Efficacy of triple therapy with a proton pump inhibitor, levofloxacin, and amoxicillin as first-line treatment to eradicate *Helicobacter pylori*

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ABSTRACT

Background: triple therapy including a proton pump inhibitor, clarithromycin, and amoxicillin (PPI-CA) is the first-choice treatment used for *H. pylori* eradication. The efficacy of this treatment is declining of late, and alternative therapies are currently under evaluation.

Objectives: to evaluate the efficacy, safety and compliance of a triple therapy with a PPI, amoxicillin and levofloxacin (PPI-LA) - replacing clarithromycin - for the eradication of *H. pylori*.

Methods: the study included 135 patients (65% women), mean age 53 years, with dyspeptic symptoms and *H. pylori* infection proven by a positive urease rapid test, histological analysis, or C13-urea breath test. **Diagnosis:** non-investigated dyspepsia 48.9%, functional dyspepsia 36.3%, and ulcerative dyspepsia 14.8%. Treatment was indicated with a proton pump inhibitor at usual doses, amoxicillin 1 g, and levofloxacin 500 mg, administered jointly during breakfast and dinner for 10 days. We studied the performance of this triple therapy and its effects using a questionnaire, and effectiveness by the negativity of the C13-urea breath test after 6-8 weeks after treatment discontinuation. Per protocol, we compared the effectiveness of PPI-LA with a control group of 270 patients treated with PPI-CA for 10 days.

Results: 130 patients (96.2%) could complete the treatment and follow-up protocol. Effectiveness (intention to treat) was 71.8% (97/135) and 74.6% (per protocol) (97/130). Sixteen patients (11.8%) had well-tolerated adverse effects, except for 5 subjects (3.7%) who dropped out. PPI-CA was effective (per protocol) in 204 patients out of 270 (75.5%) in the control group.

Conclusions: triple therapy with a PPI, amoxicillin and levofloxacin for 10 days is a well-tolerated treatment that is easy to comply with; however it has low efficiency - less than 80% - and is not recommended as a first-choice treatment for *H. pylori* eradication. Similar results were obtained with the classic triple therapy using a PPI, clarithromycin and amoxicillin.

Key words: Triple therapy. Levofloxacin. *Helicobacter pylori*.

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INTRODUCTION

Triple therapy combining a proton pump inhibitor (PPI) with two antibiotics, preferably clarithromycin and amoxicillin (PPI-CA), is the first-choice treatment in the eradication of *Helicobacter pylori* (*H. pylori*) (1-3). The efficacy of this treatment has declined in recent years, being now usually below 80% and, in some studies, lower than 70% (4-9), probably due to increased resistance to clarithromycin. Recent publications show a higher efficacy (> 80%) of a new triple therapy combining a PPI, amoxicillin and levofloxacin (PPI-LA) replacing clarithromycin as first-line treatment to eradicate *H. pylori*, this being considered an alternative treatment because of the lack of effectiveness of triple therapy with PPI-CA (10-15). In this study we determined the effectiveness, compliance and safety of PPI-LA triple therapy for 10 days, given as first-line treatment to eradicate *H. pylori* in our health area.

METHODS

Study design: a prospective, observational, single-center study. Period of study: 2007-2008.

We included 135 consecutive patients with dyspeptic symptoms and *H. pylori* infection diagnosed by positivity

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for the C13-urea breath test, urease rapid test, or histological analysis. It was determined that a patient was infected when having a positive result for any of these tests. Eighty-eight patients (65%) were female and 47 (35%) were male, with an average age of 53 years (18-80); 33 were smokers (24.5%). Patients under 18 years of age were not included, as well as patients with alleged difficulty in complying with therapy, serious illnesses, previous eradicating treatment, gastric surgery, intolerance, or allergy to any of the drugs included in the study. In 69 of 135 cases (51%) an oral endoscopic analysis was performed, obtaining antral gastric mucosa biopsies for histological analysis and/or urease rapid test, and the following diagnoses were made: functional dyspepsia = 49 cases (36.3%), and peptic ulcer disease or ulcerative dyspepsia = 20 cases (14.8%). The remaining 66 cases (48.9%) were diagnosed using the C13-urea breath test and managed with the "test and treat" strategy (non-investigated dyspepsia).

