

Efficacy of levofloxacin, amoxicillin and a proton pump inhibitor in the eradication of *Helicobacter pylori* in Brazilian patients with peptic ulcers

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OBJECTIVES: The eradication of *Helicobacter* (*H.*) *pylori* allows peptic ulcers in patients infected with the bacteria to be cured. Treatment with the classic triple regimen (proton pump inhibitor, amoxicillin and clarithromycin) has shown decreased efficacy due to increased bacterial resistance to clarithromycin. In our country, the eradication rate by intention to treat with this regimen is 83%. In Brazil, a commercially available regimen for bacterial eradication that uses levofloxacin and amoxicillin with lansoprazole is available; however, its efficacy is not known. Considering that such a treatment may be an alternative to the classic regimen, we aimed to verify its efficacy in *H. pylori* eradication.

METHODS: Patients with peptic ulcer disease infected with *H. pylori* who had not received prior treatment were treated with the following regimen: 30 mg lansoprazole bid, 1,000 mg amoxicillin bid and 500 mg levofloxacin, once a day for 7 days.

RESULTS: A total of 66 patients were evaluated. The patients' mean age was 52 years, and women comprised 55% of the sample. Duodenal ulcers were present in 50% of cases, and gastric ulcers were present in 30%. The eradication rate was 74% per protocol and 73% by intention to treat. Adverse effects were reported by 49 patients (74%) and were mild to moderate, with a prevalence of diarrhea complaints.

CONCLUSIONS: Triple therapy comprising lansoprazole, amoxicillin and levofloxacin for 7 days for the eradication of *H. pylori* in Brazilian peptic ulcer patients showed a lower efficacy than that of the classic triple regimen.

KEYWORDS: Peptic ulcer therapy; *Helicobacter pylori* drug effects; levofloxacin; amoxicillin therapeutic use and adverse effects.

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INTRODUCTION

Curing peptic ulcers in patients infected with *Helicobacter* (*H.*) *pylori* can be achieved by eradicating the bacteria (1). This task is made easier using a triple regimen that includes an antisecretory agent, which is most often a proton-pump inhibitor (PPI), with two antibiotics (2). For years, the most commonly used triple regimen has been called the "classic" regimen, which is the combination of a PPI, amoxicillin and clarithromycin administered for 7 to 14 days (3).

In Brazil, the classic regimen has been used as the first-choice therapy for approximately 10 years (4–6), preferably with a treatment duration of 7 days provided as commercially available blister packs containing the daily treatment of 4 capsules in the morning and 4 capsules in the evening (1 PPI capsule, 2 capsules of amoxicillin and 1 capsule of clarithromycin). This regimen is inexpensive, has few adverse effects and has a per-protocol efficacy >85% (7–10). Treatment or retreatment regimens that replace clarithromycin with nitroimidazole compounds are questionable, as evidence in our country has shown a low eradication efficacy as a consequence of the high prevalence of resistant bacteria (11–13). For the retreatment of *H. pylori* infection when the classic regimen fails, we have proposed regimens including PPIs and furazolidone, tetracycline or levofloxacin, which have shown good eradication rates in our country (14,15).

Overall, a worldwide increase in *H. pylori* resistance to clarithromycin has been observed, causing a decrease in the

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efficacy of the classic regimen (16,17). In Brazil, this decrease has not occurred homogeneously due to the size of the country and the major health and socioeconomic differences between regions. In our service, probably due to low clarithromycin use in the treatment of other infections, the classic regimen still shows a high eradication rate and low primary resistance to clarithromycin (10,11).

A commercially available regimen that includes lansoprazole with amoxicillin and levofloxacin (18) with a 10-day treatment duration was recently launched in the market as a retreatment option when the classic regimen fails, but this regimen has not been tested in Brazil as either a retreatment or a first treatment. In the literature, this regimen has shown good efficacy as both a first-choice treatment (19,20) and a retreatment (21,22).

The objective of the present study was to assess the eradication efficacy of treatment with 30 mg lansoprazole bid, 1000 mg amoxicillin bid and 500 mg levofloxacin once a day administered for 7 days in peptic ulcer patients infected with *H. pylori*.

