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Review

Clopidogrel pharmacogenetics: metabolism and drug interactions

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Abstract

The thienopyridine, clopidogrel bisulfate (clopidogrel), is the most widely prescribed antiplatelet therapy in the world. Clopidogrel, alone or in conjunction with aspirin as part of a dual antiplatelet therapy regimen, is the standard of care for reducing ischemic events in patients with acute coronary syndrome, recent myocardial infarction, recent stroke, or established peripheral artery disease. Initially approved for use in 1997, the label was updated by both the USA Food and Drug Administration and the European Medicines Agency in 2009 to include information regarding cytochrome P450 (CYP) genotype status and concomitant proton pump inhibitor use. Labeling warns of reduced effectiveness in those with impaired *CYP2C19* function and to avoid concomitant clopidogrel use with drugs that are strong or moderate *CYP2C19* inhibitors, such as omeprazole. The interpretation of this warning and the implementation in clinical practice is not without controversy. The following review provides a summary of the published evidence regarding *CYP2C19* function, both genotype status and drug inhibition from concomitant proton pump inhibitors use, and response to clopidogrel.

Keywords: antiplatelet therapy; clopidogrel; *CYP2C19*; cytochrome P450; proton pump inhibitors.

Clopidogrel conversion to active moiety

Inhibition of platelet aggregation, the pharmacodynamic response to clopidogrel (1), has substantial interindividual variability that has been correlated with the risk of recurrent cardiovascular events (2–6). This variable response to clopidogrel and the risk of cardiovascular events is the result of multiple genetic and environmental factors. Factors that are suggested to contribute to the interindividual variability in clopidogrel responsiveness include the patients' age, body mass index, diabetes status, ejection fraction, number of stents, compliance with medication, and smoking status (3–6). Other reports have suggested that the genetic polymorphisms of the drug receptors and platelet membrane receptors could contribute to the observed variable response (4). The clopidogrel mechanism of action, metabolic conversion to its active form, and the pharmacokinetic study results provide additional candidates with biological plausibility. Clopidogrel is a prodrug requiring in vivo conversion to its pharmacologically active thiolactone (Figure 1). The thiol moiety of the active metabolite binds specifically and irreversibly to cysteine residues of the platelet $P2Y_{12}$ receptor, inhibiting adenosine-5-diphosphate (ADP) mediated platelet activation and preventing occlusive vascular events. The generation of the active thiolactone is subject to major competing metabolic pathways, such as the hydrolysis by esterases, primarily human carboxylesterase 1 (*hCE1*), resulting in generation of inactive metabolites. Consequently, only a small percentage, 10%–15%, of a clopidogrel dose is ultimately converted to the active metabolite (7). The in vivo conversion of the prodrug to active metabolite occurs in the liver mediated by cytochrome P450 enzymes (CYPs). As interindividual differences in exposure to active metabolite have been correlated with variability in responsiveness to clopidogrel, both the dependence on CYPs for generation of the pharmacologically active metabolite and the competing pathways to inactive metabolites make clopidogrel active metabolite levels susceptible to influence from CYP enzyme function. This impact of CYP enzyme function might be either through functional genetic variation or through direct inhibition by drugs.

CYP1A2 was identified in rats as involved in producing the pharmacologically active metabolite from clopidogrel (8). Later, human studies identified the involvement of the *CYP3A* system (9). Kurihara et al. confirmed the involvement of the *CYP3A* system, identifying it as the major contributor to the formation of the active metabolite from the thiolactone (10). The involvement of the *CYP3A* system was further supported by ketoconazole and itraconazole study data. Following a ketoconazole dose of 400 mg/day and a clopidogrel dose of 300 mg/75 mg, active metabolite levels as measured by area under the time concentration curve (AUC) and the maximal concentration (C_{max}) and inhibition of platelet aggregation were reduced (11). Owing to the involvement of the *CYP3A* system in the formation of the active thiolactone, both *CYP3A* functional polymorphisms and drugs that interfere with *CYP3A* function are hypothesized

