

Use of Prasugrel in a Patient with Clopidogrel Hypersensitivity

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Clopidogrel, a second-generation thienopyridine antiplatelet agent, is considered the standard of care for preventing coronary stent thrombosis in patients diagnosed with ST-segment elevation myocardial infarction (STEMI) who have undergone percutaneous coronary intervention (PCI) with coronary stenting.¹ Emerging evidence has also led to recommendations for clopidogrel therapy in patients with acute coronary syndromes (ACS) even when a noninvasive strategy is employed. Clopidogrel is also indicated for use in patients with peripheral arterial disease and for secondary prevention in stroke.²

Allergic and hematologic complications occurred in approximately 1% of patients receiving clopidogrel in randomized clinical trials.^{2,3} These types of reactions often require discontinuation of the drug and leave the clinician with limited, and frequently undesirable, options, including clopidogrel desensitization as well as ticlopidine and other therapies with less compelling clinical data (ie, warfarin plus aspirin, cilostazol, ticagrelor).⁴ Ticlopidine, a first-generation thienopyridine, is not first-line therapy for reduction of subacute stent thrombosis in coronary stent implantation, because of its adverse effect profile and potential cross-reactivity.^{5,6} The third-generation thienopyridine prasugrel became available in 2009. As with ticlopidine, prasugrel is structurally similar

OBJECTIVE: To report a case of successful use of prasugrel following percutaneous coronary intervention with placement of a bare metal stent in a patient with a documented hypersensitivity reaction to clopidogrel.

CASE SUMMARY: A 61-year-old male with a history of coronary artery disease with coronary stent placement presented with ST-elevation myocardial infarction. The patient had developed Stephens-Johnson syndrome 6 years earlier following clopidogrel administration, characterized by erythematous plaques and subsequent desquamation of the hands and feet; clopidogrel was discontinued and he was subsequently treated with ticlopidine in addition to aspirin. The third-generation thienopyridine prasugrel was initiated as a therapeutic alternative to clopidogrel after placement of a bare metal stent; a 60-mg dose was administered after extubation, followed by 10 mg/day. No signs of allergic reaction were observed in the days, weeks, and months following administration.

DISCUSSION: Thienopyridines, specifically clopidogrel, are the standard of care for prevention of coronary stent thrombosis; however, there are few data available on cross-hypersensitivity between these agents. One study demonstrated that 27% of patients who developed an allergic or hematologic reaction to clopidogrel developed a similar reaction to ticlopidine. Other therapeutic options for patients with clopidogrel hypersensitivity who are undergoing a percutaneous coronary intervention with stent placement include clopidogrel desensitization, warfarin plus aspirin, cilostazol, ticagrelor, and ticlopidine. However, these options are limited by efficacy and/or toxicity. With its approval in 2009, prasugrel has become a potential treatment option.

CONCLUSIONS: Prasugrel may be considered a therapeutic alternative in some patients allergic or intolerant to clopidogrel, but additional data are warranted to make a strong conclusion.

KEY WORDS: allergy, clopidogrel, hypersensitivity, prasugrel, thienopyridine.

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to clopidogrel (Figure 1)⁷; however, little is currently known about its cross-reactivity, as patients with an intolerance or allergy to ticlopidine or clopidogrel were excluded from the registration trials.⁸ There is only one published case report to date describing the successful use of prasugrel in a patient with clopidogrel hypersensitivity.⁹

Author information provided at end of text.

We describe the successful use of prasugrel in a patient who had previously developed Stevens-Johnson syndrome after taking clopidogrel.

Case Report

A 61-year-old white male presented to the emergency department of an outside hospital with a 2-hour history of substernal chest pain and pressure, radiating to both medial arms and the jaw, associated with diaphoresis and nausea. The onset of pain was not immediately preceded by eating or any increased exertion. His history was significant for coronary artery disease, including placement of a drug-eluting stent in the right coronary artery 6 years earlier and a subsequent STEMI with placement of 2 drug-eluting stents in the left circumflex and first obtuse marginal arteries; gastroesophageal reflux disease, with Barrett's esophagus and multiple esophageal ablations; hypertension; and hyperlipidemia. He was known to have allergies to sulfa drugs and clopidogrel; sulfa exposure resulted in a rash. Clopidogrel therapy following his stent placement 6 years earlier yielded a severe reaction suspicious for Stevens-

