Pharmacogenomics and Personalized Medicine

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ORIGINAL RESEARCH

CYP3A and CYP2C19 activity in urine in relation to CYP3A4, CYP3A5, and CYP2C19 polymorphisms in Russian peptic ulcer patients taking omeprazole

This article was published in the following Dove Press journal:
Pharmacogenomics and Personalized Medicine

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Background: Proton pump inhibitors (PPIs) are metabolized by cytochrome P450. CYP2C19 is the main isoenzyme for the majority of PPI, whereas CYP3A family is a secondary enzyme for PPI biotransformation.

Purpose: The aim of the study was to find if _CYP3A4*22, CYP3A5*3, CYP2C19*2, CYP2C19*3,_ and _CYP2C19*17_ genotypes are connected with CYP3A and CYP2C19 activities in Russian peptic ulcer patients taking omeprazole.

Patients and methods: Forty-eight gastric or duodenal ulcer patients (15 men, 33 women; mean age 55.0±15.3 years, age range 18–91 years) from Moscow region of Russia were enrolled. Peripheral venous blood was collected for DNA extraction, and real-time polymerase chain reaction was performed for _CYP3A5*3_ ^{A6986G} (rs776746), _CYP3A4*22_ C>T in intron _6_ (rs35599367), _CYP2C19*2_ ^{G681A} (rs4244285), _CYP2C19*3_ ^{G636A} (rs4986893), and _CYP2C19*17_ $^{C-806T}$ (rs12248560) polymorphism analyses. Urine samples of patients were collected in the morning between 6 and 9 am before food or drug intake. Urine cortisol and 6β-hydroxycortisol concentrations (for CYP3A activity) and omeprazole and 5-hydroxyomeprazole concentrations (for CYP2C19 activity) were measured using high-performance liquid chromatography/mass spectroscopy.

Results: We found a connection between _CYP2C19_ genotypes and CYP3A activity. Median metabolic ratios 6β-hydroxycortisol/cortisol (25%–75% percentiles) were 2.84 (1.99–4.39) for CYP2C19 extensive metabolizers (EMs), 2.51 (1.86–4.73) for CYP2C19 ultra-rapid metabolizers (UMs), and 1.45 (1.12–2.16) for CYP2C19 intermediate metabolizers (IMs) + poor metabolizers (PMs). A statistically significant difference in CYP3A activity (Mann–Whitney test) was found between CYP2C19 EMs vs CYP2C19 IMs+PMs (p=0.006), between CYP2C19 UMs vs CYP2C19 IMs+PMs (p=0.018), and in multiple comparison Kruskal–Wallis test (p=0.014).

Conclusion: In CYP2C19 IMs+PMs, CYP3A activity was significantly lower than in CYP2C19 EMs and UMs.

Keywords: pharmacogenetics, phenotyping, metabolomics, proton pump inhibitor

Introduction

Proton pump inhibitors (PPIs), which are widely used in peptic ulcer patients' treatment, are metabolized by cytochrome P450. CYP2C19 is the main isoenzyme for the majority of PPI, whereas CYP3A family is a secondary enzyme for PPI biotransformation.[1] CYP2C19 polymorphisms are studied in detail and their impact on PPI efficacy is established in guidelines of Dutch Pharmacogenetics Working Group of the Royal Dutch Pharmacists Association.[2]

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http://dx.doi.org/10.2147/PGPM.S159708

CYP3A family includes at least 3 members: CYP3A4, CYP3A5, and CYP3A7.[3]

CYP3A4 and CYP3A5 are the main significant isoenzymes of CYP3A family in adults.[4] CYP3A4 metabolizes about 60% of all known drugs.[5] Metabolism of PPI involves CYP3A enzymes, and CYP3A may become the main pathway especially in CYP2C19 poor metabolizers (PMs).[6] CYP3A4 activity may be detected using 6β-hydroxycortisol/cortisol ratios in urine.[7] CYP3A4 genetic polymorphisms are being studied. CYP3A4*22, found in 2011, is associated with low *CYP3A4* expression and low CYP3A4 activity.[8] CYP3A4*22 allele influences efficacy of tacrolimus, statin, and cyclosporine therapy.[8–11]

It was shown that CYP3A5 and CYP3A4 have common substrates.[12–14] Studies showed that CYP3A5 genotypes reflect CYP3A4 activity.[12] So, CYP3A5 genetic polymorphisms may also have impact on PPI metabolism.[15] It was shown that CYP3A5*3 allele is associated with lack of activity of the enzyme compared with wild-type CYP3A5*1 allele.[3]

