

Clopidogrel Desensitization After Drug-Eluting Stent Placement

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Objectives	We hypothesized that a standardized outpatient clopidogrel desensitization protocol would be safe and effective.
Background	Adverse reactions to clopidogrel are not uncommon, and affected patients must switch to ticlopidine after drug-eluting stent placement, despite its more malignant side-effect profile, because of the risk of ischemic events associated with premature discontinuation of dual antiplatelet therapy.
Methods	Patients with suspected clopidogrel sensitivity were treated with escalating doses of clopidogrel administered orally in solution until either a clinically significant reaction occurred or the full 75-mg tablet of clopidogrel was tolerated. Desensitization was performed on an outpatient basis except in cases in which the subjects were inpatients at the time of enrollment. Follow-up was performed at 2 to 4 weeks and 6 months after treatment. Successful desensitization was defined as the ability to take clopidogrel 75 mg daily without a mucocutaneous, bronchial, or anaphylactic response.
Results	We enrolled 24 consecutive patients with suspected reactions to clopidogrel after DES implantation, 20 of whom were outpatients. During desensitization, allergic-type reactions occurred in 4 patients and angina occurred in 1 patient. Desensitization was acutely successful in all 24 patients, and by 6-month follow-up, 1 patient had persistent but improved pruritus controlled with oral antihistamines and 23 remained asymptomatic, with only 2 patients requiring repeat desensitization.
Conclusions	Clopidogrel desensitization is safe and effective, induces a sustained remission, and could be advantageous in treating outpatients who are at-risk for premature discontinuation of dual antiplatelet therapy. (J Am Coll Cardiol 2007;50:2039–43) © 2007 by the American College of Cardiology Foundation

Drug-eluting stents (DES) significantly reduce the rate of restenosis and the need for repeat revascularization compared with bare-metal stents (1,2). Premature discontinuation of dual therapy with aspirin and a thienopyridine is strongly associated with stent thrombosis and major adverse coronary events (3). Although the optimal duration of clopidogrel therapy has yet to be defined, recent guidelines recommend at least 1 year of clopidogrel after DES implantation (4) because of the potential risk of thrombotic events caused by delayed vascular healing and re-endothelialization. Potentially allergic reactions to clopidogrel have been reported to occur in approximately 4% of patients (5), usually requiring drug discontinuation. The alternative thienopyridine, ticlopidine, is more expensive, dosed more often, and associated with a more frequent and serious adverse side-effect profile, includ-

ing blood dyscrasias (6), limiting its clinical safety and utility.

Desensitization protocols exist for several medications (7,8). Aspirin-desensitization protocols have had a significant impact on the management of patients with cardiovascular disease (9). We hypothesized that patients treated with DES who suffered from clopidogrel sensitivity could be safely and effectively maintained on clopidogrel with a standardized outpatient desensitization protocol.

Methods and Materials

Patients. All patients screened for clopidogrel desensitization between September 2005 and June 2006 were followed prospectively. Patients who developed a clopidogrel reaction after their cardiac intervention were identified and referred to our allergy division for a detailed history, physical, and review of the medical record.

There are currently no immunoglobulin-based assays for clopidogrel sensitivity, so clinical criteria were used instead. Patients were not enrolled if more likely causes for their reactions were identified (e.g., history of intravenous [IV]-

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**Abbreviations
and Acronyms****DES** = drug-eluting stent(s)**IV** = intravenous**PCI** = percutaneous
coronary intervention

contrast sensitivity, other drug exposures, or if the history and physical were clearly inconsistent with drug sensitivity). Exclusion criteria included exfoliative dermatitis; toxic epidermal necrolysis; Stevens-Johnson rash; anaphylaxis; upper- or lower-airway

compromise, including angioedema or respiratory failure; or other life-threatening reactions to clopidogrel or ticlopidine. This study was approved by the Scripps Clinic institutional review board, and all patients provided informed consent.

