

Effects of *CYP2C19*, *MDR1*, and interleukin *1-B* gene variants on the eradication rate of *Helicobacter pylori* infection by triple therapy with pantoprazole, amoxicillin, and metronidazole

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Abstract

Objective Eradication of *H. pylori* is an important treatment strategy in peptic ulcer patients. Current regimens of eradication consist of proton pump inhibitor (PPI) and two antibiotics. Effects of PPI may depend on their metabolism, and other factors important for the pathophysiology of peptic ulcer disease. Aim of the present study was to evaluate an association of *CYP2C19*, *MDR1*, and *IL-1B* polymorphisms with the eradication rate of *H. pylori* in Polish Caucasian patients treated with a triple therapy of pantoprazole, amoxicillin, and metronidazole.

Methods A total of 139 peptic ulcer patients, positive for *H. pylori* infection, were treated with triple therapy (pantoprazole + amoxicillin + metronidazole). Subsequently, the patients were divided into two groups (group 1, success, and group 2, failure of eradication after therapy) and genotyped by the PCR-RFLP method for the presence of *CYP2C19* variant alleles (*2, *3, and *17), and *MDR1* 3435C>T and *IL-1B* +3954C>T polymorphisms. Pantopra-

zole serum concentrations were measured using the HPLC method.

Results No significant differences in frequency or distribution of *CYP2C19* genotypes were found between the two groups of patients (i.e., with successful *H. pylori* eradication and treatment failure). However, any carrier of defective *CYP2C19**2/*2 genotype was found among patients with treatment failure. Similarly, *MDR1* and *IL-1B* genotypes were found to be significantly associated with the success or failure of *H. pylori* eradication. Univariate and multivariate analysis of the genotypes did not reveal any significant association between the genotypes and *H. pylori* eradication. Pantoprazole concentrations differed significantly, and were the highest in patients with defective allele *CYP2C19**2 carriers and lowest in hyperactive genotype homozygotes *CYP2C19**17/*17.

Conclusion The results suggest that the *CYP2C19* genotype contrary to *MDR1* and *IL-1B* genotypes may have an impact on the efficacy of *H. pylori* eradication in peptic ulcer patients treated with pantoprazole in Polish Caucasian peptic ulcer patients administered pantoprazole, amoxicillin, and metronidazole.

Keywords *CYP2C19* · *MDR1* · Interleukin-1 β · Genetic polymorphism · Peptic ulcer · *H. pylori* · Pharmacogenetics

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Introduction

Eradication of *H. pylori* is an important treatment strategy in a variety of upper gastrointestinal disorders, such as peptic ulcer, chronic gastritis, and mucosa-associated

lymphoid tissue lymphoma. Current regimens of eradication consist of proton pump inhibitor (PPI) and two antibiotics (amoxicillin and either clarithromycin or metronidazole). A PPI is a key drug in *H. pylori* eradication, as it makes antibiotics more stable by raising intragastric pH [1]. Additionally, a neutral level of intragastric pH allows bacteria to go into the growth phase, and become more sensitive to antibiotics [2]. The PPIs are metabolized in liver by the cytochrome P450 (CYP) system. The principal enzyme involved in the metabolism is CYP2C19, and to a lesser extent, CYP3A4 [3, 4]. Pantoprazole is metabolized via CYP2C19 to demethylated pantoprazole and via CYP3A4 to pantoprazole sulfone [5, 6].

There are interindividual differences in CYP2C19 activity, mainly due to genetic polymorphism: subjects carrying two defective *CYP2C19* alleles are poor metabolizers (PMs) of enzyme substrates [7]. One common variant allele is responsible for the great majority of PM phenotypes in Caucasians (*CYP2C19**2), while inactive *CYP2C19**3 is additionally found in Asians. It was demonstrated that PPI-based eradication therapy is more effective, not only in PMs, but also in intermediate metabolizers (IM), heterozygotes with one wild-type and one defective *CYP2C19* allele, compared with wild-type homozygotes (rapid extensive metabolizers) [8–10]. In PMs and IMs mean plasma levels of PPIs are higher, what makes therapy with standard drugs' doses more effective compared with wild-type homozygotes [11]. Recently, a novel *CYP2C19* gene variant (*CYP2C19**17), associated with increased gene transcription, and thus faster metabolism of *CYP2C19* substrates was described [12]. Contrary to defective *CYP2C19**2 and *3 alleles, *CYP2C19**17 is likely to cause therapeutic failures in treatment with PPIs. However, limited clinical data are available on the *CYP2C19**17 allele's cure rate of *H. pylori* eradication [12, 13], contrary to the large number of studies suggesting higher cure rates in *CYP2C19**2 and *CYP2C19**3 carriers.

