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Anti-Platelet Therapy in Mild Cerebral Infarction Patients on the Basis of CYP2C19 Metabolizer Status

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Abstract

This study aimed to investigate the effects of CYP2C19 metabolizer status on the clinical therapeutic efficacy of cerebral infarction. Patients with cerebral infarction ($n = 180$; NIHSS score ≤ 5) were recruited and divided into Group A and Group B according to CYP2C19 metabolizer status. In Group A, patients received routine clopidogrel therapy for 1 year; in Group B, the patients with extensive metabolizer (EM) were treated with clopidogrel, and patients with intermediate metabolizer (IM) and poor metabolizer (PM) were treated with aspirin for 1 year. On admission, National Institutes of Health Stroke Scale score was determined, and the therapeutic efficacy was evaluated with Modified Rankin Scale score after 1 year of treatment. The outcomes and adverse effects were recorded during the treatment. After routine clopidogrel treatment, the efficacy in EM patients was significantly better than in PM and IM patients. After adjustment of therapeutic protocol, the therapeutic efficacy in PM and IM patients was markedly improved, which was accompanied by significant reduction in recurrence rate of cerebral infarction. Although the adverse effects increased in patients receiving aspirin treatment, they resolved after symptomatic therapy. CYP2C19 metabolizer status is closely related to the clinical efficacy of clopidogrel. Thus, it is necessary to adjust the anti-platelet treatment according to the CYP2C19 metabolizer status to maximize therapeutic efficacy without increasing recurrence and adverse effects.

Keywords

CYP2C19, metabolizer status, clopidogrel, clinical efficacy, recurrence rate

Introduction

Patients having a history of ischemic stroke or transient ischemic attack (TIA) usually possess elevated risk for subsequent vascular events, including stroke, myocardial infarction (MI), and death from cardiovascular causes[1]. –The annual risk of a recurrent ischemic event after an initial ischemic stroke or TIA is, on average, approximately 3–4%[2]. Therefore, antiplatelet therapy for the prevention of these events has been a cornerstone of treatment in patients with ischemic stroke and TIA[3]. Aspirin and clopidogrel are commonly used in anti-platelet therapy. Several studies have shown that short-term aspirin, in combination with clopidogrel, is more effective as secondary prevention of stroke or TIA without increasing the risk of hemorrhagic stroke and major bleeding events as compared to monotherapy. However, long-term combination therapy cannot reduce the risk of stroke recurrence and is associated with increased major bleeding events[4].

Clopidogrel is a thienopyridine prodrug and metabolized in the liver to form an active metabolite that selectively and irreversibly inhibits the P2Y12 class of adenosine diphosphate (ADP) receptors on platelets to prevent aggregation. The metabolism of clopidogrel into its active metabolite has

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involvement of several CYP450 enzymes including cytochrome P450, family 2, subfamily C, and polypeptide 19 (CYP2C19). However, the efficiency of clopidogrel in preventing platelet aggregation is inconsistent among patients[5]. The difference in the efficiency of clopidogrel is related to the individual and genetic factors. The CYP2C19 enzyme is responsible for 45% of the first step and 20% of the second step in hepatic biotransformation of clopidogrel[6]. Polymorphisms in the CYP2C19 gene have been consistently implicated in clopidogrel responsiveness heterogeneity[7]. CYP2C19 is located on chromosome 10 among a cluster of CYP genes including CYP2C18, CYP2C9, and CYP2C8[8]. The genetic polymorphisms of CYP2C19 may lead to variable hepatic expression, which then alters the function of the resultant protein (i.e., CYP2C19 enzyme).

To date, more than 30 CYP2C19 alleles have been identified. The normal, or wild-type, allele is usually denoted *1 (e.g., homozygous wild type *1/*1). The most extensively studied loss-of-function (LOF) alleles are *2 and *3 alleles[9]. CYP2C19*4, *5, *6, *7, and *8 alleles have also been associated with CYP2C19 LOF, but these variants are rare (<1% allelic frequency) and less studied[10]. In addition, there is also a gain-of-function (GOF) variant of CYP2C19: the variant CYP2C19*17[9]. All these CYP2C19 genotypes confer five phenotypes: extensive (or normal) metabolizers (EMs) (*1/*1), poor metabolizers (PMs) (*2/*2, *2/*3, or other combination of two LOF alleles), intermediate metabolizers (IMs) (*1/*2, *1/*3, *2/*17 or other genotypes with a single LOF allele), rapid metabolizers (RMs) (*1/*17), and ultrarapid metabolizers (UMs) (*17/*17).

