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Case Report

The Individualized Antiplatelet Therapy in a Patient with Renal Insufficiency Following Percutaneous Coronary Intervention: A Case Report

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Abstract

Clopidogrel plays a key role in inhibiting platelet adhesion, activation, and aggression. It has been widely recommended by current guidelines in patients undergoing PCI. We discuss the clinical application of VerifyNow P2Y12 assay in the evaluation of clopidogrel resistant in this patient with clopdiogrel resistance. We also introduced the hepatic cytochromes (CYP450) enzymes metabolic pathways of clopidogrel and the pivotal role of CYP2C19 genotype on outcome of clopidogrel therapy. However, under the circumstance of discontinuing clopidogrel, this clopidogrel resistance patient with renal insufficient suffered from a cerebral hemorrhage. The optimal individualized antiplatelet therapy in patients with clopidogrel resistance following PCI, especially concurrence renal insufficient still need further to be studied.

Keywords: CYP2C19 Genotype; Renal Insufficiency; Verifynow Antiplatelet Assay

Case Presentation

Clinical Data

A 62-year-old coronary heart disease man who had experienced paroxysmal ischemic chest pain for fifteen years came to the cardiology department after an episode of chest pain at ten o'clock on September 12, 2016.

Past History

He had three stents implanted in 2001, three stents implanted in 2008, and one stent implanted in 2014. He was with no history of hypertension and diabetes mellitus. He was without hepatitis and tuberculosis.

Personal History

No history of smoking or drinking.

Course of Analysis

His blood pressure at presentation was 100/70 mmHg, heart rate 70 bpm, afebrile, oxygen saturation (SaO_2 99%). His bed side Electrocardiogram (ECG) showed atrial fibrillation. Biochemistry test results revealed renal insufficiency (creatinine 180.9 umol/L), and high total cholesterol 5.22 mmol/L. Creatine Kinase-MB (CK-MB) 11 U/L and B-natriuretic peptide (BNP) 2516 pg/mml were also present.

On hospital day2, the patient underwent coronary angiography on September 13, 2016. The imaging showed that the patency after left main coronary artery stenting, the patency of the stent of the proximal Left Anterior Descending (LAD), while 90% stenosis of the distal LAD. There is about 90% obstruction of the first diagonal branch of the LAD. The stent patency was in the proximal left circumflex coronary artery. There was the complete occlusion in the distal of the left circumflex coronary artery. Restenosis after stent implantation was in the right coronary artery with non-calcified and mixed plaques, and the complete occlusion of the middle of right coronary artery. We implanted a Giwei stent（2.5*28 mm) on the distal Left Anterior Descending

(LAD). Angiography revealed a good result at the site of stent deployment.

We tested the platelet aggregation with the PFA-100 platelet function analyzer in hospital outpatient department (2016-10-16). The results showed that ACA 8.6% (55.0-90.0%) and ADP 53.1% (55.0-90.0%). The blood routine examination showed PLT：240 $\times 10^9$/L. According to the severity of coronary artery disease, the incidence of chest distress recently, and the platelet function monitoring by PFA-100 platelet function analyzer, we adjust his antiplatelet therapy using aspirin 100 mg QD + ticagrelor 90 mg BID and other routine treatment (2016-10-16).

Forty days after his discharge (2016-10-24), the patient returned with chest congestion and dyspnea. His blood pressure at presentation was 110/70 mmHg, heart rate 78 bpm, afebrile, oxygen saturation (SaO_2 99%). We performed a complete echocardiographic examination identifying the patient with left ventricular Ejection Fraction (EF) about 39% and diffuse hypokinetic left ventricular wall motion and the result was similar with previous one. He discharged from our hospital in 2016-10-27. We thought that dyspnea might be due to the side effect of ticagrelor, so we adjust the antiplatelet agents once again, using aspirin 100 mg QD and clopidogrel 75 mg QD. We tested the platelet function with the VerifyNow antiplatelet assay (2016-11-09). Results showed that P2Y12 Reaction Unit (PRU) value of 330 (reference range for PRU from 95 to 208 PRU), with the rate of inhibition of 0%, and baseline 329 PRU. The result of VerifyNow platelet-function testing showed the patient with high on-clopidogrel platelet reactivity, which means the patient with clopidogrel resistance. We detected CYP2C19 genotyping for clopidogrel in 2016-11-11, with the result of genetic testing CYP2C19*3/*3 (636AA, 681 GG). We readjusted his antiplatelet therapy using aspirin 100 mg QD + Clopidogrel 75mg QD+ Cilostazol 100 mg BID after discharge from the hospital. We did telephone follow-up after discharge and got feedback that the patient occurred chest distress and fatigue once in a while, without severe chest pains and dyspnea. The patient came to subsequent visit in 2016-11-21. After the routine assessment, we did the platelet function with the VerifyNow antiplatelet assay (2016-11-09). Results showed that P2Y12 Reaction Unit (PRU) value of 276PRU, with the rate of inhibition of 8%, and baseline 299 PRU. The ECG revealed atrial fibrillation and ST-T change. The patient was instructed in the use of aspirin 100 mg QD + Clopidogrel 75mg QD+ Cilostazol 100 mg BID. We informed him to contact us if he felt discomfort immediately. However, he didn't follow the doctor's advice due to personal reason, stopping Cilostazol and taking clopidogrel irregularly.

