RESEARCH ARTICLE

Effects of the CYP2C19 Genetic Polymorphism on Gastritis, Peptic Ulcer Disease, Peptic Ulcer Bleeding and Gastric Cancer

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Abstract

Background: The CYP2C19 genotype has been found to be an important factor for peptic ulcer healing and *H. pylori* eradication, influencing the efficacy of proton pump inhibitors (PPIs) and the pathogenesis of gastric cancer. The aim of this study was to investigate clinical correlations of the CYP2C19 genotype in patients with gastritis, peptic ulcer disease (PUD), peptic ulcer bleeding (PUB) and gastric cancer in Thailand. Materials and Methods: Clinical information, endoscopic findings and *H. pylori* infection status of patients were assessed between May 2012 and November 2014 in Thammasat University Hospital, Thailand. Upper GI endoscopy was performed for all patients. Five milliliters of blood were collected for *H. pylori* serological diagnosis and CYP2C19 study. CYP2C19 genotypes were determined by polymerase chain reaction (PCR) and restriction fragment length polymorphism analysis (RFLP) and classified as rapid metabolizer (RM), intermediate metabolizer (IM) or poor metabolizer (PM). Results: A total of 202 patients were enrolled including 114 with gastritis, 36 with PUD, 50 with PUB and 2 with gastric cancer. Prevalence of CYP2C19 genotype was 82/202 (40.6%) in RM, 99/202 (49%) in IM and 21/202 (10.4%) in PM. Overall *H. pylori* infection was 138/202 patients (68.3%). *H. pylori* infection was demonstrated in 72% in RM genotype, 69.7% in IM genotype and 47.6% in PM genotype. Both gastric cancer patients had the IM genotype. In PUB patients, the prevalence of genotype RM (56%) was highest followed by IM (32%) and PM(12%). Furthermore, the prevalence of genotype RM in PUB was significantly greater than gastritis patients (56% *vs* 36%: p=0.016; OR=2.3, 95%CI=1.1-4.7). Conclusions: CYP2C19 genotype IM was the most common genotype whereas genotype RM was the most common in PUB patients. All gastric cancer patients had genotype IM. The CYP2C19 genotype RM might be play role in development of PUD and PUB. Further study in different population is necessary to verify clinical usefulness of CYP2C19 genotyping in development of these upper GI diseases.

Keywords: CYP2C19 genotype - gastritis - peptic ulcer disease - gastric cancer

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Introduction

CYP2C19 genotype has been found to be an important factor in peptic ulcer healing rate, *H. pylori* eradication, influences the therapeutic efficacy of proton pump inhibitors (PPI) and development of gastric cancer (Sugimoto et al., 2009; Furuta et al., 2010; Prasertpetmanee et al., 2013). CYP2C19 genotypes can be determined by polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) analysis and divided into 3 groups in relation to PPI metabolism; rapid metabolizer (RM), intermediate metabolizer (IM) or poor metabolizer (PM). Genotype RM experience rapid clearance of PPI and generally has less effective than PM (Yamada et al., 2001; Furuta et al., 2001; Sugimoto et al., 2009; Furuta et al., 2010; McNicholl et al., 2012). Among phenotypic RM and IM, higher dose of PPI or frequent dosing of PPI may require increasing efficacy of gastroprotective effect. Prior study suggested that it was difficult to assess the effect of CYP2C19 genotype on PPI because of small number studies, inadequate CYP2C19 genotype testing and lack of control (Estany-Gestal et al, 2011). The aim of this study was to investigate status and clinical correlation of CYP2C19 genotype in patients with gastritis, peptic ulcer disease (PUD), peptic ulcer bleeding (PUB) and gastric cancer in Thailand.

