Alimentary Pharmacology & Therapeutics

Omeprazole may be superior to famotidine in the management of iatrogenic ulcer after endoscopic mucosal resection: a prospective randomized controlled trial

B. D. YE*, J. H. CHEON†, K. D. CHOI‡, S. G. KIM*, J. S. KIM*, H. C. JUNG* & I. S. SONG*

*Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine; †Department of Internal Medicine, Yonsei University College of Medicine; ‡Division of Gastroenterology, Department of Internal Medicine, Asan Medical Center, Seoul, Korea

Correspondence to:
Dr H. C. Jung, Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine, 28 Yongon-dong, Chongno-gu, Seoul 110-799, Korea.
E-mail: hyunchae@plaza.snu.ac.kr

Publication data
Submitted 25 April 2006
First decision 1 May 2006
Resubmitted 3 June 2006
Resubmitted 26 June 2006
Accepted 27 June 2006

SUMMARY

Background
Acid suppressing agents are widely used to treat the iatrogenic ulcers following endoscopic mucosal resection for gastric neoplasms. However, the relative merits of proton pump inhibitor or histamine$_2$-receptor antagonist for endoscopic mucosal resection-induced ulcers are not known.

Aim
To prospectively compare omeprazole and famotidine for the healing of endoscopic mucosal resection-induced ulcers and for bleeding control.

Methods
After endoscopic mucosal resection, patients were randomly assigned to omeprazole (20 mg/day) or to famotidine (40 mg/day) group for a 28-day treatment period. The ulcer sizes and stages, bleeding rates and ulcer-related symptoms were compared.

Results
A total of 100 patients were randomized equally to each group. Forty-one patients in each group were finally compared. The two groups were comparable in terms of baseline characteristics. Twenty-eight days after treatment, the two groups were not different with respect to ulcer stage ($P = 0.137$) or ulcer reduction ratio ($P = 0.380$). No difference was observed with respect to ulcer-related symptoms ($P = 0.437$) and no bleeding episode occurred in any of the 82 patients. In subgroup that underwent endoscopic submucosal dissection, fewer patients in the omeprazole group showed active ulcers than those in the famotidine group ($P = 0.035$).

Conclusion
Our results demonstrate that omeprazole may be superior to famotidine for iatrogenic ulcers following endoscopic mucosal resection, especially for large ulcers.

Aliment Pharmacol Ther **24**, 837–843

doi:10.1111/j.1365-2036.2006.03050.x

INTRODUCTION

Endoscopic mucosal resection (EMR) is widely performed as a curative treatment modality for gastric neoplasms such as early gastric cancer (EGC) and adenoma in many centres. Iatrogenic gastric ulcers invariably follow EMR and acid-suppressing agents are administered to prevent bleeding and to induce rapid ulcer healing. Proton pump inhibitor (PPI) is a specific inhibitor of the enzyme H^+/K^+-ATPase, which is found on the secretory surface of the parietal cells.[1] PPI is a more potent inhibitor of gastric acid secretion than histamine$_2$-receptor antagonists (H_2RA) like cimetidine,[2] and is known to be superior to H_2RA with respect to healing gastric[3–8] and duodenal ulcers.[9, 10] Moreover, PPIs are widely used as first-line drugs for the treatment of peptic ulcers, but it is unclear which one is better at promoting the healing of iatrogenic ulcers after EMR between PPI and H_2RA. Studies that have compared PPI and H_2RA in terms of efficacy of healing iatrogenic ulcers and preventing bleeding after EMR have not shown any differences,[11, 12] but it is difficult to generalize those results because of the small sample sizes. This study was conducted to elucidate the optimal treatment regimen for iatrogenic ulcers following EMR by comparing PPI and H_2RA in terms of ulcer healing and the prevention of bleeding in a prospective randomized controlled design.

