The Platelet Activity After Clopidogrel Termination (PACT) Study

Andrew L. Frelinger III, PhD; Marc R. Barnard, MS; Marsha L. Fox, RN, MS; Alan D. Michelson, MD

Background—“Rebound” platelet hyperreactivity after discontinuation of clopidogrel has been proposed to lead to increased thrombotic risk, including late stent thrombosis. However the hypothesis that discontinuation of clopidogrel results in platelet hyperreactivity has never been rigorously tested. We therefore performed a randomized, double-blind, placebo-controlled, crossover study: the Platelet Activity after Clopidogrel Termination (PACT) study.

Methods and Results—Platelet reactivity in 15 healthy subjects was measured at baseline, during clopidogrel 75 mg or placebo daily for 14 days, and on days 1, 4, 8, 11, 15, and 45 after discontinuation of clopidogrel or placebo. Platelet reactivity was assessed by (1) platelet surface activated GPIIb-IIIa and surface P-selectin (by whole blood flow cytometry) in response to ADP 0.5, 1, and 20 μmol/L; thrombin receptor activating peptide (TRAP) 1 and 20 μmol/L; and collagen/epinephrine 5 μg/mL/5 μmol/L, (2) light transmission aggregation with ADP 2.5, 5, and 20 μmol/L; TRAP 2 and 20 μmol/L; and collagen 6 μg/mL, (3) whole blood impedance aggregation with ADP 1.6 and 6.5 μmol/L; TRAP 4 and 32 μmol/L; and collagen 3.2 μg/mL, and (4) plasma soluble CD40 ligand (by ELISA). Immature platelet fraction was measured in the Sysmex XE-2100. At no time point after discontinuation of clopidogrel was platelet reactivity, as determined by any assay end point, or the immature platelet fraction significantly greater than after discontinuation of placebo.

Conclusions—This randomized, double-blind, placebo-controlled, crossover study demonstrates that discontinuation of clopidogrel does not result in “rebound” platelet hyperreactivity, as determined by multiple time points, assays, agonists, and agonist concentrations.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00619073.

Key Words: platelets • clopidogrel • pharmacology • thrombosis

Increased platelet function has been reported after discontinuation of antiplatelet drugs, for example, aspirin1–3 and GPIIb-IIIa antagonists.4–6 This “rebound” platelet hyperreactivity has been hypothesized to result in increased thrombotic risk.1–7 More recently, the concept of platelet hyperreactivity after discontinuation of clopidogrel therapy, with an associated increased thrombotic risk, has been proposed in patients with coronary artery disease treated medically or by percutaneous coronary intervention.1,8–12 However, whether or not platelet hyperreactivity after discontinuation of clopidogrel occurs has never been rigorously tested; for example, all previous studies have lacked the necessary control of a baseline measurement before the initiation of clopidogrel. An alternative explanation for the reported increased risk of thrombosis after the discontinuation of clopidogrel9–11,13–16 is recovery of platelet reactivity to pretreatment levels.

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In the present study, we therefore rigorously tested the hypothesis that discontinuation of clopidogrel results in platelet hyperreactivity. We performed a randomized, double-blind, placebo-controlled, crossover study: the Platelet Activity after Clopidogrel Termination (PACT) study. In this study, platelet reactivity in healthy subjects was measured by sensitive assays before, during, and after exposure to clopidogrel or placebo.

Methods

Study Design

The PACT study was a prospective, randomized, double-blind, placebo-controlled, crossover study (www.clinicaltrials.gov/ct2/show/NCT00619073). The study design is shown in Figure 1. Fifteen healthy subjects were randomly assigned to either clopidogrel 75 mg plus aspirin 81 mg or to placebo plus aspirin 81 mg orally daily for 14 days. The study drug (ie, clopidogrel or placebo) was then discontinued and aspirin continued for another 45 days. After a period of 0 to 30 days of no study drug and no aspirin, subjects were crossed over to either clopidogrel 75 mg plus aspirin 81 mg or to placebo plus aspirin 81 mg orally daily for 14 days. The study drug (ie, clopidogrel or placebo) was then discontinued and aspirin continued for another 45 days. Blood samples were drawn at 8 time points daily for 14 days, and on days 1, 4, 8, 11, 15, and 45 after discontinuation of clopidogrel or placebo.