Materials and Methods

Patients who underwent gastroscopic examination at Thammasat University Hospital, Thailand for dyspeptic symptoms and UGIB were recruited between May 2012 and November 2014. Entry criteria included age over 18 years and those who had never received *H. pylori* eradication and had indication for upper GI endoscopy. We excluded those who were receiving anticoagulants, who had previously undergone gastric surgery and those patients with significant systemic diseases eg. congestive

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Table 1. The CYP2C19 Genotype of All Patients

CYP2C19 Genotype	Gastritis (N=114)	PUB (N=50)	PUD (N=36)	Gastric cancer (N=2)	Total (N=202)
Rapid metabolizer (RM)	41 (36%)	28 (56%)*, **	13 (36.1%)	0	82(40.6%)
Intermediate metabolizer (IM)	60 (52.6%)	16 (32%)	21 (58.3%)	2 (100%)	99(49%)
Poor metabolizer (PM)	13(11.4%)	6 (12%)	2 (5.6%)	0	21(10.4%)

**p=0.016 OR=2.3 (95%CI=1.1-4.7) when compare with gastritis; ** p=0.068 OR=2.3 (95%CI=0.9-6) when compare with PUD

heart failure, chronic renal failure and AIDS, patients who abused drug or alcohol, and women who were breast feeding or had child-bearing potential without using effective contraception. Informed consent was obtained before participating in this study. The diagnosis of gastritis, PUD, PUB and gastric cancer was made according to symptomatic assessment and endoscopic findings. Dyspeptic patients with normal endoscopy and those with gastric inflammation without erosions or ulcer were considered of having gastritis. Five milliliters of blood was collected for *H. pylori* serological diagnosis (Anti-*H. pylori* ELISA IgG) and for CYP2C19 study. CYP2C19 genotype was determined by PCR and RFLP analysis and divided into 3 groups: rapid metabolizer (RM), intermediate metabolizer (IM) or poor metabolizer (PM) and was performed as described previously (Furuta et al., 2001). After upper GI endoscopy, gastritis, PUD and gastric cancer patients continued to receive standard treatment from Thammasat university hospital and all PUB patients were received intravenous pantoprazole and the dose and duration of intravenous pantoprazole was introduced to these patients as suggested from the International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding (Barkun et al., 2010).

Statistical analysis

The demographic information and frequencies of adverse effects were compared using chi-squared and Fisher's exact test. The P-values <0.05 were considered to be statistically significant. For each variable, the odds ratio (OR) and 95% confidence interval (CI) were calculated. The data analysis was performed using SPSS version 19 (SPSS Inc., Chicago, IL, USA). 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. All subjects signed informed consent to participate in this study.

Results

Total of 202 patients were enrolled (109 males and 93 females, mean age of 53 years). There were 114 patients with gastritis, 36 patients with PUD, 50 patients with PUB and 2 patients with gastric cancer.

The CYP2C19 genotype

CYP2C19 genotype was performed in all patients. Overall, the prevalence of genotype IM (49%) was the most common genotype followed by RM (40.6%) and PM genotype (10.4%). All gastric cancer patients had genotype IM. In PUB patients, the prevalence of RM genotype (56%) was highest followed by IM (32%) and PM genotype (12%). Furthermore, the prevalence of RM genotype in PUB was significantly more common than gastritis patients (56% *vs* 36%: p=0.016; OR= 2.3, 95%CI= 1.1-4.7). Genotype RM in PUB had higher than PUD patients (56% *vs* 36.1%: p=0.068; OR= 2.3, 95%CI= 0.9-6) but the difference did not achieve significance (Table 1).

Table 2. The CYP2C19 Genotype and *H. pylori* Infection

CYP2C19 Genotype (N=202)	*H. pylori* infection
Rapid metabolizer (RM) (N=82)	59 (72%)
Intermediate metabolizer (IM) (N=99)	69 (69.7%)
Poor metabolizer (PM) (N=21)	10 (47.6%)

Table 3. CYP2C19 Genotype and Short Term Rebleeding Rate

	CYP2C19 Genotype		
	Rapid metabolizer (N=28)	Intermediate metabolizer (N=16)	Poor metabolizer (N=6)
Short term rebleeding	3 (10.7%)	0 (0%)	0 (0%)

H. pylori infection and CYP2C19 genotype

Overall *H. pylori* infection was 138/202 patients (68.3%). H .pylori infection was demonstrated in 59/82 (72%) in genotype RM, 69/99 (69.7%) in genotype IM and 10/21 (47.6%) in genotype PM. However, there was not significant difference between CYP2C19 genotype and *H. pylori* infection in all group patients (Table 2).

