

## EFFECTS OF *CYP2C19* GENOTYPE ON THE ERADICATION RATE OF *HELICOBACTER PYLORI* INFECTION IN DUODENAL ULCER PATIENTS BY QUADRUPLE THERAPY WITH RABEPRAZOLE, BISMUTH, TETRACYCLINE AND TINIDAZOLE

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### SUMMARY

**Objectives:** To investigate the impact of *CYP2C19* genotype on the eradication rate of *Helicobacter pylori* (*H. pylori*) in duodenal ulcer patients by quadruple therapy with rabeprazole, bismuth, tetracycline and tinidazole (RBTT). **Subjects and methods:** A total of 102 duodenal ulcer patients infected with *H. pylori* completed initial treatment with 20 mg of rabeprazole twice/day, 120 mg of bismuth subcitrate 4 times/day, 500 mg of tetracycline 4 times/day and 500 mg of tinidazole twice/day for 2 weeks. Patients were administered 20 mg of rabeprazole twice/day for 2 weeks after the quadruple therapy. Gastroduodenoscopy was performed after 4 weeks completing the therapy to assess the treatment response. *CYP2C19* genotypes were determined with realtime polymerase chain reaction. **Results:** The eradication rate of *H. pylori* was 91.3% (95%CI, 84.8 - 96.7%). The cure rates of *H. pylori* in the extensive metabolizer (EM), intermediate metabolizer (IM), and poor metabolizer (PM) groups were 87.5%, 94.4%, and 100%, respectively. However, the genotypes of *CYP2C19* were not significantly associated with successful *H. pylori* eradication ( $p > 0.05$ ). **Conclusions:** The 14-day quadruple therapy with RBTT was effective in the *H. pylori* eradication. *CYP2C19* genotype did not influence the eradication of *H. pylori* infection.

\* Keywords: *CYP2C19*; *H. pylori* eradication; Duodenal ulcer.

### INTRODUCTION

*H. pylori* infection is associated with gastrointestinal disorders, such as peptic ulcer disease, chronic gastritis, gastric mucosal-associated lymphoid tissue (MALT) lymphoma and gastric cancer [2]. Eradication of *H. pylori* is the first-line therapy in peptic ulcer disease, which is proven to be beneficial for prevention and treatment of this disease.

According to the Vietnam Association of Gastroenterology (2013), the standard 3-drug regimen with PPI, amoxicilline and clarithromycine is not recommended to treat *H. pylori* because of its ineffectiveness. A quadruple therapy with bismuth should be used within 7 - 14 days, including PPIs, bismuth, tetracycline, metronidazole (or tinidazole) [1].

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Metabolism of PPI depends on the cytochrome P450 in the liver, mainly *CYP2C19*. The *CYP2C19* genotype exists in the form of three polymorphisms with different effects on pharmacodynamics of PPIs. EM, the most popular form, contains two normal alleles, the PPI metabolism genotype with high speed. Therefore, EM limits the bioavailability of some drugs and consequently reduces the antisecretory effect. The IM contains one purebred allele and one mutant allele. This genotype metabolizes PPI more slowly. In the PM group, both types of allele are mutated, and the metabolism is the least. As a result, antisecretory effect increases [3]. Many reports have suggested that differences in the *CYP2C19* genotype are associated with *H. pylori* eradication rate [4]. The metabolism of rabeprazole is less dependent on *CYP2C19* than other PPIs [5]. Therefore, we used rabeprazole in *H. pylori* treatment to achieve the best results for patients.

Thus, this study aimed: *To investigate the effect of CYP2C19 genotype of eradication rate of H. pylori in duodenal ulcer patients by quadruple therapy with RBTT.*

## SUBJECTS AND METHODS

### 1. Subjects

- 102 duodenal ulcer patients with positive *H. pylori*. These patients had never undergone the *H. pylori* eradication therapy and were examined at Can Tho University of Medicine and Pharmacy Hospital, from 1/ 2015 - 12/2016.

#### \* Inclusion criteria:

Patients were diagnosed with duodenal ulcer by gastroduodenoscopy, a duodenal ulcer with a diameter of  $\geq 5$  mm, measured by biopsy pliers, diagnosed with *H. pylori* infection when rapid urease test and histopathology are positive, and they agreed to take part in the study.

#### \* Exclusion criteria:

Patients < 18 years old, with severe internal medicine diseases (liver, kidney, cardiovascular, respiratory), pregnant women, stomach cancer, gastrointestinal bleeding, history of gastric bypass surgery, history of allergy of drugs in research protocols.

## 2. Methods

- A cross-sectional descriptive, and longitudinal study.

#### \* Procedures:

Endoscopic examinations were carried out before the treatment. Each patient had 4 biopsy specimens from the antrum and the body of the stomach. 2 biopsy specimens from the antrum and the body were subjected to rapid urease testing (Clo test, Nam Khoa Co., Ho Chi Minh city) and the 2 biopsy specimens from the antrum and the body were fixed in formalin and assessed for the presence of *H. pylori* by histopathology analysis. The patients were positive with *H. pylori*, determined by rapid urease test and histopathologic result.

Genomic DNA for *CYP2C19* genotype was extracted from leukocytes obtained from peripheral venous blood. The *CYP2C19* genotypes were determined by the

realtime PCR and divided into 3 groups: (1) EM: \*1/\*1, (2) IM: \*1/\*2 or \*1/\*3, and (3) PM: \*2/\*2, \*3/\*3 or \*2/\*3.

