Sofalcone, a mucoprotective agent, increases the cure rate of \textit{Helicobacter pylori} infection when combined with rabeprazole, amoxicillin and clarithromycin

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INTRODUCTION

\textit{Helicobacter pylori} (\textit{H. pylori}) causes type B chronic gastritis and plays a critical role in the pathogenesis of peptic ulceration\cite{1,2}. Eradication of \textit{H. pylori} infection facilitates ulcer healing and prevents recurrence\cite{8}. In the quest for optimal choice of drugs, dosage and duration, various therapeutic regimens have been studied extensively during the past few years. Among these, short-term low-dose triple therapy, comprising of one proton pump inhibitor and two antimicrobials from the choice of clarithromycin, amoxicillin and metronidazole, is currently considered the gold standard regimen\cite{6,7}. The new proton pump inhibitor-based triple therapies provide high eradication rates, which are generally more than 80\%. In fact, we reported that a 7-d course of rabeprazole, a novel potent proton pump inhibitor, 10 mg b.d plus amoxicillin 750 mg b.d. and clarithromycin 200 mg b.d. showed satisfactory results\cite{8}. Nevertheless, there are still some disadvantages to be addressed such as drug resistance when considering the PPI-based triple therapies\cite{14,15}. With the rising prevalence of resistance of \textit{H. pylori} to metronidazole or clarithromycin, failure rates of the PPI-based regimens are expected to increase\cite{14-21}.

A variety of gastric mucoprotective agents have been used as anti-ulcer drugs, usually in combination with antacids, in the upper gastrointestinal tract\cite{14}. Among these, rebamipide, ecabet sodium, sofalcone, polaprezinc, plaunotol and sucralfate are uncomplicated by drug resistance and have anti-\textit{H. pylori} activities\cite{14-21}. Therefore, the theoretical rationale for adding such mucoprotective drugs to ordinary...
eradication regimens is that these may meet demands of improved treatment outcome without the development of resistance.

There are several reports on the additive effects of mucoprotective drugs in eradication regimens, but most of the study designs were not randomized and the sample sizes were limited\(^4\)\(^{22-27}\). In addition, there is little information on the most effective mucoprotective drugs. This prospective, randomized study was designed to determine whether the inclusion of sofalcone or polaprezinc increases the cure rate of \(H. pylori\) infection when combined with the rabeprazole-amoxicillin-clarithromycin therapy.

**MATERIALS AND METHODS**

**Patients**

The present study was designed as a prospective, open, randomized and controlled trial, which was performed between January 1999 and December 2002. The study was conducted according to Good Clinical Practice and the Declaration of Helsinki. All patients gave informed consent prior to their inclusion in the study.

The patient population comprised 165 consecutive outpatients with peptic ulcer and \(H. pylori\) infection. Exclusion criteria were: age <18 years, pregnancy or lactation, severe concomitant diseases, previous medications effective against \(H. pylori\) such as bismuth compounds, proton pump inhibitors, or antibiotics during the last 3 mo, alcohol abuse, drug addiction, chronic corticosteroid or nonsteroidal anti-inflammatory drug use, and previous gastroduodenal surgery. Information on alcohol intake and smoking habits was obtained at entry into the study. Ex-smokers and social drinkers were considered as nonsmokers and nondrinkers respectively.

**Diagnosis of \(H. pylori\) infection**\(^{28,29}\)

The presence of \(H. pylori\) was confirmed by serology (anti-\(H. pylori\) Immunoglobulin G antibody, HEL-p TEST, AMRAD Co., Melbourne, Australia), rapid urease test (Helicocheck, Otsuka Pharmaceutical Co., Tokushima, Japan) and histology (Giemsa staining) using two biopsy specimens obtained during endoscopy from each the antrum (within 2 cm of the pyloric ring) and the corpus (along the greater curvature). Patients were considered to be infected with \(H. pylori\) when at least two of these examinations gave positive results. Patients were classified as \(H. pylori\)-negative when all test results were negative. Patients who had only one positive result were not included.