Johnson syndrome, characterized by fever, rash, and desquamation of skin on the palms and soles. The rash resolved with clopidogrel discontinuation and administration of diphenhydramine. Treatment was subsequently maintained with aspirin and ticlopidine for 9 months without complications. According to the Naranjo probability scale, which was used retrospectively, clopidogrel was the possible cause of the reaction.¹⁰

Home medications prior to the current admission included aspirin 81 mg orally daily, simvastatin 40 mg orally nightly, and omeprazole 20 mg orally twice daily. Family history was significant only for vague knowledge of heart disease on both the maternal and paternal sides, and no known medication allergies other than sulfa drugs and clopidogrel. The patient had smoked 1 pack of cigarettes daily for 45 years and did not use alcohol or illicit drugs.

At the outside hospital, vital signs were normal and results of the physical examination were unremarkable. An electrocardiogram demonstrated ST-segment elevation in the inferolateral leads, and cardiac enzyme levels were elevated, consistent with the diagnosis of an acute STEMI. The patient was given nitroglycerin, aspirin, morphine, and oxygen and was then immediately transferred by helicopter to our facility for emergent cardiac catheterization. At time of admission, the patient's vital signs remained normal and results of the physical examination were unremarkable. The patient was 178 cm and weighed 110 kg. A chest X-ray showed no acute cardiopulmonary pathology. Laboratory tests included a complete blood cell count, basic metabolic panel, lipid panel, and cardiac enzymes. All results were within normal limits except for the following: white blood cell count 13,400 cells/ μ L (reference range 4000-10,000), high-density lipoprotein cholesterol 27 mg/dL (40-60), creatine kinase (CK) 535 U/L (38-120), CK-MB 44.5 ng/mL (0-3), CK-index 8.3% (0-3), and troponin T 0.967 ng/mL (<0.4).

The patient was taken emergently to the cardiac catheterization laboratory; immediately upon injection of iohexol contrast dye into the right coronary artery, he started coughing violently and had mild respiratory distress, presumed to be secondary to an allergic reaction to the contrast dye. Given the immediate need for catheterization and intervention, he was intubated. The remainder of the catheterization was uneventful, and he was found to have 100% occlusion of the mid-left circumflex artery at the site of a prior stent, 70% occlusion of the first obtuse marginal branch, and 50% occlusion of the mid-right coronary artery at the site of a prior stent. The first intervention was thrombectomy with bare metal stent placement and angioplasty of the lesion in the mid-left circumflex artery, with 0% residual stenosis. The second intervention was balloon angioplasty of the 70% occlusion in the first obtuse marginal branch, resulting in 40% residual stenosis. Medications given intravenously during the catheterization were fentanyl 100 μ g,

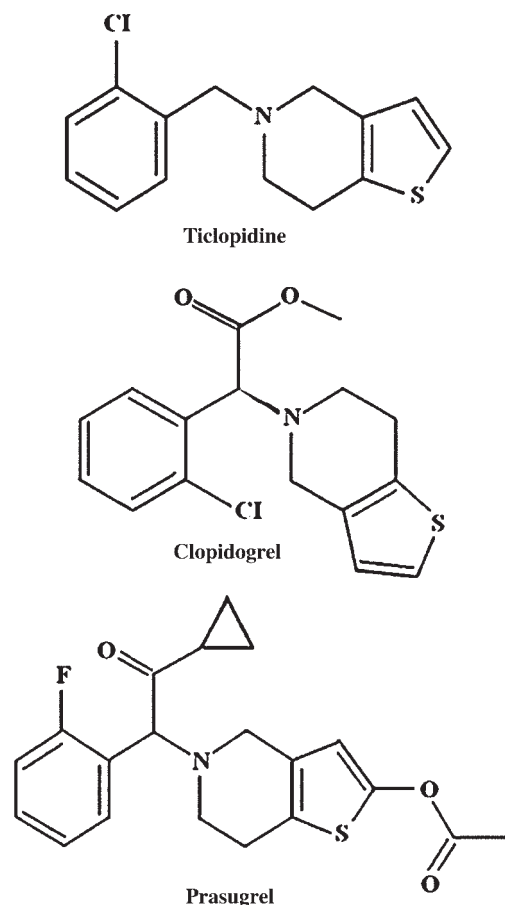


Figure 1. Biochemical structures of thienopyridines.⁷ © The Author 2008. Used with permission of Oxford University Press on behalf of the Association of Physicians.

midazolam 2 mg, abciximab 27 mg, heparin 1000 units, diphenhydramine 50 mg, famotidine 20 mg, and hydrocortisone 100 mg. A total of 85 mL of iohexol contrast dye was administered by catheter into the right and left coronary arteries.

