



RAPID COMMUNICATION

## Quadruple therapy with furazolidone for retreatment in patients with peptic ulcer disease

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**CONCLUSION:** The association of bismuth, furazolidone, amoxicillin and a proton-pump inhibitor is a valuable alternative for patients who failed to respond to other eradication regimens. It is an effective, cheap and safe option for salvage therapy of positive patients.

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**Key words:** Gastric ulcer; Duodenal ulcer; *Helicobacter pylori*; Retreatment; Furazolidone

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### Abstract

**AIM:** To establish the efficacy and safety of a 7-d therapeutic regimen using omeprazole, bismuth subcitrate, furazolidone and amoxicillin in patients with peptic ulcer disease who had been previously treated with other therapeutic regimens without success.

**METHODS:** Open cohort study which included patients with peptic ulcer who had previously been treated unsuccessfully with one or more eradication regimens. The therapeutic regimen consisted of 20 mg omeprazole, 240 mg colloidal bismuth subcitrate, 1000 mg amoxicillin, and 200 mg furazolidone, taken twice a day for 7 d. Patients were considered as eradicated when samples taken from the gastric antrum and corpus 12 wk after the end of treatment were negative for *Helicobacter pylori* (*H. pylori*) (rapid urease test and histology). Safety was determined by the presence of adverse effects.

**RESULTS:** Fifty-one patients were enrolled. The eradication rate was 68.8% (31/45). Adverse effects were reported by 31.4% of the patients, and these were usually considered to be slight or moderate in the majority of the cases. Three patients had to withdraw from the treatment due to the presence of severe adverse effects.

### INTRODUCTION

Since the discovery of the etiological role of *Helicobacter pylori* (*H. pylori*) in peptic ulcer disease<sup>[1]</sup>, its eradication became the main objective of therapy, and several treatment regimens were developed. Currently, triple therapy with omeprazole, amoxicillin, and clarithromycin remains the best therapeutic option<sup>[2]</sup>. Despite its efficacy, 10% to 20% of the patients present with treatment failure, demanding alternative therapeutic regimes with variable success rates<sup>[3,4]</sup>. The reasons for this considerable rate of failure are several, including low patient compliance with treatment<sup>[5]</sup>, and bacterial resistance to antimicrobial agents<sup>[6,7]</sup>. The development of effective salvage treatments is of paramount importance in this situation.

Furazolidone is a synthetic nitrofurantoin derivative with bactericidal or bacteriostatic activity against Gram-positive and Gram-negative bacteria, and it is well absorbed in the intestine with no tissue accumulation<sup>[8]</sup>. It has anti-*H. pylori* activity and resistant strains appear to be rare or non-existent in many areas<sup>[9]</sup>, characteristics

that make it a potential option for retreatment of peptic ulcer disease caused by *H pylori*. One of the main limitations for its widespread use is the relatively high incidence of significant adverse effects, reported mainly in European studies<sup>[10]</sup>. In a country such as Brazil, which has large populations with low socioeconomic levels and a high bacterial resistance to metronidazole<sup>[11]</sup>, furazolidone emerges as an interesting option.

This study aimed to establish the efficacy and safety of a 7-d therapeutic regimen for *H pylori* eradication (omeprazole, bismuth subcitrate, furazolidone, and amoxicillin) in patients with peptic ulcer disease who had been previously treated with other therapeutic regimens without success.

## MATERIALS AND METHODS

The study was performed in accordance with the declaration of Helsinki, and was approved by the institutional Ethics Review Board for clinical research, and all patients signed an informed written consent form.

Sample size calculation was determined for a descriptive study of a dichotomous variable, considering the prevalence of peptic ulcer with resistant *H pylori* in 2% of the general population.

