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Personalized Approaches to Clopidogrel Therapy: Are We There Yet?

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Abstract

Clopidogrel is one of the most commonly prescribed medications world-wide. Recent advisories from the US Food and Drug Administration (FDA) have drawn attention to the possibility of personalized decision-making for individuals who are candidates for clopidogrel. As is the case with antihypertensives, statins and warfarin, common genetic sequence variants can influence clopidogrel metabolism and its effect on platelet activity. These genetic variants have, in multiple studies, been associated with adverse clinical outcomes. Concurrent medication use also influences the body's handling of clopidogrel. Proton pump inhibitors, widely prescribed in conjunction with clopidogrel, may blunt its effectiveness. We address implications for bedside decision-making in light of accumulated data and current FDA advisories, and conclude that genetic testing for CYP2C19 genotype and limitation of PPI interactions do not yet appear to offer an opportunity to optimize treatment given the current state of knowledge.

Keywords

antiplatelet; genetics; stroke; review

Introduction

Clopidogrel, in combination with aspirin, is standard treatment for both medical and interventional management of acute coronary syndrome (ACS). Dual antiplatelet therapy reduces the risk of repeat ACS events and death compared with aspirin alone [1,2], and helps prevent stent thrombosis in patients undergoing percutaneous interventions (PCI) [2]. Patients presenting to neurovascular clinics are often on dual antiplatelet therapy because of coincident cardiac disease. Alternatively, clopidogrel monotherapy may be used as a first-

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line agent, or in the setting of an aspirin allergy or suspected aspirin ineffectiveness, in secondary prevention of ischemic stroke.

Concerns have been raised, however, regarding this agent's efficacy in specific subgroups. In November 2009, the Food and Drug Administration (FDA) published a post-market drug safety information announcement detailing drug-drug interactions between clopidogrel and omeprazole, urging against the concomitant use of these medications [TABLE 2]. In March 2010, the FDA announced that clopidogrel would require a new “black-box” warning regarding reduced effectiveness in individuals who are poor metabolizers of the medication, recommending testing for CYP2C19 genotype to aid clinical management [TABLE 3].

Both FDA announcements reflect increasing awareness of inter-individual differences in medication efficacy, and a growing desire to apply genetic discoveries to clinical medicine. These announcements place the clinician in the difficult position of weighing circumstantial and often contradictory information in pursuit of evidence-based practice. In this review, we discuss current evidence regarding the effect of CYP2C19 genotype and concurrent proton pump inhibitor (PPI) use on patients receiving clopidogrel for management of cardiovascular disease. We provide recommendations for clinical care and highlight areas of research that may clarify future practice.

Inter-Individual Variation in Clopidogrel Metabolism and Response

Common DNA sequence variants, called single nucleotide polymorphisms (SNPs), appear within genes, creating different alleles of that gene within the population. In the case of clopidogrel, variants have been identified in multiple genes which account for some, but not all, of the inter-individual variability in clopidogrel's antiplatelet effect. Several of these variants are fairly common, as represented by their allele frequency in the population, making them attractive targets for genetic screening. However, the effect size for these variants is small [3], with the consequence that the presence of any one accounts for only a small percentage of the inter-individual variation in clopidogrel response.

As with many medications, clopidogrel is dependent on multiple genetic and environmental factors to determine its circulating metabolite concentrations as well as its antiplatelet effect. As a result, there is wide inter-individual variability in response to clopidogrel [3–6]. A genetic test, if it is to be clinically useful, must explain enough of the inter-individual variation to provide sufficient predictive value to alter clinical decision making. Furthermore, there must be effective, presumably evidence-based, treatment alternatives for individuals who are tested.

Genetic Modifiers of Clopidogrel Response

Inter-individual variation in response to clopidogrel is driven by the pathways involved in the drug's pharmacokinetics and pharmacodynamics. The pharmacokinetics (absorption and metabolism) of clopidogrel is analyzed by measurement of the maximum blood concentration of clopidogrel or its metabolites (C_{max}), or the area under the curve of clopidogrel's blood concentration over 24 hours ($AUC_{0–24}$). The pharmacodynamics (end-organ effect) of clopidogrel are tested using techniques to examine the residual platelet function after dosing of the drug. The standard pharmacodynamic measurement is aggregometry, in which a blood sample is exposed to ADP, and the resulting platelet aggregation provides a measure of residual platelet reactivity [7]. Newer methods employ flow cytometry to measure vasodilator stimulated phosphoprotein (VASP), a direct marker of residual ADP-receptor activity [7]. Both pharmacodynamic assays detect residual platelet function in the presence of clopidogrel, although the differences in technique prevent the results from being directly comparable between studies.

