

RESEARCH ARTICLE

Seven-Day Bismuth-based Quadruple Therapy as an Initial Treatment for *Helicobacter pylori* Infection in a High Metronidazole Resistant Area

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Abstract

Background: The prevalence of metronidazole-resistant *H. pylori* is almost 50% in Thailand which severely limits the use of this drug for eradication therapy. The aims of this study were to evaluate the efficacy and safety profiles of 7-day bismuth-based quadruple therapy including metronidazole as an initial treatment for *H. pylori* infection in a high metronidazole resistance area. **Materials and Methods:** This study was performed at Thammasat University Hospital and King Chulalongkorn Memorial Hospital during January 2009 to October 2010. Patients with non-ulcer dyspepsia (NUD) with active *H. pylori* infection were assigned to receive seven days of quadruple therapy (pantoprazole 40 mg bid, bismuth subsalicylate 1,048 mg bid, amoxicillin 1 gm bid and metronidazole 400 mg tid). *H. pylori* infection was defined as positive *H. pylori* culture or two positive tests (rapid urease test and histology). Antibiotic susceptibility test for metronidazole by Epsilonometer test (E-test) was performed in all positive cultures. At least four weeks after treatment, ¹³C urea breath test (¹³C-UBT) was performed to confirm *H. pylori* eradication. **Results:** A total of 114 patients were enrolled in this study, 50 males and 64 females with a mean age of 49.8 years. All 114 patients had a diagnosis of NUD. Overall eradication as confirmed by negative ¹³C-UBT was achieved in 94 out of 114 patients (82.5%). 44 patients had positive cultures and success for E-test. *In vitro* metronidazole resistance was observed in 22/44 (50%) patients. Eradication rate in patients with metronidazole resistant strains was 16/22 (72.7%) and 20/22 (90.1%) with metronidazole sensitive strains (72.7% vs 90.1%, p-value=0.12; OR=3.75 [95% CI=0.6-31.5]). Minor adverse reactions included nausea, bitter taste, diarrhea and black stools but none of the patients dropped out from the study. **Conclusions:** Initial treatment with 7-day bismuth-based quadruple therapy including metronidazole, amoxicillin and pantoprazole is highly effective and well tolerated for metronidazole-sensitive *H. pylori* infections. However, the efficacy markedly decline with metronidazole resistance. Longer duration of this regimen might be required to improve the eradication rate and larger multi-center studies are needed to confirm this hypothesis.

Keywords: Bismuth - quadruple therapy - *Helicobacter pylori* eradication - Thailand

Asian Pac J Cancer Prev, 16 (14), 6089-6092

Introduction

Helicobacter pylori is the common chronic infection leading to gastritis, peptic ulcer disease, gastric cancer and gastric lymphoma. (Vilaichone et al., 2001; Vilaichone, et al 2006). Effective eradication regimens are required to reduce the consequences of *H. pylori* infection. Standard triple therapy is commonly used regimen recommended by many guidelines. However, the efficacy of triple therapy has recently decline worldwide to 70-75% which is unacceptable (Vilaichone et al., 2006; Vilaichone et al, 2011). Improvement of eradication regimens

depends on local data of antibiotic resistant pattern in each particular area. Metronidazole resistance has been detected approximately 40-50% in Thailand (Vilaichone et al, 2013). Metronidazole resistance, however, has lesser impact on eradication rate compared to clarithromycin resistance. Bismuth has anti-*H. pylori* property that could suppress the bacterial load and was widely used in quadruple therapy (Vilaichone et al., 2006). It has been suggested that bismuth-based quadruple therapy is either as effective as or more effective than standard triple therapy and might be used as first-line treatment (Ferreira and Moss et al., 2014).

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Newer regimens are required in Thailand for effective *H. pylori* eradication. This study was aimed to evaluate the efficacy and safety of bismuth containing quadruple regimen as first line therapy for *H. pylori* eradication in Thailand. We also compared the eradication rates of this quadruple therapy between metronidazole resistant and sensitive groups.

