RESEARCH ARTICLE

High Efficacy of Levofloxacin-Dexlansoprazole-Based Quadruple Therapy as a First Line Treatment for *Helicobacter pylori* Eradication in Thailand

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Abstract

Background: Levofloxacin is an effective medication for second line *Helicobacter pylori* (*H. pylori*) eradication. However, limited studies have approved its use as an effective antibiotic in first line therapy. Dexlansoprazole is a new PPI and lacks of evidence in support of a role in *H. pylori* eradication. This study was designed to evaluate efficacy of levofloxacin-dexlansoprazole-based quadruple therapy for *H. pylori* eradication in Thailand. Materials and Methods: This prospective randomized control study was performed during June 2014 to December 2014. *H. pylori* infected gastritis patients were randomized to receive 7- or 14-day levofloxacin-dexlansoprazole based on quadruple therapy (levofloxacin 500 mg OD, dexlansoprazole 60 mg bid, clarithromycin MR 1000 mg OD, bismuth subsalicylate 1048 mg bid). CYP2C19 genotyping and antibiotic susceptibility tests were conducted for all patients. A 13C urea breath test was performed to confirm *H. pylori* eradication at least 4 weeks after treatment. Results: A total of 100 patients were enrolled, comprising 44 males and 56 females (mean age of 52.6 years). Eradication rate by PP analysis was 85.7% (42/49) with the 7-day regimen and 98% (48/49) with the 14-day regimen (85.7% *vs* 98%; p-value=0.059). ITT analysis was 84% and 96% with 7- and 14-day regimens, respectively (84% *vs* 96%; p-value=0.092). Antibiotic susceptibility testing demonstrated 35.1% resistance to metronidazole, 18.3% to clarithromycin, and 13.5% to levofloxacin. CYP2C19 genotyping revealed 54.1% RM, 34.7% IM and 11.2% PM. The 14-day regimen provided 100% eradication in patients with clarithromycin or dual clarithromycin and metronidazole *H. pylori* resistant strains. Moreover, the eradication rate was 96.6% in patients with CYP2C19 genotype RM. Conclusions: The 14-day levofloxacin-dexlansoprazole based quadruple therapy provides high *H. pylori* eradication regardless of CYP2C19 genotype, clarithromycin or dual clarithromycin and metronidazole resistant strains. This regimen could be use as an alternative first line therapy for *H. pylori* eradication in Thailand.

Keywords: Levofloxacin - dexlansoprazole - quadruple therapy - *Helicobacter pylori* eradication - Thailand

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Introduction

Helicobacter pylori (*H. pylori*), a gram-negative bacterium found on the luminal surface of the gastric epithelium, was first isolated in 1984 (Marshall and Warren, 1984). It induces chronic inflammation of the underlying mucosa resulting in the development of important upper gastrointestinal diseases such as gastritis, peptic ulcer diseases, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer (Rauws and Tytgat, 1990; Parsonnet et al., 1991; Bayerdorffer et al., 1995; Vilaichone and Mahachai, 2001). Moreover, a recent meta-analysis has shown that *H. pylori* eradication potentially reduces the incidence of gastric cancer, especially in high prevalence area of gastric cancer (Ford et al., 2014).

For years, *H. pylori* has been regarded as a difficult-to-treat infection due to the bacterium's nature, and readily acquired resistance to commonly used antibiotics. Therefore, standard triple therapy with proton pump inhibitor (PPI), amoxicillin and clarithromycin is no longer recommended as an empiric choice in most countries (Chey and Wong, 2007; Mahachai et al., 2011). Levofloxacin-based triple therapy for *H. pylori* eradication has been shown to increase cure rate with minimal side effects. However, levofloxacin-based triple therapy provided excellent results only in levofloxacin sensitivity (Antos et al., 2006). Interestingly, recent studies have demonstrated the positive effect of adding bismuth salt to levofloxacin-based triple therapy for *H. pylori* eradication, especially in levofloxacin resistance (Liao et al., 2013).

We conduct this study for searching an optimal

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combination of drugs and duration for first line *H. pylori* eradication in Thailand. We reported a prospective randomized trial evaluating *H. pylori* eradication by using levofloxacin-dexlansoprazole based quadruple therapy for 7- or 14-day. The effects of CYP2C19 genotype and antibiotic resistance were also examined.

