

Pharmacogenetic approach to clopidogrel resistance: recurrent stent thrombosis in two brother

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Özet

Klopidogrel direncine farmakogenetik yaklaşım: iki erkek kardeşte tekrarlayan stent trombozisi olgusu

Klopidogrel, koroner stent implantasyonundan sonra tromboz gelişiminin önlenmesi için günümüzde tercih edilen ilaçlardan (prasugrel/velicagrelor) biridir. Bununla birlikte birçok hastada stent trombozisi gelişmeye devam etmektedir. Tekrarlayan iskemik komplikasyonların nedeninin yetersiz klopidogrel yanıtından kaynaklandığını gösteren çalışmaların sayısı gün geçtikçe artmaktadır. Yetersiz klopidogrel yanıtına neden olan mekanizmaların tartışılması kayda değerdir. Bu olgu sunumunda olası klopidogrel direnci ile birlikte tekrarlayan stent trombozisi bulunan hastada tıbbi literatür desteği ile klopidogrel direncinin mekanizmaları tartışılacaktır.

Anahtar kelimeler: klopidogrel, stent, trombozis

Abstract

Clopidogrel, is the antiplatelet treatment choice for prevention of thrombosis after coronary stent implantation. However, despite the use of clopidogrel, a considerable number of patients continue to have stent thrombosis. There is a growing degree of evidence that recurrence of ischemic complications may be attributed to poor response of clopidogrel. It is noteworthy to elucidate the mechanisms leading to poor clopidogrel effects. We report recurrent stent thrombosis with possible clopidogrel resistance and aimed to discuss the mechanisms of clopidogrel resistance in the light of the medical literature.

Keywords: clopidogrel, stents, thrombosis

Introduction

Stent thrombosis remains an important and potentially lethal clinical problem which often seems to be associated with clopidogrel resistance (1, 2). Studies have shown that major cardiac events still may occur despite the treatments to prevent stent thrombosis (3). Clopidogrel is administered to the majority of patients following the coronary stent implantation. It is a prodrug that requires in vivo conversion to an active metabolite to exert its antiplatelet effect. CYP3A4 is the responsible enzyme for this conversion. There is evidence that significant part of clopidogrel resistance may be due to insufficient production of its active metabolite (4, 5). It is crucial

to recognize the importance of clopidogrel resistance in order to increase detection of at-risk patients. In the present article we report two cases, two brothers, of recurrent stent thrombosis associated with clopidogrel resistance after an acute myocardial infarction.

A 57-year-old male patient came to our hospital for his routine control. He has a history of hypertension, hyperlipidemia and coronary artery disease. Also, he had a coronary by-pass surgery eleven years ago and pulmonary embolism history one year ago. According to his positive history, he underwent an elective cardiac catheterization. Coronary angiography revealed 80 % stenosis of the left anterior descending (LAD) coronary artery. LAD stenosis was successfully stented with two zotarolimus drug-eluting stents with an excellent angiographic result. Medication with aspirin, statin, beta-blocker, dalteparin sodium and

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clopidogrel (75 mg/day) was administered, and patient was discharged from hospital after 2 days. Approximately one month after this hospitalization, the patient suffered again from chest pain and electrocardiography suggested an acute closure of LAD. Immediately he was admitted to the catheterization laboratory. The angiography revealed 100 % stent thrombosis in the proximal section of LAD which was recanalized by percutaneous transluminal coronary angioplasty (PTCA). After two days, he was discharged on aspirin, beta-blocker, statin and his clopidogrel dose regime was increased to 150 mg/day and he continued dalteparin sodium for five days. Four days later, he presented to our hospital again, with a sudden, sharp, left-sided chest pain. He was immediately moved to the catheterization laboratory. There was a 100 % stent stenosis of LAD coronary artery. After balloon angioplasty was carried out two times, and TIMI III flow was established. His previous therapy was continued with dalteparin sodium, clopidogrel, aspirin and beta-blocker. After three days, the patient was discharged without any complications. On the other hand, our patient's brother who was 55-year-old had the same history almostly. He experienced two stent-thrombosis and four additional stent implantation on LAD because of recurrent stent thrombosis.

