Role of CYP2C19 alleles in the management of recurrent ischemic stroke

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Abstract

Purpose of review

CYP2C19 is the primary enzyme involved in the activation of clopidogrel, an antiplatelet agent used for secondary stroke prevention. An individual's *CYP2C19* alleles are used to understand their *CYP2C19*-clopidogrel metabolizer phenotype. Single nucleotide polymorphisms of the *CYP2C19* gene result in altered metabolism of this prodrug.

Recent findings

Three ischemic stroke cases were treated with clopidogrel. Despite confirming adequate drug exposure, medication adherence, and ruling out drug-drug interactions, all had recurrent ischemic stroke. Each case had a *CYP2C19* *2/*17 genotype, categorizing them as intermediate clopidogrel metabolizers. Even with the gain-of-function allele, the loss-of-function allele resulted in lack of prodrug activation, leading to decreased efficacy in platelet inhibition.

Summary

These cases illustrate the importance of a thoughtful approach to secondary stroke prevention and demonstrate the utility of pharmacogenomic testing in clopidogrel hyporesponders. Recognition of the importance of *CYP2C19* genotyping has the potential to enable better selection of appropriate secondary prevention strategies.

Clinical cases

Clinical case 1

A 75-year-old Caucasian woman with a medical history of hypertension, hyperlipidemia, previous stroke, and 4 subsequent transient ischemic attacks (TIAs, over a 3-month interval consisting of worsening right-sided weakness and dysarthria with no medical treatment sought between the initial stroke and the last TIA) presented to the emergency department with her fifth TIA stating that her symptoms persisted longer than the previous episodes. She had been managed with clopidogrel 75 mg daily since her initial stroke, had adequate control of her vascular risk factors, and had previously had a negative evaluation for a cardioembolic source. She was admitted and found to have a new left internal capsule infarction. Her workup revealed a combination of both mild intracranial atherosclerosis and small vessel disease, and repeat echocardiography and telemetry monitoring were not suggestive of cardioembolism. Using pharmacy records, her clopidogrel adherence was calculated as proportion of days covered >80%.¹ Platelet aggregometry showed hyporesponse to clopidogrel.

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An Accu-Type CP, Clopidogrel CYP2C19 Genotype using PCR with allele-specific primer extension was used to test for *CYP2C19* loss-of-function (LoF) variants (*2, *3, *4, *5, *6, *7, *8, *9, *10, and *12) and the *CYP2C19* gain-of-function (GoF) variant (*17).² She was found to have one *CYP2C19**2 LoF allele (associated with reduced platelet inhibition) and one *CYP2C19**17 GoF allele (associated with enhanced platelet inhibition). Her *CYP2C19* *2/*17 genotype was translated to its corresponding metabolizer phenotype, resulting in an intermediate clopidogrel metabolizer phenotype.³ This phenotype has been associated with reduced platelet inhibition, increased residual platelet aggregation, and increased risk of adverse cardiovascular events.⁴ As a result of her *CYP2C19* genotype, her antiplatelet therapy for secondary stroke prevention was changed from clopidogrel to aspirin/extended-release dipyridamole (ASA-ERDP) 25/200 mg twice daily. At nearly 1-year follow-up, she is tolerating her antiplatelet therapy without side effects and has not had any recurrent cerebrovascular symptoms or events.

Clinical case 2

A 42-year-old African American man with a medical history of hypertension, tobacco abuse, and previous stroke presented with new left facial weakness and dysarthria. He was found to have a subcortical infarction involving the right corona radiata and basal ganglia on MRI, attributable to focal intracranial atherosclerosis involving the proximal right middle cerebral artery. The remainder of his stroke evaluation, including echocardiography, was unremarkable. He was placed on aspirin 81 mg daily and clopidogrel 75 mg daily in addition to a high dose of statin therapy for 90 days. Starting on day 91, he was advised to discontinue his aspirin and continue clopidogrel monotherapy.

The patient returned to the hospital 8 months later with transient left lower extremity weakness lasting 1 hour, consistent with a TIA. Using the Morisky 8-item medication adherence questionnaire, his clopidogrel adherence was medium to high (7/8).⁵ Although his other vascular risk factors were controlled, he did continue to smoke. Given that this recurrent cerebrovascular event occurred while adherent to clopidogrel, platelet aggregometry was performed. It demonstrated a partial response to ADP, consistent with clopidogrel hyporesponse.

As with case number 1, genotyping revealed one *CYP2C19**2 loss-of-function allele and one *CYP2C19**17 gain-of-function allele, translating to the intermediate clopidogrel metabolizer phenotype. Based on these results, his antiplatelet therapy was switched from clopidogrel to aspirin. Clopidogrel was listed as an “allergy” in his medical record to prevent subsequent administration. He remained free of stroke symptoms while adherent to aspirin. Nine months later when his medication adherence dropped below 80%, his stroke symptoms returned.