MATERIALS AND METHODS

Patients

We enrolled patients who underwent EMR for gastric mucosal neoplasm between October 2004 and 2005 at the Seoul National University Hospital. The exclusion criteria employed were as follows; (i) age below 16 or above 76; (ii) women either pregnant or at risk of pregnancy; (iii) lactating women; (iv) previous gastro-oesophageal surgery; and (v) the use of PPI, H_2RA, aspirin, a non-steroidal anti-inflammatory drug or glucocorticoid within 7 days of EMR. At enrolment, baseline characteristics like sex, age, comorbidity and the presence of epigastric pain were recorded. Written informed consents were obtained from all participants and the ethics committee of the Seoul National University Hospital approved the study protocol.

EMR

Endoscopic mucosal resection was performed by using one of the following methods; (i) by endoscopic submucosal dissection (ESD) using an insulation-tipped electrosurgical knife; (ii) by precutting and resecting using a snare (EMR-P); (iii) by using a transparent cap (EMR-C); or (iv) by snare polypectomy. Before EMR, maximal diameter and location of a lesion were recorded. After EMR, ulcer dimensions were calculated by multiplying the maximal diameter by its perpendicular diameter. Diameters were measured with a biopsy forceps (FB-24K-1; Olympus, Tokyo, Japan) placed on the ulcer surface, based on the width between the full-opened forceps (7 mm).[11] The presence of *Helicobacter pylori* (*H. pylori*) infection was determined by histological evaluation (modified Giemsa staining) on antrum and body mucosa and by the rapid urease test (CLOtest; Kimberley-Clark, Draper, UT, USA) using a specimen from the lesser curvature side of the antrum. When one of these tests was positive, then we defined it as the presence of *H. pylori* infection. Haemoglobin and haematocrit levels and coagulation profiles (prothrombin time and activated partial thromboplastin time) were also checked 1 day before EMR. After EMR, patients were randomly assigned to either the OMP group (omeprazole 20 mg daily for 28 days) or the FMT group (famotidine 20 mg twice daily for 28 days). Study subjects were unaware of the therapeutic regimen administered, which was performed as follows; patients in the OMP group were administered omeprazole (20 mg) with a famotidine placebo in the morning and placebos of omeprazole and famotidine in the evening; whereas patients in the FMT group were administered famotidine (20 mg) with a omeprazole placebo in the morning and evening. Endoscopists and interviewers were also unaware of the regimens administered. Patients were instructed not to take any other gastrointestinal medications during the 28 days study period.

Evaluation after 4 weeks

Upper gastrointestinal endoscopy was performed 28 days after EMR. Ulcer stages were assessed using a six-stage system as proposed by Sakita and Fukutomi (Table 1),[13] and ulcer dimensions were determined as described above at EMR. This measurement was taken when ulcers were active (A1 and A2) or in the healing

Table 1. Gastric ulcer stages using a six-stage system

Stage	Finding
A1 (active stage 1)	Ulcer that contains mucus coating, with marginal elevation because of oedema
A2 (active stage 2)	Mucus-coated ulcer with discrete margin and less oedema than active stage 1
H1 (healing stage 1)	Unhealed ulcer covered by regenerating epithelium <50 %, with or without converging folds
H2 (healing stage 2)	Ulcer with a mucosal break but almost covered with regenerating epithelium
S1 (scar stage 1)	Red scar with rough epithelialization without mucosal break
S2 (scar stage 2)	White scar with complete re-epithelialization

English version of ulcer stages as classified by Sakita and Fukutomi.[13]

Table 2. Grading system of epigastric pain

Grade	Severity
None	Without epigastric pain
Mild	Minimal epigastric pain
Moderate	With epigastric pain, without disturbing activities of daily living
Severe	With epigastric pain with disturbing activities of daily living

stage (H1 and H2), but not in the scar stage because there was no measurable mucosal break. Epigastric pain was recorded using a four-grade system (Table 2). Compliance with medication was evaluated by counting the remaining tablets and adverse events over the 4 weeks study period were recorded. Patients with ulcers in the active or healing stage 28 days after EMR were administered omeprazole 20 mg/day for additional 4 weeks.

Exclusion criteria at final analyses

After counting the remaining tablets on the 29th day after EMR, patients who had taken <75% of the prescribed medications were excluded from final analyses. Patients whose post-treatment endoscopic evaluations were performed more than 7 days after completing medication were also excluded from final analyses.

