MEDICAL SCIENCE MONITOR

LAB/IN VITRO RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2016; 22: 310-315
DOI: 10.12659/MSM.894868

Received: 2015.06.01
Accepted: 2015.07.28
Published: 2016.01.29

Roles of *CYP2C19* Gene Polymorphisms in Susceptibility to POAG and Individual Differences in Drug Treatment Response

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Source of support: Departmental sources

Background: The aim of this study was to investigate the roles of *cytochrome P450 2C19* (*CYP2C19*) polymorphisms in primary open-angle glaucoma (POAG) susceptibility and individual responses to drug treatment.

Material/Methods: This case-control study consisted of 93 cases with POAG and 125 controls. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used to analyze *CYP2C19* single-nucleotide polymorphisms (SNPs). After timolol treatment, patients were classified into side effect (SE) group and non-side effect (NSE) group. According to drug treatment responses, patients were divided into 3 groups: excellent group (Ex) (IOP ≥8 mm Hg); utility group (Ut) (5 <IOP ≤8 mm Hg), and ineffective group (In) (IOP ≤5 mm Hg). Data analysis was performed using SPSS software.

Results: We found no statistical differences in the alleles and genotypes frequencies of *CYP2C19* between the case group and the control group (both $P>0.05$). Frequencies of extensive metabolizer phenotype and poor metabolizer phenotype or poor metabolizer phenotype and intermediate metabolizer phenotype were significantly different between the SE group and NSE group (both $P<0.05$). The distribution of intermediate metabolizer phenotype and extensive metabolizer phenotype were significantly different among Ex group, Ut group, and In group (all $P<0.05$).

Conclusions: We found no evidence that *CYP2C19* polymorphisms are associated with susceptibility to POAG. However, different *CYP2C19* metabolizer phenotypes were identified and observed to have important effects on the individual differences in drug treatment response.

MeSH Keywords: Biomarkers, Pharmacological • Glaucoma, Open-Angle • Polymorphism, Genetic • Timolol

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/894868

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Background

Glaucoma is the most common cause of visual impairment or visual loss worldwide, and primary open-angle glaucoma (POAG) is the most prevalent type of glaucoma [1]. An estimated 70 million people suffer from glaucoma, and Asian ethnic minorities are more susceptible to this visual disease [2]. POAG is a chronic and aggressive optic neuropathy characterized by loss of optic nerve fibers, leading to elevated intraocular pressure (IOP), visual field abnormality, and occurrence of open anterior chamber angle (*http://www.lifesciencesite.com/lsj/life1101/003_21749life1101_18_26.pdf*). The POAG etiology is partly attributed to advanced age, ethnicity, and family history [3]. IOP is considered the major risk factor for POAG, and an elevated IOP (>21 mmHg) influences both the incidence and the progression of POAG; therefore, lowering IOP is the primary goal of current treatments in POAG patients [4,5]. Timolol is a non-selective beta-adrenergic receptor antagonist that has been widely used for the treatment of elevated IOP and glaucoma. Timolol is actively metabolized by the drug-metabolizing enzyme cytochrome P450 2C19 (*CYP2C19*), improving the efficacy of medical treatment [6].

Timolol is mostly used for treating heart attacks, hypertension, and glaucoma [7]. The use of timolol in POAG patients can improve retinal vascular autoregulatory function, including ocular blood flow and blood pressure, thereby reducing the loss of retinal ganglion cells and vision damage [8,9]. Inactive prodrugs require biotransformation into active forms, and drug metabolism is mediated by the hepatic cytochrome P450 (CYP450) system [10]. The hepatic *CYP2C19* enzyme, belonging to the CYP450 superfamily, metabolizes several important drugs such as mephenytoin, antidepressants, benzodiazepines, clopidogrel, and timolol [11]. The *CYP2C19**1, *2 and *3 alleles are the most common loss-of-function alleles that affect *CYP2C19*-mediated bioactivation of inactive drugs to active metabolites, consequently leading to poor drug pharmacodynamics and intestinal absorption [12]. Patients carrying the *CYP2C19**1 variant have full drug-metabolizing capacity, and *CYP2C19**2 and *3 carriers exhibit attenuation of CYP function and impaired drug response; therefore, individual differences in drug treatment response may be attributed to *CYP2C19**2 and *3 genetic polymorphisms (*http://www.davidpublishing.com/davidpublishing/Upfile/8/14/2014/2014081408950324.pdf*). The present study investigated the *CYP2C19**2 and *3 genetic polymorphisms for their association with the susceptibility to POAG and individual differences in drug treatment response.

