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Furazolidone, tetracycline and omeprazole: a low-cost alternative for *Helicobacter pylori* eradication in children

Rodrigo Strehl Machado,[1] Marcello Ruiz da Silva,[2] Aírton Viriato[3]

Abstract

Objectives: To evaluate furazolidone, tetracycline and omeprazole as first line therapy for *Helicobacter pylori* in children with digestive symptoms.

Methods: Prospective and consecutive open trial. The study included patients older than 8 years old with functional dyspepsia, functional abdominal pain, severe histological abnormalities (intestinal metaplasia, gastric atrophy or mucosa-associated lymphoid tissue lymphoma) or peptic ulcer. *H. pylori* status was defined based both upon histology and rapid urease test. Drug regimen was a 7-day course of omeprazol, tetracycline (or doxycycline) and furazolidone twice daily. Eradication was assessed by upper endoscopy 2 months after treatment (histology and rapid urease test). Further clinical evaluation was done 7 days and 2 months after treatment.

Results: Thirty-six patients (21 female/15 male) were included. Age ranged from 8 to 19 years (mean 12.94±2.89 years). On intention-to-treat analysis (n = 36), eradication rate was 83.3% (95%CI 77.1-89.5) whereas in per-protocol analysis (n = 29), it was 89.7% (95%CI 84.6-94.7). Compliance was better when doxycycline was used, but the success rates were similar for the two tetracyclines. There was no variable associated with treatment failure. Side effects were reported in 17 patients (47.2%), mainly abdominal pain (11/30.5%), nausea (seven/19.4%) and vomiting (five/13.9%).

Conclusion: Triple therapy with furazolidone and tetracycline is a low-cost alternative regimen to treat *H. pylori* infection.

J Pediatr (Rio J). 2008;84(2):160-165: Furazolidone, tetracycline, *Helicobacter pylori* treatment, child, clinical trial.

Introduction

Helicobacter pylori infection has been associated with gastric cancer, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and peptic ulcer disease, and its eradication may cure gastric MALT lymphoma and prevent peptic ulcer recurrence.[1,2] The infection is highly prevalent worldwide, mainly in developing countries. *H. pylori* related disease is rare in children, but most of infected patients acquire the infection at this age. Despite the fact that "test and treat" strategy is not recommended in children with abdominal pain or functional dyspepsia, if symptoms are recurrent or severe, upper gastrointestinal endoscopy with biopsies is warranted. It is controversial whether *H. pylori* treatment is helpful in children with functional gastrointestinal disorders,[3] but the treatment is generally indicated if the infection was diagnosed, mainly due to long-term morbidity.

Nevertheless, the best regimen for eradication therapy is an open question in children. The most used drug regimen is the Maastricht triple therapy, with clarithromycin, amoxicillin and a proton pump inhibitor, but there is an increasing prevalence of clarithromycin-resistant strains and this has produced suboptimal cure rates in children.[4,5] Additionally, the

1. Doutor. Serviço de Apoio Diagnóstico e Terapêutico, Hospital Infantil Cândido Fontoura, São Paulo, SP, Brazil.
2. Mestre. Departamento de Pediatria, Hospital Guilherme Álvaro, Santos, SP, Brazil.
3. Mestre. Serviço de Apoio Diagnóstico e Terapêutico, Hospital Infantil Cândido Fontoura, São Paulo, SP, Brazil.

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high cost of clarithromycin impairs its generalized use in developing countries. Amoxicillin resistance is considered rare in most countries, but it is the most prescribed antibiotic for children in Brazil and up to 38% *H. pylori* strains have been reported to be resistant to this antibiotic in our country.[6] Metronidazole is a suitable alternative in countries with less than 40% of resistance to the drug, but in Brazil resistance to metronidazole is reported in 55% of the strains.[1,6] Tetracyclines and furazolidone are old antimicrobial drugs, and nowadays they are not frequently prescribed in children. They are cheaper than traditional *H. pylori* treatment drugs, and the resistance rate of *H. pylori* to these drugs is lower than that reported to clarithromycin and metronidazole.[5] Tetracycline-based therapy against *H. pylori* has not been evaluated in children to date.

Recently, a 7-day furazolidone-based therapy against *H. pylori* was demonstrated to be effective in children in Brazil, with 84.8% per protocol, but with a 73.7% intention to treat eradication rate.[7] This study aims to evaluate furazolidone, a tetracycline and omeprazole treatment, in children older than 8 years old with *H. pylori* infection.

