

# CLINICAL AND ENDOSCOPIC EVALUATION OF GASTROESOPHAGEAL REFLUX DISEASE IN PATIENTS SUCCESSFULLY TREATED WITH ESOMEPRAZOLE

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**ABSTRACT – Background** – Esomeprazole, an S-isomer of omeprazole, is the first proton pump inhibitor developed as an optical isomer, and it has shown high healing rates in erosive esophagitis. **Aim** – To evaluate the efficacy and tolerability of esomeprazole in subjects with erosive esophagitis, according to the Los Angeles classification study design: an open, multi-center clinical study. **Material and Methods** – Two hundred and eighteen subjects with reflux esophagitis confirmed by endoscopy were included in an open, multi-center study in Brazil. All of them received esomeprazole 40 mg, once daily, for a 4-week period. Subjects who had unhealed esophagitis by week 4 continued the treatment for another 4 weeks. The primary efficacy endpoint was the healing rates by weeks 4 and 8. The secondary endpoints were the number of patients with symptom resolution by week 4, the number of days to sustained symptom resolution, number of symptom-free days and nights and safety and tolerability of the drug. **Results** – Healing rates by weeks 4 and 8 were 82% (confidence interval: 77.4%-87.6%) and 96.1% (confidence interval: 93.5% – 98.8%), respectively. Ninety-nine (99%) of the patients had heartburn resolution by week 2. The most common adverse events were headache (4%), diarrhea (2.6%) and epigastric pain (2.2%). **Conclusion** – For the studied period, esomeprazole was shown to be a safe and well-tolerated drug, providing significant healing rates of mucosal breaks, regardless of LA classification, in patients with erosive esophagitis. Esomeprazole was also shown to be effective in quickly relieving symptoms.

**HEADINGS** – Gastroesophageal reflux. Esophagitis, peptic. Heartburn. Proton pumps. Esomeprazole.

## OVERVIEW

The last two decades were marked by a considerable improvement in the diagnosis of the gastroesophageal reflux disease (GERD), making it one of the most frequent disorders of the digestive tract.

According to the concept adopted at the I Brazilian Consensus of Gastroesophageal Reflux Disease<sup>(18)</sup>, GERD is defined as a chronic disorder resulting from the retrograde reflux of part of the gastric and duodenal contents to the

esophagus and/or adjacent organs, causing a wide range of esophageal and extra-esophageal symptoms and/or signs, that may or may not be associated to tissue damage.

Heartburn is an excellent marker of GERD, and when associated with acid regurgitation, makes it possible, in about 90% of cases, to establish the diagnosis of GERD. Some surveillance studies in the United States concluded that 15% of the population present heartburn once a month, 13%, once a week and 7%, daily<sup>(18)</sup>. More recent data suggest that once a week symptoms may be present in 19,8%<sup>(17)</sup>.

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It should be emphasized that GERD may be related to other dyspeptic symptoms, which may have atypical presentations, such as labyrinthitis, chronic cough, asthma, non-cardiac chest pain, or even be asymptomatic<sup>(13, 20)</sup>.

The presence of heartburn, including its frequency, does not predict an endoscopic finding. Only about 50% to 60% patients that have this symptom, presented erosive esophagitis when submitted to endoscopic evaluation<sup>(25)</sup>. Therefore, the diagnosis of GERD is not dependent on the presence of endoscopy-verified esophagitis; it is a chronic condition that requires judicious, individual, permanent and sometimes prolonged treatment.

It is important to emphasize that in the same manner as the number of cases of GERD is increasing, so is the number of cases of distal esophagus and gastroesophageal junction cancer. To prove how important and worrying this fact is, only in the year 2000, 341 articles were published in English<sup>(21)</sup> about this.

Several international meetings have tried to reach a consensus for the treatment of GERD, and most of them have proposed the use of proton pump inhibitors (PPI) as first line treatment. Also, it is known that some goals need to be met, such as symptom relief, healing of mucosal breaks, and prevention of relapse and complications.

These goals can be met if an adequate acid suppression is achieved, keeping the pH above 4 for at least 16 to 18 hours of the day. Considering this, PPI may be considered as the first choice treatment.

Esomeprazole, a recently developed S-isomer of omeprazole, is part of this class of drugs. One of its features is a greater systemic bioavailability, which may be translated into greater and more prolonged acid suppression, offering the perspective of better clinical efficacy and efficient management of the disease.

Considering this scenery, the present study was designed to assess the clinical and endoscopic response as well as the safety and efficacy of esomeprazole 40 mg once daily (od) in the treatment of GERD.

