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Efficacy of low-dose lansoprazole in the treatment of non-erosive gastroesophageal reflux disease. Influence of infection by *Helicobacter pylori*

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ABSTRACT

Introduction: proton pump inhibitors (PPIs) are the most effective drugs to cure peptic esophagitis and control the symptoms of gastroesophageal reflux disease (GERD). In most patients with GERD esophagitis is not detected by endoscopy, which represents GERD with a negative endoscopy or non-erosive reflux disease (NERD). The influence of infection by *H. pylori* in the evolution of GERD is controversial since a protective action is identified by some studies, but not all. We conducted a clinical trial to assess the efficacy of lansoprazole 15 mg/day in the initial control of NERD symptoms, and as a secondary endpoint the impact of *H. pylori* infection on response to treatment.

Patients and methods: a pilot, single-center clinical trial was conducted –single-blind regarding the experimental medication (unknown to patients), and double-blind regarding the information concerning *H. pylori* infection. Sixty (60) patients with NERD were initially included, who had suffered from daytime or nocturnal heartburn for 1-2 days in each of the last two weeks. Nine patients were excluded for failing to comply with the study protocol. The 51 remaining patients, 35 women and 16 men, with a mean age of 49 years, comprised the per protocol analysis population. Patients received treatment for two weeks with a capsule of the study medication (15 mg/day of lansoprazole), with daily controls on the presence and severity of daytime and nocturnal heartburn. Treatment was considered effective when, upon completion, patients referred a maximum of one episode of mild heartburn as defined in the protocol, or answered the following question in the affirmative: "Does the medication you are receiving satisfactorily control the symptoms of your disease?".

During diagnostic endoscopy we obtained biopsies of the gastric body and antrum to investigate infection by *H. pylori* by means of a urease test. Treatment efficacy was assessed with no patients or doctors responsible for the study being aware of urease test results.

Results: 41 patients (80.3%) reported that treatment had satisfactorily controlled their symptoms, and 34 patients (66.6%) had a maximum of one episode of mild heartburn in the last week. Forty-two (42) patients (82.3%) had infection by *H. pylori*. No significant differences were observed in the response to treatment between patients with or without *H. pylori* infection.

Conclusions: with the limitations of a pilot study, these results suggest that lansoprazole 15 mg/day is an effective treatment in the control of NERD symptoms, that it may be a good initial therapeutic strategy, and that, according to data available, *H. pylori* infection has no significant effect on the response to treatment.

Key words: Lansoprazole. Non-erosive reflux disease. *Helicobacter pylori.*

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INTRODUCTION

Gastroesophageal reflux disease (GERD) is a highly prevalent (10-20% of population) condition that may have a significant impact on quality of life and lead to a high use of healthcare resources. The etiopathogenesis of this disease is multifactorial, and the main factor responsible for it is a dysfunction of the lower esophageal sphincter (1-4).

In GERD there is a poor correlation between symptom severity (heartburn, acid regurgitations) and the presence of esophagitis. Approximately 65% of patients have non-erosive GERD (NERD), and 35% have erosive esophagitis (5-7).

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Proton pump inhibitors (PPIs) are the most effective drugs to control GERD symptoms, and to endoscopically cure esophagitis (8,9).

The efficacy of PPIs, and specifically of lansoprazole, is superior to that of H2-antagonists and, on the other hand, lansoprazole 30 mg/day is more effective than lansoprazole 15 mg/day in the curing of GERD with esophagitis (10-12). However, both these doses have similar efficacy as maintenance treatment for preventing a esophagitis relapse (13,14). The efficacy of PPIs is greater in the population with GERD and esophagitis *versus* those with NERD. Ritcher et al. observed that lansoprazole 15 mg/day is no less effective than lansoprazole 30 mg/day in the treatment of NERD, with both doses being more effective than placebo or ranitidine 300 mg/day (15,16).

The influence of infection by *Helicobacter pylori (H. pylori)* on GERD's outcome and response to treatment is controversial. According to some studies, it has a protective effect decreasing the severity of symptoms or the prevalence of esophagitis, while other claim otherwise (17-33).

