High On-Treatment Platelet Reactivity Associated With Prasugrel

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Abstract

Objective: To report a case of high on-treatment platelet reactivity (HTPR) with prasugrel maintenance therapy despite adequate initial platelet response to a loading dose. **Case Summary:** A 51-year-old woman presented to the emergency department complaining of chest pain. She was diagnosed with acute-on-chronic systolic heart failure and non-ST-elevated myocardial infarction (MI). She had a previous MI with bare metal stent placement and was taking aspirin and prasugrel 10 mg daily. Once admitted, a P2Y₁₂ assay revealed HTPR (331 PRU); therefore, prasugrel was reloaded (60 mg). The next day a P2Y₁₂ assay showed adequate platelet reactivity inhibition (118 PRU), so prasugrel 10 mg daily was continued in the hospital and on discharge. Seventeen days after discharge she was readmitted for possible ischemia. On day 3 of admission, a P2Y₁₂ assay revealed HTPR (278 PRU); subsequently, prasugrel was discontinued and ticagrelor started. After 3 doses of ticagrelor, a P2Y₁₂ assay was 97 PRU, so ticagrelor was continued. Five months have passed since discharge. The patient continues to take ticagrelor and has had no further cardiac events. **Discussion:** HTPR indicates hypo- or nonresponsiveness for antiplatelet agents and may result in serious adverse events. HTPR has rarely been reported with prasugrel or ticagrelor. An objective causality assessment of our case revealed a probable association between HTPR and prasugrel. **Conclusion:** Patient education and recognition of signs and symptoms associated with prasugrel HTPR may prevent morbidity and mortality from treatment failure. Additional research may determine incidence, risk factors, and optimal management of HTPR with prasugrel.

Keywords

adherence, adverse drug reactions, antiplatelets, cardiology, cardiovascular drugs

Dual antiplatelet therapy with clopidogrel and aspirin has been a primary treatment strategy for preventing major adverse cardiovascular events in patients with acute coronary syndrome and those undergoing percutaneous coronary intervention (PCI) for more than a decade. When compared to aspirin alone, the combination of clopidogrel plus aspirin significantly reduces the occurrence of these events, including recurrent myocardial infarction (MI) and stent thrombosis.^{1,2} Despite this pharmacologic treatment advance, residual ischemic events continue to be a clinical challenge due to medication nonadherence and variability in clopidogrel responsiveness.

High-on-treatment platelet reactivity (HTPR) is an indicator of hypo- or nonresponsiveness for antiplatelet agents (Table 1). Current guidelines suggest platelet function testing be considered if testing results may alter management or in patients at high risk for poor clinical outcomes.^{3,4} Multiple assays are available to assess platelet reactivity including light transmittance aggregometry, Multiplate Analyzer, the vasodilator-stimulated phosphoprotein-phosphorylation (VASP-P) assay, and the VerifyNow P2Y₁₂ assay.⁵ The definition and cutoff values for determining HTPR vary by

assay; however, specific cutoff values for adequate platelet response have been established for the most commonly used assays (Table 1).⁵⁻⁷ It has been reported that up to 40% of clopidogrel-treated patients have variable responses and experience HTPR.⁸ Patient factors associated with clopidogrel HTPR include type 2 diabetes, body mass index (BMI) ≥ 30 kg/m², renal failure, increased age, drug–drug interactions, and genetic polymorphisms of cytochrome P450 (CYP) enzymes (2C19 [*2], 2C9 [*2,*3], and 3A4).⁹ Because of the interindividual response and relatively high rate of HTPR associated with clopidogrel that may lead to serious adverse outcomes, novel antiplatelet agents, prasugrel and ticagrelor, have been developed. Unfortunately, rare cases of HTPR associated with prasugrel and ticagrelor have recently been described.¹⁰⁻¹⁵ We report the first case of

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Table 1. Platelet Reactivity Cutoff Values for High On-Treatment Platelet Reactivity (HTPR)⁵⁻⁷.

Assay	Cutoff Value for HTPR
LTA, RPR induced by 5 μ mol/L ADP	>46%
LTA, RPR induced by 20 μ mol/L ADP	>64.5%
Multiplate Analyzer	≥ 468 AU
VASP-P	PRI > 50%
VerifyNow P2Y ₁₂	PRU > 235

Abbreviations: ADP, adenosine diphosphate; AU, arbitrary aggregation units; LTA, light transmittance aggregometry; PRI, platelet reactivity index; RPR, residual platelet reactivity; PRU, platelet reactivity unit; VASP-P, vasodilator-stimulated phosphoprotein-phosphorylation.

documented HTPR with prasugrel maintenance therapy despite initial response to a loading dose.