**Clinical trial**

The enrolled patients were randomized by drawing a sealed envelope that contained pre-assigned treatment instructions. They were allocated to one of the following three groups and were medicated for 7 d: group A, which received rabeprazole 10 mg b.d., clarithromycin 200 mg b.d. and amoxicillin 750 mg b.d.; group B, which received sofalcone [2’-carboxymethyl 4, 4’-bis (3-methyl-2-butenyloxy) chalcone] 100 mg t.i.d., in combination with rabeprazole 10 mg b.d., clarithromycin 200 mg b.d. and amoxicillin 750 mg b.d.; group C, polaprezinc, zinc L-carnosine [N-aminopropionyl-L-histidinato zinc (II)] 150 mg b.d. in combination with rabeprazole 10 mg b.d., clarithromycin 200 mg b.d. and amoxicillin 750 mg b.d. Both the sofalcone and polaprezinc were prescribed as the standard daily dosage. If an active ulcer (defined as a circumscribed break in the mucosa measuring at least 5 mm in diameter with apparent depth and covered with an exudate\(^30\)) was found at baseline endoscopy, it was treated with an \(H_2\)-receptor antagonist (famotidine 20 mg twice daily) for 4 wk after the eradication therapy. In cases of peptic ulcer scar, no other ulcer healing drugs were provided throughout the study. Participants returned at the conclusion of therapy for interview regarding adverse events. Compliance with medication was checked immediately after stopping treatment by counting the number of returned pills. Four weeks after cessation of eradication therapy, repeat endoscopy was performed to assess \(H. pylori\) status by the rapid urease test and histology as before treatment. In patients with peptic ulcer in the active phase, the endoscopy-based tests were performed 4 wk after stopping famotidine (8 wk after the completion of eradication). Ulcer healing (defined as complete re-epithelialization) was assessed at the time of repeat endoscopy. Furthermore, we adopted the \(^1\)C-urea breath test for the evaluation of \(H. pylori\) cure 4 wk or longer after completion of treatment. In patients with active peptic ulcer, the \(^1\)C-urea breath test was performed 4 wk or longer after completion of the ulcer treatment with famotidine (at least 8 wk after completion of the eradication therapy). The urea breath test was performed as described previously\(^31\). Briefly, \(^1\)C-urea at 100 mg (Otsuka Pharmaceutical Co.) was dissolved in 100 mL of water. The test solution was ingested while in the sitting position, followed immediately by mouth rinsing. The patient was subsequently placed in the left decubitus position for 5 min and then in the sitting position for 15 min. Breath samples were collected, at baseline and 20 min after dosing and then analyzed using an isotope-selected nondispersive infrared spectrometer; UBIT-IR200 (Otsuka Electronics Co., Hirakata, Japan). The cut-off value was set at 2.5%; eradication of \(H. pylori\) was considered successful if all test results were negative\(^30\).

**Statistical analysis**

\(H. pylori\) cure rate was evaluated by intention-to-treat (ITT) and per protocol (PP) analyses. ITT analysis included all enrolled patients and patients who dropped out were regarded as treatment failures. PP analysis included all patients who took at least 80% of each study medication as prescribed and returned for assessment of \(H. pylori\) cure\(^34\).

The cure rate was calculated together with 95% confidence intervals (CI). Statistical analyses were performed using the \(\chi^2\), Fisher’s exact and Student’s \(t\)-tests, as appropriate. A \(P\) value less than 0.05 was accepted as statistically significant.

**RESULTS**

The enrolled patients comprised 125 men and 40 women, with a mean age of 46 years (range, 21-73). They included 101 patients with gastric ulcer, 59 with duodenal ulcer and 5 with gastroduodenal ulcer. The peptic ulcer was in the
active phase in 87 patients. The baseline characteristics of the study population are listed in Table 1. The three treatment groups were well matched for gender, age, body weight, alcohol intake, smoking habits and baseline diagnosis. Of the 165 patients enrolled in this study, 4 patients (1 from group A, 1 from group B and 2 from group C) were lost to follow-up. Furthermore, 5 patients (1 from group A, 3 from group B and 1 from group C) were excluded from PP analysis as their compliance was less than 80%, leaving 156 patients for PP analysis.

Table 1 Patients' characteristics

|                      | Group A | Group B | Group C |
|----------------------|---------|---------|---------|
| Mean age, yr (range) | 45.3    | 47.2    | 45.6    |
| Male/female          | 41/14   | 42/12   | 42/14   |
| Mean weight, kg (range) | 60.7(42.5-70.0) | 59.8(40.5-70.0) | 58.7(38.5-79.0) |
| Smokers (%)          | 23(41.8) | 28(51.6) | 24(42.6) |
| Alcohol drinkers (%) | 21(38.1) | 28(51.6) | 23(41.1) |
| Gastric ulcer (%)    | 34(61.8)| 31(57.4)| 36(64.3)|
| Duodenal ulcer (%)   | 19(34.5)| 21(38.9)| 19(33.9)|
| Gastruduodenal ulcer (%) | 2(3.6)   | 2(3.7)  | 1(1.8)  |
| Active ulcer (%)     | 27(49.1)| 32(59.3)| 28(50.0)|
|                       | Per protocol (%) | 95% CI | Per protocol (%) | 95% CI | Per protocol (%) | 95% CI |
| A                     | 78.2(43/55)      | 66.9-89.4 | 81.1(43/53)  | 70.2-92.0 |
| B                     | 87.0(47/54)      | 77.8-96.4 | 94.0(47/50)  | 87.2-100.0 |
| C                     | 80.4(45/56)      | 69.6-91.1 | 84.9(45/53)  | 73.1-93.6 |

