

Characterization of Clopidogrel Hypersensitivity Reactions and Management With Oral Steroids Without Clopidogrel Discontinuation

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Objectives	The purpose of this study was to characterize clopidogrel hypersensitivity and describe its successful management with oral steroids without clopidogrel discontinuation.
Background	Hypersensitivity reactions to clopidogrel are poorly understood and present difficulty in management.
Methods	Patients diagnosed with clopidogrel hypersensitivity after percutaneous coronary intervention underwent evaluation and received oral prednisone without clopidogrel discontinuation. Cutaneous testing was performed after completion of clopidogrel therapy for diagnosis and assessment of cross-reactivity.
Results	Sixty-two patients representing 1.6% of the percutaneous coronary intervention population developed clopidogrel hypersensitivity during the study period. The mean age was 62 ± 11 years, 71% of patients were male, and 35% reported prior adverse drug reaction. Clopidogrel hypersensitivity manifested as generalized exanthema in 79%, localized skin reaction in 16%, and angioedema or urticaria in 5% of patients. Biopsy of affected areas demonstrated a lymphocyte-mediated delayed hypersensitivity reaction. Complete resolution of hypersensitivity reaction was observed in 61 patients (98%) with a short course of oral prednisone. Cutaneous testing confirmed delayed hypersensitivity reaction to clopidogrel in 34 (81%) and immediate hypersensitivity in 3 of 42 patients (7%) tested. Allergic cross-reactivity was observed for ticlopidine in 10 (24%), prasugrel in 7 (17%), and both ticlopidine and prasugrel in 3 patients (7%). Histological examination showed lymphocyte-mediated hypersensitivity in abnormal patch test areas.
Conclusions	Clopidogrel hypersensitivity is manifested as generalized exanthema and is caused by a lymphocyte-mediated delayed hypersensitivity in most patients. This can be managed with oral steroids without clopidogrel discontinuation. Allergic cross-reactivity with ticlopidine, prasugrel, or both is present in a significant number of patients with clopidogrel hypersensitivity. (J Am Coll Cardiol 2011;58:1445–54) © 2011 by the American College of Cardiology Foundation

Clopidogrel is an oral thienopyridine widely used in the management of patients with cardiovascular disease (1–3). In addition, long-term administration of clopidogrel with aspirin is recommended after drug-eluting stent (DES) placement for prevention of late stent thrombosis (4,5). Development of hypersensitivity reactions after clopidogrel administration is a recognized complication and presents difficulty in management. The characteristics and mechanism of clopi-

dogrel hypersensitivity are poorly understood, and treatment options remain limited. Most patients with clopidogrel hypersensitivity have been managed by switching to ticlopidine, until recently when the availability of prasugrel offered another

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alternative. However, ticlopidine or prasugrel may not be suitable for all patients because of allergic cross-reactivity (6,7) and potential serious side effects (8–11). Desensitization protocols have also been described but require clopidogrel discontinuation (12–14). In this report, we characterize morphological and histological features of clopidogrel hypersensitivity and describe successful resolution with oral corticosteroids without clopidogrel discontinuation or desensitization.

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Abbreviations and Acronyms

DES = drug-eluting stent(s)
Ig = immunoglobulin
PCI = percutaneous
coronary intervention

Methods

All patients with suspected clopidogrel hypersensitivity after percutaneous coronary intervention (PCI) at St. Michael's Hospital from July 2006 to March 2010 were referred for focused evaluation and management. Detailed

history and physical examination were performed according to the European Network of Drug Allergy guidelines (15), and assessment of clopidogrel hypersensitivity was conducted as per Naranjo et al. (16). All patients diagnosed with probable or definite clopidogrel hypersensitivity after February 2007 were prescribed a 3-week tapering course of oral prednisone starting at 30 mg twice per day for 5 days followed by a decrease of 5 mg/day every 3 days for 15 days. Diphenhydramine 25 to 50 mg every 6 to 8 h was prescribed for pruritus if present. Long-term follow-up was completed in all patients by office visit.

Hematologic analysis. Complete blood counts with automated differential for leukocyte, lymphocyte, eosinophil, and platelet count were obtained before initiation of clopidogrel therapy and at 24 h after PCI in all patients as part of routine care and repeated on initial presentation with clopidogrel hypersensitivity.

Platelet aggregation analysis. Venous blood was collected in Vacutainer blood-collecting tubes (BD Canada, Mississauga, Ontario, Canada) containing 3.8% trisodium citrate after the first 3 ml of free-flowing blood was discarded. Measurement of platelet aggregation was carried out less than 120 min after the blood draw with an impedance aggregometer (model 700, Chrono-log Corporation, Havertown, Pennsylvania) using 5 μ M adenosine diphosphate as an agonist. Platelet aggregation studies were performed at initial presentation with clopidogrel hypersensitivity and repeated after 4 to 12 weeks on maintenance clopidogrel therapy. An impedance value ≤ 5 ohms at 6 min identified clinically therapeutic inhibition of platelet aggregation (17).

