Journal of Pharmacokinetics & Experimental Therapeutics

Pereira, J Pharmacokinet Exp Ther 2022, 6:3

Case Report Open Access

A Study of CYP2C19 Activity in Populations of European and Japanese Ancestry Using a Physiologically Based Pharmacokinetic Model of Clopidogrel

Naveen Pereira*

MD, Department of Cardiovascular Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905

Abstract

Clopidogrel treatment response is linked to CYP2C19 activity, which is measured by the active H4 metabolite. The researchers wanted to create a physiologically based pharmacokinetic (PBPK) model of clopidogrel and its metabolites for European ancestry populations, predict pharmacokinetics in the Japanese population using the CYP2C19 phenotype, and look into the impact of clinical and demographic parameters. Using plasma data from previous research, a PBPK model was created and proven to describe the two metabolic routes of clopidogrel (H4 metabolite, acyl glucuronide metabolite) for a population of European ancestry.

Introduction

Following that, the model's predictions in the Japanese population were assessed. The pharmacokinetics of clopidogrel and its metabolites were then studied in relation to CYP2C19 activity, fluvoxamine Coad ministration (a CYP2C19 inhibitor), and population-specific variables (age, sex, BMI, body weight, cancer, hepatic, and renal impairment). Clopidogrel and metabolite exposure parameters had acceptable predicted/observed ratios (twofold acceptance criteria). The steady-state AUC0- of the H4 metabolite was lower in the Japanese population (e.g., EM, 7.69 [6.26–9.45] ngh/ml; geometric mean [95 percent CI]) than in the European population (EM, 24.8 [20.4–30.1] ngh/ml, p.001) [1]. Fluvoxamine coadministration, hepatic, and renal dysfunction were shown to lower H4 metabolite concentrations but not acyl glucuronide metabolite concentrations, in addition to the CYP2C19-poor metabolizer phenotype. This is the first PBPK model of clopidogrel's two key metabolic pathways that can be applied to European and Japanese people with the CYP2C19 phenotype. The influence of variable CYP2C19 liver activity appears to be the primary determinant of the disparities between the two populations.

Description

Another common measure taken to mitigate the risk of complications from excessive bleeding is to instruct patients who usually take antiplatelet medications to discontinue these medications prior to shoulder arthroplasty. However, this instruction does not come without some potential risk. In addition to aspirin, one of the most common medications in this class is clopidogrel (Plavix), which is typically prescribed to patients to prevent thrombosis of a recently placed cardiac stent. Premature discontinuation of clopidogrel after stent placement has been correlated with an increased risk of coronary stent thrombosis [2]. Moreover, there are some patients who remain on lifelong clopidogrel after cardiac or vascular events. Additionally, patients undergoing noncardiac surgery relatively soon after stent placement are at a higher risk of major adverse cardiac events (ACEs) occurring postoperatively. This highlights the importance of adherence to antiplatelet therapy.

Carriers of these loss-of-function alleles have significantly reduced clopidogrel active metabolite levels and high on-treatment platelet reactivity when treated with clopidogrel, resulting in an increased risk of major adverse cardiovascular events, especially after percutaneous coronary intervention. The Food and Drug Administration has issued a black box warning, encouraging physicians to seek alternate treatment options in CYP2C19 poor metabolizers who may be given clopidogrel, and to identify such patients using genotyping [3-4]. Clinical guidelines, however, do not support systematic genotyping for CYP2C19 loss-of-function alleles in patients having percutaneous coronary intervention due to a lack of prospective evidence. TAILOR-PCI (Tailored Antiplatelet Initiation to Lessen Outcomes due to Decreased Clopidogrel Response after Percutaneous Coronary Intervention) is a large, pragmatic, randomised trial comparing point-of-care genotype-guided antiplatelet therapy with routine care to see if identifying CYP2C19 loss-of-function allele patients and prescribing alternative antiplatelet therapy is beneficial [5].