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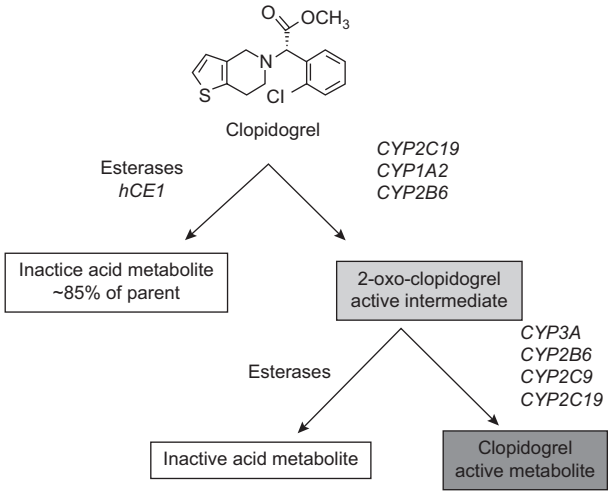

Figure 1 Clopidogrel metabolism: conversion of clopidogrel to the active metabolite in the liver. CYP, cytochrome P450; *hCE1*, human carboxylesterase 1.

to impact the formation of the clopidogrel active metabolite. Drugs that are substrates or inhibit *CYP3A4*, such as the lipophilic statins, might result in decreased antiplatelet effects following co-administration with clopidogrel. However, the published results are inconsistent and the data controversial (4). In patients who could not express *CYP3A5*, itraconazole inhibition of *CYP3A4* resulted in decreased platelet response and increased rate of atherothrombotic events (12). The first step in the conversion, the generation of 2-oxo clopidogrel, is dependent on *CYP2C19* with *CYP2B6* as the next most significant contributor (10, 13). As the second step also involves *CYP2C19*, *CYP2C19* function is also a biologically plausible candidate for impacting generation of the active moiety.

CYP2C19 functional polymorphisms

In fact, the most extensive data regarding CYP impact on clopidogrel response involves *CYP2C19*. Common polymorphisms in *CYP2C19* result in altered function. One allele resulting in an upregulation is *CYP2C19**17. Carriers of at least one *CYP2C19**17 allele represent approximately 35%–40% of the Caucasian population and those with two *CYP2C19**17 alleles represent 14%–16%. Those with two *CYP2C19**17 alleles have a 35%–40% increase in function. Those with one *CYP2C19**17 and no other polymorphism in *CYP2C19* have approximately a 20% increase in function (14). However, when the *CYP2C19**17 allele is present with other polymorphisms, the effect on gene function is ambiguous. Therefore, when evaluating the results of *CYP2C19**17 care must be taken to consider the presence of other functional polymorphisms. A prominent role for *CYP2C19**17 polymorphisms in the risk of bleeding and cardiovascular event rate has been suggested (15). However, this finding has failed to be replicated (16, 17). The effect of carrying a *CYP2C19**17 allele on the function of the enzyme and clopidogrel response warrants further investigation.

Other common *CYP2C19* polymorphisms result in ablation of gene function (14, 18, 19). Carriers of at least one null allele (*2, *3, *4, *5, *6, *7, *8) represent approximately 25%–30% of Caucasians, 35% of Africans, and 60% of Asians (20). The most common null allele is *CYP2C19**2 which is present in 85% of individuals with dysfunctional alleles. Healthy subject carriers of at least one reduced function allele, heterozygote or homozygote for *2 or *3, generate less active metabolites than those with two normal activity *CYP2C19* alleles, *1/*1 (no *2 or *3 alleles, classified as extensive metabolizers). Decreased active metabolite generation was observed following clopidogrel loading doses (LD), 300 mg and 600 mg, and maintenance doses (MD), 75 mg and 150 mg (20–30). In a report of 349 healthy subjects, in carriers of at least one reduced function *CYP2C19* allele, the plasma AUC of the clopidogrel active metabolite was reduced 53% after a 300-mg LD of clopidogrel, resulting in a 19 percentage point lower reduction in maximal platelet aggregation at 4 h following LD (29). In another study of healthy subjects, Kim et al. demonstrated that exposure to clopidogrel prodrug was related in a dose-dependent manner to *CYP2C19* carrier status but was only statistically significant in carriers of two reduced function alleles (25). In another study of 40 healthy subjects categorized by *CYP2C19* genotype into four groups, ultrarapid, extensive, intermediate, and poor metabolizers (UMs, EMs, IMs, PMs, respectively) and treated with 300/75 mg and 600/150 mg in a crossover design, significantly reduced exposure and decreased inhibition of platelet aggregation was observed only in PMs, homozygous for two reduced function alleles (1). This study, in part, led to the USA Food and Drug Administration (FDA) placing a boxed warning on clopidogrel stating that the drug has a diminished effect specifically in PMs, or approximately 2%–4% of Caucasians, 4%–5% of Africans, and 12%–14% of Asians (14). In a study of patients with coronary artery disease receiving a clopidogrel 600 mg LD followed by 75-mg MD, an association between *CYP2C19* genotype, carrying either one or two reduced function alleles, and decreased exposure to active metabolite and decreased inhibition of platelet aggregation was observed (30). The impact of *CYP2C19* genotype on platelet response has been confirmed in carriers of at least one reduced function allele, across doses, up to 1200 mg LD and 150 mg MD, and in larger populations of patients (22, 23, 31–33).

