Prilagodba doze klopidozela u akutnom koronarnom sindromu i inicijalno povišenoj ostatnoj reaktivnosti trombocita – može li se nadvladati smanjena aktivnost izoenzima CYP2C19?

Clopidogrel dose adjustment in acute coronary syndrome and initial high on-treatment platelet reactivity – can we overcome reduced activity of isoenzyme CYP2C19?

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KEYWORDS: clopidogrel, acute coronary syndrome, percutaneous coronary intervention, platelet reactivity, CYP2C19.

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UVOD: Klopidozel je prolijek koji se mora preko citokrom P450 enzinskog sustava biotransformirati u aktivni metabolit. Prisutnost alela CYP2C19*2 povezana je sa stvaranjem nefunkcionalnoga enzima što dovodi do slabije biotransformacije klopidozela i u konačnici, oslabljenog učinka lijeka i lošijih kliničkih ishoda. U inicijalnoj studiji randomizirali smo 87 bolesnika s akutnim koronarnim sindromom (AKS) i povišenom reaktivnosti trombocita (RT) nakon perkutane koronarne intervencije (PCI) u skupinu kojoj će se kontinuirano prilagođavati doza klopidozela prema RT i skupinu liječenu standardnim dozama klopidozela. Pokazali smo da su u intervencijskoj skupini kontrola RT-a i ishodi bolesnika bili bolji. Cilj ovog istraživanja je ispitati utjecaj nosilaštva alela CYP2C19*2 na RT u obje skupine ispitanika.

PACIJENTI I METODE: U analizu je uključeno 85 ispitanika kojima je izrađen genotip CYP2C19 (97,7%). Analizirani su podatci o RT tijekom 12 mjeseci praćenja – 2., 3., 7. i 30. dan te 2., 3., 6., 9. i 12. mjesec od PCI. Uspoređivana je RT između nositelja i nenositelja alela CYP2C19*2 posebno za svaku skupinu ispitanika.

REZULTATI: U skupini bolesnika s prilagođavanom dozom klopidozela nije bilo statistički značajne razlike u RT tijekom cijelog razdoblja praćenja između nositelja alela CYP2C19*2 i onih koji nisu bili nositelji CYP2C19*2 ($p=0,187$) dok su u skupini ispitanika liječenih standardnom dozom nositelji alela CYP2C19*2 imali statistički značajno veću RT od nenositelja alela CYP2C19*2 ($p<0,05$).

ZAKLJUČAK: Rezultati ukazuju da bi se serijskim prilagođavanjem doze klopidozela prema testovima RT kod bolesnika s inicijalno povišenom ostatnom RT nakon PCI mogao nadvladati utjecaj genske komponente oslabljenog učinka klopidozela.

INTRODUCTION: Clopidogrel is a prodrug that undergoes cytochrome P450 enzyme mediated biotransformation into the active metabolite. The presence of the CYP2C19*2 allele is associated with the formation of a non-functional enzyme. Therefore, CYP2C19*2 carriers have diminished biotransformation of clopidogrel and consequently, manifest reduced drug effect and poorer clinical outcome. In the initial study, we randomly assigned 87 acute coronary syndrome (ACS) patients with high on-treatment platelet reactivity (HTPR) after percutaneous coronary intervention (PCI) to interventional group which underwent serial clopidogrel dose adjustment based on platelet function tests (PFT) and standard-dose clopidogrel group. We observed better PR control and patient outcomes in the interventional group. The aim of this study was to investigate the effect of genetic variant affecting clopidogrel pharmacodynamics - CYP2C19*2, on PR control in both groups.

PATIENTS AND METHODS: The analysis included 85 patients with determined CYP2C19 genotype (97.7%). We analyzed PR measurements during 12 months follow up – on 2nd, 3rd, 7th and 30th day, and on 2nd, 3rd, 6th, 9th and 12th month after PCI. PR levels were compared between CYP2C19*2 carriers and non-carriers for each study group separately.

RESULTS: In the interventional group there was no statistically significant difference in RT during the entire follow-up period between the CYP2C19*2 carriers and non-carriers ($p=0,187$), whereas in the standard group CYP2C19*2 carriers had significantly higher PR levels than non-carriers ($p<0,05$).

CONCLUSION: We hypothesize that serial adjustment of clopidogrel dose based on PFT in ACS patients with initial HTPR after PCI can overcome the genetic cause of reduced clopidogrel efficacy.

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