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RESEARCH ARTICLE

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CYP2C19 genetic variation and individualized clopidogrel prescription in a cardiology clinic

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ABSTRACT

Background: Clopidogrel (Plavix) is an antiplatelet medication that is routinely used in patients with cardiovascular disease. Cytochrome P2C19 enzymes play a major role in its metabolism, which determines its varied therapeutic level and its effectiveness.

Objectives: To customize clopidogrel therapy and evaluate its efficacy by using CYP2C19 genotypic and phenotypic information to improve clinical outcomes in patients.

Methods: A total of 465 patients with underlying cardiovascular disease were selected from our out-patient cardiology clinic. DNA sequences of CYP2C19 were analyzed in 465 patients.

Results: Of 465 patients, 183 were wild-type homozygous (*1/*1) and 18.8% gain-of function and 19.8% loss-of-function alleles in our patient population The following changes were made: 1) Switching to prasugrel in patients whose genotype noted them to be "Slow metabolizers. This medication adjustment improved clinical outcomes in this patient group.

2) Discontinuing or lowering clopidogrel doses in patients whose genotypes noted them to be "Fast or ultra-fast metabolizes" to decrease bleeding risk. For those who were not on clopidogrel but carried abnormal allele(s), "clopidogrel caution" was documented. These individuals were followed up for 3 years and there has not been any cardiac clinical symptoms, cardiac death or excessive bleeding reported.

Conclusions: Given the varied effectiveness of clopidogrel due to its metabolism by CYP2C19 enzyme, and the relatively high frequency of both gain-of-function (18.8%) and loss-of-function (19.8%) alleles in our patient population, we believe that genotyping CYP2C19 is clinically important in order to improve patient outcomes and minimize patient risk.

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CYP2C19; clopidogrel; pharmacogenetic

1. Introduction

Clinicians often treat patients based on data gathered from large clinical trials. As a consequence, similar treatment is recommended for all patients with the same disease or medical condition, without consideration of genetic data [1]. Yet, the use of the personalized data can reveal more differences among patients than similarities, especially with regards to pharmacogenetics and pharmacokinetics. In fact, based on pharmacogenomic data, we can better predict how an individual may process and how well they may respond to their medications [1].

Over the past few years, several institutions including Mayo Clinic have utilized pharmacogenomic information to personalize (individualize) pharmacologic therapy [1–4]. There is significant genetic variability between patients; and each individual may have a different response to commonly prescribed cardiovascular medication. These include warfarin, clopidogrel, statins, and b-blockers, among others. For some individuals, prescribing these medications would provide no significant clinical benefit whereas others may experience potentially fatal side effects. Personalizing (individualizing) the treatment plan provides the opportunity to prescribe medications safer and enables us to better predict the potential efficacy as well as prevent the development of significant side effects [5].

Clopidogrel, which is a commonly used anti-platelet medication in cardiovascular disease, is metabolized in our body by various hepatic enzymes. CYP2C19, which is the principal hepatic enzyme involved in converting clopidogrel to its active metabolite primary activator, is a highly polymorphic enzyme, with more than 25 alleles. Based on the different alleles, the enzyme is categorized into 4 major phenotypes: Ultra rapid metabolizer (UM), Extensive metabolizer (EM), Intermediate metabolizer (IM) and Poor metabolizer (PM).

The *1 is the wild-type allele and is associated with normal enzyme activity and the 'extensive metabolizer' phenotype. The *17 allele is associated with increased enzyme activity due to increased gene transcription [6] and individuals with one or two copies of the *17 allele are typically classified as 'ultra-fast metabolizers'.

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Individuals who carry one and two reduced-activity or non-functioning CYP2C19 alleles are 'intermediate' and 'poor metabolizers', respectively.

The most common loss-of-function variant is CYP2C19*2, which is the most important factor responsible for the variable clopidogrel effect in different individuals. This was not recognized until 2006 [6]. It contains a 681G>A variant in exon 5 which creates a cryptic splice site and premature stop codon 20 amino acids leading to the production of a truncated and non-functioning protein.

The other loss of function allele are *3, *4, *5, *6, *7, and *8.

Given that the efficacy of clopidogrel is, in part, dependent upon it being metabolized by CYP2C19 to an active metabolite, intermediate and poor metabolizers can have reduced antiplatelet responses when treated with clopidogrel. Based on this information, the FDA issued a boxed drug label warning indicating potential for reduced efficacy (increased adverse cardiovascular outcomes) in March 2010. This warning demonstrated the importance of genotypic determination of the patients who are taking clopidogrel [1].

