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Frequency of Allergic or Hematologic Adverse Reactions to Ticlopidine Among Patients With Allergic or Hematologic Adverse Reactions to Clopidogrel

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Background—Clopidogrel and ticlopidine are structurally very similar. In patients with an allergic or hematologic adverse reaction to either one of these drugs, the likelihood that an allergic or hematologic adverse effect will develop to the other is unknown. It is also unknown whether a reaction to the second thienopyridine is likely to be life threatening.

Methods and Results—Medical records from 2 academic institutions were reviewed to identify patients who had an allergic or hematologic adverse reaction to either of the 2 currently commercially available thienopyridines and who were subsequently prescribed the other thienopyridine. Patient demographics, details of the adverse reactions, and subsequent clinical course were reviewed. A total of 76 patients were identified with an allergic or hematologic adverse reaction to clopidogrel or ticlopidine who had also received the other thienopyridine. Fourteen (27%; 95% CI, 16 to 41) patients who had an allergic or hematologic adverse reactions to clopidogrel had a similar reaction to ticlopidine; none developed a life-threatening reaction. The most common reaction was a rash (93%).

Conclusions—In patients with an allergic or hematologic adverse reaction to one thienopyridine, there seems to be an increased frequency of such reactions to the other thienopyridine. However, no patient had a life-threatening reaction after exposure to the alternative thienopyridine. (*Circ Cardiovasc Intervent.* 2009;2:348-351.)

Key Words: platelet aggregation inhibitors ■ hemorrhage ■ thienopyridine ■ clopidogrel ■ ticlopidine ■ allergy ■ cross-reactivity

Recent studies demonstrate that drug-eluting stents may pose a higher risk of late stent thrombosis than bare metal stents because of delayed healing.¹ This has led to guidelines recommending dual antiplatelet therapy for at least 1 year after the placement of drug-eluting stents.² Premature cessation of dual antiplatelet therapy can be catastrophic.³

Clinical Perspective on p 351

Clopidogrel, a second-generation thienopyridine structurally similar to ticlopidine, was developed to be equally efficacious to ticlopidine but with fewer adverse effects.^{4,5} However, allergic or hematologic reactions occur in approximately 1% of patients taking clopidogrel and, when severe, require discontinuation.⁶ Substituting ticlopidine for clopidogrel is the most common practice in patients who develop a severe allergic or hematologic adverse reaction to clopidogrel. However, the frequency and severity of allergic cross-reactivity between the agents are not known.

Methods

Patients

The electronic health records from the Geisinger Clinic (Danville, Pa) and the Mayo Clinic (Rochester, Minn) were reviewed to identify patients older than 18 years with an allergy to a thienopyridine in their medical record between January 1995 and June 2007. These patients were sorted into 3 groups based on whether their allergy was either to 1 of the 2 currently available thienopyridines or to both. Of the patients with an allergy to only one thienopyridine, only those who had also received the other thienopyridine, as determined by a query of their electronic medication lists, were selected for inclusion in this analysis. These medication lists include all medications prescribed by all physicians throughout the Geisinger or Mayo systems and are reconciled at each clinic visit with those the patient is actually taking. For each patient thus identified, medical records were reviewed to assess adverse reaction details and subsequent clinical course. Only patients whose adverse reactions met the study criteria of allergic or hematologic adverse reactions (defined later) were included in this analysis. Demographic data, indication for thienopyridine use, and baseline cardiovascular characteristics were collected as well. This study was approved by the institutional review boards of both institutions.

