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World J Gastroenterol 2005;11(11):1680-1684
World Journal of Gastroenterology ISSN 1007-9327

• *BRIEF REPORTS* •

One-year follow-up study of *Helicobacter pylori* eradication rate with ^{13}C-urea breath test after 3-d and 7-d rabeprazole-based triple therapy

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Received: 2004-09-30 Accepted: 2004-10-18

Abstract

AIM: To investigate the long-term role of a 3-d rabeprazole-based triple therapy in patients with *Helicobacter pylori* (*H pylori*)-infected active peptic ulcers.

METHODS: We prospectively studied 115 consecutive patients with *H pylori*-infected active peptic ulcers. *H pylori* infection was confirmed if any two of *H pylori* DNA, histology, and rapid urease test were positive. Patients were assigned to either an open-labeled 3-d course of oral amoxicillin 1 000 mg b.i.d., clarithromycin 500 mg b.i.d., and rabeprazole 20 mg b.i.d., or 7-d course of oral amoxicillin 1 000 mg b.i.d., clarithromycin 500 mg b.i.d., and rabeprazole 20 mg b.i.d. Subsequently, all patients received oral rabeprazole 20 mg once daily until the 8th wk. Three months after therapy, all patients were followed-up endoscopically for the peptic ulcer, *H pylori* DNA, histology, and rapid urease test. One year after therapy, *H pylori* infection was tested using the ^{13}C-urea breath test.

RESULTS: The ulcer healing rates 3 mo after therapy were 81.0% *vs* 75.4% for the 3-d and 7-d groups [intention-to-treat (ITT) analysis, $P = 0.47$] respectively, and 90.4% *vs* 89.6% for the 3-d and 7-d groups [per-protocol (PP) analysis, $P = 0.89$] respectively. The eradication rates 3 mo after therapy were 75.9% *vs* 73.7% for the 3-d and 7-d groups (ITT, $P = 0.79$) respectively, and 84.6% *vs* 87.5% for the 3-d and 7-d groups (PP, $P = 0.68$) respectively. One year after therapy, seventy-five patients returned to receive the ^{13}C-urea breath test, and the eradication rates were 78.4% *vs* 81.6% in 3-d and 7-d groups (PP, $P = 0.73$) respectively.

CONCLUSION: Our study showed the eradication rates against *H pylori* infection 3 and 12 mo after triple therapy were not different between the 3-d and 7-d rabeprazole-based groups. Therefore, the 3-d rabeprazole-based triple therapy may be an alternative treatment for peptic ulcers with *H pylori* infection.

Key words: Eradication rate; Short-term triple therapy

Wang HH, Chou JW, Liao KF, Lin ZY, Lai HC, Hsu CH, Chen CB. One-year follow-up study of *Helicobacter pylori* eradication rate with ^{13}C-urea breath test after 3-d and 7-d rabeprazole-based triple therapy. *World J Gastroenterol* 2005; 11(11): 1680-1684
http://www.wjgnet.com/1007-9327/11/1680.asp

INTRODUCTION

Helicobacter pylori (*H pylori*), a gram-negative spiral organism, was isolated from the mucosal biopsies of patients with chronic active gastritis by Marshall and Warren in 1983[1]. *H pylori* infection plays an important role in the pathogenesis of peptic ulcer disease, type B gastritis, gastric carcinoma, gastroesophageal reflux disease and lymphoma of mucosa-associated lymphoid tissue[2-6].

At present, the eradication of *H pylori* infection is considered to be a cost-effective method in the treatment of peptic ulcer disease[7,8]. Furthermore, in a recent randomized controlled trial, Wong *et al*[9] found that in *H pylori* carriers without precancerous lesions, eradication of *H pylori* significantly decreased the development of gastric cancer in a high-risk region of China. One-week proton pump inhibitor (PPI)-based triple therapy has been widely accepted as the standard treatment for *H pylori* eradication[10-12]. The *H pylori* eradication rate is higher than 90.0% with the combination of two antimicrobials and a PPI.

There has been recent studies in the eradication of *H pylori* infection[13,14] using short-term (<7-d duration) PPI-based therapy. This is because if a short-term eradication regimen is proven to be effective, it would provide advantages in cost-saving and better patient compliance. Rabeprazole is a newly developed PPI with potent and rapid acid-suppression[15]. It has been demonstrated in one study to have a higher eradication rate than omeprazole[16]. The long-term role of a 3-d rabeprazole-based triple therapy against *H pylori* infection is not known at present. We, therefore,

conducted a randomized, prospective study in patients with active peptic ulcer disease and *H pylori* infection to compare the efficacy and one-year eradication rates between 3-d and 7-d rabeprazole-based triple therapy.

