

Helicobacter pylori treatment with alternative drugs: good and cheap for developing countries furazolidone-based treatment- omeprazole, furazolidone and tetracycline open-label trial in a developing country: why not?

Abstract

Objective: To analyze eradication rate and evaluate collateral effects of an existing alternative dosage, comprised of Omeprazole, tetracycline and furazolidone for 7 days in patients with gastric and/or duodenal ulcers and first-degree relatives of family members with a diagnosis of gastric cancer with positive study for *Helicobacter pylori* (*H. pylori*) and treatment-naïve.

Design and location: The out patients from the Clinic of the Gastroenterology Department of the ABC Medical School, Santo Andre, SP-Brazil.

Patients and methods: Study including treatment-naïve patients with a duodenal or gastric ulcer or first-degree relatives of family members with a diagnosis of gastric cancer with a positive study for *H. pylori* confirmed by non-invasive: breath test (C 13), or serology (IgG) or invasive: Rapid Urease Test or gastric histology by biopsy obtained of upper gastro duodenal endoscopy (UGE). The medication schedule: Omeprazole 20mg TID (before meals) plus Tetracycline 500mg TID (after meals) and Furazolidone 200mg TID (after meals) for 7 days. Diagnostic tests for eradication rates were performed 90 days after the treatment. Adverse effects were considered as: light, mild or severe, and include: nausea, vomiting, rash, headache.

Results: 85 patients were included in the study of which 55 completed the treatment. 95% of the patients had an adequate adherence to the treatment. 49% of the patients analyzed by protocol had at least one side effect, with the most common being nausea (24%) and there was no statistical difference between the relation of side effects and lapse of treatment for *H. pylori* 5% (3 patients) interrupted the treatment. The eradication rate per protocol (PP) was 96% (95%CI: 84% to 100%) for patients who completed the treatment.

Conclusion: The therapy based on Omeprazole, tetracycline and furazolidone in the dosages proposed represents a good and low-cost alternative to the first-line therapy to eradicate infection by *H. pylori* in treatment-naïve patients in a developing country.

Keywords: *helicobacter pylori*, treatment, eradication, furazolidone, tetracycline, omeprazole

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Abbreviations: MALT, mucosa-associated lymphoma tissue; PPI, proton pump inhibitor; RUT, rapid urease test; UGE, upper gastro duodenal endoscopy; NSAIDs, non-steroid anti-inflammatory drugs; ITT, intention to treat; PP, per protocol; IARC, international agency for research on cancer

Introduction

Helicobacter pylori (*H. pylori*) is the microorganism responsible for the most frequent and persistent infection of the gastrointestinal tract worldwide. The *H. pylori* infection affects almost half of the world's population. In developed countries (except Japan), the prevalence is below 40%, whereas in developing countries the prevalence infection is as high 90%.¹ In Brazil the prevalence of *H. pylori* infection is about 82% and mostly infected younger ages.² The infection by *Helicobacter pylori* is associated to diseases like the duodenal/ gastric ulcer, acute and chronic gastritis, gastric adenocarcinoma, and mucosa-associated

lymphoma (MALT) and possible B-cell gastric lymphoma and the importance of its eradication is well established [3]. According to the consensus of Maastricht III, the eradication of *H. pylori* is strongly recommended in:

- Past or present duodenal and/or gastric ulcer, with or without complications.
- Following resection of gastric cancer.
- Gastric mucosa-associated lymphoma tissue (MALT) lymphoma.
- Atrophic gastritis.
- Functional dyspepsia.
- Patients with first-degree relatives with gastric cancer.
- Patient's wishes.⁴

Maastrich IV consensus suggests that the treatment regimen should be selected according to areas of low or high clarithromycin (Clari) resistance. Low prevalence of clarithromycin is defined if it is below 20% and High prevalence of clarithromycin resistance if it is higher than 20%. The first-line treatment regimen in regions of low clarithromycin resistance is: Proton Pump Inhibitor (PPI)+Clari+ Amoxicillin/Metronidazole or Bismuth Quadruple. In regions with high clarithromycin resistance the first choice is Bismuth Quadruple and if it is not available the sequential or concomitant regimens.⁵

What is the ideal *H. pylori* eradication regimen? First of all, the following factors need to be taken account when choosing a particular treatment approach: they may vary in different continents, countries, and regions:

- a. Prevalence of *H. pylori*.
- b. Prevalence of gastric cancer.
- c. Resistance to antibiotics.
- d. Cost level and available budget.
- e. Availability of bismuth.
- f. Availability of endoscopy, *H. pylori* tests.
- g. Ethnicity.
- h. Drug allergies and tolerance.
- i. Previous treatments outcome.
- j. Effectiveness of local treatment.
- k. Ease of administration.
- l. Adverse effects.
- m. Recommended dosages and treatment duration.²

Although *H. pylori* is susceptible to several antimicrobials, this infection has proven challenging to cure because of increasing prevalence of bacterial strains that are resistant to the most commonly used antimicrobials, particularly to clarithromycin. An effective (i.e.>90%) first-line therapy is mandatory for preventing the development of secondary resistance.⁶

Unfortunately the eradication rates following the standard triple therapy (proton pump inhibitor plus amoxicillin and clarithromycin) for *H. pylori* are declining worldwide. Several first-line strategies have been proposed to increase the eradication rate including extending the treatment duration to 14 days.⁶ The treatment options also suggest the use of a four drug regimen (bismuth-containing quadruple, sequential and concomitant treatments) and the use of novel antibiotics, such as fluoroquinolones. However, the efficacy of these regimens is controversial. A first-line eradication regimen should be based on what works best in a defined geographical area and must take into account the prevalence of antimicrobial resistance in that region.⁶

In an urban area of Brazil a recent study of the *H. pylori* resistance of antibiotics in adults, showed that resistance to metronidazole was 51%, to clarithromycin 8%, to levofloxacin 23% and to bismuth 5%. There was no observed resistance to amoxicillin, tetracycline or Furazolidone.⁷ In 2013 another Brazilian study was done to search for the *H. pylori* antibiotic resistance in children and adolescents. The mean age was 11.1±3.9 years (3-20 years) and included 77 patients. Global rate resistance was 49.3%: 40% of strains were resistant to metronidazole, 19.5% to clarithromycin and 10.4%

to amoxicillin. All of tested *H. pylori* strains were susceptible to furazolidone and tetracycline. They conclude that the high resistance rate to metronidazole and clarithromycin could exclude them to empirical eradication treatment and otherwise there is no resistance to furazolidone and tetracycline, so we need to think about risks and benefits of using these drugs.⁸

Furazolidone, a drug of the Nitrofurans class composed of a furan ring with a group of nitro, has been used in the treatment of *H. pylori* in developing countries. This drug present low bacterial resistance and it is effective against the strains of *H. pylori* and have a reduced cost.^{2,7-9} In 2002, Eisig et al.⁷ proposed a 7-day treatment based on furazolidone and tetracycline combined to a pump inhibitor (Omeprazole) in patients that had been previously treated. Not so good rates of eradication were observed (75% by protocol and 69% with intention-to-treat), with many side effects which impeded the continued use of these medications.¹⁰

In developing countries the furazolidone is available and it is allowed to the current use. The therapeutic scheme of Omeprazole, furazolidone and tetracycline was advantageous, because it did not induce bacterial resistance, had a good adherence due to its easy posology and cost less. Nonetheless, the high rates of side effects in other studies make it necessary to search for a better-tolerated alternative. Is it a good first choice for naïve treated patients? The objective of this study was to evaluate the eradication rate and side effects of a 7-days therapeutic regimen comprising Omeprazole, tetracycline and furazolidone in a dosage alternative to the existing one in treatment-naïve patients with gastric and/or duodenal ulcers or first-degree relatives of family members with a diagnosis of gastric cancer with a positive infection for *H. pylori*.

Patients and methods

This study was done in the out-patients of the clinic of the Gastroenterology Department of the ABC Medical School (Faculdade de Medicina do ABC) between the years 2004-2011. This was an open-label and prospective trial. The study was open to those older than 18 years of age and having a duodenal or gastric ulcer or both and first-degree relatives of family members with a diagnosis of gastric cancer and positive test for *H. pylori* infection (one or two diagnostic methods positive). All patients that met the inclusion criteria and signed the consent agreement terms were included. Patients having less than 18 years, without an ulcer, testing negative for *H. pylori*, having an allergy to one of the medical components being used and those who had previously been treated for *H. pylori* with a different therapeutic scheme were excluded. The study was approved by the Research Ethics Committee of Faculdade de Medicina do ABC under number 027/ 2004 and all the patients must signed terms of consent agreeing to participate in the study.

