SCH 602539, a Protease-Activated Receptor-1 Antagonist, Inhibits Thrombosis Alone and in Combination With Cangrelor in a Folts Model of Arterial Thrombosis in Cynomolgus Monkeys

Madhu Chintala, John Strony, Bo Yang, Stan Kurowski, Qiu Li

Objective—To determine the antithrombotic effects of SCH 602539, an analog of the selective protease-activated receptor (PAR)-1 antagonist vorapaxar (formerly SCH 530348) currently in advanced clinical development, and the P2Y12 ADP receptor antagonist cangrelor, alone and in combination.

Methods and Results—Multiple platelet activation pathways contribute to thrombosis. The effects of SCH 602539 and cangrelor alone and in combination on cyclic flow reductions were evaluated in a Folts model of thrombosis in cynomolgus monkeys. The effects of these treatments on ex vivo platelet aggregation and coagulation parameters were also monitored. Dose-dependent inhibition of cyclic flow reductions was observed after treatment with SCH 602539 alone and cangrelor alone ($P<0.05$ versus vehicle for the 2 highest concentrations of each agent). The combination of SCH 602539 and cangrelor was associated with synergistic antithrombotic effects ($P<0.05$ versus vehicle for all combinations tested). The 2 highest doses of SCH 602539 inhibited platelet aggregation in response to PAR-1–selective high-affinity thrombin receptor agonist peptide by greater than 80% but did not affect platelet aggregation induced by other agonists; also, they did not affect any coagulation parameters.

Conclusion—The combined inhibition of the PAR-1 and the P2Y12 ADP platelet activation pathways had synergistic antithrombotic and antiplatelet effects. The addition of a PAR-1 antagonist to a P2Y12 ADP receptor antagonist may provide incremental clinical benefits in patients with atherothrombotic disease, both in short- and long-term settings. These hypotheses need to be tested clinically. (Arterioscler Thromb Vasc Biol. 2010;30:2143-2149.)

Key Words: thrombin ■ thrombosis ■ PAR-1 antagonist ■ antiplatelet ■ platelet activation pathways

Atherothrombotic disease is associated with considerable morbidity and mortality.1 Although the benefits of dual antiplatelet therapy with aspirin and a P2Y12 adenosine diphosphate (ADP) receptor antagonist have been demonstrated in a broad range of patients with atherothrombotic disease, many of these patients continue to have recurrent ischemic events.2,3 This high residual risk can be attributed to the fact that aspirin and P2Y12 ADP receptor antagonists (eg, clopidogrel and prasugrel) only have a partial inhibitory effect on platelet-mediated thrombosis because they each target only 1 of many platelet activation pathways.4,5 As a result, thrombosis mediated by other platelet activation pathways, including stimulation of protease-activated receptor (PAR)-1 by thrombin, continues to occur even in the presence of aspirin and a P2Y12 ADP receptor antagonist, leading to ischemic events.

Thrombin is the most potent platelet agonist because it stimulates platelet activation at low subnanomolar concentrations.6,7 PAR-1 is the principal receptor for thrombin on human platelets, whereas the secondary PAR-4 receptor may contribute to platelet activation at high concentrations of thrombin.4,8 Because the PAR-1 pathway is a key contributor to platelet-mediated thrombosis, PAR-1 is a valid therapeutic target for the development of novel antiplatelet agents.4,8 Previous preclinical studies9,10 with PAR-1 antagonists have demonstrated antithrombotic activity without an effect on bleeding time or coagulation parameters, supporting the clinical potential of this therapeutic approach.

The present study was designed to evaluate the antithrombotic efficacy of SCH 602539, a thrombin receptor antagonist selective for PAR-1 (SCH 602539 is an analog of vorapaxar [previously known as SCH 530348], a PAR-1 antagonist currently in phase 3 clinical development), alone and in combination with a P2Y12 ADP receptor antagonist cangrelor in a Folts model of thrombosis.11 SCH 602539 and cangrelor were chosen as the prototypes for the antagonism of the PAR-1 and P2Y12 ADP receptors because both agents can be administered parenterally and titrated.
Methods

Animals
Given the existence of species differences in the platelet thrombin receptor, we used cynomolgus monkeys because they have the same distribution of thrombin receptors (PAR-1 and PAR-4) on their platelets as do humans. Animal experiments were conducted in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act, in a program accredited by the American Association for Accreditation of Laboratory Animal Care.