Clopidogrel is a pro-drug that must be absorbed and then metabolized into the active compound R-130964 in order to affect platelet function [FIGURE 3]. Absorbed chiefly in the duodenum, it passes into enterocytes and into the portal circulation [7–9]. On the luminal surface of the enterocyte, p-glyocoprotein (encoded by ABCB1) actively pumps clopidogrel back into the duodenum. Polymorphisms in ABCB1 influence the bioavailability of clopidogrel, and in some studies affect outcomes after ACS in patients on the drug [8,9].

After absorption, clopidogrel passes into the liver. Hepatic metabolism of clopidogrel involves two steps, each catalyzed by members of the cytochrome P450 (CYP) system: oxidation to 2-oxo-clopidogrel and conversion to the active R-130964 [FIGURE 4]. Sequence variants in multiple CYP isoenzymes in the cytochrome P450 system have been implicated in inter-individual variation in the pharmacokinetics and pharmacodynamics of clopidogrel [4,10,11]. Hepatic esterases, which are active during both stages of metabolism, compete with the CYP enzymes to generate inactive metabolites. As a result, just 5–10% of ingested clopidogrel is ultimately converted to R-130964 [10].

From the liver, R-130964 passes into the general circulation, where it irreversibly binds the ADP-receptor on the platelet surface, preventing activation of glycoprotein IIb/IIIa [12]. The ADP receptor is encoded by the P2RY12 gene, and sequence variants within this gene have been associated with decreased antiplatelet effect in some studies [12], but not others [13].

In summary, the protein products of numerous genes [FIGURE 3, 4] are involved in the pharmacokinetics and pharmacodynamics of clopidogrel, with relevant sequence variants identified for several of them [7]. Of these genes, CYP2C19 has been the most thoroughly investigated.

CYP2C19*2 Genotype an Inter-individual differences in clopidogrel response

CYP2C19 is a critical enzyme in clopidogrel metabolism, instrumental in both the oxidation of clopidogrel to 2-oxo-clopidogrel, and conversion of this intermediate to R-130964 [10,14]. Presently, more than 33 distinct alleles of CYP2C19 gene have been identified [http://www.cypalleles.ki.se/cyp2c19.htm]; however, many of these alleles are rare in the general population. Each allele is defined by variations in DNA sequence, which can result in conformational and/or functional changes in the CYP2C19 enzyme. The CYP2C19*1 allele, the most common in individuals of European origin, enables extensive metabolism of clopidogrel to its active compound.

The CYP2C19*2 allele is a common alternative variant allele in Asian, Caucasian, and African American individuals, appearing in 30%, 15%, and 17% of these populations, respectively [7]. Healthy volunteer carriers of the CYP2C19*2 allele have reduced clopidogrel C_{max} and $AUC_{0–24}$ [11,14,15], both after initial loading doses and steady state dosing. Most studies have demonstrated an allelic dose-dependence of effect, with homozygous *1/*1 carriers showing higher blood concentrations of clopidogrel's active metabolite than *1/*2 carriers [15]. Pharmacodynamic studies on healthy volunteers have shown similar results, with significantly increased on-clopidogrel residual platelet activity (RPA, as determined by aggregometry), representing reduced drug effectiveness in carriers of the *2 allele [14,15]. Carriers of a reduced function CYP2C19 allele in one study had 9% higher residual platelet activity on clopidogrel, compared with CYP2C19*1/*1 individuals [15]. Furthermore, a genome-wide association study of platelet aggregation in volunteers taking clopidogrel revealed a strong association between high RPA and a variant genetically associated (i.e. in high linkage disequilibrium) with the marker defining the CYP2C19*2

allele [3]. Of note, this unbiased genetic survey showed that CYP2C19*2 status explained only 12% of the variability in clopidogrel response of individuals involved in the study.

Pharmacodynamic studies have also been performed in individuals presenting with ACS, receiving clopidogrel either prior to PCI or for medical management. These studies have shown similar results to those described above, with CYP2C19*2 carriers demonstrating significantly higher RPA on clopidogrel than *1/*1 individuals [3,16]. It should be noted, however, that although CYP2C19*2 status was associated with statistically significant differences in RPA, the very wide interquartile ranges within each genotype reported in these studies demonstrate substantial dramatic inter-individual variability beyond that explained by CYP2C19 genotype [3].