Following cardiac catheterization the patient was extubated; he recovered without incident in the cardiovascular intensive care unit and was transferred to the cardiac ward the following day. Abciximab was continued as an intravenous infusion for 12 hours following the catheterization. Prasugrel 60 mg orally was administered after extubation. He was started on oral therapy with aspirin 325 mg/day, prasugrel 10 mg/day, metoprolol tartrate 25 mg twice daily, simvastatin 80 mg/day, pantoprazole 40 mg/day, prednisone 60 mg/day for 3 days, diphenhydramine 25 mg every 6 hours for 1 day, and famotidine 20 mg every 12 hours for 1 day. On the second hospital day, he was started on lisinopril 5 mg/day orally, nicotine 21 mg/day transdermally, and heparin 5000 units every 8 hours subcutaneously. The remainder of his hospital course was uneventful. A follow-up transthoracic echocardiogram the day after catheterization revealed a left ventricle of normal size with normal systolic and diastolic function, right ventricle of normal size with normal systolic function, atria of normal size, and no significant valvular disease. Medications prescribed on discharge included oral therapy with aspirin 325 mg/day for 1 month and 81 mg/day thereafter, prasugrel 10 mg/day, metoprolol succinate 50 mg/day, lisinopril 5 mg/day, simvastatin 80 mg nightly, and omeprazole 20 mg twice daily; sublingual nitroglycerin 0.4 mg as needed for chest pain; and transdermal nicotine 21 mg/day. He was instructed to postpone any procedures that would require him to forego aspirin or prasugrel, including a previously planned esophageal ablation, for at least 1 month.

The patient was seen in the clinic for follow-up 2 weeks later. He was doing well with no additional symptoms, and had used no tobacco. Vital signs and physical examination results were unremarkable. All of his discharge medications were continued, he was referred to cardiac rehabilitation, continued smoking cessation was encouraged, and he was instructed to return to the clinic in 6 months. No signs or symptoms of hypersensitivity were noted at the 6-month clinic visit.

Given that he had 2 myocardial infarctions in the past, with the most recent related to in-stent thrombosis, the patient was advised to continue aspirin 81 mg orally daily and prasugrel 10 mg orally daily indefinitely.

Discussion

Therapeutic options are limited for patients with clopidogrel hypersensitivity who are undergoing a PCI with stent placement. Warfarin in combination with aspirin has

been studied for use in patients with coronary stents and has been shown to be inferior in preventing stent thrombosis when compared to aspirin plus a thienopyridine.¹¹⁻¹³ Furthermore, the administration of warfarin poses distinct disadvantages, such as frequent laboratory monitoring and the need for patient awareness of several food and drug interactions. The 2008 American College of Chest Physicians (ACCP) guidelines for antithrombotic therapy recommend against the use of a vitamin K antagonist for patients who have undergone PCI who have no other indication for a vitamin K antagonist and recommend triple antithrombotic therapy for patients undergoing stent placement with a strong concomitant indication for a vitamin K antagonist.¹⁴ The 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guidelines for the management of unstable angina (UA)/non-ST-segment elevation myocardial infarction (NSTEMI),¹⁵ as well as the 2004 American College of Cardiology/AHA guidelines for the management of STEMI¹⁶ state that warfarin may be a reasonable alternative for patients who are intolerant of clopidogrel.