Folts Model of Thrombosis in Anesthetized Monkeys
The procedures used in this study are similar to the acute artery occlusion model developed by Folts and others. Cynomolgus monkeys were sedated with ketamine hydrochloride, 10 mg/kg IM, followed by anesthetization with sodium pentobarbital, 20 mg/kg IV bolus and 5 mg/kg per hour IV infusion for the duration of the experiment. The body temperature was maintained at 37°C to 39°C, and fluids infused were adjusted to body temperature. The right carotid artery was exposed and dissected free of surrounding tissue, and an appropriately sized transonic flow probe was placed around the vessel. A constrictor (Lexan; 5-mm length) was placed onto the carotid artery. The constrictor was sized to abolish reactive hyperemia and to reduce mean carotid blood flow by no more than 50% to 60%. Mechanical damage to the endothelium was induced in the constricted segment of the artery. Cyclic flow reductions (CFRs) because of platelet-dependent thrombus formation occurred shortly after placement of the constrictor over the region of endothelial damage. These gradual declines in carotid blood flow were occasionally interrupted spontaneously but frequently required manual restoration by gently shaking the vessel. Flow reductions would typically return in 3 to 4 minutes. The CFR frequency was calculated as the number of such cycles (CFRs) over a 30-minute period. Based on the pilot studies, CFRRs were evaluated in a maximum of 4 consecutive 30-minute collection periods, and mechanically mediated endothelial injury was performed at 30-minute intervals to ensure exposure of the thrombogenic endothelium.

Animals instrumented to produce CFRRs were administered SCH 602539, cangrelor, or a combination of SCH 602539 and cangrelor. The dosing regimens of the PAR-1 antagonist SCH 602539 were selected to provide complete inhibition of PAR-1–selective high-affinity thrombin receptor agonist peptide (haTRAP)–induced ex vivo platelet aggregation observed with the PAR-1 antagonist SCH 602539, cangrelor, or a combination of SCH 602539 and cangrelor.

Evaluation of Synergy
The in vivo effect of coadministration of PAR-1 and P2Y_{12} ADP receptor antagonists on the inhibition of CFRRs (synergy, additivity, or antagonism) was tested using the RACT cartridges (Medtronic). Briefly, 0.2 mL of citrated whole blood was added to each well of the cartridge and the test was initiated by inserting the cartridge into the machine (ACT II). The end point, clot formation, was measured by the rate of fall of the plunger-flag mechanism contained in each cartridge. The plunger assembly falls rapidly through an unclotted sample, but the fibrin web formed during clotting impedes the rate of descent, which can be detected by a photo-optical system and displayed. These measurements were performed in duplicate.

ACT Evaluation
The ACT test measures the clotting time of fresh whole blood and was performed in an automated coagulation timer (ACT II; Medtronic) using the RACT cartridges (Medtronic). Briefly, 0.2 mL of citrated whole blood was added to each well of the cartridge and the test was initiated by inserting the cartridge into the machine (ACT II). The end point, clot formation, was measured by the rate of fall of the plunger-flag mechanism contained in each cartridge. The plunger assembly falls rapidly through an unclotted sample, but the fibrin web formed during clotting impedes the rate of descent, which can be detected by a photo-optical system and displayed. These measurements were performed in duplicate.

Evaluation of Synergy
The in vivo effect of coadministration of PAR-1 and P2Y_{12} ADP receptor antagonists on the inhibition of CFRRs (synergy, additivity, or antagonism) was tested using the criteria described by Berenbaum. Briefly, CFR frequency was plotted versus drug dose administered and fitted to dose-response curves using inhibitory effect E_{max} modeling. Estimates of the dose regimens needed for 50% reduction in CFRRs (EC_{50}) were calculated using the following equation: E = E_{max} (1 - [C/(1 + EC_{50})]), where E is the CFR frequency, assuming maximum frequency (E_{max}) is achieved at dose level (C) 0 and 0 frequency at dose level infinity. The EC_{50} value refers to the concentration of the antplatelet agent required to reduce maximum CFR frequency by 50%.

