Between a rock and a hard place: a high-risk patient with resistance to multiple P2Y₁₂ antagonists

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Impaired response to P2Y₁₂ receptor antagonists, such as clopidogrel and prasugrel, can have devastating consequences for patients that require prolonged or indefinite therapy with these agents, including those with a left ventricular assist device (LVAD). While loss-of-function (LOF) alleles in *CYP2C19* have been elucidated as contributing to high on treatment platelet reactivity (HTPR) during clopidogrel therapy, genetic variations in the metabolic pathway of prasugrel have not been shown to elicit this same effect. Moreover, limited studies have assessed the effect of coexisting genetic variations in pharmacokinetic and pharmacodynamic pathways. Herein, we report a left ventricular assist device patient exhibiting high on treatment platelet reactivity during clopidogrel and prasugrel therapy. Genotyping revealed variants in pharmacokinetic (*CYP2B6*), and pharmacodynamic pathways, with multiple variants in P2Y₁₂, the target receptor.

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Heart failure (HF) is one of the leading causes of morbidity and mortality in the USA. It affects 5.7 million patients, with an increase to 8 million expected by 2030 [1]. In approximately 150,000 to 250,000 patients with end stage HF, medical management is no longer sufficient. While cardiac transplantation remains the gold standard therapy for end stage HF, limited donor organ availability restricts the number of patients that can receive a transplant. Left ventricular assist devices (LVADs) are becoming increasingly used as destination therapy (DT), in patients who do not meet the criteria for a transplant, or as bridge to transplant (BTT), in patients on the transplant list [2].

While LVADs are a life-saving measure for HF patients, thromboembolic complications including stroke and pump thrombosis significantly increase morbidity and mortality [3]. Current guidelines recommend anticoagulation with warfarin with a target international normalized ratio (INR) of 2–3, and aspirin (81–325 mg/day). Additional antiplatelet agents, typically a thienopyridine agent (e.g., clopidogrel), are added based on clinical needs of the patient. Herein, we describe a LVAD patient experiencing repeated pump thrombosis requiring escalation of antithrombotic therapy exhibiting nonresponsiveness to clopidogrel and prasugrel.

Case

A 25-year-old African-American female developed postpartum cardiomyopathy, with an ejection fraction of 15–20%. Her past medical history was significant for rheumatoid arthritis. For 2 years, she maintained on digoxin, metoprolol, spironolactone, losartan and furosemide, until she presented with acute decompensated HF and cardiogenic shock. After evaluation, she underwent placement of a HeartMate II LVAD.

Her early postsurgical period was complicated by right ventricular dysfunction and ventricular tachycardia requiring prolonged inotropic support with milrinone, sildenafil and amiodarone. Antithrombotic therapy including warfarin and aspirin was initiated.

Two weeks later, she developed multiple hematomas in her mediastinal and intra-abdominal cavities in the setting of a supratherapeutic INR of 8.3. She was treated with vitamin K and fresh frozen plasma. No surgical interventions were performed. After resolution of the hemorrhage, she was discharged on aspirin (325 mg daily) and warfarin (with target INR 2–3).

Over the next 2 years, she was hospitalized numerous times for recurrent infections including driveline infections with methicillin resistant *Staphylococcus aureus* (MRSA) and *Proteus mirabilis* and candidemia. These events and the associated extended treatment with antibiotics and antifungals made warfarin management difficult, requiring frequent dose adjustments. Throughout the duration of the therapy, response to aspirin was consistent as demonstrated by whole blood platelet aggregation (WBPA) assays using arachidonic acid (AA) as the agonist.

Two years postimplant, at a routine clinic visit, labs revealed elevated lactate dehydrogenase (LDH; 619 units/l), elevated plasma free hemoglobin (80 mg/dl) and an INR of 2.8. Due to concern for pump thrombosis, secondary to elevated hemolysis labs, clopidogrel (75 mg daily) was added to her antiplatelet regimen as adjunctive therapy, in an attempt to decrease her risk of thromboembolic complications. However 4 days later she was admitted for suspected pump thrombosis. Relevant labs included LDH (1173 units/l), INR of 2.3 and platelet aggregation demonstrating response to aspirin, but not clopidogrel (assessed via WBPA using adenosine diphosphate [ADP] as the agonist). During the hospitalization, she was maintained on eptifibatide, aspirin and warfarin. After her LDH and plasma-free hemoglobin normalized, she was discharged on aspirin, clopidogrel and warfarin. As repeat platelet function testing confirmed no therapeutic response to clopidogrel, clopidogrel was discontinued and prasugrel 10 mg daily, was initiated. Prasugrel was selected over ticagrelor due to cost constraints. At this time, no generic formulation of ticagrelor was available on the market.