Materials and Methods

Patients

Eligible patients age 18-75 years who underwent gastroscopic examination at Thammasat University Hospital, for dyspeptic symptoms between June 2014 and December 2014 were enrolled. After the endoscopy, those with diagnosis of non-ulcer dyspepsia, which was established during gastroscopy with normal finding or mild gastritis, were considered for entry in this study. Exclusion criteria included patients with a history of prior *H. pylori* eradication, previous gastric surgery, pregnancy, lactation, major systemic diseases, cardiovascular disease or administration of antibiotics, bismuth and PPI drugs in the preceding 4 weeks, or allergy to any one of the given medication in the regimens. All patients provided written informed consent.

The diagnosis of H. pylori infection

During the endoscopy, 4 biopsy samples from gastric antrum were obtained for rapid urease test, *H. pylori* culture and Epsilometer test (E-test) or GenoType®HelicoDR, histological examination and CYP2C19 genotype. The results of CYP2C19 genotype testing were expressed as: rapid metabolizer (RM), intermediate metabolizer (IM) or poor metabolizer (PM). The presence of *H. pylori* was defined as: (1) positive *H. pylori* culture, or (2) positive tests (rapid urease test or histology).

Therapeutic regimens

Randomization was made by reference to a computer-generated list. The two different groups were given for 7-day or 14-day of 500mg levofloxacin once daily, 60mg dexlansoprazole twice daily, 1g long acting clarithromycin MR once daily, and 1048mg bismuth subsalicylate twice daily.

Post-therapy follow-up

At least 4 weeks after completion of therapy, 13C-urea breath test (UBT) was carried out in all patients to assess *H. pylori* eradication. Successful eradication was defined as a negative result from UBT. Pill count was conducted, and drug consumption over 90% was defined as good compliance. Side effects were assessed by personal interview using open-ended questions. The potential adverse events listed in the questionnaires were diarrhea, bitter taste, nausea, vomiting, palpitation, and skin rashes. New symptoms and exacerbation of pre-existing symptoms during the treatment period were considered to be therapy-related adverse events. Serious adverse events were defined as events that disturbed on daily activities.

Statistical analysis

We expected the eradication rate of levofloxacin-dexlansoprazole based quadruple therapy as an empiric therapy to be≥90%. Treatment success was pre-specified as a cure rate of≥95% (i.e. grade A) as described in previous studies (Graham et al., 2007), and failure as a cure rate of<90% per protocol. The demographic characteristics and frequencies of adverse effects were compared using chi-squared, Fisher's exact and student's t-test. The p-value<0.05 was considered to be statistically significant. The study was conducted according to the good clinical practice guideline, as well as the Declaration of Helsinki, and was approved by our local ethics committee.

Results

Total of 100 patients were included in this study, 44 men and 56 women with a mean age of 52.6 years. All 100 patients were randomized in to 2 groups as previously described. When compared, the patients with 7-day regimens were significantly younger and predominate with women. The baseline demographic data are shown in Table 1. One patient in each group discontinued treatment due to side effects.

Eradication of H. pylori infection

The results analyzed by both intention-to-treat (ITT) and per-protocol (PP) analyses were demonstrated as shown in Figure 1. The eradication rates by ITT analysis was 84% (42/50) with 7-day regimen and 96% (48/50)

Table 1. Baseline Demographic Data of All Patients

Characteristic data	7-day regimen (n = 50)	14-day regimen (n = 50)	P-value
Age (years)	49.72	55.64	0.008
Sex no. (%)			0.026
Male	16 (32)	28 (56)	
Female	34 (68)	22 (44)	
Underlying disease no. (%)			
Hypertension	7 (14)	11 (22)	0.436
Dyslipidemia	3 (6)	5 (10)	0.715
Smoking no. (%)	4 (8)	6 (12)	0.741
Alcohol consumption no. (%)	13 (26)	11 (22)	0.815

Table 2. Results of CYP2C19 Genotype and Eradication Rate

CYP2C19 genotype (n=98)	7-day regimen (n=49)	14-day regimen (n=49)
RM (n=53; 54.1%)	24 (87.5%)	29 (96.6%)
IM (n=34; 34.7%)	20 (85%)	14 (100%)
PM (n=11; 11.2%)	5 (100%)	6 (100%)

Table 3. Adverse Events in Each Regimen

Adverse events	7-day regimen (n=50)	14-day regimen (n=50)	P-value
Bitter taste	45 (90%)	44 (88%)	1
Nausea/Vomiting	5 (10%)	2 (4%)	0.436
Diarrhea	1 (2%)	2 (4%)	1
Black stool	47 (94%)	48 (96%)	1