Histological analysis. Punch biopsy of the clopidogrel hypersensitivity-affected area was performed for histological analysis, except in patients with angioedema or isolated involvement of the face and/or neck. The biopsy tissue was embedded in paraffin after fixation and cut into 4- μ m thick sections. The hematoxylin and eosin-stained sections were used for histological examination under light microscopy. Periodic acid-Schiff staining was performed for detection of fungi.

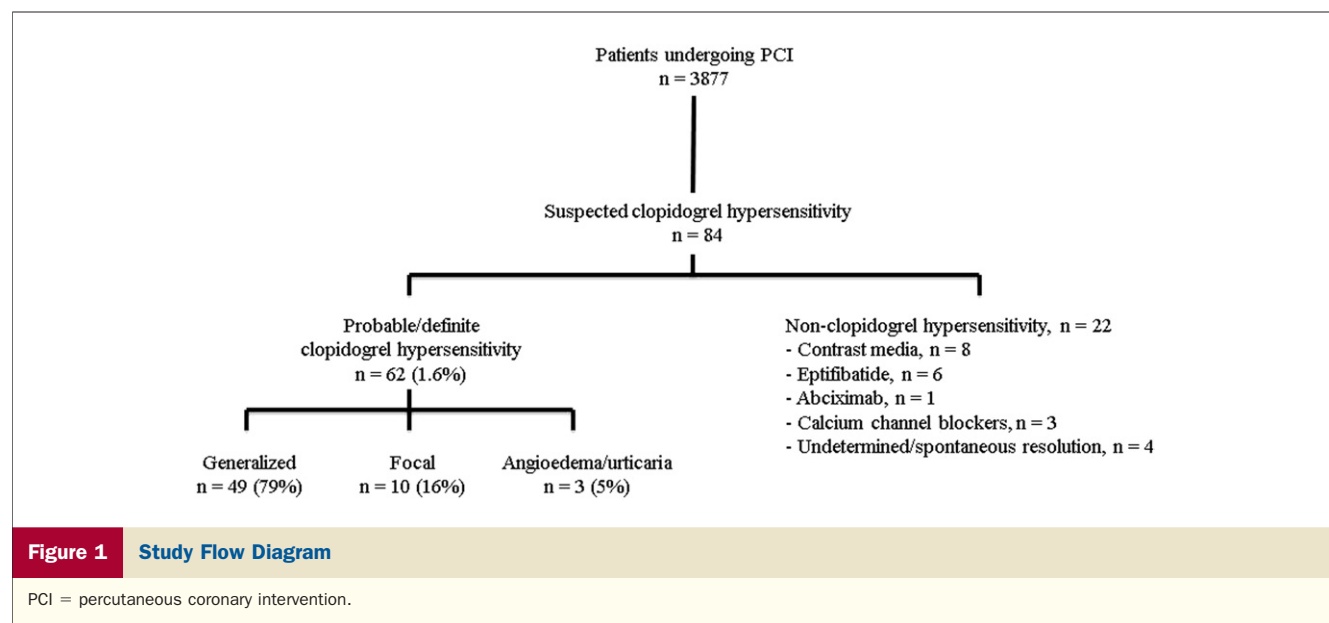
Drug allergy testing. Skin testing for clopidogrel allergy and cross-reactivity with ticlopidine and prasugrel was performed after completion of prescribed clopidogrel therapy and a minimum of 4 weeks drug free. The patients continued aspirin while undergoing drug allergy testing. Skin prick testing on the forearm and intradermal testing on the upper arm were performed with clopidogrel (0.75 mg/ml), ticlopidine (0.625 mg/ml), and prasugrel (0.5

mg/ml) using standard technique. For skin prick testing, a single drop of test agent was placed on the volar surface of the forearm, and the Prick Lancetter (Hollister-Stier Laboratories, Spokane, Washington) was pierced through the drop into the upper dermis and withdrawn. For intradermal testing, a 1-ml syringe with 26-gauge short-bevel needle was used for intradermal injection of test agent (0.2 ml). Sterile saline was used as a negative control, and test sites were examined at 15 and 30 min routinely and at 24 h for reactions appearing after 30 min. A positive skin prick or intradermal reaction was defined as urticarial wheal with surrounding erythema ≥ 3 mm in diameter. For patch testing, clopidogrel (20% in petrolatum alba and 30% in water), ticlopidine (75% in water), and prasugrel (5% in water) were applied using IQ Ultra patch testing chambers (Chemotechnique Diagnostics, Vellinge, Sweden) on the outer surface of the upper arm. The patch was removed at 48 h for scoring at 72 h (18,19). Additional readings were performed up to 7 days later for reactions appearing after 72 h. Sterile water and petrolatum alba were used as negative controls for skin (prick and intradermal) and patch testing, respectively. No positive control was used during skin (prick and intradermal) testing.

Statistical analysis. Continuous data are expressed as mean $\pm$ SD, and dichotomous data are expressed as absolute values and percentages. Clopidogrel hypersensitivity onset time was compared across presentation type (generalized rash, focal rash, or angioedema/urticaria) with the Kruskal-Wallis test and between the 2 loading dose (300 mg and 600 mg) groups with the Wilcoxon rank-sum test. Leukocyte, neutrophil, lymphocyte, eosinophil, and platelet counts at baseline, 1 day after PCI, and at clopidogrel hypersensitivity onset were analyzed with repeated-measures analysis of variance; Bonferroni correction was applied for multiple comparisons. All analyses were performed using SAS version 9.1 (SAS Institute, Inc., Cary, North Carolina). A *p* value of <0.05 was considered statistically significant.