Clopidogrel desensitization protocol. When possible, clopidogrel was discontinued and patients were transitioned to ticlopidine 250 mg orally twice a daily for 5 days before desensitization for both drug elimination and symptom resolution. Clopidogrel desensitization was performed in an outpatient setting, except for those patients who were already hospitalized for other clinical reasons. The protocol was administered by a dedicated drug desensitization nurse and supervised by an allergist, who confirmed and treated any reactions during the protocol. The use of steroids, antihistamines, and antileukotrienes was stopped for 7 days before desensitization if feasible. Beta-blockers were held on the day of desensitization if possible. No premedication was administered. Intravenous access was obtained on all patients before desensitization.

The protocol involved oral administration of an aqueous solution containing increasing amounts of clopidogrel. The approach was modified from earlier, smaller studies of clopidogrel desensitization used predominantly on inpatients (10,11). Three different methods to solubilize clopidogrel were used. For inpatients, finely crushed clopidogrel was combined with a small amount of Ora-Plus compounding agent (Paddock Laboratories Inc., Minneapolis, Minnesota) then diluted with Ora-Sweet (Paddock Laboratories Inc.) to final concentrations of 0.5 and 5 mg/ml. Alternatively, when Ora-Plus was unavailable, ethanol was used as a solvent to dissolve finely crushed clopidogrel and was titrated to 0.5 and 5 mg/ml using purified drinking water. For outpatients, analogous clopidogrel solutions were provided by a compounding pharmacy. Solution-stability investigations were deemed unnecessary given the speed with which we used our stock solutions.

The first dose given was solvent-only, followed 30 min later by 0.005 mg of clopidogrel in solution. Thereafter, doubling doses of dilute clopidogrel were given every 30 min until a single 75-mg tablet was given (Table 1). All patients were monitored for adverse reactions. If a potentially allergic reaction occurred, the patient was given diphenhydramine (oral or IV) or oral cetirizine for symptom control. Once symptoms subsided and 30 min had elapsed since the previous dose of clopidogrel had been given, the same dose was repeated. If no reaction occurred, then the aforementioned protocol was continued. If a reaction reoccurred, the patient was given the same treatment as mentioned previously, and once the symptoms

Table 1 Clopidogrel Desensitization Schedule

Time	Dose (mg)	Concentration (mg/ml)	ml
8:00 AM	0	0	0.01
8:30 AM	0.005	0.5	0.01
9:00 AM	0.01	0.5	0.02
9:30 AM	0.02	0.5	0.04
10:00 AM	0.04	0.5	0.08
10:30 AM	0.08	0.5	0.16
11:00 AM	0.16	0.5	0.32
11:30 AM	0.3	0.5	0.6
12:00 PM	0.6	0.5	1.2
12:30 PM	1.2	5	0.24
1:00 PM	2.5	5	0.5
1:30 PM	5	5	1
2:00 PM	10	5	2
2:30 PM	20	5	4
3:00 PM	40	5	8
3:30 PM	75	75-mg tablet	N/A

Adapted from Camara and Almeda (10) and Walker *et al.* (11).

had subsided and a minimum of 30 min had elapsed, then the next dose of clopidogrel given was half of the provoking dose. After desensitization, patients were instructed to continue clopidogrel 75 mg daily and to follow-up with their cardiologist within 2 weeks. Telephone follow-up was performed by the lead author at both 2 to 4 weeks and 6 months after desensitization to monitor for recurrent symptoms.

Results

A total of 24 consecutive patients were screened for clopidogrel desensitization after DES implantation. All 24 were considered to have reactions likely due to clopidogrel. No patients had to have steroids or antileukotrienes stopped. The mean age was 62 years, 63% were male, and an average of 2.3 DES were implanted per patient. Outpatient desensitization was performed in 20 patients (83%).