Table 3 Adverse events in the three treatment groups (n, %)

|                      | Group A | Group B | Group C |
|----------------------|---------|---------|---------|
| Diarrhea or soft stool | 8(14.5)| 7(13.0)| 9(16.1)|
| Heartburn            | 1(1.8)  | 4(7.4)  | 1(1.8)  |
| Nausea               | 1(1.8)  | 1(1.9)  | 0(0.0)  |
| Skin rash            | 0(0.0)  | 0(0.0)  | 1(1.8)  |
| Total                | 10(18.2)| 12(22.2)| 11(19.6)|

At the following endoscopy, ulcer healing was comparably observed in 24 out of 27 patients in group A (88.9%, 95%CI = 76.2-100%), 28 out of 32 in group B (87.5%, 95%CI = 75.4-99.6%) and 24 out of 28 (85.7%, 95%CI = 71.9-99.5%). Adverse events were noted in 10 patients from group A, 12 from group B and 11 from group C. These included diarrhea or soft stools, heartburn, nausea and skin rash (Table 3), and resulted in discontinuation of treatment in one patient from group B due to skin rash. Overall, the adverse events were mild and self-limited. No significant differences in the incidence and proportion of adverse events were observed among the three groups.

DISCUSSION

The generally assumed mechanisms of action of mucoprotective agents involve up-regulation of gastric mucosal defense during the process of recovery from mucosal injury[14]. Some of these drugs are also reported to have anti-H pylori activities through different mechanisms[14-21]. Amongst this background, a series of trials have been carried out in which such mucoprotective agents were added to the original dual or triple therapy regimens in an attempt to improve the efficacy[22-27]. The meta-analysis study of Hojo et al[14], supported the view that the eradication rates can be enhanced by adding mucoprotective agents to dual therapies. However, such agents could not be employed as alternative drugs for antimicrobials such as metronidazole and clarithromycin as dual therapies plus any mucoprotective agents were still unacceptable for the treatment of H pylori infection[14,22,26]. On the other hand, Hojo et al[14], could not validate the positive effect of mucoprotective agents in triple therapies. While this lack of additive efficacy may be due to high eradication rates already provided by triple therapy regimens, most trials were not randomized and the sample sizes were limited. Thus, we sought to evaluate the efficacy of sofalcone or polaprezinc when combined with the new triple therapy. To our knowledge, this is the first prospective, randomized and controlled trial undertaken to determine which of the two mucoprotective agents produces better H pylori eradication.

Sofalcone is a type of flavonoid and a synthetic derivative of sophoradine isolated from the root of the Chinese medicinal plant Sophora subprostrata[22]. Besides its mucosal protective action, sofalcone has a direct bactericidal effect on H pylori, with a minimum inhibitory concentration of 55-222 μmol/L, anti-urease activity and reduces the adhesion of this organism to gastric epithelial cells[18,19]. Polaprezinc is an insoluble chelate compound consisting of a zinc ion and L-carnosine and exerts potent mucoprotective activities[23]. It also inhibits the growth of H pylori, in addition to its urease activity and adhesion to gastric mucin[17,20]. Thus, we expected additive effects of the two mucoprotective drugs in the original proton pump inhibitor-based triple therapy. This was the case in the inclusion of sofalcone, but not polaprezinc. A 7-d course of quadruple therapy consisting of sofalcone, rabeprazole, amoxicillin and
clarithromycin demonstrated satisfactory treatment outcome, *H pylori* eradication rate being not less than 94% on the PP basis. On the other hand, the co-prescription of polaprezinc did not improve the cure rate, which was comparable to the existing rabeprazole-amoxicillin-clarithromycin regimen.

