Acute Antithrombotic Effect of a Front-Loaded Regimen of Clopidogrel in Patients With Atherosclerosis on Aspirin


Abstract—There is a need for a rapid antithrombotic effect after the administration of antiplatelet drugs in the setting of acute coronary syndromes and percutaneous interventions. Clopidogrel, a new thienopyridine derivative, is an efficient antiplatelet agent. However, the standard regimen of clopidogrel (75 mg/d) requires 2 to 3 days before significant antithrombotic effects. Patients with stable arterial disease on chronic aspirin therapy (n=20) were treated with clopidogrel either with a front-loaded regimen, 300 mg the first day and 75 mg/d the next 7 days, or with a standard regimen, 75 mg/d for 8 days. Blood thrombogenicity was assessed by quantification of platelet-thrombus formation in an ex vivo perfusion chamber, by ADP-induced platelet aggregation, and by ADP-induced fibrinogen binding. At 2 hours, mean total thrombus area with the standard regimen was not significantly reduced. In contrast, at 2 hours, the mean total thrombus area with the front-loaded regimen was significantly decreased by 23.1±8.5% versus baseline (P<0.05). ADP-induced platelet aggregation (with 5 and 10 μmol/L) was also significantly (P<0.05) reduced with the front-loaded regimen at 2 hours, with the mean platelet aggregation being 82.2±4.4% and 81.8±4.5%, respectively, versus baseline. Similarly, flow cytometry demonstrated a significant decrease (P<0.05) in the ADP-induced fibrinogen binding (with 0.12 and 0.6 μmol/L) at 2 hours in this front-loaded regimen group (36.1±2.0% and 53.2±9.3%). With the standard regimen, platelet activity was not significantly reduced at 2 hours. Our data suggest that a front-loaded regimen of clopidogrel added to aspirin achieves a significant antithrombotic effect at 2 hours in patients with known atherosclerotic disease on chronic aspirin therapy. This provides a rationale for using front-loaded clopidogrel in combination with aspirin in percutaneous coronary interventions. (Arterioscler Thromb Vasc Biol. 2000;20:2316-2321.)

Key Words: platelet aggregation inhibitors thrombus atherosclerosis

The central role of platelets in arterial thrombosis is well established.1 Platelet activity and thrombin and thromboxane generation are markedly increased after myocardial infarction, thrombolysis, unstable angina, and percutaneous coronary interventions.1,2 Numerous studies have shown that antiplatelet agents like aspirin or ticlopidine are effective for secondary prevention of coronary and cerebrovascular events.3 Combined antiplatelet therapy with aspirin and ticlopidine improves clinical outcome after stent implantation compared with aspirin alone or aspirin plus full anticoagulation.4–7 New antiplatelet drugs, including glycoprotein IIb/IIIa antagonists and clopidogrel, a new ADP-receptor antagonist, also reduce coronary events.8,9

Aspirin inhibits cyclooxygenase, whereas clopidogrel inhibits the binding of ADP to its platelet receptor, which leads to reduced binding of fibrinogen to glycoprotein IIb/IIIa receptors.10,11 Given the different mechanisms of action and proven safety of these combined drugs, combined therapy appears logical and has already given encouraging results in nonrandomized comparisons in patients undergoing coronary stenting.12–15 There is a need for rapid efficacy after the administration of antiplatelet drugs in the setting of percutaneous interventions and acute coronary syndromes. However, the standard regimen of clopidogrel (75 mg/d) requires 2 to 3 days before significant effects occur in platelet aggregation.16

The major objective of this study was to investigate whether a front-loaded regimen of clopidogrel added to aspirin could achieve a significant antithrombotic activity 2 hours after its administration. Antithrombotic activity was assessed by evaluating (1) the quantitative growth of thrombus in a well-validated ex vivo perfusion chamber, (2) ADP-induced platelet aggregation, and (3) ADP-induced fibrinogen binding by flow cytometry in patients with atherosclerosis receiving chronic aspirin therapy.17 No clinical or experimental study has assessed, in patients with atherosclerosis, the acute antithrombotic effect of the combination of clopidogrel and aspirin (load and no-load) compared with aspirin alone. Therefore, the secondary objective was to compare the antithrombotic effect at day 8 of the standard regimen of clopidogrel versus the antithrombotic effect of

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baseline aspirin therapy alone in atherosclerotic patients on chronic aspirin therapy.

