Pharmacogenomics and Personalized Medicine

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ORIGINAL RESEARCH

The frequency of CYP2C19 genetic polymorphisms in Russian patients with peptic ulcers treated with proton pump inhibitors

This article was published in the following Dove Press journal:
Pharmacogenomics and Personalized Medicine
27 May 2015
Number of times this article has been viewed

DA Sychev[1,2]
NP Denisenko[1,2]
ZM Sizova[2]
AV Grachev[3]
KA Velikolug[4]

[1]Russian Medical Academy of Post-Graduate Education, [2]I.M. Sechenov First Moscow State Medical University, [3]SM-Clinic, [4]Out-patient department Number 51 branch 3, Moscow, Russia

Introduction: Proton pump inhibitors, which are widely used as acid-inhibitory agents for the treatment of peptic ulcers, are mainly metabolized by 2C19 isoenzyme of cytochrome P450 (CYP2C19). *CYP2C19* has genetic polymorphisms, associated with extensive, poor, intermediate or ultra-rapid metabolism of proton pump inhibitors. Genetic polymorphisms of *CYP2C19* could be of clinical concern in the treatment of peptic ulcers with proton pump inhibitors.

Aim: To investigate the frequencies of CYP2C19*2, CYP2C19*3, and CYP2C19*17 alleles and genotypes in Russian patients with peptic ulcers.

Methods: We retrospectively reviewed the cases of 971 patients of Caucasian origin with Russian nationality from Moscow region with endoscopically and histologically proven ulcers, 428 males (44%) and 543 females (56%). The mean age was 44.6±11.9 years (range: 15–88 years). DNA was extracted from ethylenediaminetetraacetic acid whole blood samples (10 mL). The polymorphisms CYP2C19 681G>A (CYP2C19*2, rs4244285), CYP2C19 636 G>A (CYP2C19*3, rs4986893) and CYP2C19 -806 C>T (CYP2C19*17, rs12248560) were evaluated using real-time polymerase chain reaction.

Results: Regarding *CYP2C19* genotype, 317 patients (32.65%) out of 971 were CYP2C19*1/*1 carriers classified as extensive metabolizers. Three hundred and eighty-six (39.75%) with CYP2C19*1/*17 or CYP2C19*17/*17 genotype were ultra-rapid metabolizers. Two hundred and fifty-one people (25.85%) were intermediate metabolizers with CYP2C19*1/*2, CYP2C19*2/*17, CYP2C19*1/*3, CYP2C19*3/*17 genotypes. Seventeen patients (1.75%) with CYP2C19*2/*2, CYP2C19*3/*3, CYP2C19*2/*3 genotypes were poor metabolizers. The allele frequencies were the following: CYP2C19*2 – 0.140, CYP2C19*3 – 0.006, CYP2C19*17 – 0.274.

Conclusion: There is a high frequency of *CYP2C19* genotypes associated with modified response to proton pump inhibitors in Russian patients with peptic ulcers. Genotyping for *CYP2C19* polymorphisms is suggested to be a useful tool for personalized dosing of proton pump inhibitors.

Keywords: CYP2C19, proton pump inhibitors, peptic ulcer, Russian

Introduction

Cytochrome P450 is known to be a major enzyme responsible for the oxidative metabolism of drugs in the liver. Proton pump inhibitors, which are widely used as acid-inhibitory agents for the treatment of peptic ulcers, are mainly metabolized by CYP2C19, and by CYP3A4 to a lesser extent. CYP2C19 is the main isoenzyme which is related to the metabolism of omeprazole and esomeprazole, while both CYP2C19 and CYP3A4 undertake the metabolism of pantoprazole and lansoprazole. As for

Correspondence: NP Denisenko
109443 Unih Lenintsev, 75k3, 22, Moscow, Russia
Email natalypilipenko3990@gmail.com

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http://dx.doi.org/10.2147/PGPM.S78986

rabeprazole it undergoes non-enzymatic conversion and therefore has less reliance on CYP2C19. All the metabolites produced are inactive.[1,2]