The most common reaction to clopidogrel was a pruritic macular erythematous confluent rash that began either on the face, chest, or abdomen, which then secondarily generalized to cover most of the face, chest, back, abdomen, and proximal extremities (Table 2). In 7 patients (29%), the rash progressed to cover the entire body, including their palms and soles. One patient experienced pruritus without a rash and one patient experienced a nonpruritic rash. Four patients experienced urticaria.

The median time between clopidogrel exposure/percutaneous coronary intervention (PCI) and symptom development (Table 3) was 6 days (interquartile range 3 to 9 days). The median time between symptom development and clopidogrel desensitization was 11.5 days (interquartile range 6 to 66 days). One patient on ticlopidine experienced a reaction to clopidogrel approximately 2.5 years before desensitization and could not recall specifics surrounding the event aside from the characteristics of the rash.

Table 2 Days of Clopidogrel Use and Extent of Initial Clopidogrel Reaction

Patient #	Days of Clopidogrel Use	Extent of Initial Clopidogrel Reaction
1	11	Neck to hips
2	4	In ears to chest and back
3	7	Chest and back
4	10	Chest, back, and proximal extremities
5	3	Diffuse pruritus
6	9	Abdomen, chest, back, and proximal extremities
7*	1,546	Total body, including palms and soles
8	11	Axillae, palms, and soles
9	36	Chest and back. Incidental antecubital fossae eczema
10	20	Total body, including palms and soles
11*	6	Lower anterior abdomen
12	1	Periocular to thighs
13	Unknown	Perioral
14	9	Total body, including palms and soles
15	6	Back and thighs
16	6	Chest and back
17	2	Upper chest, and back
18	5	Face, chest, and back
19	7	Chest and back to proximal thighs
20	2	Total body, including palms and soles
21	8	Face, chest, and proximal extremities
22	8	Chest to buttocks
23	9	Total body, including palms and soles
24	40	Total body, including palms and soles

*Re-desensitized patients.

Cutaneous reactions during desensitization occurred in 4 patients (17%) and did so at dissimilar doses (Table 4). Pruritus was the primary symptom in all of these patients. One of these patients developed a pruritic rash that dissipated during desensitization, and 3 experienced pruritus alone. Of the 3 patients that did not complete a 5-day washout of clopidogrel while receiving ticlopidine, 1 (33%) reacted during desensitization, compared with 3 of 21 patients (14%) who completed the washout period.

Angina occurred in one patient during desensitization. There were no electrocardiographic changes consistent with ischemia, and the patient was hemodynamically stable. The patient's angina resolved with one sublingual nitroglycerin spray and desensitization was completed without further incident.

Desensitization was acutely successful in all 24 patients. Telephone follow-up was complete in all patients. All patients were still taking clopidogrel 75 mg daily at 6-month follow-up. Repeat desensitization was required and successful in 2 patients (8%). The first patient missed 3 doses of clopidogrel, which resulted in recurrent symptoms. The second patient required repeat desensitization 2 days after initial desensitization because of a persistent rash that eventually dissipated spontaneously. Two additional patients had antecedent nonallergic rashes before enrollment. One patient had low-grade pruritus that was well controlled with oral antihistamines at both 4

weeks and 6 months after desensitization. Twenty-three of the 24 patients (96%) remained entirely free of their original clopidogrel-induced symptoms at 6-month follow-up.

Discussion

Unlike previous reports (10,11), this single-center, prospective study of patients with clopidogrel sensitivity after DES implantation demonstrates that primarily outpatient-based clopidogrel desensitization is feasible, safe, and effective and induces a sustained remission for at least 6 months. This series is the largest reported to date of patients receiving clopidogrel desensitization to date.

The observation that 2 patients required repeat desensitization by 6-month follow-up reflects the inherent limitations of this approach to clopidogrel sensitivity. A sustained response to desensitization requires excellent patient compliance as even brief discontinuation of the offending drug can cause symptoms to recur once the drug is restarted. Therefore, the recurrence of clopidogrel sensitivity in patients who have been previously desensitized may serve as a warning of noncompliance.