Results

A total of 84 patients were referred and evaluated for suspected clopidogrel hypersensitivity during the study period. Sixty-two patients had findings consistent with probable or definite hypersensitivity reactions attributable to clopidogrel. This represented 1.6% (62 of 3,877) of the patient population undergoing PCI during the study period (Fig. 1). Baseline and procedural characteristics of the study sample and PCI cohort are shown in Table 1. The information for presence of asthma, family history of allergy, and prior drug allergy in individual patients was not systemically collected except for patients presenting with clopidogrel hypersensitivity. There were no significant differences in cardiac risk factors, concurrent medications, and procedural variables between patients with clopidogrel hypersensitivity and the entire patient cohort undergoing PCI during the study period except for use of DES (71% in patients with



clopidogrel hypersensitivity vs. 56% in the entire PCI cohort; $p = 0.02$). The recommended minimum duration for clopidogrel therapy was 4 weeks for bare-metal stents and 12 months for DES. All patients with clopidogrel hypersensitivity were able to continue clopidogrel for the recommended minimum duration without recurrence of clopidogrel hypersensitivity after treatment with oral ste-

roids. All patients were continued on aspirin 81 mg per day after completion of clopidogrel therapy.

Clinical outcomes. Clinical follow-up was completed in all patients for a median of 576 days (25th to 75th percentile: 308 to 763 days). During follow-up, there was 1 death, 1 myocardial infarction, and 6 target vessel revascularization procedures. One patient died at 8 months of follow-up after experiencing a stroke. One myocardial infarction occurred at 8 months on continued dual antiplatelet therapy with aspirin and clopidogrel, and 3 patients with target vessel revascularization had received bare metal stents. All patients had completed the minimum recommended duration of clopidogrel therapy. None of the study patients suffered from stent thrombosis.

Clinical manifestations of clopidogrel hypersensitivity. Patients with clopidogrel hypersensitivity presented with 3 distinct clinical patterns. Group 1 contained 49 patients (79%) who developed a generalized, pruritic, exanthematous rash predominantly affecting the trunk with or without involvement of the upper and lower extremities (Fig. 2). The rash was limited to the chest, abdomen, and back in 40 (65%) and extended to the proximal part of the upper and lower extremities in 9 patients (15%). Group 2 consisted of 10 patients (16%), in whom the rash was limited to a localized area in a focal or symmetrical manner (Fig. 3). These reactions involved the neck, face, back, axilla, palm of the hand, and/or sole of the feet. Group 3 had 3 patients (5%); 2 presented with symptoms and signs of angioedema, with swelling of the tongue and lips, and 1 with generalized urticaria (Fig. 4). Two patients (3%) reported symptoms of fever and arthralgia. The median time to development of clopidogrel hypersensitivity after clopidogrel use was 5 ± 1 days for group 1, 5 ± 2 days for group 2, and 1 ± 0 days for group 3 ($p = 0.01$). There was no difference in time to clopidogrel hypersensitivity onset or severity of allergic

Table 1 Baseline and Procedural Characteristics

	Clopidogrel Hypersensitivity Patients (n = 62)	Entire PCI Cohort (n = 3,815)	p Value
Baseline characteristics			
Age, yrs	62 $\pm$ 11	62 $\pm$ 11	NS
Female	18 (29)	1,145 (30)	NS
Diabetes	22 (35)	1,012 (26)	NS
Hypertension	49 (79)	3,128 (82)	NS
Dyslipidemia	56 (90)	3,510 (92)	NS
Prior MI	15 (24)	763 (20)	NS
Asthma	3 (5)	NA	—
Family history of allergy	10 (16)	NA	—
Prior drug allergy	22 (35)	NA	—
Concurrent medications			
Beta-blockers	51 (82)	3,052 (80)	NS
ACE inhibitors	41 (66)	2,671 (70)	NS
Aspirin	62 (100)	3,777 (99)	NS
Statin	56 (90)	3,586 (94)	NS
Procedural characteristics			
Clopidogrel loading			
300 mg	20 (32)	1,106 (29)	NS
600 mg	39 (63)	2,289 (60)	NS
No. of vessels	2 $\pm$ 1	2 $\pm$ 1	NS
No. of stents	2 $\pm$ 1	2 $\pm$ 1	NS
Drug-eluting stent use	44 (71)	2,136 (56)	0.02

Values are mean $\pm$ SD or n (%).

ACE = angiotensin-converting enzyme; MI = myocardial infarction; NA = not available; NS = nonsignificant; PCI = percutaneous coronary intervention.