CYP2C19*2 and clinical outcome in Patients on Clopidogrel

The effect of CYP2C19*2 on clopidogrel's pharmacokinetics and pharmacodynamics appears to be sufficient to influence clinical outcomes. Data from the EXCELSIOR trial have shown an association between higher RPA on clopidogrel and adverse clinical outcomes [17]. Multiple studies have examined the association between CYP2C19 allele status and clinical outcomes such as recurrent cardiovascular events, in-stent thrombosis, and mortality in individuals on clopidogrel after ACS presentations [3,8,15,17,18]. A recent meta-analysis of all published studies on CYP2C19*2 and outcomes identified a risk OR = 1.96 (95% confidence interval (CI) 1.14 – 3.37) for recurrent cardiovascular events per CYP2C19*2 allele [19] and a risk OR = 3.82 (95% CI 2.23 – 6.54) per allele for stent thrombosis.

The mechanism for increased adverse outcomes associated with the CYP2C19*2 genotype is likely related to attenuated effect of clopidogrel on platelet aggregation, rather than another unmeasured cause. In one study which both performed platelet aggregometry and followed clinical outcomes in patients on clopidogrel after ACS events, carriers of the CYP2C19*2 allele had higher on-clopidogrel RPA as well as increased incidence of adverse outcomes [3]. This association between CYP2C19*2 and outcome was not observed after controlling for RPA in regression analysis. Hence, while unmeasured physiologic changes conferred by the CYP2C19*2 allele could theoretically impact outcome, the available evidence suggests that the increased risk of adverse outcomes is primarily mediated by impaired onclopidogrel platelet inhibition in carriers of this allele.

Proton Pump Inhibitors and Clopidogrel

Proton pump inhibitors are widely prescribed in conjunction with antiplatelet therapy. Current American Heart Association guidelines recommend that all patients on dual antiplatelet therapy be prescribed a PPI regardless of H. pylori status or gastrointestinal bleeding risk [20]. PPIs are inhibitors of CYP2C19 in vitro, with omeprazole showing more potent inhibition than newer generation PPIs such as pantoprazole [21]. Based on this evidence, several studies have assessed RPA in patients co-prescribed clopidogrel and a PPI. For omeprazole, there is a significant increase in RPA in individuals prescribed both clopidogrel and a PPI compared to clopidogrel alone [22]. The results for other PPIs, particularly pantoprazole, are less clear. One study showed that RPA in ACS patients on clopidogrel and pantoprazole was similar to those on clopidogrel alone [23], suggesting a compound-specific effect.

Despite the evidence that at least some PPIs affect residual platelet function in patients taking clopidogrel, the results of studies seeking to link this effect to adverse outcomes in ACS patients have been inconsistent. Multiple retrospective analyses, involving thousands of participants, have demonstrated a significant association between PPI/clopidogrel co-

prescription and adverse cardiovascular outcomes and death [24,25]. These results might be confounded, however, by greater illness severity among individuals prescribed PPIs. Attempts to control for this confounding by indication using propensity matching indeed weaken the association between PPI use and adverse outcome [22,25]. The yet-to-be published COGENT trial, the only randomized, double-bind, placebo-controlled trial of ACS patients discharged on either clopidogrel alone or clopidogrel and PPI demonstrated no association between co-prescription and outcome [26]. Among the 3627 participants on clopidogrel after ACS events, the hazard ratio for combined endpoints of vascular events and death was 1.02 (95% CI 0.70–1.51). The survival curves for individuals taking and not taking PPIs were entirely superimposable. In a recent meta-analysis of all available outcome studies, there was a risk OR = 1.43 (95% CI 1.15 – 1.77) for adverse outcomes in patients co-prescribed clopidogrel and a PPI [25]. Meta-analysis restricted to only propensity-matched and randomized trials showed no association with outcome, with OR = 1.15 (95% CI 0.89 – 1.48) [25]. In contrast with the pharmacodynamic studies (which showed a compound-specific effect for RPA on clopidogrel), analyses of adverse outcomes have not demonstrated that pantoprazole and other “newer” PPIs have effects that differ from those of older PPIs such as omeprazole [24,27].

Should genetic testing for CYP2C19 status be routinely performed?

There is good evidence that CYP2C19*2 is associated with increased residual platelet function on clopidogrel compared with CYP2C19*1. Furthermore, CYP2C19*2 genotype has been reliably associated with increased risk of adverse cardiovascular outcomes in ACS patients [3,8,19]. The mechanism for this association appears to be through reduction in clopidogrel's antiplatelet effect [3].