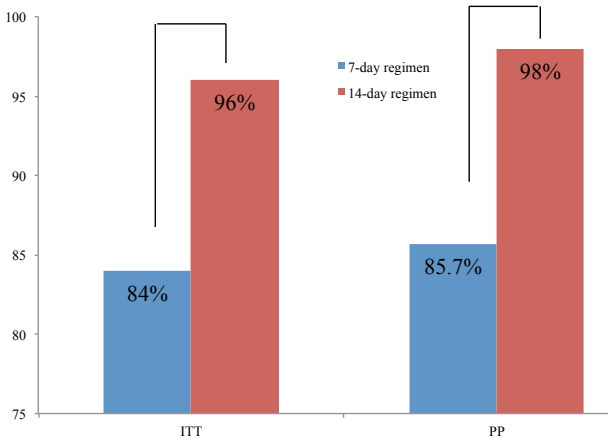

Figure 1. Eradication Rates According to Treatment Regimens

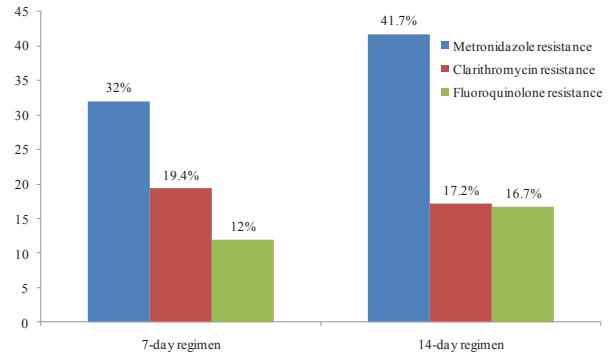

Figure 2. Prevalence of Antibiotic Resistance

with 14-day regimen. PP eradication results were 85.7% (42/49) and 98% (48/49) with 7- and 14-day regimen, respectively. The cure rate was higher in 14-day regimen than those in 7-day regimen from both ITT and PP and could achieve cure rate of grade A (≥95%) as detail in Figure 1.

Antibiotic susceptibility tests were performed in 60 strains (37 from E-test and 23 from GenoType®HelicoDR), which demonstrated 35.1% of metronidazole resistant, 18.3% of clarithromycin resistant and 13.5% of levofloxacin resistant strains as detail in Figure 2. CYP2C19 genotype tests were performed in 98 cases (49 from each 7-day and 14-day regimen). The CYP2C19 genotype tests revealed 54.1% RM, 34.7% IM and 11.2% PM. The prevalence of CYP2C19 genotype was similar in all groups of patients as in Table 2.

Adverse events

The common side effects include diarrhea, bitter taste, nausea, and vomiting which were found in all groups. Two patients (one from each study group) were withdrawn from treatment regimens because of side effects. Documented adverse reactions are shown in Table 3. None of subject experienced any major adverse event.

Discussion

At present, several epidemiological and experimental data support a pathological role between *H. pylori* and the development of gastric cancer (Basiri et al., 2014; Demirel et al., 2013; Rauws and Tytgat, 1990). It was estimated that *H. pylori* infection accounts for approximately 650,000 new cases of gastric cancer annually (de Martel et al., 2012). The eradication rate of *H. pylori* by standard triple therapy with clarithromycin-containing regimen was reported to be less than 70% in many countries worldwide, including Thailand (Vilaichone et al., 2006; Graham, 2009). It has been suggested that clarithromycin-containing regimens should be renounced as an empiric therapy especially in high clarithromycin resistance area.

Bismuth has long been known as an anti-*H. pylori* drug with minimal side effects. The previous study demonstrated that adding bismuth might be a good option to improve the eradication by standard triple therapy apart from increasing the dosage and duration of PPI (Srinarong et al., 2014). Several studies also demonstrated that administration of bismuth in quadruple therapy increased the eradication rate of *H. pylori* up to 90%, comparing to standard triple therapy (Ford et al., 2008; Fock et al., 2009).

Fluoroquinolones have been suggested as alternative drug but generally the results of fluoroquinolone triple therapy was less than 90% (Gisbert and Morena, 2006; Graham and Shiotani, 2012). In addition, recent studies have demonstrated that longer duration with 14-day fluoroquinolone triple therapy provided treatment success of 95% (Miehlke et al., 2011).

Our study supported this idea and also demonstrated high eradication rate (grade A) of *H. pylori* infection from 14-day levofloxacin-dexlansoprazole quadruple therapy as a first line treatment regardless of CYP2C19 genotype, clarithromycin or dual clarithromycin and metronidazole resistant strains. Only minor side effects were observed from this regimen. Furthermore, this 14-day regimen could achieve high cure rate with levofloxacin resistant strains. However, larger multi-center controlled studies are needed to confirm this hypothesis.

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