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CASE REPORT

Use of prasugrel in the setting of clopidogrel hypersensitivity: Case report and systematic review of the literature

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Abstract

Allergic reactions to clopidogrel soon after coronary stent implantation pose an important and challenging clinical problem. We describe a 44-year-old man who developed a diffuse maculopapular rash four days after initiation of clopidogrel with drug-eluting coronary stent placement. An initial treat-through strategy was unsuccessful due to patient intolerance to corticosteroids. Because of persistent hypersensitivity, clopidogrel was substituted with prasugrel which was continued successfully for one year without reaction. A systematic review of the literature was performed which identified 10 prior case reports of patients with clopidogrel hypersensitivity who were subsequently treated with prasugrel. Patient characteristics and clinical outcomes of these patients plus the current case were reviewed. There were 9 men and 2 women with ages from 44 to 76 years. All patients had undergone coronary stent procedures. Prasugrel was successfully used without cross-reactivity in 9 of the 11 patients (82%). Cross-reactivity was reported in two patients who developed hypersensitivity reactions to prasugrel similar to those experienced on clopidogrel. In conclusion, prasugrel can be used successfully in most patients with a history of clopidogrel hypersensitivity. However, potential cross-reactivity between these two thienopyridines may occur in some patients.

KEYWORDS

Antiplatelet drugs, clopidogrel, hypersensitivity, prasugrel, thienopyridine

History

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Introduction

Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel plays an essential role in preventing coronary stent thrombosis [1]. Furthermore, DAPT is beneficial after thromboembolic events such as acute coronary syndromes and stroke [2]. Clopidogrel hypersensitivity reactions occur in 2–6% of treated patients and lead to its discontinuation in 1–2% of cases [3–6]. Typically, allergic manifestations develop during the first two weeks of therapy. Discontinuation of clopidogrel soon after percutaneous coronary intervention (PCI) is especially problematic due to the risk of stent thrombosis.

Various approaches have been proposed to manage patients with clopidogrel hypersensitivity. These include conventional desensitization methods and treating-through techniques with corticosteroids and antihistamines which are effective in approximately 90% of patients and allow continued long-term therapy with clopidogrel. An alternative strategy is to discontinue clopidogrel and substitute a different P₂Y₁₂ inhibitor. In this case report, we describe the successful use of prasugrel in a patient with clopidogrel hypersensitivity after a treat-through approach with corticosteroids failed.

Case report

A 44-year-old man with type 2 diabetes, hypertension, dyslipidemia, and tobacco abuse presented with escalating chest pain.

Pharmacologic stress testing demonstrated anterior ischemia. Cardiac catheterization was performed and a drug-eluting stent was placed to treat a severe lesion in the left anterior descending coronary artery. DAPT with aspirin and clopidogrel was initiated. The patient had no history of previous drug allergy. On the fourth day of clopidogrel therapy, the patient developed a pruritic, diffuse maculopapular eruption on his arms, back, chest, and scalp. An initial plan was to “treat through” the drug reaction with a 6-day methylprednisolone taper (Medrol dosepak) and antihistamines without discontinuation of clopidogrel. However, the patient’s rash persisted and he developed intolerable gastrointestinal discomfort and nausea, similar to the patient’s previous experience with steroids. As there were no contraindications, the alternative thienopyridine, prasugrel, was initiated. Clopidogrel and corticosteroids were discontinued. The rash resolved and the patient subsequently went on to successfully complete a one-year course of DAPT without any adverse events.

Systematic review of the literature

A systematic review of the English language literature (through March 2016) was performed using PubMed (MEDLINE), Scopus, Ovid, and Cochrane Central Register of Controlled Trials. No restrictions were placed on publication date. Search terms included: clopidogrel hypersensitivity, prasugrel, and thienopyridine cross-reactivity. References cited by retrieved articles were also reviewed. Inclusion criteria for this review required a prior history of clopidogrel hypersensitivity and subsequent therapy with prasugrel. The primary outcome assessed was a successful therapeutic substitution with prasugrel without hypersensitivity cross-reaction.

Table I. Reported cases using prasugrel in patients with clopidogrel hypersensitivity.