■ MATERIALS AND METHODS

Study population

Considering that the eradication efficacy expected for this regimen is 85%, a sample approximately 70 patients was proposed for the study to obtain a confidence level of 95% and an error of 20%. All of the patients were recruited from the outpatient clinic of the Division of Gastroenterology and Clinical Hepatology, Hospital das Clínicas, Universidade de São Paulo after being evaluated and agreeing to sign the free and informed consent form approved by the hospital Research Ethics Committee.

Inclusion criteria were as follows: being older than 14 and younger than 85 years; being capable of understanding the study objectives; having a peptic ulcer and being infected with *H. pylori*.

Exclusion criteria were as follows: having undergone previous eradication treatment for the bacteria; having previously used quinolone compounds; having a complicated ulcer; having undergone upper digestive tract surgery; being pregnant or lactating; having symptomatic intestinal or biliary diseases; having decompensated diseases, including endocrine, respiratory, cardiac, and renal disease, among others; continuously using anti-inflammatory drugs, even at low doses; and having Los Angeles grade C or D esophagitis.

Study design

Because this study used an uncontrolled trial design, it was not registered on international clinical trial sites.

After the initial visit, eligible patients underwent a 30-day "wash-out" period after the use of PPIs or H₂ blockers was suspended; the patients were switched to antacids or prokinetic drugs. After this period, the patients underwent a videoendoscopy, during which gastric mucosa samples were obtained to diagnose *H. pylori* infection by histopathological analysis and rapid urease testing. Patients with positive results for both tests were considered infected.

On a second visit, after the inclusion and exclusion criteria were assessed, the patients received the medications and were properly advised regarding drug use, care and treatment adherence. On a third visit, held one week later, the patients were reassessed, the remaining pills were counted, and adverse treatment effects were assessed. The

patients were also advised to avoid using other acid suppressants, especially PPIs, as well as anti-inflammatory drugs or other medications harmful to the digestive mucosa until cured or controlled.

Twelve weeks after completing the antibiotic therapy, patients underwent a C-13-labeled urea breath test, according to a previously described technique (23). Patients with negative test results then underwent endoscopy. Cases were considered treatment failures if the breath test results were positive, and such patients were referred for retreatment with another eradication regimen. In cases for which there was disagreement between the breath test assessment and histological analysis control or rapid urease test results, the patient underwent a new respiratory test after four weeks. If the test was positive, it was considered a treatment failure; and if negative, the patient was considered to be cured.

The presence of *H. pylori* in the initial and control histological examination was evaluated by two pathologists experienced in ulcer disease using hematoxylin-eosin (HE) and Giemsa stains.

Treatment

Patients were treated with a commercial product, which is sold in blister packs for daily use, containing a 30 mg capsule of lansoprazole, one 500 mg capsule of levofloxacin and two 500 mg capsules of amoxicillin for use in the morning, and one 30 mg capsule of lansoprazole and two 500 mg capsules of amoxicillin for use at night. Enough medicine was supplied for a seven-day treatment period.

Adverse effects assessment

Patient-reported adverse events were recorded and classified as mild when they did not hinder the patient's daily activities, moderate when they hindered the patient's daily activities but did not require the discontinuation of medication, and severe when they hindered the patient's daily activities and required treatment or the discontinuation of medications.

Statistical analysis

Data were analyzed using the SPSS v.10 statistical program, and the frequencies of categorical and continuous variables were determined; the 95% confidence interval (CI) was also calculated for the eradication rate.

Ethics

The study was approved by the Ethics Committee for Analysis of Research Projects – CAPPesq – of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. All patients were informed about the purpose of the study and its methodology and agreed to sign the free and informed consent form.

■ RESULTS

Seventy-one patients were invited to participate in the study, but five were excluded: two because they had no evidence of ulcer in the upper digestive endoscopy examination in the inclusion period and three because the *H. pylori* detection tests were negative. Therefore, a total of 66 patients were available for analysis, of which one did not return for the control examinations.

The mean age of the patients was 52 years; there was a predominance of women in the sample, and duodenal ulcers



Table 1 - Patient data.

Variable	Value
Age	
Mean	52 years
Range	19–82 years
Sex	
Female	36 (55%)
Smoking	14 (21%)
Symptoms duration	
Up 1 year	14 (21%)
1 to 5 years	16 (24%)
Over 5 years	36 (65%)
Ulcer type	
Gastric	20 (30%)
Duodenal	33 (50%)
Gastric + duodenal	13 (20%)
Ulcer stage	
Sakita A	8 (12%)
Sakita H	12 (18%)
Sakita S	46 (70%)

Table 2 - Eradication rates.