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Flow cytometric assay. This assay was chosen as the primary end point because of its sensitivity to clopidogrel19,20 and because its dynamic range allows the detection of platelet hyperreactivity.

Secondary end points were (1) platelet surface activated GPIIb-IIIa and platelet-poor plasma by ELISA, and (5) immature platelet fraction (IPF, measured in the Sysmex XE-2100).

Blood Collection
Blood was collected by peripheral venipuncture with a 21-gauge butterfly needle into evacuated tubes containing either 3.2% (0.105 mol/L) sodium citrate (BD Biosciences, San Jose, Calif) or 25 μg/mL hirudin (Dynabyte, Munich, Germany). Where indicated, platelet-rich plasma was prepared by centrifugation of blood for 10 minutes at 150 g and platelet-poor plasma by centrifugation of blood for 10 minutes at 2000 g.

Platelet Surface Activated GPIIb-IIIa and Platelet Surface P-Selectin
The method has been previously described in detail.19,21 Citrate anticoagulated whole blood was allowed to rest for exactly 30 minutes at 37°C before assay. Anticoagulated whole blood (10 μL) was added to a mixture (15 μL) of fluorescein isothiocyanate-conjugated PAC1 (BD Biosciences; a monoclonal antibody specific for the activated conformation of GPIIb-IIIa17), phycoerythrin-conjugated CD62P (BD Biosciences, clone AK4; a P-selectin-specific monoclonal antibody), CD41-phycoerythrin-Cy5 (Beckman Coulter; as a platelet identifier), and a platelet agonist. Final concentrations of the platelet agonists were: ADP 0.5, 1, and 20 μmol/L (BioData); TRAP 1 and 20 μmol/L (Bachem); and a combination of collagen 5 μg/mL (Chromo-Log) and epinephrine 5 μmol/L (BioData). After 15 minutes of incubation at room temperature, the reaction was stopped by fixation with 800 μL 1% formaldehyde, 10 mmol/L HEPES, 0.15 mol/L NaCl, pH 7.4. Nonspecific PAC1 binding was determined by a parallel sample in which specific PAC1 binding was blocked by an excess (2.5 μg/mL) of the GPIIb-IIIa antagonist epifibatide (Menillium Pharmaceuticals). Samples were analyzed for PAC1 binding to platelets (reflecting platelet surface activated GPIIb-IIIa) and AK4 binding to platelets (reflecting platelet surface P-selectin) in a FACSCalibur flow cytometer (Becton Dickinson), as previously described.19,21

Light Transmission Aggregometry
Light transmission aggregation was performed in a Chrono-Log 560Ca lumiggregometer (Havertown, Pa) using platelet-rich plasma obtained from the citrated blood, as previously described.22,23 Platelet aggregation was performed without adjustment of platelet count in the platelet-rich plasma. Platelet aggregation was initiated by addition of 1/10th volume ADP (2.5, 5, or 20 μmol/L final concentration), TRAP (2 or 20 μmol/L final concentration), or collagen (6 μg/mL final concentration).

Impedance Aggregometry
Impedance aggregometry was performed in a Multiplate analyzer (Dynabyte, Munich, Germany) using blood collected in hirudin,
according to the manufacturer’s instructions. Briefly, hirudin-anticoagulated whole blood 300 µL was mixed with saline 300 µL and warmed for 3 minutes at 37°C. Platelet aggregation was initiated by addition of 20 µL agonist solution and followed for 6 minutes. Final agonist concentrations were: ADP 1.6 and 6.5 µmol/L, TRAP 4 and 32 µmol/L, and collagen 3.2 µg/mL. Results are reported as area under the curve (AUC) in arbitrary units. The Multiplate analyzer reports the average AUC of the 2 pairs of electrodes in each cartridge.