Infectious diagnosis

The diagnosis for *H. pylori* was realized using non- invasive tests: Urea 13C- breath test or antibodies for *H. pylori* (IgG) or invasive tests: Rapid Urease Test (RUT) or by gastric histology obtained by biopsy using an Upper Gastro duodenal Endoscopy (UGE).

Treatment

The schedule treatment consisted of 20mg Omeprazole 1 pill before each meal (breakfast, lunch and dinner), 500mg tetracycline-1 pill and also 200 mg furazolidone-1 pill of each, after meals (breakfast, lunch and dinner) for 7 days (9 pills/ day). The cost of the entire treatment was approximately USD 16,00 (R\$40,00 reais, Brazilian

money). One week later we checked: the compliance, pills count, and the correct use of medication and the occurrence of side effects. These were evaluated qualitatively as light; mild or severe (need treatment interruption/hospital care). They were: nausea, vomiting, headaches, diarrhea and others.

Treatment evaluation

The infection of *H. pylori* was considered cured if one of the diagnostic tests were negative (the Urea 13C- Breath Test or the Rapid Urease Test or gastric histology). The search was done 90 days after the end of treatment. The statistical determination was done using the SPSS program, software package 10.0 (SPSS Inc. USA).

Results and discussion

The sample consists of 85 patients with *H. pylori* positive in at least one diagnostic test, naive-treatment for *H. pylori*. We search for: age, gender, tobacco users (present or past, any amount of cigarette), alcohol users (present or past: more than 30-40g of alcohol/more than 5 years), Regular users of non-steroid anti-inflammatory drugs (NSAIDs) and tests for *H. pylori*. In all of the patients at least one method of detecting *H. pylori* was realized and 82% (70 patients) had done two. Those that did two tests (91%) received a positive result in both, and in 10% there was a discrepancy between the two (gastric histology was the gold-standard). Smokers (39%) and alcohol users (18%) were a minority, as were chronic users of NSAIDs (26%). The clinical data of the studied population is showed in Table 1.

Table 1 Clinical information of the initial sample

Patients	n=85	
Age (Years)	52.8 (18-84)	
Mean/Interval		
Female	62/85	53%
Male	23/85	47%
Tobacco Users	46/85	39%
Alcohol Users	21/85	18%
NSAIDs Users	30/85	26%
Initial Upper Endoscopy		
Duodenal Ulcer	51/85	60%
Gastric Ulcer	20/85	24%
Duodenal + Gastric Ulcer	8/85	9%
Gastritis/Esoophagitis	6/85	7%

The initial upper endoscopy of the total sample is showed in Table 1: Duodenal Ulcer (DU) in 51/85 (60%), Gastric Ulcer (GU) in 20/85 (24%), DU/GU in 8/85 (9%) and esophagitis /gastritis in 6/85 (7%). Of the 85 patients in the sample, 55 (65%) ended the treatment, took medication and underwent the final diagnostic test to assess *H. pylori* eradication. The dropout rate was 35% (30 patients). Of those that did not complete the treatment, 21 (70%) did not return to consult number 1 (For the orientation on taking the medication) and the remainder (9 patients) received the orientation but got lost in the follow-up. Table 2 indicates the clinical information about the patients with complete treatment and follow-up. The initial group (85 patients) was similar to the final group (55 patients) including age and gender. Analyzing the final group we find 49% of DU, 31% of GU, 13% of both and other alterations (gastritis or esophagitis) 7%. Initial search for *H. pylori* infection was done in at least 1 test. Forty-eight of

the 55 realized 2 tests to verify the *H. pylori* infection. Of these, 88% (42 patients) had a positive result for *H. pylori* in the 2 tests. Users of tobacco, alcohol and NSAIDs continued being the minority (Table 2).

Table 2 Main information of final sample

Patients	n=55	
Age (Years)	53.7 (18-84)	
Mean/Interval		
Female	30/55	55%
Male	25/55	45%
Tobacco Users	18/55	18%
Alcohol Users	8/55	15%
NSAIDs Users	14/55	25%
Initial Upper Endoscopy		
Duodenal Ulcer	27/55	49%
Gastric Ulcer	17/55	31%
Duodenal + Gastric Ulcer	7/55	13%
Gastritis/Esoophagitis	4/55	7%

Adequate adherence to the treatment was realized by 95% of the patients, who claimed they had taken the medication correctly, respecting the hours and doses as oriented. Three patients, 5% (3/55), discontinued the medication or did not conclude the 7 days of treatment. None of them needed medical assistance for the collateral effects. There is no statistical evidence between the patients who took the medication correctly and had side effects and those who did not take the medication correctly and had side effects (P=0.6 in Fisher exact test). Of the final group of 55 patients analyzed, 26 (49%) had at least one side effect, with the most common being nausea which was reported by 13 patients (24%). There was no statistical difference between the side effects and the relapse of treatment for *H. pylori* (p=1.00 in Fisher exact test).