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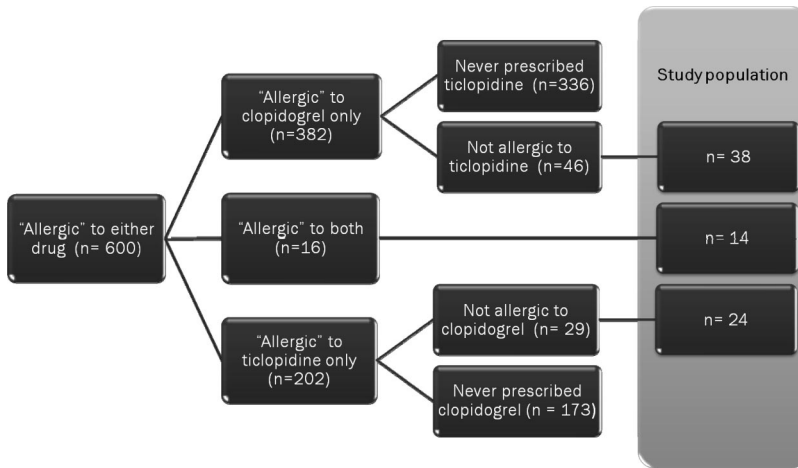


Figure. Schematic overview of the study population.

Criteria for Allergic or Hematologic Adverse Reactions

Because there are currently no assays available to confirm an allergy to clopidogrel or ticlopidine, an allergy or hematologic adverse reaction was determined by the clinical history. Allergic reactions included in this study were anaphylaxis, angioedema, and rash. Although it is not clear whether hematologic adverse reactions to thienopyridines are truly allergies, such reactions were included in our study, given their clinical importance, implications for continuing the thienopyridine, and evidence of associated antibodies in some cases of drug-induced neutropenia, thrombocytopenia, and thrombotic thrombocytopenic purpura.^{7,8} Specific attention was paid to the time course of the development and resolution of the allergic or hematologic reaction relative to the time of administration of the thienopyridine and all other medications initiated at the same time. Each reaction thought to be an allergic or hematologic reaction to a thienopyridine, at the time of its occurrence, by the patient's physician was further evaluated by review of electronic health records by a physician at each of the 2 centers and by an additional physician if there was a discrepancy between the 2 that the thienopyridine was the causative agent for the allergic or hematologic reaction. If other medications were started concomitantly with the thienopyridine, the adverse reaction was only considered to represent an allergic or hematologic reaction to the thienopyridine if it subsided with discontinuation of the thienopyridine while continuing the other medications. If the thienopyridine was discontinued and the patient was subsequently able to tolerate reinitiation of the thienopyridine medication without recurrence of the adverse reaction, the reaction was not considered to represent an allergy to the thienopyridine. Gastrointestinal intolerance and bleeding were not considered to represent allergic reactions. Patients at Geisinger Clinic or Mayo Clinic who had opted not to be included in any research study were excluded.

Statistical Analysis

Patients were assigned to 1 of 3 groups: patients with an allergic or hematologic reaction to both thienopyridines, patients with an allergic or hematologic reaction to clopidogrel but who tolerated ticlopidine, or patients with an allergic or hematologic reaction to ticlopidine but who tolerated clopidogrel. Data from both centers were analyzed together. Data are presented as means and percentages with 95% confidence intervals (CIs). The CIs were calculated using normal approximation to the binomial distribution. STATXACT (version 5.0) statistical software was used.

Results

Six hundred patients were identified by their physician as having an allergic or hematologic reaction to either ticlopidine or clopidogrel. We identified 91 of the 600 patients who

had received both thienopyridines. Of these 91 patients, 76 patients (41 from the Geisinger Clinic and 35 from the Mayo Clinic) were confirmed for an allergic or hematologic adverse reaction, using rigid study criteria (Figure). These 76 patients formed the study population; their baseline characteristics are shown in the Table.

Indication for Thienopyridine

A percutaneous coronary intervention was the indication for the thienopyridine for most patients (n=57; 75%). Other indications included prior stroke (n=10; 13%), a percutaneous intervention for peripheral arterial disease (n=5; 7%), allergy or intolerance to aspirin (n=3; 4%), and coronary artery disease (n=1; 1%).

Type of Allergic Reactions or Hematologic Adverse Effects

Seventy-one of the 76 patients had a rash (93%), 4 (5%) had angioedema, 3 (4%) had thrombocytopenia, and 2 (3%) had neutropenia. No patients with thrombotic thrombocytopenic purpura were included in this analysis because no patients were administered the alternative thienopyridine after having developed thrombotic thrombocytopenic purpura.

