



Comparison of four proton pump inhibitors for the short-term treatment of esophagitis in elderly patients

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Abstract

AIM: To compare efficacy and tolerability of four proton pump inhibitors (PPIs) commonly used in the short-term therapy of esophagitis in elderly patients.

METHODS: A total of 320 patients over 65 years with endoscopically diagnosed esophagitis were randomly assigned to one of the following treatments for 8 wk: (1) omeprazole 20 mg/d; (2) lansoprazole 30 mg/d; (3) pantoprazole 40 mg/d, or (4) rabeprazole 20 mg/d. Major symptoms, compliance, and adverse events were recorded. After 8 wk, endoscopy and clinical evaluation were repeated.

RESULTS: Per protocol and intention to treat healing rates of esophagitis were: omeprazole = 81.0% and 75.0%, lansoprazole = 90.7% ($P = 0.143$ vs omeprazole) and 85.0%, pantoprazole = 93.5% ($P = 0.04$ vs omeprazole) and 90.0% ($P = 0.02$ vs omeprazole), rabeprazole = 94.6% ($P = 0.02$ vs omeprazole) and 88.8% ($P = 0.04$ vs omeprazole). Dividing patients according to the grades of esophagitis, omeprazole was significantly less effective than the three other PPIs in healing grade 1 esophagitis (healing rates: 81.8% vs 100%, 100% and 100%, respectively, $P = 0.012$). Pantoprazole and rabeprazole (100%) were more effective vs omeprazole (89.6%, $P = 0.0001$)

and lansoprazole (82.4%, $P = 0.0001$) in decreasing heartburn. Pantoprazole and rabeprazole (92.2% and 90.1%, respectively) were also more effective vs lansoprazole (75.0%, $P < 0.05$) in decreasing acid regurgitation. Finally, pantoprazole and rabeprazole (95.2% and 100%) were also more effective vs lansoprazole (82.6%, $P < 0.05$) in decreasing epigastric pain.

CONCLUSION: In elderly patients, pantoprazole and rabeprazole were significantly more effective than omeprazole in healing esophagitis and than omeprazole or lansoprazole in improving symptoms. *H. pylori* infection did not influence the healing rates of esophagitis after a short-term treatment with PPI.

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Key words: Elderly; Esophagitis; Proton pump inhibitors

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INTRODUCTION

Old age is known to be a significant risk factor for severe esophagitis^[1,2], chronic relapses^[3], as well as severe complications of the disease^[1,4]. Clinical features of esophagitis in elderly patients are quite different from those of young or adult subjects. Indeed, elderly patients present less frequently the typical symptoms of heartburn, acid regurgitation and/or epigastric pain. Conversely, the prevalence of other non-specific symptoms, i.e. anorexia, weight loss, anaemia, and/or vomiting significantly increases with age^[2]. Thus, the diagnosis of reflux esophagitis may be missed in the elderly, and a substantial number of patients may suffer subclinical relapses of the disease^[5].

The treatment of esophagitis is based on gastric acid suppression with antisecretory drugs. Proton pump inhibitors (PPIs) are widely used and their effectiveness and safety have been demonstrated also in patients of old age^[6]. Currently, five PPIs are available on the market:

omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole. Some age-associated differences in pharmacokinetics and pharmacodynamics of the PPIs have been reported^[7]. However, it is unknown if these differences are associated with different clinical effects, i.e. healing rates and/or symptom relief, particularly in older patients.

The aim of this study was to compare the clinical efficacy and tolerability of four PPIs used for the short-term therapy of esophagitis in elderly patients.

MATERIALS AND METHODS

Study design

This was an open, single-centre, randomized study including elderly subjects that consecutively underwent an upper gastrointestinal endoscopy. It was conducted according to the Declaration of Helsinki and the guidelines for Good Clinical Practice. All patients gave their informed consent prior to participation in the study.

