CYP450 pharmacogenomics: a cardiology perspective

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Key words: clopidogrel • myocardial infarction • outcomes • pharmacogenomics • warfarin

Contemporary evidence-based medicine: ideal for populations but not always the individual

The contemporary practice of cardiology is based principally on clinical evidence derived from large-scale, randomized clinical trials and registry databases. The pharmaceutical agents available for the treatment of cardiovascular diseases continue to expand. However, the evidence-base for these pharmacotherapeutics was developed from population-level analyses, where the efficacy and safety of a given agent were determined by comparing the mean rates of clinical events with the standard of care or placebo. Despite the necessity of clinical trials for advancing the practice of medicine, their results do not account for the complexities surrounding an individual’s response to a drug. The intra- and inter-individual variability of a drug’s effect is determined, at least in part, by an individual’s pharmacokinetic (PK) and pharmacodynamic (PD) response, which can account for clinical failure or toxicity in a subset of patients. PK/PD are influenced by intrinsic (e.g., age, race, ethnicity, gender, co-morbid disease, renal and hepatic function, genetics) and extrinsic (e.g., diet, smoking, drug–drug interactions) factors. Adverse drug reactions are common, costly, and can be fatal [1]; especially in an aging population, where polypharmacy can significantly influence drug PK/PD response. Thus, a tailored pharmacotherapeutic approach would have potentially important advantages.

CYP450 genetic polymorphisms: a cardiologist’s gateway to personalized medicine?

The hepatic cytochrome P-450 (CYP) isoenzymes comprise an enzyme family responsible for the metabolism of approximately 75% of drugs via oxidative biotransformation [2]. There are 57 human CYPs encoded by 57 genes (and 58 pseudogenes); five (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4) are responsible for roughly 95% of the enzymatic activity [3]. Genetic variants within the genes encoding these isoenzymes strongly influence PK/PD responses [3] and can be responsible for the significant heterogeneity of responses to drugs among individuals. For cardiologists, genetic variants in CYP genes (CYP) represent a major determinant of the clinical efficacy and safety of many cardiovascular drugs and provide a unique backdrop to paint the landscape of pharmacogenetic therapy. Herein, we discuss two examples of the intersection between cardiovascular therapeutics, clopidogrel and warfarin, and the influence of CYP variants.

Clopidogrel on-treatment variability influences clinical outcomes: a pharmacogenetic phenomenon

Platelet activation and aggregation are the predominant mechanisms responsible for adverse clinical events following an acute coronary syndrome (ACS) and/or coronary stenting [4]. The addition of clopidogrel to aspirin compared with aspirin alone was found to significantly decrease subsequent adverse ischemic events and dual antiplatelet therapy is currently the standard of care.
following ACS or stenting [4]. However, clinical failure in efficacy or safety occurs in a subgroup of patients on clopidogrel treatment [4,5]. On an individual level, the clinical response to clopidogrel can result in the desired effect or, alternatively, higher or lower platelet inhibition [6]. Though the proposed mechanisms responsible for clopidogrel response are multifactorial, variability in the metabolism of clopidogrel to its active metabolite is one of the most important putative mechanisms [6].

Clopidogrel is absorbed as a prodrug and converted to its active metabolite using the CYP isoenzymes [5]. Significant variation in the production of clopidogrel’s active metabolite by CYP isoenzymes can result in high- or low- on-treatment platelet reactivity and is influenced by a number of factors that interact with the CYP enzymatic system, including drug–drug interactions and genetic polymorphisms [6].

The most studied and well-known genetic polymorphism in the gene encoding is the CYP2C19 isoenzyme, an enzyme critical in clopidogrel metabolism [6]. Two important genetic polymorphisms of CYP2C19 include the *2 (i.e., loss-of-function) and *17 (i.e., gain-of-function) alleles, which result in significant differences in clopidogrel’s active metabolite generation, platelet reactivity and clinical outcomes [7]. Carriers of CYP2C19*2 have reduced platelet inhibition, high on-treatment platelet reactivity and a higher rate of ischemic events, whereas CYP2C19*17 carriers have the highest platelet inhibition, low on-treatment platelet reactivity and a higher risk for bleeding [7]. To date, large-scale clinical trials have not demonstrated that changing one group’s antiplatelet regimen based on real-time assessment of platelet reactivity (the phenotype for clopidogrel metabolism) results in improved clinical outcomes [6]. However, evidence continues to emerge on the complexities of the pharmacogenomics of the CYP isoenzymes, clopidogrel metabolism and clinical outcomes. As an example, genetic polymorphisms in different CYPs have been associated with different outcomes, and with outcomes that vary by race. Among patients with an acute myocardial infarction (MI) treated with clopidogrel, Caucasian carriers of the CYP2C19*2 allele have increased mortality and increased rates of recurrent MI whereas African-American carriers of the CYP2C19*17 and CYP1A2*1C alleles have increased mortality and a higher rate of bleeding events compared with noncarriers [8].