CYP2C19 has genetic polymorphisms that correlate with its activity. All the individuals may be classified as extensive metabolizers (EMs), poor metabolizers (PMs), intermediate metabolizers (IMs), and ultra-rapid metabolizers (UMs) according to their CYP2C19-based ability to metabolize proton pump inhibitors.[3,4]

Individuals with CYP2C19*1/*1 genotype are EMs, they carry two wild-type alleles and have no mutation, whereas those who have CYP2C19*2 (681G>A) or CYP2C19*3 (636 G>A) mutation alleles are designated as IMs, if heterozygous, and PMs, if homozygous. IMs and especially PMs have superior acid suppression with conventional doses of proton pump inhibitors.[5–7] The CYP2C19*17 (−806 C>T) allele, a novel allele identified by Sim et al[8] is associated with ultra-rapid phenotype and provides decreased acid suppression with standard recommended doses of proton pump inhibitors.[9–11] The areas under the concentration-time curve of proton pump inhibitors are higher in PMs than in EMs, whereas IMs are intermediate between the two; UMs have the lowest area under the concentration-time curve. Thus, proton pump inhibitors may not provide sufficient acid suppression in EMs and especially UMs.

Genotyping for *CYP2C19* polymorphisms reveals considerable interethnic differences. Most PMs are to be found among Asian and African-American population (allele frequencies are 30% and 17% for CYP2C19*2; 5% and 0.4% for CYP2C19*3, respectively). CYP2C19*2 is also relatively common in Caucasians with an allele frequency of 15% compared to 0.04% for CYP2C19*3 allele.[2] Thus, genetic polymorphism of *CYP2C19* could be of clinical concern in the treatment of peptic ulcers with proton pump inhibitors.

The aim of the study – to investigate the frequencies of CYP2C19*2, CYP2C19*3, and CYP2C19*17 alleles and genotypes in Russian patients with peptic ulcers.

Methods

We retrospectively reviewed the cases of 971 patients of Caucasian origin with Russian nationality from the Moscow region with endoscopically and histologically proven ulcers, 428 males (44%) and 543 females (56%). The mean age was 44.6±11.9 years (range: 15–88 years). We selected patients who were tested for *CYP2C19* polymorphism. In all patients, *CYP2C19* polymorphism testing and gastroduodenoscopy with biopsy were done after informed consent was obtained.

DNA was extracted from ethylenediaminetetraacetic acid whole blood samples (10 mL) and isolated from peripheral lymphocytes. The polymorphisms CYP2C19 681G>A (CYP2C19*2, rs4244285), CYP2C19 636 G>A (CYP2C19*3, rs4986893), and CYP2C19 −806 C>T (CYP2C19*17, rs12248560) were evaluated using real-time polymerase chain reaction. We used LightMix for CYP2C19*2 and CYP2C19*3 and LightSNiP for CYP2C19*17 (Roche®; Hoffman-La Roche Ltd, Basel, Switzerland) in a LightCycler 2.0 system.[12]

Patients were referred to as EMs, PMs, IMs or UMs according to the Dutch Pharmacogenetics Working Group Guideline of the Royal Dutch Pharmacists Association (http://www.pharmgkb.org/guideline/PA166104957).

The correspondence of the distribution of the genotype frequencies to the Hardy-Weinberg equilibrium was assessed using a χ^2 test with Yates correction. A P-value <0.05 was considered statistically significant. The statistical analysis was performed using SPSS Statistic 20.

Results

Regarding *CYP2C19* genotype, 317 patients out of 971 were CYP2C19*1/*1 carriers classified as EMs, 386 with CYP2C19*1/*17 or CYP2C19*17/*17 genotype were UMs, 251 were IMs, and 17 were PMs (Table 1).

The allele frequencies were the following: CYP2C19*2 – 0.140, CYP2C19*3 – 0.006, CYP2C19*17 – 0.274 (Table 2). Genotype frequencies are summarized in Table 3.