The inclusion criteria were: (1) age 65 years or over and (2) endoscopic diagnosis of esophagitis grade I to IV according to the Savary-Miller classification^[8]. Major exclusion criteria were: history of Zollinger-Ellison syndrome, pyloric stenosis, previous surgery of the esophagus and/or gastrointestinal tract (except for appendectomy and cholecystectomy), and gastrointestinal malignancy. Patients were excluded if they had received antacids, sucralfate, prokinetics, H₂-blockers, and/or PPIs for more than 7 d in the four weeks prior to the start of the study.

Assessments

At the initial visit, demographic data, medical history, clinical symptoms, non-steroidal anti-inflammatory drug (NSAID) use, and antisecretory therapy were recorded. At study entry, an endoscopy was performed to diagnose acute esophagitis (inclusion criteria). After 2 mo of treatment, endoscopy was repeated to evaluate healing of acute esophagitis. All patients were examined during therapy to record side effects and to count tablets. Compliance was defined as "good" when more than 90% of the tablets had been taken by the patients. Adverse events were rated by the investigator as not related, unlikely, possibly related, or likely related to the medication.

Endoscopic diagnoses

Reflux esophagitis was endoscopically defined by epithelial defects according to the Savary-Miller criteria^[8] and classified as grade I: non-confluent erosions; grade II: confluent erosions; grade III: lesions extending to the entire circumference of the lower esophagus; and grade IV: deep ulcer or esophagitis with complications, i.e. stenosis and/or hemorrhagic lesions. Patients with diffuse erythema and/or fragility of the lower esophagus were not included. Hiatus hernia was diagnosed when the Z-line and the gastric folds extended 2 cm or more above the diaphragmatic hiatus^[9]. Patients with Barrett's esophagus were not included unless erosive esophagitis was also present.

Histology and *H. pylori* infection

During endoscopy, six gastric biopsies were taken from

both the antrum (three biopsies), and from the body (three biopsies). Two antral and two body biopsies were used for histological analysis, while one from each site was used for the rapid urease test (CLO test, Delta West Pty Ltd, Western Australia). For histological examination, biopsy specimens were immediately fixed in buffered neutral formalin and embedded in paraffin. Sections were stained with hematoxylin-eosin and modified Giemsa for the detection of *H. pylori* and evaluated according to the Sydney classification^[10]. Patients were considered *H. pylori* negative if both histology and the rapid urease test were negative; patients were considered *H. pylori* positive if either their histology or rapid urease test, or both, were positive for Hp infection^[11].

Symptomatology

Symptoms were assessed during a structured interview. The patient was questioned about the principal symptoms, i.e. acid regurgitation, heartburn, and other symptoms of reflux esophagitis, i.e. epigastric pain, dysphagia, vomiting, and anaemia (loss of ≥ 3 grams of haemoglobin during the last 3 mo) and expressed as absent/present.

Treatments

Patients included in the study were consecutively assigned to one of the following regimens for two months: omeprazole 20 mg once daily, lansoprazole 30 mg once daily; pantoprazole 40 mg once daily, or rabeprazole 20 mg once daily. Randomization was performed by a computer-generated list in blocks of four with a 1:1:1:1 ratio. All PPIs were taken in the morning fasting just before breakfast. Patients who resulted *H. pylori* positive were treated with the PPI plus two antibiotics i.e., amoxicillin 1g twice daily and claritromycin 250 mg twice daily or metronidazole 250 mg four times daily for 7 d^[12].

Statistical analysis

Statistical analysis was performed by means of the SPSS version 13. Results were evaluated using both "per protocol" (PP) and "intention-to-treat" (ITT) analyses; the 95% confidence intervals (95% CI) were also calculated. The ITT population was defined as all patients initially enrolled who had taken at least one dose of study medication. Statistical analysis was performed using the χ^2 test (comparison of outcomes with the treatments) and Fisher exact test (healing rates related to *H. pylori* infection, symptoms). All p values were two-tailed with statistical significance indicated by a value of $P < 0.05$.

