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Effect of cytochrome P450 2C19 polymorphisms on the *Helicobacter pylori* eradication rate following two-week triple therapy with pantoprazole or rabeprazole

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Abstract. – OBJECTIVE: Cytochrome P450 2C19 (CYP2C19) polymorphisms play an important role in the metabolism of proton pump inhibitors. Rabeprazole is primarily metabolized via non-enzymatic pathways. In this study, we determined whether rabeprazole- and pantoprazole-based eradication treatments were influenced by CYP2C19 polymorphisms.

PATIENTS AND METHODS: A total of 200 patients infected with *Helicobacter pylori* were treated with either 40 mg of pantoprazole or 20 mg of rabeprazole plus 500 mg of clarithromycin, 1000 mg of amoxicillin twice daily for 2 weeks. CYP2C19 genotype status was determined by Polymerase Chain Reaction (PCR)-restriction-fragment-length polymorphism. The genotypes of cytochrome P450 2C19 were classified as homozigote extensive metabolizer (HomEM), heterozigote metabolizer (HetEM) and poor metabolizer (PM). The CYP2C19 genotype of all patients, the effectiveness of the treatment, the effect of the genotypic polymorphism on the treatment were assessed.

RESULTS: The frequencies of HotEM, HetEM, PM were 78%, 19.5% and 2.5%, respectively. 48% (n = 96) of the patients received treatment with rabeprazole and 52% (n = 104) with pantoprazole. The eradication rate was 64.7% for HomEM, 79.4% for HetEM, 100% for PM (p = 0.06). In HetEM, PM, are considered as a single group, the eradication rates were higher in patients with the HetEM and PM (HetEM+PM) genotypes than in those with the wild-type genotype (81.8 *vs*. 64.7% p = 0.031). Among the patients treated with rabeprazole, the eradication rates were significantly lower in those with the HomEM genotype than in those with the HetEM+PM genotypes (60% *vs*. 85.7% p = 0.023).

CONCLUSIONS: The genotypic polymorphism is effective on the rate of eradication. Eradication treatment rate with rabeprazole is influenced by CYP2C19 genotype.

Key Words:
Helicobacter pylori, CYP2C19, Polymorphism, Pantoprazole, Rabeprazole.

Introduction

Helicobacter pylori (H. pylori) infection is a global health problem and the main underlying cause of peptic ulcer disease and noncardiac gastric cancer. Although the prevalence of *H. pylori* infection is decreasing in developed countries, about one-third of the adult northern European and North American populations is infected[1]. The prevalence of *H. pylori* infection has been reported to be 50-80% in Southern and Eastern Europe, Asia and Africa[2]. In a recent study in Turkey, 82.5% of the general population tested positive by urea breath testing[3]. According to the recent Maastricht Consensus Guidelines[4], in populations with an *H. pylori* prevalence of > 20%, a test-and-treat strategy is appropriate to manage patients with dyspepsia in the absence of alarm findings. In addition to management of dyspepsia, *H. pylori* eradication also improves public health by preventing peptic ulcer disease, gastric cancer and other complications of the infection[4]. All current treatment options for the eradication of *H. pylori* infection involve the combination of

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a proton pump inhibitor (PPI) and antibiotics[5]. PPIs are indispensable in the eradication of *H. pylori* infection, and the rationale for their use involves some potential mechanisms. PPI components with antisecretory properties increase gastric pH, therefore stabilizing acid-labile antibiotics in the stomach, and increase gastric luminal antibiotic concentrations[6-8]. Moreover, PPIs also enhance the efficacy of antibiotics by reducing the rate of antibiotic decay in gastric fluid and increasing the sensitivity of *H. pylori* to antibiotics.

PPI metabolism and pharmacokinetics are regulated by cytochrome P450 enzymes in the liver, mainly S-mephenytoin-4-hydroxylase, which is encoded by cytochrome P450 2C19 (CYP2C19)[9-10]. The three possible genotypes for CYP2C19 each has a distinct effect on the pharmacodynamics of PPIs[11]. Homozygote extensive metabolizers (HomEM) have two wild-types (non-mutant) (*1/*1) alleles. HomEM is associated with increased enzyme activity, which increases the rate of PPI metabolism. Heterozygote extensive metabolizers (HetEM) have one wild-type allele (*2 or *3); therefore, PPI metabolism tends to be slower. The PM type has two mutant alleles (*2/*2, *2/*3 or *3/*3) and extremely slow PPI metabolism[12]. This distinction plays an important role in the treatment of *H. pylori* infection. Intragastric pH, which is required for eradication, is lowest in EM homozygotes, followed by heterozygotes, and highest in PM[13]. In EM homozygotes, an insufficient increase in intragastric pH results in decreased anti-*H. pylori* efficacy of the antibiotics and, therefore, lower eradication rates.