Case

A 51-year-old African American woman weighing 113 kg and standing 162.5 cm (BMI 42.8 kg/m²) was transported to the emergency department (ED) of an 865-bed level 1 trauma center with a chief complaint of chest pain. During transport the patient was hypertensive (215/120), and an electrocardiogram (ECG) showed normal sinus rhythm (NSR) with T wave inversion in V1 and AVL. After arriving to the ED, the patient reported having a nonproductive cough and progressively worsening dyspnea that developed over the past 24 to 48 hours. The patient's past medical history included diabetes, depression, peripheral neuropathy, hypertension, and peripheral arterial disease. Additionally, 18 months prior to presentation she had a left superficial femoral artery (SFA) stent placed and a right SFA artherectomy, for which she was prescribed clopidogrel 75 mg daily. Twelve months later the patient had an MI and underwent PCI with placement of a bare metal stent to the left anterior descending artery (LAD). Clopidogrel was discontinued and dual antiplatelet therapy (ie, aspirin 81 mg daily and prasugrel 10 mg daily) was prescribed. The patient had no known drug allergies, and her active home medication list included sertraline 100 mg daily, gabapentin 300 mg 3 times daily, human insulin 70/30: 75 units twice daily, amlodipine 10 mg daily, aspirin 81 mg daily, atorvastatin 40 mg daily, carvedilol 25 mg twice daily, furosemide 40 mg daily, potassium chloride 10 mEq daily, lisinopril 40 mg daily, prasugrel 10 mg daily, nitroglycerin 0.4 mg sublingual as needed, and acetaminophen 325 mg every 4 to 6 hours as needed. The patient reported medication adherence; however, chart review revealed a history of medication nonadherence. Family and social history were noncontributory. On examination, bilateral crackles throughout both lung fields and 1+ pedal edema bilaterally were identified. A repeat ECG showed a regular heart rate and rhythm without ST-T changes, and remarkable

laboratory results included an elevated troponin I (1.17 ng/mL), B-type natriuretic peptide (BNP; 550 pg/mL), white blood cell count (15×10^9), and blood glucose (240 mg/dL). All other cardiac enzymes and laboratory results were within normal limits. A chest X-ray revealed significant patchy opacities throughout the right lung, stable cardiomegaly, and a small left pleural effusion. The patient was diagnosed with acute on chronic systolic heart failure, non-ST elevated MI, and presumed community-acquired pneumonia for which she received a nitroglycerin IV drip, aspirin PO 325 mg, furosemide IV 40 mg, morphine IV 4 mg, and levofloxacin PO 500 mg. Accordingly, she was admitted to the cardiac intensive care unit (CICU) for further evaluation.

Within hours of being transferred to the CICU, a P2Y₁₂ assay (VerifyNow) was ordered to determine platelet reactivity. Assay results were high (331 platelet reactivity units [PRU]; ≤ 235 for adequate platelet reactivity inhibition), indicating HTPR. Since the patient had a suspected history of nonadherence, she was reloaded with oral prasugrel 60 mg once, and all home medications (except for carvedilol) and levofloxacin were continued. Approximately 19 hours later a repeat P2Y₁₂ assay was drawn and results showed adequate inhibition of platelet reactivity (118 PRU); therefore, a maintenance dose of prasugrel 10 mg daily was started. Unfortunately, the patient continued to be medically unstable with acute decompensated heart failure and pneumonia, so a cardiac catheterization was not performed until hospital day 5. When compared to her earlier cardiac catheterization report, reduced left ventricular ejection fraction, elevated left ventricular end diastolic pressure, and progression of distal LAD disease was found. Consequently, balloon angioplasty was performed and an XIENCE Xpedition drug eluting stent was placed in the LAD. On hospital day 6, the patient was stable and discharged on all home medications (including prasugrel) plus levofloxacin 500 mg daily to complete a 10-day course of antibiotics.