Patients were selected from the Outpatient Gastroenterology Clinic of Hospital das Clínicas, Faculty of Medicine, University of Sao Paulo. Fifty-one patients with peptic ulcer who had previously been treated unsuccessfully with one or more eradication regimens for *H pylori* were included in the study. Bacterial persistence after treatment was confirmed by positive rapid urease test and histological examination through a modified Giemsa staining method. Gastric mucosa samples were obtained from the antrum and corpus during upper digestive endoscopy.

Patients younger than 18 years of age were excluded, as were those who presented with severe comorbidity, pregnant patients, infants, patients who had previously undergone gastrectomy, patients with a known history of allergy to the therapeutic regimen drugs, and patients who had used non-steroidal anti-inflammatory drugs, antibiotic therapy, or bismuth salts up to 4 wk before study inclusion.

In an open, cohort study, the patients were invited to use a therapeutic regimen for 7 d that consisted of 20 mg omeprazole, 240 mg colloidal bismuth subcitrate, 1000 mg amoxicillin, and 200 mg furazolidone, taken twice a day. Patients were advised not to ingest alcoholic beverages and to avoid foods related to potential side effects determined for drugs similar to monoamine oxidase (MAO) inhibitors. They were also encouraged to take the full medication regularly and were informed about the importance of adequate use of the medication for 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

Table 1 Clinical data

Clinical data	n
Patients	51
Age (yr)	
Mean	49
Median	48
Interval	23-77
Women	32
Duodenal ulcers	39
Gastric ulcers	7
Duodenal and gastric ulcers	5
Tobacco users	16

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 12 wk after the end of treatment.

A confidence interval of 95% was calculated for the eradication rate percentiles. The  $\chi^2$  method with Pearson coefficient was used for the comparison among the variables, eradication rate for previous treatment, gender, and age, with significance value of  $P < 0.05$ . Statistical analysis was performed with the statistics software, version 10.0 (SPSS Inc., USA).

## RESULTS

Among the 51 patients enrolled in the study, there was no predominance regarding gender, and the median age was 48 years. Duodenal ulcer was most commonly observed (Table 1). Five (10%) patients had already undergone three or more previous treatments (32 and 14 had undergone one and two, respectively). Six patients were excluded from the analysis, three for not undergoing follow-up evaluation, and three for early interruption of the treatment due to adverse effects.

The eradication rate was 68.8% (31/45). Eradication rates were similar regardless of the number of previous treatments (one treatment: 21/32, 65.6%; two treatments: 8/14, 57.1%; three or more treatments: 2/5, 40%). Age and gender did not correlate with eradication rates ( $P > 0.05$ ). Adverse effects were reported by 31.4% of the patients, most of which were considered to be slight or moderate. Three patients had to withdraw from the treatment due to the severe adverse effects (one with nausea, one with diarrhea, and one with dizziness).

## DISCUSSION

*H pylori* infection is highly prevalent in Brazil. Among blood donors without gastrointestinal complaints, positive serology for *H pylori* is found in 68%<sup>[12]</sup>. In a country with more than 200 million inhabitants, we may estimate that 140 millions individuals are currently infected. If we consider a 10% incidence of peptic ulcer disease or gastric cancer, we will find 14 million people in whom eradication of *H pylori* is mandatory. Despite the good eradication rates achieved with the combination

of omeprazole, amoxicillin, and clarithromycin, 10% to 15% of the patients present with treatment failure<sup>[2]</sup>. In face of this reality, it is interesting to pursue the development of alternative therapeutic regimens with satisfactory eradication rates, low incidence of adverse effects, and low cost.

The efficacy of different regimens varies according to patient compliance and bacterial resistance to the antibiotics<sup>[13]</sup>. Clarithromycin, quinolones and metronidazole should not be used more than once, due to *H pylori* intrinsic or induced resistance<sup>[14,15]</sup>. For patients with primary treatment failure it would be ideal to test the *H pylori* antimicrobial sensitivity, but the high cost and the lack of laboratories capable of adequately performing sensitivity tests limit this strategy. Retreatment must be based on knowledge of the antimicrobial agents previously used.