### Plasma Soluble CD40 Ligand

Freshly prepared platelet-poor plasma samples were frozen at −80°C until assay for plasma soluble CD40L. Before analysis, plasma samples were thawed and centrifuged at 15,000g for 5 minutes. Plasma soluble CD40L was measured by ELISA using a kit from Bender MedSystems (San Bruno, Calif), as previously described.24

### Immature Platelet Fraction

IPF and a complete blood count were measured in a Sysmex XE2100 (Sysmex, Kobe, Japan), which, through automation of sample staining and the use of preprogrammed data analysis algorithms to identify immature platelets, provides more consistent and reproducible results than traditional manual thiazole orange staining and flow cytometry.25–27 The Sysmex XE2100 identifies the IPF using a combination of a proprietary fluorescent RNA stain (which preferentially binds young platelets) and light scatter characteristics.25–27 The immature platelet count was derived from the platelet count (measured in the XE2100) and the IPF %.

### Statistics

The study was powered (α=0.05, β=0.8) to detect a 10% difference in platelet reactivity between samples collected at corresponding times in the clopidogrel versus placebo treatment arms as determined by the primary end point (0.5 µmol/L ADP-induced platelet surface activated GPIIb-IIIa complex). The D’Agostino and Pearson omnibus normality test was used to determine if results followed a normal distribution. Normally distributed results were analyzed by 2-way (time and treatment) repeated-measures ANOVA, followed by Bonferroni posttest analysis of results from corresponding times in the clopidogrel versus placebo treatment arms. Non-normally distributed results were analyzed using the repeated-measures Friedman test with Dunn multiple comparison posttest analysis of results from corresponding times in the clopidogrel versus placebo treatment arms. For consistency, all figures show significant differences as determined by Dunn analysis.

### Results

The study population consisted of 12 women and 3 men, with an age of 44.7±2.4 (mean±SEM) years. Blood counts at study entry (platelet count, 231±9.8×10^9/L; hematocrit, 40.4±0.7%; and white cell count, 6.2±0.4 10^9/L; mean±SEM) were within normal ranges and did not differ significantly over the course of the study.

Figure 2A shows the results for the primary end point: 0.5 µmol/L ADP-induced platelet surface activated GPIIb-IIIa, as reported by monoclonal antibody PAC1 in a whole blood flow cytometric assay. As expected, compared with placebo, clopidogrel resulted in a marked, statistically significant reduction in ADP-induced platelet surface activated GPIIb-IIIa. Also as expected, discontinuation of clopidogrel resulted in a gradual return of ADP-induced platelet surface activated GPIIb-IIIa toward normal levels. Normal levels of platelet surface activated GPIIb-IIIa were achieved 8 to 11 days postclopidogrel discontinuation—a time frame consistent with the life span of platelets and the irreversible binding of the active metabolite of clopidogrel to P2Y12 receptors.29 However, at no time point after discontinuation of clopidogrel (days 1, 4, 8, 11, 15, and 45 postclopidogrel discontinuation) was platelet reactivity, as determined by 0.5 µmol/L ADP-induced platelet surface activated GPIIb-IIIa, significantly greater than after discontinuation of placebo (Figure 2A).
In both the absence (baseline [day −15]) and presence of clopidogrel, increasing concentrations of ADP resulted in increasing platelet surface activated GPIIb-IIIa (Figure 2A through 2C—note differing y-axis scales). Similarly, in both the absence (baseline [day −15]) and presence of clopidogrel, increasing concentrations of TRAP resulted in increasing platelet surface activated GPIIb-IIIa (Figure 2D and 2E—note differing y-axis scales). These data demonstrate the wide dynamic range of this assay and indicate that the assay had the capacity to detect increased platelet reactivity, if present. However, at no time point after discontinuation of clopidogrel was platelet reactivity significantly greater than after discontinuation of placebo, as determined by platelet surface activated GPIIb-IIIa in response to ADP 0.5 μmol/L (Figure 2A), ADP 1 μmol/L (Figure 2B), ADP 20 μmol/L (Figure 2C), TRAP 1 μmol/L (Figure 2D), TRAP 20 μmol/L (Figure 2E), or the combination of 5 μg/mL collagen and 5 μmol/L epinephrine (Figure 2F).