In this study we assessed, as our primary endpoint, the efficacy of lansoprazole at lower-than-conventional doses in the control of NERD, an increasingly prevalent condition with a growing impact on healthcare expenditure, and as our secondary endpoint the possible influence of *H. pylori* infection on response to treatment.

MATERIAL AND METHODS

Study protocol

We conducted a pilot, single-center clinical trial –single-blind with regards to the experimental medication (lansoprazole 15 mg/day), unknown to patients, and double-blind with regards to *H. pylori* infection, which could be the basis for more comprehensive studies. We included 60 consecutive patients clinically diagnosed with GERD who complied with inclusion and exclusion criteria as shown in table I. During endoscopy we investigated *H. pylori* infection by means of a urease test on biopsies of the gastric body and antrum (Jatrox-Test). Infection by *H. pylori* was considered to be present when the urease test was positive for one or both locations within 24 hours. Patients provided their informed consent in writing, and were allowed to voluntarily withdraw from the study. The study was approved by the hospital's Ethic and Research Committees. A description of the study population, including demographic and clinical data, is shown in table II.

The capsules of the study medication, lansoprazole 15 mg, were to be taken once a day, 20-30 minutes before breakfast. During this treatment, the use of other PPIs, H2-antagonists, antibiotics, or drugs that could alter gastroesophageal reflux extent, induce dyspepsia, or interfere with the metabolism of lansoprazole was not permitted.

Table I. Inclusion and exclusion criteria

Inclusion criteria	*Exclusion criteria*
Age > 18 years	Pregnant or breastfeeding women or women of childbearing age without effective contraception
Non-erosive GERD	
Two or more heartburn episodes per week	History of allergy to lansoprazole
Study of infection by *H. pylori* by urease test on gastric body and antrum	History of esophagitis, gastroduodenal ulcer or digestive surgery
Absence of relevant gastric or duodenal disease	Liver or kidney impairment
	Treatment in the 4 previous weeks with anti-secretory agents (PPIs and H2-antagonists) or antibiotics
Ability to correctly follow the study instructions	Treatment in the 2 previous weeks with NSAIDs and drugs able to alter GER extent: theophylline, prokinetic drugs, calcium antagonists, beta-adrenergic agonists, meperidine, diazepam, antidepressants, anticholinergic drugs, etc.)
Informed consent in writing	

NSAIDs: non-steroidal anti-inflammatory drugs. PPIs: proton pump inhibitors. Anti-H2: histamine H2 receptor antagonists. GER: gastroesophageal reflux.

Table II. Demographic and clinical data of the study populations

	ITT population (No. 57)	*PP population (No. 51)*
Mean age	49.29 years	49.12 years
Mean weight	74.51 k	73.95 k
Mean height	163 cm	162 cm
Men	16 (28%)	16 (31.4%)
Women	41 (72%)	35 (68.6%)
Mean time with GERD	7.08 years	6.93 years
Mean days of daytime heartburn (2 previous weeks)	10 days	9.8 days
Severity of daytime heartburn:		
Absent	01 (01.7%)	01 (01.9%)
Mild	15 (26.3%)	13 (25.4%)
Moderate	41 (71.9%)	37 (72.5%)
Severe	–	–
Mean days of nocturnal heartburn (2 previous weeks)	5.02 days	4.41 days
Severity of nocturnal heartburn:		
Absent	26 (45.6%)	24 (47.0%)
Mild	12 (21.0%)	10 (19.6%)
Moderate	19 (33.3%)	17 (33.3 %)
Severe	–	–
Smoking	10 (17.5%)	10 (19.6%)
Alcohol consumption (> 40 g)	18 (31.5%)	17 (33.3%)
Coffee or tea consumption	22 (38.5%)	20 (39.2%)
Infection by *H. pylori:*	47 (82.4%)	42 (82.3%)
Positive		
Negative	10 (17.5%)	09 (17.6%)

ITT: intent-to-treat population; PP: per protocol population; GERD: gastroesophageal reflux disease. (*) = In the two weeks prior to inclusion in the study.