Several studies have investigated the influence of CYP2C19 genotypes and metabolizer status on the efficacy of clopidogrel[11–13]. Although these studies consistently suggest CYP2C19 genotypes are closely related to the clopidogrel response, the influence of CYP2C19 metabolizer status on the clopidogrel response is still inconclusive. In addition, there is no consensus as to whether the diminished pharmacologic response leads to increased clinical adverse events in patients with ischemic stroke (IS) or TIA, and whether aspirin as an alternative to clopidogrel can improve the efficacy in patients with resistance to clopidogrel therapy[14]. In this study, the clopidogrel response was investigated in stroke patients, and the response was further explored after adjustment of anti-platelet therapy according to the CYP2C19 metabolizer status. Our findings may provide evidence on the clinical prevention of stroke and TIA with anti-platelet therapy.

Materials and Methods

Patients

Unrelated patients with acute non-cardiogenic cerebral infarction were recruited into present study from October 2015 to October 2016. The inclusion criteria were as follows: (1) Patients were aged 45–80 years; (2) patients were diagnosed with acute cerebral infarction within 24 h after symptom onset according to the diagnostic criteria for cerebral infarction (2010) developed by the Chinese Society for Neuroscience, and National Institutes of Health Stroke Scale (NIHSS) score was $\leq$5; (3) non-cardiogenic cerebral infarction was confirmed by imaging examinations in all patients. The exclusion criteria were as follows: (1) Patients had a history of stroke; (2) patients had received anti-coagulation therapy recently; (3) patients had contradictions to clopidogrel; (4) patients had severe heart, liver, and kidney disease; (5) patients received surgery or had a history of hemorrhage within 3 months prior. Informed consent was obtained from each patient before study, and this study was approved by the Ethics Committee of the First People's Hospital of Wujiang District (No: 2015036).

Measurements and Observations

On admission, all patients were assessed with the NIHSS, and received routine examinations (routine blood test, routine urine test, kidney function test, liver function test [kits from Shanghai Zhicheng, Shanghai, China; Beijing Lideman, Beijing, China], chest X-ray, blood lipids [kits from Kyowa Chemical Industry Co., Ltd, Sakaka, Japan], cranial CT, cranial MRI, cranial MRA or CTA, carotid ultrasonography, ECG, etc.). In addition, venous blood was collected for the detection of CYP2C19 gene polymorphism with real-time polymerase chain reaction (PCR) technology system (Cobas Z 480, Roche, Basel, Switzerland) and human CYP2C19 genotyping kit (YZY Bio, Wuhan, China) by physicians blind to the study. Patients were phenotyped according to the CYP2C19 alleles (*1, *2, and *3).

Detection of CYP2C19 Gene Polymorphism

Venous blood (1–2 ml) was collected before treatment, anticoagulated with EDTA (Sinoreagent, Shanghai, China) and stored at 4°C. DNA was then extracted and purified according to a standard protocol, and processed for amplification by PCR. PCR products were subjected to hybridization and visualization. BE2.0 Biochip reader was used to collected images which were then analyzed with V2.0 Gene chip image analysis software (Affymetrix, Thermo Fisher, Waltham, MA, USA). The CYP2C19 1 (wild type), CYP2C19 *2 (c.681G>A), and CYP2C19 *3 (c.636G>A) were detected. The reaction was done with 23 μl of reaction mixture, 1 μl of enzyme, and sample DNA (or quality control) at 95°C for 3 min, 40 cycles of 95°C for 30 s, 56°C for 30 s, and 65°C for 45 s, and finally 25°C for 1 min.