Premature discontinuation of dual antiplatelet therapy has been clearly shown to be a strong, independent risk factor for stent thrombosis, which frequently results in Q-wave myocardial infarction and death. Therefore, efforts to reduce discontinuation of clopidogrel up to 12 months after DES implantation are crucial (12). As observed in our study, the most common period for the onset of clopidogrel reactions was within the first 10 days after PCI. This time-frame coincides with the highest risk of stent thrombosis when not treated with a thienopyridines (13); moreover, discontinuation of clopidogrel within 30 days after primary PCI with DES for ST-segment elevation myocardial infarction is associated with increased rates of mortality at 1 year (14). Outpatient clopidogrel desensitization may therefore be an important approach to prevent discontinuation and subsequent major adverse cardiac events in clopidogrel-sensitive patients after DES.

Study limitations. Limitations of the current study include the nonrandomized, small, and unblinded nature inherent to a pilot study. The potential for confounding IV contrast and medication reactions is also recognized. Use of antihistamines pre-desensitization could not be controlled for adequately, given their ubiquitous presence in over-the-counter medications. The resolution of reactions with discontinuation of clopidogrel argues against other drug exposures as the etiologic factors for those reactions. Also, the observation that all patients remained improved or asymptomatic post-desensitization argues that clopidogrel was likely the offending drug. Thus, desensitization was highly effective both by the end of the procedure and for up to 6 months after it. Other reactions to DES have been reported (15), but until a specific antibody assay is developed to diagnose clopidogrel sensitivity, it will be impossible to completely exclude other agents as etiologic factors. Given

Table 3 List of Patients by Status, Days From Clopidogrel Exposure/PCI to Reaction, Days From Reaction to Desensitization, and Type of Reaction During Desensitization

Patient #	Status	Days From Clopidogrel Exposure/PCI to Reaction	Days From Reaction to Desensitization	Type of Reaction During Desensitization
1	Outpatient	9	37	—
2	Outpatient	1	10	Pruritus
3	Outpatient	7	97	—
4	Outpatient	1	17	—
5	Outpatient	3	738	—
6	Outpatient	6	11	—
7*	Inpatient	1,546	78	Pruritic rash at 20 mg
8	Inpatient	10	11	—
9	Outpatient	33	6	—
10	Outpatient	20	22	—
11*	Outpatient	3	13	—
12	Outpatient	0	66	—
13	Outpatient	Unknown	2.5 yrs	Angina at 2.5 mg clopidogrel
14	Outpatient	8	334	—
15	Outpatient	6	3	Pruritus
16	Outpatient	6	8	—
17	Outpatient	0	6	—
18	Inpatient	5	5	—
19	Outpatient	5	12	—
20	Outpatient	2	9	Pruritus
21	Outpatient	4	11	—
22	Inpatient	7	2	—
23	Outpatient	7	2	—
24	Outpatient	30	400	—

*Re-desensitized patients.

PCI = percutaneous coronary intervention.

the overwhelming safety we observed with our protocol, desensitization may be appropriate even when the offending agent cannot be definitively identified, as the desensitization procedure itself may be of diagnostic utility. Moreover, the instantaneous and prolonged therapeutic benefit of clopidogrel desensitization may obviate the need for an antibody assay. The clopidogrel solubilization technique differed among inpatients; however, this would have been unlikely to significantly affect the solutions' concentrations or absorption rates.

Previous publications speculate as to the cause of clopidogrel sensitivity (10,16,17), but until the mechanism is found, the terms "allergy" and "hypersensitivity" should not be used as these relate only to immunoglobulin E-mediated reactions. Interestingly, all of our study participants reacted to clopidogrel on their first continuous exposures to the drug. Thus, if we are to blame antibody production for clopidogrel sensitivity, another common antigen may exist. Similarly, the mechanisms for drug desensitization and

tolerance-induction are unknown. It has been proposed that if a drug reaction is immunoglobulin E-mediated, antibody-specific mast cell degranulation occurs and a refractory period is then entered and sustained by subsequent continuous drug dosing (18).