Statistical analysis

Patient baseline characteristics were compared using the chi-squared test, the Student's *t*-test or the Mann–Whitney test. Ulcer reduction ratios were calculated by dividing ulcer dimensions at 4 weeks after EMR by initial ulcer dimensions.[12, 14] Ulcer reduction ratios were compared using the Mann–Whitney test. Ulcer stages, symptoms during treatment and the frequencies of adverse events were compared using the chi-squared test. *P*-values of <0.05 were considered to be statistically significant. Statistical analysis was performed using SPSS for Windows (version 12.0; SPSS Inc., Chicago, IL, USA).

Sample size was calculated based on the assumption that the endoscopic ulcer healing rate of the OMP group was higher than that of the FMT group by 30%.[15] More than 39 patients were needed per group using a 5% significance level and a statistical power of 80%.[16] Fifty patients were enrolled in each group due to an expected 20% loss caused by loss during follow-up and protocol violations.

RESULTS

A total of 100 patients were enrolled and randomly assigned equally to the two groups. Nine patients in each group were excluded from the final analyses because of loss during follow-up or a failure to meet the requirements of the final analyses. Baseline characteristics, e.g. sex, age, comorbidity, epigastric pain, blood test and *H. pylori* positivity (Table 3) and characteristics, such as lesion size and location, EMR method used and haemostasis after EMR and histopathology (Table 4) were not significantly different between the two groups.

The stages of the 82 ulcers on follow-up endoscopy were compared between the two groups (Figure 1) and no significant difference was found in terms of ulcer stage distribution ($P = 0.137$). Twenty-three patients

Table 3. Characteristics of patients in both groups

Variables	Omeprazole group ($n = 41$)	Famotidine group ($n = 41$)	*P*-value
Male	28 (68.3%)	24 (58.5%)	0.359
Age (mean ± s.d.)	61.2 ± 9.0	58.5 ± 9.4	0.186
Comorbidity	22 (53.7%)	15 (36.6%)	0.120
Epigastric pain			
None	31 (75.6%)	29 (70.7%)	0.534
Mild	9 (22.0%)	8 (19.5%)	
Moderate	1 (2.4%)	4 (9.8%)	
Haemoglobin (g/dL) (mean ± s.d.)	13.8 ± 1.5	13.8 ± 1.4	0.951
Haematocrit (%) (mean ± s.d.)	40.6 ± 4.2	40.7 ± 4.0	0.910
Prothrombin time (INR) (mean ± s.d.)	1.02 ± 0.09	1.02 ± 0.06	0.629
Activated partial thromboplastin time (s) (mean ± s.d.)	35.9 ± 4.6	35.3 ± 6.3	0.607
Helicobacter pylori positivity	25 (61.0%)	23 (56.1%)	0.654

INR, International normalized ratio.

Table 4. Characteristics of gastric lesions in the two groups

Variables	Omeprazole group ($n = 41$)	Famotidine group ($n = 41$)	*P*-value
Maximal diameter (cm) (mean ± s.d.)	1.14 ± 0.53	1.11 ± 0.46	0.740
Location			
Upper third	1 (2.4%)	1 (2.5%)	0.903
Mid third	13 (31.7%)	11 (26.8%)	
Lower third	27 (65.9%)	29 (70.7%)	
Method of EMR			
Snare polypectomy	5 (12.2%)	8 (19.5%)	0.712
EMR-C	3 (7.3%)	3 (7.3%)	
EMR-P	7 (17.1%)	9 (22.0%)	
ESD	26 (63.4%)	21 (51.2%)	
Haemostasis after EMR	31 (75.6%)	25 (61.0%)	0.154
Histopathology			
Adenoma, low grade	16 (39.0%)	24 (58.5%)	0.071
Adenoma, high grade	5 (12.2%)	8 (19.5%)	
Adenocarcinoma, W/D	10 (24.4%)	3 (7.3%)	
Adenocarcinoma, M/D	5 (12.2%)	1 (2.5%)	
Others	5 (12.2%)	5 (12.2%)	

EMR-C, endoscopic mucosal resection using a transparent cap; EMR-P, endoscopic mucosal resection by precutting and resecting using a snare; ESD, endoscopic submucosal dissection; W/D, well differentiated; M/D, moderately differentiated.

among 41 patients (56.1%) in each groups were remained in stage A2 or H1 in both groups; however, a much smaller proportion (one among 41 patients; 2.4%) of patients in the OMP group showed stage A2 than that (seven among 41 patients; 17.1%) of patients in the FMT group. When stages of ulcers were classified using a three-stage system, i.e. active, healing or scar stage, the distribution of ulcer stages differed with marginal significance between the two study groups ($P = 0.057$).