Dose-response curves were constructed for SCH 602539 and cangrelor. Equitropin dose values obtained for the tested combinations were fitted to the equation for each individual compound. These equipotent doses were then applied to the following equation used by Berenbaum for the determination of the synergy factor.
Results

Of the 24 monkeys studied, 22 exhibited stable CFRs after instrumentation. There was minimal reduction in blood flow in the context of abolishing hyperemic blood flow. The heart rate, blood pressure, and body temperature were unchanged for the duration of the study.

Antithrombotic Effects in the Folts Model of Thrombosis

The results of 22 experiments with the vehicle are shown in Figure 2A. The stability and utility of the surgical model were demonstrated by the consistent and reproducible CFRs achieved in animals treated with vehicle for the 2-hour study period. In the 22 experiments, the control frequency of the CFRs was a mean ± SEM of 8.9 ± 1.8 per 30 minutes (range, 7–13) (Figure 2A).

Intravenous bolus doses of SCH 602539 reduced the number of CFRs in a dose-dependent manner (Figure 2B). The CFR frequency was reduced from baseline by approximately 50% with the 0.1-mg/kg dose and by greater than 80% with the 0.3- and 1.0-mg/kg doses (P < 0.05 versus vehicle for both). The CFRs were completely abolished in 4 of 6 animals with both the 0.3- and 1.0-mg/kg doses.

Continuous infusions of cangrelor reduced the CFR frequency from baseline by approximately 40%, 70%, and 90% with the 0.1-, 0.2-, and 0.3-μg/kg per minute 30-minute infusion doses, respectively (Figure 2C). The reductions achieved with the 2 highest doses were statistically significant versus vehicle. The intermediate and highest doses of cangrelor completely prevented CFRs in 3 and 5 of 6 animals, respectively. No complete suppression was evident in any of the animals treated with the lowest dose of cangrelor.

To assess the antithrombotic effects of SCH 602539 in combination with cangrelor, doses of each agent that provided only modest inhibition of CFRs when used alone were chosen (SCH 602539, 0.1 mg/kg; and cangrelor, 0.1 μg/kg per minute). Doses of SCH 602539 and cangrelor that were estimated not to affect CFR frequency when administered alone (SCH 602539, 0.05 mg/kg; and cangrelor, 0.05 μg/kg per minute), and a slightly higher dose of SCH 602539, 0.15 mg/kg, were used to explore the possibility that the antithrombotic effects of a PAR-1 antagonist and a P2Y12 ADP receptor antagonist were synergistic. Initial treatment with SCH 602539, 0.05 mg/kg, plus cangrelor, 0.05 μg/kg per minute, significantly reduced the mean CFR frequency to 2.4 and completely abolished CFRs in 2 of 5 animals (Figure 2D). Treatment with a combination of SCH 602539, 0.1 mg/kg, plus cangrelor, 0.1 μg/kg per minute, completely abolished the CFRs in 4 of 5 animals and reduced the number of CFRs by approximately 50% in the remaining animal (Figure 2D). Similar antithrombotic effects were observed with a combination of SCH 602539, 0.15 mg/kg, plus cangrelor, 0.1 μg/kg per minute (Figure 2D).

Evaluation of Synergy Resulting From Dual P2Y12 and PAR-1 Inhibition

The Folts model of CFRs, resulting from fixed stenosis of an arterial bed, is the result of the in vivo interplay of platelet-sensitive vasoactive molecules, which closely mimics the clinical scenario of unstable angina. The mean ± SEM EC50 values calculated from dose-response curves are 0.100 ± 0.042 mg/kg and 0.099 ± 0.039 μg/kg per minute for SCH 602539 and cangrelor, respectively.

