

## ORIGINAL RESEARCH

A FURAZOLIDONE-BASED QUADRUPLE THERAPY FOR *HELICOBACTER PYLORI* RETREATMENT IN PATIENTS WITH PEPTIC ULCER DISEASE

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Eisig JN, Silva FM, Rodriguez TN, Hashimoto CL, Barbuti RC. A furazolidone-based quadruple therapy for *helicobacter pylori* retreatment, in patients with with peptic ulcer disease. Clinics. 60(6):485-8.

**PURPOSE:** Many of the currently used eradication regimens against *Helicobacter pylori* fail to cure the infection either due to antimicrobial resistance or to poor patient compliance. The infection leads to increased risk of developing potentially severe complications, such as gastric cancer. This study was aimed at assessing the efficacy and safety of a quadruple therapy with furazolidone for *H. pylori* retreatment.

**METHODS:** Patients who had failed one or more eradication regimens against *H. pylori* infection underwent upper gastrointestinal endoscopy. Biopsy specimens were taken from the gastric antrum and corpus for histology and for a urease test and. Patients received omeprazole 20 mg, bismuth citrate 240 mg, tetracycline 500 mg, and furazolidone 200 mg, all twice daily for 7 days. Therapeutic success was evaluated by endoscopy and biopsies 8 weeks after the end of treatment.

**RESULTS:** Sixty two patients were enrolled, and 58 completed the study. Under this protocol, *H. pylori* eradication was achieved in 39/58 patients (67%). Mild adverse events were reported.

**CONCLUSION:** The short quadruple therapy course with furazolidone is well tolerated, inexpensive, and effective in retreatment for *H. pylori* infection. It is a good option for developing countries.

**KEYWORDS:** Peptic ulcer treatment. *Helicobacter pylori* eradication. Resistant *Helicobacter pylori*. Quadruple therapy. Furazolidone.

The importance of *H. pylori* as an etiological factor in gastrointestinal ulcer is well established, and its eradication is the main objective in the treatment of peptic ulcer disease.<sup>1-3</sup>

First-line eradication therapies for *H. pylori* associate a proton-pump inhibitor with 2 types of antibiotics; this results in eradication rates of 80% to 90%. Consequently, 10% to 20% of patients will constitute therapeutic failure,<sup>4,5</sup> the main reasons being low patient compliance with treatment<sup>6</sup> and bacterial resistance to the antimicrobial agents,<sup>7</sup> especially to clarithromycin and metronidazole.<sup>8</sup>

The best retreatment regime has yet to be established. Some international consensus statements recommend the use of a quadruple therapy regime with a proton-pump inhibitor, bismuth subcitrate, metronidazole, and tetracycline

for 1 week, resulting in eradication rates of 57% to 95%, with an average of 77%.<sup>4</sup>

A retreatment option that is more practical in Brazil involves the use of furazolidone. In a country such as ours, which has large populations with low socioeconomic levels and high bacterial resistance to metronidazole,<sup>8</sup> a simple, inexpensive regime that is reasonably well tolerated by patients is one that substitutes metronidazole with furazolidone.

This study aimed at establishing the efficacy and safety of a 7-day therapeutic regimen used in the eradication of *H. pylori* using omeprazole, bismuth subcitrate, tetracycline, and furazolidone in a group of patients with peptic ulcer disease who had been previously treated with other therapeutic regimens without success.

## METHODS

Patients were selected from the Outpatient Gastroenterology Clinic of Hospital das Clinicas, Faculty of Medicine,

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University of São Paulo (HCFMUSP). The study was approved by the institutional Ethics Review Board for clinical research, and all patients signed an informed written consent form. Sixty-two patients with peptic ulcer who had previously been treated unsuccessfully with one or more eradication regimens for *Helicobacter pylori* (Table 1) were included in the study. Bacterial persistence after treatment was confirmed by positivity of the rapid urease test and histological examination through a modified Giemsa staining method. Gastric mucosa samples were obtained from the antrum and corpus through upper digestive endoscopy.

Patients who were younger than 18 years of age were excluded, as were those who presented severe comorbidity, pregnant patients, infants, patients who had previously undergone gastrectomy, patients with a known history of allergy to the therapeutic regime drugs, and patients who had used nonsteroidal antiinflammatory drugs (NSAIDs), antibiotic therapy, or bismuth salts up to 4 weeks before study inclusion.