Sakaki et al[23], reported that 7-d omeprazole-amoxicillin-clarithromycin combination therapy yielded satisfactory results by the addition of sofalcone. Moreover, adding this drug improved the eradication rate in dual therapy with lansoprazole and amoxicillin[34]. Kodama et al[35], reported that combination therapy of clarithromycin and sofalcone yield 69.2% of eradication rate without the incorporation of anti-secretory drug. Although the study designs were non-randomized and the sample sizes were not large enough to find any significant differences, it is of clinical importance that sofalcone may possess the ability to latently increase the efficacy in *H pylori* eradication.

In contrast to our study, the addition of polaprezinc to triple therapy with lansoprazole, amoxicillin and clarithromycin significantly improved the cure rate of *H pylori* in a randomized controlled trial[35]. Kuwayama et al[36] reported that this agent in combination with low dose metronidazole (750 mg/d) and amoxicillin (750 mg/d) produced a 100% *H pylori* eradication. The exact reason for this discrepancy remains unknown, but many factors may affect eradication efficacy such as physical structure of the patient, smoking habits, compliance in taking the therapeutic drugs, genetic predisposition of cytochrome p450 2C19, which metabolizes proton pump inhibitors, and frequency of strains resistant to antimicrobials[37,39,40]. In the present study, there were no significant differences in the baseline characteristics among the trial arms. The incidence of adverse events was comparable among the three treatment groups, affecting approximately 20% of patients, which is similar to previous data[19,39]. These adverse events were generally mild, causing discontinuation of therapy in only one patient. Thus, each treatment regimen was well tolerated, leading to excellent compliance in the current study. In addition, the action of rabeprazole is known to be less affected by genetic susceptibility of *H pylori* has been considered a key factor in determining the outcome of anti-*H pylori* therapies[10,12,13,28], and it might influence treatment results of the present eradication regimens incorporating this drug. Further studies should be conducted to determine the efficacy of mucoprotective agents in treating clarithromycin-resistant *H pylori*.

In conclusion, our results indicated that sofalcone provides a significant additive effect in the eradication of *H pylori* infection, when combined with rabeprazole, amoxicillin and clarithromycin. In contrast, polaprezinc inclusion did not improve treatment outcome of the original triple therapy. Each treatment arm yielded equally good acceptability and compliance. In clinical practice, further work should be conducted to identify the most effective mucoprotective agents with anti-*H pylori* activities when combined with existing eradication regimens.