The *MDR1* gene product P-glycoprotein (P-gp) is probably one of the most important and best defined transporters for drug disposition in humans. P-gp transports a wide range of substrates with diverse chemical structures, among them proton pump inhibitors [14, 15]. P-gp is expressed in the apical membrane of cells with excretory functions such as the liver, kidney, small intestine, stomach, the blood–brain barrier, and functions as an efflux pump for lipophilic and amphipathic substrates. It was documented that *MDR1* 3435C>T polymorphism is a good predictor of P-gp activity, with 3435TT subjects having low transporter activity [14]. The 3435TT *MDR1* genotype has been associated with successful PPI treatment (most cases omeprazole medicated) in patients with acid-related disorders with *H. pylori* infection [8].

Interleukin-1 β (IL-1 β) is not only an amplifier of the immune response, but also a potent inhibitor of stomach acid secretion [16]. Studies carried out in Caucasian and Asian populations have demonstrated that the *IL-1B* polymorphism is associated with an increased risk of hypochlorhydria and gastric carcinoma as well as peptic ulcer disease [17, 18]. Scarce data were provided for the role of *IL-1B* polymorphism and treatment outcome of peptic ulcer disease. Furuta et al. and Take et al. demonstrated that IL-1beta-511 polymorphism was one of the determinants of successful eradication of *H. pylori* using triple therapy with PPI, amoxicillin, and clarithromycin, together with the *CYP2C19* genotype [19, 20]. The observations from Asian populations suggest that the *IL-1B* polymorphism can influence the treatment outcome of peptic ulcer disease. However, any data from Caucasian populations are available. The *IL-1B* gene displays many SNPs among which polymorphisms at the position +3954 influence the rate of production of the cytokine. Considering the +3954 *IL-1B* polymorphism, homozygous individuals for the T allele produce a four-fold higher amount of IL-1 β than individuals displaying the C/C genotype. Heterozygous individuals have intermediary production of IL-1 β [21].

In the light of the aforementioned data the study was aimed at the evaluation of an association of *CYP2C19*, *MDR1*, and *IL-1B* polymorphisms' with the *H. pylori* eradication rate in Polish Caucasian patients treated with triple therapy of pantoprazole, amoxicillin, and metronidazole.

Materials and methods

Patients of Caucasian origin with Polish nationality were included in the study after giving informed consent. The local Ethics Committee of the Pomeranian Medical University, Szczecin, Poland approved the protocol of the study. A total of 139 unrelated patients (74 female, 65 male, mean age 51.0 \pm 14.4 years, range 20–80 years) suffering from peptic ulcer, positive for *H. pylori* infection, were included in the study. All subjects underwent physical examination, gastroduodenoscopy, and laboratory tests (rapid urease test, histopathological examination). The patients exhibited normal liver function according to clinical laboratory tests. None of the subjects consumed extensive amounts of alcohol or had a smoking habit. The patients were treated with triple therapy (pantoprazole 40 mg \times 2 per day, amoxicillin 1,000 mg \times 2 per day, and metronidazole 500 mg \times 2 per day) for 1 week, then only 40 mg pantoprazole a day was given for 5 weeks. All the patients confirmed that they fully complied with physicians' instructions. Negative results

Table 1 *CYP2C19* allele frequencies in peptic ulcer patients ($n=139$)