In a similar fashion, proton pump inhibitors (PPIs) are metabolized by the CYP450 isoenzymes, including CYP2C19, and have been associated with an impaired clopidogrel pharmacodynamic response (i.e., drug–drug interaction) [5,9]. Despite the association between PPIs and worse cardiovascular outcomes in clopidogrel-treated patients [5], only one randomized trial has studied whether there is any association between PPI use and adverse clinical outcomes, and that trial failed to demonstrate any increased cardiovascular risk by the addition of a PPI to clopidogrel and aspirin among patients with coronary artery disease [10]. However, a recent study examining PPI use according to CYP genotype determined that the risk of adverse outcome associated with PPI use among patients receiving clopidogrel and aspirin after an MI may be influenced by an individual’s genotype for CYP2C19 [11].

The association between an impaired clopidogrel PD response, genetic polymorphisms among CYPs, drug–drug interactions, and worse clinical outcomes is an area of intense research that remains incompletely defined and controversial. Yet, it represents an excellent example of the obstacles and ongoing research required to reach the goal of personalized antiplatelet therapy following ACS and/or coronary stenting.

**Optimizing warfarin dosing: a pharmacogenetic panacea?**

Warfarin is a vitamin K antagonist widely used for the treatment of arterial and venous thromboembolic disease. It inhibits vitamin K dependent clotting factors (II, VII, IX and X) by inhibiting the vitamin K epoxide reductase multiprotein complex, subunit 1 (VKORC1) [12]. Warfarin dosing is complicated by a narrow therapeutic range which requires frequent monitoring. Wide intra- and interindividual variability exists with warfarin, which can lead to sub- or supra-therapeutic anticoagulation and a risk for a thrombotic or bleeding event, respectively [13]. Up to 55% of the variability in warfarin response can be explained by patient factors and genetic polymorphisms (e.g., in CYP2C9, CYP4F2 and VKORC1) [14].

The active metabolite of warfarin is inactivated by CYP isoenzymes, predominantly CYP2C9 [15]. Two loss-of-function alleles have been identified, CYP2C9*2 and *3, which significantly reduce the enzymatic metabolism (i.e., inactivation) of the potent active metabolite of warfarin [15]. Reduced metabolism can lead to supratherapeutic levels of warfarin and a risk for hemorrhage [15]. Both alleles have been associated with an increased risk of bleeding compared with individual without the loss-of-function allele [15]. Carriers of either allele require reductions in warfarin dosage to reduce the risk of bleeding; where carriers of the *2 or *3 alleles require a 17–19% or 33–37%, respectively, lower mean daily warfarin dose compared with individuals who do not have the reduced function allele (i.e., CYP2C9*1) [15,16]. Additionally, homozygotes of the *2 and *3 alleles require an even greater reduction (36 and 78%, respectively) in the daily warfarin dose [16]. Genetic polymorphisms have...
also been identified in CYP4F2, a gene that encodes an enzyme responsible for metabolizing Vitamin K1, that results in the need for higher warfarin dosages [17]. Similarly, multiple genetic polymorphisms have been identified in the promoter region of the gene encoding VKORCl; the promoter regulates gene expression of warfarin’s pharmacologic target, and carriers of these variants therefore require lower or higher daily warfarin doses based on the polymorphism’s effect on expression [14,18,19].

To date, clinical trials have failed to demonstrate statistically significant improvements in maintaining a therapeutic range during the initiation of warfarin dosing using a genotype-guided strategy compared with standard care (20,21). Nevertheless, variability in metabolism based on genetic polymorphisms in CYP2C9 and VKORCl is important for warfarin dosing. The Food and Drug Administration recently endorsed the importance of pharmacogenomics for warfarin dosing, and guidelines that implement the pharmacogenetic evidence available for warfarin are emerging (22,23). Additionally, available online calculators for warfarin dosing utilize the genetic polymorphisms as part of the algorithm for determining the optimal warfarin dose (see [24]). The influence of pharmacogenetics on warfarin dosing is a model of how tailoring a pharmaceutical therapy to the individual has the potential to impact clinical practice.

Conclusion

The goal of tailoring diagnostic and treatment strategies to the individual is being driven by an explosion of pharmacogenomic research and development. As demonstrated with clopidogrel and warfarin, the incorporation of an individual’s genotype into therapeutic strategies has the potential to have a profound impact on clinical management. Guidelines are beginning to emerge that incorporate pharmacogenetic evidence and offer us an important glimpse of the horizon of personalized medicine. Continued efforts to determine the impact of genotype–phenotype associations are essential. The final goal will be to integrate vital genetic information within the patient record to allow for real-time personalized therapeutic decisions to maximize efficacy and reduce harm.

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