

CLOPIDOGREL PHARMACOGENETICS: A VALID METHOD TO ASSURE EFFECTIVENESS AND APPROPRIATENESS OF THE ANTIPLATELET THERAPY

1)Conti V.. 2)Manzo V.. 3)Sellitto C.. 4)Iannaccone T.. 5)Costantino M.. 6)Corbi G.. 7)Malangone P.. 8)Tarallo S.. 9)Iannello F.. 10)Nicoletta G.. 11)Accarino G.. 12)Filippelli A..

University Hospital of Salerno

Clopidogrel, the best characterized member of thienopyridine derivatives, irreversibly inhibits the platelet purinergic receptor P2Y₁₂, thereby reducing platelet aggregation. It is commonly administered with aspirin to prevent thromboembolic events in patients with peripheral arterial disease or acute coronary syndrome after stent placement. Clopidogrel is a pro-drug that needs to be converted into its active metabolite by hepatic cytochromes, including CYP2C19 (Kam PC et al., 2003).

Despite its good efficacy and safety, there is a remarkable variability in the therapeutic response to such antiplatelet agent, partially due to three polymorphisms indicated as CYP2C19-*2; -*3 and -*17. CYP2C19-*2 and -*3, whose presence identifies individuals as intermediate and poor metabolizers, reduce the conversion of clopidogrel to its active form, thereby decreasing the drug's antiplatelet activity (Saab YB et al., 2015).

The effectiveness of clopidogrel might be affected also by drug-drug interaction with proton pump inhibitors (especially omeprazole and esomeprazole) that strongly inhibit CYP2C19. Food and Drug Administration and European Medicine Agency have added a boxed warning to the label for clopidogrel, advising clinicians to avoid the concomitant use of proton pump inhibitors mainly in patients who are CYP2C19 intermediate or poor metabolizers (Guérin A. et al., 2016).

We report three cases of men with carotid artery stenosis admitted to Vascular and Endovascular Surgery Unit of the University Hospital "San Giovanni di Dio e Ruggi d'Aragona", Salerno-Italy for elective surgery of percutaneous transluminal angioplasty (PTA). The patients was on treatment with clopidogrel 75 mg, aspirin 100 mg and omeprazole (20 mg).

Platelet function testing was performed to assess the rate of patient's antiplatelet aggregation using an aggregometer (Multiplate analyzer, Roche Diagnostics), largely used for antiplatelet therapy monitoring.

Clopidogrel pharmacogenetic testing was made at Service of Clinical Pharmacological and Pharmacogenetics of the University Hospital of Salerno to identify CYP2C19-*2; -*3 and -*17 polymorphisms by Real-Time PCR with allelic discrimination assay SNIp kit (Real Gene S.r.l., RC, Italy).

Moreover, a standardized self-reported questionnaire named Morisky Medication Adherence Scale (MMAS) was administered to evaluate patients' adherence to pharmacological treatment (Morisky DE. et al., 2008).

Before PTA, the patients had an aggregation corresponding to a value occurring in the absence of treatment with thienopyridines. In addition, pharmacogenetic testing revealed that patients were heterozygous carriers for CYP2C19*2 polymorphism.

Taking into account the insufficient platelet aggregation inhibition, the presence of CYP2C19*2 allele revealing a phenotype of intermediate metabolizer, and considering the inappropriate use of omeprazole, the therapy was changed by replacing omeprazole with ranitidine (150 mg bid) and by administering a 75 mg supplemental dose of clopidogrel.

After 20 days, the patients repeated platelet functional testing, showing a platelet aggregation rate well suited with a therapeutic effect of clopidogrel.

In conclusion, an impaired drug metabolism due to genetic factors and/or comedications often affects clopidogrel effectiveness. Patients who do not adequately respond to clopidogrel have a 5-10 fold increased risk for stent thrombosis, whereas the regular responders' risk is very low (0,2%). The described case series report emphasizes the importance of monitoring the antiplatelet therapy and confirms the role of the pharmacogenetics in informing therapeutic decisions making and assuring pharmacological appropriateness into the context of individualizing care.

Kam PC et al. (2003). *Anaesthesia*. 58(1):28-35.

Saab YB et al. (2015). *Ther Clin Risk Manag*. 11: 1421-7

Guérin A et al. (2016). *PLoS One*. 11(1):e0145504

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