Methods

Patient Population

The study population included patients with stable coronary or peripheral arterial disease (n=20). All patients were receiving chronic aspirin therapy (325 mg/d) for ≥3 months. The presence of coronary artery disease was documented by coronary angiography, history of previous myocardial infarction, or typical angina pectoris with a positive stress test. The existence of peripheral disease was documented by lower-extremity claudication, previous peripheral angioplasty, bypass grafting, or >50% stenosis in any artery distal to the aortic bifurcation by angiography or ultrasound. Exclusion criteria included hemoglobin <12 g%, history suggestive of recurrent blood loss, or poorly controlled hypertension (>180/100 mm Hg). The study was approved by the Institutional Review Board, and all patients signed informed consent to participate.

The selected patients were randomized to 1 of 2 treatment groups in a double-blind, placebo-controlled design. The front-loaded regimen received a loading dose of clopidogrel (four 75-mg tablets) and 75 mg/d of clopidogrel on the first day, followed by 75 mg/d for the next 7 days. The standard regimen group received a loading dose of 3 identical placebo capsules plus a 75-mg clopidogrel capsule on the first day followed by 75 mg/d of clopidogrel for the next 7 days. All patients continued taking 325 mg/d of aspirin for the duration of the study. The CAPRIE Trial used a dose of 75 mg/d clopidogrel, which is approved by the FDA.5 The effects of the 2 treatments were studied at serial time points throughout the study and were compared with their respective pretreatment values. This design allowed each patient to serve as his or her own control. The investigators performing the perfusion and platelet studies, described further below, were blinded as to treatment assignment.

Quantification of Platelet-Thrombus Formation

Quantification of platelet-thrombus formation was assessed at baseline, after 2 hours, and on day 2. The effect of clopidogrel on ex vivo arterial thrombus formation was assessed by measuring the area of thrombus formation in a perfusion chamber. The description, validity, and reliability of the Badimon perfusion system to study arterial thrombus formation were reported previously.17-19 In brief, a 19-gauge needle was carefully inserted into an antecubital vein. After the first 5 mL of blood had been discarded, the needle was connected to the perfusion chamber. Native, nonanticoagulated blood was directly perfused from the antecubital vein to the perfusion chambers at a constant flow rate with a peristaltic pump (Masterflex, Cole-Parmer Instruments) distal to the chambers. The Plexiglas perfusion chamber consists of a cylindrical flow channel (1-mm diameter, 2.5-cm length) that allows the blood to flow over the thrombogenic substrate. All perfusions were performed for a period of 5 minutes at a flow rate of 10 mL/min (calculated shear rate of 1690/s; Reynolds number of 60; average blood velocity 21.2 cm/s). The selected dynamic conditions model the local rheology associated with mildly stenosed coronary arteries. Previous work has demonstrated that these rheological conditions result in consistent thrombus formation in a perfusion chamber. The description, validity, and reliability of the Badimon perfusion system to study arterial thrombus formation were assessed at serial time points throughout the study and were compared with their respective pretreatment values. This design allowed each patient to serve as his or her own control. The investigators performing the perfusion and platelet studies, described further below, were blinded as to treatment assignment.

To mimic the in vivo situation of severe arterial injury, porcine aortic tunica media was used as the substrate to trigger thrombus formation. Segments of porcine aorta were cut into segments (2.8×0.8 cm) and surgically prepared to expose the deeper components of the arterial wall as previously described.17 The histological assessment of thrombus formation was performed by histomorphometry as previously described.17-19 In brief, after blood perfusion, the segments were removed from the chambers, fixed in 4% paraformaldehyde, and embedded in paraffin. Sections (5 μm) were cut and stained with a combined Masson’s trichrome-elastin to visualize the total thrombus formed on the exposed substrates. Morphometric analysis of thrombus was conducted at 400-fold magnification. Images were digitized with a Sony DKC-5000 camera using Adobe Photoshop 4.0 software on a PowerMacIntosh 8500 computer. The thrombus area on each section was measured by computerized planimetry using Image Pro-plus software (Media Cybernetic). Results are given as the average of the analyzed sections (n=6) per chamber and expressed as the percentage of thrombus area compared with baseline. The measurements were performed by a single investigator blinded to the assigned therapy.

Platelet Aggregation

Platelet aggregation was performed at baseline, 2 hours, 6 hours, day 2, and day 8. Blood (16 mL) was drawn from an antecubital vein through a 19-gauge needle into 2 mL of 110 mmol/L trisodium citrate solution. Platelet-rich plasma and platelet-poor plasma were prepared by differential centrifugation. Platelet concentration in platelet-rich plasma was adjusted to 2.5×10^10/L by the addition of platelet-poor plasma. ADP (Chronolog) at concentrations of 5 and 10 μmol/L served as an agonist to trigger platelet aggregation. The aggregation response was recorded for 6 minutes after addition of the agonist in an aggregometer (Chrono-log model 440, Chrono-log Corp). Platelet aggregation was expressed as the mean percentage of maximum platelet aggregation compared with baseline.