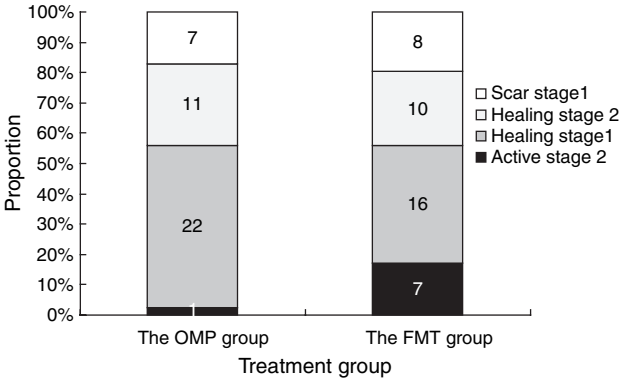

Figure 1. The distribution of ulcer stages on follow-up endoscopic examination. The numbers in graph indicate the number of patients in each stage. No significant difference was found between the omeprazole (OMP) and famotidine (FMT) groups ($P = 0.137$).

The ulcer reduction ratios of the 67 ulcers that were remained in the active or healing stage on follow-up endoscopy (34 ulcers in the OMP group and 33 ulcers in the FMT group) were also compared. Figure 2 shows the initial and follow-up mean dimensions of ulcers in the two groups. In the OMP group, the initial mean ulcer dimension 1042.9 ± 873.1 mm^2 reduced to 35.9 ± 30.6 mm^2 after 28 days (mean ulcer reduction ratio $= 0.072 \pm 0.159$) and in the FMT group, it reduced from 912.6 ± 744.0 mm^2 to 40.3 ± 42.2 mm^2 after 28 days (mean ulcer reduction ratio $= 0.058 \pm 0.062$) and ulcer reduction ratios were not significantly different ($P = 0.380$). Moreover, the distribution of the severity of epigastric pain during the study period was not different in the two groups ($P = 0.437$, Table 5). Bleeding episodes or adverse events were not observed in any of 82 study subjects.

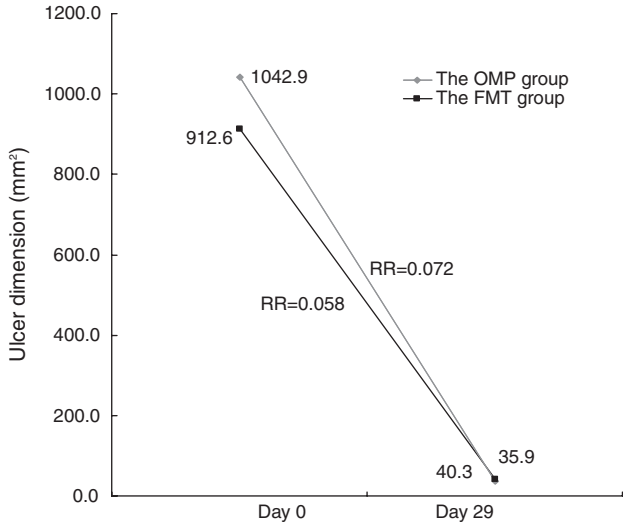

Figure 2. Mean initial and final (on follow-up endoscopy) ulcer dimensions of the both groups. Ulcer reduction ratios (RRs) were not significantly different ($P = 0.380$).