## OBJECTIVES

### Primary

- To confirm the efficacy of esomeprazole 40 mg (Nexium®) in healing mucosal breaks in patients with GERD.

### Secondary

- To confirm the efficacy of esomeprazole 40 mg (Nexium®) in improving symptoms in patients with GERD.
- To assess the safety and tolerability of esomeprazole 40 mg (Nexium®) during the treatment period for the healing of GERD.

## SAMPLE SIZE AND METHODS

This was a prospective, multi-center, open, non-controlled study, with competitive inclusion of 218 patients from May until August 2001.

It was conducted according to the ethical guidelines for clinical research studies in humans of the Declaration of Helsinki (WHO), and with the previous approval of the Independent Ethics Committees of the Institutions.

The inclusion criteria for the study were symptoms of reflux esophagitis, previously confirmed (up to 7 days) by endoscopy (Los Angeles Guidelines), in patients of any gender, over 18 years old. The patients had to give their informed consent to be included in the study. The exclusion criteria were previous gastrointestinal surgery; esophageal malignancy; gastric or duodenal ulcer disease; presence of complications of GERD, such as Barrett's esophagus and/or esophageal stricture; previous gastrointestinal diseases that might impair the assessment of the study objective, such as Zollinger-Ellison syndrome; motility disorders of the esophagus such as achalasia, scleroderma and esophageal spasms; continuous treatment with any acid-suppressing drug for more than 7 days within the 30 days previous to inclusion; any contra-indications for the use of omeprazole and esomeprazole; any "alarm signs" indicating severe diseases, such as weight loss, hematemesis, melena, fever, etc.; pregnancy and lactation; history of illicit drugs or alcohol abuse; complications not related to the study method but that might prevent the conclusion of the study period, and previous inclusion in this study.

All patients included took esomeprazole in a daily dosage of 40 mg as the only treatment, to be taken in the morning, fasting, for 4 weeks.

After this period, an endoscopy of the upper digestive tract was repeated, to assess the presence or absence of reflux esophagitis. All patients whose esophagitis was not healed at this moment continued on an identical treatment regimen for another 4 weeks, and were then submitted to a new endoscopy to assess the presence or absence of reflux esophagitis.

The symptoms of reflux esophagitis, heartburn, regurgitation and/or epigastric pain were assessed after 2 to 4 weeks.

In each visit, treatment adherence, protocol failure and/or adverse events, that might cause the patient's withdrawal, were assessed.

The results obtained were submitted to statistical analysis, using the confidence interval of 95%, significant level of 5% ( $P < 0.05$ ), from which any differences were considered significant.

## RESULTS

### Patient population

Two hundred and twenty seven patients were enrolled in this study; three (1.3%) were excluded due to protocol deviations, and six (2.6%)

left the study prematurely. Thus, 218 patients were considered for the efficacy evaluation. Among these 218 patients who had erosive esophagitis confirmed by upper digestive tract endoscopy, 191 (87.6%) presented Los Angeles grades A and B. Three patients were withdrawn due to adverse events.

The intention-to-treat (ITT) analysis included 218 patients. The per protocol analysis (PP) included the 215 patients who completed the study treatment.

Among the 218 patients, 108 were males and 110 were females; 190 (87.2%) were Caucasian; the mean age was 44.7 ( $\pm$  13.4) years. Eighty seven (39.9%) patients referred having had GERD symptoms for more than 5 years and 169 (77.5%) had been presenting the symptoms for 1 to 5 years.

The treatment adherence rate was high, since the number of patients who took treatment medication correctly was 98.6%.

### Efficacy

The healing rate in the ITT analysis was 82.5% (CI 95% = 77.5%-87.5%) after 4 weeks, and 93.6% (CI 95% = 90.4%-96.9%) after 8 weeks of treatment (Figure 1). The PP analysis results were similar: 83.7% (CI 95% = 78.8%-88.6%) after 4 weeks, and 94.9% (CI 95% = 91.9%-97.8%) after 8 weeks of treatment

The analysis of treatment efficacy for the different grades of esophagitis showed that, by the end of week 4, the healing rate was higher in patients with esophagitis grade A than in patients with more severe esophagitis, but this difference was not statistically significant. By the end of week 8, the healing rates in groups A and B was 97.3% and 96%, respectively, much higher than the ones in groups C and D. However, due to the small number of patients in these latter groups, a comparison of data was not possible (Figure 2).