RESULTS

A total of 320 consecutive elderly (156 males and 164 females, mean age 77.4 ± 7.9 years, range from 65 to 93 years) with an endoscopic diagnosis of acute esophagitis, grades 1 to 4 according to the Savary-Miller classification, were included in the study. Demographic and clinical characteristics of patients are shown in Table 1.

Nineteen patients (5.9% of the total population) dropped-out from the study due to: adverse events (2 patients), low compliance (11 patients), and refusal of endoscopy after two months of treatment (6 patients).

Table 1 Demographic and clinical characteristics of the study population

	All patients	Omeprazole	Lansoprazole	Pantoprazole	Rabeprazole
Number of patients	320	80	80	80	80
Males/Females	156/164	44/36	36/44	39/41	37/43
Mean age (yr)	77.4 ± 7.9	77.9 ± 6.4	77.8 ± 9.2	76.8 ± 6.1	77.0 ± 9.5
Age Range (yr)	65-93	65-93	65-92	65-88	65-93
Esophagitis <i>n</i> (%)					
-Grade I°	96 (30.0)	34 (42.5)	26 (32.5)	20 (25.0)	16 (20.0)
-Grade II°	152 (47.5)	27 (33.8)	33 (41.3)	42 (52.5)	50 (62.5)
-Grade III°-IV°	72 (22.5)	19 (23.8)	21 (26.2)	18 (22.5)	14 (27.6)
Hiatus hernia <i>n</i> (%)	194 (60.6)	43 (53.8)	48 (60.0)	50 (62.5)	53 (66.3)
<i>H. pylori</i> infection <i>n/n</i> (%)	202/306 (66.0)	52/76 (68.4)	61/76 (80.3)	51/77 (66.2)	38/77 (49.3)
NSAIDs/Aspirin use <i>n</i> (%)	78 (24.4)	18 (22.5)	17 (21.3)	26 (32.5)	17 (21.3)

Table 2 Healing rates, drop-out patients, and side effects in elderly patients divided according to the different PPI regimens

Regimen	No. of patients	Per protocol analysis		Intention to treat analysis		Drop outs	Side effects
		Cure rates % (N° of patients)	95% CI	Cure rates % (N° of patients)	95% CI		
Omeprazole	80	81.0 60/74	72.0-89.9	75.0 60/80	65.0-84.0	6 (7.5)	1
Lansoprazole	80	90.7 68/75	84.1-97.2	85.0 68/80	77.0-92.8	5 (6.3)	1
Pantoprazole	80	93.5 ¹ 72/77	87.9-99.0	90.01 72/80	83.4-96.5	3 (3.8)	1
Rabeprazole	80	94.6 ² 71/75	89.4-99.7	88.82 71/80	81.5-95.6	5 (6.3)	1
Total	320	90.0 271/301	86.6-93.4	84.7 271/320	80.7-88.6	19 (5.9)	4 (1.4)

¹Pantoprazole vs Omeprazole: PP analysis: $P = 0.039$, ITT analysis $P = 0.022$; ²Rabeprazole vs Omeprazole: PP analysis: $P = 0.022$, ITT analysis $P = 0.040$.

Table 3 Healing rates of esophagitis after eight weeks of PPI treatment in elderly patients with esophagitis divided according to the grades of severity of esophagitis according to the Savary-Miller classification

Severity grades	Omeprazole		Lansoprazole		Pantoprazole		Rabeprazole	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
I grade ^a	27/33	81.8	25/25	100	20/20	100	14/14	100
II grade ^c	18/22	81.8	28/29	96.5	36/40	90.0	46/48	95.8
III-IV grades ^e	15/19	78.9	15/21	71.4	16/17	94.1	11/13	84.6

^a $P = 0.012$; ^c $P = 0.215$; ^e $P = 0.458$.

