

Prasugrel use in a patient allergic to clopidogrel: Effect of a drug shortage on selection of dual antiplatelet therapy

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Dual antiplatelet therapy with aspirin and a thienopyridine (clopidogrel or prasugrel) is currently recommended in patients with unstable angina or non-ST-segment elevation myocardial infarction who have undergone the placement of a drug-eluting stent.¹ Unfortunately, up to 4% of patients treated with clopidogrel develop hypersensitivity reactions, ranging from a mild maculopapular rash to life-threatening reactions including angioedema and Stevens–Johnson syndrome.^{2,3}

Clopidogrel desensitization regimens have been described^{4,5}; however, desensitization is a time-consuming, labor-intensive process that may not be appropriate or effective in all cases of clopidogrel allergy. To date, the most commonly employed alternative to clopidogrel in patients with a history of clopidogrel allergy is ticlopidine, a structurally similar first-generation thienopyridine. In a series of 52 patients with allergy or hematologic adverse effects during clopidogrel use, 38 (73%) were able to tolerate ticlopidine, whereas 14 (27%) had similar non-life-threatening reactions to ticlopidine.⁶

Purpose. A case illustrating multiple considerations in choosing safe and effective dual antiplatelet therapy for a patient with a history of clopidogrel allergy—including concerns relating to a national drug shortage—is described.

Summary. A 75-year-old woman required dual antiplatelet therapy (aspirin plus a thienopyridine) after a cardiac catheterization procedure; during a prior emergency department visit for acute coronary syndrome, she had experienced an allergic reaction within 24 hours of receiving dual therapy including clopidogrel. A team of pharmacy and allergy staff determined that challenging the patient with prasugrel was the best treatment option. Key considerations in the decision-making process included (1) concerns that an alternative thienopyridine, ticlopidine, might be unavailable for long-term outpatient use due to an ongoing national drug shortage, (2) the patient's concomitant use of metopro-

lol (cessation of β -blocker use is recommended for four days before attempted clopidogrel desensitization), and (3) recent reports of the safe use of prasugrel in three patients with a history of clopidogrel allergy. In the case described here, prasugrel administration was effective and did not result in adverse effects; however, the risk of cross-reactivity of clopidogrel and ticlopidine or prasugrel remains largely unknown. The case highlights the importance of careful consideration of a number of patient- and drug-specific factors in the selection of the most appropriate antiplatelet dual therapy for patients with a history of allergic reactions to clopidogrel.

Conclusion. A shortage of ticlopidine prompted the use of prasugrel in a clopidogrel-allergic patient requiring dual antiplatelet therapy. Prasugrel therapy was well tolerated, with no evidence of allergic reaction.

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Prasugrel offers another potential alternative for patients with a history of clopidogrel allergy; however, published data to help assess the safety of administering prasugrel to such patients are limited. A search of MEDLINE 1996 to September 2012 using the meSH

terms *clopidogrel*, *prasugrel*, *drug hypersensitivity* and *cross-reaction* led to the identification of only three cases of the successful use of prasugrel in patients with a history of clopidogrel allergy.⁷⁻⁹

This article describes the case of a patient with a past history of

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clopidogrel allergy who was able to tolerate ticlopidine but was not able to continue therapy due to a national drug shortage. Our choice to initiate alternative dual antiplatelet therapy with aspirin plus prasugrel was influenced by not only the patient's history of clopidogrel allergy but also by a shortage of ticlopidine. This case illustrates some of the challenges posed by the contemporary issue of widespread drug shortages.

Case report

A 75-year-old white woman (61 kg, 170 cm) was referred for cardiac catheterization at Tufts Medical Center after a positive stress test indicating inferolateral ischemia. The initial indication for stress testing was recurrent chest discomfort with shortness of breath, exertional dyspnea, and fatigue. The patient's past medical history was significant for untreated seasonal allergies; hypothyroidism; hypertension; cardiac arrest; myocardial infarction; and coronary artery disease, with stent placement in the left anterior descending coronary artery, the second obtuse marginal branch of the circumflex coronary artery, and the right coronary artery (RCA).

At the time of the hospitalization described here, her oral medications were amlodipine 10 mg daily, aspirin 325 mg daily, calcium with vitamin D, clorazepate dipotassium 15 mg at bedtime as needed for sleep, isosorbide mononitrate 60 mg daily, levothyroxine 75 µg daily, lisinopril 20 mg daily, metoprolol tartrate 100 mg twice daily, and simvastatin 80 mg daily; she was also receiving nitroglycerin 0.4 mg sublingually as needed. The patient reported recent self-discontinuation of ticlopidine (prescribed pursuant to the aforementioned stent placements), which she attributed to its lack of availability from her community pharmacy due to a national drug shortage.

A review of the woman's allergy history revealed clopidogrel-induced

angioedema, described as swelling of the mouth, cheeks, hands, and fingers that occurred within 24 hours of receiving clopidogrel 75 mg during an emergency department (ED) visit for acute coronary syndrome. The angioedema had necessitated a return visit to the ED, where she underwent observation but did not require treatment. Subsequent to that ED visit, the patient was started on ticlopidine, which she tolerated for more than two years. The patient had no other known allergies and reported no history of tobacco or alcohol use.

At the time of catheterization, she had a temperature of 37.6 °C, a heart rate of 69 beats/min, blood pressure of 145/65 mm Hg, a respiratory rate of 16 breaths/min, and a pain score of 5 on a 10-point visual analog scale. The patient's general chemistry values were all within normal limits; the results of a complete blood cell count indicated a white blood cell count of 5800 cells/mm³ with 5% eosinophils, a hemoglobin concentration of 13.2 mg/dL, a hematocrit of 39.1%, and a platelet count of 208,000 platelets/mm³.