*\* Eradication therapy for H. pylori:*

Patients were treated with quadruple therapy: rabeprazole (20 mg twice/day), bismuth subcitrate (120 mg, 4 times/day), tetracycline (500 mg, 4 times/day) and tinidazole (500 mg twice/day) for 2 weeks. Patients were administered 20 mg of rabeprazole twice/day for 2 weeks after the quadruple therapy. 4 weeks after the therapy, the outcome of eradication was diagnosed based on the rapid urease test and histopathology result. *H. pylori* treatment is considered successful when *H. pylori* is negative in both rapid urease test and histopathology.

*\* Statistical analysis:*

Data was analyzed using SPSS 18.0 software. Comparison of the ratio among the EM, IM, and PM group was performed using the  $\chi^2$ -test, Fisher's exact test. The average values of continuous variables and analysis of the correlation between various parameters and the result of eradication were performed by  $\chi^2$ -test, the Fisher's exact test and student's T-test. The difference was statistically significant with  $p < 0.05$ .

**RESULTS AND DISCUSSIONS**

**1. Patient characteristics**

The mean age of patients was  $43.8 \pm 13.9$  (range, 19 - 84) and the mean bodyweight was  $59.7 \pm 8.5$  kg. There were more male (77.5%) than female patients (22.5%).

For the endoscopic characteristics of duodenal ulcer, 84.3% of patients had an ulcer whose size under 15 mm was present in 85.3%.

**2. H. pylori eradication rate**

Table 1: *H. pylori* eradication rate.

Results	n	%	95%CI
Success	84	91.3	84.8 - 96.7
Failure	8	8.7	
Total	92	100	

Among 102 patients enrolled, 92 patients completed the research according to the protocol. 10 patients were excluded from the analysis because of their withdrawal. Therefore, the eradication rate on a per-protocol was 84 patients (91.3%), who were successfully eradicated the infection, determined by rapid urease test and histopathology result of the second endoscopy. The failure rate was found in 8 patients (8.7%).

The eradication rate of RBTT in this study got 91.3%. According to the present studies, the eradication rates of the quadruple therapy widely varied, ranging 87 - 90.8% with using as the second line rescue therapy [6]. The most recent guidelines recommended bismuth quadruple therapy as the first-line treatment in regions with clarithromycin resistance exceeding 20% [7]. In our study, RBTT was used as a first-line treatment in duodenal ulcer patients because clarithromycin resistance of *H. pylori* was 30.4% in the South of Vietnam [1].

### 3. Frequency of *CYP2C19* genotype

Table 2: *CYP2C19* genotype frequencies in duodenal ulcer patients.

Phenotype	Genotype	n	%
EM	*1/*1	51	50.0
IM	*1/*2, *1/*3	43	42.2
PM	*2/*2, *2/*3, *3/*3	8	7.8
Total		102	100

The frequencies of EM, IM and PM in the duodenal ulcer patients with *H. pylori* were 50.0%, 42.2%, and 7.8%, respectively. The frequency of EM given in this study is much lower than that in Ormeci A. et al's on Caucasians subjects, namely Turkish (78%) [8]. In contrast, the percentage of EM in Vietnamese subjects is much higher than that in Furuta et al's in Japan (34%) [9]. Obviously, the racial distribution of the *CYP2C19* genotypes is different among nations in the world.

### 4. Effects of *CYP2C19* genotype on the eradication rate of *H. pylori*

Table 3: Effects of *CYP2C19* genotype on the eradication rate of *H. pylori*.

Results	Phenotype						p
	EM		IM		PM		
	n	%	n	%	n	%	
Success	42	87.5	34	94.4	8	100	> 0.05
Failure	6	12.5	2	5.6	0	0	
Total	48	100	36	100	8	100	

Cure rate with RBTT for 2 weeks showed that 100% of the patients had PM genotype, which was higher than EM and IM genotype (87.5% and 94.4%, respectively). However, the distribution of EM, IM and PM in the successful eradication group was not significantly different ( $p > 0.05$ ) than that in the failure group.

Many studies showed that genotype of *CYP2C19* affected the *H. pylori* eradication rate. Patients who had rapid metabolism of *CYP2C19* genotype got the lower cure rate than cases with the poor

and intermediate metabolism [4]. Although the result of this study showed that the *CYP2C19* genotype had statistically non-significant association with the success or failure of the *H. pylori* eradication ( $p > 0.05$ ) probably due to the small sample size, they still have higher cure rate among cases with PM or IM genotypes than cases with EM genotypes. In the study by Kuo et al [10], *CYP2C19* genotype did not influence the cure rate of quadruple therapy with rabeprazole. According to a meta-analysis on *CYP2C19* genotypes,

rabeprazole was not influenced, but other PPIs such as omeprazole, lansoprazole were [4]. Most PPI are metabolized by *CYP2C19* and *CYP3A4* P450 in liver, but this dependence varies for each PPI. Rabeprazole was mainly metabolized by non-enzymatic pathway beside *CYP2C19* and *CYP3A4* [7]. Therefore, regulating the type and dose of PPI is recommended as a clinical practical approach guideline in the future.

### CONCLUSION

The eradication rate of *H. pylori* infection in duodenal ulcer patients by RBTT was 91.3%. The cure rates of *H. pylori* in the EM, IM, and PM group of *CYP2C19* genotype were 87.5%, 94.4%, and 100%, respectively. *CYP2C19* genotype had no effects on the eradication of *H. pylori* infection.

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