Clinical case 3

A 49-year-old Filipino man with a history of tobacco and cocaine abuse was admitted with symptoms of vertigo,

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He was found to have occlusion of the right cervical vertebral artery on CT angiography. His posterior circulation symptoms initially resolved after being started on aspirin 325 mg and clopidogrel 75 mg. MRI demonstrated scattered infarcts in the right cerebellar hemisphere. On hospital day 4, he acutely developed recurrence of his dysarthria, vertigo, diplopia with nystagmus, and subsequent right hemiparesis. Given his rapid progression of neurologic deficits, he was taken for emergent catheter angiography and found to have a distal basilar occlusion secondary to right vertebral artery dissection with distal embolization. He had a successful mechanical thrombectomy, and follow-up MRI showed 2 new small infarcts within the right cerebellar hemisphere.

After his recurrent stroke, platelet aggregometry was performed on hospital day 6, indicating appropriate response to aspirin and reduced response to clopidogrel. Although he was not loaded on clopidogrel and platelet inhibition may have not been fully achieved, there was enough concern to proceed with genotyping, given the high-risk nature of his condition. He was found to have the same genotype as the previous 2 cases (*CYP2C19* *2/*17). Clopidogrel was discontinued and the decision was made to add anticoagulation therapy (warfarin) to aspirin monotherapy. At 6-month follow-up, he had no residual neurologic deficits, and follow-up CT angiography showed complete recanalization of the vessel. At that time, warfarin was discontinued with the plan to continue aspirin alone.

Before performing platelet function studies and pharmacogenomic testing

In each case presented, the patient displayed a hyporesponse to clopidogrel. Before ordering platelet function studies or pharmacogenetic testing, it is important to consider modifiable factors that may be influencing platelet function studies, such as the patient's dosing regimen, medication adherence, and potential drug-drug interactions. For patients loaded with clopidogrel, it is important to consider the loading dose of clopidogrel and the amount of time that has passed since the load was administered. In patients not loaded with clopidogrel, one must consider the maintenance dose and the duration of therapy. In a similar manner, it is essential to confirm that the patient has been adherent to clopidogrel before performing platelet function studies by asking about recent

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use leading up to the study and using a validated medication adherence tool.^{1,5} The goal is to ensure that the patient has had adequate exposure to the drug before performing platelet function studies. The provider should check for potential drug-drug interactions (DDIs), such as proton pump inhibitors, lipophilic statins, and possibly calcium channel blockers, that may lower the efficacy of clopidogrel.⁶ In each of the cases presented, platelet function studies were performed only after confirming adequate drug exposure, medication adherence, and ruling out potential DDIs. When hyporesponse to clopidogrel was noted under these circumstances, we performed pharmacogenomic testing. Last, the provider should be aware of the platelet function assay being used, as well as the characteristics and limitations of each device.⁷

CYP2C19-clopidogrel: an important pharmacokinetic pharmacogene-drug pair

Clopidogrel is a prodrug, or a biologically inactive compound, that must undergo metabolism (biotransformation) to be activated.³ Once activated, clopidogrel can bind to the P2Y₁₂ receptor and inhibit platelet aggregation. Clopidogrel is absorbed in the small intestine and activated through a two-step oxidative process in the liver.⁸ The main enzyme involved in clopidogrel activation is CYP2C19—a protein coded by a gene of the same name.⁹ Polymorphisms in the CYP2C19 gene are associated with altered clopidogrel metabolism. Common CYP2C19 alleles include *17 (GoF allele), *1 (wild-type allele), and *2-*8 (LoF alleles). An individual's CYP2C19 alleles are used to predict their CYP2C19-clopidogrel metabolizer phenotype.³ When LoF alleles fail to activate the prodrug clopidogrel, there is less active metabolite and consequently decreased efficacy in terms of platelet inhibition.³ Of interest, the genotype for all 3 cases described here was CYP2C19 *2/*17. Despite *17 being a GoF allele, evidence to date indicates that this allele is unable to completely compensate for the *2 no function/LoF allele.^{8,10} Thus, the 3 patients were classified as intermediate metabolizers.^{3,8}

CYP2C19-clopidogrel: an equally important pharmacodynamic pharmacogene-drug pair

The Secondary Prevention of Small Subcortical Strokes (SPS3) randomized controlled trial (RCT) included a genetic substudy (SPS3-GENES) that genotyped CYP2C19*2 and CYP2C19*17 in 522 lacunar stroke patients. SPS3-GENES found that patients with one CYP2C19 LoF allele (LoF carriers) had higher odds of stroke recurrence compared with no CYP2C19 LoF alleles (noncarriers) during the more than 3 years of follow-up.¹¹ A

preplanned substudy of the Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) RCT genotyped CYP2C19*2, CYP2C19*3, and CYP2C19*17 in 2,933 Chinese patients with minor stroke or high-risk TIA and found that CYP2C19 LoF carriers had 1.5 times the risk of recurrent ischemic or hemorrhagic stroke as noncarriers at 90 days.¹² A meta-analysis combining data from these 2 RCTs with 13 cohort studies demonstrated that clopidogrel-treated LoF carriers have 1.8 times the risk of recurrent ischemic or hemorrhagic stroke as noncarriers, whereas individuals with 2 LoF alleles have 2.5 times the risk of recurrent ischemic or hemorrhagic stroke as noncarriers,¹³ signifying a biologic gradient.¹⁴

