Evaluation of platelet reactivity using P2Y12 reaction units in acute coronary syndrome with essential thrombocythemia: A case report

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ABSTRACT

Essential thrombocythemia (ET) has been reported to cause acute coronary disease. However, the efficacy of anti-platelet therapy for ET is unclear since there are individual differences in the platelet function of ET patients. Here we report a case of a 62-year-old man with ET who was admitted to our hospital because of acute coronary syndrome. He underwent coronary angioplasty. Dual anti-platelet therapy with aspirin (81 mg/day) and clopidogrel (75 mg/day) was subsequently initiated. We evaluated platelet reactivity in P2Y12 reaction units, and subsequently determined anti-platelet drugs and corresponding doses.

<Learning objective: Essential thrombocythemia (ET) is a myeloproliferative disorder that causes acute coronary disease. As there are individual differences in the platelet function of patients with ET, the efficacy of anti-platelet therapy for these patients varies. Evaluation of platelet reactivity using P2Y12 reaction units is useful in determining appropriate anti-platelet drugs and corresponding doses.>

Introduction

Essential thrombocythemia (ET) is a myeloproliferative disorder that causes thrombus formation in systemic arteries including the coronary arteries. A previous study reported that the incidence of acute coronary events in ET patients was 9.4% [1]. Paradoxically, ET can cause secondary von Willebrand disease, which is characterized by excessive bleeding, especially when platelet count is over 1,000,000–1,500,000/mm³ [2]; however, thrombosis is more frequent than hemorrhage in patients with ET.

There are individual differences in the platelet function of ET patients. Furthermore, studies have shown that the efficacy of clopidogrel has interpatient variability because of genetic factors, especially in Asian people [3]. Since clopidogrel is a prodrug that requires metabolism by cytochrome P450 (CYP) enzymes, the efficacy of clopidogrel is affected by CYP genetic variation. Platelet reactivity to clopidogrel can be measured in P2Y12 reaction units (PRU) using VerifyNow® (Accumetrics, San Diego, CA, USA).

There are some reports of acute coronary syndrome (ACS) with ET, however, there are few reports focused on anti-platelet therapy. Here we present a case of ET accompanied by ACS with percutaneous coronary intervention (PCI). We determined the dose of anti-platelet therapy while evaluating the platelet reactivity using PRU in order to prevent recurrent thrombosis and hemorrhage events.

Case report

A 62-year-old man was admitted to our hospital with severe chest pain. He had been experiencing episodes of chest pain for three weeks. One evening, severe chest pain occurred and did not subside until the following evening, when he visited our hospital. He was a current smoker and had a previous history of ET treated with hydroxyurea (500 mg/day) 25 years earlier. He had wild-type JAK2 V617F. He had a family history of coronary artery disease. His vital signs on admission revealed blood pressure of 156/91 mmHg, a
heart rate of 84 bpm, and body temperature of 36.2 °C. Laboratory evaluation revealed his platelet count was 1,200,000/mm³. Electrocardiography showed ST elevation in leads II, III, and aVF, and ST depression in leads I, aVL, and V2–6. The transthoracic echocardiogram showed a hypokinesia of wall motion in the posteroinferior region. These findings indicated ACS and therefore oral aspirin (162 mg) was initiated prior to a coronary angiogram (CAG). The CAG showed 99% stenosis in the proximal right coronary artery (Fig. 1A). Intravascular ultrasound (IVUS) showed a large amount of thrombus in the culprit lesion (Fig. 1B). Aspiration thrombectomy was performed, and white thrombus was withdrawn. Pre-dilatation and stenting (3.5 mm × 18 mm biolimus-eluting stent) were performed successfully with Thrombolysis In Myocardial Infarction grade 3 coronary flow. The maximum creatine kinase level reached was 382 IU/L. Dual anti-platelet therapy (DAPT) with aspirin (81 mg/day) and clopidogrel (75 mg/day) was initiated after 300 mg clopidogrel loading. Although the patient’s platelet count on admission was high (1,200,000/mm³), von Willebrand factor antigen levels (136%) and ristocetin cofactor activity levels (99%) were normal. We increased the dose of hydroxyurea to decrease his platelet count and prevent thrombosis and hemorrhage (Fig. 2).

His genotype of CYP2C19 was wild-type (CYP2C19*1/*1), namely extensive metabolizer. PRU measured by VerifyNow® are only available when platelet count is less than 741,000/mm³; therefore, we measured PRU at 35 days after administration when his platelet count was 557,000/mm³. A PRU value of 5 was obtained by VerifyNow®. Although the efficacy of clopidogrel was potent, we decided to continue DAPT with the same drugs at the same doses because the patient was classified as high risk for thrombosis due to age and thromboembolic complication [2]. The patient’s platelet count decreased to within normal range, and the PRU value changed from 5 to 72. We performed follow-up CAG and optical coherence tomography (OCT) six months after stenting. CAG showed normal coronary artery and no in-stent restenosis, and OCT images showed that most of the struts were covered, and that there were uncovered struts and peri-strut low intensity area (Fig. 3). We decided to continue DAPT with the same drugs at the same doses for one year. Seven months have passed since we performed stenting. There has been no major thrombosis or bleeding event.