<i>CYP2C19</i> allele	Group 1, successful <i>H. pylori</i> eradication ($n=103$), n (%; 95% CI)	Group 2, failure of <i>H. pylori</i> eradication ($n=36$), n (%; 95% CI)	p value
*1 ($n=165$)	117 (56.80; 49.73–63.66)	48 (66.67; 54.57–77.34)	0.16
*2 ($n=35$)	30 (14.56; 10.05–20.13)	5 (6.94; 2.29–15.74)	0.10
*17 ($n=78$)	59 (28.64; 22.57–35.33)	119 (26.39; 16.70–38.10)	0.76

on all examinations, including gastroduodenoscopy, rapid urease test, histopathological examination, and ^{13}C -urea breath test at 6 weeks after initiation of the therapy were judged indicative of *H. pylori* eradication. Patients were subsequently divided into two groups, i.e., group 1, patients with successful eradication after the first cycle of the therapy, and group 2, patients who failed the first cycle of the treatment.

Blood for pantoprazole concentration assay was sampled 3 h post-dose during a control visit at 6 weeks from the beginning of the study, centrifuged for plasma separation and then stored at -20°C till analysis. Plasma pantoprazole concentrations were measured using the HPLC method published by Storms and Stewart [22]. The detection limit of the method (LOQ) was set at $0.5\ \mu\text{g/ml}$.

Genomic DNA was extracted from peripheral leukocytes using a non-organic and non-enzymatic extraction method [23]. Genotyping of each subject for the presence of common *CYP2C19* variants (19154G>A, specific for *2, and 17948G>A, for *3 allele) was performed using previously described a PCR/RFLP assay [24]. Two single nucleotide polymorphisms (SNPs), specific for *CYP2C19**17 alleles, were analyzed by PCR-RFLP ($-3402\text{C}>\text{T}$) and allele-specific amplification methods ($-806\text{C}>\text{T}$), described by Sim et al. [12].

The *MDR1* C3435T polymorphism was identified by the PCR-RFLP method as described by Cascorbi et al. [25]. Digestion with the restriction enzyme *Sau3AI* resulted in the classification of evaluated genotypes into the following three groups: 3435 CC, CT, and TT.

The *IL-1B* 3954C>T polymorphism was assessed using the PCR-RFLP method by Hodge et al. [26]. Based on the *TaqI* digestion pattern the patients were classified

into the following three genotype groups: 3954 CC, CT, and TT.

Allele and genotype frequencies were determined by the direct counting of the alleles. Concordance of genotype distribution with the Hardy–Weinberg equilibrium and associations between categorical variables were assessed by Fisher's exact test, using Statistica 6.0 (Statsoft). The study with 139 patients has over 80% power to detect differences in allele frequency between the groups stratified according to treatment outcome if it exceeds 14%, under the assumption that the treatment success rate is 75% and the minor allele frequency in the population is 15%. Odds ratios and confidence intervals were calculated using the Newcombe–Wilson method without continuity correction. The effect of the *CYP2C19*, *MDR1*, and *IL-1B* genotypes as well as treatment regimens on eradication of *H. pylori* infection after the first cycle of triple therapy was evaluated using univariate and multivariate logistic regression analysis. The multivariate analysis was adjusted for age, gender, and smoking status. The Kruskal–Wallis test was applied to evaluate an influence of *CYP2C19* genotypes on pantoprazole plasma concentration. A p value less than 0.05 was considered significant.

Results

Based on haplotype estimation analysis, two SNPs specific for the *CYP2C19**17 allele ($-3402\text{C}>\text{T}$ and $-806\text{C}>\text{T}$) were found in complete linkage in the studied population. On the other hand, SNPs distinctive for the *17 and *2 alleles occurred separately, none of the patients homozygous for the *17 allele carried the 19154G>A SNP. The

Table 2 *CYP2C19* genotype frequencies in peptic ulcer patients ($n=139$)

