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Case Report

Antiplatelet Pharmacogenomic Assessment in a Case of Coronary Artery Bypass

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Abstract

If not contraindicated, it is reasonable to use DAPT, starting in the CABG postoperative period, using ASA in association with clopidogrel. There is no specific guideline indicating pharmacogenomic testing for DAPT, but the FDA recommends it when using clopidogrel. In the present case pharmacogenomics was used for the evaluation of DAPT one year after CABG. The results indicate that despite the platelet hyper-responsiveness to ADP, clopidogrel might not be indicated, due to an increased P-gp dependent intestinal efflux, and its use should be reconsidered to substitute it with a different drug, like ticlopidine, or to administer it concomitant with P-gp antagonists.

Keywords: Personalized Medicine; Precision Medicine; Pharmacogenomics; Coronary Artery Disease; Platelet Aggregation; Antiplatelet therapy; Clopidogrel

Abbreviations:

ABCB1: ATP-Binding Cassette, sub-family B, member 1;

ACS: Acute Coronary Syndrome;

ADP: Adenosine diphosphate;

ASA: Acetylsalicylic acid;

BP: Blood Pressure;

CABG: Coronary Artery Bypass Grafting;

CAD: Coronary Artery Disease;

CBC: Count Blood Cells;

CYP2C19: Cytochrome P450 2C19;

DAPT: Dual Antiplatelet Therapy;

FDA: Food and Drug Administration;

HR: Heart Rate;

P2RY12: Purinergic Receptor P2Y, G Protein-coupled, 12;

PAD: Peripheral Arterial Disease;

PCI: Percutaneous Coronary Intervention;

P-gp: P-glycoprotein;

RFLP-PCR: Restriction Fragment Length Polymorphism of PCR-Amplified Fragments;

SNPs: Single Nucleotide Polymorphisms

Background

Though a growing number of guidelines for the application of pharmacogenomic testing for the personalization of therapies is available from national health agencies like FDA, these are still limited in number, despite the important information that can be obtained which can potentially improve the pharmacologic outcome. In the cardiovascular field multidrug associations are common; often to prevent life threatening conditions and pharmacogenomics could help the optimization of the effectiveness of therapeutic regimens.

Clinical Case

A 67 year-old female, 1 year after coronary artery bypass graft, referred to the personalized medicine ambulatory for the evaluation of her current antiplatelet therapy with aspirin (ASA) and clopidogrel. During anamnestic evaluation the patient did not complain any ischemic cardiac symptom and no other medical condition was referred, but she reported a history of hypercholesterolemia currently treated with atorvastatin. There was no history of hypertension, diabetes, or tobacco smoke. Finally she reported a family history of cardiovascular and cerebrovascular ischemic diseases, which occurred in first degree relatives in old age.

Since the beginning of her postoperative antiplatelet therapy all the follow up cardiac controls and routine blood tests had been regular, and current therapy consisted of atorvastatin, metoprolol, pantoprazole, ASA and clopidogrel.

On physical examination, BP was 120/80 mmHg and 60 beats per minute HR was recorded. The remaining physical examination was normal, including no petechiae or intramuscular hematomas or history of bleeding, no splenomegaly or global or focal neurological signs. Following examination a blood sample was taken and the laboratory test results showed no significant alterations of the CBC parameters.

While aspirin use alone can be considered relatively safe, adding clopidogrel increases bleeding risk. In these conditions clopidogrel pharmacokinetics and pharmacodynamics can be assessed with pharmacogenomic analysis to verify potential efficacy and side effects of the polypharmaceutical association. The pharmacogenomic assessment of the main known factors that contribute to the biological antiplatelet activity of clopidogrel was performed by analyzing the allelic variants of genes modulating the absorption (ABCB1), metabolic activation (CYP2C19) and biological activity (P2RY12) of clopidogrel [1- 4].

The results, obtained by RFLP-PCR and direct DNA sequencing, indicated that the following SNPs were present in the ABCB1 gene: 3435TT (rs1045642), 2677TT (rs2032582), 1236TT (rs1128503). These allelic variants are associated to P-glycoprotein over-expression and therefore to a reduced absorption of clopidogrel [3- 5].

Further, the analysis of CYP2C19 gene indicated that the two allelic variants rs4244285 and rs4986893 were absent, thus suggesting a normal and effective metabolic activation of clopidogrel [3, 6, 7]. Lastly the analysis of the P2RY12 gene indicates the presence of an H1/H2 haplotype (rs2046934, rs10935838, rs5853517, rs6809699). The H2 haplotype heterozygosity has been shown to be associated with increased platelet reactivity, coronary artery disease and peripheral arterial disease, due to increased platelet aggregation in response to ADP-mediated activation [3, 6, 7].

Discussion

After acute coronary syndrome (ACS), in some cases dual antiplatelet therapy (DAPT) is the standard of care for both invasive management with percutaneous intervention and noninvasive (medical) management [1,2]. In particular aspirin and clopidogrel DAPT is currently recommended for the prevention of atherothrombotic events in patients after coronary artery bypass graft (CABG) or after percutaneous coronary intervention (PCI). However, even with the use of such therapy, a substantial number of subsequent ischemic events still occur [1, 2].