In an open, cohort study, the patients were invited to use a therapeutic regime for 7 days that consisted of 20 mg omeprazole, 240 mg colloidal bismuth subcitrate, 500 mg tetracycline, and 200 mg furazolidone, taken twice a day. Patients were warned not to ingest alcoholic beverages and to avoid foods related to potential side effects determined for drugs similar to monoamine oxidase inhibitors. They were also encouraged to take the full medication regularly and were informed about the importance of an adequate use of the medication for a successful treatment. No other medication was allowed until the end of the treatment, when patients were evaluated regarding compliance by counting the remaining tablets. Adverse effects were recorded in a questionnaire, and each adverse effect was specifically investigated.

Treatment efficacy was determined by bacterial negativity at the rapid urease test and histological examination of gastric antrum and corpus mucosa samples taken during digestive endoscopy performed 8 weeks after the end of treatment.

### Statistical Analysis

Sample size calculation was determined for a descriptive study of a dichotomous variable, considering the prevalence of peptic ulcer with resistant *Helicobacter pylori* in 2% of the general population and an expected eradication efficacy of 70%. The eradication rates were calculated by intention to treat and per protocol analysis.

All patients enrolled in the study were analyzed as intention to treat (ITT). All the patients enrolled who took more than 80% of the medication and those who returned and agreed to undergo the control endoscopy were considered for the per protocol (PP) analysis. A confidence in-

terval of 95% was calculated for the eradication rate percentiles. The chi-square method with Pearson coefficient was used for the comparison among the variables, eradication rate for previous treatment, gender, and age, with a significance value of  $P < .05$ .

Statistical calculations were performed with the SPSS statistics software, version 10.0 (SPSS Inc., USA).

### RESULTS

Of the 62 patients enrolled in the study, a few had already undergone 3 or more previous treatments (Table 1). There was no predominance regarding gender, and the average and median age of patients was 45 years. The prevalence of duodenal ulcer was high, and the prevalence of smokers was similar to that in the Brazilian population<sup>9</sup> (see Table 2). Four patients were excluded from the analysis by protocol, 2 for failing to undergo the control endoscopy, 1 for taking the medication inadequately, and 1 who interrupted the treatment early due to the presence of adverse effects (nausea and headaches).

The eradication rates were 67% (39/58) for the PP group and 63% (39/62) for the ITT group (Table 3). There was no difference in the eradication rates in relation to the number of previous treatments the patient had undergone (Table 4). Age and gender did not correlate with eradication rates either. Adverse effects were reported by 10% of the patients, and these were usually considered to be slight. Only 1 patient had to withdraw from treatment due to the presence of nausea and headaches.

**Table 1** - Unsuccessful previous treatments

| Therapies | Patients |
|-----------|----------|
| 1         | 37       |
| 2         | 20       |
| 3 or more | 5        |
| Total     | 62       |

**Table 2** - Clinical data

|                  |         |
|------------------|---------|
| Patients         | 62      |
| Age (years) mean | 45      |
| Median           | 45      |
| Interval         | 18 - 74 |
| Women            | 50%     |
| Duodenal ulcer   | 71%     |
| Tobacco users    | 22%     |

**Table 3** - Eradication rates

|                    | %           | 95% Confidence Interval |
|--------------------|-------------|-------------------------|
| Per protocol       | 67% (39/58) | 80% - 55%               |
| Intention to treat | 63% (39/62) | 51% - 75%               |

**Table 4** - Eradication rates and previous treatments

| Treatments | Rates       |
|------------|-------------|
| 1          | 65% (23/58) |
| 2          | 74% (14/58) |
| 3 or more  | 60% (3/5)   |

## DISCUSSION

In recent years, an increase in the number of patients who present therapeutic failure with *H. pylori* eradication regimens has been observed. Antimicrobial resistance has been described as the main reason for this failure. Thus, several alternative therapeutic regimens have been tested with the objective of attaining an effective retreatment of such patients.

In our country, it is costly and unfeasible to verify antimicrobial sensitivity in all patients who need retreatment, even for large centers, and few of them perform the bacterial sensitivity test. Hence, retreatment regimens are not based on the antibiogram of the resistant *Helicobacter*, but rather on the knowledge of the previously used antibiotic therapy.