CYP3A phenotype may be predicted on the basis of CYP3A4*22 and CYP3A5*3 carrier. Persons with CYP3A4*1/*1 genotype (no CYP3A4*22) together with CYP3A5*1 carrier were classified as CYP3A EMs. CYP3A IMs were CYP3A4*22 together with CYP3A5*1 carrier or CYP3A4*1/*1 with CYP3A5*3/*3 genotypes. CYP3A PMs were CYP3A4*22 and CYP3A5*3/*3 carriers.[16]

The aim of the study was to find if CYP3A4*22, CYP3A5*3, CYP2C19*2, CYP2C19*3, and CYP2C19*17 genotypes are connected with CYP3A and CYP2C19 activities in Russian peptic ulcer patients.

Patients and methods

Study design and patients

Forty-eight gastric or duodenal ulcer patients (15 men, 33 women; mean age 55.0±15.3 years, age range 18–91 years) from Moscow region of Russia were enrolled in the study after providing written informed consent to participate in the study. This study is an extension of previously published study.[17]

Peptic ulcer diagnosis was based on endoscopy and histology. There were 18 gastric ulcer patients, 25 duodenal ulcer patients, and 5 patients had both gastric and duodenal ulcers. Patients underwent gastroscopy and were prescribed omeprazole 20 mg BID for at least 7 days intake. Exclusion criteria were severe comorbidities (cardiovascular, cerebral, renal, hepatic dysfunction) and CYP3A inhibitor clarithromycin intake. The study was approved by local Ethics Committee of First Moscow State Medical University (Sechenov University, Moscow, Russia).

Statins (atorvastatin or simvastatin), which refer to weak CYP3A inducers, were prescribed to 3 patients.

Genotyping

Peripheral venous blood (6 mL) of patients was collected in K2-EDTA tubes for DNA extraction from leukocytes. Blood samples were stored in the deep freeze at –70°C until analysis. DNA was isolated using a commercially available kit "S-sorb" (produced by "Syntol," Moscow, Russia) with silica-based sorbent. *CYP3A5*3* ^{A6986G} (rs776746) and *CYP3A4*22* C>T in intron 6 (rs35599367) polymorphisms were analyzed using real-time polymerase chain reaction (PCR). PCR was performed using a commercially available kit (produced by "Syntol") in DNA amplifier CFX96 Touch (Bio-Rad Laboratories, Hercules, CA, USA) for *CYP3A5*3* and TaqMan genotyping assay (produced by Applied Biosystems Inc., Foster City, CA, USA) for *CYP3A4*22*.

The program consisted of initial denaturation step at 95°C for 3 minutes followed by 40 cycles of 15 seconds' denaturation at 95°C, then annealing at 63°C for 40 seconds. Genotyping was repeated for 20% of patients' samples as a control for correct sample handling. Repeated genotyping revealed identical results.

CYP2C19*2, CYP2C19*3, and CYP2C19*17 genotyping have been described previously.[17]

Assay

Urine samples were stored in deepfreeze at –70°C until analysis. About 2 mL of urine was extracted with 4 mL of ethyl acetate/isopranolol (85:15). After orbital mixing for 10 minutes and centrifuging at 3,000×*g* for 5 minutes, the upper organic layer was separated and transferred to glass tube. About 2 mL 1 M sodium hydroxide solution was added to organic layer, then followed orbital mixing for 10 minutes. and centrifuging at 3,000×*g* for 5 minutes to separate organic layer and evaporation to dryness under gentle stream of air was finished dissolving dry residue in 1 mL of ethanol.

Phenotyping

Endogenous cortisol transforms to 6β-hydroxycortisol selectively by CYP3A isoenzyme; thus, the metabolic ratio of 6β-hydroxycortisol/cortisol in urine is suggested to reflect the activity of CYP3A. The higher the urine metabolic ratio of 6β-hydroxycortisol/cortisol, the higher the activity of CYP3A. As cortisol concentration is the highest in the morning, urine samples of patients were collected between 6 and 9 am before food or drug intake.