Material and Methods

Ethics statement

This case-control study was performed in accordance with the guidelines received from the local Ethics Committee of the Affiliated Hospital of Beihua University. The enrolled patients provided written informed consent for the procedures and agreed to genetic analyses. The study conformed to the Declaration of Helsinki.

Study subjects

The study consisted of 93 POAG subjects (male 64, female 29; age range, 19~78; average age, 44.8±10.3; BMI, 17~31) and 125 controls (male 73, female 52; age range, 20~76; average age, 43.1±10.7; BMI, 17~31), divided into 2 groups (case and control groups). All patients in this study were recruited between March 2013 and May 2014 at the Department of Ophthalmology, the Affiliated Hospital of Beihua University. The diagnosis of POAG was based on diagnostic criteria published by the Chinese Medical Association Glaucoma Branch in 2008. The criteria for diagnosis of POAG were as follows: 1) IOP ≥21 mmHg; 2) abnormal optic disc determined by optical coherence tomography; 3) glaucomatous visual field deletion (on the basis of mean deviation and corrected pattern standard deviation); 4) retinal nerve fiber layer defect; and 5) open anterior chamber angle [13]. Patients were excluded if they had histories of chronic obstructive pulmonary diseases, bradycardia (heart rate <60 beats per min) (bpm), atrioventricular heart-block, bronchial asthma, spontaneous hypoglycemia, and diabetics under medication. All patients who used systemic and topical IOP-lowering drugs were also excluded. All patients did not use medication for 3 weeks before inclusion were excluded as well. Additionally, Han subjects in this study were not blood relatives.

DNA extraction

After all subjects fasted overnight for a period of 10–12 h, peripheral venous blood (5 mL) was collected in ethylene diamine tetraacetic acid (EDTA) tubes and stored at –80 °C [14]. The whole-blood Genomic DNA Isolation Kit (Tiangen Biotech (Beijing) Co. Ltd) was used for genomic DNA extraction. An ultraviolet spectrophotometer was used to measure the concentration and purity of the DNA.

Single nucleotide polymorphisms analysis

*CYP2C19**2 and *3 single-nucleotide polymorphisms (SNPs) were analyzed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RLFP) method. The PCR primers were designed by Primer Premier 5.0 software (Sangon Biotech, Shanghai, China) and were synthesized by Shanghai Sangon Biological Engineering Technology and Service Co., Ltd. Primer sequences are listed in Table 1. The 50 µL-PCR system consisted of 5 µL 10× PCR buffer, 1 µL dNTP (10 mmol/L), 2 µL primer compound, 0.5 µL Taq enzyme (5 U/µL) (TaKaRa), and 1 µL genomic DNA. The amplification conditions were as

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Table 1. Primer sequences of forward primers and reverse primers of *CYP2C19**2 and *3 single nucleotide polymorphism.

SNP	Primer sequences
CYP2C19*2	5'-AATTACAACCAGAGCTTGGC-3'
	5'-TATCACTTTCCATAAAAGCAAG-3'
CYP2C19*3	5'-TATTATTATCTGTTAACTAATATGA-3'
	5'-ACTTCAGGGCTTGGTCAATA-3'

SNP – single nucleotide polymorphism.

follows: an initial denaturation step (94°C for 5 min) and 35 cycles of denaturation (94°C for 60 s), followed by annealing and extension steps (53°C for 30 s and 70°C for 1 min). The Sam I restriction digestion reaction consisted of 1 μL Sam I, 2.0 μ L 10× T Buffer, 2 μ L 0.1% BSA, 10 μL DNA, and 5 μL double distilled water. The BamHI restriction digestion reaction was as follows: 1 μL BamH I, 2.0 μ L 10× K Buffer, 12 μL DNA, and 5 μL double-distilled water. The digestion products were separated on 3% agarose gels containing ethidium bromide and sequenced directly on an ABI 370 automated DNA sequencer (ABI Systems).