Conclusions

Clopidogrel desensitization appears safe and highly effective in inducing a sustained remission in clopidogrel-sensitive patients who require prolonged dual antiplatelet therapy after DES. Our data support that this approach should be considered in all stable outpatients with clopidogrel sensitivity who meet our inclusion and exclusion criteria to avoid the potential adverse effects of ticlopidine and to avoid the thrombotic risk of discontinuation of thienopyridine therapy.

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REFERENCES

- Moses JW, Leon MB, Pompa JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315–23.

Table 4 Reactions During Desensitization

Reaction	n = 24 (% Total)
Pruritus alone	3 (13)
Rash alone	0
Pruritic rash	1 (4)
None	20 (83)

2. Stone GW, Ellis SG, Cox DA, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350:221–31.
3. Iakovou I, Schmidt T, Bonizzoni E, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. *JAMA* 2005;293:2126–30.
4. Eisenstein EL, Anstrom KJ, Kong DF, et al. Clopidogrel use and long-term clinical outcomes after drug-eluting stent implantation. *JAMA* 2007;297:159–68.
5. Plavix (clopidogrel bisulfate) package insert. New York, NY: Bristol-Myers Squibb Company & Sanofi-Synthelabo, revised May 2006.
6. Steinhubl SR, Tan WA, Topol EJ. Incidence and clinical course of thrombotic thrombocytopenic purpura due to ticlopidine following coronary stenting. EPISTENT Investigators. Evaluation of Platelet IIb/IIIa Inhibitor for Stenting. *JAMA* 1999;281:806–10.
7. Patterson R, DeSwarte RD, Greenberger PA, Grammer LC. Drug allergy and protocols for management of drug allergies. *N Engl Reg Allergy Proc* 1986;7:325–42.
8. Stevenson DD. Desensitization of aspirin-sensitive asthmatics: a therapeutic alternative? *J Asthma* 1983;20:131–8.
9. Gollapudi RR, Teirstein PS, Stevenson DD, Simon RA. Aspirin sensitivity: implications for patients with coronary artery disease. *JAMA* 2004;292:3017–23.
10. Camara MG, Almeda FQ. Clopidogrel (Plavix) desensitization: a case series. *Catheter Cardiovasc Intervent* 2005;65:525–7.
11. Walker NE, Fasano MB, Horwitz PA. Desensitization for the management of clopidogrel hypersensitivity: initial clinical experience. *J Invasive Cardiol* 2006;18:341–4.
12. Grines CL, Bonow RO, Casey DE Jr., et al. Prevention of premature discontinuation of dual antiplatelet therapy in patients with coronary artery stents: a science advisory from the American Heart Association, American College of Cardiology, Society for Cardiovascular Angiography and Interventions, American College of Surgeons, and American Dental Association, with representation from the American College of Physicians. *J Am Coll Cardiol* 2007;49:734–9.
13. Cutlip DE, Baim DS, Ho KK, et al. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation* 2001;103:1967–71.
14. Spertus JA, Kettelkamp R, Vance C, et al. Prevalence, predictors, and outcomes of premature discontinuation of thienopyridine therapy after drug-eluting stent placement: results from the PREMIER registry. *Circulation* 2006;113:2803–9.
15. Nebeker JR, Virmani R, Bennett CL, et al. Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J Am Coll Cardiol* 2006;47:175–81.
16. Doogue MP, Begg EJ, Bridgman P. Clopidogrel hypersensitivity syndrome with rash, fever and neutropenia. *Mayo Clin Proc* 2005;80:1368–70.
17. Lee-Wong M, Gadhvi D, Resnick D. Clopidogrel desensitization. *Ann Allergy Asthma Immunol* 2006;96:756–7.
18. Naclerio R, Mizrahi E, Adkinson NF Jr. Immunologic observations during desensitization and maintenance of clinical tolerance to penicillin. *J Allergy Clin Immunol* 1983;71:294–301.