Table 3 shows the distribution according to side effects presented. Other side effects reported included vertigo, sleepiness weakness, fainting, mild cramps, lower abdominal pain, dryness of the mouth, metallic taste in the mouth and itching. Of the three patients that discontinued the medication, one had nausea and vomiting, one had vertigo and one did not have any side effect. After 90 days, we did diagnostic tests to verify eradication rates of the *H. pylori* (Urea 13C-breath test, or Rapid Urease Test or gastric histology). The majority (91%) had the gastric histology obtained by UGE. The eradication rate by Intention to Treat (ITT) was 62% (53/85) (95%CI 0.5 - 0.73).The eradication rate Per Protocol (PP) was 96% (53/55) (95% CI 0.91-1.0). The high drop-out tax explained the high difference between the ITT and PP.

Table 3 Side effects of treatment omeprazole/ furazolidone/ tetracycline

Side Effects	n	%
Headache	5	9
Nausea	13	24
Vomiting	7	13
Diarrhea	1	2
Others	19	35
At least one Side Effect	26	49

Table 4 shows the distribution of patients according to eradication rate. Our results showed a good rate for the eradication *H. pylori*. Besides the collateral effects, the patients could conclude the

treatment and took correctly the medications. Is this schedule a good choice for *H. pylori* eradication? The treatment for infection by *H. pylori* has been difficult to deal because there is a growing resistance to the established antibiotics being used in numerous countries. It is therefore necessary to seek out alternative medication regimes. In the last few years, it has been observed a decrease in the eradication rates in triple therapies. The first-line therapy established world-wide to treat infection by *H. pylori*, comprised of clarithromycin, amoxicillin and metronidazole, and has declined from eradication rates of 90% down to 70-80% success rates. So, new effective therapies are needed.¹¹

Table 4 Patients according to eradication rate

Intention to Treat (ITT)	53/85 (62%)	(95% CI 0.5-0.73)
Per Protocol (PP)	53/ 55 (96%)	(95% CI 0.91-1.0)

Therapy failure mainly depends on both primary bacterial resistance towards antibiotics and patient compliance. In developing countries, there is a high prevalence of primary and secondary resistance to metronidazole and also to levofloxacin is present, and the bismuth compounds are very difficult to achieve. To overcome these limitations, furazolidone-based treatments have been suggested in developing countries by the World Gastroenterology Organization and Latin-America guidelines.^{2,12,13} On the other hand, the low rate of primary *H. pylori* resistance toward furazolidone in developed countries may render appealing the use of this drug also in these geographic areas.^{14,15} Furazolidone is a synthetic nitro furan with a broad spectrum of antimicrobial activities widely used in the treatment of bacterial and protozoal infections in both humans and animals. However, some concerns recently arose in using furazolidone, such as a molecule harboring a potential carcinogenic effect. The use of Furazolidone in *H. pylori* therapies results in lots of controversy in the literature. Zullo et al.¹⁶ argued forward the potential harmful effects of the furazolidone based on studies of the literature.¹⁷⁻²¹

On the other hand Graham et al.¹⁴ questioned the warning about the carcinogenic potential of furazolidone.²² They are cautioned that furazolidone may be a carcinogen. They believed that this warning was not completely accurate citing determinations of The International Agency for Research on Cancer (IARC). It categorizes agents in categories or groups: Group 1: Carcinogenic to humans. Group 2A: Probably carcinogenic to humans (substances for which there is a lesser degree of evidence in humans but sufficient evidence in animal studies, or degrees of evidence considered appropriate to this category, e.g., unequivocal evidence of mutagenicity in mammalian cells), Group 2B: Possibly carcinogenic to humans, (substances for which there is sufficient evidence in animal tests, or degrees of evidence considered appropriate to this category), Group 3: Unclassifiable as to carcinogenicity in humans, Group 4: Probably not carcinogenic to humans. Furazolidone is a category 3 agent. The IARC report states: "Furazolidone has been produced commercially since 1955. It is used in human and veterinary medicine as an antibacterial and antiprotozoal agent. No data were available to assess the teratogenicity or chromosomal effects of this compound in humans. No case report or epidemiological study of the carcinogenicity of furazolidone was available to the Working Group. Evaluation: No evaluation of the carcinogenicity of furazolidone to experimental animals could be made. In the absence of epidemiological data, no evaluation of the carcinogenicity of furazolidone to humans could be made".²³

Furazolidone was last updated in 1998 and group 3 drugs have been typically excluded from more recent complications of carcinogens.