Materials and Methods

Dyspeptic patients who had performed upper GI endoscopy and found to have *H. pylori* infection confirmed by positive *H. pylori* culture; or two positive tests (rapid urease test and histology) were recruited into this study at Thammasat University Hospital and King Chulalongkorn Memorial Hospital during January 2009 to October 2010. Patients must be over 18 years of age and had never received *H. pylori* treatment or received proton pump inhibitor, H2 receptor antagonists, and any antibiotics in the past 1 month. More exclusion criteria included patients with a history of prior gastric surgery, pregnancy, major systemic diseases such as cardiovascular disease, chronic renal and liver diseases or history of allergy to any one of medication in the regimens. Written Informed consents were done before participating in this study. Diagnosis was made according to endoscopic findings. Patients with normal endoscopy and those with gastritis were diagnosed to have non-ulcer dyspepsia (NUD). During endoscopy, three biopsy samples from gastric antrum were collected; one for rapid urease test, one for histology and another biopsy for *H. pylori* culture and antibiotic susceptibility test.

H. pylori culture and antibiotic susceptibility test

H. pylori isolates were obtained by inoculating the specimens on nonselective media (Columbia agar supplemented with 7% sheep blood) under a microaerophilic atmosphere for at least 7 days. The colonies were identified by gram staining, oxidase, catalase and urease production. Susceptibility for metronidazole was tested by the Epsilometer test (E-test). The minimum inhibitory concentration (MIC) was defined as the lowest concentration of antimicrobial agent which completely inhibited any visible growth. Metronidazole resistance was defined as MIC above 8 µg/ml.

Treatment regimen

Only those patients with *H. pylori* infection received seven days of quadruple therapy consisting of pantoprazole 40 mg bid, bismuth subsalicylate 1,048 mg bid, amoxicillin 1 gm bid and metronidazole 400 mg tid. Patients did not receive further PPI therapy.

Post-treatment follow up

Patients returned for follow-up visit at the end of the eradication therapy for assessment of compliance and side effects. Pill count was conducted and drug consumption over 90% was defined as good compliance. Side effects were assessed by personal interview using opened ended questions. New symptoms and exacerbation of pre-existing symptoms during the treatment period were considered to

be therapy-related side effects. ¹³C urea breath test (UBT) was performed to assess *H. pylori* eradication at least 4 weeks after completion of the treatment.

Statistical analysis

We expected the eradication rate of 7-day bismuth-based quadruple therapy as an empiric therapy to be ≥90%. Treatment success was identified 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 association between eradication rate of patients with metronidazole resistance and sensitive was evaluated by using chi-squared. Association between categorical variables were determined using odds ratio and 95% confidence interval (95% CI). The p values <0.05 were considered to be statistically significant. The data analysis was performed by using SPSS version 19 (SPSS Inc., Chicago, IL, USA). The study was conducted according to the good clinical practice guidelines, as well as the Declaration of Helsinki and was approved by our local ethics committee.

Results

A total of 114 patients were enrolled in this study. There were 50 male and 64 female patients with the mean age of 49.8 years. All 114 patients had diagnosis of NUD. Overall eradication rate as confirmed by negative ¹³C-UBT was achieved in 94 out of 114 patients (82.5%). 44 patients had positive cultures and success for E-test. *In vitro* metronidazole resistance determined by E-test was identified in 22/44 (50%) of these patients. Eradication rate of patients with metronidazole resistant strain was 16/22 (72.7%) and 20/22 (90.1%) with metronidazole

Table 1. Adverse Events in All Patients

Adverse events	7-day bismuth-based quadruple therapy (n=114)
Bitter taste	38 (33.3%)
Nausea/Vomiting	14 (12.3%)
Diarrhea	3 (2.6%)
Black stool	102 (89.5%)