<i>CYP2C19</i> genotype	Group 1, successful <i>H. pylori</i> eradication ($n=103$), n (%; 95% CI)	Group 2, failure of <i>H. pylori</i> eradication ($n=36$), n (%; 95% CI)	p value
*1/*1 ($n=47$)	32 (68.09; 52.88–80.91)	15 (31.91; 19.09–47.12)	0.49
*1/*2 ($n=24$)	19 (79.17; 57.85–92.87)	5 (20.83; 7.13–42.15)	
*1/*17 ($n=47$)	34 (72.34; 57.36–84.38)	13 (27.66; 15.62–42.64)	
*2/*2 ($n=2$)	2 (100.0; 15.81–100.0)	0 (0.00; 0.00–84.19)	
*2/*17 ($n=7$)	7 (100.0; 59.04–100.0)	0 (0.00; 0.00–40.96)	
*17/*17 ($n=12$)	9 (75.00; 42.81–94.51)	3 (25.00; 5.49–57.19)	

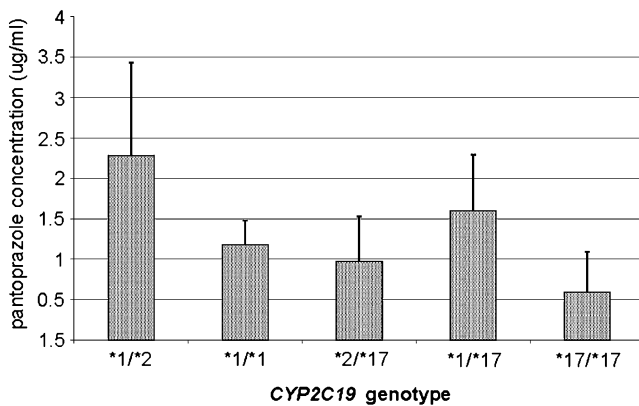


Fig. 1 Pantoprazole plasma concentrations (mean, SD) 3 h after administration of 40 mg pantoprazole in patients with different *CYP2C19* genotypes

genotype frequency distribution was in concordance with the Hardy–Weinberg equilibrium. No significant differences in the frequency or distribution of the *CYP2C19* allele (allele *3 was not detected, Table 1) and genotypes (Table 2) were found between the two groups of patients (i. e., with those with successful *H. pylori* eradication and those with treatment failure). However, no carriers of a defective *CYP2C19**2/*2 genotype were found among the patients with treatment failure (Table 2). Classification of patients into subgroups of extensive, EM, (genotypes *1/*1, *1/*17, *17/*17); intermediate, IM, (*1/*2, *2/*17); and poor, PM, metabolizers (*2/*2) did not reveal significant differences in cure rates. Eradication was observed in 70.8% (95% CI 61.1–79.2) EM, 83.9% (95% CI 66.3–94.5) IM, and 100% (95% CI 15.8–100) PM patients. Failure of treatment was demonstrated in 29.2% (95% CI 20.8–38.9) EM, 16.1% (95% CI 5.5–33.7) IM, and 0% (95% CI 0–84.2) PM subjects.

Pantoprazole plasma concentrations were evaluated in 24 patients: 6 carriers of *1/*1 genotype, 7-*1/*2, 6-*1/*17, 3-*2/*17, and 3-*17/*17. The values of the drug concentrations were as follows: *1/*1–1.18±0.30 µg/ml, *1/*2–2.28±1.15 µg/ml, *1/*17–1.60±0.69 µg/ml, *2/*17–0.97±0.56 µg/ml, and *17/*17–0.59±0.50 µg/ml. The concentrations of pantoprazole among the studied genotypes differ significantly ($p=0.030$, Kruskal–Wallis test). The highest concentrations were observed in heterozygous subjects, carriers of *CYP2C19**1/*2 genotypes ($p=0.073$ vs *1/*1,

Mann–Whitney test; unfortunately, we were not able to measure pantoprazole concentrations in *2/*2 patients), and the lowest in the case of *17/*17 (Fig. 1).

Similar to *CYP2C19*, the *MDR1*, and *IL-1B* genotypes were not found to be significantly associated with success or failure *H. pylori* eradication. Distribution of allele and genotype frequencies were similar in both subgroups of the study (Tables 3, 4).

Univariate and multivariate analysis of the evaluated genotypes, i.e., *CYP2C19*, *MDR1*, and *IL-1B* did not reveal any significant association between the genotypes and the *H. pylori* eradication rate (Table 5).