Seventeen days after discharge, the patient was readmitted to the hospital after arriving to the ED complaining of chest pain radiating bilaterally to the shoulders. In the ED, the patient was hypertensive (systolic blood pressure = 214 mm Hg) with an elevated BNP (712 pg/mL). ECG results showed concerning changes in lateral leads as compared to previous ECG results; however, cardiac enzymes were unremarkable. A chest X-ray and myocardial perfusion imaging were inconclusive for an MI or ischemia, so the patient was admitted for further examination. All home medications, including aspirin 81 mg daily and prasugrel 10 mg daily, were continued. On day 3 of the current admission, the patient continued to complain of atypical chest pain with new onset pain radiating to the left side of her jaw. Although a repeat ECG revealed nonsignificant inferior ST elevation and cardiac enzymes were negative, differences from the baseline ECG were noted, so heparin and

nitroglycerin drips were initiated and continued for 48 hours for possible ischemia. Also at this time, a repeat P2Y₁₂ assay was performed that showed HTPR (278 PRU). Since this level was consistent with HTPR and drawn after 3 observed in hospital doses, prasugrel therapy was discontinued and oral ticagrelor 90 mg every 12 hours was started. After 3 doses of ticagrelor, a P2Y₁₂ assay was 97 PRU, showing adequate inhibition of platelet reactivity. Once stabilized, the patient was transferred to inpatient rehabilitation and discharged home 2 weeks later on dual antiplatelet therapy (ticagrelor 90 mg every 12 hours and aspirin 81 mg daily) in addition to her home antihypertensive and congestive heart failure regimen. Five months have passed since discharge. The patient continues to take ticagrelor and has had no further cardiac events.

Discussion

In the case described, the patient had adequate inhibition of platelet reactivity (118 PRU) after receiving a loading dose (60 mg once) of prasugrel; however, after approximately 3 weeks of maintenance therapy (10 mg daily), with the last 3 maintenance doses documented as given in the hospital medical record, a repeat assay showed HTPR (278 PRU). Application of the Naranjo probability scale¹⁶ to our patient case yielded a score of 6 out of a possible 13, indicating a probable association between HTPR and prasugrel. Specifically this case was scored as a probable association as the patient had a similar previous event, other reports of HTPR with prasugrel exist, HTPR was confirmed by VerifyNow P2Y₁₂ assay, there was a temporal association, and HTPR responded when transitioned to ticagrelor. The adverse drug event was reported through our institution's adverse drug event reporting program and to the MedWatch program of the Food and Drug Administration. Our case highlights response variability with prasugrel resulting in HTPR.

Prasugrel is a novel antiplatelet agent that is rapidly activated by esterase-mediated hydrolysis and a single CYP oxidative step. The efficient transformation of prasugrel to its active metabolite through a single CYP oxidative step results in faster, less variable, and more potent platelet inhibition than clopidogrel. As prasugrel has more efficient metabolism with less reliance on CYP activation, it is associated with fewer drug-drug interactions than clopidogrel.^{17,18} In the TRITON-TIMI 38 trial prasugrel plus aspirin produced a significant reduction in MI and stent thrombosis when compared with clopidogrel plus aspirin. Despite this reduction, a portion of patients randomized to prasugrel had residual ischemic events.¹⁹ A subset analysis of TRITON-TIMI 38 revealed that thienopyridine hyporesponsiveness, defined as a VASP platelet reactivity index (PRI) >50%, occurred in 57% of prasugrel-treated patients at 1 to 2 hours post-PCI and 24% at 30 days.²⁰ Reported rates of HTPR

with maintenance prasugrel dosing vary (0% to 24%) and are dependent on sample timing, platelet assay used, threshold for HTPR definition, and patient population sampled.²¹

The clinical significance of HTPR with prasugrel therapy has not been extensively investigated. One prospective, observational study evaluated the relationship between platelet reactivity and ischemic events in prasugrel-treated patients. HTPR, defined as a VASP $\geq 50\%$ within 6 to 12 hours of prasugrel 60 mg load, occurred in 25.2% of patients. Patients with HTPR had a significantly increased risk of ischemic events at 30 days when compared with those with adequate prasugrel response (9.2% vs 0.4%, $P < .001$).²² It should be noted that, despite clinical significance, the overall event rate was low. In our patient case stent thrombosis was not documented; however, the patient did exhibit ischemic changes and chest pain while on prasugrel therapy. Further investigation into the association of HTPR with prasugrel and ischemic events is warranted.