Discussion

Acute coronary syndromes (ACS) are still life-threatening conditions with a high rate of morbidity and fatality. In patients with ACS, dual-antiplatelet therapy with aspirin and clopidogrel has been found to minimise cardiovascular events [6-7]. However, due to irreversible binding to P2Y12 receptors, there is significant inter-individual heterogeneity in response to clopidogrel treatment, as well as a lengthy recovery of platelet reactivity. Genetic polymorphisms in the genes encoding for cytochrome (CYP) 2C19, which impact clopidogrel's pharmacokinetics, have been linked to the substantial inter-individual variability in treatment response. While the FDA has issued a boxed warning for CYP2C19 poor metabolizers due to the possibility of reduced efficacy in these patients, multivariate analyses suggest that other factors such as age, sex, obesity, concurrent diseases,

***Corresponding author:** Naveen L. Pereira, MD, Department of Cardiovascular Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA, E-mail: preira.naven@mayo.edu

Received: 02-Jun-2022, Manuscript No. jpet-22-65666; **Editor assigned:** 04-Jun-2022, PreQC No. Jpet-22-65666 (PQ); **Reviewed:** 18-Jun-2022, QC No. jpet-22-65666; **Revised:** 21-Jun-2022, Manuscript No. jpet-22-65666 (R); **Published:** 28-Jun-2022, DOI: 10.4172/jpet.1000144

Citation: Pereira N (2022) A Study of CYP2C19 Activity in Populations of European and Japanese Ancestry Using a Physiologically Based Pharmacokinetic Model of Clopidogrel. J Pharmacokinet Exp Ther 6: 144.

and drug-drug interactions may all play a role in the overall between-subject variability in treatment response. However, it is currently unknown how much each of these elements contributes to overall variability and how they are related. The goal of this study is to offer a complete update on the various parameters that influence clopidogrel's pharmacokinetics and pharmacodynamics, as well as how they contribute mechanistically to inter-individual variability in response to clopidogrel medication [8].

Clopidogrel (CLOP) is routinely used in patients with coronary artery disease (CAD) who have or do not have diabetes (DM), however CLOP resistance is widespread in these individuals, especially those with diabetes. The goal of this study was to create a physiologically-based pharmacokinetic-pharmacodynamic (PBPK-PD) model to describe the pharmacokinetics and pharmacodynamics of clopidogrel active metabolite (CLOP-AM) in CAD patients with and without diabetes mellitus (DM). The PBPK-PD model was developed and validated in healthy people before being used to CAD patients with or without diabetes [9-10]. The effects of CYP2C19, CYP2C9, CYP3A4, carboxylesterase 1 (CES1), gastrointestinal transit rates ($K_{t,i}$), and platelet response to CLOP-AM (k_{irre}) on predicted pharmacokinetics and pharmacodynamics, as well as their individual and combined effects on CLOP-AM pharmacokinetics due to changes in DM status, were investigated [11].

Conclusion

Similar to how a surgeon considers surgical complications when deciding how to manage clopidogrel in the perioperative shoulder arthroplasty period, he or she must also take into account the incidence of postoperative ACEs in this patient population. In our study, the patients who continued clopidogrel had a 0% 30-day ACE incidence compared to 3% of patients who held clopidogrel. This was not statistically significant, and the incidence for both groups is comparable to other studies that examined the ACE rate after shoulder arthroplasty. Singh et al reviewed 3480 patients who underwent shoulder arthroplasty and found a 2.6% incidence of 90-day ACEs20 while Chalmers et al found a 0% incidence in their series of 127 patients [12].

The majority of forecasts were within 0.5–2.0 folds of observations, indicating that they were correct. The contributions of interesting factors to pharmacodynamics were CES1> k_{irre}> $K_{t,i}$> CYP2C19 > CYP3A4> CYP2C9, according to sensitivity analysis. Increased CES1 activity, followed by decreased CYP2C19 activity, were found to be the main reasons for CLOP-AM exposure being reduced by DM. The created PBPK-PD model was successful in predicting the pharmacokinetics and pharmacodynamics of CLOP-AM. Clopidogrel resistance in DM was caused by alterations in $K_{t,i}$, CYP2C19, CYP3A4, CES1, and k_{irre}.

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