Among the 301 patients who completed the study, 271 had healed esophagitis and 30 were unhealed. The overall PP and ITT healing rates of esophagitis were 90.0% (95% CI = 86.6-93.4) and 84.7% (95% CI = 80.7-88.6), respectively. Dividing patients according to treatments, the PP and ITT healing rates of esophagitis were: omeprazole = 81.0% and 75.0%, lansoprazole = 90.7% ($P = 0.143$ vs omeprazole) and 85% ($P = 0.167$ vs omeprazole), pantoprazole = 93.5% ($P = 0.04$ vs omeprazole) and 90.0% ($P = 0.02$ vs omeprazole), rabeprazole = 94.6% ($P = 0.02$ vs omeprazole) and 88.8% ($P = 0.04$ vs omeprazole) respectively (Table 2). Dividing patients according to the grades of esophagitis, a significantly lower healing rate was observed in patients with grade 1 esophagitis treated with omeprazole com-

pared to patients treated with lansoprazole, pantoprazole, or rabeprazole (healing rates: 81.8% vs 100%, 100% and 100%, respectively, $P = 0.012$). Omeprazole was less effective than the three other PPIs also in patients with grade 2 esophagitis (healing rates: 81.8% vs 96.5% vs 90% vs 95.8%, respectively) and than pantoprazole and rabeprazole in grade 3-4 esophagitis (healing rates: 78.9% vs 94.1% vs 84.6%, respectively); probably due to the low number of patients, however, the differences were not statistically significant (Table 3).

At baseline 188 of 288 patients (65.3%) were identified as infected with *H. pylori* in the gastric mucosa. No differences were observed in the healing rates of esophagitis between *H. pylori* positive and *H. pylori* negative patients (90.4% vs 89.0%, $P = \text{NS}$). After two months, 149 of 188 (79.3%) who were treated with triple therapies for one week were *H. pylori* negative while 39 patients (20.7%) remained *H. pylori* positive after treatment. No significant differences in the healing rates of esophagitis were observed between successfully and unsuccessfully treated *H. pylori* patients (negative *H. pylori* vs still-positive after treatment: 89.9% vs 92.3%, $P = \text{NS}$) (Table 4).

After two months of PPI treatment, a significant reduction of symptoms as compared to baseline was observed both in healed and in unhealed patients. While heartburn improved significantly more effectively in healed patients than unhealed patients (rates of heartburn

Table 4 Healing rates of esophagitis in elderly patients divided according to *H pylori* infection

	Omeprazole (<i>n</i> = 71)	Lansoprazole (<i>n</i> = 71)	Pantoprazole (<i>n</i> = 74)	Rabeprazole (<i>n</i> = 72)	All (<i>n</i> = 288)
<i>H pylori</i> positive <i>n</i> = 188	38/49 77.6%	54/57 94.7%	45/48 93.8%	33/34 97.1%	170/188 90.4%
<i>H pylori</i> negative <i>n</i> = 100	19/22 86.4%	11/14 78.6%	24/26 92.3%	35/38 92.1%	89/100 89.0%
	Omeprazole (<i>n</i> = 49)	Lansoprazole (<i>n</i> = 57)	Pantoprazole (<i>n</i> = 48)	Rabeprazole (<i>n</i> = 34)	All (<i>n</i> = 188)
<i>H pylori</i> cured <i>n</i> = 149	24/32 75.0%	43/46 93.5%	39/42 92.6%	28/29 96.6%	134/149 89.9%
<i>H pylori</i> still-positive <i>n</i> = 39	14/17 82.4%	11/11 100%	6/6 100%	5/5 100%	36/39 92.3%

Table 5 Symptoms in elderly patients with esophagitis before and after two months of PPI therapy