Unlike clopidogrel, risk factors for HTPR with prasugrel are less well established. A registry review of PCI-treated patients on prasugrel maintenance therapy identified obesity (BMI ≥ 30 kg/m²), history of clopidogrel hyporesponsiveness, and a reduced prasugrel maintenance dose of 5 mg as predictors of HTPR.²³ Chronic renal failure with hemodialysis is another potential predictor, with 19% of hemodialysis-dependent prasugrel-treated patients having HTPR in one analysis.²⁴ In our patient the only identified risk factor for HTPR with prasugrel was obesity (BMI = 42.8 kg/m²). Though HTPR with clopidogrel was not documented, the patient did experience an MI while on clopidogrel therapy. It should also be noted that the patient was a poorly controlled diabetic (HbA1c 12%), and diabetes is an established risk factor for increased platelet reactivity.²⁵

Hypothesized mechanisms of HTPR with prasugrel include genetic variations in the CYP enzymes responsible for prasugrel activation (eg, CYP2B6, CYP2C9), P2Y₁₂ receptor polymorphisms, and drug interactions.^{26,27} Specific drug interactions that may result in decreased serum concentrations of prasugrel's active metabolite include strong CYP3A4 inhibitors, ranitidine, and rifampin.²⁸ In our patient no drug interactions were identified that would be expected to affect prasugrel responsiveness. Management options for patients with identified HTPR with prasugrel are currently anecdotal. Reported strategies have included increased prasugrel maintenance dosing (eg, 20 mg daily) and transitioning to ticagrelor.^{13,26} In a preliminary study managing HTPR, the prasugrel maintenance doses were doubled in 4 patient cases and adequate platelet inhibition was achieved without adverse bleeding events.²⁴ Case reports have also demonstrated successful management of prasugrel HTPR with ticagrelor.^{10,12-14} Similar to these previous reports, transitioning our patient to ticagrelor therapy resulted in adequate platelet inhibition without adverse bleeding events.

This case demonstrates HTPR with prasugrel maintenance therapy following previously documented responsiveness to prasugrel loading. A PubMed Search (1966-July 2014) using the search terms high on-treatment platelet reactivity, HTPR, clopidogrel, prasugrel, and ticagrelor revealed 5 other cases of possible HTPR with prasugrel.¹⁰⁻¹⁴ In 4 of these cases, HTPR was documented during prasugrel maintenance dosing; in 1 case HTPR was documented following a single prasugrel loading dose. The PRINCIPLE TIMI-44 trial previously documented that HTPR could occur with prasugrel maintenance dosing despite initial response to prasugrel loading as no patients demonstrated HTPR 24 hours postload but 2.4% to 8.1%, depending on the assay used, had HTPR with maintenance dosing.²⁹ Similarly, our patient demonstrated appropriate platelet inhibition following a single prasugrel loading dose but subsequently developed HTPR during prasugrel maintenance therapy. Prasugrel hyporesponsiveness was associated with chest pain and ischemic ECG changes requiring ICU admission. This case report is consistent with the current literature in that HTPR resolved with transition to the non-thienopyridine P2Y₁₂ inhibitor ticagrelor. While adequate platelet inhibition was demonstrated following 3 ticagrelor doses, it is unclear if this response will be maintained. It should be noted that a case report of stent thrombosis and HTPR with ticagrelor has recently been published.¹⁵ Given the patient's history, consideration will be given to reevaluating platelet reactivity with ticagrelor maintenance dosing.

Prasugrel therapy has rarely been implicated with HTPR. However, patients receiving prasugrel who present with signs and symptoms or specific adverse cardiovascular events (eg, ischemic ECG changes, chest pain, MI) should be evaluated for HTPR, and therapy modified based on the assay results. Patient education and early recognition of signs and symptoms associated with prasugrel HTPR by health care providers may help prevent morbidity and possible mortality from treatment failure. Further research is necessary to determine the incidence, risk factors, clinical significance, and optimal management of HTPR with prasugrel.

Conclusion

A 51-year-old woman developed HTPR with prasugrel maintenance therapy despite initial response to a loading dose. Decreased responsiveness to prasugrel was associated with ischemic ECG changes and chest pain. HTPR resolved with discontinuation of prasugrel and transition to ticagrelor.

Declaration of Conflicting Interests

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