In our country, *H pylori* strains show an intrinsic resistance to metronidazole that reaches 50%, which decreases the efficacy of schemes containing this drug or other nitroimidazoles<sup>[16-19]</sup>. Furazolidone is widely available in public health care facilities in Brazil. Despite that no decrease in susceptibility has been observed<sup>[20]</sup>, and bacterial resistance appears to be rare or non-existent in many areas<sup>[18,21,22]</sup>, even among metronidazole-resistant isolates<sup>[23]</sup>. The main concern regarding its use is the adverse effects observed, especially among individuals who do not adhere to the dietary restrictions recommended, since this drug belongs to the group of the MAO inhibitors. Asian and European studies have reported a relatively high incidence of adverse effects (31.4%-35%)<sup>[10,24,25]</sup>. Conversely, two South American<sup>[26,27]</sup> studies have shown fewer undesirable symptoms when compared to the previously mentioned studies. In the present study, despite a comparable incidence of adverse effects during treatment, only three patients had severe symptoms demanding treatment discontinuation. Lower doses of furazolidone could decrease the incidence of undesirable symptoms, but this strategy can also lead to a lower eradication rate<sup>[22,28,29]</sup>.

The prevalence of smokers was similar to that in the Brazilian population and no significant differences in the results were observed when analyzing the number of previous treatments, gender and age. Even though compliance was good, and the length of treatment was short, this regimen ought to be considered only as an alternative for patients with previous treatment failures. Extending the antibiotic course to 10 d or 14 d could improve eradication rates, despite a greater likelihood of adverse effects<sup>[30,31]</sup>.

Furazolidone appears to be an excellent choice for combination therapy for *H pylori* infection, especially as a substitute for metronidazole in quadruple therapy regimens in areas with high prevalence of metronidazole-resistant strains<sup>[32]</sup>. In our study, the eradication rate was 68.8%, which was superior to that previously reported<sup>[33,34]</sup>, and, considering the efficacy, safety and potential cost-effectiveness, it seems reasonable to introduce furazolidone-based regimens following the failure of initial eradication attempts<sup>[32]</sup>. The differences

regarding the safety profile between South American and American and European studies may be attributed to the limited clinical experience with this drug in the former regions, where it is unavailable and expensive<sup>[33]</sup>.

In conclusion, our study shows that the association of bismuth, furazolidone, amoxicillin and a proton-pump inhibitor is a valuable alternative for patients who failed to respond to an initial therapeutic regime in a country with high prevalence of *H pylori* metronidazole-resistant strains. This scheme is an effective, cheap and safe option for salvage therapy of *H pylori* positive patients.

## COMMENTS

### Background

Since the discovery of the etiological role of *Helicobacter pylori* (*H pylori*) in peptic ulcer disease, its eradication became essential to allow for adequate healing and prevention of recurrence. It is well established that triple therapy with omeprazole, amoxicillin and clarithromycin is the first-line treatment, but it fails in 10% to 20% of the patients, demanding alternative therapeutic regimens.

### Research frontiers

Furazolidone has anti-*H pylori* activity, low incidence of resistance, is cheap, and is widely available. Despite these characteristics, not many studies have been performed to evaluate its efficacy for retreatment.

### Innovations and breakthroughs

This study provides further evidence of the efficacy and tolerability of a short-term furazolidone-based quadruple regimen in South America.

### Applications

Furazolidone-based regimens may be an interesting option for retreatment due to their low cost and low resistance rate, especially in developing countries such as Brazil, where metronidazole-resistant strains are common.

### Peer review

Quadruple therapy with the medicine used in this study is not a new regimen. It has been used widely in China with good results. Unfortunately, it is not popularly used outside China. The present study was a small series with not very satisfactory results (efficacy rate 68.8%). However, I think it is still worthwhile to be published in our journal, at least indicating that the regime was also used in a South American country with some success.

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