Presented with this data, the question arises whether testing for CYP2C19 allele status would be beneficial for patient care. A genetic test is clinically useful when it guides practice, through the reliable identification of individuals who are likely to benefit from a change in therapy. Because CYP2C19 genotype alone has a relatively small influence on an individual's response to clopidogrel, and there is dramatic inter-individual variation in residual platelet function on clopidogrel, knowledge of CYP2C19 status is insufficient to inform physicians of clopidogrel's effect on an individual patient. Numerous environmental, medical, and genetic factors play a role in clopidogrel pharmacology, including adherence to therapy, age, BMI, diabetes status, and drug and dietary inhibitors of hepatic metabolism [5,6]. CY2C19*1 carriers could have high residual platelet function for other reasons, and carriers of the *2 allele could have low residual platelet activity, limiting the predictive value of the test.

A further limitation on the clinical utility of CYP2C19 genetic testing is that there are no proven therapies that can supplant clopidogrel as part of a dual anti-platelet regimen for active cardiovascular disease. Clopidogrel dose escalation has been studied in a small case-series of CYP2C19*2 carriers, and has not been shown to significantly change residual platelet activity [28]. Additional studies of dose escalation in perceived clopidogrel resistance are needed, particularly given that alternative antiplatelet strategies such as prasugrel are as yet unproven. At this time, therefore, it is reasonable to conclude that there is currently no change in practice dictated by knowledge of CYP2C19*2 allele status.

Should patients routinely receive PPIs and clopidogrel?

Although co-prescription of clopidogrel and PPI medications appears to result in reduced antiplatelet effect, evidence linking co-prescription to outcome is far less clear. Multiple large retrospective studies have found such an association, but the fact that several propensity-matched studies and one randomized controlled trial did not validate this finding

raises concern for confounding. Additionally, the utility of alternate forms of gastrointestinal prophylaxis is unclear. Although the FDA update [TABLE 2] points out that H2 blockers do not inhibit CYP2C19, their use in patients taking dual antiplatelets is not currently recommended by consensus guidelines [20]. In a recent case-control study of 2777 patients with history of upper-GI bleeding and 5532 controls, individuals on either non-steroidal anti-inflammatory drugs, aspirin, or clopidogrel were treated with either PPI, H2 blocker, or nitrates for GI prophylaxis. In those receiving clopidogrel therapy, only patients treated with PPIs had a significant reduction in GI bleeding risk [29]. In addition to this data, withdrawal of PPIs from individuals taking clopidogrel could have unintended gastrointestinal bleeding consequences, which have not yet been effectively weighed against the potential increase in adverse cardiovascular outcomes [27].

Recommendations

Based upon available evidence, systematic CYP2C19 genotype testing for individuals on clopidogrel appears to be of limited benefit to bedside decision-making [TABLE 1]. Further research into clinically useful platelet function analysis is likely to be of greater utility, as residual platelet function on clopidogrel represents the “final common pathway” of environmental and genetic factors affecting clopidogrel efficacy. Further insight into clopidogrel dose escalation strategies or other antiplatelet medications is also needed for CYP2C19 genetic testing to become a useful part of the vascular physician's armamentarium.

One situation where alternative therapies to clopidogrel have been established is secondary stroke prevention. Neurovascular patients on clopidogrel monotherapy could potentially benefit from knowledge of CYP2C19 genotype, as presence of the CYP2C19*2 allele could be used to justify re-trial of aspirin or a switch to an alternative antiplatelet agent. We note that the utility of this strategy has not yet been explored.

Finally, given conflicting evidence for association between co-prescription of clopidogrel and PPIs and adverse outcomes, it appears premature to recommend discontinuation of PPI therapy in individuals on clopidogrel as part of a dual antiplatelet regimen [TABLE 1]. Further research is needed to understand the ramifications of any increase in gastrointestinal bleeding events in clopidogrel users off PPIs. In management of neurovascular patients on clopidogrel monotherapy, testing for H. pylori and review of gastrointestinal risk factors could be entertained, with possible discontinuation of PPI therapy in low-risk patients to minimize any possible interactions.

Conclusion

Clopidogrel is a commonly-prescribed medication, and has been proven useful in the prevention of recurrent cardiovascular and cerebrovascular events. It is natural to want to guarantee that our therapy is having its desired effect in every patient. In the case of clopidogrel, CYP2C19 genetic testing and limitation of PPI interactions do not yet appear to offer an opportunity to optimize treatment given the current state of knowledge.