Methods

Patients

This is an open, not controlled, prospective and consecutive clinical trial. Patients older than 8 years old with *H. pylori* infection were consecutively recruited in two outpatient facilities of pediatric gastroenterology (Hospital Infantil Cândido Fontoura, São Paulo, and Hospital Guilherme Álvaro, in Santos) with the following criteria: severe histological abnormalities (intestinal metaplasia, gastric atrophy or MALT lymphoma), functional abdominal pain, functional dyspepsia or peptic ulcer. Functional dyspepsia and functional abdominal pain were defined according to Rome II criteria.[8] The study period was 16 months (April 1, 2005 to July 31, 2006). These patients had been evaluated by upper gastrointestinal endoscopy performed at discretion of the assistant doctor, to investigate either persistent or recurrent symptoms. Exclusion criteria were previous eradication therapy for *H. pylori* infection, inability to ingest pills and refusal to participate.

During this period, 441 patients underwent upper endoscopy, 80 of them with a positive rapid urease test, and 59 older than 8 years old. Clinical inclusion criteria were filled out by 39 children, but three refused to participate in the trial. Thirty-six patients participated in the study, with ages ranging from 8 to 19 years old.

The study was conducted according to Good Clinical Practice and the Declaration of Helsinki, and was approved by the local ethics committees. Patients and parents were invited to participate voluntarily in the study. Parents were given a written consent form to sign, and patients were asked to verbally consent to the study protocol.

Endoscopy

The exam was performed by the authors (MRS or RSM). Esophagus, stomach, and proximal duodenum mucosa were examined under deep sedation or general anesthesia, supervised by an anesthesiologist. Two biopsy fragments were collected from the gastric antrum at approximately 2 cm from the pylorus, one for a rapid urease test and one for histological analysis. The latter was fixed in 100 mL/L formaldehyde, placed on filter paper and stained with hematoxylin-eosin and modified Giemsa. Histological diagnosis of the infection was established by the typical appearance of the bacterium along the mucus layer covering the gastric mucous membrane. Histological evaluation was performed according to the modified Sydney system.[9] The rapid urease test was performed with a non-commercial solution (100 mg/mL aqueous urea solution with 10 mg/mL phenol red).[10] The patient was considered infected when both tests were positive and noninfected when both were negative.

H. pylori *treatment*

The regimen was administered for 10 days with omeprazole 20 mg once a day (40 mg if > 30 kg), furazolidone 100 mg twice a day (200 mg if > 30 kg) and a tetracycline. Most patients were provided tetracycline 50 mg/kg/day four times a day, but this drug was replaced during the study period with doxycycline 50 mg twice a day (100 mg if > 30 kg) due to commercial availability. The drugs used were generic and the total cost of this regimen was R$ 20.06 per patient (US$ 11.14, maximum dose). The antibiotic drugs were ingested after meals, and the omeprazole was ingested 30 min before the first meal. On the last day of the treatment, patients were clinically evaluated with a complete physical examination. All medicines were given to the patients, and during this examination, the patients were asked about side effects, compliance was controlled by return of empty medication blisters. Compliance with treatment was defined as over 90% intake of the prescribed doses.

Eradication control

A second endoscopic evaluation was scheduled at least 8 weeks after the end of the treatment. During this evaluation, two biopsy fragments were collected from the gastric antrum and gastric body, one for rapid urease test and one for histological analysis. Successful treatment was defined by both rapid urease test and negative histology (gastric body and gastric antrum).

Statistical analysis

The main outcome measure was the eradication rate of the infection in intention-to-treat analysis. Sample size was estimated to be 34. The hypothesis was that the regimen would reach 90% (95%CI 80-100) success in intention-to-treat analysis. Continuous variables were expressed by calculation of mean and standard deviation.

Table 1 - *Helicobacter pylori* eradication rate estimated according to intention-to-treat and per-protocol analysis in 36 children treated with tetracycline (or doxycycline), furazolidone and omeprazol

Drug	n	Dropouts n (%)	ITT analysis % (95%CI)	PP analysis % (95%CI)
Tetracycline	21	6 (28.6)	85.7 (78.1-93.3)	93.3 (86.9-99.8)
Doxycycline	15	1 (6.7)	80.0 (69.7-90.3)	85.7 (76.3-95.1)
Total	36	7 (19.4)	83.3 (77.1-89.5)	89.7 (84.6-94.7)

95%CI = 95% confidence interval; ITT = intention to treat; PP = per protocol.

Eradication rates were expressed by calculation of proportion and a 95%CI. Qualitative outcomes were tested in contingency tables using Pearson's chi square test or Fisher's exact test when necessary. $P < 0.05$ was considered significant, while p values ≥ 0.05 and < 0.1 were considered marginally significant.