The observed genotype frequencies were in the Hardy-Weinberg equilibrium ($P>0.05$) for the majority of *CYP2C19* polymorphisms. We did not calculate CYP2C19*3 deviation from the Hardy-Weinberg equilibrium because CYP2C19*3 mainly occurs in Asian populations and is rare in Caucasians.

Discussion

The incidence of peptic ulcer in different countries of the world varies from 5% to 15%. It has been reported that *CYP2C19* polymorphism affects cure rates of peptic ulcers.[4–7] CYP2C19*2 and CYP2C19*3 alleles are associated with high eradication rates of Helicobacter pylori in patients with peptic ulcers, when triple therapy is administered.[6] The data on CYP2C19*17 allele are very scarce. It is reported, that patients carrying ultra-rapid CYP2C19*17 allele have lower levels of proton pump inhibitors in plasma.[7]

Our study provides data on *CYP2C19* genetic polymorphisms and is the first that has investigated CYP2C19*17 allele frequency in Russian patients with peptic ulcers.

Table 1 *CYP2C19* genetic polymorphisms frequency in Russian patients with peptic ulcers

CYP2C19 phenotype	CYP2C19 genotype	Number of patients	Frequency, %
Extensive metabolizers	*1/*1	317	32.65
Intermediate metabolizers	*1/*2	165	25.85
	*2/*17	78	
	*1/*3	7	
	*3/*17	1	
Poor metabolizers	*2/*2	14	1.75
	*3/*3	1	
	*2/*3	2	
Ultra-rapid metabolizers	*1/*17	320	39.75
	*17/*17	66	

Table 2 *CYP2C19* allele frequency in Russian patients with peptic ulcers

Genetic polymorphism	Allele	Number of alleles	Frequency
CYP2C19*2	G	1,669	0.860
	A	273	0.140
CYP2C19*17	C	1,411	0.726
	T	531	0.274

Table 3 *CYP2C19* genotype frequency in Russian patients with peptic ulcers

Genetic polymorphism	*P*-value	Genotype	Number of patients	Frequency
CYP2C19*2	0.17	GG	712	0.73
		GA	245	0.25
		AA	14	0.02
CYP2C19*17	0.29	CC	506	0.52
		CT	399	0.41
		TT	66	0.07

Table 4 CYP2C19*2 allele frequency in Russian patients with peptic ulcers compared to healthy Russian volunteers

Allele	Patients with peptic ulcer	Healthy volunteers[13]	χ^2 and *P*-value
G	1,669 (86.0%)	514 (88.6%)	P=0.1118
A	273 (14.0%)	66 (11.4%)	χ^2=2.528

Table 5 CYP2C19*2 genotype frequency in Russian patients with peptic ulcers compared to healthy Russian volunteers

Genotype	Patients with peptic ulcer	Healthy volunteers[13]	χ^2 and *P*-value
GG	712 (73.33%)	229 (79.0%)	P=0.1409
GA	245 (25.23%)	56 (19.3%)	χ^2=3.919
AA	14 (1.44%)	5 (1.7%)	

We compared CYP2C19*2 allele and genotype frequency in our study and in Gaikovitch et al's study on healthy volunteers from Voronezh area, Russia, and no statistically significant difference was found, $P>0.05$ (Tables 4 and 5).[13]

The frequency of CYP2C19*2 allele in our study is also comparable with data described for healthy volunteers from Slovenia (15.9%), Italy (9.4%), Croatia (15%), the Netherlands (13.3%), Germany (15%), and Greece (13.1%).[14–19]

CYP2C19*17 allele frequency in Russian patients tended to be higher than in Swedish (18%) and Chinese (4%) populations, thus a standard dose of proton pump inhibitors may not be effective in this group.[8]

Conclusion

There is a high frequency of *CYP2C19* genotypes associated with modified response to proton pump inhibitors in Russian patients with peptic ulcers. Genotyping for *CYP2C19* polymorphisms is suggested to be a useful tool for personalized dosing of proton pump inhibitors.

Disclosure

The authors declare no conflicts of interest.

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