Cortisol and 6β-hydroxycortisol concentrations in urine were measured using Agilent 1290 Infinity (Agilent Technologies, Santa Clara, CA, USA) high-performance liquid chromatography with mass spectrometry. The isolation of drug and its metabolite was performed on Waters Symmetry C18 Column (150×4.6 mm; 5.0 µm, Waters Corporation, Milford, MA, USA). The column temperature was maintained at 35°C. UV detector wavelength was set at 246 nm. The mobile phase contained of 55% water formic acid solution (1 L of water:1 mL of formic acid) and 45% acetonitrile. The flow rate was 0.5 mL/min. Volumes of 10 µL were injected. The mass spectrometer was operated using the following conditions: positive polarity, MM–ES+APCI ionization.

CYP2C19 phenotyping using omeprazole and 5-hydroxyomeprazole concentrations in urine was described previously.[17]

Statistical analysis

The statistical analysis was performed using SPSS Statistics 22 (IBM Corporation, Armonk, NY, USA). A p-value <0.05 was considered statistically significant. The normality of metabolic ratio distribution was analyzed by Kolmogorov–Smirnov test. Nonparametric statistics was used to compare metabolic ratio in different genotypes. The observed and expected genotype frequencies were calculated by using Hardy–Weinberg equilibrium. Fisher's exact test was used to evaluate deviation of genotype frequencies in the studied population from Hardy–Weinberg equilibrium.

Results

CYP2C19, CYP3A4, and CYP3A5 genotyping results

Of 48 patients, there were 46 (95.8%) CC (*CYP3A4*1/*1*), 1 (2.1%) CT (*CYP3A4*1/*22*), and 1 (2.1%) TT (*CYP3A4*22/*22*) carriers of *CYP3A4*22* (Table 1). Genotypes were not in accordance to Hardy–Weinberg equilibrium (χ^2=20.7, p=0.00). The *CYP3A4*22* allele frequency was 3.1%.

Of 48 patients, there were 4 (8.3%) GA (*CYP3A5*1/*3*) and 44 (91.7%) GG (*CYP3A5*3/*3*) carriers of *CYP3A5*3*^{A6986G} (Table 2). Genotypes were in accordance to Hardy–Weinberg equilibrium, p>0.05 (χ^2=0.09, p=0.76). The *CYP3A5*3* allele frequency was 95.8%.

Of 48 patients, there were 4 (8.3%) CYP3A extensive metabolizers (EMs), 42 (87.5%) CYP3A intermediate metabolizers (IMs), and 2 (4.2%) CYP3A PMs (Table 3).

Results of CYP2C19 genotyping for 59 patients were described previously in detail.[17] Eleven patients from the previous study were excluded for the current analysis because of clarithromycin, a CYP3A inhibitor, intake. Results of CYP2C19 genotyping for 48 patients are described in Tables 2 and 3.

Table 3 *CYP3A4* and *CYP3A5* genotypes and predicted CYP3A phenotype in Russian peptic ulcer patients

CYP3A phenotype	CYP3A4*22 genotype	CYP3A5*3 genotype	Total, patients
EMs	CC	GA	4
IMs	CT+TT	AA+GA	–
	CC	GG	42
PMs	CT+TT	GG	2
Total			48

Abbreviations: EMs, extensive metabolizers; IMs, intermediate metabolizers; PMs, poor metabolizers.

Table 1 *CYP3A4* and *CYP2C19* genotypes in Russian peptic ulcer patients

CYP3A4*22 C>T in intron 6	CYP2C19							Total, patients
	*1/*1	*1/*17	*1/*2	*2/*17	*2/*2	*3/*17	*17/*17	
CC	19	13	8	2	2	1	1	46
CT	–	1	–	–	–	–	–	1
TT	1	–	–	–	–	–	–	1
Total	20	14	8	2	2	1	1	48

Table 2 *CYP3A5* and *CYP2C19* genotypes in Russian peptic ulcer patients

CYP3A5 A6986G	CYP2C19							Total, patients
	*1/*1	*1/*17	*1/*2	*2/*17	*2/*2	*3/*17	*17/*17	
GG	19	13	7	2	1	1	1	44
GA	1	1	1	–	1	–	–	4
Total	20	14	8	2	2	1	1	48

CYP3A activity and its relationship to CYPs genotypes

Because distribution of metabolic ratio of 6β-hydroxycortisol/cortisol was not normal (Kolmogorov–Smirnov Test *p*=0.001) median and 25%–75% percentiles for data description and nonparametric statistics for samples' comparison were used.