Whether this observed *CYP2C19* effect on exposure and platelet response translates into a clinically relevant effect on cardiovascular event rates has been investigated in multiple studies (6, 16, 17, 29–40). Although not observed in all studies (39, 40), a significant effect of *CYP2C19* genotype status was observed for major adverse cardiovascular events (MACEs) and stent thrombosis in the majority of the studies (6, 30–38). Meta-analyses confirm that the cumulative evidence supports an increased risk of cardiovascular events and stent thrombosis in those patients undergoing percutaneous intervention (PCI) who carry one or two reduced function *CYP2C19* alleles, heterozygotes and homozygotes (41–44). Among 9865 patients [91.3% who underwent PCI and 54.5% with acute coronary syndromes (ACS)], a significantly increased risk of

MACE was observed in both heterozygotes [hazard ratio (HR) 1.55, 95% confidence interval (95% CI) 1.11–2.17, p=0.01) and homozygotes (HR 1.76, 95% CI, 1.24–2.50, p=0.002) for reduced function *CYP2C19* alleles, as compared with non-carriers (43). In this analysis, the risk of stent thrombosis was also significantly increased in heterozygotes (HR 2.67, 95% CI 1.69–4.22, p<0.0001) and homozygotes (HR 3.97, 95% CI 1.75–9.02, p<-0.001). In another meta-analysis of 11,959 patients, carriers of at least one *CYP2C19**2 had a 30% increase in the risk of MACE [odds ratio (OR) 1.20, 95% CI 1.12–1.49, p<0.001], increased mortality (OR 1.79, 95% CI 1.10–2.91, p=0.019), and an increased risk of stent thrombosis (OR 3.45, 95% CI 2.14–5.57, p<0.001) when compared with non-carriers (44).

Conversely, no hazard associated with *CYP2C19* genotype (HR 0.86, 95% CI 0.63–1.17) was observed for patients in the genetic substudy of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial (17). Patients in this trial were conservatively managed with only 15.5% undergoing PCI with stenting. Clopidogrel treatment was associated with a 20% reduction in cardiovascular death, myocardial infarction (MI) or stroke, a modest effect when compared with the 75%–85% clopidogrel effect seen in a population undergoing PCI. Therefore, with the overall dampened drug effect, the genotype effect would also be expected to be of lower magnitude. Another trial seeming to demonstrate no significant effect of *CYP2C19* genetic status is the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization Management and Avoidance (CHARISMA) trial (40). In this trial, not all patients had established coronary disease and only 22% underwent a PCI. Clopidogrel treatment in this population did not reduce adverse cardiovascular events. It is not surprising that no effect of *CYP2C19* genotype on response was observed in a trial that had no measurable drug response. Thus, despite some conflicting results when evaluated in total, the data supports the impact of *CYP2C19* genotype in both heterozygous and homozygous carriers of reduced function alleles on exposure to active metabolites, attenuation of platelet aggregation, and subsequent cardiovascular event rates.