Two weeks later, the patient was readmitted with suspected pump thrombosis, in the setting of elevated LDH (1629 units/l), elevated plasma free hemoglobin (50 mg/dl), INR (2.6) and platelet aggregation demonstrating response to aspirin, but not prasugrel. This result was confirmed through repeat testing 12 days later, with adherence validated by medication administration records. Over the course of her admission, she was continued on aspirin, prasugrel and warfarin, and ultimately discharged on the same regimen.

One week after discharge, she developed shortness of breath, fatigue and dark urine. On presentation, laboratory studies revealed elevated LDH (2221 units/l), elevated plasma free hemoglobin (230 mg/dl) and a supratherapeutic INR (5.2). She was admitted again for suspected pump thrombosis and was initiated on heparin. Despite therapeutic heparin, her hemolysis labs remained elevated. Due to her complications, her LVAD was exchanged with another HeartMate II device.

Post-LVAD exchange, she developed sepsis with bilateral pneumonia and a right pleural effusion resulting in significant volume overload resistant to diuretic therapy. She developed hypotension requiring therapy with multiple vasopressors and inotropes, acute kidney injury with oliguria and was placed on continuous renal replacement therapy (CRRT). Despite treatment, her condition deteriorated to multisystem organ failure and she died 3 weeks after her LVAD exchange.

Methods & results

Platelet aggregation

AA and ADP-induced WBPA were used to determine platelet reactivity. This testing exposes the patient's platelets to the aforementioned agonists. If the platelets are functioning normally, they will aggregate on the device's electrodes causing electrical resistance/impedance (measured in Ohms). Per the manufacturer's instructions, a measurement of <6 Ohms is consistent with sufficient responsiveness of an ADP receptor antagonist and <5 Ohms for an AA antagonist. Results were verified by a board certified pathologist and reported as a qualitative result of responsive or nonresponsive to collagen, ADP and AA.

Our patient demonstrated consistent response to aspirin, evidenced by nonresponse to AA on 33 of 33 tests performed over a 2-year period (data not shown). For all 33 tests, consistent response to collagen was also observed. However, inconsistent response to ADP was noted during treatment for both clopidogrel and prasugrel (Figure 1). Over a period of 2–3 months, 11 WBPA tests were performed. Of these, three demonstrated therapeutic response, while eight demonstrated no response. One case of response occurred while the patient was receiving eptifibatide (platelet receptor GIIb/IIIa antagonist) inpatient.

Figure 1. Adenosine diphosphate-induced whole blood platelet aggregation results. (+) denotes response to ADP, no therapeutic response to P2Y₁₂ receptor antagonists. (-) denotes no response to ADP, therapeutic response to P2Y₁₂ receptor antagonists.

ADP: Adenosine diphosphate.

Table 1. Genotyping results.

Gene (SNP)	Genotype	Metabolizer phenotype
CYP2C9		
CYP2C9*2 (c.430C>T; rs1799853)	C/C	Normal activity
CYP2C9*3 (c.1075A>C; rs1057910)	A/A	Normal activity
CYP2C19		
CYP2C19*2 (c.681G>A; rs4244285)	G/G	Normal activity
CYP2C19*3 (c.636 G>A; rs4986893)	G/G	Normal activity
CYP2C19*17 (c. -806 C>T; rs12248560)	†	
CYP2B6		
CYP2B6*5 (c.1459 C>T; rs3211371)	C/C	Normal activity
CYP2B6*6 (c.516 G>T; rs3745274)	T/G	Decreased activity
CYP2B6*27(c.593 T>C; rs36079186)	T/T	Normal activity
P2Y₁₂		
(c.36 T>G; rs6809699)	C/C	
(c. -15 + 742C>T; rs2046934)	G/A	
(c. -180 + 2739T>C; rs6787801)	G/A	

† Genotyping for CYP2C19*17 returned as a no call.