Drugs used in animals can easily enter the human food chain and are thus rigorously controlled. As they note, furazolidone was removed from animal use. Clinical usage of all drugs is dictated by risks and benefits. Clinical usage of most drugs is often short such that the benefits can easily outweigh possible but low risks. They also questioned the situation of the metronidazole, which is listed as a definite carcinogen in animals and as a category agent 2B in human and also the tinidazole: why not be worried about these drugs? Most regimens or "recipes" have never been optimized and furazolidone-containing regimens are no exception.²⁴⁻²⁶ They recommend Furazolidone combination therapy for areas with high rates of resistance and for patients with multiple prior treatment failures.

A few caveats are necessary when using furazolidone. The drug is an monoamine oxidase inhibitor and thus interacts with many other drugs and foods (e.g. we provide patients with an information sheet that cautions against aged cheese, sausage including bologna, salami and pepperoni, lima beans, lentils, snow peas, and soybeans, canned figs and raisins, beer, ale and wines, licorice, soy sauce and any food product that is made with soy sauce, monoamine oxidase inhibitors, phenylpropanolamine, ephedrine, and phenylephrine).²² They conclude that "Furazolidone is an underutilized drug especially useful in areas where resistance is widespread and multiple. To make excellent French bread requires a proven recipe; the ideal use of any anti-*H. pylori* therapy requires an optimized regimen. The lack of specifics by authors of the review limits its applicability for the clinician and their misunderstanding of the data about carcinogenicity unfairly maligns what should otherwise be a useful drug".²²

Recently, Jiang et al. find a novel application to furazolidone: as an anti-leukemic drug in acute myeloid leukemia. In vitro studies demonstrated that furazolidone was shown to inhibit bone marrow transformation mediated by several leukemia fusion proteins and is promising drug in acute myeloid leukemia.²⁷ In Brazil other studies were done with the same antibiotics. Our study presented a side effects rate of 49%, compatible with the scientific literature, which advocates between 34-59.7%.^{9,10} In Silva et al.¹⁰ the rate of reported side effects for the same therapeutic scheme was 34% 10, while in Machado et al.⁹ it was 47.2%.

In spite of the apparently high rates of side effects reported in our study, the majority corresponded to vague complaints, which might not necessarily be related to the treatment for *H. pylori*. The occurrence of side effects, nonetheless, was not the determinant factor for discontinuing the treatment, and able to consider that the proposed therapeutic scheme was well-tolerated.^{9,10} The therapy proposed for this study avoids using clarithromycin, due to high antibiotic resistance and advocates the use of furazolidone, a drug which has proven to be efficient in fighting infection by *H. pylori* in Brazil. The low complexity of the therapeutic scheme favors patients adherence to the treatment and, consequently, success which can be seen in the high eradication rates obtained (96%). Furthermore, this therapeutic scheme had its efficacy proved by two other studies: Silva et al. found an intention-to-treat efficacy of 69% and in Machado et al.⁹ *H. pylori* eradication rates were 83.3% patients in intention-to-treat analysis and 89.7% in per-protocol analysis.^{9,10}

Conclusion

Most of the studies for the eradication of *H. pylori* are, as in the present study, non-comparative tests, of a single treatment and with a low population sample, which limits its generalization. Furazolidone used in patients naive to treatment has the main advantage of not

inducing bacterial resistance, allowing for a gamut of therapeutic options if there is a need to change medication course. For these reasons, the triple medication scheme, proposed in this study, composed of omeprazole, tetracycline and furazolidone should be considered as a viable alternative for the treatment of infection by *H. pylori* in Brazil. In Brazil the furazolidone is still available, with some recommendations in national and international guidelines “the triple therapy composed of IBP, tetracycline and furazolidone as the low-cost alternative triple treatment for Brazil”, we think that this is a good option: cheap, ease and effective, but we must be careful with collateral effects.

Conflicts of Interest

The author declares that there is no conflicts of interest.

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