He was admitted to our department with an outbreak of dizziness and vomiting for 1 hour in 2017-01-14. The patient said that he felt dizzy and then vomited gastric content after defaecation. Physical examination at admission revealed an irregular heart rate of 75 beats/min (bmp), blood pressure 168/80 mmHg, respiratory rate 20 per min. Bilateral muscle strength is asymmetry and the right side of the limb was graded as grade 4. Bilateral pathological signs were negative. The ECG revealed atrial fibrillation and ST-T change. Cranial CT（2017-01-14）: left thalamic hemorrhage breaking into ventricular, left frontal lobe encephalomalacia and brain atrophy. Lung CT: bilateral interstitial pneumonia, upper lobe bronchiectasis, and bilateral pleural effusion. A hemogram showed a high D-dimer 8.26 mg/L and fibrinogen 6.32g/L. Biochemistry test results revealed renal insufficiency (creatinine 439.9 umol/L), and total cholesterol 2.42 mmol/L. Creatine Kinase-MB (CK-MB) 14 U/L were also present. After acute consultant, the patient was transferred to the department of neurology for further treatment. He was discharged from neurology department after the specialized treatment.

Diagnosis: The final diagnosis was coronary atherosclerotic heart disease and unstable angina after percutaneous coronary stents placement, with class III systolic heart failure, atrial fibrillation, cerebral hemorrhage, and chronic renal failure.

Discussion

The patient has been treated in our department for several times since 2014. He had eight stents implanted totally, without a history of hypertension and diabetes mellitus. We did platelet function analysis by LTA and Verifynow after his last percutaneous coronary intervention with stenting. The results showed clopidogrel resistance in this patient. Furthermore, we explicit the CYP2C19 loss of function allele *3 variants might be responsible for clopidogrel resistance. We weight the risk of bleeding and ischemic event by the platelet function analysis and CHA_2DS_2-VASC/HAS-BLED score. Based on these results, we did adjust the antiplatelet therapy with aspirin + ticagrelor or aspirin + clopidogrel + cilostazol. However, the patient was intolerable to the changes. Due to personal reasons, he did not follow the doctor's advice, stopping Cilostazole and taking clopidogrel irregularly. Finally, this renal insufficient patient with clopidogrel resistance suffered a cerebral hemorrhage.

Chronic Kidney Disease (CKD) is related to an increased risk of cardiovascular adverse events in patients following percutaneous coronary intervention, even if in patients with the renal function only moderately disturbed [1,2]. Previous studies have found that patients with chronic kidney disease might have the less therapeutic benefit of antiplatelet therapy [3,4]. The relationship between the renal function and the platelet reactivity is the current research hotspot. Clinical data on the relationship between the renal function and the platelet reactivity in patients on dual antiplatelet therapy (aspirin and clopidogrel) are controversial [5-9].

Several international guidelines have already recommended dual use of aspirin and clopidogrel for the prevention of ACS and MACE after Percutaneous Coronary Intervention (PCI) [10-13]. It is well known that clopidogrel has a wide variability in platelet responsive. Thought antiplatelet treatment of clopidogrel correctly, there still exists 5-10% of patient's experience thrombosis events after percutaneous coronary intervention [14,15]. In general, clopidogrel resistance refers to the occurrence of adverse cardiovascular events despites adequate antiplatelet treatment and compliance [16,17]. Clopidogrel resistance also call non-responsiveness. It has been published several definitions for clopidogrel resistance based on Light Transmission Aggregometry (LTA) assay: <10% absolute decrease in LTA-ADP max from the baseline, or LTA-ADP max value >50% during treatment [18,19]. Recently, the Verifynow-P2Y12 assay is considered to be a reliable, accurate, sensitive device for clinical monitoring platelet inhibition with clopidogrel [20,21].