Treatments

All the patients in the acute phase received dual antiplatelet therapy (clopidogrel was administered at a loading dose of 300 mg, and thereafter at 75 mg/day; aspirin was simultaneously administered at 100 mg/day) for 21 days. After detection of CYP2C19 genotype, patients were divided into

Table 1. General Characteristics of Patients in this Study ($\bar{\chi} \pm SD$).

Variables	Group A	Group B	*p* value
Gender (M/F)	60/30	52/38	0.282
Age (years) ($\bar{\chi} \pm SD$)	69.0 ± 3.4	68.9 ± 3.7	2.467
Hypertension (*n*)	58	55	0.758
DM (*n*)	19	15	0.568
LDL-C (mmol/L)	2.72 ± 0.04	2.73 ± 0.05	0.338
HDL-C (mmol/L)	1.20 ± 0.06	1.19 ± 0.06	0.227
TC (mmol/L)	4.48 ± 0.31	4.57 ± 0.30	0.733

DM: diabetes mellitus; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol.

Group A and Group B according to the CYP2C19 metabolizer status. A total of 180 patients were recruited into present study ($n = 90$ per group). In Group A, patients received antithrombotic therapy with clopidogrel (Sanofi Pharmaceutical Co., Ltd, Shandong, China; Lot No: J20080090; 75 mg/tablet) at 75 mg/day for 1 year. In Group B, the therapeutic protocol was adjusted according to the CYP2C19 phenotypes. In brief, original treatment remained for EM patients (clopidogrel at 75 mg/day); IM and PM patients were treated with aspirin enteric-coated tablets (Bayer HealthCare Manufacturing S.r.l. Leverkusen, Germany; Lot No: H20160685; 100 mg/tablet) at 100 mg/day for 1 year. During the treatment, patients could withdraw from this study according to the severity of adverse effects.

Observations

Patients were assessed with NIHSS before therapy, and the clinical efficacy was assessed with Modified Rankin Scale after 1-year treatment[9]. During the whole study, the recurrence of cerebral infarction was recorded. The endpoints of this study included cerebral infarction, cerebral hemorrhage, myocardial infarction, and events of other organs. Adverse effects (such as hemorrhage and gastrointestinal reactions) were recorded during hospitalization.

Statistical Analysis

Statistical analysis was performed with Statistical Product and Service Solutions version 13.0 (SPSS, Inc., Chicago, IL, USA). Quantitative data are expressed as mean $\pm$ standard deviation ($\bar{\chi} \pm SD$) and compared with t test. Qualitative data are presented as percentage and compared with Chi square test. A value of $p < 0.05$ was considered statistically significant.

Results

General Characteristics

A total of 180 patients were recruited into present study. There were 112 males and 68 females. Gender, age, hypertension, diabetes mellitus (DM), and blood lipid profile are shown in Table 1. There were 90 patients in Group A and 90 patients in Group B (Table 1).

Table 2. Frequency of CYP2C19 Genotypes and Phenotypes in Patients of Present Study.

Variables	Group A (*n* [%])	Group B (*n* [%])	*p* value
Genotypes			
*1/*1	46 (51.2)	45 (50.0)	$p > 0.05$
*1 /*2	20 (22.2)	21 (23.4)	
*1/*3	10 (11.1)	9 (10.0)	
*2/*2	9 (10.0)	10 (11.1)	
*2/*3	3 (3.3)	3 (3.3)	
*3/*3	2 (2.2)	2 (2.2)	
Phenotypes			
EM	46 (51.2)	45 (50.0)	$p > 0.05$
IM	30 (33.3)	30 (33.3)	
PM	14 (15.5)	15 (16.7)	

Table 3. NIHSS and Modified Rankin Scale Scores in Patients with Different Phenotypes.

	Group A		Group B	
Phenotypes	NIHSS	Modified Rankin Scale	NIHSS score	Modified Rankin Scale
EM	4.31 ± 0.41	1.51 ± 0.27	4.47 ± 0.47	1.49 ± 0.25
IM	4.41 ± 0.42	$2.13 \pm 0.7^{\#}$	4.44 ± 0.47	$1.64 \pm 0.31^{\#\$}$
PM	4.10 ± 0.87	$2.52 \pm 0.35^{\#*}$	4.05 ± 0.72	$2.01 \pm 0.34^{\#*\$}$

NIHSS: National Institutes of Health Stroke Scale.
$^{\#}p < 0.05$ vs EM patients; $^{*}p < 0.05$ vs IM patients; $^{\$}p < 0.05$ vs Group A.