Table. Baseline Clinical Characteristics of the Study Population

Mean age, y	69
Male, n (%)	53 (70)
Hypertension, n (%)	62 (82)
Hyperlipidemia, n (%)	64 (84)
Diabetes, n (%)	15 (20)
Active tobacco abuse, n (%)	10 (13)
Former tobacco abuse, n (%)	40 (53)
Chronic kidney disease, n (%)	12 (16)
Peripheral arterial disease, n (%)	20 (26)
Previous myocardial infarction, n (%)	37 (49)
Previous percutaneous coronary intervention, n (%)	58 (76)
Previous coronary artery bypass grafting, n (%)	15 (20)

Frequency of Allergic Cross-Reactivity and Severity

Of the 52 patients with allergic or hematologic adverse reactions to clopidogrel, 14 (27%; 95% CI, 16% to 41%) had similar reactions to ticlopidine. Most of the remaining 38 patients (36; 95%) were able to tolerate ticlopidine for the entire recommended therapy: 1 patient ultimately discontinued ticlopidine because of gastrointestinal side effects, and the other was later successfully desensitized to clopidogrel and resumed treatment with clopidogrel.

Of the 38 patients with allergic or hematologic adverse reactions to ticlopidine, 14 patients (37%; 95% CI, 22% to 54%) developed similar reactions to clopidogrel.

Of the 14 patients allergic to both thienopyridines, 12 had received clopidogrel first, and 2 had received ticlopidine first. Thus, 50 patients allergic to clopidogrel had not yet been exposed to ticlopidine; 12 of them (24%) subsequently developed an allergic reaction to ticlopidine.

Severity of the Allergic or Adverse Reaction

None of the 76 patients with an allergic or hematologic adverse reaction to one thienopyridine developed a life-threatening reaction to the other thienopyridine. In patients who had a rash in response to a thienopyridine, allergic reactions to the alternative thienopyridine were primarily limited to a rash; none required emergency therapy. One patient with angioedema from clopidogrel had recurrent angioedema of lesser severity after taking ticlopidine. In 2 patients who developed thrombocytopenia from taking clopidogrel, recurrence was seen with ticlopidine. None of these 3 patients required hospital admission or emergency therapy, and none of the reactions were thought to be life threatening.

Discussion

The principal finding of this study is that patients allergic or intolerant because of a hematologic adverse reaction to clopidogrel had an approximately 1 in 4 chance of also being unable to tolerate ticlopidine. However, the adverse reaction was not life threatening in any of the cases.

Background

An allergic reaction may recur if a patient allergic to 1 drug is exposed to another drug of the same class or with a similar structure.⁸ Termed cross-reactivity, this presents a dilemma because it reduces the therapeutic options available to a patient. Data on allergic cross-reactivity within most classes of drugs are scarce, because true drug allergies are rare and patients allergic to a drug are often excluded from clinical trials of other drugs within the same class.⁹

Clopidogrel is chemically very similar to ticlopidine, differing only by the addition of a carboxymethyl group. All metabolites of clopidogrel carry either the carboxymethyl ester group or a carboxylic acid group.¹⁰ Therefore, the occurrence of an allergic or hematologic adverse reaction to both thienopyridines cannot be explained on the basis of a common metabolite.

Case reports of patients with allergic reactions to both clopidogrel and ticlopidine have been described.^{11,12} The current study is the first to identify a relatively large number

of patients with an allergic or hematologic adverse reaction to one thienopyridine who received the other thienopyridine, and to suggest that the frequency of cross-reactivity between the 2 agents is clinically significant.

