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

Alberto Pilotto, Mariilisa Franceschi, Gioacchino Leandro, Carlo Scarcelli, Luigi Piero D'Amбросio, Francesco Paris, Vito Annese, Davide Seripa, Angelo Andriulli, Francesco Di Mario

Alberto Pilotto, Mariilisa Franceschi, Carlo Scarcelli, Luigi Piero D'Amбросio, Francesco Paris, Davide Seripa, Geriatric Unit, Department of Medical Sciences & Gerontology and Geriatrics Laboratories, Department of Research, IRCCS “Casa Sollievo della Sofferenza”, San Giovanni Rotondo (FG), Italy

Marilisa Franceschi, Francesco Di Mario, Gastroenterology Department, University of Parma, Parma, Italy

Gioacchino Leandro, Gastroenterology Unit, IRCCS De Bellis, Castellana Grotte, Bari, Italy

Angelo Andriulli, Vito Annese, Gastroenterology Unit, Department of Medical Sciences, IRCCS “Casa Sollievo della Sofferenza”, San Giovanni Rotondo (FG), Italy

Supported by “Ministero della Salute”, IRCCS Research Program, Ricerca Corrente 2006-2008, Linea n. 2 “Malattie di rilevanza sociale”

Correspondence to: Alberto Pilotto, Geriatric Unit, IRCCS “Casa Sollievo della Sofferenza”, Viale Cappuccini, 71013 San Giovanni Rotondo (FG), Italy. alberto.pilotto@operapadrepio.it

Telephone: +39-882-410271 Fax: +39-882-410271

Received: 2007-05-16 Accepted: 2007-06-04

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.

@2007 WJG. All rights reserved.

Key words: Elderly; Esophagitis; Proton pump inhibitors

Pilotto A, Franceschi M, Leandro G, Scarcelli C, D’Amбросio LP, Paris F, Annese V, Seripa D, Andriulli A, Di Mario F. Comparison of four proton pump inhibitors for the short-term treatment of esophagitis in elderly patients. World J Gastroenterol 2007; 13(33): 4467-4472

http://www.wjgnet.com/1007-9327/13/4467.asp

INTRODUCTION

Old age is known to be a significant risk factor for severe esophagitis, chronic relapses, as well as severe complications of the disease. 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. 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. 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. 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[11]. 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, protonics, 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[12] 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[8]. 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[13]. 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[14].

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 clarithromycin 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 χ2 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).
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 severity of esophagitis, a significantly lower healing rate was observed in patients with grade 1 esophagitis treated with omeprazole compared 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 no 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 = 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 = 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
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 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%): orticaria, 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 subjects 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 pantoprazole 20 mg daily (n = 3.137

---

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

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

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

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

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

| Treatment            | Omeprazole | Lansoprazole | Pantoprazole | Rabeprazole |
|----------------------|------------|--------------|--------------|-------------|
| Heartburn            | 86.9%      | 82.4%        | 100%         | 100%        |
| Acid regurgitation   | 100%       | 79.6%        | 92.2%        | 90.1%       |
| Epigastric pain      | 95%        | 82.6%        | 95.2%        | 100%        |
| Dysphagia            | 100%       | 100%         | 100%         | 100%        |
| Vomiting             | 100%       | 100%         | 100%         | 100%        |
| Anaemia              | 100%       | 100%         | 100%         | 100%        |

*P < 0.05 Omeprazole vs Pantoprazole and Omeprazole vs Rabeprazole; ^P = 0.0001 Lansoprazole vs Pantoprazole; ^P = 0.005 Lansoprazole vs Rabeprazole; ^P = 0.0001 Lansoprazole vs Omeprazole; ^P < 0.05 Lansoprazole vs Pantoprazole, Lansoprazole vs Rabeprazole; ^P < 0.05 Lansoprazole vs Omeprazole and Lansoprazole vs Pantoprazole; ^P = 0.0001 Lansoprazole vs Rabeprazole.

www.wjgnet.com
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%)[10]. 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[3].

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[20]. 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 esomperazole 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 = NS)[21] 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 = NS)[22]. 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[23]. 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[24].

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.