Rabeprazole is metabolized mainly through non-enzymatic pathways; however, cytochrome P450 plays a role[14]. In addition, previous studies have reported that the clinical efficacy of triple therapy with rabeprazole is not affected by CYP2C19 genetic polymorphisms. In contrast, pantoprazole is metabolized primarily by O-demethylation by CYP2C19.

Few studies have compared the *H. pylori* eradication rates of rabeprazole and pantoprazole according to CYP2C19 genotypic polymorphism. Our main aim was to evaluate the effect of this polymorphism on rabeprazole and pantoprazole treatment for *H. pylori* eradication.

Patients and Methods

Patients

Study participants were recruited from consecutive patients undergoing upper endoscopy at the Istanbul University, Istanbul Medical Faculty, Department of Gastroenterology, between May 2011 and January 2012. 200 patients with the diagnosis of non-ulcer dyspepsia were selected for the study. Inclusion criteria were age 18-75 yr, presence of endoscopic evidence of gastritis, presence of *H. pylori*.

H. pylori was detected by rapid urease test from the biopsy samples which were obtained from the antrum (two samples) and corpus (two samples) mucosa by endoscopy. The exclusion criteria were concomitant renal or hepatic impairment, pregnancy, lactation, body mass index (BMI) ≥ 25, previous *H. pylori* eradication therapy failure, and treatment with an anticoagulant, acid suppressant or antibiotic during the 4 weeks prior to study enrollment. The local Ethics Committee of University Medical Faculty approved this study, and all participants signed an informed consent form.

Study Protocol

For *H. pylori* eradication, all patients were treated with 40 mg of pantoprazole or 20 mg of rabeprazole plus 500 mg of clarithromycin and 1000 mg of amoxicillin twice daily for two weeks. Eradication rates were evaluated according to the presence of *H. pylori* antigen in stool samples obtained from patients during the third month of routine treatment.

Patients were allocated into two groups according to patients follow-up charts, receiving either pantoprazole or rabeprazole in combination with amoxicillin and clarithromycin (PAC or RAC), including 104 patients and 96 patients, respectively. Initial treatment of the patients was started without knowing their CYP2C19 phenotype and genotype. The end point of the study was the eradication of *H. pylori*.

CYP2C19 Genotyping

Written informed consent was obtained. Blood samples were taken from 200 patients for CYP2C19 genotyping analysis. Genomic DNA was extracted from 1 ml venous blood of all patients (MagNA Pure Compact Nucleic Acid Isolation system, Roche Applied Science Indianapolis, IN, USA). All the patients were screened for the G681A point mutation in exon 5 of CYP2C19*2 and the G636A transition in exon 4 of CYP2C19*3 by polymerase chain reaction–restriction-fragment-length polymorphism (PCR-RFLP). Genotyping for the CYP2C19 gene was carried out with the ampli-

fication of genomic DNA for exon 5 by using a forward primer of 5'- CTG CAA TGT GAT CTG CTC CA-3'and a reverse primer of 5'- TCA GGG CTT GGT CAA TAT AG-3'and for exon 4 by using a forward primer of 5'- CAG AGC TTG GCA TAT TGT ATC -3'and a reverse primer of 5'- GAT GCT TAC TGG ATA TTC ATG C-3'. The procedure consisted of an initial denaturation step at 95°C for 5 minutes, followed by 38 cycles of denaturation at 95°C for 30 seconds, annealing at 62°C for 60 seconds, extension at 72°C for 30 seconds, and a final extension step at 72°C for 5 minutes. The amplified PCR products were 300 bp for CYP2C19*2 and 270 bp for CYP2C19*3.

The PCR products were digested with restriction endonucleases (SmaI for CYP2C19*2 and BamHI for CYP2C19*3). (Thermo Fisher Scientific, Cleveland, OH, USA).The digested PCR products were analyzed on 2% agarose gels and stained with ethidium bromide.

CYP2C19 has polymorphisms that result in three genotypes: homozygous EMs (HomEMs) harboring two wild-type alleles (*1/*1), heterozygous EMs (HetEMs) carrying one loss-of-function variant allele (frequently *2 or *3), and PMs, with two loss-of-function variant alleles (*2/*2, *2/*3 or *3/*3). Serum samples were used to identify cases with mutant (Het EM+PM) or without (HomEM) mutations in exons 4 or 5 of the CYP2C19 gene.