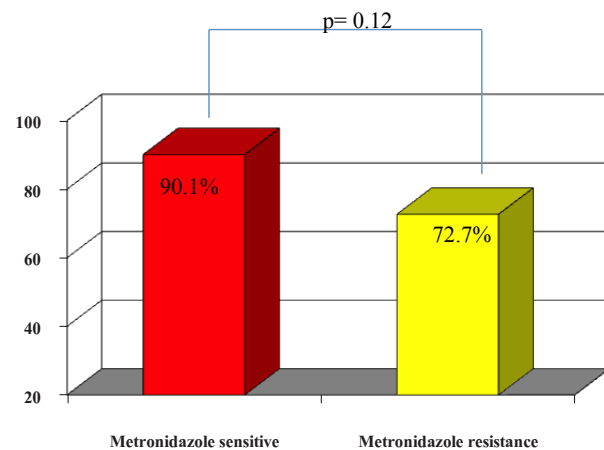


Figure 1. *H. pylori* Eradication Rate Of 7-Day Bismuth-Based Quadruple Therapy in Metronidazole Resistant and Metronidazole Sensitive Strains

sensitive strains (72.7% vs 90.1%, p-value=0.12; OR=3.75 [95%CI=0.6-31.5]). Minor adverse reactions were commonly occurred included nausea, bitter taste, diarrhea and black stools as detail in Table 1. None of the patients dropped out from the study. The side effects disappeared after cessation of the medications.

Discussion

Many epidemiological and experimental data demonstrated a significant role between *H. pylori* and pathogenesis of gastric cancer. It was estimated approximately 700,000 new cases of gastric cancer annually and gastric cancer was document to be the first GI cancer related death. (Rauws and Tytgat, 1990; Demirel et al., 2013; Basiri et al., 2014; Srinarong et al., 2014; Vilaichone et al., 2014; Naghavi et al., 2015). The eradication of *H. pylori* by the high efficacy regimen should be the appropriate tool to reduce and prevent the development of this particular cancer. Standard triple therapy is no longer recommended as a first regimen in several countries (Chey and Wong, 2007; Mahachai et al., 2011). Bismuth based quadruple therapy might be an alternative first line regimen even in metronidazole resistance era. Metronidazole resistance has little impact on eradication rate of quadruple therapy and can be used effectively in the area with high metronidazole resistance (Vilaichone et al., 2006).

Bismuth has long become available in Thailand with an inexpensive price and acceptable side effects such as nausea, vomiting, numbness and metallic taste. Another possible adverse reaction of bismuth is black stools which should be warned to patients and should not confuse with melena from upper GI bleeding. Bismuth has antibacterial activity and prevents bacterial colonization to gastric epithelium and has no prior resistance report to *H. pylori* (Vilaichone et al., 2006). This study demonstrated high eradication rate (>90%) of a 7-day bismuth based quadruple regimen in metronidazole sensitive strain. However, the efficacy of this regimen was reduced to 72.7% in metronidazole resistant group. A longer duration of treatment (eg. 14 days) might give a higher eradication rate but perhaps more side effects can be occurred. In Thailand, 10-day course of sequential therapy and 10-day concomitant therapy provided high *H. pylori* eradication rate (>95%) (Mahachai et al., 2011; Kongchayanun et al., 2012). Thus, sequential and concomitant therapies might be reliable first line for *H. pylori* eradication in our country. Recently, another study from Thailand which used 14-day levofloxacin-dexlansoprazole quadruple therapy demonstrated high eradication rate of *H. pylori* infection regardless of CYP2C19 genotype, clarithromycin or dual clarithromycin and metronidazole resistant strains (Prapitpaiboon et al., 2015). However, this new quadruple therapy should consider testing in other clinical trials before granting as a first line *H. pylori* eradication in our country.

A seven day bismuth-based quadruple therapy is highly effective eradication regimen that is well tolerated in metronidazole-sensitive *H. pylori*. However, the efficacy was markedly decline in metronidazole resistance. Longer

duration of this regimen might be required to improve the eradication rate and larger multi-center studies are needed to confirm this hypothesis.

Acknowledgements

This work was partially supported by the National Research University Project of Thailand Office of Higher Education Commission and the Excellence Center GI Endoscopy Research Fund at King Chulalongkorn Memorial Hospital.

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