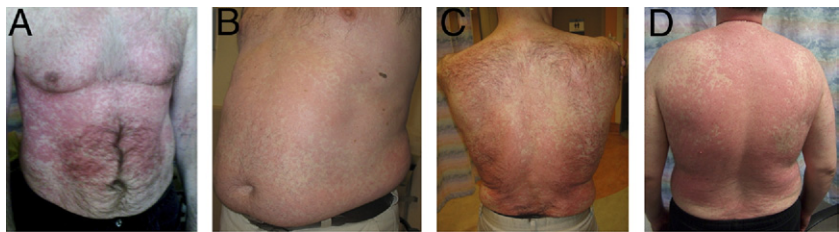


Figure 2 Clopidogrel Hypersensitivity Manifesting as Generalized Exanthema

Generalized exanthema affected the chest, abdomen, and upper and lower back after clopidogrel administration with varying severity (A to D).

reaction for patients receiving a 300- or 600-mg loading dose ($p = \text{NS}$). The findings are summarized in Table 2. **Oral steroids for clopidogrel hypersensitivity.** All patients were able to complete the oral prednisone as prescribed, and 59 patients (95%) reported complete resolution of clopidogrel hypersensitivity at 5 ± 2 days. The first patient with angioedema was hospitalized and monitored in an intensive care unit while oral steroids were given, but this treatment was accomplished without stopping clopidogrel. All other patients were treated in the outpatient setting. One patient with incomplete response and one with recurrence after tapering of steroids required a second course of oral steroids, with successful resolution. One patient (Fig. 3F) with hyperkeratotic psoriasiform rash affecting the soles of both feet continued clopidogrel and topical steroids with partial

response until completion of prescribed clopidogrel therapy. The affected area improved after clopidogrel was stopped. All patients were able to continue clopidogrel for the recommended duration without recurrence of clopidogrel hypersensitivity. Four patients were re-exposed to clopidogrel after drug discontinuation, resulting in recurrence of clopidogrel hypersensitivity in all 4 patients. Oral steroids were prescribed again and resulted in clopidogrel hypersensitivity resolution without clopidogrel discontinuation. There were no significant differences in baseline or procedural characteristics for patients with or without recurrence of clopidogrel hypersensitivity. **Hematologic profile and platelet aggregation studies.** Hematologic counts and platelet aggregation data were available for 48 (77%) and 42 (68%) patients, respectively, and are summarized in Table 3. The neutrophil count was



Figure 3 Clopidogrel Hypersensitivity Manifesting as Localized Reactions

Local reactions after clopidogrel administration. (A) Erythematous and desquamative rash on face. (B) Fixed drug reaction on back. (C) Focal erythema of neck. (D) Symmetrical bilateral erythematous rash in axilla. (E) Symmetrical bilateral desquamation of palms. (F) Symmetrical, bilateral hyperkeratotic psoriasiform lesions on soles.



Figure 4 Clopidogrel Hypersensitivity Manifesting as a Type I Hypersensitivity Reaction

Angioedema (A and B) and urticaria (C) after clopidogrel administration.

significantly higher and lymphocyte count was significantly lower at 1 day after PCI compared with baseline values. The leukocyte and neutrophil counts were significantly higher and lymphocyte count was significantly lower at clopidogrel hypersensitivity onset compared with those at baseline. No significant change in eosinophil counts was present at any

Table 2 Phenotypic Patterns of Clopidogrel Hypersensitivity

Rash distribution	
Generalized	49 (79)
Localized	10 (16)
Angioedema/urticaria	3 (5)
Time to symptom onset after clopidogrel exposure, days*	
Generalized hypersensitivity group	5 ± 2
Localized hypersensitivity group	5 ± 1
Angioedema/urticaria group	1 ± 0
Time to symptom onset after clopidogrel exposure, days†	
600-mg loading dose	5 ± 3
300-mg loading dose	5 ± 2
Systemic symptoms	
Arthralgia	2 (3)
Fever	2 (3)

Values are n (%) or mean ± SD. *p = 0.01 for comparison between groups by Kruskal-Wallis test. †p = NS by Wilcoxon rank-sum test.

time compared with baseline. The platelet count was significantly lower at 1 day after PCI and significantly higher at clopidogrel hypersensitivity onset compared with baseline values. Impedance aggregometry identified clinically therapeutic inhibition of platelet aggregation in 38 (90%) of tested patients. The values (means ± SD) at initial presentation with clopidogrel hypersensitivity and on maintenance clopidogrel therapy were 2.42 ± 2.95 ohms and 2.84 ± 3.75 ohms, respectively.

Histological characterization of clopidogrel hypersensitivity. Punch biopsy of affected areas was performed in patients with generalized (n = 7) and local (n = 6) clopidogrel hypersensitivity. Skin biopsy was not performed in patients with angioedema and urticaria. The microscopic examination of tissue specimens (Fig. 5) showed parakeratosis and spongiotic crusting on the skin surface. There was evidence of epidermal spongiosis, intercellular edema, and acanthosis. Perivascular and interstitial lymphocytes were present, with extension into epidermal layers (lymphocytic exocytosis). Rare eosinophils were seen in the affected areas.

