of *H. pylori* colonization of gastric mucosa were assessed according to the Mitchell's grading system [22]. The presence of mononuclear cells in the lamina propria (score between 0 and 3) and the presence and density of intraepithelial neutrophils (from 0 to 3) were each assessed separately. The presence and number of *H. pylori* present in mucosa sections were excluded from calculating the gastritis total score. The criteria were slightly modified as follows: the presence and severity of mucus depletion (from 0 to 2) were assessed also, and were included when calculating gastritis total score. Briefly, gastritis was graded from 0 to 8.

All the patients infected with *H. pylori* received the combination of bismuth subcitrate (De-Nol, Yamanouchi Europe b.V., Leiderdorp, the Netherlands; 8 mg/kg/day, q.d.s.), amoxicillin (Hiconcil, KRKA, Slovenia; 50 mg/kg/day, q.d.s.), and nifuratel (Macmiror, Doppel pharmaceutici S.r.l., Piacenza, Italy; 30 mg/kg/day, q.d.s.) for 10 days.

Exclusion criteria were: allergy to one or more above-listed drugs, severe liver and kidney disease, favism and use of tricyclic antidepressants or monoamine oxidase inhibitors, medications containing phenylpropanolamine, ephedrine or phenylephrine, and common colds remedies. Patients who had been treated with some other medications (bismuth salts, H_2-blockers, PPI, antacids, antibiotics, nonsteroidal anti-inflammatory drugs) in the previous month were also excluded.

In 4–6 weeks after the completion of treatment, all *H. pylori*-positive patients were invited to undergo a follow-up upper gastrointestinal endoscopy with biopsies. The criterion of eradication of *H. pylori* was the absence of bacterial bodies in follow-up biopsy specimens by histologic examination. Eradication results were reported as intention-to-treat (ITT) analysis and per-protocol (PP) analysis with 95% confidence intervals (CI). Eradication failure was defined as positive histology 4–6 weeks after the completion of management. Side-effects were graded as: mild, self-limiting despite continuation of all drugs; moderate, some loss of capacity for daily activities despite continuation of all drugs; and severe, interruption or discontinuation of some or all of the prescribed drugs.

Those patients, who were *H. pylori*-negative at the entrance to the study, were treated with PPI/H_2-blockers and/or prokinetic agents during 1–2 months.

Fully written informed consent of all the patients (or their parents) was obtained for every procedure that was performed. Verbal and printed instructions were given to the patients and their parents. For ethical reasons, no placebo group was included. The study protocol was reviewed and approved by the Ethical Committee of the Hospital. The choice of treatment regimen was justified in the light of general recommendations of Medical Statement of Russian *Helicobacter pylori* Study Group, 2001.

Results are reported as mean ± SD (standard deviation). In statistical analysis, parametric Student's *t*-test was used. Statistical significance was taken at $p < .05$.

Results

The study group (90 patients) consisted of 56 female (62.2%) and 34 male (37.7%) subjects, age range 9–15 years (mean age was 12.7 years). Seventy-three children (81%) were *H. pylori* positive. Endoscopic finding included 27 with nodular antritis, 14 with gastric incomplete erosions, and 32 with erythema of gastric and/or duodenal mucosa. No patients had peptic ulcer disease.

H. pylori was cured in 63 patients of 73 infected patients. Thus, by ITT analysis the eradication rate was 86.3% (86%; 95% CI: 76.6–93.2; intention-to-treat and per-protocol). All 73 *H. pylori*-positive patients completed the course of therapy. Compliance was excellent in all the patients (patients used > 90% of their medications). Ten children (13.7%), who failed *H. pylori* therapy had persisting antral erythema and/or nodular hyperplasia, although in 8 (80%) gastric histology was improved.

Side-effects were mild and well tolerated. There was no hospitalization related to the treatment regimen. The most common adverse symptoms were trivial (dark stools, urine discoloration in 72 patients, and blackening of tongue in 37 children). Other side-effects occurred in five children (nausea in four, skin rash in two patients, anorexia and fatigue were associated with vomiting and reported by one patient).