CYP3A4*22

Median metabolic ratio of 6β-hydroxycortisol/cortisol for all genotypes was 2.30 (1.47–4.13). Median 6β-hydroxycortisol/cortisol ratio for *CYP3A4*1/*1* was 2.27 (1.46–3.70), and for *CYP3A4*1/*22+CYP3A4*22/*22*, it was 8.65.

We found statistically significant difference in urine metabolic ratio of 6β-hydroxycortisol/cortisol between patients with *CYP3A4*1/*1* genotype vs *CYP3A4*1/*22 +CYP3A4*22/*22* carriers (Mann–Whitney test, *p*=0.03). So, we found that CYP3A activity was significantly higher in *CYP3A4*22* carriers, which contadicts the data of previous studies.

CYP3A5*3

Median metabolic ratio of 6β-hydroxycortisol/cortisol for *CYP3A5*1/*3* was 2.27 (1.45–4.20), and for *CYP3A5*3/*3*, it was 2.27 (1.40–4.34).

No statistically significant difference in CYP3A activity (Mann–Whitney test) was found between *CYP3A5*1/*3* vs *CYP3A5*3/*3* carriers (*p*=0.63).

CYP2C19*2, *3, and *17

Patients were referred to as *CYP2C19* EMs, PMs, IMs, or ultra-rapid metabolizers (UMs) according to the Dutch Pharmacogenetics Working Group Guideline of the Royal Dutch Pharmacists Association.[2] Median metabolic ratio of 6β-hydroxycortisol/cortisol for CYP2C19 EMs was 2.84 (1.99–4.39), UMs – 2.51 (1.86–4.73), and IMs+PMs – 1.45 (1.12–2.16).

Statistically significant difference in CYP3A activity (Mann–Whitney test) was found between EMs vs IMs+PMs (*p*=0.006), between UMs vs IMs+PMs (*p*=0.018), and in multiple comparison Kruskal–Wallis test (*p*=0.014) (Table 4).

Both CYP3A4*22 and CYP3A5*3

When comparing CYP3A activity between CYP3A EMs and a combined group of CYP3A IMs+PMs, the results correspond to the comparison of CYP3A5*3 genotypes with no statistically significant difference between groups (*p*=0.63).

CYP2C19 activity and its relationship to CYPs genotypes

CYP2C19*2, *3, and *17

The results have been previously published.[17]

CYP3A4*22

Median metabolic ratio of 5-hydroxyomeprazole/omeprazole in urine for all genotypes was 1.23 (0.80–1.99); for *CYP3A4*1/*1*, it was 1.23 (0.79–1.88), and for *CYP3A4*1/*22+CYP3A4*22/*22*, it was 1.62.

No statistically significant difference in CYP2C19 activity (Mann–Whitney test) was found between *CYP3A4*1/*1* vs *CYP3A4*1/*22+CYP3A4*22/*22* carriers (*p*=0.76).

CYP3A5*3

Median metabolic ratio of 5-hydroxyomeprazole/omeprazole in urine for *CYP3A5*1/*3* was 2.40 (0.76–2.98) and for *CYP3A5*3/*3* was 1.17 (0.80–1.79).

No statistically significant difference in CYP2C19 activity (Mann–Whitney test) was found between *CYP3A5*1/*3* vs *CYP3A5*3/*3* carriers (*p*=0.22).

Both CYP3A4*22 and CYP3A5*3

When comparing CYP2C19 activity between CYP3A EMs and a combined group of CYP3A IMs+PMs, the results

Table 4 *CYP2C19* genotypes and CYP3A activity and in Russian peptic ulcers patients

Enzyme activity	**CYP2C19 genotype**							
	EMs		**UMs**		**IMs+PMs**		**Total**	
	Median	**Percentiles 25%–75%**	**Median**	**Percentiles 25%–75%**	**Median**	**Percentiles 25%–75%**	**Median**	**Percentiles 25%–75%**
CYP3A activity	2.84	1.99–4.39	2.51	1.86–4.73	1.45	1.12–2.16	2.30	1.47–4.13
	EMs vs UMs		**EMs vs IMs+PMs**		**UMs vs IMs+PMs**		**EMs vs UMs vs IMs+PMs**	
CYP3A activity	*p*=0.790		***p*=0.006**		***p*=0.018**		***p*=0.014**	

Note: *p*<0.05 for bold text.
Abbreviations: EMs, extensive metabolizers; IMs, intermediate metabolizers; PMs, poor metabolizers; UMs, ultra-rapid metabolizers.

correspond to comparison of CYP3A5*3 genotypes with no statistically significant difference between groups (*p*=0.22).