Table 3 Hematologic Findings in Patients With Clopidogrel Hypersensitivity

	Baseline (n = 48)	1 Day After PCI (n = 48)	Clopidogrel Hypersensitivity Onset (n = 48)
Leukocytes, $\times 10^9/l^*$	8.2 ± 2.4	8.6 ± 2.3	10.7 ± 4.0
Neutrophils, $\times 10^9/l^\dagger$	4.95 ± 2.0	5.98 ± 2.0	7.92 ± 4.3
Eosinophils, $\times 10^9/l^\ddagger$	0.21 ± 0.13	0.21 ± 0.15	0.22 ± 0.22
Lymphocytes, $\times 10^9/l^\S$	2.25 ± 0.79	1.78 ± 0.72	1.80 ± 0.77
Platelets, $\times 10^9/l^\parallel$	234 ± 67	215 ± 67	278 ± 92

Values are mean ± SD. Analyzed by repeated-measures analysis of variance with Bonferroni correction. *p = 0.009 (overall); p = 0.009 for baseline versus clopidogrel hypersensitivity onset. †p = 0.006 (overall); p = 0.005 for baseline versus 1 day after percutaneous intervention (PCI); p = 0.003 for baseline versus clopidogrel hypersensitivity onset. ‡p = NS for all comparisons. §p = 0.005 (overall); p = 0.004 for baseline versus 1 day after PCI; p = 0.05 for baseline versus clopidogrel hypersensitivity onset. ||p = 0.001 (overall); p = 0.004 for baseline versus 1 day after PCI; p = 0.026 for baseline versus clopidogrel hypersensitivity onset; p = 0.002 for 1 day after PCI versus clopidogrel hypersensitivity onset.

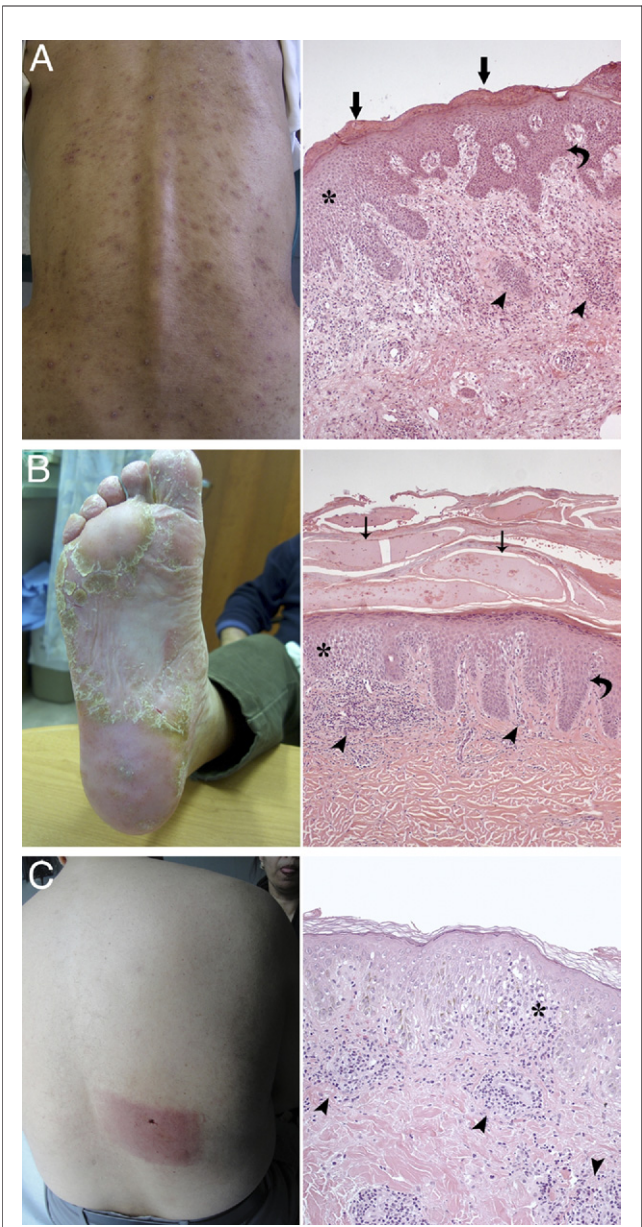


Figure 5 Histological Findings for Punch Biopsy of Area Affected by Clopidogrel Hypersensitivity

The microscopic sections of generalized (A) and localized (B and C) clopidogrel hypersensitivity showed lymphocyte infiltration of dermis and epidermis and early development of hyperkeratosis. **Thick arrow** = parakeratosis; **curved arrow** = epidermal acanthosis; **thin arrow** = spongiotic crusting; **arrowhead** = lymphocytic infiltration; **asterisk** = lymphocytic exocytosis and spongiosis.