Tolerability and Compliance

All patients were reached by telephone during the first and second weeks of treatment and were asked to keep a treatment log for any side effects or treatment breaks. In addition, all patients were given emergency mobile contact numbers in the event of a missed dosage.

Statistical Analysis

Statistical analyses were performed by using IBM SPSS v17 (IBM SPSS Inc., Chicago, IL, USA). Descriptive statistical methods (mean, standard deviation, frequency, and ratio) were used to evaluate the data and Student's *t*-test was used to compare numerical data between groups. Qualitative data were compared using the chi-squared test, Yates corrected chi-squared test, and Fisher's exact test. Significance was considered at $p < 0.05$.

Results

Study Groups

Two hundred dyspeptic patients 118 females, 82 males were enrolled in the study. Their mean age was 40 ± 13 years (range: 18-72 years). Rabeprazole and pantoprazole regimens were administered to 48% (n = 96) and 52% (n = 104) of the patients, respectively.

According to the CYP2C19 genotype analyses, HomEM, HetEM and PM comprised 78% (n = 156), 19.5% (n = 39) and 2.5% (n = 5), respectively, of the patient population. Descriptive characteristics of patients with H. *pylori* infection according to CYP2C19 phenotype groups in Table I. Cases with polymorphisms (heterozygous and homozygous mutant) comprised 22% (n = 44) of the total number of cases.

The PAC group comprised 77.9% (n = 81), 21.1% (n = 22) and 1% (n=1), respectively, HomEM, HetEM, and PM patients, while the genotypes in the RAC group were 78.1% HomEM (n = 75), 17.7% HetEM (n = 17), and 4.2% PM (n = 4), respectively. Frequencies of CYP2C19 genotypes among treatment groups in Table II.

Table I. Descriptive characteristics of patients with H. pylori infection according to CYP2C19 phenotype groups.

	HomEM (n = 156) n (78%)	HetEM (n = 39) n (19.5%)	PM (n = 5) n (2.5%)	Totally (n = 200)
Age (range; years) mean ± SD	18-70 (40.4 ± 13.46)	19-72 (41.0 ± 11.6)	25-56 (39.4 ± 13.4)	18-72 (40 ± 13)
Gender				
Male	67 (42.9%)	13 (33.3%)	2 (60%)	82 (41%)
Female	89 (57.1%)	26 (66.7%)	3 (40%)	118 (59%)
Treatment				
Rabeprazole	75 (48.1%)	17 (43.6%)	4 (80%)	96 (48%)
Pantoprazole	81 (51.9%)	22 (56.4%)	1 (20%)	104 (52%)

HomEM: homozygous extensive metabolizer; HetEM: heterozygous extensive metabolizer; PM: poor metabolizer.

Table II. Frequencies of CYP2C19 genotypes among the treatment groups.

	Allele	Clinical phenotype	PAC treatment	RAC treatment	Total
HomEM	CYP2C19 *1/*1	HomEM	81 (77.9%)	75 (78.1%)	156 (78%)
HetEM	CYP2C19*1/*2	HetEM	21 (20.1%)	16 (16.7%)	37 (18.5%)
	CYP2C19*1/*3	HetEM	1 (1%)	1 (1%)	2 (1%)
PM	CYP2C19 *2/*2	PM	1 (1%)	1 (1%)	2 (1%)
	CYP2C19*2/*3	PM	0	3 (3.2%)	3 (1.5%)
	CYP2C19*3/*3	PM	0	0	0

HomEM: homozygous extensive metabolizer; HetEM: heterozygous extensive metabolizer; PM:, poor metabolizer; *1, wild type (wt); *2, CYP2C19 mutation in exon 5; *3, CYP2C19 mutation in exon 4; *1/*1, homozygous for the wt alleles in both exon 5 and exon 4; *1/*2, heterozygous for the CYP2C19*2 mutation without the CYP2C19*3 mutation; *1/*3, heterozygous for the CYP2C19*3 mutation without the CYP2C19*2 mutation;*2/*3, heterozygous for the CYP2C19*2 mutation and the CYP2C19*3 mutation; *2/*2, homozygous for the CYP2C19*2 mutation without the CYP2C19*3 mutation. RAC: rabeprazole, amoxicillin, clarithromycin. PAC: pantoprazole, amoxicillin, clarithromycin.