Stent thrombosis is an uncommon but serious complication of percutaneous coronary intervention that often results as a myocardial infarction or death. About 1% to 1.9 % of the patients continue to experience stent thrombosis. Although, clopidogrel in combination with aspirin, is currently the antiplatelet treatment choice for prevention of stent thrombosis, clopidogrel resistance is an emerging topic (6, 7). This phenomenon can result from alterations or abnormalities in intestinal absorption or hepatic conversion to active metabolites. Drug-drug interactions as well as receptor polymorphisms may also contribute to clopidogrel response variability. Clopidogrel is an inactive prodrug that requires two-step oxidation by the hepatic cytochrome P450 system to generate an active metabolite. *In vitro*, the first step is catalyzed by several enzymes including CYP2C19, CYP1A2 and CYP2B6 and the second by CYP3A4/5, CYP2B6, CYP2C19 and CYP2C9. *In vivo*, CYP3A4, CYP2C19 and CYP1A2 are considered the main enzymes involved (8). Drugs that inhibit the CYP3A4 isoenzyme can potentially interfere with the conversion of clopidogrel into its active metabolite, leading to reduced antiplatelet effects. It was observed

that the effectiveness of clopidogrel was diminished in patients who were taking lipophilic statins (7, 9). The present two cases have also been using rosuvastatin 40 mg/d for 10 years. Rosuvastatin was metabolized principally by the CYP2C9 isoenzyme and with little involvement of CYP3A4 which may indicate less interaction. It has been recently documented that co-treatment with CYP3A4 metabolized statins did not attenuate the bioactivation of clopidogrel which is contrast to the conventional (10, 11). Other possible effects of ongoing medications in our patients are unknown. On the other hand as a prodrug, clopidogrel also requires metabolism by CYP2C19 for fully activation. Another challenge for clopidogrel disactivation is the presence of loss-of-function alleles of CYP2C19. In patients with these alleles, no active metabolite could be detected in plasma and the risk for stent thrombosis was more than three-fold increased compare to the rate of noncarriers (12-14). Therefore the elucidation and verification of CYP2C19 polymorphism as a cause of clopidogrel resistance should be an important step forward to deal with this problem.

In addition to the commonly known genetic factors in clopidogrel resistance, there are also several recently pronounced genetic factors associated with stent thrombosis. Gene studies found variants in platelet endothelial aggregation receptor-1 (PEAR1) to be strongly associated with altered function and aggregation (15). Goodall and et al., identified other possible novel regulators in platelet function. They examined COMM domain-containing protein 7 (COMMD7) and leucine-rich repeat (in FLII) interacting protein 1 (LRRFIP-1) and, showed that these proteins were in association with myocardial infarction because of their effects on thrombus formation and function as a component of the platelet cytoskeleton (16). Other genetic studies were interested with genes which were employed in regulating platelet function. For example, it was recently announced that connexin37 (Cx37) protein family was responsible for a mechanism to limit thrombus propensity in platelets. Deletion of Cx37 gene in mice shortened bleeding time and increased thrombus propensity (17). In addition, we cannot rule out the importance of paraoxonase-1 and SR-B1 genes in this case. These genes concern a significant impact in atherosclerosis process (18). Our two patients' history has gone away through ten years. This period is a sufficient time for atherosclerosis developing process.

Taken together, the clopidogrel resistance in the present two cases as being close relatives may be related to these kinds of deletions or variations (Table 1). Patients with multiple stent thrombosis or history of stent thrombosis in his family should alert physicians to consider a genetic polymorphism or drug-drug interactions in order to evaluate and quantify the degree of preventable risk and initiate therapy to modify risk. Further investigations are going on with our patients, in order to document if there was any genetic polymorphism.

Table 1: Potential genetic factors associated with stent thrombosis

Genes	Literature evidence
CYP3A4	Campo G, Fileti L, et al. (2010) Lau WC, Waskell LA, et al. (2003)
CYP2C19	Collet JP, Hulot JS, et al. (2009) Silvano M, Zambon CF, et al. (2011)
PEAR1	Faraday N, Yanek LR, et al. (2011)
CX37	Angelillo-Scherrer A, Fontana P, et al. (2011)
Paraoxonase-1	Bouman HJ, Schömig E, et al. (2011)
SR-B1	Bouman HJ, Schömig E, et al. (2011)
COMMD7	Goodall AH, Burns P, et al. (2011)
LRRFIP-1	Goodall AH, Burns P, et al. (2011)

As a conclusion, this case emphasizes the complexity of mechanisms underlying resistance to clopidogrel. Thus, it is important to consider clopidogrel resistance in patients with recurrent stent thrombosis or a similar event in his family. Genotyping analysis besides non-genetic risk factors (drug-drug interaction) are needed to be verified for their potential benefit in individualization of antithrombotic therapy.

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