Immediately prior to the patient's cardiac catheterization, the medical center's departments of pharmacy and allergy were consulted regarding her history of clopidogrel hypersensitivity. After weighing the available options for dual antiplatelet therapy, prasugrel was recommended by members of both departments as an alternative thienopyridine. The catheterization procedure revealed a lesion causing a 95% blockage of the circumflex artery, as well as 95% distal in-stent restenosis of the RCA. The other previously placed stents were patent. Two drug-eluting stents were placed, and the patient received the following drugs intraprocedurally: an i.v. bolus of bivalirudin 47 mg (diluted to 5 mg/mL in 5% dextrose injection) followed by an infusion of bivalirudin 109.5 mg/hr (delivered from the same solution) for 42 minutes, a 60-mg oral loading dose of prasugrel, 200 µg of intracoronary nitroglycerin, a total of

75 µg of i.v. fentanyl, and a total of 1.5 mg of i.v. midazolam.

After the catheterization procedure, the patient was observed in the coronary care unit, where she remained stable with no signs of an allergic reaction to prasugrel. She was discharged home 24 hours later with instructions to continue her routine medications, with the addition of prasugrel 10 mg orally daily for at least one year and lifelong aspirin therapy (325 mg orally daily). During a follow-up phone call three months later, the patient reported that she was doing well clinically and still taking the prasugrel as prescribed without adverse events.

Discussion

This case illustrates the challenges of providing dual antiplatelet therapy to a patient with a history of clopidogrel allergy. Treatment options for these patients include a clopidogrel rechallenge with concomitant administration of corticosteroids and antihistamines, attempted desensitization to clopidogrel, and administration of an alternative antiplatelet agent.² Each of these options has been successful in selected patients.

The initiation of a three-week tapering course of oral prednisone along with continued clopidogrel therapy was shown to be successful in 62 patients with clopidogrel allergy described by Cheema et al.¹⁰ The majority of these patients had a history of generalized (79%) or localized (15%) exanthematous reactions to clopidogrel; only 2 (3%) had a history of angioedema similar to that reported by our patient.

A variety of clopidogrel desensitization regimens administered over hours to days have been described for use in both inpatients and outpatients.^{4,5} Although successful in the majority of reported cases, desensitization regimens have not been validated for general use, are associated with a risk of breakthrough reactions, and are preferable for use in patients

not concomitantly treated with β -blocker therapy. Before attempting clopidogrel desensitization, it is recommended that β -blocker therapy be withheld for four days to allow for unopposed β stimulation of mast cells should an allergy reaction occur.¹¹

Based on the nature of our patient's hypersensitivity to clopidogrel (i.e., angioedema not requiring treatment) and concomitant β -blocker therapy with metoprolol, a challenge with an alternative antiplatelet agent was deemed to be the preferred treatment option.

Prasugrel is a third-generation thienopyridine that has the thiophene and pyridine ring structures also common to both clopidogrel and ticlopidine. Although these agents share structural similarities, it is not known whether hypersensitivity to clopidogrel is elicited by the parent drug or a reactive metabolite unique to clopidogrel. As such, the degree of risk of cross-reactivity between the thienopyridines is largely unknown. In premarketing clinical trials of prasugrel, patients with documented intolerance or allergy to either clopidogrel or ticlopidine were excluded. Since prasugrel's marketing approval, three cases of the successful use of the drug in patients with a history of clopidogrel allergy have been published.⁷⁻⁹ In two of the three cases, the patients had manifestations of clopidogrel allergy similar to that of our patient (i.e., angioedema)^{7,8}; in another similarity to our patient (who had tolerated ticlopidine for two years before developing adverse effects), one of the three patients had previously been able to tolerate ticlopidine.⁹ In all three cases, the patients were able to tolerate prasugrel for follow-up periods ranging from weeks to six months. Each of these factors influenced our decision to recommend the use of prasugrel in the patient whose case is described here.

In our patient's case, the reinstitution of ticlopidine was not an option.

Since 2009, the original supplier of ticlopidine and five manufacturers of generic ticlopidine have stopped the drug's production, leaving only one known manufacturer of ticlopidine.¹² The potential lack of access to ticlopidine for continued outpatient use precluded our recommendation to resume ticlopidine therapy.

An additional treatment option not explored in this case was the use of ticagrelor, a nonthienopyridine P2Y₁₂ inhibitor. Ticagrelor is currently indicated for the management of acute coronary syndrome (ACS) and recommended over clopidogrel for patients with ACS, with or without percutaneous coronary intervention and stent placement.¹³ Our patient did not have ACS at the time of hospitalization, and ticagrelor was not available on our hospital formulary at that time. Ticagrelor's structural dissimilarity from other thienopyridines suggests that the drug may have a role in managing clopidogrel allergy; however, currently there are no published data to support this contention.

In a patient with a history of clopidogrel allergy, the potential for and degree of risk of cross-reactivity to alternative thienopyridines are largely unknown. In one case series of patients who had experienced allergy or hematologic toxicity to clopidogrel, 73% of the patients were subsequently able to tolerate ticlopidine.⁶ Our patient, who had documented clopidogrel allergy, was able to tolerate ticlopidine but not able to continue therapy due to a national drug shortage, prompting a decision to use prasugrel, which was well tolerated. In this time of multiple drug shortages, current and potential future interruptions in product availability must be a consideration when making clinical decisions regarding dual antiplatelet drug therapy.

Conclusion

A shortage of ticlopidine prompted the use of prasugrel in a clopidogrel-allergic patient requiring

dual antiplatelet therapy. Prasugrel therapy was well tolerated, with no evidence of allergic reaction.

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