CYP2C19 Gene Polymorphism

There were six CYP2C19 genotypes identified in these patients: CYP2C19 *1/*1, CYP2C19 *1/*2, CYP2C19 *1/*3, CYP2C19 *2/*2, CYP2C19 *2/*3, and CYP2C19 *3/*3. The frequency of CYP2C19 *1, CYP2C19 *2, and CYP2C19 *3 alleles was 67.7%, 24.5%, and 7.8%, respectively, in these patients. According to the genotypes, the phenotypes were determined. In Group A, there were 46 patients with EM, 30 patients with IM and 14 patients with PM; in Group B, there were 45 patients with EM, 30 patients with IM and 15 patients with PM (Table 2).

Clinical Efficacy of Anti-Platelet Therapy

There was no marked difference in the NIHSS score between Group A and Group B as well as among EM, IM, and PM patients in each group ($p > 0.05$) (Table 3).

In Group A ($n = 90$), 12 were lost to follow up within 1-year clopidogrel treatment. In 78 patients completing this study, the Modified Rankin Scale score in EM patients was significantly lower than in PM patients and IM patients ($p < 0.05$) and significant difference was also noted between PM and IM (Table 3).

In Group B ($n = 90$), 13 patients were lost to follow up after 1-year treatment. In remaining 77 patients, the Modified Rankin Scale score was significantly different between

Table 4. Different End Points in Group A and Group B.

End points	Group A ($n = 78$)	Group B ($n = 77$)	p value
Cerebral infarction n (%)	3 (3.8%)	1 (1.3%)	>0.05
Cerebral hemorrhage n (%)	1 (1.3%)	0 (0%)	>0.05
Myocardial infarction n (%)	0 (0%)	1 (1.3%)	>0.05
Other events	2 (2.6%)	1 (1.3%)	>0.05

EM patients and PM patients, between IM patients and PM patients, and between EM patients and IM patients. When compared with Group A, the Modified Rankin Scale score in IM and PM patients was significantly reduced in Group B ($p < 0.05$) (Table 3). This indicates that the clinical efficacy is improved after adjustment of therapeutic protocol according to the CYP2C19 genotypes.

End Points and Adverse Effects

As shown in Table 4, when compared with Group A, the adjusted therapeutic protocol reduced the recurrence rate of cerebral infarction in Group B although significant difference was not observed, and recurrence was found mainly in IM and PM patients. In respect of other end points, cerebral hemorrhage was found in one patient, and events of other organs were noted in two patients of Group A; myocardial infarction was found in one patient, and events of other organs were noted in one patient of Group B (Table 4). No significant differences were noted in the incidence of other end points between two groups ($p > 0.05$).

Routine blood and urine examinations, coagulation examination, and detection of kidney and liver functions showed normal in both groups before and after treatment. In Group A, evident adverse effects were not observed. In Group B, abdominal pain (occult blood test showed negative), and diarrhea were found in seven patients, and these adverse effects resolved after symptomatic therapy and did not cause discontinuation of treatment. In Group A, cranial CT showed intracranial hemorrhage in one patient after treatment, and other adverse effects were not present during the follow up period. In Group B, the incidence of adverse effects was significantly higher than in Group A ($p < 0.05$).