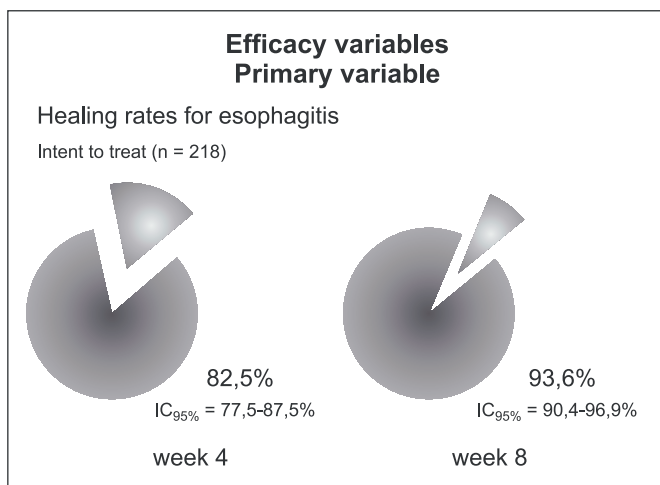


FIGURE 1 – Healing rates after 4 and 8 weeks of treatment

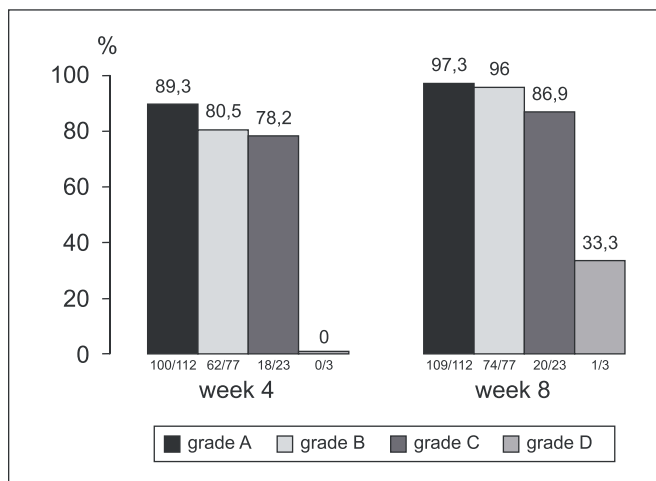


FIGURE 2 – Healing percentage of mucosal breaks at weeks 4 and 8, in patients treated with esomeprazol 40 mg od, per protocol analysis, evaluated according to esophagitis severity at inclusion, using the LA classification

The healing of mucosal breaks was not influenced by the use of nonsteroidal anti-inflammatory drugs (NSAIDs), smoking status, alcohol intake or family history of GERD. We observed that male patients had twice less chance of healing the week 4 ( $P = 0.049$ ) than the females, but this difference was not seen by the end of week 8.

Esomeprazole was highly efficacious in completely relieving heartburn, acid regurgitation, dysphagia and epigastric pain. After 2 weeks of treatment, 80.6% patients had no heartburn, and at the end of week 4 this rate reached 90%. Acid regurgitation had a similar behavior (Table 2), with significant improvement of dysphagia and epigastric pain.

We have not observed association between heartburn and healing of mucosal breaks. Of 22 patients with heartburn at the 4<sup>th</sup> week of treatment, 17 (77.3%) presented healing of their esophagitis; 12 had grade A esophagitis; 4 had grade B esophagitis and 1 had grade C esophagitis. Of the remaining five, three had healed esophagitis at the end of week 8 and remained asymptomatic.

TABLE 1 – Distribution of included patients (n = 218) according to esophagitis level (LA classification)

LA classification	n (%)
grade A	114 (52,3%)
grade B	77 (35,3%)
grade C	24 (11,0%)
grade D	3 (1,4%)
Total	218 (100%)

**TABLE 2** – Symptom resolution in patients treated with esomeprazol 40 mg od (per protocol analysis)

Severity	Baseline n = 218	Week 2 n = 217	Week 4 n = 215	Week 8 n = 35	Week 4 + 8 n = 215
<b>Heartburn (%)*</b>					
none	14 (6.4)	175 (80.6)	193 (89.8)	33 (94.3)	196 (91.2)
mild	42 (19.3)	31 (14.3)	19 (8.8)	-	15 (7.0)
moderate	111 (51.0)	10 (4.6)	3 (1.4)	1 (2.9)	3 (1.4)
severe	50 (22.9)	1 (0.5)	-	1 (2.9)	1 (0.5)
N/A	1 (0.5)	-	-	-	-
<b>Acid regurgitation (%)**</b>					
none	63 (28.9)	178 (82.0)	193 (89.8)	34 (97.1)	197 (91.6)
mild	56 (25.7)	28 (12.9)	19 (8.8)	1 (2.9)	16 (7.4)
moderate	72 (33.0)	9 (4.1)	3 (1.4)	-	2 (0.9)
severe	26 (11.9)	2 (0.9)	-	-	-
N/A	1 (0.5)	-	-	-	-