Genetic studies

Genotyping for *CYP2C19**2, *CYP2C19**3, *CYP2C19**17, *CYP2B6**5, *CYP2B6**6, *CYP2B6**27, *CYP2C9**2, *CYP2C9**3 and the *P2Y₁₂* SNPs rs6809699, rs2046934 and rs6787801 was performed as part of a research study under the approval of the University of Alabama at Birmingham's (UAB) institutional review board. Genotyping results are presented in Table 1. Genetic testing revealed variants in *CYP2B6* and *P2Y₁₂* with no variants detected in either *CYP2C19* or *CYP2C9*.

Discussion

LVADs are a viable alternative and bridge to cardiac transplantation, given the limited availability of donor organs, as well as factors limiting transplant candidacy, such as obesity or other comorbid conditions. Although life-saving for many patients, thrombotic complications (pump thrombosis, systemic thromboembolism) remain a significant issue, necessitating indefinite warfarin and antiplatelet therapy [4–6].

Optimal medication management is critical to maintain pump function and minimize the risk of thromboembolic and hemorrhagic complications. However, responsiveness to medications is variable across patients and within a patient across time. At UAB, all LVAD patients undergo weekly INRs and monthly platelet aggregation studies to monitor and optimize therapy. The frequency of these studies can differ based on a patient's clinical presentation. For patients with an LVAD, resistance or complete unresponsiveness (i.e., high on treatment platelet reactivity [HTPR]) to antiplatelet medications can have devastating consequences. While HTPR is more frequently observed

Figure 2. Pathways of activation and metabolism for the P2Y₁₂ receptor antagonists.

in patients treated with clopidogrel, [7] it has also been reported in prasugrel treated patients. Up to 19% of patients receiving hemodialysis exhibit HTPR during prasugrel therapy [8]. Additionally, 25% of patients treated with prasugrel after acute coronary syndrome displayed HTPR. Compared with patients demonstrating adequate response to prasugrel, patients with HTPR have higher rates of thrombotic events [9]. Major factors contributing to HTPR during clopidogrel therapy include poor compliance, inadequate dosage, age >63 years, BMI >30 kg/m², diabetes, reduced ejection fraction (EF <55%), reduced renal function (serum creatinine >1.1 mg/dl) and genetic variations [10,11].

Clopidogrel, prasugrel and ticagrelor are agents that bind and inactivate the P2Y₁₂ receptor on platelets, leading to inhibition of ADP-induced platelet activation and platelet aggregation. Clopidogrel and prasugrel are both prodrugs and hepatic metabolism is required for activation. Clopidogrel has been shown to exhibit high rates of inter-individual variability, with 4–30% of patients demonstrating inadequate response [12,13]. Cytochrome P450 CYP2C19 plays a major role in the activation of clopidogrel, with lesser contribution from CYP2B6, CYP1A2, CYP3A4/5 and CYP2C9 [14–16]. Up to 30% of patients harbor loss-of-function (LOF) alleles in *CYP2C19*. LOF variants in *CYP2C19* have been consistently associated with lower platelet inhibition, higher platelet reactivity and increased risk of major adverse cardiovascular outcomes in clopidogrel-treated patients [17]. Prasugrel displays lower rates of variability, and a stronger antiplatelet response than clopidogrel [18]. Bioactivation of prasugrel is mainly through CYP3A4 and CYP2B6, with CYP2C9 and CYP2C19 having a minor role [19,20]. Ticagrelor is a reversible, direct acting antagonist of the P2Y₁₂ receptor, with CYP3A4/5 serving as the major metabolic pathway. Figure 2 depicts the processes each agent must go through before binding the P2Y₁₂ receptor.

Given the prevalence of LOF alleles in genes coding drug-metabolizing enzymes, most investigations focus on genes that influence pharmacokinetic variability. However, as we demonstrate in this case report, it is important to assess genetic underpinnings of pharmacodynamic variability. While some studies have analyzed the co-contribution of genetic factors related to pharmacokinetics and pharmacodynamics, these were primarily performed in patients with HTPR treated with clopidogrel, not ticagrelor and prasugrel. Variants in *CYP2C19* and *P2Y₁₂* or a combination thereof, were primarily assessed. Both *CYP2C19* and *P2Y₁₂* variants were found to impact residual platelet reactivity in patients treated with clopidogrel [21]. Furthermore, other investigations have found that variation in the *P2Y₁₂* SNP rs2046934, in combination with either *CYP2B6*9* or *CYP2B6*1B*, was associated with poor response to clopidogrel; with carriers of variants in *P2Y₁₂* and *CYP2B6*9* exhibiting the highest levels of ADP-induced platelet aggregation out of all studied groups [22].