Discussion

The incidence of peptic ulcer disease in the Polish population is estimated to be 5–10%, with the prevalence of duodenal ulcer (60%) [27] being an important medical pathology. In the present study, a potential association between *CYP2C19*, *MDR1*, and *IL-1B* polymorphisms and *H. pylori* eradication efficacy in Polish Caucasian patients has been analyzed. It is well documented that the *CYP2C19* polymorphism affects cure rates of peptic ulcer. Patients harboring defective alleles *CYP2C19**2 and *CYP2C19**3 are characterized by higher rates of successful *H. pylori* eradication, when omeprazole/amoxicillin/clarithromycin or pantoprazole/amoxicillin/metronidazole were administered [8, 10]. Therapy including amoxicillin and clarithromycin are gastric pH-dependent, while the effects of metronidazole are independent [1, 28]. Our observations support the published data, as all carriers of *CYP2C19**2/*2 genotypes responded to the administered triple therapy of pantoprazole, amoxicillin, and metronidazole. The data for hyperactive allele *CYP2C19**17 are very scarce. In our previous study, which included mainly patients medicated with omeprazole, we did not document any association between *H. pylori* eradication and *CYP2C19**17 [13]. Our current observations are in keeping with the former report, i.e., no effect of *CYP2C19**17 allele on the cure rate in patients medicated with pantoprazole (along with amoxicillin and metronidazole). However, the study revealed that the *CYP2C19* polymorphism influences significantly the metabolic rate of pantoprazole, as defective allele carriers

Table 3 *MDR1* 3435C>T genotype frequencies in peptic ulcer patients ($n=139$)

<i>MDR1</i> 3435C>T genotype	Group 1, successful <i>H. pylori</i> eradication ($n=103$), n (%; 95% CI)	Group 2, failure of <i>H. pylori</i> eradication ($n=36$), n (%; 95% CI)	p value
3435CC ($n=44$)	33 (75.0; 59.66–86.81)	11 (25.0; 13.19–40.34)	0.99
3435CT ($n=61$)	45 (73.77; 60.93–84.20)	16 (26.23; 15.80–39.07)	
3435TT ($n=34$)	25 (73.53; 55.64–87.12)	9 (26.47; 12.88–44.36)	

Table 4 *IL-1B 3954C>T* genotype frequencies in peptic ulcer patients (*n*=139)

<i>IL-1B 3954C>T</i> genotype	Group 1, successful <i>H. pylori</i> eradication (<i>n</i> =103), <i>n</i> (%; 95% CI)	Group 2, failure of <i>H. pylori</i> eradication (<i>n</i> =36), <i>n</i> (%; 95% CI)	<i>p</i> value
3954TT (<i>n</i> =80)	56 (70.00; 58.72–79.74)	24 (30.00; 20.26–41.28)	0.40
3954CT (<i>n</i> =47)	38 (80.85; 66.74–90.85)	9 (19.15; 9.15–33.26)	
3954CC (<i>n</i> =12)	9 (75.00; 42.81–94.51)	3 (25.0; 5.49–57.19)	

showed highest drug concentrations, with the lowest for the hyperactive *CYP2C19*17* allele. This finding is in line with data reported by Sim et al. [12], who estimated that *CYP2C19*17* homozygotes would attain up to 40% lower omeprazole AUC values than subjects homozygous for the *CYP2C19*1* allele after a single dose of the drug. Similar to our observations, higher pantoprazole concentrations in poor *CYP2C19* metabolizers have been reported by others [11].

Limited data indicate that the *MDR1 3435C>T* polymorphism affects PPI (lansoprazol) pharmacokinetics, but no marked PPI pharmacodynamic effects (i.e., intragastric pH) of the polymorphism were determined [29]. There are few data on the association of *MDR1* polymorphism with *H. pylori* eradication. Furuta et al. found that the polymorphism of *MDR1* was one of the determinants of successful eradication of *H. pylori* by the triple therapy with lansoprazole, amoxicillin, and clarithromycin, together with the *CYP2C19* genotype and bacterial susceptibility to clarithromycin, with the lowest response rate in 3435TT carriers [30]. In our previous study, similar to observations by Furuta et al. [30], lower cure rates were noted in *MDR1 3435TT H. pylori*-positive peptic ulcer patients treated predominantly with omeprazole as the PPI component of triple therapy, with the *MDR1* polymorphism being found to be an independent risk factor [8]. However, the results of the present study did not confirm the significant role of the *MDR1* gene polymorphism in *H. pylori* eradication in patients medicated with pantoprazole, amoxicillin, and metronidazole.