Management of Patients Allergic to Clopidogrel

In patients who develop an allergic reaction to clopidogrel, the reaction is often mild, and clopidogrel may be continued. Sometimes, antihistamines and/or steroids are effective in allowing continuation of the thienopyridine. However, if the allergic reaction fails to respond to these measures or if the reaction is severe, clopidogrel may have to be discontinued. In such patients, several different therapeutic options exist, none of which is ideal, particularly in patients who have recently received a coronary stent. Discontinuing the thienopyridine and administering warfarin is one option. However, although anticoagulation with warfarin is better than aspirin alone, it is inferior to dual antiplatelet therapy.^{13,14} Data suggest that cilostazol and aspirin may be as effective as ticlopidine plus aspirin in preventing major adverse cardiac events after coronary stent implantation, but this combination has not been studied in large randomized clinical trials.¹⁵

Among patients in whom clopidogrel must be discontinued, immediate substitution with ticlopidine is the most evidence-based and commonly used approach to minimize the risk of stent thrombosis. Ticlopidine is as efficacious as clopidogrel.⁵ Ticlopidine, however, is associated with serious hematologic side effects, including neutropenia and thrombotic thrombocytopenic purpura; accordingly, monitoring of complete blood counts is recommended every 2 weeks for the first 3 months.^{4,10} To minimize the duration of ticlopidine treatment, desensitization protocols for clopidogrel have been described after the allergic reaction to clopidogrel has resolved.^{12,16,17} However, patients are generally transitioned to ticlopidine to allow for the symptoms to resolve and for elimination of all clopidogrel from the blood before beginning desensitization.¹⁸ Furthermore, if the patient misses 1 to 3 days of clopidogrel after reinitiation, desensitization may need to be repeated.

Because no patients allergic to clopidogrel or ticlopidine have been included in the trials of prasugrel, it is currently unknown whether prasugrel, which is also structurally similar to the other 2 thienopyridines, will be an option for patients allergic to either clopidogrel or ticlopidine.

Study Limitations

This is a retrospective study subject to the limitations of such studies. It is possible that patients may have developed allergic reactions or intolerance to a thienopyridine and received care somewhere other than Geisinger Clinic or Mayo Clinic, in which case, the observed frequency of adverse reactions reported in this study may be an underestimate. It is possible that the 509 patients with an allergic reaction to a thienopyridine who did not receive the alternative thienopyridine may have had more severe allergic reactions and not have had a compelling clinical indication for a thienopyridine. This bias may have resulted in an underestimation in the percentage of dual adverse effects, which might be true particularly for the patients with the most severe

reactions. In the absence of immunologic testing, we cannot be certain that the apparently allergic reactions our patients suffered were due to true allergic reactions to thienopyridines. However, we used strict criteria for subjects with apparent allergic or hematologic reactions for inclusion in this study, and the high frequency of cross-reactivity with adverse reactions that were similar to those that developed in response to the previously administered thienopyridine suggests that most adverse reactions were indeed due to an allergic reaction to the thienopyridines.

Conclusions

Patients who develop an allergic or hematologic adverse reaction to clopidogrel may be safely treated with ticlopidine without fear of a life-threatening allergic reaction to ticlopidine. However, our data suggest that 24% of patients will develop an allergic or hematologic adverse reaction to ticlopidine as well.

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Disclosures

Dr Berger has served as consultant/advisor for Accumetrics, The Medicines Company, Eli Lilly/Daiichi-Sankyo, Novartis/Portola, and Guerbet; has received research support from Thrombovision, Helena Laboratories, Accumetrics, AstraZeneca, Hemoscope, and The Medicines Company; and owns stock in Lumen Inc. Dr Blankenship is a member of a speaker's bureau for Sanofi-Aventis. The other authors report no potential conflicts of interest.

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CLINICAL PERSPECTIVE

Clopidogrel and ticlopidine are structurally similar. We conducted a retrospective study among patients who had received both drugs and had an allergic or hematologic adverse reaction to one of these drugs to determine the extent and severity of allergic cross-reactivity. Seventy-six patients met the study criteria. Of the 52 patients with an allergic or hematologic adverse reaction to clopidogrel, 14 (27%) were also unable to tolerate ticlopidine. No patient with an allergic reaction to one thienopyridine developed a life-threatening reaction to the other.