Metabolic phenotypes of *CYP2C19* polymorphisms

The polymorphisms of *CYP2C19**2 and *3 were divided into 3 phenotypes according to definition of metabolic phenotype: *CYP2C19**1/*1 (extensive metabolizers); *CYP2C19**1/*2 and *CYP2C19**1/*3 (intermediate metabolizers); and *CYP2C19** 2/ *2, *CYP2C19** 2/* 3, and *CYP2C19** 3/* 3 (poor metabolizers) [15].

Drug treatment and IOP measurement

The case group received 1 drop of 0.5% timolol without punctal occlusion, twice daily at 8 am and 6 pm. After the instillation, IOP was measured on days 1, 3, 7, 14, 21, and 28 with a Perkins hand-held applanation tonometer (Perkins), in the sitting position [16]. The IOP daily curve was taken after measurements, and HR of patients was also recorded.

Individual differences in drug response

Patients who showed HR lower than 60 bpm after timolol treatment or lower than 20 bpm for the first-time measurement were considered as the side effect group (SE), and the remaining patients were considered as the non-side effect group (NSE). If patients had HR lower than 45 bpm or symptoms of chest stuffiness, general fatigue, or palpitations at any time during the study, they were requested to immediately stop drug use and consult a doctor.

Based on the effects of drug treatment and degree of IOP improvement, patients were divided into 3 groups: the excellent group (Ex) (IOP ≥8 mm Hg); the utility group (Ut) (5 <IOP ≤8 mm Hg); and the ineffective group (In) (IOP ≤5 mm Hg).

Statistical analysis

Data analysis was performed using SPSS software for Windows (Version 18.0; SPSS, Chicago, IL). Measurement data are expressed as mean ±SD and compared using the *t* test. Enumeration data are presented by percentage or rate and compared using the χ^2 test. The different genotypes of *CYP2C19**2 and *3 polymorphisms were estimated by odds ratios (ORs) with 95% confidence intervals (CIs). All tests were 2-sided, and *P* values less than 0.05 were considered to be statistically significant.

Results

CYP2C19 genotypes distributions of the study subjects

All patients with different allelic and genotypic frequencies were in Hardy-Weinberg equilibrium. The frequencies of *CYP2C19* alleles and genotypes are shown in Table 2, and it showed that there were no statistically significant differences in frequencies of *CYP2C19* alleles and genotypes between the case group and the control group (both $P>0.05$). The results suggest that *CYP2C19**2 and *3 polymorphisms were not associated with susceptibility to POAG.

CYP2C19 metabolizer phenotype distributions in SE group and NSE group

No differences in sex, age, or BMI existed between the SE group and NSE group (all $P>0.05$). However, statistically significant differences were observed in *CYP2C19* metabolizer phenotypes between the SE group and NSE group. As seen in Table 3, the frequencies of extensive metabolizer phenotype and poor metabolizer phenotype or poor metabolizer phenotype and intermediate metabolizer phenotype were significantly different (both $P<0.05$), but the distributions of intermediate metabolizer phenotype and extensive metabolizer phenotype showed no statistically significant differences ($P>0.05$). These results

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Table 2. Distributions of allele and genotype frequencies of *CYP2C19**2 and *3 polymorphisms in both the case group and the control group.