Studies using DAPT in the population of patients presenting with ACS who undergo coronary artery bypass grafting are conflicting. The appropriate antiplatelet regimen after CABG remains an area of controversy. On the balance, plaque stability, prevention of graft closure, and secondary thrombosis form the basis for using a second antiplatelet drug, whereas the risk of bleeding and the potential lack of effectiveness weighs in against it [1, 2, 8]. There is interindividual variability in the response to clopidogrel, depending on the lab test or agonist used and the timing of the trombo-cytometric assessment [9,10]. Recommendations from national guidelines differ, varying from single antiplatelet therapy with aspirin, or DAPT with the combination of aspirin and clopidogrel [1, 2].

Clopidogrel is absorbed in the intestinal lumen as a prodrug, thus requiring metabolism after adsorption and before it can inhibit ADP-induced platelet aggregation. Intestinal absorption, metabolic activation, and intrinsic biologic activity are known to be affected by specific genetic polymorphisms [11]. In the personalized and precision medicine ambulatory pharmacogenomic tests are used to identify such pharmacologically relevant genetic patterns so that therapeutic choices and regimens can be optimized. Single nucleotide polymorphisms (SNPs) indicating the individual's response to drugs, can guide the choice of a drug and its use.

Today pharmacogenomic evaluation can give important insights both on clopidogrel bioavailability and on its effectiveness, and can guide its use and dosage. While FDA guidelines recommend pharmacogenomic testing when using the antiplatelet drug clopidogrel, these are limited to CYP2C19 testing [12,13], the enzyme responsible for its bioactivation, while no specific recommendation is given about other mutations that are known to impact its pharmacological outcome, like those affecting adsorption and ADP sensitivity. Considering that the mechanisms leading to a poor response to clopidogrel are multifactorial and not solely linked to poor metabolic activation, it would be beneficial to test pharmacokinetic and pharmacodynamic characteristics as well, when evaluating the potential effectiveness of clopidogrel treatment.

In the present study the three groups of polymorphisms known to affect clopidogrel activity were analyzed: genes modulating the absorption (ABCB1), metabolic activation (CYP2C19) and biological activity (P2RY12) [1-4].

The drug-efflux transporter, P-glycoprotein (P-gp), encoded by the ABCB1 gene, limits the bioavailability of many drugs, like clopidogrel, by effluxing them from the intestinal epithelia. In the present case, analysis of ABCB1 showed the presence of a hyper-expressed form of the transporter, thus indicating a poor clopidogrel absorption [3- 5]. In this particular context, the co-administration of pantoprazole and atorvastatin, two molecules competing for the P-gp transporter, might improve clopidogrel adsorption.

The second group of SNPs (CYP2C19) was normal, indicating a regular clopidogrel pro-drug transforming activity. The last group of SNPs indicated that the patient was strongly sensitive to ADP stimulation, thus suggesting that aspirin by itself would not be effective for the antiplatelet activity [3, 6, 7].

Taken together the results indicate that the antiplatelet DAPT therapy is recommended in the patient, given the ASA inability of effectively inhibiting an enhanced ADP-mediated activation. The results also confirm that clopidogrel can be effectively transformed into the active metabolite, thus supporting its use. On the other hand the P-glycoprotein over-expression indicates that clopidogrel might be poorly absorbed, thus suggesting its substitution with a different drug like ticlopidine, which acts on the ADP mediated pathway, but is not known to be a P-gp substrate. Ticlopidine has also been reported to be more effective when administered with Ginkgo biloba extract [14]. This combination could also be considered in substitution of clopidogrel, but the use of three antiplatelet agents, including ASA, would require a special monitoring of potential bleeding side effects.

Although clopidogrel substitution would probably be the best choice given the pharmacogenomics results, the current antiplatelet therapy with aspirin and clopidogrel, might still be effective, thanks to the presence of pantoprazole and atorvastatin which, in addition to their primary gastroprotective and lowering cholesterol activities, respectively, limit the availability on P-glycoprotein for clopidogrel, thus reducing its efflux. In this case though, attention must be paid to the timing of drug administration, to optimize the P-gp competing effect. This last aspect might not be feasible though, given the different timing of dosage of the drugs. One further option would then be to administer Ginkgo biloba extract in association with clopidogrel, given the anti P-gp activity of the flavonoids present in its phytocomplex [15]. This last option would also benefit from the synergistic antithrombotic activity of ginkgolides [16], which might allow modulation of the doses of clopidogrel and/or aspirin, thus reducing the possibility of side effects.

Conclusion

In conclusion, the case presented here brings an example of pharmacogenomics application in the cardiovascular context of aspirin-clopidogrel administration after artery bypass graft, where a dual antiplatelet therapy can be indicated. A selected panel of genetic variants was analyzed to ascertain the effectiveness of the antiplatelet therapy. The results indicated the limits of the use of clopidogrel in the patient, suggesting that the use of a different antiplatelet drug might improve the pharmacologic outcome, thus dis-aligning with the standard practice, but at the same time demonstrating the advantages of using a full spectrum personalized approach when choosing a pharmacological regimen.

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