Symptoms	Before therapy	After therapy		
	All	Healed	Unhealed	Healed vs unhealed
	<i>n</i> = 301	<i>n</i> = 271	<i>n</i> = 30	<i>P</i> value
Heartburn (<i>n</i> , %)	131 (43.5)	9 (3.3)	6 (20.0)	0.0001
Acid regurgitation (<i>n</i> , %)	39 (13.0)	4 (1.5)	0 (0.0)	0.874
Epigastric pain (<i>n</i> , %)	143 (47.5)	10 (3.7)	2 (6.6)	0.781
Dysphagia (<i>n</i> , %)	10 (3.3)	0 (0.0)	0 (0.0)	--
Vomiting (<i>n</i> , %)	60 (19.9)	0 (0.0)	0 (0.0)	--
Anaemia (<i>n</i> , %)	28 (9.3)	0 (0.0)	0 (0.0)	--

disappearance = 96.7% *vs* 80%, *P* = 0.001), other symptoms improved significantly both in healed and unhealed patients (Table 5). The rates of symptom disappearance in the four treatment groups, i.e. omeprazole, lansoprazole, pantoprazole, and rabeprazole, were 86.9%, 82.4%, 100%, and 100% for heartburn, 100%, 75.0%, 92.9%, and 90.1% for acid regurgitation, and 95.0%, 82.6%, 95.2, and 100% for epigastric pain, respectively (Table 6). Comparisons between the four PPIs demonstrated that pantoprazole and rabeprazole were more effective than omeprazole (100% *vs* 86.9, and 100% *vs* 86.9%, respectively, *P* < 0.05) and than lansoprazole (100% *vs* 82.4%, *P* = 0.0001 and 100% *vs* 82.4%, *P* = 0.005, respectively) in decreasing heartburn. Lansoprazole was less effective in improving acid regurgitation and epigastric pain than omeprazole (*P* = 0.0001, *P* = 0.033, respectively), pantoprazole (*P* = 0.005, *P* = 0.028, respectively), and rabeprazole (*P* = 0.026, *P* = 0.0001, respectively) (Table 6).

All four PPIs were well tolerated. Adverse events were reported only by four patients (1.3%): urticaria, glossitis, nausea, and headache. Two patients discontinued therapy due to treatment-related side effects. No significant differences were found in the prevalence of adverse events among the four treatment groups.

DISCUSSION

This study demonstrates that in patients over 65 years PPI therapy for 2 mo is very effective in healing acute esophagitis. The pooled ITT and PP healing rates were 84.7% and 90.0%, respectively. These are comparable to previous data from double-blind studies carried out in non-elderly sub-

Table 6 Symptom disappearance after therapy in elderly patients divided according to PPI regimens %

	Omeprazole	Lansoprazole	Pantoprazole	Rabeprazole
Heartburn	86.9 ^a	82.4 ^{b,d}	100	100
Acid regurgitation	100	75.0 ^{c,f}	92.2	90.1
Epigastric pain	95	82.6 ^{e,h}	95.2	100
Dysphagia	100	100	100	100
Vomiting	100	100	100	100
Anemia	100	100	100	100

^a*P* < 0.05 Omeprazole *vs* Pantoprazole and Omeprazole *vs* Rabeprazole;

^b*P* = 0.0001 Lansoprazole *vs* Pantoprazole; ^d*P* = 0.005 Lansoprazole *vs* Rabeprazole; ^f*P* = 0.0001 Lansoprazole *vs* Omeprazole; ^c*P* < 0.05 Lansoprazole *vs* Pantoprazole, Lansoprazole *vs* Rabeprazole; ^e*P* < 0.05 Lansoprazole *vs* Omeprazole and Lansoprazole *vs* Pantoprazole; ^h*P* = 0.0001 Lansoprazole *vs* Rabeprazole.

jects treated for 8 wk with omeprazole 20 mg or lansoprazole 30 mg daily^[13], pantoprazole 40 mg daily^[14], or rabeprazole 20 mg daily^[15]. In this population of older patients, pantoprazole and rabeprazole were significantly more effective in healing esophagitis than omeprazole. Moreover, pantoprazole and rabeprazole were more effective than lansoprazole and omeprazole in improving heartburn, and than lansoprazole in improving acid regurgitation and epigastric pain.