REFERENCES

1. Blaser MJ. Helicobacter pylori and the pathogenesis of gastroduodenal inflammation. J Infect Dis 1990; 161: 626-633
2. Graham DY. Campylobacter pylori and peptic ulcer disease. Gastroenterology 1989; 96: 615-625
3. Graham DY, Lew GM, Evans DG, Evans DJ, Klein PD. Effect of triple therapy (antibiotics plus bismuth) on duodenal ulcer healing. A randomized controlled trial. Ann Intern Med 1991; 115: 266-269
4. Hopkins RJ, Girardi LS, Turney EA. Relationship between Helicobacter pylori eradication and reduced duodenal and gastric ulcer recurrence: a review. Gastroenterology 1996; 110: 1244-1252
5. Tytgat GN. Review article: treatments that impact favourably upon the eradication of Helicobacter pylori and ulcer recurrence. Aliment Pharmacol Ther 1994; 8: 359-368
6. Malfertheiner P, Megraud F, O’Morain C, Hungin AP, Jones R, Axon A, Graham DY, Tytgat G. Current concepts in the management of Helicobacter pylori infection—the Maastricht 2-2000 Consensus Report. Aliment Pharmacol Ther 2002; 16: 167-180
7. Pounder RE. New developments in Helicobacter pylori eradication therapy. Scand J Gastroenterol Suppl 1997; 223: 43-45
8. Isomoto H, Furusu H, Morikawa T, Mizuta Y, Nishiyama T, Omegari K, Murase K, Inoue K, Murata I, Kohno S. 5-day vs. 7-day triple therapy with rabeprazole, clarithromycin and amoxicillin for Helicobacter pylori eradication. Aliment Pharmacol Ther 2000; 14: 1619-1623
9. Ducons JA, Santolaria S, Guirao R, Ferrero M, Montoro M, Gomollon F. Impact of clarithromycin resistance on the effectiveness of a regimen for Helicobacter pylori: a prospective study of 1-week lansoprazole, amoxicillin and clarithromycin in active peptic ulcer. Aliment Pharmacol Ther 1999; 13: 775-780
10. Miwa H, Misawa H, Yamada T, Nagahara A, Ohtaka K, Satô N. Clarithromycin resistance, but not CYP2C-19 polymorphism, has a major impact on treatment success in 7-day treatment regimen for cure of *H pylori* infection: a multiple logistic regression analysis. Dig Dis Sci 2001; 46: 2445-2450
11. Hoshiyama S, Watanabe K, Tokunaga K, Tanaka A, Ninomiya H, Shingaki I, Itoh T, Saito S, Ishida H, Takahashi S. Relationship between eradication therapy and clarithromycin-resistant Helicobacter pylori in Japan. J Gastroenterol 2000; 35: 10-14
12. Nagahara A, Miwa H, Ohkura R, Yamada T, Sato K, Hojo M, Sato N. Strategy for retreatment of therapeutic failure of eradication of Helicobacter pylori infection. J Gastroenterol Hepatol 2001; 16: 613-618
13. Megraud F. Resistance of Helicobacter pylori to antibiotics. Aliment Pharmacol Ther 1997; 11 Suppl 1: 43-53
14. Hojo M, Miwa H, Kikuchi S, Sato N. Do mucosal defensive agents improve the cure rate when used with dual or triple therapy regimens for eradicating Helicobacter pylori infection? Aliment Pharmacol Ther 2000; 14: 193-201
15. Hayashi S, Sugiyama T, Amako K, Isogai H, Isogai E, Aihara M, Kikuchi M, Asaka M, Yokota K, Oguma K, Fujii N, Hirai Y. Effect of rebamipide, a novel antiulcer agent, on Helicobacter pylori adhesion to gastric epithelial cells. Antimicrob Agents Chemother 1998; 42: 1895-1899
16. Shibata K, Ito Y, Hongo A, Yasoshima A, Endo T, Ohashi M. Bacterial activity of a new antiulcer agent, ecabet sodium, against Helicobacter pylori under acidic conditions. Antimicrob Agents Chemother 1995; 39: 1295-1299
17. Sunairi M, Tanaka N, Kuwayama H, Nakajima M. Effect of Z-103, a new antiulcer agent, on Helicobacter pylori—antimicrobial, antiurease, and antiahesive activities. Jpn
Isomoto H et al. Effect of sofalcone on H pylori eradication rate

Pharmacol Ther 1994; 22: 31-35

Sunairi M, Watanabe K, Suzuki T, Tanaka N, Kuwayama H, Nakajima M. Effects of anti-ulcer agents on antibiotic activity against Helicobacter pylori. Eur J Gastroenterol Hepatol 1994; 6 Suppl 1: S121-S124

Nagata T, Numata K, Hanada K, Kondo I. The susceptibility of Campylobacter pylori to agents and antibiotics. J Clin Gastroenterol 1990; 12 Suppl 1: S135-S138

Koga T, Kawada H, Utsui Y, Domon H, Ishii C, Yasuda H. Bactericidal effect of pluotanol, a cytoprotective antiulcer agent, against Helicobacter pylori. J Antimicrob Chemother 1996; 38: 387-397

Slomiany BL, Piotrowski J, Slomiany A. Suppression of Helicobacter pylori urease activity by sucralate and sulglycotide. Biochem Mol Biol Int 1997; 42: 155-161

Hahn KB, Lee KJ, Kim YS, Kim JH, Cho SW, Yim H, Joo HJ. Augmented eradication rates of Helicobacter pylori by new combination therapy with lansoprazole, amoxicillin, and rebamipide. Dig Dis Sci 1998; 43: 233-240

Kodama R, Fujikura T, Fujiyama K, Kawasaki H, Kubota T, Nasu M. Combination therapy with clarithromycin and sofalcone for eradication of Helicobacter pylori. Eur J Gastroenterol Hepatol 1994; 6 Suppl 1: S125-S128

Sakaki N, Arakawa T, Kozawa H, Yamada Y, Kato H, Komisawa T, Momma K. Preliminary study on a novel quadruple eradication therapy with a mucoprotective drug, sofalcone, for Helicobacter pylori infection. J Clin Gastroenterol 1998; 27 Suppl 1: S187-S191

Kashimura H, Suzuki K, Hassan M, Ikezawa K, Sawahata T, Watanabe T, Nakahara A, Mutoh H, Tanaka N. Polaprezinc, a mucosal protective agent, in combination with lansoprazole, amoxicillin and clarithromycin increases the cure rate of Helicobacter pylori infection. Aliment Pharmacol Ther 1999; 13: 483-487