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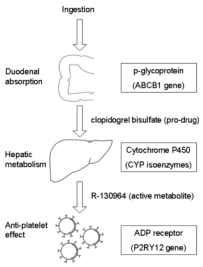

Figure 3.
Clopidogrel metabolism
ADP = adenosine diphosphate. Proteins and genes listed in boxes play the dominant role in the pharmacokinetics and pharmacodynamics of clopidogrel.

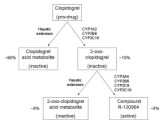

Figure 4.

Hepatic metabolism of clopidogrel

Hepatic enzymes catalyzing each reaction are shown adjacent to each arrow. Percentages represent the amount of each metabolite that his produced from each dose that reaches the liver [10].

Table 1

Summary and recommendations

CYP2C19*2 and clopidogrel pharmacokinetics/pharmacodynamics	
Summary	Clopidogrel's anti-platelet effect depends on multiple genetic and environmental factors, and there is substantial inter-individual variability in clopidogrel response. The CYP2C19*2 allele is associated with a decrease in both loading-dose and steady state concentrations of clopidogrel's active metabolite, as well as higher residual platelet function in patients on clopidogrel. However, CYP2C19 status appears to account for no more than 12% of the inter-individual variation in clopidogrel response.
Recommendation	Genotyping CYP2C19 status alone is insufficient to inform clinicians about on-clopidogrel residual platelet function.
CYP2C19*2 and clopidogrel-associated clinical outcomes	
Summary	The CYP2C19*2 allele is associated with increased risk of adverse cardiovascular outcomes, stent thrombosis, and death in individuals placed on clopidogrel after acute coronary events.
Recommendation	In the absence of clinical evidence for effective alternative therapies, the impact of CYP2C19*2 status on clinical management is unclear. Further research is needed into the utility and safety of clopidogrel dose escalation, as well as the potential utility of alternate antiplatelet agents less sensitive to CYP2C19 genotype.
Proton-pump inhibitor (PPI) use and clopidogrel-associated clinical outcomes	
Summary	Multiple retrospective studies have found an association between the dual prescription of clopidogrel and PPIs and increased risk of adverse cardiac outcomes and death in individuals placed on clopidogrel after acute coronary events. Other retrospective studies and one prospective randomized trial have not replicated this association.
Recommendation	The association between PPI use in conjunction with clopidogrel and adverse outcomes is unclear. Potential unmeasured confounders may have influenced the results of retrospective analyses. Further randomized trials are needed.

Table 2

FDA Information for Healthcare Professionals: Update to the labeling of Clopidogrel Bisulfate (marketed as Plavix) to alert healthcare professionals about a drug interaction with omeprazole (marketed as Prilosec and Prilosec OTC)

- The concomitant use of omeprazole and clopidogrel should be avoided because of the effect on clopidogrel's active metabolite levels and anti-clotting activity. Patients at risk for heart attacks or strokes, who are given clopidogrel to prevent blood clots, may not get the full protective anti-clotting effect if they also take prescription omeprazole or the OTC form (Prilosec OTC).
- Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.
- Other drugs that should be avoided in combination with clopidogrel because they may have a similar interaction include: esomeprazole (Nexium), cimetidine (which is available by prescription Tagamet and OTC as Tagamet HB), fluconazole (Diflucan), ketoconazole (Nizoral), voriconazole (VFEND), etravirine (Intelence), felbamate (Felbatol), fluoxetine (Prozac, Serafem, Symbyax), fluvoxamine (Luvox), and ticlopidine (Ticlid).
- At this time FDA does not have sufficient information about drug interactions between clopidogrel and PPIs other than omeprazole and esomeprazole to make specific recommendations about their co-administration. Healthcare professionals and patients should consider all treatment options carefully before beginning therapy.
- There is no evidence that other drugs that reduce stomach acid, such as most H2 blockers ranitidine (Zantac), famotidine (Pepcid), nizatidine (Axid), except cimetidine (Tagamet and Tagamet HB - a CYP2C19 inhibitor) or antacids interfere with the anti-clotting activity of clopidogrel. Ranitidine and famotidine are available by prescription and OTC to relieve and prevent heartburn and antacids are available OTC to relieve heartburn.
- Talk with your patients about the OTC medicines they take. Be aware that patients may be taking non prescription forms omeprazole and cimetidine.

FDA = Food and Drug Administration.

Table reprinted from the U.S. Food and Drug Administration.

Http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm190787.htm (Accessed 8/1/2010).

Table 3

FDA Black box warning on clopidogrel (Plavix)

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19.
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function.
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy.
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers.

FDA = Food and Drug Administration.

Table reprinted from the U.S. Food and Drug Administration.

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s042lbl.pdf (Accessed 8/1/2010).