Discussion

*CYP3A5*3* allele is frequently seen among Caucasians (frequency 88%–97%), whereas in Hispanic and Asian population, it is more rare (66%–75%). As for African Americans and Africans, the frequency of *CYP3A5*3* allele is about 37% or less.[18] Studies found 96.6%–97.7% *CYP3A5*3* allele frequency in Russians.[19,20] We found 95.8% *CYP3A5*3* allele frequency in our study of Russian peptic ulcer patients, which corresponds to data[19,20] described for Caucasians, and particularly Russians.

CYP3A4*22 allele is less frequent and is found in 5%–7% of Caucasians.[16] We found 3.1% CYP3A4*22 allele frequency in our study to be lower than data described for Caucasians, and CYP3A4*22 genotypes in our study were not in accordance with Hardy–Weinberg equilibrium.

CYP3A4 and CYP3A5 have overlapping substrate specificity, so it is important to genotype both CYP3A4 and CYP3A5 as well as to study CYP3A activity.

We did not find connections between CYP3A activity and CYP3A4 and CYP3A5 genotype, except the data that CYP3A activity was significantly higher in *CYP3A4*22* carriers. CYP3A activity was studied in some previous works, and no evidence was found for the fact that large interindividual differences in its activity were based on genotype.[21–24] In another study, midazolam and erythromycin were used for CYP3A phenotyping, and there were connections between CYP3A activity and CYP3A4*22 genotype and partly (only for midazolam) for CYP3A5*3 genotype.[16]

We did not find connections between CYP2C19 activity and CYP3A4 and CYP3A5 genotypes, but found a connection between CYP2C19 genotype and CYP2C19 activity in a previously published study.[17]

We found a relationship between CYP2C19 genotype and CYP3A activity: in CYP2C19 IMs+PMs, CYP3A activity was significantly lower than in CYP2C19 EMs (*p*=0.001), and it also was significantly lower than in CYP2C19 UMs (*p*=0.011). The findings contradict our hypothesis that there is an increased CYP3A activity in CYP2C19 IMs and PMs compared to CYP2C19 EMs and UMs.

One of the limitations of our study was the following: we estimated CYP3A activity using 6β-hydroxycortisol/cortisol ratio in urine, not omeprazole sulfoxidation index (omeprazole sulfone/omeprazole in plasma), so it was not possible to identify the potential activation of the secondary metabolic route of conversion of omeprazole to omeprazole sulfone in CYP2C19 IMs and PMs. Other limitations of the study were that only one single nucleotide polymorphism genotyping was done for CYP3A4 and also for CYP3A5, the low sample size, and the fact that CYP3A4*22 genotypes are not in Hardy–Weinberg equilibrium.

Conclusion

We found a connection between *CYP2C19* genotypes and CYP3A activity, measured using 6β-hydroxycortisol/cortisol ratio in urine in Russian peptic ulcer patients. In *CYP2C19* IMs+PMs, CYP3A activity was significantly lower than in *CYP2C19* EMs (*p*=0.006). Also, *CYP2C19* IMs+PMs had significantly lower CYP3A activity compared with *CYP2C19* UMs (*p*=0.018). There were no connections between CYP3A activity and *CYP3A5*3*. *CYP3A4*22* carriers had significantly higher CYP3A activity. No connections were found between CYP2C19 activity, measured using 5-hydroxyomeprazole/omeprazole ratio in urine and *CYP3A5*3* and *CYP3A4*22* genotypes.

Acknowledgment

This work is supported by Russian Scientific Foundation (project number 16-15-00227: "Fundamental research and exploratory research in priority areas of research") for CYP2C19*2 and CYP2C19*3 genotyping reagents and consumables and CYP2C19 and CYP3A phenotyping reagents and consumables and University Grant of First Moscow State Medical University (Sechenov University) ("Prognosing the efficacy of peptic ulcer therapy on the basis of pharmacogenomics, pharmacometabolomic and pharmacoproteomic technologies of personalized medicine") for CYP2C19*17, CYP3A4*22, and CYP3A5*5 genotyping reagents and consumables.

Disclosure

The authors report no conflicts of interest in this work.

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