MATERIALS AND METHODS

Selection of patients

From February 2002 to February 2003, we prospectively studied 115 consecutive outpatients (73 male and 42 female, Table 1) documented with *H pylori* infection as well as active gastric ulcers or duodenal ulcers or both at the China Medical University Hospital. All peptic ulcers were confirmed by the first upper gastrointestinal endoscopy.

Table 1 Demographic data of patients who underwent triple therapy

	3-d group	7-d group
Patients (M/F)	36/22	37/20[1]
Age (yr)	48.3 ±12.4	48.7±15.4[2]
Peptic ulcers[3]		
Gastric ulcers	9	12
Duodenal ulcers	40	38
Both	9	7

[1]P = 0.75 (χ^2 test); [2]P = 0.99 (two-sample t-test); [3]P = 0.70 (χ^2 test).

Patients were not allowed to receive aspirin, H_2-receptor blockers, antibiotics or any non-steroidal anti-inflammatory drugs (NSAIDs) in the 4 wk prior to the study. All females with active gastrointestinal bleeding, pregnancy, lactation, delayed last menstrual period or previous curative therapy for *H pylori* infection were excluded. Patients with a history of hypersensitivity to PPIs, penicillin groups, amoxicillin, or clarithromycin, concurrent serious systemic disease including malignancy, renal, hepatic or cardiac insufficiency, or previous esophageal or gastric surgery were also excluded.

The present study was approved by the Ethics and Science Committee of the hospital. Written informed consent was obtained from all patients before the study.

Diagnosis of H pylori infection

During the first endoscopic examination, two biopsy specimens were obtained from the gastric antrum within 2 cm proximal to the pyloric ring. One antral biopsy specimen was assessed for *H pylori* DNA. The *H pylori* DNA was detected using PCR. Another antral biopsy specimen was sent for rapid urease test (RUT) (CLO test, Ballard Medical Products, Draper, UT, USA). In addition, one biopsy specimen was taken from the gastric corpus and sent for histological examination for *H pylori* using hematoxylin-eosin staining or Giemsa staining if necessary. For those patients with gastric ulcers, additional biopsies were made from four sites of the margin of gastric ulcers to rule out possible malignancy. Patients were considered to have *H pylori* infection if they were positive for any two of the three tests.

Clinical treatment

All patients were randomly assigned into two groups. Group I patients received a 3-d course of oral amoxicillin 1 000 mg b.i.d., clarithromycin 500 mg b.i.d., and 7-d course of oral rabeprazole 20 mg b.i.d., Group II patients received a 7-d course of oral amoxicillin 1 000 mg b.i.d., clarithromycin 500 mg b.i.d., and rabeprazole 20 mg b.i.d. All patients further received oral rabeprazole 20 mg once daily until the end of the 8th wk. All the medications were open-labeled. Both groups of the patients were questioned about the occurrence and intensity of adverse effects one week later after triple therapy.

Three months follow-up

Three months after the completion of triple therapy, a repeat endoscopy was performed for examination of the peptic ulcers, *H pylori* DNA, RUT, and histology. *H pylori* infection was considered to be eradicated if all the three tests were negative.

Long-term follow-up

One year after the completion of triple therapy, *H pylori* infection was diagnosed using the ^{13}C-urea breath test (^{13}C-UBT) (Pei Li Pharmaceutical Industrial Ltd, Taichung, Taiwan).Patients were not permitted to receive antacids within 4 wk prior to the ^{13}C-UBT. A negative ^{13}C-UBT indicated no *H pylori* infection.

Statistical analysis

The eradication and healing rates of ulcers were evaluated by intention-to-treat (ITT) analysis and per protocol (PP) analysis. The ITT analysis included all enrolled patients including those cases dropped from the study. The PP analysis included all patients who took at least 80.0% of each study medication and returned for assessment of eradication of *H pylori* infection after three months and one year. Two-sample test or χ^2 test was used to assess significant differences between values in various groups of patients. The eradication rate and ulcer healing rate were calculated for 95.0% confidence intervals. A P-value of less than 0.05 was regarded as statistically significant. Statistical analysis was performed using commercial software (SAS v.8.0, SAS Institute Inc., Cary, NC, USA).

Results were expressed in the form of mean±SD.

RESULTS

Of the 115 patients, 21 patients had gastric ulcers, 78 had duodenal ulcers and 16 had both ulcers. Fifty-eight patients received the 3-d course and 57 received the 7-d course of triple therapy. Fifteen patients, who did not complete the 3-mo follow-up after treatment, were dropped from the study; six of the dropped patients were from the 3-d group and nine patients from the 7-d group.

The ulcer healing rate 3 mo after triple therapy showed no difference with 81.0% in 3-d group and 75.4% in 7-d group (ITT, P = 0.47), and 90.4% in 3-d group and 89.6% in 7-d group (PP, P = 0.89, Table 2).

