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ORIGINAL RESEARCH

Do *CYP2C19* and *ABCB1* gene polymorphisms and low CYP3A4 isoenzyme activity have an impact on stent implantation complications in acute coronary syndrome patients?

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Aim: The aim of this study was to determine the impact of *CYP2C19* and *ABCB1* gene polymorphisms and CYP3A4 isoenzyme activity on stent implantation complications among patients with an acute coronary syndrome (ACS) who underwent percutaneous coronary intervention (PCI).

Patients and methods: Seventy-six patients (median age 63, range 37–91 years) with an ACS who underwent PCI were screened for *CYP2C19* and *ABCB1* gene polymorphisms with real-time polymerase chain reaction: *CYP2C19*2*, *CYP2C19*17*, and *ABCB1 3435*. CYP3A4 isoenzyme activity was determined by urine cortisol and 6-beta-hydroxycortisol levels. Stent implantation complications such as stent thrombosis (n=2) and restenosis (n=1) were observed among drug-eluting stent recipients.

Results: Low mean 6-beta-hydroxycortisol/cortisol ratio is indicative of impaired CYP3A4 activity and was associated with higher risk of thrombosis (β coefficient=0.022, SE 0.009, p=0.021 in the linear regression model). The increase in the length of the implanted stent was associated with higher risk of restenosis (β coefficient=0.006, SE=0.002, p=0.001 in the linear regression model). The presence of the *CYP2C19*2* polymorphism did not affect the incidence of stent thrombosis (β coefficient=−1.626, SE=1.449, p=0.262 in the logistic regression model), nor did the *CYP2C19*17* (β coefficient=−0.907, SE=1.438, p=0.528 in the logistic regression model) and *ABCB1 3435* polymorphisms (β coefficient=1.270, SE=1.442, p=0.378 in the logistic regression model).

Conclusion: We did not find evidence that the presence of *CYP2C19*2*, *CYP2C19*17*, and *ABCB1 3435* polymorphisms may jeopardize the safety of stent implantation in patients with an ACS. Patients with low CYP3A4 isoenzyme activity may have increased risk of stent thrombosis.

Keywords: acute coronary syndrome, clopidogrel, complications, polymorphism, stents

Essentials

- Due to the relatively high costs of ticagrelor and prasugrel, the use of clopidogrel continues to be prevalent among patients with an acute coronary syndrome (ACS) who underwent percutaneous coronary intervention (PCI).
- Seventy-six patients with an ACS who underwent PCI were screened for *CYP2C19* and *ABCB1* gene polymorphisms. CYP3A4 isoenzyme activity was determined by urine cortisol and 6-beta-hydroxycortisol levels.
- No evidence was found supporting that the presence of *CYP2C19*2*, *CYP2C19*17*, and *ABCB1 3435* polymorphisms may jeopardize the safety of stent implantation in patients with an ACS.

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- Patients with low CYP3A4 isoenzyme activity may have increased risk of stent thrombosis, and this matter needs further investigation.

Introduction

Patients with an ACS require dual antiplatelet therapy with both $P2Y_{12}$ receptor inhibitors and aspirin treatment for 12 months.[1] Due to the relatively high costs of ticagrelor and prasugrel, the use of clopidogrel continues to be prevalent. Clopidogrel is a thienopyridine $P2Y_{12}$ receptor inhibitor which consequently inhibits the activation of the GPIIb/IIIa complex mediated by adenosine diphosphate, thus inhibiting platelet aggregation. Clopidogrel is a prodrug which undergoes 2-step hepatic metabolism by several cytochrome P450 isoforms. The first step is mediated mostly by CYP2C19 enzyme followed by further oxidation where the intermediate metabolite 2-oxo-clopidogrel turns into an active metabolite by CYP3A4, CYP2C19, CYP2B6, and CYP2C9 isoenzymes.[2] The absorption of the drug itself in the duodenum requires P-glycoprotein involvement in the intestinal transport which is subsequently coded by the *ABCB1* gene.[3] If a loss-of-function variant of gene coding any of these isoenzymes is present, this may result in complications associated with suboptimal blood-thinning levels, such as stent thrombosis as well as other major adverse cardiovascular events. In this study, we tried to assess the impact of *CYP2C19* and *ABCB1* gene polymorphisms and CYP3A4 isoenzyme activity on the incidence of stent implantation complications in patients with an ACS.