Discussion

Patients having a history of IS or TIA usually possess elevated risk for recurrent ischemic events, and a recurrent stroke carries twice the probability of death and increased complications compared with the first stroke and as such can be serious. For patients with non-cardioembolic stroke or TIA, antiplatelet therapy has been the mainstay for secondary prevention[3]. Aspirin was the most widely studied antiplatelet agent, and clopidogrel may reduce serious vascular events by $10\% \pm 4\%$ compared with aspirin. Some studies also investigate the dual therapy with clopidogrel and aspirin for the secondary prevention, but current recommendation is the short-term dual therapy because long-term dual therapy has the risk of increasing vascular events[4]. Thus, it is recommended that monotherapy with clopidogrel is appropriate if patients are intolerant to aspirin because of allergy or gastrointestinal side effects or to dipyridamole because of headache. However, the clinical response to clopidogrel varies widely in patients with cardiovascular and/or cerebrovascular diseases and it is closely related to the CYP2C19 gene polymorphism[11–13]. For example, some studies show CYP2C19*2 carriers have lower levels of active clopidogrel metabolites, higher on-treatment platelet aggregation, and higher risk for major adverse cardiovascular events as compared to noncarriers[15]. Although increasing evidence indicates the influence of CYP2C19 gene polymorphism on the clopidogrel responsiveness in stroke patients, the efficacy of antiplatelet agents for the secondary prevention of stroke according to CYP2C19 genotype status remains unclear, and little is known about the influence of CYP2C19 metabolizer status on the clopidogrel responsiveness. The US Food and Drug Administration implements a boxed warning on the clopidogrel label describing the relationship between CYP2C19 pharmacogenetics and drug response, particularly noting the drug's diminished effectiveness in PM patients[16]. In this study, we further investigated clopidogrel responsiveness after adjustment of antiplatelet therapy according to CYP2C19 metabolizer status. In the clopidogrel treated patients (Group A), the Modified Rankin Scale score in EM patients was significantly lower than in PM patients and IM patients, and significant difference was also noted between PM and IM. This suggests that CYP2C19 metabolizer status may affect clopidogrel responsiveness: EM patients have a better responsiveness to clopidogrel. In Group B, the antiplatelet therapy was adjusted according to the CYP2C19 metabolizer status: EM patients still received clopidogrel therapy, but IM and PM patients were treated with aspirin at 100 mg/day (doses of 75 to 150 mg daily were at least as effective as higher daily doses)[4]. Results showed aspirin therapy in IM and PM patients was able to improve the Modified Rankin Scale score, and the responsiveness was better in IM patients as compared to PM patients. Moreover, the adjusted therapy significantly reduced the incidence of stroke recurrence without increasing the bleeding events in these patients. Although the incidence of adverse effects (abdominal pain, diarrhea, and melena) after adjustment for antiplatelet therapy was higher than after clopidogrel therapy, these adverse effects resolved after symptomatic therapy and did not cause the discontinuation of antiplatelet therapy.

There were still limitations in this study. The LOF of CYP2C19 alleles was not comprehensively detected, and only the GOF of CYP2C19 was examined in these patients. Thus, the specific relationship between other metabolizer statuses and clopidogrel responsiveness and the response to aspirin in patients with other metabolizer statuses is still unclear. There are reports that variants in other genes such

as ABCB1, P2YR12, and PON1 may also affect clopidogrel metabolism and/or its efficacy. In addition, the sample size was small, and this was a non-randomized, prospective study. More prospective studies with large sample size and long-term follow up are needed to confirm our findings. In fact, follow up is ongoing in these patients. Moreover, there is evidence showing that DM, old age, higher body mass index, and glycemic control may increase the on-treatment residual platelet aggregation, and the use of certain proton pump inhibitors also affects clopidogrel responsiveness[1].

Taken together, our study further confirms that the clopidogrel responsiveness is related to CYP2C19 metabolizer status, and anti-platelet therapy with aspirin with PM or IM may improve the efficacy in patients with mild cerebral infarction. This provides evidence for the clinical secondary prevention of stroke and TIA in patients with a history of stroke or TIA. In China, approximately 35% of the populations are carriers of CYP2C19 LOF alleles, which is higher than in Caucasians and Africans (15%)[17]. Thus, this finding is particularly important for stroke patients.

Ethical Approval

This study was approved by the Ethics Committee of the First People's Hospital of Wujiang District (No: 2015036).

Statement of Human and Animal Rights

Informed consent was obtained from each patient before study. This study was approved by the Ethics Committee of the First People's Hospital of Wujiang District (No: 2015036).

Statement of Informed Consent

Informed consent was obtained from each patient before study.

Declaration of Conflicting Interests

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