Drug inhibition of *CYP2C19* function

Some proton pump inhibitors (PPIs), notably omeprazole and lansoprazole, competitively inhibit *CYP2C19* (1, 45–47). PPIs have been used in conjunction with antiplatelet therapy to reduce the risk of gastrointestinal bleeding, an adverse event associated with antiplatelet therapy. Whether or not this competitive inhibition of *CYP2C19* has any relevance to treatment with clopidogrel is an area of ongoing debate. Ex vivo studies have suggested that the co-administration of omeprazole or lansoprazole decrease the antiplatelet effect of clopidogrel (1, 48–52). The interaction between PPIs and clopidogrel resulting in decreased exposure and higher residual platelet reactivity was confirmed following administration of clopidogrel (1, 51, 53, 54). Subjects administered a 300-mg LD followed by 75 mg/day with 80 mg/day of omeprazole demonstrated 40%–46% less exposure to active metabolite, as measured by C_{max} and AUC on day 1 and day 5 following dosing. Also platelet inhibition was decreased 39% on day 1 and 21% on day 5 in the same subjects. Similar data were observed whether the omeprazole was administered concurrently or 12 h apart from the clopidogrel (1). Similar to the results observed in healthy subjects, when patients taking clopidogrel 75 mg/day for 7 days were randomly assigned to either omeprazole 20 mg/day or placebo, those taking omeprazole were observed to have significantly decreased platelet inhibition (48). In patients undergoing coronary stent implantation, omeprazole significantly reduced the ability of clopidogrel to inhibit platelet aggregation (48).

The potential clinical relevance of the observed interaction on pharmacokinetic and platelet activity has largely been evaluated in observational and retrospective cohort studies (55–61). The retrospective cohort and observational trials report an increased risk of cardiovascular events when patients are prescribed clopidogrel and a PPI (Table 1) (55–59). These studies include >80,000 patients and a reported increased risk of 22%–51%. Conversely, post-hoc analyses from large clinical trials have failed to show such an association (60). A post-hoc analysis of the Clopidogrel for the Reduced of Events During Observation (CREDO) trial suggests that the increased rate of cardiovascular events

Table 1 Observational and cohort studies investigating risk of cardiovascular event with concomitant PPI and clopidogrel use vs. clopidogrel alone.

Reference	n	Result	Clinical measure	Follow-up	Study population
Ho et al., J Am Med Assoc 2009 (55)	8205	Odds ratio 1.25 95% CI (1.11–1.41)	Risk of death or recurrent ACS	>1 year	Veterans cohort
Juurlink et al., Can Med Assoc J 2009 (56)	13,636	Odds ratio 1.27 95% CI (1.03–1.57)	Risk of recurrent MI	>90 days	Elderly cohort
Kreutz et al., Pharmacotherapy 2010	16,690	Hazard ratio 1.51 95% CI (1.39–1.64)	Incidence of MACE	1 year	Prescription cohort
Rassen et al., Circulation 2009 (58)	18,565	Hazard ratio 1.22 95% CI (0.99–1.51)	Incidence of death or MI	180 days	Claims database
Charlot et al., Ann Inter Med 2010 (59)	24,702	Hazard ratio 1.29 95% CI (1.21–1.37)	Incidence of MACE	1 year	National registry

ACS, acute coronary syndrome; MI, myocardial infarction; MACE, major adverse cardiovascular event; 95% CI, 95% confidence interval.

might be observed with PPI use alone (61). The incidence of ischemic endpoints was increased at 1 year in those receiving a PPI regardless of whether or not they received clopidogrel and no effect of PPI on clopidogrel efficacy was observed. These results sparked debate that the previously observed PPI effect was due to an increased morbidity overall among those prescribed PPIs. However, the FDA conducted two safety reviews in 2007 and concluded that in the absence of clopidogrel therapy, PPIs do not independently contribute to the risk of cardiovascular events (62, 63). In the only randomized controlled trial, Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) study, patients with ACS and/or PCI were randomized to a fixed-dose combination of controlled release omeprazole 20 mg/clopidogrel 75-mg/day or to clopidogrel alone. This randomized controlled trial was discontinued early with 3627 patients enrolled rather than the 5000 planned for enrollment and after a median follow-up of only 133 days. In total, only 109 patients experienced a cardiovascular event. In this limited number of patients, no significant increase in risk was observed for those receiving the omeprazole and clopidogrel combined therapy (HR 0.99, 95% CI 0.68–1.44) (64).