Results

The study included 36 patients (15 males/21 females), with ages ranging from 8 to 19 years (mean 12.94±2.89 years). Most patients had functional dyspepsia (28, 77.8%), and other indications to treat the infection were duodenal ulcer (four, 11.1%), functional abdominal pain (three, 8.3%) and severe histological abnormality (intestinal metaplasia, one patient, 2.8%). Endoscopy found nodular gastritis in 27 patients (75%), duodenal ulcer in three (8.4%), erosive gastritis in three (8.3%), hyperemic gastritis in two (5.6%) and normal mucosa in two (5.6%). One patient with duodenal ulcer also had nodular gastritis, and one patient had had a previous duodenal ulcer with uninvestigated *H. pylori* status, but had only nodular gastritis at the time of inclusion in this study. All patients had active gastritis, which was mild in 11 (30.6%), moderate in 18 (50%) and intense in seven (19.4%) patients. One patient also had intestinal metaplasia in the antrum biopsy.

The tetracycline was tetracycline in 21 (58.3%) and doxycycline in 15 (41.7%). All patients were considered in intention-to-treat analysis, but only 29 were considered in per-protocol analysis. One patient lost follow-up (this patient was compliant but the eradication was not verified) and six patients were not compliant, with one patient taking only 28-50% of the doses of the three medicines, one patient taking only 30% of furazolidone doses and four patients taking 43 to 86% of tetracycline doses. All patients treated with doxycycline were compliant (Fisher's exact test, $p = 0.03$). All poorly compliant patients had functional dyspepsia (Fisher's exact test, $p = 0.30$).

H. pylori eradication rates are displayed in Table 1. Overall, 30/36 (83.3%) patients were successfully treated in an intention-to-treat analysis and 26/29 (89.7%) in per-protocol analysis. There was no difference between success rates between tetracycline and doxycycline. Patients with functional dyspepsia had a similar eradication rate to the entire group (78.6% by intention to treat, 95%CI 70.1-86.3; 85.7% per protocol, 95%CI 78.1-94.7).

Adverse effects were reported by 17 (47.2%) patients. There was a marginal significance of the relationship between adverse effects and treatment failure (five out of six patients with treatment failure reported side effects vs. 12 out of 30 successfully treated, Fisher's exact test, $p = 0.081$). The commonest side effect reported was abdominal pain, by 11 patients (30.5%), which was epigastric in seven patients (19.4%). Other adverse events reported were nausea (seven, 19.4%), vomiting (five, 13.9%), metallic taste (three, 8.3%), fatigue (one, 2.8%) and dizziness (one, 2.8%).

Outcomes

After treatment, 35 patients were examined by upper endoscopy 8 to 26 weeks (mean 10.17±4.91) after treatment, five of them with unsuccessful treatment. Four of these patients remained with nodular gastritis and one evolved from hyperemic gastritis to erosive gastritis. On the other hand, 23 successfully treated patients had a normal endoscopy, five remained with nodular gastritis and two with hyperemic gastritis. There was a remarkable improvement of histological abnormalities, with only six patients with active gastritis, five of them unsuccessfully treated patients, and the remaining with either inactive gastritis (moderate in three, mild in 14) or normal gastric histology (12).

All patients with functional abdominal pain had the *H. pylori* infection eradicated, and 2/3 were asymptomatic after 2 months and 1/3 improved their symptoms. All patients with

duodenal ulcer were successfully treated, 3/4 were asymptomatic and 1/4 were improved 2 months later. Finally, 27/28 patients with functional dyspepsia were evaluated after 2 months, 14 of them were asymptomatic (one remained infected), 11 reported partial relief of their symptoms (two remained infected) and two reported no clinical improvement (treatment failure). These patients were given a second treatment with clarithromycin, amoxicillin and omeprazol, and their *H. pylori* infection was cleared.

Discussion

The study has demonstrated tetracycline is a suitable alternative antibiotic to constitute *H. pylori* eradication regimens. Furazolidone has been demonstrated to be an effective drug in *H. pylori* treatment in Brazil, with eradication rates in adult patients up to 90% by intention to treat.[11] In children, its efficacy is lower, but it is at least similar to that exhibited by the traditional Maastricht regimen.[5,7] Furazolidone has not been tested in conjunction with tetracycline in children, and this is the main contribution of this study. Furthermore, the triple therapy was well tolerated, with mild adverse effects.

This study is not comparative, and this is an important limitation to its generalization. It lacks comparative studies concerning the cost effectiveness of the *H. pylori* treatment because the studies are generally single-treatment trials with a small sample.[12] On the other hand, placebo-controlled trials are not needed to test drug regimens because the spontaneous eradication of the infection is unusual.[13] The present study was not designed as a comparative study because this regimen has never been tested in children, and it should be needed to establish the feasibility of this treatment in children. Finally, the health facilities participating in this study are not tertiary centers, which could lead to better treatment results.

