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• *BRIEF REPORTS* •

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

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CONCLUSION: The addition of sofalcone, but not polaprezinc, significantly increased the cure rate of *H pylori* infection when combined with the rabeprazole-amoxicillin-clarithromycin regimen.

Key words: *Helicobacter pylori* ; Sofalcone; Mucoprotective agents

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Abstract

AIM: The mucoprotective agents, sofalcone and polaprezinc have anti-*Helicobacter pylori* (*H pylori*) activities. We determined the therapeutic effects of sofalcone and polaprezinc when combined with rabeprazole, amoxicillin and clarithromycin for *Helicobacter pylori* infection.

METHODS: One hundred and sixty-five consecutive outpatients with peptic ulcer and *H pylori* infection were randomly assigned to one of the following three groups and medicated for 7 d. Group A: triple therapy with rabeprazole (10 mg twice daily), clarithromycin (200 mg twice daily) and amoxicillin (750 mg twice daily). Group B: sofalcone (100 mg thrice daily) plus the triple therapy. Group C: polaprezinc (150 mg twice daily) plus the triple therapy. Eradication was considered successful if ^{13}C-urea breath test was negative at least 4 wk after cessation of eradication regimens or successive famotidine in the cases of active peptic ulcer.

RESULTS: On intention-to-treat basis, *H pylori* cure was achieved in 43 of 55 (78.2%) patients, 47 of 54 (87.0%) and 45 of 56 (80.4%) for the groups A, B and C respectively. Using per protocol analysis, the eradication rates were 81.1% (43/53), 94.0% (47/50) and 84.9% (45/53) respectively. There was a significant difference in the cure rates between group A and B. Adverse events occurred in 10, 12 and 11 patients, from groups A, B and C respectively, but the events were generally mild.

INTRODUCTION

Helicobacter pylori (*H pylori*) causes type B chronic gastritis and plays a critical role in the pathogenesis of peptic ulceration[1,2]. Eradication of *H pylori* infection facilitates ulcer healing and prevents recurrence[3-5]. 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[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[8]. Nevertheless, there are still some disadvantages to be addressed such as drug resistance when considering the PPI-based triple therapies[9-13]. With the rising prevalence of resistance of *H pylori* to metronidazole or clarithromycin, failure rates of the PPI-based regimens are expected to increase[12,13].

A variety of gastric mucoprotective agents have been used as anti-ulcer drugs, usually in combination with antacids, in the upper gastrointestinal tract[14]. Among these, rebamipide, ecabet sodium, sofalcone, polaprezinc, plaunotol and sucralfate are uncomplicated by drug resistance and have anti-*H pylori* activities[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[14,22-27]. 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 ^{13}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 ^{13}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, ^{13}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[31].

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[24]. The cure rate was calculated together with 95% confidence intervals (CI). Statistical analyses were performed using the χ^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[1]	Group B[1]	Group C[1]
Mean age, yr (range)	45.3 (21-73)	47.2 (27-71)	45.6 (21-71)
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)
Gastroduodenal ulcer (%)	2 (3.6)	2 (3.7)	1 (1.8)
Active ulcer (%)	27 (49.1)	32 (59.3)	28 (50.0)

[1]Group A: triple therapy with rabeprazole (10 mg twice daily), clarithromycin (200 mg twice daily) and amoxicillin (750 mg twice daily). Group B: sofalcone (100 mg thrice daily) plus the triple therapy. Group C: polaprezinc (150 mg twice daily) plus the triple therapy. Patients received the medications for 7 d in each group.

Table 2 shows ITT and PP *H pylori* eradication rates in each treatment group. In the ITT analysis, there were no significant differences in *H pylori* cure rates among the three groups, while the PP-based eradication rate in group B was significantly higher than that in group A ($P<0.05$). Background characteristics including age, gender, body weight, current tobacco use, alcohol intake and baseline diagnosis did not affect treatment outcome.

Table 2 Intention-to-treat and per protocol cure rates of *H pylori* infection

Group[1]	Intention-to-treat (%)	95% CI[2]	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

[1]See Table 1 for the definition of each group. Patients received the medications for 7 d in each group; [2]CI: Confidence intervals.

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.

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

	Group A[1]	Group B[1]	Group C[1]
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)

[1]See Table 1 for the definition of each group. Patients received the medications for 7 d in each group.

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]. Amidst 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*[32]. 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[33]. It also inhibits the growth of *H pylori*, in addition to its urease activity and adhesion to gastric mucin[17,25]. 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*[24], 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*[23], 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[25]. Kuwayama *et al*[35] 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[9-13,36,37]. 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[28-30]. 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 polymorphisms of the metabolic enzyme[38]. In this study, susceptibility of *H pylori* to antibiotics was not assessed, although we did endeavor to minimize the risk of antibiotic resistance by excluding patients who had taken medications, effective against the organism. However, Hoshiya *et al*[11], reported that based on the current wide use of clarithromycin, no less than 12.5% of their *H pylori* infected patients showed primary resistance to this agent. Clarithromycin resistance 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.

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