Cilostazol has a unique mechanism of action mediated by phosphodiesterase inhibition of cyclic adenosine monophosphate degradation and possesses antithrombotic, vasodilatory, and antiproliferative effects.^{17,18} Cilostazol plus aspirin has been found to be comparable to clopidogrel plus aspirin for reducing the incidence of subacute stent thrombosis or major cardiac adverse events, including death, myocardial infarction, and target lesion revascularization.¹⁹ In this study, the cessation of therapy because of adverse effects was not significantly different between the groups. However, the routine use of cilostazol as an alternative to clopidogrel is less desirable because of numerous drug interactions, twice-daily administration, and overall lack of patient tolerance of commonly reported adverse effects such as headache and diarrhea.²⁰ The most current ACCP guidelines for antithrombotic therapy recommend clopidogrel or ticlopidine over cilostazol after stent placement.¹⁴ Cilostazol is not mentioned in the most current guidelines for the management of UA/NSTEMI or STEMI.^{1,15}

Ticagrelor is a novel reversible P2Y₁₂ inhibitor that has a quicker onset of action and more pronounced platelet inhibition than clopidogrel.²¹ Treatment with ticagrelor, when compared to clopidogrel, significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke in patients with ACS; however, these patients also had higher rates of intracranial bleeding, major bleeding not related to coronary artery bypass graft surgery, and dyspnea.²² Additionally, ticagrelor was not commercially available in the US at the time of our patient's presentation. More data are needed to make the conclusion that ticagrelor may be an alternative to clopidogrel. Ticagrelor is not mentioned in the most current ACCP guidelines for antithrombotic therapy.¹⁴ Similar to cilostazol, ticagrelor is

also not mentioned in the most current guidelines for the management of UA/NSTEMI or STEMI.^{1,15}

Ticlopidine is a therapeutic alternative to clopidogrel and has been successfully used for the prevention of graft occlusion after stent placement and for secondary prevention of stroke and myocardial infarction.²³⁻²⁷ However, ticlopidine use is often limited by its adverse effects: neutropenia, gastrointestinal adverse effects, and, rarely, thrombotic thrombocytopenia purpura.⁶ For these reasons, ticlopidine is listed as an alternative to first-line therapy with clopidogrel in major guidelines for the management of PCI, UA/NSTEMI, and STEMI.^{1,15,16,23-25}

Prasugrel is indicated for patients with ACS undergoing PCI.⁸ The most recent updates of the ACCF/AHA guidelines for management of patients with UA/NSTEMI or STEMI list prasugrel as an alternative to clopidogrel.^{1,15} Prasugrel, the most potent of the thienopyridines, is associated with an increased risk of bleeding and is contraindicated in patients with prior stroke to transient ischemic attack.⁸ In addition to the bleeding risk, data from clinical trials have led to a restriction in its use to patients younger than 75 years and more than 60 kg.^{28,29} In contrast, patients with ACS and diabetes mellitus had a greater reduction in cardiovascular death, nonfatal myocardial infarction, and/or stroke than those without diabetes mellitus.²⁹ Although prasugrel appears to be a promising alternative to clopidogrel, patients with a history of intolerance or allergy to aspirin or thienopyridines (ticlopidine or clopidogrel) were excluded from the TRITON-TIMI 38 study, which leads to uncertainty regarding its use in this patient population.²⁹

This case describes the successful use of prasugrel in a patient with a serious allergy to clopidogrel; however, more information on the cross-reactivity between these 2 agents is needed. It is known that all thienopyridines are structurally similar, but how these similarities relate to hypersensitivity has yet to be elucidated (Figure 1).⁷ Only one study to date has examined the frequency of cross-reactivity between clopidogrel and ticlopidine.⁵ Through retrospective chart review, 76 patients were identified who had an allergic or hematologic adverse reaction to either clopidogrel or ticlopidine and had received both drugs (38 patients allergic to clopidogrel, 24 patients allergic to ticlopidine, and 14 patients allergic to both medications). Of the 52 patients who had previously developed an allergic or hematologic reaction to clopidogrel, 14 (27%) developed an allergic or hematologic reaction to ticlopidine. None of the 76 patients developed a life-threatening reaction to the other thienopyridine. Although this study was retrospective, with a relatively small sample size, it does provide some insight into this clinical situation and is currently the only published data, outside of case reports, on the cross-reactivity between clopidogrel and ticlopidine. Unfortunately, this trial cannot be extrapolated to prasugrel and, to date, there is only one other published case report docu-

menting the safe administration of prasugrel to a patient allergic to clopidogrel.⁹

Our patient, who had a known hypersensitivity to clopidogrel, tolerated treatment with prasugrel without complication. Prasugrel may be considered as an alternative antiplatelet agent when indicated; however, additional data are needed to confirm a lack of cross-reactivity across a broad spectrum of clopidogrel allergy manifestations.

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