Table 5. Severity of epigastric pain during the 28 days treatment period

Severity of epigastric pain	Omeprazole group ($n = 41$)%	Famotidine group ($n = 41$)%	P-value
None	26 (63.4)	22 (53.7)	0.437
Mild	11 (26.8)	12 (29.3)	
Moderate	4 (9.8)	4 (9.7)	
Severe	0 (0)	3 (7.3)	

We performed subgroup analysis for patients who underwent ESD (26 patients in the OMP group and 21 patients in the FMT group). Baseline characteristics were comparable between the two groups (data not shown). In comparing ulcer stages using a six-stage system, the distribution was not significantly different ($P = 0.097$). When stages of ulcers were classified using a three-stage system as stated above, the distribution of ulcer stages was significantly different ($P = 0.035$, Figure 3), i.e. a smaller proportion of patients in the OMP group (3.8%) remained in the active stage

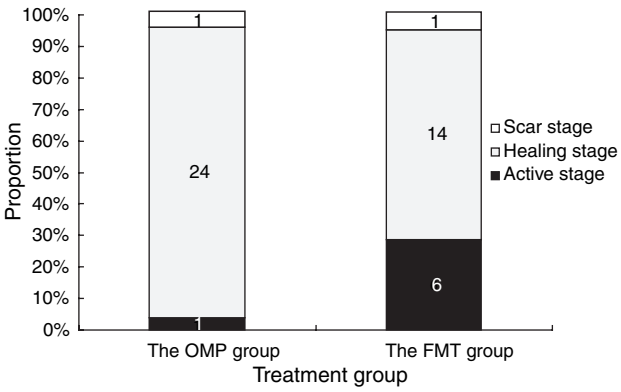

Figure 3. The distribution of ulcer stages on follow-up endoscopic examination of patients who underwent endoscopic submucosal dissection. The numbers in graph indicate the number of patients in each stage. This shows significant difference in the distribution of ulcer stages ($P = 0.035$).

than that of the FMT group (28.6%). We also compared the ulcer reduction ratios of 25 ulcers following ESD in the OMP group and 20 ulcers following ESD in the FMT group. The mean ulcer reduction ratios were not significantly different (0.034 ± 0.028 in the OMP group vs. 0.057 ± 0.076 in the FMT group, $P = 0.293$). The distribution of severity of ulcer-related symptoms was also comparable ($P = 0.290$, data not shown).

DISCUSSION

This study was conducted to compare the efficacies of PPI and H_2RA in terms of inducing ulcer healing and preventing bleeding after EMR for a gastric mucosal neoplasm. Many reports have compared PPI with H_2RA in terms of healing peptic ulcers and some have reported that PPI is superior to H_2RA in this respect.[3–10] Similarly, for bleeding peptic ulcers, omeprazole was found to be more effective than H_2RA in terms of reducing rebleeding episodes in patients who underwent initial endoscopic haemostasis,[17] or who did not undergo endoscopic haemostasis.[18–21] EMR is widely applied for curative treatment of gastric mucosal neoplasms like EGC or adenoma. Recently, the ESD technique has been adopted by many centres in Korea for en-bloc resection of a lesion. However, after ESD, a larger artificial ulceration is created than those produced by snare polypectomy or EMR-P. Because ulcer dimensions are larger and the resection depths are greater than those associated with the conventional method like snare polypectomy or EMR-P, the risk of bleeding is believed to be higher. Thus, rapid ulcer healing through clot stabilization at an elevated intragastric pH is required.

Generally, PPI or H_2RA is used for inducing the rapid healing of artificial gastric ulcers after EMR. Because PPI is known to be more potent at elevating the intragastric pH than H_2RA, it can be assumed that PPI induces ulcer healing more rapidly and prevents bleeding episodes more efficiently than H_2RA after EMR. However, in one study which compared omeprazole and famotidine, ulcer healing rates (assessed using ulcer sizes) were not different.[11] But the sample size (eight patients in each treatment group) was small and ulcer reduction ratios based on initial ulcer sizes were not calculated. Recently, in one randomized prospective study, no difference was found between famotidine and omeprazole in terms of bleeding rates and ulcer reduction ratios after EMR.[12]