Author (year)	Age (years)	Gender	Cardiac presentation	Stent type	Reaction to clopidogrel	Time of clopidogrel reaction	Follow-up on prasugrel	Outcome with prasugrel
van Werkum (2011) [7]	69	Male	STEMI	BMS	Fever, rash, angioedema	14 days	NR	No reaction
Chopra (2011) [8]	62	Male	ACS	DES	Hives, pruritus, facial and eye swelling	4 days	12 weeks	No reaction
Peppard (2011) [9]	61	Male	STEMI	BMS	Fever, rash, desquamation of palms/soles; Stevens-Johnson syndrome	NR	6 months	No reaction
Raccach (2011) [10]	76	Female	ACS	DES	Rash	NR	1 month	Prasugrel discontinued (rash)
Kanadiya (2011) [11]	52	Male	ACS	DES	Itching, fever, polyarthritis	14 days	9 weeks	No reaction
Coulter (2012) [12]	64	Male	ACS	NR	Fever, polyarthritis	8 days	8 weeks	No reaction
Felix-Getzik (2013) [13]	75	Female	ACS	DES	Angioedema	24 h	3 months	No reaction
Agrawal (2013) [14]	64	Male	ACS	DES	Fever, polyarthritis	4 days	1 month	No reaction
Williams (2014) [15]	72	Male	Elective PCI	BMS	Fever, polyarthritis	14 days	6 weeks	No reaction
Chin (2015) [16]	57	Male	Elective PCI	DES	Urticaria, angioedema	2 h	NR	Prasugrel discontinued (angioedema)
Siu (2016) (this paper)	44	Male	ACS	DES	Rash	4 days	1 year	No reaction

ACS, acute coronary syndrome; BMS, bare metal stent; DES, drug-eluting stent; NR, not reported; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

This systematic review identified 10 case reports of patients with clopidogrel hypersensitivity who were subsequently treated with prasugrel [7–16]. Table I summarizes the clinical features of these patients in addition to the patient of the current report. There were 9 men and 2 women, ages 44 to 76 years. All patients had undergone PCI with coronary stents and 9 of the 11 patients presented with an acute coronary syndrome. Hypersensitivity manifestations included rash or urticaria in six patients, angioedema in three patients, fever/polyarthritis in four patients, and Stevens–Johnson syndrome in one patient. In seven patients, prasugrel was prescribed post-PCI for hypersensitivity soon after clopidogrel initiation. In the remaining four patients, prasugrel was used because of a remote history of clopidogrel hypersensitivity during previous exposure.

Prasugrel was successfully used without cross-reactivity in nine patients (82%). Cross-reactivity was reported in two patients who developed hypersensitivity reactions to prasugrel similar to those experienced with clopidogrel; prasugrel was discontinued in both cases. In these two patients, clopidogrel was successfully reinstituted – one after desensitization and one using a treat-through approach.

Discussion

Clopidogrel hypersensitivity occurs in 2–6% of patients [3–6]. The wide use of clopidogrel in the management of cardiovascular disease necessitates awareness of treatment options in the presence of hypersensitivity reactions. This is most often manifested as a pruritic generalized exanthema but may also present as localized cutaneous reactions, urticaria, angioedema, or systemic symptoms including fever and arthralgias [6]. Clopidogrel hypersensitivity is especially problematic in patients with newly implanted coronary stents. Premature discontinuation of clopidogrel therapy after recent PCI is the most important risk factor for stent thrombosis [1]. Typically, clopidogrel hypersensitivity occurs during the first two weeks after initiation, when drug discontinuation carries the greatest risk for stent thrombosis [3].

Traditional desensitization protocols may successfully enable resumption of clopidogrel but require stopping the drug for a wash-out period while hypersensitivity symptoms resolve [17,18]. Without

clopidogrel discontinuation, treating-through methods with corticosteroids and antihistamines are successful in over 88% of cases, and appear as effective as desensitization [6,19]. While most patients with clopidogrel hypersensitivity can be successfully treated with desensitization or treating-through techniques, a subset of patients will fail or relapse with these approaches. For these patients, alternative strategies are required.

Prasugrel, a third-generation thienopyridine has greater platelet inhibition than clopidogrel [20]. When compared to clopidogrel in patients with acute coronary syndromes undergoing PCI, prasugrel was associated with a significant reduction in cardiovascular events [21]. Prasugrel is contraindicated in patients with prior stroke or transient ischemic attack, age greater than 75 years, weight less than 60 kg, or significant bleeding. With prasugrel's proven cardiovascular efficacy, substitution with prasugrel in instances of clopidogrel hypersensitivity presents a potential therapeutic option. The first-generation thienopyridine, ticlopidine has also been used in these circumstances, but ticlopidine is associated with high risk (27%) for cross-reactivity and potentially serious hematological effects [3,6,22].