The last genotype evaluated in the present study was functional *IL-1B 3954C>T*. Take et al. [20] reported that *IL-1B-511* genetic polymorphism, although not an inde-

pendent factor in the treatment outcome of peptic ulcers (PPI applied: omeprazole, lansoprazole, or rabeprazole), influenced the impact of the *CYP2C19* genotype on the cure rate of 1-week triple therapy for *H. pylori* infection. Logistic regression analysis of clinical study by Furuta et al. [19] showed that the *IL-1B-511C>T* polymorphism, as well as the *CYP2C19* genotype of patients and the clarithromycin resistance of *H. pylori*, was associated with successful eradication. Eradication rates for *H. pylori*, the highest among carriers of the *-511 T/T* genotypes of *IL-1B*. Therefore, the *IL-1B-511* polymorphism could be one of the determinants of the successful eradication of *H. pylori* using triple therapy with a PPI (omeprazole or lansoprazole), amoxicillin, and clarithromycin. In the present study we evaluated the effects of different functional SNPs of *IL-1B 3954C>T* of pantoprazole-based triple therapy on the *H. pylori* eradication rate in a Caucasian population (contrary to the reports cited above from Asian populations). The *IL-1B 3954C>T* is functional as it was documented that monocytes from homozygous subjects carrying allele 2 of the *IL-1B* gene produced significantly more IL-1 β than those from heterozygotes [21]. Our results did not replicate the observations of Take et al. and Furuta et al., i.e., no significant association of the *IL-1B* polymorphism and *H. pylori* eradication in pantoprazole-treated patients was documented. As a summary of our study we performed multivariate analysis, and did not reveal any significant association between the genotypes, i.e., *CYP2C19*, *MDR1*, and *IL-1B* and the *H. pylori* eradication rate in Polish Caucasian peptic ulcer patients receiving pantoprazole, amoxicillin, and metronidazole. However, other factors may also be responsible for a failure to eradicate *H. pylori*, i.e., the high incidence of

Table 5 Univariate and multivariate analysis for factors predicting success of cure of *H. pylori* infection after the first cycle of triple therapy

Factor	Univariate analysis OR (95% CI)	<i>p</i> value ^a	Multivariate analysis ^b OR (95% CI)	<i>p</i> value ^a
<i>CYP2C19*2*2+*1*2+*2*17</i> vs <i>*1*1+*1*17+*17*17</i>	2.32 (0.85–6.37)	0.10	1.99 (0.68–5.83)	0.20
<i>MDR1 3435 C</i> carriers vs <i>T/T</i>	0.96 (0.40–2.33)	0.93	0.98 (0.39–2.45)	0.97
<i>IL-1B 3954 T/T</i> vs <i>C</i> carriers	1.68 (0.75–3.74)	0.20	1.53 (0.66–3.54)	0.32

^a No statistically significant differences were documented^b Adjusted for age, gender, and smoking status

H. pylori resistance to metronidazole (30–40% in Poland) [31], an antimicrobial agent included in triple therapy of studied patients, or undetermined drug interactions. It should also be stated that the effects of the *CYP2C19* and *MDR1* polymorphisms, which influence PPI pharmacokinetics, may be more prominent in patients medicated with PPI/amoxicillin/clarithromycin than in those with PPI/amoxicillin/metronidazole, as the antimicrobial efficacy of amoxicillin and clarithromycin depend on gastric pH, contrary to metronidazole [1].

On the basis of our results, one can conclude that the *CYP2C19* genotype, contrary to the *MDR1* and *IL-1B* genotypes, may have an impact on the efficacy of *H. pylori* eradication in Polish Caucasian peptic ulcer patients receiving pantoprazole, amoxicillin, and metronidazole.

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