Friedman test(baseline, weeks 2 e 4):

\*  $\chi^2_2 = 334.34 -P < 0.000001$ ,

\*\*  $\chi^2_2 = 221.26 -P < 0.00001$

Of the 193 patients whose heartburn had disappeared at the end of week 4, 163 (84.5%) had healed mucosal breaks at endoscopy. At week 8, 196 patients did not have heartburn and of those, 187 (95.4%) did not present esophagitis at endoscopy.

**Safety and tolerability**

All the patients who took at least one dose of esomeprazole 40 mg were included in the ITT analysis of safety and tolerability.

At least one adverse event was reported by 37 (16.3%) of the treated patients, related or not to esomeprazole (Table 3) and 3 (1.3%) patients had to be withdrawn from the treatment.

There were no serious adverse events that were life threatening, nor clinically important changes through the study.

At least one adverse event, drug related or not, was observed in 37 (16.3%) patients, with the majority being of mild intensity (75.9%) and the most frequent (although observed in only 4.4%) being headache.

**TABLE 3** – Main adverse events that occurred during esomeprazole treatment

Event	n	%
headache	10	4.4
diarrhea	6	2.6
epigastric pain	6	2.6
nausea	4	1.8
flu	3	1.3

**DISCUSSION**

Gastroesophageal reflux disease (GERD) results from frequent and prolonged contact of gastric contents with esophageal mucosa. Hydrochloric acid (HCl) is the main responsible for the aggression to esophageal mucosa and for symptom severity<sup>(3, 12, 14, 15)</sup>, which has negative impact on patients' quality of life.

The main purpose of GERD treatment is to neutralize HCl production, maintaining intragastric pH above 4.0 for a period longer than 16 hours<sup>(2)</sup>. When intragastric pH is bellow 4.0, pepsinogen activation is an aggravating factor, not only for the occurrence of mucosal breaks, but also for symptom intensity<sup>(12, 23)</sup>.

PPIs are the most potent and effective drugs available for the sustained control of gastric pH, and thus, are considered first line treatment for GERD<sup>(6, 10)</sup>. They allow quick symptom resolution and high healing rates of mucosal breaks<sup>(4, 5, 8)</sup>. Esomeprazole, an S isomer of omeprazole, is a step ahead in relation to previous PPIs, and has a smaller first pass hepatic metabolism and a reduced systemic clearance, with a higher and more persistent plasmatic concentration<sup>(11)</sup>. This increase in bioavailability results in a more intense and more prolonged suppression of gastric acidity, offering a perspective of greater efficacy in the treatment of acid related diseases<sup>(16)</sup>, particularly GERD.

Our results in 218 patients with erosive esophagitis confirm the high efficacy of esomeprazole (Nexium®) in providing symptom relief and healing of mucosal breaks in patients with GERD.

Most of the studied patients (77.5%) had a clinical history of GERD lasting for over 1 year, and 40% of them had had GERD for more than 5 years, which confirms the chronic character of this disease.

Regardless the analysis criteria used, the healing rate was highly satisfactory, that is, 82.5% (ITT) and 83.7% (PP) at week 4 and 93.6% (ITT) and 94.9% (PP) at week 8. These values were similar to values already published in other studies<sup>(15, 22)</sup>.

In patients with grades A and B esophagitis, the healing rates observed at week 4 were 89.3% e 80.5%, respectively; at week 8, they were 97.3% e 96%, respectively. This meant a therapeutic gain of 8% in grade A and 15.5% in grade B. Thus, for every 25 patients treated with esomeprazole 40 mg, only one will not heal after 8 weeks. These data suggest that the length of treatment of GERD with esomeprazole should be 8 weeks, preferably, and also, that there is no need for a control endoscopy, according to what has been suggested in recent consensus meetings<sup>(6, 18)</sup>.

Of the patients with esophagitis grade C, 78.2% were healed by the end of week 4 and 86.9% at week 8. These data suggest that due to its higher intensity, grade C esophagitis needs a longer period of treatment or, higher doses (double, for instance) to achieve healing, according to some authors<sup>(1, 19, 24)</sup>. Due to the small number of patients studied by us (23 with grade C and 3 with grade D esophagitis) it was not possible to reach definitive conclusions.