The eradication rate of *H pylori* infection three months after triple therapy showed no difference with 75.9% in 3-d group and 73.7% in 7-d group (ITT, P = 0.79), and 84.6% in 3-d group and 87.5% in 7-d group (PP, P = 0.68).

Table 2 Eradication rate of patients who underwent triple therapy

	3-d group	7-d group	*P*	OR (interval)
Ulcer healing rate				
Patients number	58	57		
ITT	47 (81.0%)	43 (75.4%)	0.47	0.72 (0.30-1.75)
PP	47 (90.4%)	43 (89.6%)	0.89	0.92 (0.25-3.38)
Eradication rate				
3 mo after therapy				
Patients number	58	57		
ITT	44 (75.9%)	42 (73.7%)	0.79	0.89 (0.3-2.07)
PP	44 (84.6%)	42 (87.5%)	0.68	1.27 (0.41-3.98)
One year after therapy				
Patients (M/F)	37 (23/14)	38 (24/14)	0.93[1]	1.22 (0.39-3.80)
PP	29 (78.4%)	31 (81.6%)	0.73	0.82 (0.26-2.54)

ITT, Intention-to-treat analysis; PP, Per-protocol analysis, [1]$P = 0.93$ (χ^2test).

One year after triple therapy, seventy-five patients had ^{13}C-UBT for the assessment of *H pylori* infection; the eradication rate showed no difference between 3-d and 7-d groups (78.4% *vs* 81.6%; $P = 0.73$, PP). Eight patients in the 3-d group were positive for ^{13}C-UBT. There were 4 cases with treatment failure at 3 mo after treatment, including 1 case of gastric ulcer and 3 cases of duodenal ulcer. Seven patients in the 7-d group were positive for ^{13}C-UBT. There were 4 cases with treatment failure at 3 mo after treatment, including 2 cases of gastric ulcer and 2 cases of duodenal ulcer.

The eradication rate (PP) decreased from 84.6% to 78.4% in the 3-d group and from 87.5% to 81.6% in the 7-d group from 3 mo to 12 mo after rabeprazole-based triple therapy.

During the period of therapy, severity of symptoms such as epigastric pain, acid regurgitation, anorexia, nausea, vomiting, belching and flatulence showed rapid decline on the first 2 d after triple therapy in both groups. Drug compliance during this study was excellent - 100% in the 3-d RAC group and 99.4% in the 7-d RAC group. Both regimens were well tolerated. Adverse events in both groups were mild, which included taste disturbance, diarrhea, oral discomfort and chill sensation. Taste disturbance (bitter taste) was the most common event, comprising about 50% of cases in 3-d and 7-d triple therapies groups. The adverse events were mild and self-limiting and disappeared after one week.

DISCUSSION

Even though many different therapeutic regimens studied for *H pylori* eradication in acid-related disorders[7,8], 1-wk PPI-based triple therapy has been widely accepted for the standard treatment of peptic ulcer with *H pylori* infection[10-12,17]. However, the optimal duration of triple therapy remains to be established. More recently, many newer PPIs have been developed, and they possess potent and rapid inhibition of gastric acid secretion[18,19]. Therefore, short-term regimens (<7-d) have been suggested for the eradication of *H pylori* infection[13,14]. Lara *et al*[20] performed a randomized and prospective study for the eradication of *H pylori* infection in patients with dyspepsia. They found 1-d quadruple therapy (bismuth, metronidazole, amoxicillin and lansoprazole) was statistically similar to 7-d triple therapy (clarithromycin, amoxicillin and lansoprazole) (95% *vs* 90%, ITT). However, Wermeille *et al*[21] reported that the eradication rate of 1-d high-dose quadruple therapy (lansoprazole 30 mg t.d.s., amoxicillin 2 000 mg q.d.s., clarithromycin 500 mg q.d.s., and bismuth 240 mg q.d.s.) was significantly less (20% *vs* 80%) than 7-d triple therapy (lansoprazole 30 mg b.d., amoxicillin 1 000 mg b.d., and clarithromycin 500 mg b.d.).

More recently, a new PPI, rabeprazole, has been demonstrated to be effective in the treatment of acid-related disorders including peptic ulcer disease[22-24]. Rabeprazole has rapid and potent inhibition of gastric acid secretion[18]. In addition, this PPI can induce earlier stabilization of antibiotics and has higher eradication rate compared to other PPIs[16,22,25].