Five experiments were conducted for each of the 3 combinations partnering SCH 602539 and cangrelor. The corresponding equipotent doses for each compound compared with the different dose combinations were calculated from the respective dose-response curve (Figure 2D and Figure 3). The in vivo CFR inhibition exerted by SCH 602539 or cangrelor, when combined with its partner, was greater than that of the individual components administered alone.

The presence of a synergistic interaction is suggested by the 50% reduction in CFR frequency with SCH 602539, 0.05 mg/kg, in combination with cangrelor, 0.05 μg/kg per minute; and the complete extinction of CFR production in 4 of 5 animals receiving SCH 602539, 0.1 mg/kg, plus cangrelor, 0.1 μg/kg per minute. Similar antithrombotic effects were also observed with the combination of SCH 602539, 0.15 mg/kg, plus cangrelor, 0.1 μg/kg per minute, administered in the subsequent 30-minute period. The CFR frequency for baseline and each of the 3 doses administered, along with the calculated doses, are shown for SCH 602539 and cangrelor in Figure 2D and Figure 3, respectively.

Synergism was confirmed because the synergistic factor was less than 1 in 12 of 15 combination experiments (data not shown) and was seen in the lowest tested dosage combination of 0.05 plus 0.05. By using the model of Berenbaum,14 the calculated mean ± SEM synergistic factor for all 15 combination experiments was 0.41 ± 0.17.

Effects on Ex Vivo Platelet Aggregation

The effects of SCH 602539 alone, cangrelor alone, and the combination of SCH 602539 and cangrelor on ex vivo platelet aggregation mediated by various agonists (eg, hTRAP, ADP, thromboxane A2 mimetic U46619, and collagen) in the Folts model of thrombosis in anesthetized cynomolgus monkeys were also evaluated. Table 1 outlines the inhibition of platelet aggregation noted at each of the tested dosing regimens of study drug. The 2 highest doses of SCH 602539, 0.3 and 1 mg/kg, were associated with potent (>80%) and dose-related inhibition of ex vivo platelet aggregation induced by 3-μmol/L hTRAP but did not affect the aggregation induced by 10-μmol/L ADP, 10-μmol/L thromboxane A2 mimetic U46619, and 3-μg/mL collagen, demonstrating selectivity of SCH 602539 for the PAR-1 receptor pathway. The 2 highest doses of cangrelor, 0.2 and 0.3 μg/kg per minute, inhibited ADP-mediated platelet aggregation by approximately 50% to 60% (as targeted) but did not interfere with the aggregation stimulated by 3-μmol/L hTRAP, 10-μmol/L thromboxane A2 mimetic U46619, or 3-μg/mL collagen. Finally, the combination of SCH 602539 and cangrelor inhibited the aggregation induced by 3-μmol/L hTRAP and 10-μmol/L ADP in a dose-related manner; and
the level of inhibition was the same as for each agent used alone. No inhibition of platelet aggregation induced by 10-μmol/L thromboxane A₂ mimetic U46619 or 3-μg/mL collagen was observed. These findings suggest that the ex vivo inhibition of haTRAP- and ADP-mediated platelet aggregation pathways is not predictive of the synergistic effect of combined therapy with SCH 602539 and cangrelor on the reduction of CFRs.

Effects on Coagulation Parameters
The administration of SCH 602539 alone, cangrelor alone, and the combination of SCH 602539 and cangrelor had no effect on the coagulation parameters, including PT, aPTT, and ACT (Table 2). These findings are consistent with the fact that both SCH 602539 and cangrelor are antiplatelet agents that interact with specific platelet receptors and do not interfere with the activity of the coagulation cascade.