Patients and methods

Seventy-six patients (median age 63, range 37–91 years) with an ACS who underwent PCI at the City Clinical Hospital No. 1, Moscow, Russian Federation, and had either drug-eluting stent (n=30) or bare-metal stent (n=46) implanted, were screened for *CYP2C19* and *ABCB1* gene polymorphisms: *CYP2C19*2*, *CYP2C19*3*, *CYP2C19*17*, and *ABCB1 3435*. CYP3A4 isoenzyme activity was determined by urine cortisol and 6-beta-hydroxycortisol levels with high-performance liquid chromatography. $P2Y_{12}$ reaction unit levels utilizing VerifyNow $P2Y_{12}$ assay (Accumetrics, San Diego, CA, USA) were measured.[4] Stent implantation complications such as stent thrombosis (n=2) and restenosis (n=1) were observed among drug-eluting stent recipients. The study protocol was approved by the Ethics Committee of Russian Medical Academy of Continuous Professional Education, Moscow, Russian Federation (resolution no. KM-145), and all patients gave written informed consent for participation.

Results

Low mean 6-beta-hydroxycortisol/cortisol ratio is indicative of impaired CYP3A4 activity and was associated with higher risk of thrombosis (β coefficient=0.022, SE 0.009, p=0.021 in the linear regression model). The increase in the length of the implanted stent was associated with higher risk of restenosis (β coefficient=0.006, SE=0.002, p=0.001 in the linear regression model). The presence of the *CYP2C19*2* polymorphism did not affect the incidence of stent thrombosis (β coefficient=−1.626, SE=1.449, p=0.262 in the logistic regression model), nor did the *CYP2C19*17* (β coefficient=−0.907, SE=1.438, p=0.528 in the logistic regression model) and *ABCB1 3435* polymorphisms (β coefficient=1.270, SE=1.442, p=0.378 in the logistic regression model).

Discussion

Although it is accepted that *CYP2C19* and *ABCB1* loss-of-function variant carriers may need drug change, we did not find evidence that the presence of *CYP2C19*2*, *CYP2C19*17*, and *ABCB1 3435* polymorphisms may jeopardize the safety of stent implantation in patients with an ACS. This means that there was no need to perform analysis of $P2Y_{12}$ reaction unit levels utilizing VerifyNow $P2Y_{12}$ assay as the results of this analysis are not going to have a clinical impact and affect the results of a PCI. This is supported by the latest ACC/AHA 2016 guideline focused update where it is stated that no randomized controlled trial has demonstrated that routine platelet function testing or genetic testing to guide $P2Y_{12}$ inhibitor therapy improves outcome and is not recommended for routine use (Class III: No Benefit).[1] CYP3A4 is another enzyme that takes part in clopidogrel metabolism. The method we used to determine CYP3A4 isoenzyme activity is based on the concentration ratio of a substrate and its metabolite – cortisol and 6-beta-hydroxycortisol, respectively. If the concentration of metabolite is more than 50%, the activity of the isoenzymes, involved in the metabolism, is considered to be high; if it is less than 30%, it is considered to be low.[5] There is a correlation between the urinary level of 6-beta-hydroxycortisol and both liver microsomal cortisol 6-beta-hydroxylase activity and CYP3A4 liver content.[6] Therefore, urinary 6-beta-hydroxycortisol excretion can be used as a marker of CYP3A4 genetic polymorphism.[7]

Conclusion

The results of our study have shown that patients with low CYP3A4 isoenzyme activity may have increased risk of stent thrombosis. Low CYP3A4 isoenzyme activity can be detected with the help of a noninvasive and simple excretory test based on 6-beta-hydroxycortisol/cortisol ratio. The risk of stent

implantation complications among patients with an ACS could be stratified according to this 6-beta-hydroxycortisol/cortisol ratio, and therapeutic adjustments be made accordingly.

Author contributions

E Rytkin and KB Mirzaev conceived the study, acquired and analyzed the data, and drafted the manuscript. EA Grishina, VV Smirnov, KA Ryzhikova, and ZhA Sozaeva conceived the study, acquired and analyzed the data, and critically revised the manuscript. MI Giliarov, DA Andreev, and DA Sychev conceived the study and critically revised the manuscript. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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