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STUDY ON THE ASSOCIATION BETWEEN CLOPIDOGREL RESISTANCE IN PATIENTS WITH ACUTE CORONARY SYNDROME AND CYP2C19 POLYMORPHISMS

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Objective To investigate clopidogrel resistance (CR) in patients of Han ethnic group with acute coronary syndrome (ACS) and the association between CR and CYP2C19 polymorphisms, to provide a theoretical basis to minimise the occurrence of a variety of ischaemic cardiovascular events for clinical practice in patients with ACS, and predict CR early enough to guide individual treatment.

Methods (1) The influence on platelet aggregation was studied in patients with ACS who received a conventional prescription of clopidogrel combined with aspirin. (2) 110 patients with ACS (71 male patients, 39 female patients, mean age 65.67 ± 11.73) were enrolled, including 44 patients

undergoing elective percutaneous coronary intervention (PCI). All patients were treated regularly with aspirin 100 mg/day, clopidogrel medication for the first time (loading dose of 300 mg, maintenance dose of 75 mg/day) or drug withdrawal of clopidogrel for at least 2 weeks. 2.7 ml (0.3 ml 3.18% Sodium Citricum, 9:1 anticoagulant) of whole vein blood was collected from each enrolled patient. Most platelet aggregation ratio (MPAR) induced by 5 $\mu\text{mol/l}$ ADP was measured by Turbidimetry before medication and 24 h after clopidogrel intake and the inhibition of aggregation (IPA) was calculated: (IPA (ΔA) was equal to the platelet aggregation before treatment minus the platelet aggregation after treatment), $\Delta A \leq 10\%$ (including negative value) was defined to be clopidogrel resistance. According to the value of ΔA , the patients were divided into two groups: clopidogrel resistance group and clopidogrel sensitive group. (3) PCR-RFLP technology was used to detect the CYP2C19 681G/A polymorphisms and genotype frequencies distribution in the enrolled patients. We assessed the association between CYP2C19 681 genotypes and laboratory clopidogrel resistance after clopidogrel intake, then they were divided into groups by their genotypes. We contrasted the inhibition of aggregation, clopidogrel resistance and adverse cardiovascular events (including ACS and/or inpatient care, instant restenosis and cardiogenic sudden death) after a follow-up for 3 months between different genotype groups.

Results (1) 110 ACS patients: The inhibition of platelet aggregation in clopidogrel resistance group was lower obviously than that of clopidogrel sensitive group (3.39 ± 12.76 vs 26.79 ± 10.86 , $p < 0.01$). (2) The 110 ACS patients who were treated with clopidogrel: The patients carrying CYP2C19 681GG genotype (59/110) have a higher reduction of IPA after 24 h' clopidogrel treatment than the CYP2C19 681GA genotype (43/110) carriers, and the CYP2C19 681AA genotype (8/110) carriers were the lowest ($16.18 \pm 10.11\%$, $10.20 \pm 9.97\%$ and $8.03 \pm 5.88\%$, $p < 0.01$). The rate of CR was 23.64% (26/110), the patients carrying CYP2C19 681GG genotype occupied with 34.62% (9/26), and the patients carrying CYP2C19 681A allele (GA+AA) occupied with 65.38% ((12+5)/26, $p < 0.01$). The average rate of platelet aggregation and the incidence of laboratory clopidogrel resistance were statistically significant in patients with different genotypes of CYP2C19 after treatment. (3) 44 patients undergoing PCI: Compared with the patients carrying CYP2C19 681GG genotype (23/44), the patients carrying CYP2C19 681A allele (GA+AA) (21/44) had a lower reduction of IPA ($p < 0.01$), a higher rate of CR (10/21 vs 4/23, $p < 0.05$) after 24 h' clopidogrel treatment. (4) 110 ACS patients after clopidogrel treatment received a follow-up for 3 months. The patients carrying CYP2C19 681A allele (GA+AA) (51/110) had a higher rate of adverse cardiovascular events (16/51 vs 5/59, $p < 0.01$).

Conclusions Some patients exist deeply clopidogrel resistance in ACS and post-PCI patients' antiplatelet therapy. CYP2C19 681G>A mutation weakens the antiplatelet effect of clopidogrel, which is a major influential factor of the effect and prognosis to patients with ACS who were treated with clopidogrel.