Discussion
In the present study, we have demonstrated the antithrombotic effects of PAR-1 antagonism with SCH 602539 in a Folts model of thrombosis. More important, we have demonstrated that the in vivo antithrombotic effects of PAR-1
antagonism, in combination with P2Y12 ADP receptor antagonism, are synergistic. The inhibitory activity of SCH 602539 was specific for platelet aggregation induced by haTRAP. The aggregation induced by other agonists, such as ADP, thromboxane A2 mimetic U46619, and collagen, was not affected, demonstrating the specificity and selectivity for the PAR-1 receptor. Cangrelor specifically inhibited aggregation induced by ADP and demonstrated a modest numeric inhibition of aggregation induced by collagen, but not by haTRAP or U46619. These findings parallel those reported in the literature.16,17

As expected, neither SCH 602539 nor cangrelor (nor the combination of the 2) had any notable effect on coagulation parameters, a finding that is consistent with the fact that these agents interact with specific platelet receptors and do not interfere with the coagulation cascade. SCH 602539 is structurally related to vorapaxar, a PAR-1 antagonist being evaluated in 2 large ongoing clinical trials (secondary prevention and acute coronary syndromes; clinicaltrials.gov identifiers: NCT00526474 and NCT00527943).

Synergistic antithrombotic effects similar to those observed with the combination of SCH 602539 and cangrelor in this study have been reported with other combinations of antiplatelet agents18,19 that target distinct platelet activation pathways contributing to thrombosis. In the Folts model of thrombosis in pigs, the combination of low oral doses of clopidogrel, 0.1 mg/kg, and aspirin, 1 mg/kg, completely eliminated CFRs at 90 minutes, whereas the higher doses of each agent alone (clopidogrel, 5 mg/kg, and aspirin, 7 mg/kg) reduced, but did not completely abolish, the CFRs.18 A separate study19 in rabbits that used several different models of thrombosis demonstrated that the addition of oral aspirin to oral clopidogrel was associated with potent antithrombotic effects, and also additive bleeding effects, possibly related to the combined inhibitory activity of 2 antiplatelet agents on collagen-induced platelet aggregation. The additive antithrombotic effects of combined inhibition of the thromboxane A2 and P2Y12 ADP receptor platelet activation pathways with aspirin and clopidogrel observed in these studies are consistent with significant reductions in ischemic events with dual antiplatelet therapy over aspirin alone reported in large clinical trials.2,3,20–22 These findings suggest that in the vascular bed, platelet activation leading to thrombosis is a complex matrix mediated by multiple pathways.

The present study is the first direct demonstration of in vivo synergism with the combination of a PAR-1 antagonist and a P2Y12 ADP receptor antagonist. Although the binding of thrombin to the PAR-1 receptor represents 1 of the most potent platelet activation pathways leading to thrombosis, neither aspirin nor P2Y12 ADP receptor antagonists (including cangrelor) significantly inhibit the PAR-1 pathway. For this reason, the addition of a PAR-1 antagonist to a P2Y12 ADP receptor antagonist and aspirin can be expected to provide even greater antithrombotic efficacy and a further reduction in ischemic events. The presence of a synergistic effect, resulting from the combined administration of a P2Y12 antagonist with the direct thrombin inhibitor melagatran, has been previously described.23

There are 2 possible explanations for this synergism. The first is via the concurrent inhibition of the G protein–coupled

### Table 1. Effects of SCH 602539, Cangrelor, and Their Combination on Ex Vivo Inhibition of Platelet Aggregation Induced by Various Agents*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Baseline</th>
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<th>Period 3</th>
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<td></td>
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<td>21±4</td>
<td>19±4</td>
</tr>
<tr>
<td>Collagen</td>
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<td>24±3</td>
<td>27±4</td>
<td>29±4</td>
</tr>
<tr>
<td>SCH 602539 Baseline</td>
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<td>1.0 mg/kg</td>
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<tr>
<td>ADP</td>
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<td>14±2</td>
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*Data are presented as mean±SEM. The agents used included the following: haTRAP, 3 µmol/L; ADP, 10 µmol/L; U46619, 10 µmol/L; and collagen, 3 µg/mL.
Table 2. Effects of Vehicle, SCH 602539, Cangrelor, and the Combination of SCH 602539 Plus Cangrelor on PT, aPTT, and ACT in the Folts Model of Thrombosis in Anesthetized Cynomolgus Monkeys

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<table>
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<td>ACT, s</td>
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<td>81.0±3.7</td>
<td>87.0±3.4</td>
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*Data are presented as mean±SEM (n=5–6 per group). The PT and aPTT assays were performed with plasma, whereas the ACT assay was performed with whole blood.

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