Previous studies were focused on potential discrepancies in efficacy among the different PPIs used for treatment of reflux esophagitis. While some previous reports suggest that acid-suppressive effect of the four PPIs is different on the basis of equivalent molecular dose, clinical studies that support such a different efficacy in healing esophagitis or improving symptoms of GERD on a PPI-equivalent molecular doses are lacking. A meta-analysis of 38 studies evaluating acute therapy of esophagitis reported that the PPIs were superior to ranitidine and placebo in healing erosive esophagitis, without significant differences in efficacy between omeprazole 20 mg daily and lansoprazole 30 mg daily, or pantoprazole 40 mg daily, or rabeprazole 20 mg daily^[16]. Similarly, in another meta-analysis, no differences in healing rates of esophagitis were reported between standard doses of lansoprazole, pantoprazole, rabeprazole, and omeprazole^[17]. More recently, a meta-analysis of eleven studies with 23 treatment arms reported no significant difference in the two-month healing rates of esophagitis between omeprazole 20 mg daily (*n* = 3.137

patients, pooled healing rate = 84.5%) and other PPIs, including lansoprazole, pantoprazole, rabeprazole, and esomeprazole at standard doses ($n = 3.397$ patients, pooled healing rate = 89.4%)^[18]. However, none of the studies included in these meta-analyses were carried out specifically in elderly patients. Indeed, to our knowledge, this is the first study that compared the efficacy of different PPIs in curing esophagitis and improving symptoms in elderly patients.

Why pantoprazole and rabeprazole were more effective than omeprazole in healing esophagitis and than omeprazole and lansoprazole in improving symptoms in elderly patients is not clear. Very recently it was suggested that omeprazole has considerable potential for drug interactions since it has high affinity for the cytochrome CYP2C19 and a lower affinity for the cytochrome CYP3A4, while pantoprazole, and maybe rabeprazole, appear to have lower potential for interactions with other drugs^[19]. Data from this study cannot confirm this hypothesis since no information was collected on concomitant treatments, with the exception of NSAID and aspirin. Interestingly, a previous multicentre study, carried out in 164 elderly patients with esophagitis reported that a 2-month therapy with pantoprazole 40 mg/d was highly effective in healing reflux esophagitis (81.1% and 93.7% by ITT and PP analyses, respectively), although the majority of patients received other drugs for concomitant illnesses (76.2% of patients), without that the presence of concomitant treatments adversely affected the efficacy or tolerability of pantoprazole^[20].

Very recently, a systematic review of randomized controlled trials in patients with reflux esophagitis reported that esomeprazole demonstrated higher short-term healing rates when compared with standard dose PPIs^[21]. While no data were reported comparing rabeprazole 20 mg to esomeprazole 40 mg, two studies included in the analysis compared pantoprazole 40 mg daily to esomeprazole 40 mg daily. This comparison found no differences in healing rates between the two treatments both in patients with moderate-severe esophagitis, i.e. Los Angeles grades B and C (healing rates with pantoprazole = 83.2% *vs* esomeprazole = 80.7%, $P = \text{NS}$)^[22] and in the subgroup of 550 patients aged 65 years or over included in the large multicenter EXPO study (healing rates with pantoprazole = 87.4% *vs* esomeprazole = 90.4%, $P = \text{NS}$)^[23]. Unfortunately, information on esomeprazole was not available for the present study.

In this elderly population, *H. pylori* infection did not influence the response to short-term treatment with PPIs. This finding confirms the data of previous studies performed in elderly populations showing that *H. pylori* infection does not have a negative effect on healing of esophagitis, nor does it worsen reflux symptoms at two-month follow up^[24]. It is also evident from our study that *H. pylori* eradication does not affect the cure rate of esophagitis during a two-month course of PPI, in agreement with a recent multicentre randomized study also performed in elderly patients^[25].

In conclusion, PPIs are highly effective and well tolerated in curing gastroesophageal reflux disease in elderly patients. Pantoprazole and rabeprazole were significantly

more effective than omeprazole in healing esophagitis and than omeprazole or lansoprazole in improving symptoms. *H. pylori* infection does not influence the healing rates of esophagitis after a short-term treatment with PPI.

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