Randomized trials are the gold standard with other study designs, such as observational and retrospective cohorts often the focus of criticism. Study design concerns include the representative nature of the patient population and treatment paradigm, and biases introduced by the lack of randomization, such as imbalances in the patient populations. Additionally, unknown biases often confound the results making interpretations difficult. For example, PPIs are frequently used in those at high risk of bleeding, making it difficult to ensure that the two populations those with and without PPIs are the same. However, clinical trials despite randomization and attempts to minimize bias might also include bias and confounding variables. Additionally, the treatment regimens evaluated in a clinical trial are often different than that practiced in routine care. Other concerns include the power to detect an effect. For example, COGENT was terminated prematurely and had a limited follow-up time and low event rate, which resulted in poor power to detect an effect on cardiovascular endpoints (64). Regardless of study design, observational or randomized controlled trials, when evaluating the possibility of a PPI-clopidogrel interaction, multiple confounding factors need careful consideration. In vitro data and in vivo active metabolite exposure and platelet inhibition studies (1) suggest a relatively lower *CYP2C19* inhibitory potency of pantoprazole and rabeprazole when compared with other PPIs, suggesting that the clopidogrel-PPI interaction might be drug specific and not a class effect. However, some clinical studies have found an increased MACE risk even with pantoprazole (59). Therefore, evaluation of the specific PPIs prescribed in the studies is necessary when evaluating the reported data. Another confounder rarely considered is the patient background *CYP2C19* genetic status and the resultant function or dysfunction of the enzyme. If the patient has a genotype that ablates the function of the *CYP2C19* enzyme, the co-administration of a PPI might have no impact. These patients as a group already have decreased platelet inhibition and further dampening might not result in additional clinical events. Also, if the patient is a *CYP2C19* UM, homozygous for an increased activity allele, with a high level of platelet inhibition, a slight decrease in effect as the result of co-administration of a PPI might be similarly clinically irrelevant. The impact on platelet aggregation might only be relevant to those who are on the border between responsive and non-responsive. Co-administration of PPIs in those patients with marginal or average levels of platelet inhibition might result in a dampened effect sufficient enough to lead to an increase in clinical events. This and other factors complicate the interpretation of the results and contribute to the debate surrounding the clinical relevance of PPI-clopidogrel co-administration.

In a systematic meta-analysis those patients receiving co-administration of any PPI and clopidogrel, patients had an increased risk of MACEs (OR 1.41, 95% CI 1.34–1.48, $p<0.001$) and mortality (OR 1.18, 95% CI 1.07–1.30, $p<0.001$) when compared with those receiving clopidogrel alone (41). When the PPI omeprazole was evaluated, omeprazole use was associated with a significantly higher risk of MACEs (OR 1.37, 95% CI 1.27–1.47, $p<0.001$) and an excess of mortality (OR 1.18, 95% CI 1.07–1.30, $p<0.001$) in patients receiving clopidogrel when compared with those receiving clopidogrel alone (41). This observed PPI effect was only significant in high-risk patients or those studies where the rate of MACEs was >10% (41).

Until further data are available, careful patient selection for co-administration of PPIs and clopidogrel is suggested. Evaluation of the overall clinical risk including both cardiovascular and the risk of bleeding, particularly gastrointestinal complications, must be considered. PPI use might be appropriate for patients requiring antiplatelet therapy with multiple risk factors of gastrointestinal bleeding, but routine use for patients at lower risk of upper GI bleeding is not warranted (65–67).

Conclusions

In aggregate, the published results suggest that patients receiving clopidogrel who are carriers of a reduced function *CYP2C19* allele and patients who are co-administered PPI have an approximately 40% increased risk for MACE and an approximately 20% higher risk for death (41–43). The risk of stent thrombosis is even greater, approximately a 3-fold increased risk, in those patients who have at least one reduced function *CYP2C19* allele (41–43). Considering that the cohort of patients at risk, when including those that carry at least one null *CYP2C19* allele and those prescribed PPIs, represents at least 50% of the patient population receiving clopidogrel treatment, these results support the American College of Cardiology (ACC) consensus guidelines and recent changes in labeling (65–67). Although it has not yet been demonstrated that genotyping followed by alterations to the patient treatment regimen results in an improved benefit risk ratio for the patient, genetic status and PPI use should be considered similar to clinicians consideration of other clinical factors, such as patient age, comorbidities such as diabetes, other

concomitant medications, and smoking status when determining a patient's treatment regimen.

Conflict of interest statement

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