Skin testing for clopidogrel hypersensitivity. Results of skin prick, intradermal, and patch testing were available for 42 patients (68%) (Table 4). Skin prick testing with clopidogrel, ticlopidine, and prasugrel did not elicit a reaction in any patient. Positive response to intradermal testing was present in less than 30 min in 3 patients (7%), all presenting with angioedema or urticaria as initial clopidogrel hypersensitivity manifestation. Allergic cross-reactivity for ticlopidine and/or prasugrel by intra-

Table 4 Results of Skin Testing in Patients With Clopidogrel Hypersensitivity (n = 42)

Positive skin prick or intradermal testing for clopidogrel	3 (7)
Positive patch testing for clopidogrel	34 (81)
Allergic cross-reactivity with ticlopidine	10 (24)
Allergic cross-reactivity with prasugrel	7 (17)
Allergic cross-reactivity with ticlopidine and prasugrel	3 (7)

Values are n (%).

dermal testing was present in 2 patients (Fig. 6). Patch testing was abnormal in 34 patients (81%), with evidence of delayed hypersensitivity to clopidogrel (Fig. 7). Allergic cross-reactivity for ticlopidine was observed in 9 (26%), prasugrel in 6 (18%), and both ticlopidine and prasugrel in 3 patients (9%) on patch testing. Microscopic analysis of biopsy from patch testing sites showed parakeratosis, epidermal spongiosis, lymphocytic exocytosis, and lymphocyte infiltrates (Fig. 8). This cellular

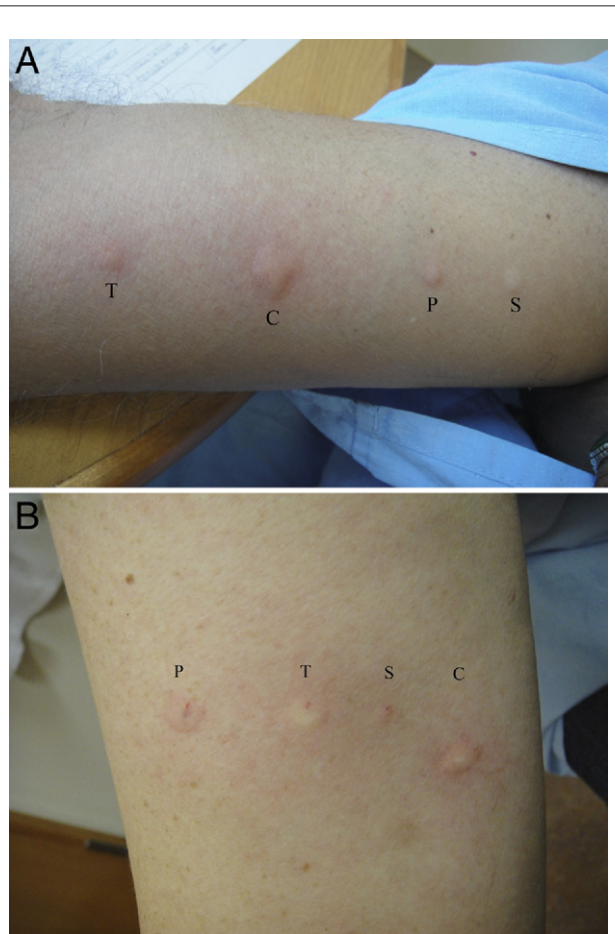


Figure 6 Positive Intradermal Testing for Clopidogrel and Allergic Cross-Reactivity to Ticlopidine and Prasugrel

Positive intradermal testing for clopidogrel (A) and clopidogrel, ticlopidine, and prasugrel (B). C = clopidogrel; P = prasugrel; S = saline; T = ticlopidine.

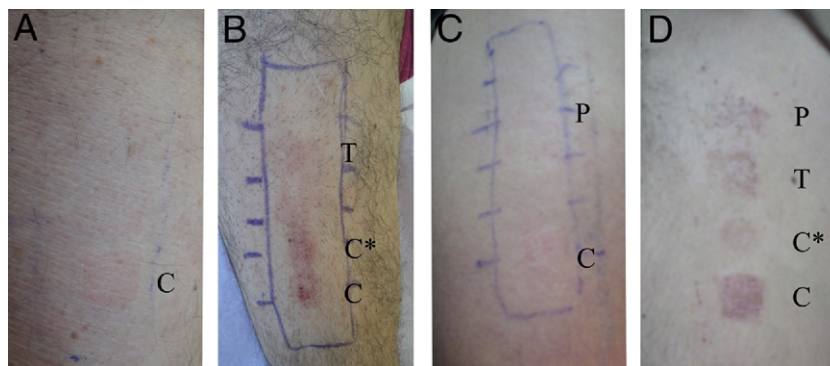


Figure 7 Positive Patch Testing for Clopidogrel and Allergic Cross-Reactivity to Ticlopidine and Prasugrel

Positive patch testing for clopidogrel (A), clopidogrel and ticlopidine (B), clopidogrel and prasugrel (C), and clopidogrel, ticlopidine, and prasugrel (D).
C = clopidogrel; P = prasugrel; T = ticlopidine.

response was similar to that observed in areas affected by clopidogrel hypersensitivity.

Discussion

The main findings of the present study were: 1) clopidogrel hypersensitivity in most patients was characterized by a generalized exanthematous rash affecting the trunk and proximal extremities a median of 5 days after clopidogrel initiation; 2) the clinical presentation, histological analysis, and results of skin testing suggested that clopidogrel hypersensitivity is a lymphocyte-mediated delayed hypersensitivity response in patients with cutaneous manifestations and an immediate hypersensitivity reaction in patients presenting with angioedema or urticaria; 3) both generalized and focal types of clopidogrel hypersensitivity can be successfully treated with a short course of oral steroids without discontinuation of clopidogrel, regardless of the type of immunologic response; and 4) a significant number of patients (40%) with an allergic cutaneous response to clopidogrel showed allergic cross-reactivity with ticlopidine or prasugrel.