In this study, many patients were referred from other medical centers and had previously been treated with different drug regimens, with clarithromycin and metronidazole being the most frequently used antibiotics.

It is known that clarithromycin and metronidazole resistance is common in all parts of the world and that it has been increasing.<sup>10-15</sup> In developing countries, where the use of metronidazole is very common in the treatment of parasitic infestations, 40% to 70% of the strains are resistant to this drug.<sup>12,16,17</sup>

Furazolidone is a synthetic nitrofurantoin derivative with bactericidal or bacteriostatic activity when used against

Gram-positive and Gram-negative bacteria, and it is well absorbed in the intestine with no tissue accumulation.<sup>18-20</sup> It has been used in China for more than 20 years in the treatment of peptic ulcer as the single therapeutic agent, with healing rates comparable to those obtained with cimetidine and displaying lower recidivation rates.<sup>21,22</sup> It is currently known that the good results are mostly due to its anti-*H. pylori* activity.<sup>23,24</sup>

Furazolidone-resistant strains<sup>25,26</sup> have not been described to date, which makes its use an alternative in the retreatment of peptic ulcer disease caused by *H. pylori*.

One of the great impediments regarding the use of furazolidone is its association with significant adverse effects, reported mainly in studies carried out in Europe, where it is no longer considered a drug of choice for retreatment regimens.<sup>27,28</sup> Our study, however, produced different results from those found in the literature, since only 1 patient had to interrupt the treatment due to the presence of side effects.

The eradication rates (67% PP and 63% ITT) were a little lower than those reported in other studies based on this therapeutic regimen.<sup>29</sup> It is possible that the use of only 1 g/day of tetracycline and 400 mg/day of furazolidone may explain the results obtained. With the aim of achieving a higher compliance rate by patients with the quadruple therapeutic regime, it was administered for only 7 days, although several consensus statements suggest a 14-day duration.<sup>30,31</sup> It is possible that a more prolonged treatment might result in better eradication rates.

In conclusion, our study showed that the association of furazolidone with a proton-pump inhibitor plus tetracycline and colloidal bismuth subcitrate could be a valuable alternative for patients who need retreatment for *H. pylori* eradication. It is an effective, affordable treatment that allows good compliance and produces low adverse effect rates.

## RESUMO

Eisig JN, Silva FM, Rodriguez TN, Hashimoto CL, Barbuti RC. Esquema quádruplo com furazolidona para retratamento do *Helicobacter Pylori*, em pacientes ulcerosos. Clinics. 60(6):485-8.

**OBJETIVO:** Muitos dos esquemas atualmente usados na erradicação do *Helicobacter pylori* não conseguem curar a infecção, pela resistência bacteriana ou pela baixa adesão do paciente. Esta condição manterá os riscos de desenvolvimento das potenciais complicações graves da infecção. Este estudo procurou determinar a eficácia e segurança de um esquema quádruplo que associou a furazolidona para o retratamento da infecção pelo *H. pylori*.

**MÉTODOS:** Pacientes que não alcançaram erradicação em um ou mais tratamentos foram submetidos à endoscopia digestiva alta e dois fragmentos do antro e do corpo foram retirados para exame histológico e de urease. Receberam então 20mg de omeprazol, 240mg de sub-citrato de bismuto, 500mg de tetraciclina e 200mg de furazolidona duas vezes ao dia por 7 dias. O sucesso terapêutico foi determinado pela negativação de nova biópsia endoscópica, após 8 semanas do tratamento.

**RESULTADOS:** Sessenta e dois pacientes foram incluídos, cinquenta e oito completaram o estudo. Por protocolo, 67% (39/58) dos pacientes conseguiram a erradicação da bactéria. Efeitos adversos leves foram relatados.

**CONCLUSÃO:** O tratamento de curto prazo, em esquema quádruplo com a furazolidona, é bem tolerado, barato e eficaz no re-tratamento do *H. pylori*. Uma boa opção de re-tratamento para países em desenvolvimento.

**PALAVRAS-CHAVE:** Úlcera péptica. Tratamento. *Helicobacter pylori*. Erradicação. *Helicobacter pylori* resistente. Terapia quádrupla. Furazolidona.

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