Flow Cytometry

Platelet activation was assessed at baseline, 2 hours, day 2, and day 8. Samples were prepared within 1 hour of collection. FITC-conjugated chicken anti-fibrinogen antibody (10 μL; Wak-Chemie Medical GmbH) was added to 3 tubes containing 230 μL HEPES buffer or HEPES-EDTA buffer for the negative control.20 Thereafter, 20 μL platelet-rich plasma was added and incubated for 10 minutes at room temperature. Twenty microliters of a solution of ADP in HEPES buffer (0, 0.12, and 0.6 μmol/L) was added to each sample tube, and 20 μL of HEPES-EDTA buffer was added to the negative control. After exactly 10 minutes of incubation, 2 mL of ice-cold HEPES buffer was added to each tube. Samples were analyzed within the next 3 hours in a Becton-Dickinson flow cytometer analyzer. Activated platelets are expressed as a percentage, and the results are expressed as the relative fibrinogen binding compared with baseline.

Blood Samples

Blood was collected at baseline and day 8 for complete blood examination. Blood (4.5 mL) was also collected in SCAT tubes (Hematologic Technologies Inc) containing PPACK, EDTA, and aprotinin. Repeated blood samples for prothrombin fragment 1+2, a marker of thrombin generation, were obtained from the 20 patients at baseline, 2 hours, and day 8. Aliquots of plasma were stored at −70°C until analysis with ELISA (Enzygnost, Dade Behring).

Statistical Analysis

As already mentioned, the study design allowed each patient to serve as his or her own control (pretreatment versus posttreatment). Continuous variables were expressed as percentage of baseline±SEM and compared by a paired Student’s t test (within-group comparisons). Statistical significance was considered as a 2-tailed probability <0.05.

Results

Study Population and Hematological Parameters

Twenty patients with stable coronary or peripheral arterial disease were studied; all of them completed the platelet reactivity data and 16 of them the perfusion chamber data. Baseline characteristics of these patients are summarized in the Table. No statistically significant differences were observed between the groups. In particular, use of antianginal and hypolipidemic drugs did not differ between groups.

There were no adverse events related to the medication. All patients received aspirin (325 mg/d) with the clopidogrel. In particular, no bleeding, gastrointestinal upset or rash was noted. Hematocrit, white cell count, and platelet count were...
measured in EDTA-blood at baseline and at day 8 and did not change significantly.

**Effects of Clopidogrel Treatments on Thrombus Area**
The effects of the 2 regimens on thrombus formation were assessed at 2 time points (2 hours and day 8) and compared with their respective baseline (aspirin-treated) values (Figure 1). No significant difference was observed in the mean thrombus formation between the 2 groups at baseline, indicating the homogeneity of the study groups. At 2 hours, mean thrombus area with the standard regimen was decreased by 9.9 $\pm$ 7.9% but was not significantly different from baseline ($P_{\text{NS}}$). In contrast, at 2 hours, the mean thrombus area in patients receiving the front-loaded regimen was 23.1 $\pm$ 8.5% less than the mean pretreatment value ($P_{0.05}$). As expected, the mean thrombus areas were significantly reduced at day 8 in both groups compared with the baseline (22.2 $\pm$ 6.9% with the standard regimen and 29.1 $\pm$ 9.1% with the front-loaded regimen).

**Effects of Clopidogrel Treatments on Platelet Aggregation**
Mean maximum percentages of ADP-induced platelet aggregation at baseline were comparable in both groups (Figure 2A and 2B). No significant inhibition of ADP-induced platelet aggregation was noted at 2 and 6 hours with ADP 5 and 10 $\mu$mol/L with the standard regimen of clopidogrel (mean platelet aggregation: 86.9 $\pm$ 8.0%, 95.0 $\pm$ 4.7% and 89.3 $\pm$ 6.8%, 96.5 $\pm$ 3.2%, respectively). At day 2, significant inhibition was achieved, the mean platelet aggregation with ADP 5 and 10 $\mu$mol/L being 66.3 $\pm$ 6.2% and 82.6 $\pm$ 6.7%, respectively.