Several studies have compared the eradication rate of short-term course with standard course rabeprazole-based triple therapy for *H pylori* infection. In a study by Gambaro *et al*[26], non-ulcer dyspepsia patients were randomized to receive rabeprazole, clarithromycin and metronidazole for 4 or 7 d, and similar *H pylori* eradication rates were achieved with both regimens (81% *vs* 78%, ITT; 88% *vs* 85%, PP). Yang *et al*[27] compared the efficacy of a 4 and a 7-d rabeprazole-based regimen (rabeprazole, clarithromycin and amoxicillin) with a 7-d omeprazole-based regimen (omeprazole, clarithromycin and amoxicillin) in the eradication of *H pylori* in peptic ulcer patients. This study showed equal efficacy among the three groups (87% *vs* 83% *vs* 88%, ITT; 91% *vs* 95% *vs* 100%, PP). Isomoto *et al*[28] randomly compared a rabeprazole-clarithromycin-amoxicillin regimen for 5 and 7 d in *H pylori*-infected patients. Their results showed 5-d regimen had lower eradication rate than the 7-d regimen (66% *vs* 84%, ITT; 70% *vs* 91%, PP [$P<0.05$]). Recently, a multicenter, double blind, randomized, parallel-group clinical study was performed by Vakil *et al*[17], in the USA. The trial results showed that 7-d therapy with rabeprazole-clarithromycin-amoxicillin is similar in efficacy to 10-d therapies and had similar efficacy in patients with and without ulcer disease. Wong *et al*[29] performed a randomized study to compare rabeprazole-amoxicillin-clarithromycin administration for 3 and 7 d. They found 3-d regimen had a lower *H pylori* eradication rate than 7-d regimen (72% *vs* 88%, ITT; 72% *vs* 91%, PP). Hence, they concluded 7-d rabeprazole-based triple therapy is superior to 3-d regimen ($P = 0.04$).

Interestingly, our study showed that a 3-d rabeprazole-based triple therapy regimen had similar eradication rates (84.6% *vs* 87.5%, PP, $P = 0.68$) against *H pylori* infection and similar ulcer healing rates (90.4% *vs* 89.6%, PP, $P = 0.89$) compared to a 7-d rabeprazole-based triple therapy regimen in 3 mo follow-up. The major differences between our study and Wong's previous study were the following. First, we gave the drugs of amoxicillin 1 000 mg, clarithromycin 500 mg twice daily for 3 d and rabeprazole 20 mg twice daily for 7-d, then tapered to once daily for 7 wk. In Wong *et al*'s study, however, they only gave additional 4-wk course of famotidine 20 mg b.i.d., for all gastric ulcer patients after *H pylori* eradication. Second, all the patients in our study suffered from active peptic ulcer with *H pylori* infection,

but not all the patients were with peptic ulcer disease in Wong *et al*'s study. Actually, we considered that the large dose of PPI combined with antibiotics in the first week of treatment may be an important factor for *H pylori* eradication.

There is no doubt that an ideal *H pylori* treatment must be safe, cheap, easy and tolerable with more than 80% eradication rate and must have a low rate of antibiotic resistance[30,31]. Although treatment failures of *H pylori* eradication are influenced by several factors[32,33], many of the currently used *H pylori* eradication regimens fail to cure the infection due to either antimicrobial resistance or poor patient compliance[34-36]. In the past, there have been concerns about antimicrobial resistance of *H pylori* eradication in many studies[37,38]. A high prevalence of metronidazole resistance has been reported in different regions in Asia[39]. However, clarithromycin resistance is still low in the United States and most communities[40,41]. In standard 1-wk PPI-based triple therapy, the large number of pills needed to be taken daily, the duration of the therapy and the presence of adverse events can limit patient compliance. A recent article has concluded that patient noncompliance is a major cause of failure of *H pylori* eradication therapy[36]. A short-term PPI-based triple regimen will have a smaller overall amount of pills and possibly fewer adverse effects, and thereby improve patient compliance compared with standard 7-d regimens. In addition, there will be health economic and cost saving advantages for patients.

Our study also showed drug compliance in the 3-d regimen was also excellent compared to the 7-d regimen (100% *vs* 99.4%). Adverse events were mild, few and self-limiting in both study groups. Taste disturbance (oral bitter taste) was the most common adverse event in both groups, but this disappeared a few d later.

To our knowledge, however, the long-term follow-up results of *H pylori* eradication after short-term triple therapy have not been reported in published scientific English literature until now. The ^{13}C-UBT is a simple, noninvasive and rapid method for the initial diagnosis of *H pylori* infection and for confirmation of *H pylori* eradication after treatment. Its sensitivity and specificity rates are more than 90%[42,43]. We therefore performed the ^{13}C-UBT to detect *H pylori* infection one year after triple therapy in our study. The eradication rates of *H pylori* infection were similar (74.8% *vs* 81.6%, PP [P = NS]) in the 3-d and 7-d rabeprazole-based triple therapy regimens after 1-year follow-up.

The study demonstrates that 3-d rabeprazole-based triple therapy has the similar efficacy and safety as standard 7-d triple therapy in *H pylori* eradication and long-term follow-up. Hence, 3-d rabeprazole-based triple therapy may be an alternative treatment for peptic ulcer disease with *H pylori* infection.

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Science Editor Guo SY **Language Editor** Elsevier HK