Discussion

ET is a myeloproliferative disorder that causes thrombus formation in systemic arteries including the coronary arteries. Furthermore, ET can cause hemorrhage events because of secondary von Willebrand disease. Secondary von Willebrand disease is caused by thrombocytes strongly binding to von Willebrand factor especially when platelet count is over 1,000,000–1,500,000/mm³ [2]. In Japan, 17.6% of ET patients have thrombosis, and 4.2% have hemorrhage [4].

In our patient, smoking and a family history of coronary artery disease were coronary risk factors in addition to ET. Moreover, the relationship of ET with the JAK2 V617F mutation is prominent. One study demonstrated that JAK2 V617F was associated with a higher number of immature platelets in ET patients [5]. This mutation was not identified in our case. Because the patient was considered as being at high risk for thrombotic complications, we reinforced myelosuppressive therapy using hydroxyurea to prevent thrombotic complications [2]. The patient had already been treated with hydroxyurea however, his platelet count was 1,200,000/mm³ on admission and therefore, we increased the doses of hydroxyurea in order to decrease his platelet count.

Aspirin (81 mg/day) with clopidogrel (75 mg/day) was initiated in our patient since it is a standard therapy for the prevention of stent thrombosis following PCI. Clopidogrel suppresses platelet aggregation inhibiting P2Y12 receptor. A previous study demonstrated that the efficacy of clopidogrel differed individually because there are factors that cause resistance to clopidogrel: genetic, clinical, and cellular factors [6]. Genetic factors are largely
due to CYP2C19 genotype because clopidogrel is mainly changed into active metabolite by CYP2C19. As the genotype of our patient was CYP2C19*1/*1, he did not have genetic resistance to clopidogrel. Clinical factors include factors associated with inadequate clopidogrel response: compliance, smoking, drug–drug interactions, diabetes mellitus, and obesity. As our patient was a smoker, smoking reinforced the efficacy of clopidogrel (PRU 5). After he quitted smoking, PRU of 72 was obtained. There is no relationship between clopidogrel and hydroxyurea because hydroxyurea is not metabolized by CYP2C19. He did have diabetes mellitus and was not obese. Cellular factors include platelet turnover and CYP activity. In addition, it is important to know whether thrombocytosis has caused secondary von Willebrand disease in ET patients. In the case presented here, the patient’s von Willebrand factor antigen levels and ristocetin cofactor activity levels were evaluated and determined to be within the normal range, meaning that he did not suffer from secondary von Willebrand disease.

We evaluated platelet reactivity using PRU to confirm the efficacy of clopidogrel objectively and to determine the appropriate doses of clopidogrel. We measured PRU according to VerifyNow®. The instrument measures platelet-induced aggregation as an increase in light transmittance and uses a proprietary algorithm to report values in PRU. Anti-platelet treatment regimens need to be within a range that is not too high or too low in order to reduce the risk of ischemic and bleeding events. In general, the therapeutic range of PRU is from 98 to 208 [6]. Previous studies have shown that clopidogrel poor response did not reduce cardiovascular death, myocardial infarction, and stent thrombosis following PCI [7]. One report suggested that all ET patients with recurrent thrombosis showed a poor response to clopidogrel [8]. Therefore, we had to confirm the efficacy of clopidogrel to prevent recurrent thrombosis events.

There are no reports of PRU in patients with thrombocytosis (platelet count >741,000/mm³); therefore, in the case presented here, we measured PRU when the patient’s platelet count had decreased to within 741,000/mm³ using hydroxyurea. PRU values from 5 to 72 were obtained. Considering that lower PRU values are associated with hemorrhage risk, there could have been an event of hemorrhage. However, because the patient was classified as at high risk for recurrent thrombosis by age >80 years and had a history of thrombosis, thrombosis risk was higher than hemorrhage risk [5]. As the therapeutic range of PRU may vary according to the patient’s phenotype, patients with a high risk of thrombosis may need high platelet aggregation inhibition [9]. Therefore, knowing that the patient’s platelet aggregation inhibition levels were high, we decided to continue DAPT with the same drugs at the same doses. To date, he has experienced no thrombosis or hemorrhagic event.

Here we present a case of ACS with ET. Evaluating PRU plays an important role in determining DAPT after PCI especially in ET since the optimal range of platelet inhibition differs between patients.

**Conflict of interest**

The authors declare no conflict of interest associated with this manuscript.

**References**