The present study involved a larger number of patients than previous studies,[11, 12] and also compared the effectivenesses of the two drugs in terms of the healing of larger ulcers than previous study.[12] We found no overall differences between the OMP and FMT groups in terms of ulcer stage or ulcer reduction ratio, although fewer patients in the OMP group showed active stage ulcers than those in the FMT group. However, in comparing subgroup that underwent ESD, active stage ulcers were significantly fewer in the OMP group than in the FMT group, although ulcer reduction ratios were not different. No comparison of ulcer stages between omeprazole and famotidine treatment groups was performed in the previous study.[12]

Our results suggest that omeprazole is superior to famotidine in terms of converting active stage ulcers into the healing stage, especially in case with a large artificial ulcer after ESD. Recently, as the ESD technique is applied more and more widely for the treatment of gastric mucosal neoplasm, the size of artificial ulcer is increasing. Our observation indicates that omeprazole is preferred for a large artificial ulcer than famotidine. Increasing the dosage of omeprazole, i.e. doubling the dose, may also be expected to accelerate ulcer healing, thereby revealing the superiority of omeprazole more clearly.

Minor bleedings, which stopped spontaneously or after endoscopic haemostasis without a need for transfusion or surgery, occurred in two of the 50 patients in the OMP group (4%) and in one of the 50 patients in the FMT group (2%). However, these three patients were excluded from the final analyses because of protocol violations. In both groups, bleeding rates were lower than previous study,[12] which may be due to more thorough application of an advanced haemostatic technique. Actually, a haemostatic procedure using haemostatic forceps and/or argon plasma coagulation was conducted in 45 (95.7%) of 47 patients treated by ESD. When *H. pylori* is detected in gastric mucosa of a patient with peptic ulcer disease, *H. pylori* eradication is a standard treatment. However, it is still uncertain whether *H. pylori* eradication therapy influences the healing of iatrogenic ulcers following EMR. Recently, *H. pylori* eradication was reported not to accelerate the iatrogenic ulcer healing although it might improve the quality of iatrogenic ulcer healing.[22] We did not eradicate *H. pylori* routinely during the study period but after the completion of study medications, seven patients of the OMP group and three patients of the

FMT group received first-line *H. pylori* eradication treatment composed of PPI with amoxicillin and clarithromycin for 7 days. Further studies are needed to elucidate the role of *H. pylori* eradication in healing of iatrogenic ulcers.

Initially, we enrolled 50 patients in each group, but nine among 50 patients (18%) were dropped out from each group. However, considering equal drop out rates and comparable incidences of adverse events, our results could be applied to the patient group having iatrogenic ulcers after EMR.

In summary, omeprazole appeared to be more effective in promoting healing of artificially induced ulcers after EMR, especially in the subgroup with ESD. A randomized controlled trial focusing on this subgroup of patients with larger artificial ulcerations will provide definitive data to confirm or refute the hypothesis that PPI is indeed superior to H_2RA after EMR.

ACKNOWLEDGEMENT

This work was supported by the 2004 General Research Fund of the Seoul National University Hospital (04-2004-006).