REFERENCES

1. Richter JE. Gastroesophageal reflux disease in the older patient: presentation, treatment, and complications. *Am J Gastroenterol* 2000; 95: 368-373
2. Pilotto A, Franceschi M, Leandro G, Scarcelli C, D’Ambrosio LP, Seripa D, Perri F, Niro V, Paris F, Andriulli A, Di Mario F. Clinical features of reflux esophagitis in older people: a study of 840 consecutive patients. *J Am Geriatr Soc* 2006; 54: 1537-1542
3. Pilotto A, Franceschi M, Leandro G, Novello R, Di Mario F, Valerio G. Long-term clinical outcome of elderly patients with reflux esophagitis: a six-month to three-year follow-up study. *Am J Ther* 2002; 9: 295-300
4. Zimmerman J, Shohat V, Tsvang E, Arnon R, Safadi R, Wengrower D. Esophagitis is a major cause of upper gastrointestinal hemorrhage in the elderly. *Scand J Gastroenterol* 1997; 32: 906-909
5. Maekawa T, Kinoshita Y, Okada A, Fukui H, Waki S, Hassan S, Matsushima Y, Kawanami C, Kishi K, Chiba T. Relationship between severity and symptoms of reflux oesophagitis in elderly patients in Japan. *J Gastroenterol Hepatol* 1998; 13: 927-930
6. Pilotto A, Franceschi M, Paris F. Recent advances in the treatment of GERD in the elderly: focus on proton pump inhibitors. *Int J Clin Pract* 2005; 59: 1204-1209
7. Klötz U. Effect of aging on the pharmacokinetics of gastrointestinal drugs. In: Aging and the Gastrointestinal Tract. Pilotto A, Malfertheiner P, Holt P, editors. Switzerland: Karger Press Basel, 2003: 28-39
8. Ollyo JB, Lang F, Fontelliet CH, Bressard E. Savary-Miller’s new endoscopic grading of reflux-oesophagitis: a simple, reproducible, logical, complete and useful classification. *Gastroenterology* 1990; 98 Suppl 1: A-100
9. Kaul B, Petersen H, Myrvold HE, Grette K, Raysland P, Halvorsen T. Hiatus hernia in gastroesophageal reflux disease. *Scand J Gastroenterol* 1986; 21: 31-34
10. Misiewicz JJ, Tytgrat GNJ, Goodwin CS et al. The Sydney system: a new classification of gastritis. Working Party Reports of the 9th World Congress of Gastroenterology, Melbourne: Blackwell Scientific, 1990: 1-10
11. Pilotto A, Salles N. Helicobacter pylori infection in geriatrics. *Helicobacter* 2002; 7 Suppl 1: 56-62
12. Pilotto A, Franceschi M, Perri F, Orsitto G, Di Mario F. Treatment options for *H pylori* infection in the elderly. *Aging Health* 2006; 2: 661-668
13. Sharma VK, Leonidias GI, Howden CW. Meta-analysis of randomized controlled trials comparing standard clinical doses of omeprazole and lansoprazole in erosive oesophagitis. *Aliment Pharmacol Ther* 2001; 15: 227-231
14. Holtmann G, Cain C, Malfertheiner P. Gastric Helicobacter pylori infection accelerates healing of reflux esophagitis during treatment with the proton pump inhibitor pantoprazole. *Gastroenterology* 1999; 117: 11-16
15. Pace F, Annese V, Prada A, Zambelli A, Casalini S, Nardini P, Bianchi Porro G. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomised, double-blind, comparative study of rabeprazole and omeprazole 20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole. *Dig Liver Dis* 2005; 37: 741-750
16. Caro JJ, Salas M, Ward A. Healing and relapse rates in gastrooesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole, and pantoprazole compared with omeprazole, ranitidine, and placebo: evidence from randomized clinical trials. *Clin Ther* 2001; 23: 998-1017
17. Edwards SJ, Lind T, Lundell L. Systematic review of proton
pump inhibitors for the acute treatment of reflux oesophagitis. *Aliment Pharmacol Ther* 2001; 15: 1729-1736

18 **Wang WH**, Huang JQ, Zheng GF, Xia HH, Wong WM, Lam SK, Wong BC. Head-to-head comparison of H2-receptor antagonists and proton pump inhibitors in the treatment of erosive esophagitis: a meta-analysis. *World J Gastroenterol* 2005; 11: 4067-4077

19 **Blume H**, Donath F, Warnke A, Schug BS. Pharmacokinetic drug interaction profiles of proton pump inhibitors. *Drug Saf* 2006; 29: 769-784

20 **Pilotto A**, Leandro G, Franceschi M. Short- and long-term therapy for reflux oesophagitis in the elderly: a multi-centre, placebo-controlled study with pantoprazole. *Aliment Pharmacol Ther* 2003; 17: 1399-1406

21 **Edwards SJ**, Lind T, Lundell L. Systematic review: proton pump inhibitors (PPIs) for the healing of reflux oesophagitis - a comparison of esomeprazole with other PPIs. *Aliment Pharmacol Ther* 2006; 24: 743-750

22 **Gillessen A**, Beil W, Modlin IM, Gatz G, Hole U. 40 mg pantoprazole and 40 mg esomeprazole are equivalent in the healing of esophageal lesions and relief from gastroesophageal reflux disease-related symptoms. *J Clin Gastroenterol* 2004; 38: 332-340

23 **Labenz J**, Armstrong D, Lauritsen K, Katelaris P, Schmidt S, Schütze K, Wallner G, Juergens H, Preiksaitis H, Keeling N, Naucler E, Eklund S. A randomized comparative study of esomeprazole 40 mg versus pantoprazole 40 mg for healing erosive esophagitis: the EXPO study. *Aliment Pharmacol Ther* 2005; 21: 739-746

24 **Pilotto A**, Franceschi M, Leandro G, Rassu M, Bozzola L, Valerio G, Di Mario F. Influence of Helicobacter pylori infection on severity of oesophagitis and response to therapy in the elderly. *Dig Liver Dis* 2002; 34: 328-331

25 **Pilotto A**, Perri F, Leandro G, Franceschi M. Effect of Helicobacter pylori eradication on the outcome of reflux esophagitis and chronic gastritis in the elderly. A randomized, multicenter, eight-month study. *Gerontology* 2006; 52: 99-106

S- Editor Liu Y  L- Editor Mihm S  E- Editor Li JL