CYP2C19 genotype and rebleeding rate

In PUB patients, there were 39 patients with gastric ulcer, 11 patients with duodenal ulcer. The short term rebleeding (within 3 days) of genotype RM had higher trend than genotypes IM and PM (10.7% *vs* 0%; p=0.08; OR= 2.1; 95%CI=1.7-2.5) (Table 3).

Discussion

CYP2C19 genotype has recently been found to have important roles on peptic ulcer healing and variable effectiveness of PPI (Yamada et al., 2001; Furuta et al., 2001). CYP2C19 genotype distributions vary among different ethnic groups. In Asian countries such as China, Japan and Vietnam, the prevalence of genotype IM was predominated (Yamada et al., 2001) whereas genotype RM was mainly found in European population (Xie et al., 2001). In our study, genotype IM was the most common genotype in Thailand same as other Asian countries. Because CYP2C19 is the main metabolizing enzyme of PPI, the variation of CYP2C19 genotype might be one of the explanations why PPI had different response between Asian and Western population.

The regimens for *H. pylori* eradication consisted of PPI and few antimicrobial agents eg. amoxicillin, clarithromycin, metronidazole and fluoroquinolone. These antimicrobial agents have uniquely pharmacologic actions. PPIs are metabolized by cytochrome P450 2C19 (CYP2C19), which is polymorphic. CYP2C19 genotypic differences might be influence the *H. pylori* eradication by variable response of PPI (pharmacokinetics and pharmacodynamics effect) in the regimens (Furuta et al., 2010). Eradication rates from PPI-based therapies might be interfering by different CYP2C19 genotype (Furuta et al., 2010). However, a recent study from Thailand demonstrated 7-day standard triple therapy plus bismuth and probiotic provided an excellent cure rate of *H. pylori* (100%) regardless of CYP2C19 genotype (Chanagune et al., 2014).

CYP2C19 genotype is also considered to be one of the factors that determine cancer susceptibility by different ability of carcinogen detoxification. CYP2C19*2 and CYP2C19*17 genotypes were associated with better survival in breast cancer patients using tamoxifen (Bai et al., 2014) and CYP2C19 polymorphisms might be significantly affect the treatment in lung cancer (Chen et al., 2014). It suggests that CYP2C19 might be participating and initiating procarcinogen and finally increase risk of these cancers. Gastric cancer is one of the important cancer in Thailand and Laos with grave prognosis (Vanarath et al., 2014; Vilaichone et al, 2014). Recent studies indicated that PM genotype of CYP2C19 had higher risk of gastric cancer (Shi et al., 2004; Sugimoto et al., 2005) and requires close monitoring future possible gastric cancer development (Sugimoto et al., 2005). Genotype PM had also appeared to be high incidence in esophagus cancer and lung cancer due to higher carcinogen level and potent cell toxicity from lower ability in carcinogenic detoxification. In our study, we demonstrated that genotype IM was found in all gastric cancer patients but only in a small number of patients. A larger group for CYP2C19 genotype in patients with gastric cancer is required for future analysis of the relevance to cancer development.

Our findings also indicated that CYP2C19 genotype RM might play an important role in the pathogenesis of PUB. Recent study from United Kingdom demonstrated that CYP2C19*17 was associated with PUD irrespective of etiology (Musumba et al., 2013). The effect of CYP2C enzymes on the metabolism of arachidonic acid, which is well known to be involved in the pathogenesis of PUD, might be the responsible mechanism (Musumba et al., 2009). Genotype RM was known to increase metabolic and clearance rate of PPI gastroprotection and finally enhancing risk of PUB. Genotype RM could also reduced mucosal gastroprotection from NSAIDS and *H. pylori* infection and might lead to develop PUD and PUB (Estany-Gestal et al., 2011; Musumba et al., 2013). Therefore, the direct effect of CYP2C19 genotype could contribute to the development of optimal therapy and pathophysiology in upper GI diseases patients. However, further large study in a different population is required to validate the usefulness of CYP2C19 genotyping in clinical practice.

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