Tetracycline had been the original drug in the present study, but, unfortunately, the protocol changed due to limited commercial availability. Tetracycline and doxycycline have similar costs and adverse effects. Doxycycline is almost completely absorbed, its absorption is less compromised by food and it is more bioavailable than tetracycline. It also has a longer half-life, and it can be used twice a day.[14] In a study comparing arms with tetracycline and doxycycline, both arms had similar eradication rates.[15] The main difference in antimicrobial resistance between the two drugs is that doxycycline can inhibit some tetracycline resistant Gram-positive bacteria.[16] Results suggest similar eradication rates, but there was significantly better compliance with doxycycline. On the other hand, the eradication rates were slightly higher in tetracycline treated patients, but have not reached statistical significance.

A recent guideline from the American College of Gastroenterology has suggested quadruple regimen with bismuth subsalicylate, ranitidine, metronidazole and tetracycline for 10-14 days as a tested first-line regimen for *H. pylori* infection in adults, alternative to the traditional clarithromycin-based regimen.[17] In our country, a recent study evaluated a regimen of lansoprazole, oxytetracycline and furazolidone as first-line therapy in adults and it described a per-protocol eradication rate of 91.8% (95%CI 81.4-99.3) and 88.4% by intention to treat (95%CI 77.5-95.1).[18] Another study evaluated the efficacy of a 7-day regimen with omeprazole, furazolidone and tetracycline in patients with duodenal ulcer and *H. pylori* infection, both naïve and previously treated with other antibiotics, and it reported a 69% eradication rate by intention-to-treat analysis (95%CI 57-80) and 75% per protocol (95%CI 63-86).[19] Similar results have been reported in other countries, with eradication rates ranging from 78.7 to 87.7 by intention-to-treat and from 85.7 to 92.5 per-protocol analysis as first-line therapy,[20,21] and between, respectively, 78-93 and 89-97% as a second-line option.[22,23] However, there is no study evaluating a tetracycline-based anti-*H. pylori* regimen in children. Tetracycline is a suitable low-cost alternative to the traditional Maastricht regimen, mainly because of the low resistance levels reported (less than 5% in adults and children), with the exception of one Chilean study, in which 26.8% of *H. pylori* strains were resistant to tetracyclines.[24,25]

Most regimens tested in children to eradicate *H. pylori* infection have suboptimal efficacy, with eradication rates ranging from 70 to 90%.[12] A recent meta-analysis showed a success rate of 71.7% (95%CI 61.4-83.0) of the Maastricht therapy (clarithromycin, amoxicillin and omeprazole) in children in randomized controlled trials.[12] This regimen was not effective in Brazilian children, with an eradication rate of 73% for a 10-day regimen (95%CI 51-95) and 50% (95%CI 19-81) for a 7-day regimen.[5] Thereafter, better results were reported by the same group with a 7-day therapy with omeprazole, clarithromycin and furazolidone, both by intention to treat (73.7%; 95%CI 65.4-82) and per protocol (84.8%; 95%CI 78.5-91).[7] These studies[5,7] had a similar study design to the present study, but they were conducted in a tertiary health facility. The eradication rate of the tetracycline-based triple therapy was slightly better in the present study, reaching 83.3% by intention-to-treat analysis and 89.7% by per protocol, and it can be attributed to the longer treatment period. Tetracycline-based triple therapy has not yet been tested in children, and the results in this first study suggest it as a promising low-cost alternative, since it costs R$ 20.06 by patient (maximum dose, with doxycycline), against R$ 74.96 (furazolidone, clarithromycin and omeprazole, maximum dose) or R$ 70.9 (amoxicillin, clarithromycin and omeprazol, maximum dose) of the traditional regimens already tested in children in Brazil.[5,7]

Side effects cited herein were mild, but frequent (47.2%). This is not surprising, as most of the patients had functional dyspepsia, and the adverse effect rates to the placebo

reported in this condition reach 37.3% in adults.[26] Side effect rates up to 34% have been reported in eradication therapy in children.[12] Previous studies with tetracycline-based regimens with adults have reported rates ranging from 34 to 59.7%, most of them mild, and the most frequent reported side effects is nausea (up to 34.6%).[18,19,27] It is interesting that the main side effect reported in the present study is abdominal pain, and it is likely that this symptom was related to the clinical condition of the patient rather than to the therapy.

In conclusion, tetracycline-based triple therapy is a low-cost alternative to first-line eradication therapy of the *H. pylori* infection. The regimen with furazolidone, tetracycline and omeprazole is well tolerated, but comparative multicenter trials are needed to establish its role in the *H. pylori* infection management.

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Correspondence:
Rodrigo Strehl Machado
Av. Dr. Altino Arantes, 894/101
CEP 04042-004 - São Paulo, SP - Brazil
Tel.: +55 (11) 3542.2737
E-mail: rodrigo@gastroped.epm.br