With consideration of FDA guidelines for clopidogrel treatment, we decided to assess the CYP2C19 polymorphism in our patients who were exposed to clopidogrel. The objective was to see if testing would help identify those at risk of adverse effects and to potentially reduce adverse outcomes with this particular drug based on an individual's genetic profile.

2. Methods

We evaluated patients at the out-patient cardiology clinic for genotyping of the CYP2C19 enzyme from September 2013 to January 2016. Out of 2000 patients, 465 consented and qualified based on insurance coverage and medical necessity. We used the Magnetic Bead-Based method for concentrating DNA, which was obtained from buccal swab leukocytes by using QiagenQiaCube instrument and MagMAX™ DNA Multi-Sample Kits. The data was reviewed and analyzed by multiple experts and specialists including a genetics expert, pharmacist and cardiologist, which was then reviewed with each patient by the cardiologist, prior to making any further modifications or recommendations.

A total of 465 consecutive qualified patients were enrolled and a consent form was signed by every patient. Enrollment consent form was approved by Copernicus Group Institutional Review Boards.

CYP2C19 alleles include wild type allele (*1), non-functional (*2,*3, *4, *5, *6, *7,*8,*9 and *10) and increased in function (*17). Based on the alleles (represented in the parenthesis), we were able to divide our patients into 3 different phenotypes: Group 1: consisted of normal metabolizers (active/active). Group 2 were the slow metabolizers (active/inactive or inactive/inactive or inactive/rapid) and Group 3 consisted of fast metabolizers (active/rapid or rapid/rapid alleles) (Figure 1).

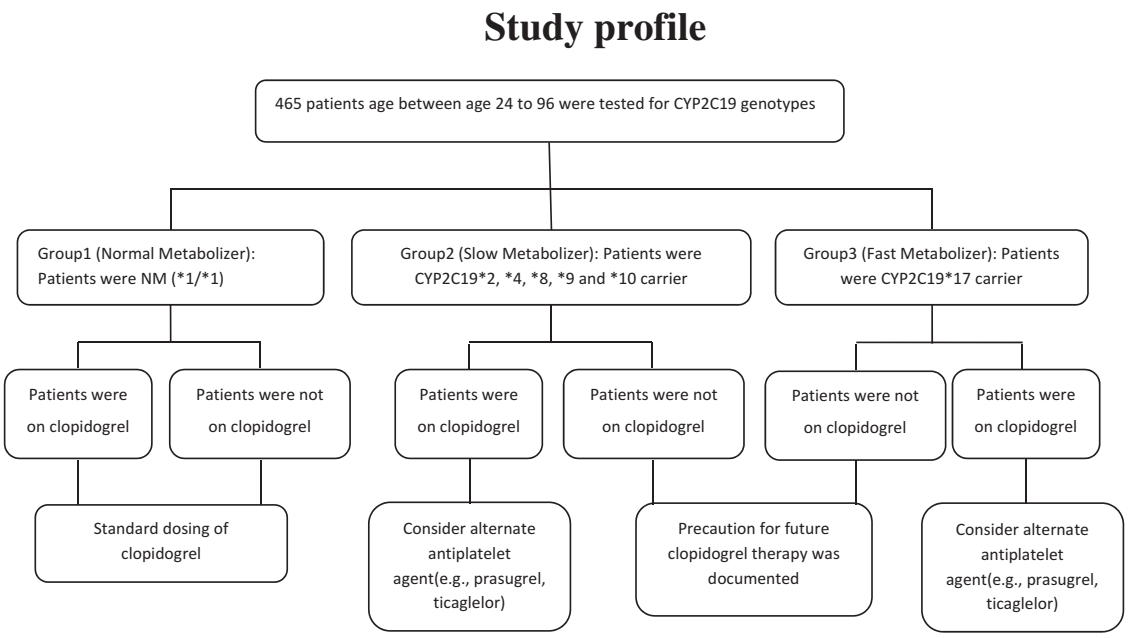

Figure 1. Study profile; Based on the results of pharmacogenetic testing, patients who were slow or fast metabolizers and on clopidogrel, were switched to another antiplatelet drug not metabolized the same enzyme (parasugrel). 'Clopidogrel precaution' was documented for the patients who were not already on it.

Table 1. Shows the correlation of likely CYP2C19 phenotypes based on CYP2C19 alleles (genotypes).