SNP	Case (n=93)		Control (n=125)		*P*	OR	95%CI	
							Down limit	Up limit
CYP2C19 * 1/* 1	37	(39.8)	50	(40.3)	0.967*	Ref	Ref	
CYP2C19* 1/* 2	36	(38.7)	47	(37.9)	0.911	1.035	0.564	1.901
CYP2C19* 1/* 3	7	(7.5)	11	(8.9)	0.776	0.860	0.304	2.430
CYP2C19 * 2/ *2	9	(9.7)	11	(8.9)	0.841	1.106	0.417	2.941
CYP2C19* 2/* 3	4	(4.3)	5	(4.0)	0.912	1.081	0.271	4.306
CYP2C19* 3/* 3	0	(0.0)	1	(1.0)	0.392	0.449	0.017	11.34
CYP2C19* 1	117	(62.9)	158	(63.2)	0.837#	Ref	Ref	
CYP2C19* 2	58	(31.2)	74	(29.6)	0.790	1.058	0.696	1.609
CYP2C19* 3	11	(5.9)	18	(7.2)	0.632	0.825	0.375	1.814

SNP – single nucleotide polymorphisms; OR – odds ratio; CI – confidence interval; * *P* values, compared among *CYP2C19* genotypes; # *P* values, compared among *CYP2C19* alleles.

Table 3. Biochemical indexes and distributions of extensive metabolizer phenotype, intermediate metabolizer phenotype and poor metabolizer phenotype in side effect group and non-side effect group.

Factors	SE group	NSE group	P
Cases	9	84	–
Sex (Male/Female)	6/3	58/26	0.145
Age/years	45.2±9.5	44.8±10.5	0.913
Body mass index	24.2±3.9	24.3±3.8	0.941
Extensive metabolizer phenotype	2	35	0.016*
Intermediate metabolizer phenotype	3	40	0.772#
Poor metabolizer phenotype	4	9	0.023**

SE – side effect; NSE – non-side effect; * *P* values, compared between extensive metabolizer phenotype and poor metabolizer phenotype; # *P* values, compared between intermediate metabolizer phenotype and extensive metabolizer phenotype; ** *P* values, compared between poor metabolizer phenotype and intermediate metabolizer phenotype.

suggest that the poor metabolizer phenotype slows the rate of timolol metabolism, thereby leading to SEs.

CYP2C19 metabolizer phenotype distributions in Ex group, Ut group, and In group

There were no differences in sex, age and BMI among Ex group, Ut group, and In group (all $P>0.05$). Distributions of poor metabolizer phenotype and intermediate metabolizer phenotype among Ex group, Ut group, and In group did not show statistically significant differences (all $P>0.05$), while the distributions of intermediate metabolizer phenotype and extensive metabolizer phenotype and extensive metabolizer phenotype and poor metabolizer phenotype among Ex group, Ut group, and In group were significantly different (all $P<0.05$) (Table 4). These results revealed that extensive metabolizers rapidly metabolize timolol, contributing to low utilization ratio of the drug and poor treatment responses.

Discussion

CYP450 metabolizes almost 90% of prescribed drugs, and *CYP2C19* is an important CYP450 that can also catalyze drugs by inducing oxidation reactions [17]. Our study found no association between *CYP2C19* polymorphisms and susceptibility

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Table 4. Biochemical indexes and distributions of extensive metabolizer phenotype, intermediate metabolizer phenotype and poor metabolizer phenotype in excellence group, utility group and inefficacy group.

Factors	Ex group	Ut group	In group	*P*
Cases	25	29	30	–
Sex (Male/Female)	17/8	20/9	21/9	0.980
Age/years	44.7±10.3	44.9±10.5	44.8±10.7	0.998
Body mass index	24.3±3.7	24.2±3.8	24.4±3.8	0.987
Extensive metabolizer phenotype	7	10	18	0.029$^{\&,*}$
Intermediate metabolizer phenotype	13	16	11	0.034$^{\&,\#}$
Poor metabolizer phenotype	5	3	1	0.246$^{\&,**}$