Patients with allergic reactions after PCI present difficulty in diagnosis and management. Many patients first have exposure to contrast media and then more recent initiation to standard therapy for coronary artery disease including statins, angiotensin-converting enzyme inhibitors, aspirin, and clopidogrel. No specific assays are available for confirming most drug-induced allergic reactions. In view of these limitations, detailed history of exposure and timing of allergic manifestations is critical for appropriate diagnosis and management. Rechallenge with evidence of recurrence remains the gold standard for diagnosis of any allergic reaction. A unique aspect of the present study was that skin patch testing was performed in a significant number of patients as an adjunct to comprehensive clinical assessment to confirm that the initial reaction was in fact due to clopidogrel.

Clopidogrel is a platelet adenosine diphosphate receptor antagonist that inhibits platelet aggregation by irreversible binding of its active metabolite to the P2Y₁₂ receptor (20), and it has been shown to reduce adverse cardiac events in

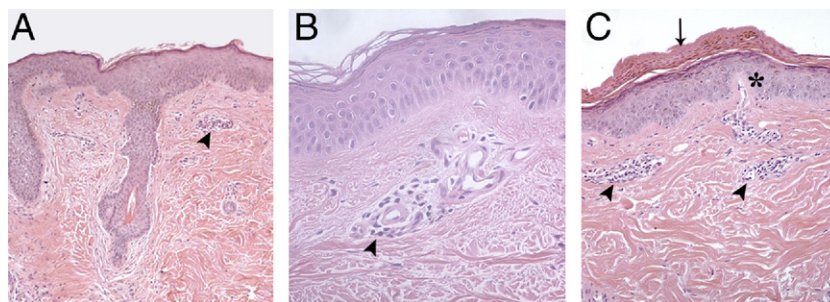


Figure 8 Histological Findings for Punch Biopsy of Positive Patch Test With Clopidogrel

The microscopic sections of positive patch test show lymphocyte infiltration of dermis and epidermis (A to C) and development of parakeratosis (C).
Arrow = parakeratosis; arrowheads = lymphocytic infiltrate; asterisk = lymphocytic exocytosis and spongiosis.

patients with both ST and non-ST-segment elevation myocardial infarction (1,2). In addition, prolonged dual antiplatelet therapy with aspirin and clopidogrel is mandatory after DES placement to prevent stent thrombosis (4,5). Clopidogrel hypersensitivity is a recognized complication of clopidogrel therapy and presents difficulty in management, particularly in patients who have received a DES. The potential ways to manage patients with clopidogrel hypersensitivity include clopidogrel desensitization or treatment with ticlopidine or possibly prasugrel. However, alternative therapy with ticlopidine and prasugrel may not be suitable for all patients because of allergenic cross-reactivity (6,7) and potential for serious side effects (8–11). In addition, clopidogrel desensitization as reported previously may not be suitable after PCI because of the need for drug discontinuation and lack of well-defined criteria for selection of patients (12–14).

Allergic reactions after PCI and clopidogrel hypersensitivity.

Adverse drug reactions are classified as type A for predictable reactions related to pharmacological activity of a drug and type B for unpredictable and rare hypersensitivity reactions. Although diverse manifestations for clopidogrel-related type B hypersensitivity, including urticaria (21), angioedema (22), arthritis (23,24), serum sickness-like reaction (25), and fixed drug reactions (26), have been reported, cutaneous reactions remain the most common presentation (3,12,13). Most patients (79%) with clopidogrel hypersensitivity in the present study presented with a generalized cutaneous exanthema, and focal reactions were seen in 21% of clopidogrel hypersensitivity cases. Focal clopidogrel hypersensitivity varied from localized skin involvement, desquamation of hands and/or feet, and dermal hyperkeratosis to cutaneous reactions similar to a fixed drug eruption. Systemic manifestations such as fever and/or arthralgia were reported by only a few patients (5%). No evidence of internal organ dysfunction, thrombocytopenia, or thrombotic thrombocytopenic purpura was observed in any patient presenting with clopidogrel hypersensitivity. No dose-response relationship between 300- and 600-mg loading doses and timing or severity of clopidogrel hypersensitivity was observed in the present study.

Immunologic mechanism of clopidogrel hypersensitivity.