The duration of treatment was 2 weeks, with two visits, one at baseline and one at the end of treatment. During the first visit we obtained a detailed history of GERD, and recorded data such as weight, height, smoking habits, and alcohol, coffee or tea consumption.

During treatment, patients recorded the presence of heartburn episodes on a daily basis, indicating time and severity, in a case report form to be returned at the 2nd visit. Heartburn severity was scored from 0 to 3. Grade 0: absence of heartburn. Grade I (mild heartburn): the patient suffered from heartburn not interfering with his or her routine activities or sleep. Grade II (moderate heartburn): the patient suffered from heartburn during a part of the day or night, which slightly or tolerably interfered with his or her routine activities or sleep. Grade III (severe heartburn): the patient suffered from heartburn during the day or night, which significantly interfered with his or her routine activities or sleep. At the 2nd visit we assessed the level of satisfaction with treatment, and the symptoms referred in the case report form; we also collected the unused medication to evaluate compliance, and asked patients about potential adverse events.

For the treatment to be considered as valid to assess its efficacy, the primary endpoint had to be available (visit 2) with a correct therapeutic compliance (at least 80%) and no use of forbidden treatments. After treatment completion (visit 2) symptoms were assessed with neither the patient nor the investigator being aware of the presence or absence of *H. pylori* infection.

Treatment efficacy was assessed in relation to the presence or absence of *H. pylori* infection, and the impact of age, sex, body mass index, smoking habit, alcohol, coffee or tea consumption, and how long the patient had suffered from GERD.

Primary endpoint

The primary endpoint to assess the efficacy of treatment was symptom control two weeks after treatment onset.

Symptoms were considered to be under control when these requisites were in place: a) heartburn was present for a maximum of one day or night, in mild form, in the last 7 days; and b) the patient answered the following question in the affirmative: "Is the medication you are receiving sufficiently controlling the symptoms of your disease?".

Secondary endpoints

Treatment efficacy during the first and second weeks. The following data were quantified: a) number of days with daytime heartburn and its severity; and b) number of days with nocturnal heartburn and its severity.

Descriptions of the analytical groups

1. *Intent-to-treat (ITT) analysis population:* it included all patients who received at least one dose of the experimental medication and attended the 2nd visit.

2. *Per protocol (PP) analysis population:* it included all patients in the ITT population with a treatment compliance over 80% who had not deviated from the protocol.

Statistical analysis

The statistical analysis compared treatment results in relation to the presence or absence of *H. pylori* infection with a subsequent evaluation of age, sex, body mass index, smoking habit, alcohol, coffee and tea consumption, and the time the patient had been suffering from disease. In order to determine the type of statistical test to be used (parametric or not) in the analysis, we tested goodness of fit with a Kolmogorov-Smirnov normal distribution test, and performed either Barlett's variance homogeneity test or Cochran's test, whichever was most restrictive.

For parametric quantitative variables we used an analysis of variance for repeated measures, associated with a t-test for paired data.

For non-parametric quantitative variables, and non-paired data, we used a non-parametric Mann-Witney U test or Kruskal-Wallis test when necessary. For paired data we used Wilcoxon's test for repeated measures.

For nominal qualitative variables we used a Chi-square test, grouping data and applying Yates' correction when necessary.

All the analyses were performed using the SAS 8.1 program, with a 5% level of significance for all hypotheses tested.

RESULTS

1. *Analysis populations:* the intention to treat (ITT) and per protocol (PP) populations comprised 57 patients and 51 patients, respectively. Six patients were excluded from the ITT population due to a treatment compliance of less than 80%, or for having used forbidden medication. The clinical data of these populations are shown in table II.

2. *Helicobacter pylori infection:* 49 patients from the total population (81.6%), 47 from the ITT population (82.4%), and 42 from the PP population (82.3%), had *H. pylori* infection. The infection was simultaneous in the gastric body and antrum in 45/49 (91.8%), 43/47 (91.4%), and 38/42 (90.4%) patients, respectively. The populations with or without infection by *H. pylori* had no significant differences in the parameters shown in table II.