Similarly, at no time point after discontinuation of clopidogrel was platelet reactivity significantly greater than after discontinuation of placebo, as determined by the following end points: (1) platelet surface P-selectin in response to ADP 0.5, 1, and 20 μmol/L; TRAP 1 and 20 μmol/L; and the combination of collagen 5 μg/mL and epinephrine 5 μmol/L.
ADP 2.5 μmol/L (Figure 3A), ADP 5 μmol/L (Figure 3B), ADP 20 μmol/L (Figure 3C), TRAP 2 μmol/L (Figure 3D), TRAP 20 μmol/L (Figure 3E), and collagen 6 μg/mL (Figure 3F); (3) whole blood impedance aggregation with ADP 1.6 μmol/L (Figure 4A), ADP 6.5 μmol/L (Figure 4B), TRAP 4 μmol/L (Figure 4C), TRAP 32 μmol/L (Figure 4D), and collagen 3.2 μg/mL (data not shown).

The concentration of plasma soluble CD40L (a measure of in vivo platelet activation\textsuperscript{24,30} [Figure 5]) and the number of young platelets (as determined by the immature platelet fraction [IPF, Figure 6A] and the immature platelet count [Figure 6B]) did not differ after discontinuation of clopidogrel versus discontinuation of placebo.

Figure 5. Plasma soluble CD40 ligand before, during, and after ingestion of clopidogrel or placebo. Open circles and dashed line: placebo. Closed squares and solid line: clopidogrel. Day refers to the number of days after study drug discontinuation. Results shown are means ± SEM, n=15.

Discussion

There is an increased risk of thrombosis after the discontinuation of clopidogrel in coronary artery disease patients treated medically or by percutaneous coronary intervention.\textsuperscript{9–11,13–16} Possible mechanisms for this phenomenon include recovery of platelet reactivity to pretreatment levels or “rebound” platelet hyperreactivity caused by increased sensitivity to ADP (eg, upregulation of ADP receptors or enhanced intraplatelet signaling\textsuperscript{1}), increased release of soluble CD40L from previously protected platelets, or release of young platelets into the circulation. The present randomized, double-blind, placebo-controlled, crossover study, the PACT study, addressed all of these mechanisms. The major findings of the PACT study are that, as determined by multiple time points, assays, agonists, and agonist concentrations, discontinuation of clopidogrel therapy: (1) results in recovery of platelet reactivity to pretreatment levels but does not result in “rebound” platelet hyperreactivity (Figure 2 to 4), (2) does not result in increased release of soluble CD40L (Figure 5), and (3) does not result in the release of young platelets into the circulation (Figure 6).

Discontinuation of clopidogrel is a risk factor for late stent thrombosis after drug-eluting stents.\textsuperscript{13–16} In a retrospective cohort study of 3137 coronary artery disease patients treated medically or by percutaneous coronary intervention, Ho et al\textsuperscript{11} observed a clustering of adverse events that peaked at approximately 45 days after discontinuation of clopidogrel, which they hypothesized was due to “rebound” platelet activation after clopidogrel discontinuation. Although this 45-day peak is well beyond the maximal platelet life span of approximately 10 days,\textsuperscript{28} we therefore studied our subjects up until 45 days after discontinuation of clopidogrel but still found no evidence of “rebound” platelet activation (Figures 2 to 4). More recently, Eisenberg et al\textsuperscript{31} reported a retrospective analysis of published cases of late stent thrombosis in patients with drug-eluting stents, which showed that only 6% of reported late stent thrombosis occurred within 10 days after discontinuation of thienopyridine therapy (median time to late stent thrombosis, 122 days after discontinuation of thienopyridine therapy). In contrast, 75% of reported cases of late stent thrombosis occurred within 10 days after discontinuation of aspirin whether thienopyridine therapy was maintained or had previously been discontinued (median time to late stent thrombosis, 7 days). These results combined with our finding that in healthy subjects discontinuation of clopidogrel does not result in “rebound” platelet hyperreactivity suggests that abrupt discontinuation of P2 \textsubscript{y}12 blockade is not associated with an immediate increase in risk for thrombosis, provided antiplatelet therapy with aspirin is maintained. Although our data and the timing of late stent thrombosis after discontinuation of clopidogrel\textsuperscript{13–15} do not support the concept of rebound, the occurrence of late stent thrombosis after discontinuation of clopidogrel\textsuperscript{13–15} may be explained the presently demonstrated recovery of platelet reactivity to preclopidogrel levels and suggests a benefit for prolonged dual antiplatelet therapy. Large-scale clinical trials, such as the ongoing Dual Antiplatelet Therapy Study (DAPT Study), (http://www.clinicaltrials.gov/ct2/show/NCT00977938), are

