PB 2.21-3

The experience of the antiplatelet therapy by clopidogrel in the West-Siberian region of Russia: the effects of CYP2C19 and ABCB1 allelic variants

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Background: Clopidogrel is known to be one of the principal drugs for modern antiplatelet therapy. However, the interindividual variability of the response to clopidogrel has been also shown. This variability depends both of the presence of certain genetic polymorphisms, in particular, allelic variants of CYP2C19 and ABCB1 genes, and of clinical factors. Clinical trials revealed the regional features of abundance of genetic polymorphisms influencing clopidogrel metabolism.

Aims: To examine frequencies of occurrence of allelic variants CYP2C19 *2, *17 and ABCB1 C3435T among the patients of the West-Siberian region of Russia receiving clopidogrel and to determine contribution of these markers to the clopidogrel laboratorial efficacy.

Methods: One hundred and fifty-eight patients with cardiologic pathology receiving clopidogrel were enrolled. The allelic variants of ABCB1 and CYP2C19 were determined by means of real-time PCR. The relative change of platelet aggregation with ADP before and 48 h after taking of loading dose of clopidogrel (600 mg) referred to as resistance index (RI) was assessed. RI was assumed to be a measure of the clopidogrel laboratorial efficacy. The relation of allelic variants of ABCB1 C3435T and CYP2C19 *2, *17 to RI was estimated. The study protocol was approved by the local ethic committee of the ICBFM SB RAS.

Results: Depending on RI the following subgroups of patients were assigned: sensitive (RI > 30%, 58.9%), semi-responders (RI = 10–30%, 20.9%), non-responders (RI = 0–10%, 7.6%), and 12.7% of patients demonstrated paradoxical laboratorial response: platelet aggregation increased after clopidogrel taking.

According to genetic analysis data, the CYP2C19 gene was presented by allelic variants *1/*2 (24.7%), *2/*2 (0.6%); *1/*17 (17.0%) and *17/*17 (1.0%), and the ABCB1 gene by 3435 CC (20.3%), CT (41.8%) and TT (37.9%) variants. The correlation analysis revealed the connection between CYP2C19*2 and RI. Both CYP2C19*17 and ABCB1 C3435T allelic variants have not been shown to make an effect in changes of platelet aggregation after clopidogrel taking. None statistically significant connection between considered genetic variants and paradoxical laboratorial response on clopidogrel was found.

Depending on the type of drug metabolism patients were divided into five subgroups: fast (*17/*17, *1/*17), extensive (*1/*1), intermediate (*1/*2, *1/*3), slow (*2/*2), 'uncertain' (*2/*17). Significant differences ($P < 0.05$) were found between average RI in groups of fast and extensive metabolizers and in groups of fast and «uncertain» metabolizers. As a result, the influence of allelic variant CYP2C19*2 is more significant than the influence of the variant CYP2C19*17 in the group of patients under study.

Summary/Conclusions: The frequencies of occurrence of CYP2C19 and ABCB1 allelic variants in a group of patients from West-Siberian region of Russia receiving clopidogrel therapy were calculated and the effect of these genetic variants on clopidogrel laboratorial efficacy was examined. 12.7% of patients in the group under study were found to demonstrate paradoxical laboratorial response on clopidogrel. Such unusual response has not been shown to be associated with genetic variants considered. CYP2C19*2 has been shown to make an effect on the laboratorial response on the clopidogrel. RI in the subgroup of fast metabolizers is higher than in subgroups of extensive and «uncertain» metabolism.

PB 2.21-4

The VerifyNow PRU is associated with optimal duration of clopidogrel interruption prior to CABG surgery: sub-Analysis of TARGET CABG study

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Background: The utility of thrombelastography (TEG) to determine the timing of CABG in pts treated with clopidogrel was evaluated in the first prospective study, TARGET CABG which showed that pts non-responsive by TEG had no greater chest tube output when operated within 24 h of last clopidogrel dose compared to clopidogrel naïve pts. The utility of VN to optimally time CABG is unknown.

Methods: In TARGET CABG, we also analyzed platelet function recovery (PFR) using VerifyNow P2Y12 assay in 81 patients on aspirin and clopidogrel therapy undergoing elective first time isolated on-pump CABG. CABG was done within 1 day (nonresponse), 3–5 days (moderate response), and > 5 days (high response) based on ADP induced platelet-fibrin clot strength (MA-ADP) as measured by thrombelastography. Proportion of patients achieving pre-surgical PRU > 208 was used indicate PFR.

Results: Baselines PRUs were in agreement with MA-ADP within each response group and there was significant difference in mean baseline PRUs between response groups ($P < 0.05$) (Figure 1). Ninety-seven percent of patients demonstrated PFR prior to surgery. The total amount of red blood cells transfused did not differ between response groups.

Conclusions: PFR by VN-P2Y12 assay agrees with TEG, suggesting that PFR specific to the P2Y12 receptor significantly influenced the primary results of TARGET-CABG. The use of platelet function testing may allow for improved pre-surgical management of $P2Y_{12}$ inhibitor therapy prior to major surgery, and further investigation is warranted.

PB 2.21-5

Comparison of the antiplatelet effect of crushed clopidogrel vs. whole tablet in diabetic patients presenting with an acute coronary syndrome

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Background: Pharmacodynamic studies have shown that persistently high residual platelet reactivity (HRPP) is common in patients with diabetes in spite of clopidogrel treatment. Even, a 600-mg clopidogrel loading dose is not sufficient to overcome this effect, especially in diabetic patients with ACS. This can be explained by altered resorption, altered liver metabolism, or altered platelet response. Recently, it was demonstrated that clopidogrel given crushed provided faster absorption and greater rate of clopidogrel inactive metabolite in healthy subjects.

Objective: The hypothesis of the study was that 600 mg clopidogrel loading dose (LD) administered crushed may provide more effective platelet inhibition than an equal clopidogrel dose taken orally as whole tablets in patients with type 2 diabetes mellitus presenting with ACS.

Methods: In a prospective, single-center, single-blind study, 30 (58.9 ± 8.4 years; 17 males) ACS diabetic patients were randomized to either 600 mg crushed clopidogrel ($n = 15$) or whole tablets ($n = 15$) follow by a maintenance dose of 150 mg, respectively. Pharmacodynamic assessment was performed by VerifyNow P2Y12 system accumetrics at 24 h and 3 days post LD. High Residual platelet reactivity (HRPR) was defined as platelet reactivity units (PRU) > 235.