Mega *et al.* demonstrated that variation in pharmacokinetic genes (*CYP2C19*, *CYP2C9*, *CYP2B6*, *CYP3A5*, or *CYP1A2*) did not influence prasugrel response [23]. However, the genetic assessment included only pharmacokinetic genes. Genes potentially influencing prasugrel pharmacodynamics (e.g., *P2Y₁₂*) were not interrogated.

Our patient carried three variant alleles, one encoding an enzyme in the metabolic pathway and two in the *P2Y₁₂* receptor. These combined heterozygous variants may explain the observed lack of response to clopidogrel and prasugrel. In instances where there is a lack of response to one of the *P2Y₁₂* receptor antagonists, it is common practice to switch therapy and use another agent in the same class. In this case, ticagrelor would have been the only alternative. However, since this agent acts on the *P2Y₁₂* receptor, it is unknown if ticagrelor would have inhibited platelet reactivity in our patient. As evidenced by the patient's response to eptifibatide, use of an antiplatelet agent with a different mechanism of platelet inhibition could have overcome the observed HTPR. While there are alternative antiplatelet agents available in intravenous formulations, oral options (e.g., aspirin/dipyridamole) are currently limited.

Cases of prasugrel resistance have been reported, and were resolved by changing therapy to ticagrelor. In the first case, the patient had variants in *CYP2C9*, *CYP2B6* and *P2Y₁₂*. While treatment with ticagrelor decreased the HTPR seen with clopidogrel and prasugrel, the patient still experienced higher platelet reactivity than expected [24]. In the second case, variants in both *CYP2B6* and *CYP2C9* were found; however, no genotyping for *P2Y₁₂* was performed [25]. Resistance to clopidogrel, prasugrel and ticagrelor has rarely been reported. A recent case report addressed three patients exhibiting resistance to all three *P2Y₁₂* antagonists. However, the mechanism of resistance was not elucidated and genotyping was not performed [26].

In addition to genetic factors, patient specific factors could have also contributed to the HTPR observed in our patient. High BMI has been found to be independently associated with HTPR during clopidogrel treatment [27]. A study by Small *et al.* found that out of all intrinsic and extrinsic factors examined, body weight played the largest role in prasugrel pharmacokinetics [15]. This patient had a BMI of 49.5 kg/m² (weight 126.2 kg), which may have made her more susceptible to HTPR during treatment. Furthermore, rheumatoid arthritis, recurrent infections and intrinsic factors of the LVAD system, put her at increased risk for thromboembolic complications, independent of her genetic risk factors for impaired medication response.

Herein, we have reported a patient who exhibited resistance to both clopidogrel and prasugrel treatment. The patient carried a variant in *CYP2B6* and multiple variants in *P2Y₁₂*. These instances of nonresponsiveness to multiple *P2Y₁₂* antagonists necessitate the need for further exploration into genetic factors that contribute to observed resistance. Variations that affect the drug target receptor, in combination with variations in the metabolizing enzymes may make the entire drug class ineffective for the patient. In patients requiring prolonged antiplatelet therapy, determining if genetic factors are contributing to a nontherapeutic response could mean the difference between optimal antiplatelet therapy and fatal thrombotic complications.

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Summary points

- Heart failure is a leading cause of morbidity and mortality in the USA.
- Due to limited donor organ availability, left ventricular assist devices (LVADs) have emerged as a viable alternative to transplantation.
- Thromboembolic complications pose a serious risk for LVAD patients, necessitating indefinite antithrombotic therapy with anticoagulant and antiplatelet agents.
- Individual variability in response to these agents can lead to hemorrhagic or thrombotic complications, and have devastating consequences.
- This report encompasses a LVAD patient exhibiting resistance to the P2Y₁₂ antagonists, clopidogrel and prasugrel.
- Genotyping revealed no genetic variants in *CYP2C19* or *CYP2C9*; however, the patient harbored a genetic variant in *CYP2B6*, in addition to multiple variants in P2Y₁₂, the target receptor.
- Most investigations focus on the genetic underpinnings of pharmacokinetic variability. As illustrated in this report, a more comprehensive approach including interrogation of pharmacodynamic genetic variants should be considered.

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