Alternate treatment strategies

Secondary stroke prevention therapy for noncardioembolic ischemic stroke generally involves antiplatelet agents such as aspirin, aspirin/extended-release dipyridamole (ASA-ERDP), or clopidogrel. Data from a randomized, double-blind, active-control trial of percutaneous coronary intervention (PCI) patients with drug-eluting stents demonstrated that doubling the dose of clopidogrel therapy provided a modest improvement in high-on-treatment platelet reactivity (HTPR), but did not reduce the risk of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis at 6 months.¹⁵ A subsequent RCT of clinically stable myocardial infarction and/or PCI patients demonstrated that although tripling the maintenance dose of clopidogrel reduces the proportion of LoF allele heterozygotes with HTPR, this approach is not effective for LoF allele homozygotes.¹⁶ The Guidelines for the Prevention of Stroke in Patients With Stroke and TIA¹⁷ provide evidence-based recommendations on antiplatelet monotherapy and dual antiplatelet therapy for noncardioembolic stroke, but do not comment on doubling or tripling the dose of clopidogrel. The newer P2Y₁₂ receptor antagonists, prasugrel and ticagrelor, have been shown to be more potent platelet inhibitors than clopidogrel.¹⁸ Although genetic variations in CYP2C19 have little effect on prasugrel pharmacokinetics,¹⁹ this drug is contraindicated in patients with previous TIA or stroke because of an increased risk of hemorrhagic complications.²⁰ Ticagrelor does not rely on CYP2C19 to be bioactivated,²¹ but data from the RCT Acute Stroke or Transient Ischaemic Attack Treated with Aspirin or Ticagrelor and Patient Outcomes found that ticagrelor was not superior to aspirin in the prevention of major vascular events in patients with nonsevere ischemic stroke or high-risk TIA.²² At this time, further study is needed to determine how to incorporate ticagrelor into secondary prevention guidelines because the current American Heart Association Guidelines only support its use when aspirin is contraindicated.²³

Discussion

The cases illustrated here highlight an important clinical dilemma in the management of ischemic stroke. Each case

presents a unique clinical scenario whereby platelet function studies and pharmacogenomic testing allowed us to determine that the patient was a hyporesponder to clopidogrel. This, in turn, affected our long-term secondary stroke prevention strategy.

Clopidogrel remains a commonly used antiplatelet for secondary stroke prevention for a variety of underlying pathophysiologic mechanisms, including minor stroke/TIA, intracranial stenosis, and in those with intracranial or extracranial stenting. Although the prevalence of clopidogrel resistance varies substantially based on patient population and testing method, some studies suggest that this abnormal platelet aggregometry may be seen in up to a quarter of patients.²⁴ Given the risk of recurrent ischemic events, it is important to remain mindful that medication adherence and drug-drug interactions may affect the efficacy of clopidogrel. We believe that it is reasonable to pursue platelet function studies such as platelet aggregometry and, when appropriate, *CYP2C19* genotyping to better understand an individual's ability to respond to this medication in patients who are at high risk of recurrent stroke or who have experienced a recurrent cerebrovascular event. These tests are frequently covered by insurers and can assist providers in selecting more appropriate antithrombotic strategies to minimize the risk of subsequent events. Providers who care for patients with cerebrovascular diseases should be cognizant of the limitations of clopidogrel and how to approach evaluation of a patient with a recurrent event despite medication adherence.

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Appendix 1 Author contributions

Name	Location	Role	Contribution
Michael J. Lyster, MD	University of Alabama at Birmingham	Author	Background research, manuscript preparation, and review
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Karen C. Albright, PhD, DO, MPH	SUNY Upstate	Author	Project conceptualization and manuscript preparation

TAKE-HOME POINTS

- Single nucleotide polymorphisms of the *CYP2C19* gene may result in altered metabolism of clopidogrel.
- Before ordering pharmacogenetic testing, it is important to consider modifiable factors that may influence platelet function studies.
- Thoughtful use of pharmacogenetics testing may allow for more appropriate selection of antiplatelet agents for secondary stroke prevention.
- Providers who care for patients with cerebrovascular diseases should be cognizant of the limitations of clopidogrel and how to approach evaluation of a patient with a recurrent cerebrovascular event.

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