Surprisingly, the male patients had twice less chance of healing at the end of week 4 than the female patients ( $P = 0.049$ ). This difference disappeared by the end of the treatment. Smoking, alcohol consumption and the use of NSAIDS do not seem related, since they have not been shown as risk or protection factors in this study.

Quality of life is decreased in patients with GERD due to symptom intensity related to acid reflux<sup>(7)</sup>, and its control is the primary objective in the treatment of this condition<sup>(24)</sup>.

In comparative studies with omeprazole, it can be observed that esomeprazole allows a quicker and more prolonged resolution of heartburn<sup>(15, 22)</sup>. The promptness of symptom disappearance with esomeprazole is, undoubtedly, of utmost importance to the patient, since it represents an improvement in quality of life<sup>(7)</sup>, allowing an earlier return to everyday activities. In our study, esomeprazole allowed a significant control of symptoms, with a complete remission of heartburn in 80.5% of patients after 14 days of treatment, and 91.2% at week 8.

Symptom disappearance is a sensitive indicator of adequate control of esophagitis<sup>(7, 24)</sup>. Our observations confirm these data, for 84.5% (163/193) and 95.4% (187/196) who did not have heartburn at weeks 4 and 8, respectively, did not have mucosal breaks.

Of the 22 patients who had heartburn at week 4, 17(77.3%) were already healed at endoscopy, the majority (12) having been classified as grade A esophagitis at inclusion. Symptom permanence can result from an increased sensitivity of the mucosa to small quantities of acid or, from the fact that the symptom is not dependent on acid<sup>(9)</sup>.

Tolerability and safety of esomeprazole were excellent in the short run, and the adverse events more frequently observed were headache (4.4%), diarrhea (2.6%), epigastric pain (2.6%) and nausea (1.8%) and none required treatment interruption.

## CONCLUSION

This study's results show that esomeprazole is a safe drug, with few side effects, allowing significant healing rates of esophageal mucosal breaks in patients with GERD. Symptom relief was significant, leading to an improvement in quality of life.

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Silva EP, Nader F, Quilici FA, Eisig JN, Zaterka S, Meneghelli U. Avaliação clínica e endoscópica da doença do refluxo gastroesofágico em pacientes tratados com esomeprazol. *Arq Gastroenterol* 2003;40(4):262-267.

**RESUMO – Racional** – O esomeprazol, um isômero-S do omeprazol, é o primeiro inibidor da bomba de prótons desenvolvido como um isômero ótico e tem apresentado altos índices de cicatrização na esofagite erosiva. **Objetivo** – Avaliar a eficácia e tolerabilidade do esomeprazol em pessoas com esofagite erosiva, classificada de acordo com a classificação de Los Angeles. **Material e Métodos** – Duzentos e dezoito pacientes com esofagite de refluxo confirmada por endoscopia foram incluídos num estudo multicêntrico, aberto, no Brasil. Todos receberam 40 mg de esomeprazol, uma vez ao dia, por um período de 4 semanas. Aqueles que não cicatrizaram a esofagite ao final da 4ª semana continuaram o tratamento por mais 4 semanas. O objetivo primário de eficácia foi a taxa de cicatrização ao final da 4ª e 8ª semanas. Os objetivos secundários foram o número de pacientes com resolução dos sintomas ao final da 4ª semana, o número de dias com resolução sustentada dos sintomas, o número de dias e noites livres de sintomas e a segurança e tolerabilidade da droga. **Resultados** – As taxas de cicatrização nas semanas 4 e 8 foram 82% (IC: 77,4%–87,6%) e 96,1% (IC: 93,5%–98,8%), respectivamente. Noventa e nove por cento dos pacientes tiveram resolução da pirose retroesternal na 2ª semana. Os eventos adversos mais comuns foram cefaléia (4%), diarreia (2,6%) e dor epigástrica (2,2%). **Conclusão** – Para o período estudado, o esomeprazol mostrou ser uma droga segura e bem tolerada, alcançando taxas significativas de cicatrização das soluções de continuidade da mucosa em pacientes com esofagite erosiva, independente do seu grau, de acordo com a classificação de Los Angeles. Mostrou-se, também, eficiente em rapidamente aliviar os sintomas decorrentes da doença do refluxo gastroesofágico.

**DESCRITORES** – Refluxo gastroesofágico. Esofagite péptica. Azia. Bombas de próton. Esomeprazol.

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