The mean gastritis score after treatment in the 63 patients, who were clear of *H. pylori*, was significantly lower compared to their mean score before treatment (3.9 ± 1 versus 1.4 ± 0.6, $p < .001$). Comparison of the mean gastritis score before and after treatment of persistently *H. pylori*-positive children showed persistence of gastric inflammation (3.8 ± 1 versus 3 ± 0.7, respectively, $p > .05$). The mean gastritis score for antibacterial treatment responders was significantly lower than that for the nonresponders (1.4 ± 0.6 versus 3.0 ± 0.7, $p < .001$).

Discussion

This study confirms that therapy with bismuth subcitrate, amoxicillin, and nifuratel is an effective regimen for the eradication of *H. pylori* in children with *H. pylori* infections. In Western countries, eradication of *H. pylori* treatment in pediatrics is often a PPI combination with amoxicillin and nitroimidazole or clarithromycin [5,6,23]. The 1-week combination of omeprazole, tinidazole, and amoxicillin in 17 children in our population yielded an eradication rate of 71% [24]. Similar less than optimal results have been reported from Western countries [25,26]. Primary resistance of *H. pylori* against metronidazole occurs frequently in East European countries (e.g., approximately 60% in the Russian Federation) [12,13]. Clarithromycin resistance is common in Western children [27,28]. However, satisfactory eradication rates have been reported in clinical practice with nitrofurans [7,10,16–18].

The combination of bismuth subcitrate, amoxicillin with a nitrofuran, furazolidone, achieved a satisfactory eradication rate in adult patients (86%) [16]. Earlier, we [29] achieved an *H. pylori* eradication rate of 81.5% in 27 children treated with a 1-week combination of bismuth, amoxicillin, and furazolidone. In a recent study [30] from China, in which a PPI was used with furazolidone and amoxicillin in a 1-week regimen, the ITT was only 52% (n = 50) with almost identical results when the therapy was extended to 14 days [17]. We found that the therapy consisting of PPI, furazolidone, and amoxicillin had eradication rates that did not exceed 66% [31]. A recent Russian study of nifuratel in triple combination with an H_2-blocker and amoxicillin showed an 80% eradication rate (n = 30), which was significantly better than when metronidazole was used instead of nifuratel (50%) [20]. In the present study, eradication was achieved in 86% of pediatric patients after 10 days of triple therapy consisting of bismuth subcitrate, nifuratel, and amoxicillin.

Nifuratel has good tolerability and has been confirmed as a highly active drug with very safe toxicological profile, which is valuable in the treatment of *H. pylori* infection in childhood [19,20]. In accordance with our preliminary work, the total number of adverse events was high in our current study, but intolerable cases were not found. Undoubtedly, a high rate of compliance was associated with absence of severe side-effects. The side-effects of treatment regimen in our work were self-limited and no patients interrupted therapy. The majority of side-effects was associated with phenomenon of formation of bismuth sulfide in the bowel and was transient in the study series.

We suggest that nifuratel definitely potentiated the action of combination of bismuth subcitrate with amoxicillin. Neither bismuth nor amoxicillin resulted in the selection of resistant strains of *H. pylori* and primary or acquired resistance of *H. pylori* against them has never been reported [11,32,33]. However, dual therapy with bismuth subcitrate and amoxicillin demonstrated low eradication rate in childhood (68–71%) [3,15,23].

In summary, the use of nifuratel in combination with bismuth subcitrate and amoxicillin can be considered an initial therapy for *H. pylori* eradication in childhood.

We are greatly indebted to Professor D. Graham for his expert review, helpful advice and friendly suggestions. We are grateful to Professor Giuseppina Oderda and Professor Peter Shcherbakov who inspired this study. We thank our friend Emil Mingazhev for technical assistance and his proficiency in English.

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