Likely phenotype	Genotypes	Examples of diplotypes
normal metabolizer (NM)	This phenotype consists of two active CYP2C19 alleles.	*1/*1
Normal/Intermediate metabolizer (NIM):	This phenotype consists of one inactive and one rapid CYP2C19 allele. CYP2C19 NIMs are likely intermediate in metabolic activity between normal and intermediate metabolizers.	*2/*17, *8/*17, *9/*17,
Intermediate metabolizer (IM):	This phenotype consists of one active (*1) and one inactive CYP2C19 allele. CYP2C19 IMs exhibit approximately one-half the normal enzyme activity.	*1/*2, *1/*3,
poor metabolizer (PM):	This phenotype consists of two inactive CYP2C19 alleles. CYP2C19 PMs have greatly decreased enzyme activity.	*2/*2, *2/*3, *3/*3
Rapid Metabolizer (RM):	This phenotype consists ofone active (*1) and one increased activity (*17) CYP2C19 alleles. CYP2C19 URMs have markedly elevated levels of enzyme activity.	*1/*17
Ultra Rapid Metabolizer (URM):	This phenotype consists of two increased activity (*17) CYP2C19 alleles. CYP2C19 URMs have markedly elevated levels of enzyme activity.	*17/*17

Table 1 shows the correlation of likely CYP2C19 phenotypes based on CYP2C19 alleles (genotypes).

Based on the results of pharmacogenetic testing, patients who were slow or fast metabolizers and on clopidogrel, were switched to another antiplatelet drug not metabolized the same enzyme (parasugrel). 'Clopidogrel precaution' was documented for the patients who were not already on it (Figure 1).

The medical history, physical examination, cardiac risk factors including diabetes, blood pressure, hyperlipidemia and BMI were assessed in every follow up visit (every 3–6 months). All medications were assessed each and every visit to eliminate any potential drug interactions. Smoking and alcohol status was documented and all clinical events were recorded by a cardiologist at every visit.

The evaluation and titration of each medication was documented and followed closely for efficacy, tolerance and any side effects for a 3-years f/u period.

We analyzed the data using a Chi-square method.

3. Results

The numbers and frequencies of CYP2C19 alleles in the 465 patients (total of 930 alleles) are [expressed as: variant: number (frequency)]:

Normal allele: *1 = N: 579(62.2%) (Table 3).

Gain-of-function allele: *17 = N: 186(20.0%)

Loss-of-function alleles: *2 = N: 158(16.9%), *4 = N:3 (0.32%), *8 = N:2 (0.21%), and *10 = N:1(0.1%).

The phenotype and genotype distributions (Table 3) are [expressed as: phenotype (patient number): genotype (patient number)]:

Slow-Metabolizer (18): *2/*2(18);

Intermediate-Metabolizer (92): *1/*2(87), *1/*4(3), *1/*8(1) and *1/*10(1);

Normal-Intermediate-Metabolizer (37): *2/*17 (35),*8/*17(1) and *9/*17(1);

Normal-Metabolizer (183): *1/*1(183);

Fast-Metabolizer (121): *1/*17(121) and

Ultra-fast-Metabolizer (14): *17/*17(14).

These patients were then grouped into 3 different phenotypes (Table 3): Group1 had 183 patients (39.3%) who were Normal Metabolizers, Group 2 had 147(31.6%) who were slow metabolizers and 135 (29%) were in Group 3, who were fast metabolizers.

Demographic, clinical and pharmacologic information of these patients including age, sex, BMI, cardiac risk factors and medication therapy were also reviewed, which did not reveal any significant difference among these three groups (Table 2).

Of the 465 patients who were tested for CYP2C19 genotype, 58 were already being treated with clopidogrel for underlying coronary artery disease, of which

Table 2. Shows demographic, clinical and pharmacologic information of patients including age, sex, BMI, cardiac risk factors and medication therapy.