Eradication Rate of H. pylori

In the whole study population, the *H. pylori* eradication rate was 68.5% (n = 138). Eradication rates in the PAC and RAC groups were 72.1% and 65.6%, respectively ($p = 0.4$, Table III).

Adverse Events

Adverse events were reported in 5 (2.5%) of 200 patients: 2 (1%) of the 96 patients in group RAC, 3 (1.5%) of the 104 patients in group PAC. The 5 adverse events were diarrhea (n = 2), dizziness (n = 2), nausea (n = 1) (Table IV). No serious adverse events or deaths occurred during the study. Rates of compliance in groups RAC, PAC were 100% (96/96), 100% (104/104) respectively.

Effect of CYP2C19 Genotype on Eradication Rate

The association between CYP2C19 genotypic polymorphisms and administered PPI treatment was evaluated. In patients treated with rabeprazole, eradication was successful in 45 of 75 patients with the HomEM genotype (60%), 14 of the 17 HetEM patients (82%), and 4 of the 4 PM patients (100%). The eradication rate among patients with the HomEM genotype was significantly lower eradication rate than in those carrying CYP2C19 polymorphisms associated with slower metabolism (60% *vs*. 85.7%, $p = 0.023$).

In patients given pantoprazole, eradication was successful in 56 of 81 patients with the HomEM genotype (69.1%), 17 of the 22 HetEM patients (77%), and the one PM patient (100%), and the difference between polymorphism carriers and non-carriers was not significant (78.3% *vs*. 69.1%, $p = 0.2$). Eradication rates for each regimen according to CYP2C19 genetic polymorphisms are shown in Table V.

Eradication rates in the HomEM, HetEM and PM groups were 64.7%, 79.5% and 100%, respectively ($p = 0.06$). The eradication rate was significantly lower in patients with the HomEM genotype than those with HetEM-PM (81.8% *vs*. 64.7% $p = 0.03$) (Table VI). The odds ratio of HomEM for eradication failure was 2.450 (95%, CI: 1.065-5.640).

Discussion

CYP2C19 genotypic polymorphisms were found to affect proton pump inhibitor (PPI) me-

Table III. Eradication rates according to the treatment group.

	Eradication		
	Eradicated (n = 137) n (%)	Not eradicated (n = 63) n (%)	p
RAC	63 (65.6%)	33 (34.4%)	0. 400
PAC	74 (72.1%)	30 (27.9%)	

RAC: 20 mg of rabeprazole plus 500 mg of clarithromycin and 1000 mg of amoxicillin twice daily. PAC: 40 mg of pantoprazole plus 500 mg of clarithromycin and 1000 mg of amoxicillin twice daily.

Table IV. Adverse events.

	PAC	RAC	Totally
Diarrhea	1	1	2
Nause	1	0	1
Dizziness	1	1	2

RAC: 20 mg of rabeprazole plus 500 mg of clarithromycin and 1000 mg of amoxicillin twice daily. PAC: 40 mg of pantoprazole plus 500 mg of clarithromycin and 1000 mg of amoxicillin twice daily.

tabolism. The effect of CYP2C19 genotypic polymorphism on PPI metabolism and eradication rates was first reported by Furuta et al[15] in 1998, who reported that *H. pylori* eradication rates in extensive metabolizers of PPIs are lower than in heterozygote extensive metabolizers and poor metabolizers.

Several subsequent studies[16,17] supported an effect of CYP2C19 on eradication rates. Similarly, in our study, we found higher eradication rates in HetEM and PM patients in comparison with those with the wild-type genotype (p = 0.03).

Further studies of the effect of CYP2C19 polymorphisms on PPI treatment efficacy have been performed. Rabeprazole is metabolized mostly by a non-enzymatic pathway, although the cytochrome P450 system is involved[14]. Since rabeprazole metabolism involves the P450 pathway to a lesser extent than does metabolism of other PPIs, it is likely less effected by genotypic polymorphisms. Studies of the influence of genotypic polymorphisms on the efficacy of rabeprazole have reported diverse results[18-20]. In a meta-analysis of 17 previous studies in Asian populations, Padol et al[21] reported that rabeprazole eradication treatments were not affected by CYP2C19 genotypic polymorphisms. However, the small number of patients included in the meta-analysis and inclusion of dual and triple therapies might have caused bias.