Figure 6. A. Immature platelet fraction and B, immature platelet count before, during, and after ingestion of clopidogrel or placebo. Open circles and dashed line: placebo. Closed squares and solid line: clopidogrel. Day refers to the number of days after study drug discontinuation. Results shown are mean ± SEM, n=15.
required to determine the relative risks and benefits of short-versus long-term dual antiplatelet therapy.

Angiolillo et al reported that after clopidogrel withdrawal in patients with diabetes and coronary artery disease, there was a significant increase in platelet surface P-selectin in both unstimulated and ADP-stimulated platelets and an increase in ADP-stimulated platelet aggregation in platelet-rich plasma. However, whether this increase represented hyperreactivity or a return to the expected preclopidogrel response remained unknown because preclopidogrel samples were not evaluated in this study. To try and overcome the problem of obtaining preclopidogrel samples from patients, Sibbing et al hypothesized that platelet hyperreactivity, if it existed, would be greater in patients who discontinued clopidogrel abruptly compared with those who discontinued clopidogrel using a tapered regimen. These authors therefore designed a study to compare platelet reactivity for these 2 treatment regimens. However, in the absence of a preclopidogrel control group, it is an unproven assumption that the tapered regimen reduced or prevented platelet hyperreactivity. Thus, comparable platelet reactivity in these 2 groups, as was observed by Sibbing, could be interpreted as either platelet hyperreactivity in both groups or lack of platelet hyperreactivity in both groups. All other previous reports of platelet hyperreactivity after discontinuation of clopidogrel therapy similarly lack the necessary control group that was included in the present study: multiple measurements of platelet reactivity in the same subjects in the absence of clopidogrel treatment.

The conclusion that discontinuation of clopidogrel therapy, as compared with discontinuation of placebo therapy, does not result in a “rebound” platelet hyperreactivity was established in the present prospective, randomized, double-blind, placebo-controlled crossover study by multiple time points (days 1, 4, 8, 11, 15, and 45 after discontinuation of clopidogrel) and multiple assays, agonists, and agonist concentrations: platelet surface activated GPIIb-IIIa and surface P-selectin (by whole blood flow cytometry) in response to ADP 0.5, 1, and 20 μmol/L; TRAP 1 and 20 μmol/L and a combination of collagen 5 μg/mL and epinephrine 5 μg/mL; light transmission aggregation with ADP 2.5, 5, and 20 μmol/L; TRAP 2 and 20 μmol/L and collagen 6 μg/mL; and whole blood impedance aggregation with ADP 1.6 and 6.5 μmol/L; TRAP 4 and 32 μmol/L; and collagen 3.2 μg/mL. It has been reported that results obtained in citrated blood samples using low concentration ADP (<10 μmol/L) as the agonist may be biased by residual thromboxane A2 generation due to incomplete aspirin inhibition of COX-1. However, even if residual thromboxane A2 was present, platelet reactivity to low concentrations of ADP after discontinuation of clopidogrel did not exceed platelet reactivity in the placebo arm of the study. Therefore, although residual COX-1 activity may contribute to a higher than desired level of platelet reactivity for some individuals on aspirin, this level of platelet reactivity was not enhanced by discontinuation of clopidogrel. In any event, similar results were obtained when samples were anticoagulated with hirudin rather than citrate and assessed by whole blood impedance aggregometry (Figure 4). The vasodilator-stimulated phosphoprotein (VASP) assay, another widely used assay for evaluating the effect of clopidogrel on platelet function, was considered as a potential additional assay in the present study for the detection of platelet hyperreactivity after clopidogrel discontinuation. However, as the VASP assay is currently configured, in uninhibited blood samples the addition of prostaglandin E1 increases VASP phosphorylation and addition of ADP attenuates VASP phosphorylation to background levels (resulting in platelet reactivity indexes close to 100%). Consequently, addition of ADP can produce no further decrease in VASP phosphorylation, even if termination of clopidogrel were to result in P2Y12-mediated platelet hyperreactivity. Therefore, the VASP assay was considered an unsuitable end point for the present study and was not included.