	All	Group1: Normal metabolizer (*1/*1)	Group2: Slow metabolizer (CYP2C19*2 carrier)	Group 3: Fast metabolizer (CYP2C19*17 carrier)	P value
	465	183 (39.3%)	147 (31.6%)	135 (29%)	
Male sex	274 (58.9%)	111 (60.7%)	84 (57.1%)	79 (58.5%)	.72
Age	71.2	72.2	70.4	70.8	.42
Clopidogrel therapy	58	21 (36.2%)	19 (32.7%)	18 (31.0%)	.53
Discontinue Plavix at Discharge	38 (65.5%)	2 (9.5%)	18 (94.7%)	18 (100.0%)	.001
BMI(kg/m2)	29.3	28.5	30.3	29.2	.13
Risk factors					
Smoking	30 (6.5%)	11 (6.0%)	8 (5.4%)	11 (8.1%)	.62
Alcohol	73 (15.7%)	32 (17.5%)	20 (13.6%)	21 (15.6%)	.63
HTN	402 (86.4%)	161 (88.0%)	130 (88.4%)	111 (82.2%)	.23
DM	126 (27.1%)	48 (26.2%)	38 (25.9%)	40 (29.6%)	.73
CAD	185 (39.8%)	74 (40.4%)	61 (41.5%)	50 (37.0%)	.73
Dyslipidemia	207 (44.5%)	77 (42.1%)	69 (46.9%)	61 (45.2%)	.67
Atrial fibrillation	195 (41.9%)	85 (46.4%)	56 (38.1%)	54 (40.0%)	.27
Other medication					
PPI	119 (25.6%)	39 (21.3%)	42 (28.6%)	38 (28.1%)	.23
Aspirin	300 (64.5%)	111 (60.7%)	94 (63.9%)	95 (70.4%)	.20

Table 3. Shows patients were grouped into 3 different phenotypes: Group1 patients (39.3%) were Normal Metabolizers; Group 2 patients (31.6%) who were Slow Metabolizers and Group 3 patinets (29%) were Fast Metabolizers.

Group	Phenotype	Genotype	Number
1: Normal Metabolizer	Normal Metabolizer (NM):	Homozygote (*1/*1)	183
2: Slow Metabolizer	Intermediate Metabolizer (IM):	Heterozygote(*1/*2)	87
	Intermediate Metabolizer (IM):	Heterozygote (*1/*4)	3
	Intermediate Metabolizer (IM):	Heterozygote (*1/*8)	1
	Intermediate Metabolizer (IM):	Heterozygote (*1/*10)	1
	Normal/Intermediate Metabolizer (NIM):	Heterozygote (*2/*17)	35
	Normal/Intermediate Metabolizer (NIM):	Heterozygote (*8/*17)	1
	Normal/Intermediate Metabolizer (NIM):	Heterozygote (*9/*17)	1
	Poor Metabolizer (PM):	Homozygote (*2/*2)	18
3: Fast Metabolizer	Ultra Rapid Metabolizer (URM):	Heterozygote (*1/*17)	121
	Ultra Rapid Metabolizer (URM):	Homozygote (*17/*17)	14

21 (36.2%) were normal metabolizers, 19 (32.7%) were slow metabolizers and 18 (31.0%) were fast metabolizers (Table 2).

According to the current CPIC guidelines, the following changes were made:

(1) Switching to prasugrel (antiplatelet medication not effected by CYP2C19) in PM genotype which improves clinical outcome;
(2) Discontinuing or lowering clopidgorel doses in RM genotype to decrease bleeding risk.

For those who are not on clopidogrel but carry abnormal allele(s), 'clopidogrel caution' was documented. Patients have been followed up for 3 years.

We considered alternate antiplatelet agents (e.g., prasugrel, ticaglelor) for the patients who were treated by clopidogrel in groups 2 and 3. Precautions for future clopidogrel therapy for the patients who were treated by clopidogrel in group 2 and 3 were documented. We continued standard dosing for clopidogrel in patients in group 1.

We discontinued clopidogrel or considered alternate antiplatelet agent (e.g., prasugrel, ticaglelor), in 2 of 21 (9.5%) in group one, 18 of 19 (94.7%) in group 2, and 18 of 18 (100%) patients in group3, who were on clopidegrol. We did not discontinue clopidogrel in 1 patients in group 2 because the patient refused new medication.

Figure 2 shows the number of patients who were on clopidegrol and we considered alternate antiplatelet agent (e.g., prasugrel, ticaglelor) based on their pharmacogenetic information in three different groups.

No adverse events were reported after two year follow up. Potential adverse events include any cardiac clinical symptoms, cardiac death or excessive bleeding.

4. Discussion

At this point, there has not been widespread implementation of pharmacogenetic testing among clinicians. Possible reasons may include lack of knowledge among clinicians about pharmacogenetic data or uncertainty about how to best utilize this information in daily practice. There are also concerns about financial and logistical aspects including the cost of genetic testing, insurance coverage and potential lack of reimbursement. Actually, CYP2C19 polymorphisms test is now available and costs $300–$400 which is covered by