Treatment

Omeprazol 20 mg/12 h (or another PPI at equivalent dose), amoxicillin 1 g/12 h, and levofloxacin 500 mg/12 h for 10 days. All three drugs should be taken together, preferably during breakfast and dinner. Other PPIs used were lansoprazole 30 mg/12 h, pantoprazole 40 mg/12 h, rabeprazole 20 mg/12 h, and esomeprazole 40 mg/12 h. We confirmed the effectiveness of triple therapy using the negativity of the C13-urea breath test at 6-8 weeks after treatment completion. The emergence of significant adverse effects and adherence to treatment were monitored through interrogation.

The analysis of results was performed using the intention-to-treat (ITT) and per protocol (PP) strategies. In the ITT analysis all patients who started treatment were included. In the PP analysis patients who completed treatment protocols, at least 90% of doses, and follow-up, keeping on the scheduled date for clinical evaluation and the breath test analysis, were included. All patients accepted the treatment provided, including levofloxacin, and were informed about the importance of *H. pylori* infection, the need for proper treatment, and the possibility of side effects.

We compared the effectiveness of the study therapy under investigation, by PP, with a control group of 270 consecutive patients with dyspepsia and *H. pylori* infection treated with omeprazole 20 mg/12 h (or another PPI at equivalent doses), clarithromycin 500 mg/12 h, and amoxicillin 1 g/12 h (PPI-CA) for 10 days, from 2006 to 2007. The control group was composed of 102 male patients (37.8%) and 168 females (62.2%), with an average age of 47 (± 30) and diagnosed as follows: non-investigated dyspepsia in 123 cases (45.6%), functional dyspepsia in 95 cases (35.2%), and ulcerative dyspepsia in 52 cases (19.2%). The diagnosis of *H. pylori* infection and the ef-

fectiveness of treatment were analyzed by the methods already described.

The present study complies with the regulations of the Ethics and Clinical Research Committees of our hospital.

RESULTS

Completion of treatment and side effects

One hundred and thirty patients out of 135 (96.2%) successfully conducted treatment with PPI-LA and underwent the C13-urea breath test on the scheduled date. Five patients (3.7%) conducted the treatment only for 3-4 days due to adverse effects. Side effects that led to treatment discontinuation were: nausea and vomiting (2 cases), nausea (2 cases), and seizures (1 case).

Sixteen patients (11.8%) had some adverse effect. They are listed in table I.

Table I. Adverse effects of triple therapy with a PPI, levofloxacin, and amoxicillin for 10 days

Adverse effect	Number of cases (%)
Nausea	8 (5.9%)
Metallic taste	4 (2.9%)
Abdominal pain	3 (2.2%)
Diarrhea	3 (2.2%)
Vomiting	2 (1.4%)
Oral thrush	2 (1.4%)
Myalgia	2 (1.4%)
Seizures	1 (0.7%)
Any adverse effect	16 (11.8%)

Effectiveness of treatment

Study group: treatment proved to be effective in 97 patients (71.8%) and failed in 33 patients (24.4%). In 5 patients of 135 (3.7%) treatment was unsuccessful.

The efficacy found was 71.8% (97/135) (95% confidence interval, 64.2-79.4%) in the intention-to-treat analysis, and 74.6% (97/130) (95% confidence interval, 67.1-82.1%) in the per protocol analysis. There was no significant difference between patients with functional, ulcerative, or non-investigated dyspepsia.

Control group: treatment using PPI-CA proved to be effective (PP) in 204 out of 270 patients (75.5%) (95% confidence interval, 70.4-80.6%), and failed in 66 out of 270 patients (24.4%). There was no significant difference in effectiveness of treatment between PPI-LA and PPI-CA.

DISCUSSION

Triple therapy combining a PPI with two antibiotics, preferably amoxicillin and clarithromycin (PPI-CA), for

at least 7 days is the first-choice regimen to eradicate *H. pylori* infection that is widely accepted in Europe and the United States. During the Second Spanish Consensus Conference (2005) it was recommended as standard first-choice regimen the use of a PPI (usual dose) together with 1 g of amoxicillin and 500 mg of clarithromycin every 12 hours, or RCB 400 mg every 12 h (this drug not currently available) with the same antibiotics. In case of allergy to amoxicillin, metronidazole 500 mg every 12 h (1,2) should be chosen. During the Third Conference of Consensus at Maastricht (2007) this triple therapy was recommended as first-line treatment. The same guideline is also present in other consensus documents produced in Italy by the "Cervia II Working Group" (2007) and in the United States by the American College of Gastroenterology (2007) (3,16,17).