In contrast, a significant inhibition of ADP-induced platelet aggregation was observed at 2 hours with the front-loaded regimen of clopidogrel. At this time, the mean platelet aggregation for ADP 5 and 10 $\mu$mol/L was 82.2 $\pm$ 4.4% and 81.8 $\pm$ 4.5%, respectively, compared with baseline (aspirin alone). Further significant inhibition ($P_{0.05}$) was observed at 6 hours, with a mean platelet aggregation of 63.5 $\pm$ 4.9% and 68.4 $\pm$ 5.2% for both concentrations of ADP used. At day 2 and day 8, no further significant inhibition of platelet aggregation was noted.

**Effects of Clopidogrel Treatments on Fibrinogen Binding to ADP-Activated Platelets**
There was no significant difference at baseline between the 2 groups (Figure 3A and 3B). With the front-loaded regimen, platelet activation, as determined by ADP-induced platelet-fibrinogen binding by flow cytometry, was significantly reduced ($P_{0.05}$) at 2 hours for ADP concentrations of 0.12 and 0.6 $\mu$mol/L, the fibrinogen binding being 36.1 $\pm$ 2.0% and 53.2 $\pm$ 9.3%, respectively, compared with baseline. In contrast, platelet activation was not significantly reduced at 2

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**Table: Baseline Characteristics in Patients Randomized to Standard (n=10) Versus Front-Loaded (n=10) Regimen of Clopidogrel**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Standard Regimen</th>
<th>Front-Loaded Regimen</th>
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<tbody>
<tr>
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<td>Long-acting nitrate</td>
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With a front-loaded regimen of clopidogrel (300 mg), it is possible to achieve a significant antithrombotic effect at 2 hours. We have shown that a front-loaded regimen of clopidogrel induces maximal antithrombotic activity as early as 2 hours after its administration, as assessed by reduction in thrombus formation and platelet reactivity. We have also demonstrated that although a significant reduction in ADP-platelet aggregation is obtained with 300 mg of clopidogrel after 2 hours, a further significant reduction is achieved at 6 hours. This confirms recent findings showing that a loading regimen of clopidogrel induces maximal inhibition of platelet aggregation at 5 hours.

The early antithrombotic effect on platelet activation we observed with a loading dose of clopidogrel, as assessed by flow cytometry, is consistent with the reduction in thrombus formation. The reduction in the fibrinogen binding obtained with a front-loaded regimen of clopidogrel is already significant at 2 hours, whereas with the standard regimen, a significant reduction was observed only at day 2. Similarly, an acceleration of platelet inhibition has been shown with a loading dose of a similar agent, ticlopidine (500 mg), in patients undergoing coronary angiography at 24 hours, but no data at 2 hours were provided.

Prothrombin fragment F1 + 2 plasma levels were similar throughout the study and between the groups. This is consistent with other published data showing that thrombin generation is not directly reduced with thienopyridines.

**Antithrombotic Effect of Clopidogrel Administration in Atherosclerotic Patients Receiving Chronic Aspirin Therapy**

We showed that the antithrombotic effect of treatment with clopidogrel for 8 days (75 mg/d) in patients with atherosclerosis receiving chronic aspirin therapy is greater than the antithrombotic effect of chronic aspirin therapy alone. In animal models, clopidogrel has antithrombotic effects in both arterial and venous thrombosis. In a porcine ex vivo model of high shear–induced stent thrombosis, intravenous clopidogrel produced a dose-dependent inhibition of stent thrombosis. In nonhuman primates, clopidogrel reduced thrombosis in a baboon model of arterial thrombosis. To the best of our knowledge, only 1 study focused on the inhibition of thrombogenesis by clopidogrel in humans. In this study, a standard regimen of clopidogrel significantly inhibited thrombus formation in healthy male subjects after 2 weeks of aspirin. To the best of our knowledge, this is the first report of quantitative reduction in thrombus formation in a patient population with documented atherosclerotic disease receiving aspirin. Previous data in normal subjects have indicated that a dose of 300 to 400 mg produced a rapid onset of the pharmacodynamic activity of clopidogrel, with levels of platelet inhibition close to steady state observed within the first hours after dosing. Our findings confirm and extend these results in patients with atherosclerotic disease receiving chronic aspirin therapy. But more importantly, we have shown that the antithrombotic effect, assessed in a perfusion chamber mimicking an arterial injury atop a mild stenosis in a coronary artery, is achieved as early as 2 hours after front-loaded regimen administration. This provides evidence for the rapid onset of an antithrombotic effect with a loading dose (300 mg) of clopidogrel in the treatment of acute coronary syndromes and in coronary stent implantation. This is important because the median time from stent implantation to stent thrombosis in patients treated with ticlopidine and aspirin is ≈12 hours. To date, it appears that a standard regimen of ticlopidine or clopidogrel does not achieve a significant early antithrombotic effect.