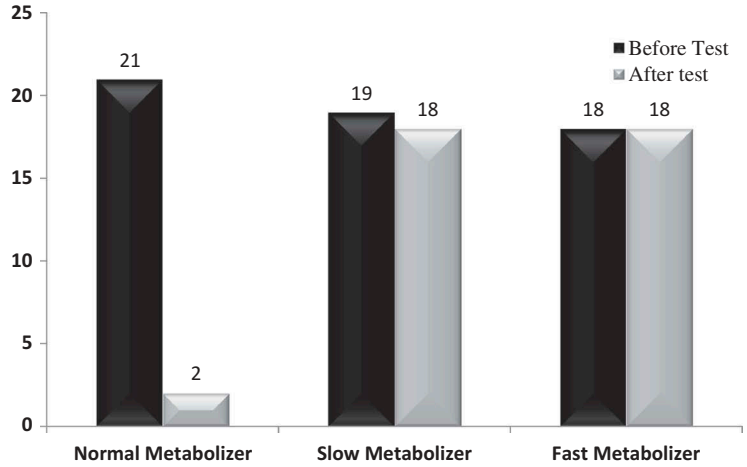

Figure 2. shows the number of patients who were on clopidegrol and we considered alternate antiplatelet agent (e.g., prasugrel, ticaglelor) based on their pharmacogenetic information in three different groups.

most insurance companies with varying co-payments [7]. There is also the challenge of obtaining the results for the genetic study in delayed turnaround time for obtaining the results for genetic information not being available after a decision about medication therapy or dose adjustment has been rendered [8,9].

Tens of millions people in the U.S. have taken clopidogrel since it was approved by FDA in1997 [10]. Its approved indications include: recent MI, cardioembolic stroke, established peripheral arterial disease and acute coronary syndrome (ACS). It is converted to an active metabolite by hepatic metabolism, which selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y12 receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation [6]. Several hepatic enzymes play a role in its activation, with the most notable one being CYP2C19.

Genetic polymorphism of variability in drug metabolism via CYP2C19 was first recognized in 1994. With more than 25 alleles attributing to varied expression of the gene, they can be categorized into 3 main phenotypes: normal, slow and rapid metabolizers.

The *1 is the wild-type allele and is associated with normal enzyme activity. The *17 allele is associated with increased enzyme activity [6] and individuals with one or two copies of the *17 allele are typically classified as 'fast metabolizers'. Individuals who carry one and two reduced-activity or non-functioning CYP2C19 alleles are 'intermediate' and 'Slow metabolizers', respectively, which are *2, *3, *4, *5, *6, *7, and *8. The most important loss-of-function allele is (*2) for CYP2C19, which is an important determinant of clopidogrel effect, was recognized only in 2006 [11], nearly a decade after its approval by the FDA.

Several studies focused on the effect of double, triple or even quadruple doses (150, 225, 300 mg daily, respectively) of clopidogrel to achieve active metabolite concentrations in *1/*2 and *2/*2 (slow metabolizers) individuals [12–14]. They evaluated on-treatment platelet reactivity and even with quadruple doses (300 mg daily), *2/*2 individuals weren't able to achieve antiplatelet effects compared to *1/*1 individuals on 75 mg daily. Simon et al. showed that among patients with an acute myocardial infarction who were receiving clopidogrel, those carrying CYP2C19 loss-of-function alleles had a higher rate of subsequent cardiovascular events than those who were not [15]. This suggests that alternate antiplatelet agents (e.g., prasugrel, ticaglelor) are better options than increasing the dose of clopidogrel in slow metabolizer patients. There are fewer studies about clopidogrel in concentration of fast metabolizers (*17 individuals), although *17 is associated with higher concentrations of active metabolites [16,17] and thus high risk of bleeding.

Given these findings, in 2013, the FDA approved drug label for clopidogrel (Plavix) warning that patients who are CYP2C19 poor metabolizers may have diminished effectiveness of the drug, leading to higher cardiovascular event rates following acute coronary syndrome or percutaneous coronary intervention, as compared to patients with normal CYP2C19 function. The drug label suggested that alternative treatment or treatment strategies are considered in patients identified as CYP2C19 poor metabolizers.

Information about the relationships between CYP2C19 genotype and pharmacokinetics, antiplatelet effect, and cardiovascular outcomes are available in the clopidogrel CYP2C19 CPIC guidelines [6].

5. Conclusion

Individualized medicine helps physicians to prescribe appropriate medication at the right dose to achieve optimal therapeutic effect while minimizing adverse effects. By studying the genotype of the CYP2C19 enzyme, we are able to identify those patients who will either not benefit from clopidogrel or will be at a higher risk for side effects and to formulate the best possible treatment plan for each patient to improve the quality of care and decreases drug related cardiac complications.

Compliance with Ethical Standards

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in this study.

Disclosure statement

No potential conflict of interest was reported by the authors.

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