As a conclusion achieved during the First Conference of Consensus at Maastricht (1997), only treatments with an efficiency higher than 80% (intention to treat) should be recommended for clinical practice (18). Graham et al., in a recent review, assess and confirm that treatment to eradicate *H. pylori* infection should have an efficiency above 80 or 85%, intention to treat or per protocol, respectively (5). Gisbert et al., (2000), published a meta-analysis on the effectiveness of triple therapy with a PPI, clarithromycin and amoxicillin or metronidazole/tinidazole, reviewing 22 previously reported studies (1996-1999). They found similar efficacy in the intention to treat and per protocol analyses (81 and 84%) (19). In this meta-analysis, the observed efficiency of the eradicating treatment was very close to or exceeded 90% (20). These results are not obtained in studies recently published, which usually show the effectiveness of classic triple therapy to be below 80%, even when treatment was extended for up to 10 days (5-9,21). Boixeda et al., (2003) found the same trend in a study of 890 patients, and detected an eradication rate of 77% (22). Calvet et al., (2005) reported an eradication rate of triple therapy (intention to treat) of 73 and 79% for 7 and 10 days of treatment, respectively (21). In our health area, during years 2005-2007, the eradication rate with the triple therapy (per protocol) was 70% for

10 days. This low efficiency led us to consider other therapeutic strategies.

Levofloxacin is a fluoroquinolone with a broad spectrum of activity against gram (+) and gram (-) bacteria, including *H. pylori*. It is highly effective for respiratory, urinary tract, skin, and soft tissue infections. In recent years, several studies have been published evaluating the effectiveness of triple therapy containing levofloxacin in the eradication of *H. pylori*. A recent meta-analysis shows that therapy with PPI-LA, especially for 10 days, is more effective and better tolerated as second-line than quadruple therapy in eradicating *H. pylori* (23). Gisbert et al. published two studies where a high multisite effectiveness of triple therapy with PPI-LA for 10 days was found as second- and third-line treatment in the eradication of *H. pylori* (24,25). The loss of effectiveness of triple therapy with PPI-CA motivates the use of triple therapy with levofloxacin replacing clarithromycin as first-line treatment for the eradication of *H. pylori*. In this regard, several studies showing an acceptable efficacy of this treatment, higher than 80% (Table II), considered it an alternative choice to standard triple therapy in areas where, due to increasing resistance to clarithromycin, a progressive loss of effectiveness was found (10-15). This situation, actually present in our health area, motivated this study. We have used high-dose levofloxacin, as previously pointed out by other authors (11,12,14,15,24,25), in order to increase treatment effectiveness. We noted that, in our experience, the effectiveness of triple therapy with PPI-LA was 75% in the per-protocol analysis, which is lower than the results reported by other authors. Treatment is simple and well tolerated, but due is not recommended in view of its low efficacy, at least in our health area, as first-choice regimen for the eradication of *H. pylori* (despite a high failure rate obtained with triple therapy using PPI-CA). The progressive increase of resistance to fluoroquinolones identified by some authors may justify the low effectiveness of triple therapy with these antibiotics. Bogaerts et al. (in Belgium) detected during the years 2003-2004 that 16.8% of *H. pylori* strains were resistant to fluoroquinolones,

Table II. Efficacy of triple therapy with levofloxacin, as first-line therapy in the eradication of *Helicobacter pylori*

References (10-15)	Number of patients	Drugs/days	Levofloxacin doses	Effectiveness ITT (%)	Effectiveness PP (%)
Cammarota et al. (2000)	50	R-L-T/7	500 mg/24 h	92	92
	50	R-L-A/7	500 mg/24 h	90	90
Antos et al. (2006)	30	E-L-A/7	500 mg/12 h	86.7	92.9
Marcio et al. (2006)	80	E-L-A/10	500 mg/12 h	93.7	93.7
Nista et al. (2006)	100	E-L-C/7	500 mg/24 h	87	90.6
Gisbert et al. (2007)	64	RBC-L-A/10	500 mg/12h	84.4	88.5
Gisbert et al. (2008)	75	O-L-A/10	500 mg/12 h	82.7	84.5

ITT: intention to treat; PP: per protocol; RBC: ranitidine bismuth citrate; R: rabeprazole; L: levofloxacin; A: amoxicillin; T: tinidazole; E: esomeprazole; O: omeprazole; C: clarithromycin.

while A. Zullo et al. (in Italy) detected in 2004-2006 a higher resistance rate (19%), particularly to levofloxacin (26-28).

The low effectiveness of PPI-CA and PPI-LA demands other treatment strategies such as the currently-discussed association of a PPI with three antibiotics: amoxicillin, clarithromycin and metronidazole, simultaneously or sequentially. These treatments have been reported to yield very good results in the eradication of *H. pylori* (29,30).

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