We have also demonstrated that although a significant reduction in ADP-platelet aggregation is obtained with 300 mg of clopidogrel after 2 hours, a further significant reduction is achieved at 6 hours. This confirms recent findings showing that a loading regimen of clopidogrel induces maximal inhibition of platelet aggregation at 5 hours.

**Acute Antithrombotic Effect of a Front-Loaded Regimen of Clopidogrel**

With a front-loaded regimen of clopidogrel (300 mg), it is possible to achieve a significant antithrombotic effect at 2 hours, an effect not obtained with the standard regimen, in patients with known atherosclerotic disease already receiving aspirin. To the best of our knowledge, this is the first report of quantitative reduction in thrombus formation in a patient population with documented atherosclerotic disease receiving aspirin. Previous data in normal subjects have indicated that a dose of 300 to 400 mg produced a rapid onset of the pharmacodynamic activity of clopidogrel, with levels of platelet inhibition close to steady state observed within the first hours after dosing. Our findings confirm and extend these results in patients with atherosclerotic disease receiving chronic aspirin therapy. But more importantly, we have shown that the antithrombotic effect, assessed in a perfusion chamber mimicking an arterial injury atop a mild stenosis in a coronary artery, is achieved as early as 2 hours after front-loaded regimen administration. This provides evidence for the rapid onset of an antithrombotic effect with a loading dose (300 mg) of clopidogrel in the treatment of acute coronary syndromes and in coronary stent implantation. This is important because the median time from stent implantation to stent thrombosis in patients treated with ticlopidine and aspirin is ≈12 hours. To date, it appears that a standard regimen of ticlopidine or clopidogrel does not achieve a significant early antithrombotic effect.

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Prothrombin fragment F1 + 2 plasma levels were similar throughout the study and between the groups. This is consistent with other published data showing that thrombin generation is not directly reduced with thienopyridines.
a standard regimen of clopidogrel. We found that the inhibition was significant at day 8 in patients with atherosclerosis receiving chronic aspirin therapy when a standard regimen of clopidogrel was used.

Large-scale, randomized, placebo-controlled trials have clearly established that oral aspirin therapy decreases the risk of thrombotic events in patients with symptomatic atherosclerotic disease by 20% to 25%. Because aspirin is only a cyclooxygenase inhibitor, its effectiveness is limited, because it fails to block platelet activation by other important agonists such as shear stress, thrombin, collagen, and ADP. Clopidogrel is an ADP-receptor antagonist that is free of the hematological side effects of ticlopidine therapy. Clopidogrel acts by irreversibly inactivating platelet ADP receptor–initiated signaling in a dose-dependent manner. In a large-scale, randomized clinical trial, clopidogrel was shown to be significantly more effective than and at least as safe as aspirin in decreasing arterial thrombo-occlusive episodes in patients with symptomatic atherosclerotic disease. However, aspirin and clopidogrel interfere with different pathways of platelet activation. Therefore, to improve the antithrombotic effect, the combination of these 2 drugs has been suggested. Additive antithrombotic effects of clopidogrel and aspirin have been demonstrated in experimental models in the rabbit. Interestingly, clopidogrel and aspirin have produced additive antithrombotic effects as assessed by measurements of In-labeled platelets and I-labeled fibrin deposition in a porcine ex vivo model of high shear–induced stent thrombosis. In our study, the combination of aspirin and clopidogrel significantly improved the antithrombotic effect of aspirin alone in patients receiving chronic aspirin therapy. The rheological conditions (1690/s) we used mimicked those typical of a mildly stenosed coronary artery. These rheological conditions were selected because ≈70% of the plaques responsible for an acute myocardial infarction have <50% stenosis.

Limitations
Our data support the added benefit of combining clopidogrel with aspirin on thrombus formation without any bleeding complications. However, this is a pilot study, and large-scale clinical trials are needed to further clarify the efficacy and safety of the combination of aspirin and clopidogrel.

Conclusions
Our data suggest that a front-loaded regimen of clopidogrel 300 mg added to aspirin achieves a significant antithrombotic effect at 2 hours, an effect not achieved with the standard regimen, in patients with known atherosclerotic disease on chronic aspirin therapy. This supports the efficacy of a loading dose of clopidogrel in acute coronary syndromes and percutaneous coronary interventions.

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