Clopidogrel, a thienopyridine, is a prodrug. In liver, about 15% absorbed clopidogrel is metabolized to an active metabolite by hepatic cytochromes (CYP450) enzymes in a 2-step process. It has been proven that CYP2C19, CYP1A2, CYP2B6 isoenzymes have a critical role in the first step, and CYP2C19, CYP3A4, CYP2C9 play a crucial role for the second step. By irreversibly binding of the P2Y12 ADP receptor on platelet surface, Clopidogrel inhibits the platelet activation and aggregation [22]. Various factors have been implicated in clopidogrel resistance, for example, clinical, cellular, and genetic factors etc. [23,24]. First, Because of patient noncompliance, clopidogrel treatment can't continue. Second, Studies have demonstrated that clopidogrel resistance is related to gene polymorphism [25,26]. Concerning clopidogrel metabolism in health individuals, carriers of a reduced-function allele of CYP2C19 had 30% lower levels of the active clopidogrel metabolite and a 25% relative reduction in platelet inhibition *ex vivo* [27]. It maybe point out that CYP2C19 does affect the pharmacodynamics of clopidogrel in patients as well. In clinical research, patients with acute MI on clinical who sustained subsequent cardiovascular events were more likely to carry CYP2C19 loss-of-function alleles compared to control group, showing an increased effect particularly in patients who underwent PCI [28]. In another study including patients treated with clopidogrel, carriers of a reduced-function CYP2C19 allele had significantly lower levels of the active metabolite of clopidogrel with diminished platelet inhibition and a higher rate of MACE (major adverse cardiovascular events) [29]. The percentage of poor CYP2C19 metabolizer subjects is about 2-4.8% worldwide, with a particularly high incidence of 22.5% among East Asians [30,31]. Furthermore, the interaction between drug-drug many is associated with the variability in the absorption of clopidogrel. Concerns have been raised about the adverse cardiovascular effects of Proton Pump Inhibitors (PPIs) especially omeprazole in patients receiving clopidogrel [32,33].

As previous recommendation, a value >208 P2Y12 Receptor Units (PRU) was defined as clopidogrel resistance or high on-treatment platelet reactivity [34]. It has been accepted recently that a PRU value > 208 can well predict death, myocardial infarction or stent thrombosis [35]. It has been indicated that CYP2C19 polymorphism plays a pivotal role in clopidogrel pharmacodynamics and pharmacokinetics. Patients can be divided into four categories based on this clopidogrel metabolism genotype [36,37]. The first kind is normal metabolizer, which is also called extensive metabolizers (EMs: wild-type for the CYP2C19 polymorphisms). The second kind is poor metabolizers (PMs: homozygous or compound heterozygous genotypes for the LOF CYP2C19 polymorphisms). The third is intermediate metabolizers (IMs: heterozygous genotype for the LOF CYP2C19 polymorphisms and wild type of the CYP2C19). The fourth is ultra-rapid metabolizer (UM: heterozygous or homozygous genotype for the CYP2C19*17 and wiled type of CYP2C19). It has been reported that the clopidogrel resistance with CYP2C19-loss-of-function allele may not be overcome through high loading doses and maintenance dose [38-41]. It has been recommended that patients with poor metabolizers should take the new type P2Y12 receptor inhibitor or triple antiplatelet treatment. It is known to all that ticagrelor could interfere with adenosine metabolism, leading to increased adenosine plasma concentration [42,43].

An increase in adenosine concentration is the reason for dyspnea. Though ticagrelor has been widely used nowadays, we should pay attention to its side effect, especially dyspnea. The clinical outcome of the patient reminds that East Asian patients might have the different risk profiles for both thromboembolism and hemorrhagic tendency compared with white patients [44,45]. Though East Asian patients have a higher level of on-treatment platelet reactivity, clinical data signified that the clinical ischemic events with East Asian patients are similar to white patients after PCI [46]. Perhaps, there might be a different 'therapeutic window' of on-treatment platelet reactivity in East Asian patients. It has been reported that increased bleeding risk in patients with impaired renal function [47]. We also speculate that the impaired renal function in this patient with clopdiogrel resistance may also contribute to the cerebral hemorrhage. In conclusion, the optimal individualized antiplatelet therapy in patients with clopidogrel resistance following PCI, especially concurrence renal insufficient still need further to be studied.

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