3. *Symptom control (primary endpoint):*

—In 35 patients from the ITT population (61.4%) and 34 patients from the PP population (66.6%) symptoms

were satisfactorily controlled, with a maximum of one episode of mild heartburn in the last week.

ITT population: 27 of 35 patients (77.1%) with controlled symptoms were *H. pylori*-positive and 8 (22.8%) were negative. Symptoms were controlled in 27 of 47 *H. pylori*-positive patients (57.4%), and 8 of 10 *H. pylori*-negative patients (80%).

PP population: 26 of 34 patients (76.4%) with controlled symptoms were *H. pylori*-positive and 8 (23.5%) were negative. Symptoms were controlled in 26 of 42 *H. pylori*-positive patients (61.9%) and 8 of 9 *H. pylori*-negative patients (88.8%).

2.42 patients from the ITT population (73.6%) and 41 from the PP population (80.3%) answered the question at visit 2 ("Is the medication you are receiving sufficiently controlling the symptoms of your disease?") in the affirmative. *H. pylori* infection was detected, respectively, in 80.9 and 80.4% of patients satisfied with their treatment.

No statistically significant differences were observed in symptom control, regardless of assessment for the presence or absence of *H. pylori* infection.

4. *Evolution of symptoms in the ITT population:*

—*No. of days with daytime heartburn and maximum severity:* in the first week of treatment 19 patients (33.3%) had no heartburn, and 6 (10.5%) had it on one day only. Thirty-two (32) patients (56.1%) had heartburn on two or more days. Severity was mild or absent in 36 patients (63.1%). In the second week of treatment 33 patients (57.8%) had no heartburn and 5 (8.7%) had it on one day only. Nineteen (19) patients (33.3%) had heartburn on two or more days. Severity was mild or absent in 48 patients (84.2%).

—*No. of days with nocturnal heartburn and maximum severity:* in the first week of treatment 23 patients (40.3%) had no heartburn and 11 (19.2%) only had it one night. Twenty-three (23) patients (40.3%) had heartburn for two nights or more. Severity was mild or absent in 45 patients (78.9%). In the second week of treatment 38 patients (66.6%) had no heartburn, and 8 (14.0%) had it only one night. Eleven (11) patients (19.2%) had heartburn for two nights or more. Severity was mild or absent in 51 patients (89.4%).

5. *Evolution of symptoms in the PP population:*

—*Daytime heartburn:* in the first week of treatment 18 patients (35.2%) had no heartburn and 6 (11.7%) had it on one day only. Twenty-seven (27) patients (52.9%) had heartburn on two or more days. Severity was mild or absent in 34 patients (66.6%). In the second week of treatment 30 patients (58.8%) had no heartburn and 5 (9.8%) had it on one day only. Sixteen (16) patients (31.3%) had heartburn on two or more days. Severity was mild or absent in 45 patients (88.2%).

—*Nocturnal heartburn:* in the first week of treatment 21 patients (41.1%) had no heartburn and 10 (19.6%) only had it one night. Twenty (20) patients (39.2%) had heartburn for two nights or more. Severity was mild or absent in 41 patients (80.3%). In the second week of treatment 34 patients (66.6%) had no heartburn and 8 (15.6%) had it on one night only. Nine (9) patients (17.6%) had heartburn for two nights or more. Severity was mild or absent in 47 patients (92.1%).

DISCUSSION

GERD is a heterogeneous disease in its pathogenesis and clinical presentation (1-4).