	Rate	95% Confidence Interval
Per protocol	74% (48/65)	63–85%
Intention to Treat	73% (48/66)	62–84%

Table 3 - Adverse events.

Variable	Value
Absent	17 (26%)
Mild	23 (35%)
Moderate	26 (39%)

were identified in half of the cases (Table 1). The per-protocol eradication rate was 74%, and the eradication rate by intention to treat (ITT) was 73% (Table 2).

Forty-nine patients reported adverse events, all of which were mild or moderate (Table 3). Complaints of diarrhea (32%) and nausea (15%) were the most frequent.

DISCUSSION

The eradication rate (73%; CI: 62–84% per ITT) for the triple regimen with lansoprazole, amoxicillin and levofloxacin found in our study was disappointing because eradication by ITT in our service was 82.7% with the classic regimen, with a CI of 79–86%. Interestingly, a study carried out in our country showed greater *H. pylori* resistance to levofloxacin (23%) than to clarithromycin (8%) (11).

A weakness of this work was that it was not conducted as a randomized, double-blind trial against the classical regimen; however, the effectiveness of that regimen has remained relatively constant in our service.

The treatment duration was possibly a factor that determined this lower efficacy, as the current tendency is to propose longer treatment regimens for *H. pylori* eradication (24,25). However, for both the classic treatment and other triple regimens, we chose to focus on shorter-term treatments, aiming to obtain lower costs, fewer adverse effects and greater adherence.

In our country, obtaining reliable information regarding the previous use of levofloxacin may be difficult because this antibiotic has been extensively used to treat respiratory infections without the patient having specific knowledge of

its use. Thus, some patients in our sample may have previously used this compound without knowing it. As we could not determine strain susceptibility to levofloxacin in this study, it was not possible to determine whether the low treatment efficacy in this sample could be associated with increased bacterial resistance to the antibiotic agent.

Evidence in the literature suggests that the secondary resistance of *H. pylori* to levofloxacin may be low (26,27), but studies also show high rates of primary resistance to levofloxacin and low rates of efficacy in treating the bacteria with this antibiotic (28,29).

There might have been a higher resistance of *H. pylori* to amoxicillin in patients from our sample, as some Brazilian studies have shown rates of resistance to this antibiotic of up to 38% (12,30). However, we did not observe resistance to amoxicillin in our service (11), and considering the good efficacy of eradication using the classic regimen in our country (10) with low bacterial resistance to clarithromycin (11), the lower efficacy of the regimen with levofloxacin is not likely due to high resistance to amoxicillin, even taking into account the frequent use of this antibiotic in our country.

Considering the limitation that our study did not determine the primary resistance of *H. pylori* to levofloxacin and amoxicillin, the efficacy of the triple regimen with levofloxacin was not superior to the classic regimen. Thus, the classic treatment is still recommended as the first-line treatment, and the triple regimen with levofloxacin is indicated as a possible retreatment.

The adverse effects of treatment were frequent but were of mild and moderate intensity, and none of the patients participating in the study stopped taking the medication. This finding is hardly surprising, as diarrhea and nausea are expected adverse effects for levofloxacin (31), as well as for amoxicillin (32), but they did not cause severe discomfort to patients. However, Di Caro et al., when comparing the adverse effects of similar treatments with quadruple therapy, reported a much lower prevalence (33) of adverse effects.

The eradication of *H. pylori* using the lansoprazole, amoxicillin and levofloxacin regimen for seven days in previously untreated Brazilian peptic ulcer patients infected with the bacteria showed low efficacy, with lower eradication rates than those obtained with the classic triple regimen of a PPI, amoxicillin and clarithromycin.

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AUTHOR CONTRIBUTIONS

All authors contributed to the design of the study and have read and approved the final manuscript. Silva FM and Queiroz EC acquired the data and performed quality control. Silva FM, Queiroz EC, Navarro-Rodríguez T, and Eisig JN analyzed and interpreted the data. Barbuti RC and Navarro-Rodríguez T performed endoscopic examinations. Lee JH and Iriya K performed histological studies. Mattar R performed laboratory tests. Silva FM drafted the manuscript.



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