In the present study, the eradication rate was 60% in extensive metabolizers (wild type), 82% in heterozygote extensive metabolizers (one mutant allele in exon 4 or 5), and 100% in poor metabolizers (two mutant alleles) treated with a regimen including rabeprazole. Eradication rates in the rabeprazole treatment group were 60% in patients with the HomEM genotype and 85.7% in those with HetEM-PM (p = 0.023). Therefore, rabeprazole efficacy is affected by CYP2C19 genotypic polymorphisms, and therapy is less likely to succeed in patients with the HomEM

Table V. Eradication rates of the various regimens according to CYP2C19 polymorphisms.

	HomEM	HetEM + PM	Overall *p-value
Pantoprazole	69.1% (56/81)	78.3% (18/23)	0.2
Rabeprazole	60% (45/75)	85.7% (18/21)	0.023
Total	64.7% (101/156)	81.8% (36/44)	0.03
$^{\alpha}$p	0.22	1	

Numbers in parentheses represent the number cured/total number. HomEM: homozygous extensive metabolizer; HetEM: heterozygous extensive metabolizer; PM: poor metabolizer. *The p-values in each row are derived from comparisons among each CYP2C19 genetic polymorphism group; the $^{\alpha}p$-values of each column are derived from comparisons between pantoprazole and rabeprazole.

Table VI. Eradication rates according to CYP2C19 polymorphisms.

		Eradicated n = 137	Not eradicated n = 63	p*
Genotypic polymorphisms	Wild type (HomEM) CYP2C19 *1/*1	101 (64.7%)	55 (35.3%)	0.031
	Mutant type (HetEM, PM) CYP2C19*1/*2 CYP2C19*1/*3 CYP2C19*2/*2 CYP2C19*2/*3	36 (81.8%)	8 (18.2%)	

*$p < 0.05$, HomEM: homozygous extensive metabolizer; HetEM: heterozygous extensive metabolizer; PM: poor metabolizer.

genotype.

One of the most important factors affecting *H. pylori* eradication therapy is gastric pH[22,23]. Although rabeprazole is metabolized mainly via non-enzymatic pathways, studies on the effect of rabeprazole on intragastric pH levels in rapid metabolizers during clinical practice have reported conflicting results[24-26]. The study by Hunfeld et al[24] of intragastric pH in rapid metabolizers reported that once daily dosage of esomeprazole and rabeprazole were both influenced by CYP2C19 polymorphism.

In the pantoprazole treatment group, the eradication rates were 69.1% in patients with the HomEM genotype, 77% in HetEM, and 100% in PM. Whether pantoprazole efficacy is affected by CYP2C19 genotypic polymorphisms is unclear. Due to the dearth of data on pantoprazole, Zao et al[16] did not include patients who received pantoprazole eradication therapy in their meta-analysis. In our study, we found that pantoprazole efficacy was not affected by CYP2C19 genotype polymorphism. However, further studies with a larger population are warranted to verify our findings.

Recently a new variant allele was described (*CYP2C19*17* allele) which is responsible for ultrarapid CYP2C19 metabolism. The CYP2C19*17 allele was documented to correlate with high CYP2C19 activity[27]. Kurzawski et al[28] found that there were no differences on *H. pylori* eradication rates in peptic ulcer patients treated with pantoprazole according to CYP2C19*1/*17 and CYP2C19*17/*17 . In the present study, we did not evaluate an effect of CYP2C19*17 on eradication rates.

The limitations of the present study include the lack of intragastric pH measurements, the small number of patients enrolled, particularly in the PM group, and the exclusion of antibiotic resistance from consideration. In the recent Maastricht Consensus Guidelines, in areas with high clarithromycin-resistant strain (> 20%), culture test will be required[4]. In our population clarithromycin-resistant strain higher than 20%. But we could not determine the clarithromycin-resistant strain[29].

Although intragastric pH levels cannot be measured in daily routine clinical practice, increased PPI dosages, especially in populations with higher prevalence of the HomEM genotype and in patients in whom a previous eradication treatment was unsuccessful, might increase the eradication rate[30,31].

Conclusions

Eradication treatment rate with rabeprazole is influenced by CYP2C19 genotype, and eradication treatments should be planned considering such genotypic polymorphisms. Increasing the PPI dosage in patients with HomEM may be effective on eradication rates. Hence, CYP2C19 genotyping prior to treatment may facilitate determination of the optimum PPI dose to improve the therapeutic outcome. However, further studies including more patients are required to confirm this hypothesis.

Disclosures

This work was presented at DDW 2013 (poster presentation).

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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