Plasma soluble CD40L concentration is a marker of platelet activation. Because clopidogrel has been reported to inhibit the release of soluble CD40L from platelets, we also examined the possibility that discontinuation of clopidogrel resulted in a surge in the release of soluble CD40L from previously protected platelets. However, this was not the case (Figure 5).

Collet and Montalescot raised the hypothesis that discontinuation of oral antiplatelet therapy is associated with a rebound of thrombotic events at least in part on the basis of the number of circulating new platelets (by the IPF in a Sysmex XE-2100, which is based on the higher messenger RNA content of young compared with old platelets). We demonstrated that discontinuation of clopidogrel did not result in the release of young platelets (Figure 6).

This study was conducted in healthy volunteers, not patients. Consequently, this study does not rule out a possible effect of cardiovascular risk factors such as smoking or diabetes, which have an impact on clopidogrel responsiveness, on platelet function after discontinuation of clopidogrel. Rigorous evaluation of the hypothesis that discontinuation of clopidogrel results in platelet hyperreactivity requires (1) a homogeneous population, which is difficult to achieve in patients due to variability in disease and treatments; (2) specific isolation of the study variable, for example, discontinuation of clopidogrel, which is also difficult to achieve in patients due to variability in disease and treatments and may raise ethical concerns in patients. These issues were, however, able to be addressed by the present randomized, double-blind, placebo-controlled, crossover study conducted in healthy volunteers. A major advantage of the placebo and crossover design is that the assessment of whether discontinuation of clopidogrel resulted in platelet hyperreactivity was not dependent on a single preclopidogrel sample, which could be unusually low due to an unknown variable(s), for example, in the diet. Furthermore, the proposed mechanisms for platelet hyperreactivity (increased sensitivity to ADP, increased release of CD40L from previously protected platelets, or release of young platelets into the circulation) are not restricted to patients and are not dependent on underlying atherothrombosis.

Conclusion

This prospective, randomized, double-blind, placebo-controlled, crossover study demonstrated by multiple time...
points, assays, agonists, and agonist concentrations that discontinuation of clopidogrel in healthy subjects does not result in “rebound” platelet hyperreactivity. This study, the first rigorous evaluation of platelet reactivity after discontinuation of clopidogrel, suggests that recovery of platelet function to pretreatment levels but not a “rebound” phenomenon accounts for the reported increased incidence of thrombotic events in patients after termination of clopidogrel therapy.

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“Rebound” platelet hyperreactivity after discontinuation of clopidogrel has been proposed to lead to increased thrombotic risk, including late stent thrombosis. This putative phenomenon is relevant to the question of when or if clopidogrel treatment after stent placement should be discontinued and whether a tapering regimen of clopidogrel treatment might reduce thrombotic complications. However, the hypothesis that discontinuation of clopidogrel results in platelet hyperreactivity has never been rigorously tested. We report a randomized, double-blind, placebo-controlled, crossover study in which platelet reactivity was measured using multiple methods, agonists, and agonist concentrations, before, during, and after exposure of subjects to clopidogrel or placebo. All subjects showed the expected inhibition of platelet reactivity during exposure to clopidogrel. However, at no time point after discontinuation of clopidogrel was platelet reactivity, as determined by any assay end point, significantly greater than after discontinuation of placebo. These results demonstrate that discontinuation of clopidogrel does not result in “rebound” platelet hyperreactivity and suggest that recovery of platelet function to pretreatment levels but not a “rebound” phenomenon accounts for the reported increased incidence of thrombotic events in patients after termination of clopidogrel therapy. Although prolonged clopidogrel treatment would prevent recovery of platelet reactivity to pretreatment levels and perhaps the associated increased incidence of thrombotic events, the optimal duration of dual antiplatelet therapy remains unknown. Large-scale clinical trials, such as the ongoing Dual Antiplatelet Therapy Study (DAPT Study), (http://www.clinicaltrials.gov/ct2/show/NCT00977938), are required to determine the relative risks and benefits of short versus long-term dual antiplatelet therapy.
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