Kagaya H, Kato M, Komatsu Y, Mizushima T, Sukeyawa M, Nishikawa H, Hokari K, Takeda H, Sugiyama T, Asaka M. High-dose ecabet sodium improves the eradication rate of Helicobacter pylori in dual therapy with lansoprazole and amoxicillin. Aliment Pharmacol Ther 2000; 14: 1523-1527

Adachi K, Ishihara S, Hashimoto T, Hirakawa K, Niigaki M, Takashima T, Kaji T, Kawamura A, Sato H, Okuyama T, Watanabe M, Kinoshita Y. Efficacy of sucralfate for eradication of Helicobacter pylori eradication triple therapy in comparison with a lansoprazole-based regimen. Aliment Pharmacol Ther 2000; 14: 919-922

Isomoto H, Inoue K, Fusuru H, Nishiyama H, Ishihara S, Omagari K, Mizuta Y, Murase K, Murata I, Kohno S. Lafortidine, a novel histamine H-receptor antagonist, versus lansoprazole in combination with amoxicillin and clarithromycin for eradication of Helicobacter pylori. Helicobacter 2003; 8: 111-119

Isomoto H, Inoue K, Fusuru H, Enjoji A, Fujimoto C, Yamakawa M, Hirakata Y, Omagari K, Mizuta Y, Murase K, Shimada S, Murata I, Kohno S. High-dose rebamipide/amoxicillin vs rebamipide/amoxicillin/metronidazole as second-line treatment after failure of the Japanese standard regimen for Helicobacter pylori infection. Aliment Pharmacol Ther 2003; 18: 101-107

Isomoto H, Inoue K, Mizuta Y, Nakazato M, Kanazawa Y, Nishiyama H, Ohara H, Urata M, Omagari K, Miyazaki M, Murase K, Murata I, Kohno S. Validation of endoscopic 13C-urea breath test with nondispersive infrared spectrometric analysis in the management of Helicobacter pylori infection. Hepatogastroenterology 2003; 50: 422-425

Ohara S, Kato M, Asaka M, Toyota T. The UBIT-100 13CO2 infrared analyzer: comparison between infrared spectrometric analysis and mass spectrometric analysis. Helicobacter 1998; 3: 49-53

Muramatsu M, Tanaka M, Suwa T, Fujita A, Otomo S, Aihara H. Effect of 2′-carboxymethoxy-4′-bis (3-methyl-2-butenylxoy) chalcone (SU-88) on prostaglandin metabolism in hog gastric mucosa. Biochem Pharmacol 1984; 33: 2629-2633

Suzuki H, Mori M, Seto K, Miyazawa M, Kii A, Suehatsu M, Yoneda T, Miura S, Ishii S. Polaprezinc attenuates the Helicobacter pylori-induced gastric mucosal leukocyte activation in Mongolian gerbils-a study using intravital videomicroscopy. Aliment Pharmacol Ther 2001; 15: 715-725

Suzuki M, Kitaohara T, Nagahashi S, Suzuki H, Mori M, Hibi T, Ishii H. Gastric urease activity is inversely associated with the success of treatment for Helicobacter pylori: effect of sofalcone. J Clin Gastroenterol 1998; 27 Suppl 1: S183-S186

Kuwayama H. Zinc compound is a novel, highly effective triple therapy for eradication of Helicobacter pylori. Gastroenterology 1995; 108: A138

Furuta T, Shirai N, Takashima M, Xiao F, Hanai H, Sugimura H, Ohashi K, Ishizaki T, Kaneko E. Effect of genotypic differences in CYP2C19 on cure rates for Helicobacter pylori infection by triple therapy with a proton pump inhibitor, amoxicillin, and clarithromycin. Clin Pharmacol Ther 2001; 69: 158-168

Miyoshi M, Mizuno M, Ishiki K, Nagahara Y, Maga T, Torigoe T, Nasu J, Okada H, Yokota K, Oguma K, Tsuji T. A randomized open trial for comparison of proton pump inhibitors, omeprazole versus rebamipide, in dual therapy for Helicobacter pylori infection in relation to CYP2C19 genetic polymorphism. J Gastroenterol Hepatol 2001; 16: 723-728

Yasuda S, Horai Y, Tomono Y, Nakai H, Yamato C, Manabe K, Kobayashi K, Chiba K, Ishizaki T. Comparison of the kinetic disposition and metabolism of E3810, a new proton pump inhibitor, and omeprazole in relation to S-mephytonin 4′-hydroxylation status. Clin Pharmacol Ther 1995; 58: 143-154

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