Most patients with GERD do not have erosive esophagitis, and this situation is known as GERD with negative endoscopy or non-erosive reflux disease (NERD). This condition is not considered a mild or initial presentation of GERD, at the opposite end of esophagitis or Barrett's esophagus, but as a form of GERD in its own right. Most patients with NERD remain stable over the years, and do not evolve to erosive esophagitis. Anti-secretory treatment is less effective in NERD than in erosive esophagitis, probably due to the different impact of pathogenic factors (34,35). NERD is a more heterogeneous condition from a pathogenic perspective than GERD with esophagitis. A study of patients with NERD using pH-metry shows that in 50-70% of cases there is an abnormal exposure of the esophagus to acid, and that in the remaining 30-50% the exposure to acid can be considered physiological. In these patients with functional heartburn we may see a positive (40%) or negative (60%) relationship between heartburn episodes and reflux. In the first case we consider the existence of a hypersensitive esophagus, and in the second case that the heartburn is provoked by non-acid stimuli. There may be a subgroup of patients with episodes of heartburn caused by minimum increases in the exposure of the esophagus to acid, even with a pH over 4 (1.6). This would explain the lower response to treatment with PPIs in NERD *versus* GERD with esophagitis, where the relation to esophageal exposure to acid is more apparent.

The relationship between infection by *H. pylori* and GERD is controversial, with contradictory data found in the literature. Some data suggest a protective or beneficial effect of *H. pylori* infection, decreasing the risk or severity of GERD. The lower prevalence of infection in more advanced levels of esophagitis, and observations regarding heartburn worsening or development after infection eradication would support this opinion. The most widespread opinion at the present time is that there is no consistent relationship between GERD and *H. pylori* infection, although an impact on certain subgroups of patients cannot be entirely ruled out (28-33).

Infection by *H. pylori* may influence GERD by altering gastric secretions and, in theory, by enhancing the effect of anti-secretory drugs. It has been considered that infection when located in the gastric antrum may favor the development of heartburn due to hypergastrinemia and gastric hypersecretion, whereas the gastric body –being diffusely affected– would cause the opposite effect.

The influence of infection has not been detected on other factors such as gastric emptying or the function of the lower esophageal sphincter, and it is not clear whether it would affect the visceral perception of the digestive tract (36,37).

NERD is a highly prevalent condition. The purpose of treatment is to control symptoms at the lowest possible dose and cost; this can be assessed either by the number of heartburn episodes and their severity, or by the patients' degree of satisfaction. In our study we assessed the efficacy of treatment considering both these parameters. Like other authors, we believe that a total absence of symptoms is not required for a treatment to be considered effective (38,39). In our study we considered that treatment was effective when a maximum of one episode of mild heartburn was detected in the last week, without affecting the patient's daily activities or sleep, or when the patient was satisfied with his or her new clinical status, aspects also evaluated in other studies. Lansoprazole, at a dose of 15 mg/day, is shown in our study to be an effective treatment in a considerable percentage of patients with NERD, with or without infection by *H. pylori*. In 66.6% of patients symptoms were controlled after two weeks of treatment according to clinical criteria as established in the protocol, and 80% of patients considered that treatment had satisfactorily controlled NERD symptoms.

During this study we observed a progressive reduction in the number of days with both daytime heartburn, absent or present only one day in 68.6% of patients, and nocturnal heartburn, absent or present only one night in 82.26% of patients in the last week of treatment. We also observed a progressive reduction in the severity of both daytime and nocturnal heartburn during treatment. These data are consistent with those provided by other studies (16,40).

The study was designed as double-blind for the absence or presence of infection by *H. pylori*, and exposure to this study factor was not assigned in a controlled manner. It is interesting to note the high prevalence of infection by *H. pylori* (82%) in our group of patients with NERD without gastroduodenal peptic disease, and the fact that in most cases the infection was simultaneous in the gastric body and antrum. These circumstances make it difficult to assess the influence of *H. pylori* infection and its location in the gastric mucosa on the response to anti-secretory treatment. The prevalence of *H. pylori* infection seen in our study is greater than initially expected (approximately 50%) and similar to that seen by Boixeda et al. in Madrid, with 74.5% in patients with GERD and esophagitis, and 76.4% in control patients with a normal endoscopy (41).

We may conclude, with the limitations inherent to a pilot study, that lansoprazole 15 mg/day is an effective treatment for NERD. Treatment with lansoprazole 15 mg would be an acceptable initial therapeutic strategy in NERD, a condition with a growing prevalence and a high impact on healthcare costs. In the patient sample studied we did not detect an impact of infection by *H. pylori* on response to treatment.

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