Ex – excellent; Ut – utility; In – inefficacy; $^{\&}$ *P* values, compared between combination of Ex group and Ut group and In group
* *P* values, compared between extensive metabolizer phenotype and poor metabolizer phenotype; # *P* values, compared between intermediate metabolizer phenotype and extensive metabolizer phenotype; ** *P* values, compared between poor metabolizer phenotype and intermediate metabolizer phenotype.

to POAG, possibly because *CYP2C19* affects drug metabolism, and thus is unlikely to be involved in the POAG disease process. However, genetic polymorphisms play a critical role in drug responses and adverse drug reactions [18]. A previous study suggested that drug-drug interactions are correlated with activities of *CYP2C19*, but the development of POAG was not linked with *CYP2C19* polymorphism [19]. We support the view that different *CYP2C19* metabolizer phenotypes impact drug treatment response to timolol in patients with POAG. Timolol monotherapy, used for management of POAG patients, lowers IOP and prevents other complications and drug-related adverse events [20]. A study conducted by Frezzotti Paolo observed that, despite the IOP-lowering effect, 2 formulations of timolol caused varying degrees of adverse events [21]. Therefore, combination therapy for glaucoma aims to achieve minimum medication, reduced IOP-lowering doses, and improved convenience and compliance for patients, leading to excellent drug effects [22,23]. Owing to the drug metabolic enzymes, treatment of POAG using timolol is improved; however, patients carrying different *CYP2C19* phenotypes may differ in drug response [24]. Carriers of 1 or more loss-of-function *CYP2C19* alleles (so-called intermediate metabolizers) prevent drug conversion to their active metabolites and enhance adverse outcomes (*http://circinterventions.ahajournals.org.proxy.its.virginia.edu/content/4/5/514.full*). Accordingly, we support the notion that *CYP2C19* genetic variants influence clinical benefits from drug treatment by modulating availability of the active drug; thus, treatment of POAG with timolol must consider these *CYP2C19* metabolizer phenotypes.

According to *CYP2C19* genotypes, there are 3 main phenotypes – extensive metabolizers, intermediate metabolizers, and poor metabolizers – that are closely correlated with drug utilization, individual response to drug treatment, and drug effects [25,26]. *CYP2C19* polymorphisms are chief pharmacogenetic contributors of individual differences in response to drug treatment because of the carrier status of the *CYP2C19* loss-of-function allele [27]. Patients carrying loss-of-function *CYP2C19* alleles are poor metabolizers [28]. Poor metabolizers have lower activities of *CYP2C19* enzyme, and the concentration of drug significantly increases, consequently leading to drug toxicity (*http://cdn.intechopen.com/pdfs-wm/39693.pdf*). In contrast, intermediate and extensive metabolizers exhibit higher drug metabolism and absorption, but the rapid metabolism lower drug effects in the clinic, causing administration of larger doses of the drug and severe side effects [29]. Our findings also suggest that different *CYP2C19* metabolizer phenotypes, due to *CYP2C19**2 and *3 polymorphisms, have important effects on individual responses to drug treatment and adverse drug reactions.

This study has some limitations that must be highlighted. First, the sample size was small and the observation period was also short. Second, the study was limited by its open-label design. Also, we did not use different timolol dosing regimens, which may be a significant study limitation. Third, the time of IOP measurement and timolol use was not matched, resulting in ignoring the peak of efficacy of drug treatment. Additionally, other factors like symptoms and ocular surface staining, which may provide useful information, were not analyzed in the study. Finally, we only discussed *CYP2C19**2 and *3 polymorphisms in this paper, but there are other genetic variants of *CYP2C19* polymorphisms that could alter the response to timolol treatment, such as *3, *5, and *17.

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Conclusions

In conclusion, *CYP2C19* polymorphisms are not associated with susceptibility to POAG. However, we observed that different *CYP2C19* metabolizer phenotypes, due to *CYP2C19**2 and *3 polymorphisms, have important effects on individual responses to drug treatment and treatment-related side effects.

Acknowledgements

We are grateful to our instructors for their valuable advice.

Competing interests

The authors have no financial or non-financial conflicts of interest to declare with regard to the study.

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