Little is known about the rate of cross-reactivity between clopidogrel and prasugrel, as patients with reported allergy to clopidogrel were excluded from enrollment in the TRITON-TIMI 38 trial [21]. The chemical structure of prasugrel bears similarities to clopidogrel, and is a proposed mechanism for hypersensitivity cross-reactivity (Figure 1). Cheema et al. performed skin testing on patients with clopidogrel hypersensitivity, and reported allergenic cross-reactivity in 7 of 42 patients (17%) with prasugrel [6]. Therefore, it remains an important, unsettled clinical question as to whether prasugrel can be used safely in patients with hypersensitivity to clopidogrel.

Our case report highlights the utility of prasugrel in a patient with an allergic reaction to clopidogrel in whom there were no good alternative management options. Since the patient developed a severe rash less than one week after coronary stent placement, desensitization was unfavorable since it would require discontinuing clopidogrel to allow drug washout during the highest risk period for stent thrombosis [19]. An initial treat-through approach was unsuccessful because of intolerable side effects from the corticosteroids. With prasugrel, the patient was able to successfully complete the desired one year course of therapy.

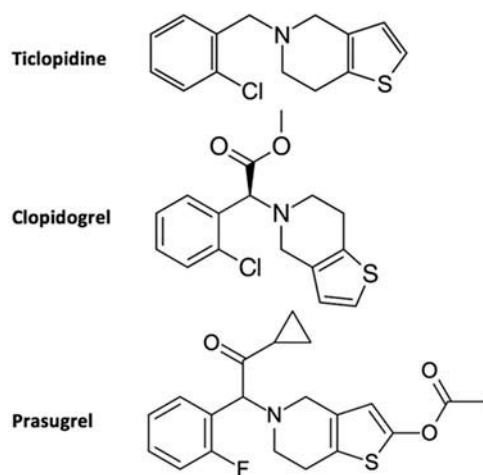


Figure 1. Chemical structures of thienopyridines.

Systematic review of the literature found case reports of 10 patients with clopidogrel hypersensitivity who were treated with prasugrel in addition to our patient [7–16]. Overall, prasugrel was safe and effective, with 9 of the 11 patients (82%) successfully treated without cross-reactivity. However, limitations of the previous case reports should be noted. The median reported follow-up after initiation of prasugrel was only 9 weeks and none of the reports had follow-up beyond 6 months. Our report is the first to demonstrate successful use of prasugrel for the recommended one-year course of DAPT after drug-eluting stents [1]. Our case report is also unique in that prasugrel was not used as the initial option to manage clopidogrel hypersensitivity but was used only after a treat-through approach had failed. None of the previously reported cases attempted either a treat-through or desensitization approach before switching to prasugrel.

Use of prasugrel was unsuccessful in 2 (18%) patients with clopidogrel hypersensitivity due to drug cross-reactivity. This incidence of clinical cross-reactivity coincides closely with the 17% incidence of cross-reactivity by skin testing reported by Cheema et al. [6]. Both of the prasugrel-failure patients went on to be successfully treated by reinstitution of clopidogrel (one with desensitization and the other with a treat-through approach).

Another alternative antiplatelet drug worthy of consideration in patients with clopidogrel hypersensitivity is ticagrelor. Because it is not a thienopyridine, ticagrelor theoretically might be advantageous as a substitute agent. However, the paucity of data on clinical cross-reactivity between clopidogrel and ticagrelor precludes any definitive comparison of the relative efficacy of ticagrelor and prasugrel in this setting. Use of ticagrelor for clopidogrel hypersensitivity has been reported in only four patients. In three of these patients ticagrelor was used successfully without cross-reactivity [23,24]. However, the fourth patient demonstrated hypersensitivity to all three drugs – clopidogrel, ticagrelor, and prasugrel [6]. For most patients with clopidogrel allergy, both prasugrel and ticagrelor are reasonable therapeutic alternatives. Because ticagrelor must be taken twice a day, the once-daily prasugrel might be preferable in patients with medication noncompliance. On the other hand, ticagrelor would be more appropriate in patients with acute coronary syndromes treated medically without PCI and in patients with specific contraindications to prasugrel (prior stroke or transient ischemic attack, age greater than 75 years, or weight less than 60 kg).

Conclusion

Prasugrel represents a viable treatment option in the management of clopidogrel hypersensitivity. While prasugrel can be used successfully

in most patients with clopidogrel hypersensitivity, clinicians should be aware that cross-reactivity between these two thienopyridines may occasionally occur.

Declaration of interest

The authors have no declaration or conflicts of interest

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