REFERENCES

1 Holt S, Howden CW. Omeprazole. Overview and opinion. *Dig Dis Sci* 1991; **36**: 385–93.
2 Walt RP, Gomes MD, Wood EC, Logan LH, Pounder RE. Effect of daily oral omeprazole on 24 hour intragastric acidity. *Br Med J (Clin Res Ed)* 1983; **287**: 12–4.
3 Lauritsen K, Rune SJ, Wulff HR, *et al*. Effect of omeprazole and cimetidine on prepyloric gastric ulcer: double blind comparative trial. *Gut* 1988; **29**: 249–53.
4 Bate CM, Wilkinson SP, Bradby GV, *et al*. Randomised, double blind comparison of omeprazole and cimetidine in the treatment of symptomatic gastric ulcer. *Gut* 1989; **30**: 1323–8.
5 Italian Cooperative Group on Omeprazole. Omeprazole 20 mg uid and ranitidine 150 mg bid in the treatment of benign gastric ulcer. *Hepatogastroenterology* 1991; **38**: 400–3.
6 Hotz J, Plein K, Schonekas H, Rose K. Pantoprazole is superior to ranitidine in the treatment of acute gastric ulcer. *Scand J Gastroenterol* 1995; **30**: 111–5.
7 Walan A, Bader JP, Classen M, *et al*. Effect of omeprazole and ranitidine on ulcer healing and relapse rates in patients with benign gastric ulcer. *N Engl J Med* 1989; **320**: 69–75.
8 Sakaguchi M, Ashida K, Umegaki E, Miyoshi H, Katsu K. Suppressive action of lansoprazole on gastric acidity and its clinical effect in patients with gastric ulcers: comparison with famotidine. *J Clin Gastroenterol* 1995; **20** (Suppl. 2): 27–31.
9 Lauritsen K, Rune SJ, Bytzer P, *et al*. Effect of omeprazole and cimetidine on duodenal ulcer. A double-blind comparative trial. *N Engl J Med* 1985; **312**: 958–61.
10 Hotz J, Kleinert R, Grymbowski T, Hennig U, Schwarz JA. Lansoprazole versus famotidine: efficacy and tolerance in the acute management of duodenal ulceration. *Aliment Pharmacol Ther* 1992; **6**: 87–95.
11 Esaki M, Aoyagi K, Matsumoto T, Kuwano Y, Shimizu M, Fujishima M. Effects of omeprazole and famotidine on fibroblast growth factor-2 during artificial gastric ulcer healing in humans. *Eur J Gastroenterol Hepatol* 2002; **14**: 365–9.
12 Yamaguchi Y, Katsumi N, Tauchi M, *et al*. A prospective randomized trial of either famotidine or omeprazole for the prevention of bleeding after endoscopic mucosal resection and the healing of endoscopic mucosal resection-induced ulceration. *Aliment Pharmacol Ther* 2005; **21** (Suppl. 2): 111–5.
13 Sakita T, Fukutomi H. Endoscopic diagnosis. In: Yoshitoshi Y, ed. *Ulcer of Stomach and Duodenum [Japanese]*. Tokyo: Nankodo, 1971: 198–208.
14 Lee SY, Kim JJ, Lee JH, *et al*. Healing rate of EMR-induced ulcer in relation to the duration of treatment with omeprazole. *Gastrointest Endosc* 2004; **60**: 213–7.
15 Tunis SR, Sheinhait IA, Schmid CH, Bishop DJ, Ross SD. Lansoprazole compared with histamine$_2$-receptor antagonists in healing gastric ulcers: a meta-analysis. *Clin Ther* 1997; **19**: 743–57.
16 Chow SC, Liu JP. *Design and Analysis of Clinical Trials: Concepts and Methodologies*, 2nd edn. New York: John Wiley and Sons, 2004: 438–52.
17 Lin HJ, Lo WC, Lee FY, Perng CL, Tseng GY. A prospective randomized comparative trial showing that omeprazole prevents rebleeding in patients with bleeding peptic ulcer after successful endoscopic therapy. *Arch Intern Med* 1998; **158**: 54–8.
18 Brunner G, Chang J. Intravenous therapy with high doses of ranitidine and omeprazole in critically ill patients with bleeding peptic ulcerations of the upper intestinal tract: an open randomized controlled trial. *Digestion* 1990; **45**: 217–25.
19 Lanas A, Artal A, Blas JM, Arroyo MT, Lopez-Zaborras J, Sainz R. Effect of parenteral omeprazole and ranitidine on gastric pH and the outcome of bleeding peptic ulcer. *J Clin Gastroenterol* 1995; **21**: 103–6.
20 Gisbert JP, Gonzalez L, Calvet X, Roque M, Gabriel R, Pajares JM. Proton pump inhibitors versus H_2-antagonists: a meta-analysis of their efficacy in treating bleeding peptic ulcer. *Aliment Pharmacol Ther* 2001; **15**: 917–26.
21 Zed PJ, Loewen PS, Slavik RS, Marra CA. Meta-analysis of proton pump inhibitors in treatment of bleeding peptic ulcers. *Ann Pharmacother* 2001; **35**: 1528–34.
22 Ueda H, Ito M, Tanaka S, *et al*. The effect of *Helicobacter pylori* eradication therapy on gastric ulcer healing after endoscopic mucosal resection. *J Clin Gastroenterol* 2006; **40**: 293–6.