Drug hypersensitivity reactions are mediated by an immune or a nonimmune mechanism. Nonimmune reactions are caused by direct mast cell activation or cytokines in susceptible individuals such as bradykinin excess after angiotensin-converting enzyme inhibitor use or leukotriene accumulation with nonsteroidal anti-inflammatory drugs. IgE- and lymphocyte-mediated drug hypersensitivity reactions are more common than antibody-, complement-, or immune complex-induced drug allergy. Reactions presenting soon after drug exposure are often mediated by IgE type I reactions, whereas most delayed-onset hypersensitivity reactions are lymphocyte-mediated type IV allergic responses (27,28). An IgE-mediated type I immune response was initially suggested for clopidogrel hypersensitivity (29), fol-

lowed by reports of successful use of clopidogrel desensitization (12–14) for its management. Although heterogeneity is not uncommon for drug hypersensitivity reactions, the present study suggested that clopidogrel hypersensitivity is a lymphocyte-mediated type IV allergic reaction in most patients. Only 3 patients (5%) with clopidogrel hypersensitivity had symptoms of angioedema and urticaria hours after clopidogrel exposure, a clinical presentation consistent with immediate drug hypersensitivity. The delayed onset of clopidogrel hypersensitivity observed in 95% of patients in the present study is consistent with timing of clopidogrel hypersensitivity reported previously (12,13) and suggests a lymphocyte-mediated hypersensitivity immune response. Furthermore, the histological analysis of clopidogrel hypersensitivity and drug allergy testing confirmed the presence of lymphocytes in biopsy specimens of patients with cutaneous manifestations of clopidogrel hypersensitivity. The mechanism of varied manifestations of clopidogrel hypersensitivity in study patients is unclear but has been described with other agents. A critical role of the major histocompatibility complex in presentation of the offending hapten for lymphocyte activation in individual patients may be responsible for this phenotypic variation (28,30).

Skin testing for clopidogrel hypersensitivity and allergenic cross-reactivity with ticlopidine and prasugrel.

Diagnostic confirmation of drug hypersensitivity reactions in clinical practice is difficult because rechallenge and drug-specific testing are not routinely employed (31,32). Drug allergy testing with skin prick and intradermal challenge has been standardized for several drugs responsible for immediate hypersensitivity reactions, but the use of patch testing as a means of controlled rechallenge in patients with delayed-onset drug hypersensitivity is not widely used. However, recent reports have described the successful use of patch testing in the diagnosis of delayed hypersensitivity reactions to antibiotics (33), anticonvulsants (34), and antiretroviral agents (35). In the present study, patch testing was abnormal in 81% of tested patients with clopidogrel hypersensitivity. In addition, patch testing showed evidence of allergenic cross-reactivity among clopidogrel, ticlopidine, and prasugrel in a significant number of patients, suggesting the presence of a common hapten among this therapeutic class. The negative patch testing in 5 patients with clinical manifestations consistent with delayed hypersensitivity does not exclude clopidogrel hypersensitivity because false-negative patch testing have been described as a result of variations in an individual's response to drug absorption and genetic differences (30,36). Skin testing demonstrated allergenic cross-reactivity for ticlopidine in 10 (24%), prasugrel in 7 (17%), and both ticlopidine and prasugrel in 3 (7%) of the tested patients. Allergenic cross-reactivity between clopidogrel and ticlopidine with clinical manifestations has been reported previously (6,7), but cross-reactivity with both ticlopidine and prasugrel in a significant number of patients with clopidogrel hypersensitivity has not been described.

Management of clopidogrel hypersensitivity without clopidogrel discontinuation. The administration of a single course of oral steroids resulted in complete resolution of clopidogrel hypersensitivity in all but one patient and offers an important treatment option for patients requiring prolonged clopidogrel therapy without drug discontinuation, switching, or desensitization. Furthermore, the steroids were effective in alleviating clopidogrel hypersensitivity in patients presenting with cutaneous manifestations, urticaria, or angioedema. The mechanism of action for successful treatment of clopidogrel hypersensitivity by oral steroids is unclear but is likely related to suppression of the immune response followed by development of immunologic tolerance in sensitive individuals. The treated patients continued on clopidogrel without interruption after tapering of steroids. However, repeat administration of clopidogrel after drug discontinuation in 4 patients resulted in recurrence of clopidogrel hypersensitivity, suggesting that steroids did not completely abolish an individual's drug sensitivity but allowed development of drug tolerance and prevented allergic manifestations. Although successful use of steroids for prevention and treatment of systemic hypersensitivity reactions has been described for other offending agents, including contrast media (37) and chemotherapeutic drugs (38,39), little is known about the utility of this approach in the treatment of delayed hypersensitivity reactions.

Study limitations. In the present study, clopidogrel hypersensitivity was observed in 1.6% of patients treated with aspirin and clopidogrel after stent placement, a rate that is lower than the 6% incidence of skin rashes reported in the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischaemic Events) study (3). However, all patients undergoing PCI were not routinely followed for detection of clopidogrel hypersensitivity. In addition, no information was available for patients who developed clopidogrel hypersensitivity and did not undergo PCI. The results of patch testing suggested the presence of allergenic cross-reactivity among clopidogrel, ticlopidine, and prasugrel, but definite clinical cross-reactivity among these drugs cannot be concluded because none of the study patients received oral ticlopidine or prasugrel.

Conclusions

Clopidogrel hypersensitivity was manifested by a generalized exanthematous eruption occurring at a median of 5 days after clopidogrel initiation and characterized by a lymphocyte-mediated delayed hypersensitivity response in most patients. The manifestations of clopidogrel hypersensitivity was successfully treated with a short course of oral steroids, regardless of the clinical manifestations, without cessation of clopidogrel therapy. Allergenic cross-reactivity with ticlopidine, prasugrel, or both was present in a significant number of patients with clopidogrel hypersensitivity.

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