Antithrombotic Effects of a Platelet Fibrinogen Receptor Antagonist in a Canine Model of Carotid Artery Thrombosis

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Background and Purpose: Platelet-fibrin thrombi in the lumen of atherostenotic carotid arteries may underlie transient ischemic attacks and cerebral infarction. For this reason, we investigated the antiplatelet and antithrombotic effects of a novel and potent platelet fibrinogen receptor (glycoprotein IIb/IIIa) antagonist (SK&F 106760).

Methods: The effects of 0.1–3.0 mg/kg i.v. SK&F 106760 on platelet aggregation were examined ex vivo in canine platelet-rich plasma (n=20). In addition, the antithrombotic effects of SK&F 106760 were compared with those of aspirin in an acute canine model of extracranial carotid artery thrombosis with high-grade stenosis. Sham-operated (n=4), vehicle-treated (n=6), SK&F 106760-treated (n=8), aspirin-treated (n=9), and SK&F 106760+aspirin-treated (n=5) dogs were examined.

Results: The intravenous administration of SK&F 106760 caused a dose-related inhibition of ex vivo platelet aggregation. In the carotid artery thrombosis model, an occlusive thrombus formed at stenotic sites in the region of the carotid bifurcation. The thrombogenic process caused a progressive reduction in carotid blood flow and reduced the cortical microvascular perfusion and electroencephalographic power. Based on nuclear magnetic resonance spectroscopy, the occlusive events depleted the stores of high-energy phosphates (adenosine triphosphate and phosphocreatine) and increased the lactate concentration in the forelimb somatosensory area of the parietal cortex. In this model, the administration of 1 mg/kg i.v. SK&F 106760 prevented thrombosis of the stenotic carotid artery. Consequently, neurophysiological, cerebral hemodynamic, and metabolic parameters were all improved significantly in the SK&F 106760-treated group. No dog receiving SK&F 106760 reocluded during the 1-hour posttreatment observation period. In contrast, thrombosis of the carotid artery was associated with neurophysiological deterioration in six of the nine dogs treated with 5 mg/kg i.v. aspirin. Both spontaneous and evoked (increased carotid stenosis) aspirin-resistant thrombosis were abolished by SK&F 106760 treatment.

Conclusions: These results suggest that antagonism of fibrinogen binding to platelet glycoprotein IIb/IIIa (the final common pathway for aggregation) may represent a new and more effective antithrombotic approach to the treatment of cerebral transient ischemic attacks and infarction associated with extracranial carotid artery disease. (Stroke 1992;23:703–711)

Keywords: glycoproteins • thrombosis • dogs

The incidence of extracranial carotid artery disease is approximately 30% in patients with carotid territory transient ischemic attacks (TIA), and the incidence of carotid TIA is 50–75% in patients experiencing carotid stroke from extracranial carotid occlusive disease.1,2 Furthermore, the risk of cerebral infarction is approximately 35% within the first 5 years after the initial TIA.2,3 These observations and the identification of occlusive platelet-fibrin thrombi in the lumen of atherostenotic carotid arteries suggest that distal hemodynamic insufficiency or cerebral emboli due to thrombosis of atherostenotic lesions in the extracranial internal carotid artery may underlie TIA and cerebral infarction.4 The initiation of an intraluminal thrombus is believed to involve platelet adherence and aggregation. Thus, platelet aggregation may play a central role in the atherothrombotic process associated with stroke. Indeed, antiplatelet agents (e.g., aspirin and ticlopidine) have been shown to reduce the incidence of stroke in high-risk patients.6,7

It has been established that fibrinogen binding to the platelet integrin glycoprotein IIb/IIIa (GP IIb/IIIa) is essential for platelet aggregation regardless of the agonist or signal transduction pathway responsible for platelet activation.8,9 For this reason, a series of experiments were performed to evaluate the antiplatelet and antithrombotic effects of a novel fibrinogen receptor antagonist, SK&F 106760 (Figure 1). SK&F 106760 is a potent and competitive antagonist of fibrinogen binding.
to platelet plasma membrane GP IIb/IIIa (fibrinogen receptor) and a potent inhibitor of human platelet aggregation induced by a variety of agonists in vitro. Unlike aspirin, SK&F 106760 is believed to inhibit the final common pathway of platelet aggregation.

We evaluated the effects of SK&F 106760 on ex vivo platelet aggregation in dogs. In addition, the antithrombotic effects of SK&F 106760 and aspirin were compared in an acute canine model of extracranial carotid artery thrombosis with high-grade stenosis.

Materials and Methods

The acute canine model of extracranial carotid artery thrombosis employed in this study was a modification of the procedure described by Uchida and Murao. Animals were housed and cared for in accordance with the Guide for the Care and Use of Laboratory Animals [DHEW (DHHS) publication No. (NIH) 85-23, revised 1985]. Procedures using laboratory animals were approved by the Institutional Animal Care and Use Committee of SmithKline Beecham Pharmaceuticals. Adult male mongrel dogs weighing 8–12 kg were anesthetized with 35 mg/kg i.v. pentobarbital and placed on a heated operating table in the supine position. All animals were then tracheotomized, paralyzed with 0.1 mg/kg i.v. tubocurarine, and artificially ventilated with room air. End-tidal CO₂ was monitored continuously, and arterial blood gas analysis was performed periodically to assure stable and adequate ventilation throughout each experiment. Polyethylene cannulas were placed in the left external jugular vein and the left and right femoral arteries and veins for drug administration, arterial blood pressure monitoring, and blood sampling, respectively. A 5–6 cm segment of the left common carotid artery was isolated in the neck just below the internal carotid artery. Anesthesia was supplemented with 5 mg/kg i.v. pentobarbital as needed.

A sternotomy was performed, and the chest was retracted to expose the aortic arch. The right and left subclavian, right and left internal thoracic, right common carotid, and left vertebral arteries were ligated to limit collateral circulation in the brain. A continuous intravenous infusion of 1 mg/ml trimethaphan camsylate was adjusted to maintain systolic arterial blood pressure at 85–110 mm Hg. All surgical wounds were then closed, and the dog was placed prone in a stereotaxic apparatus (David Kopf Instruments, Tujunga, Calif.). The scalp was reflected, and the left parietal bone was exposed. A craniectomy 1.8 cm in diameter was performed over the forelimb somatosensory area of the left parietal cortex (identified by somatosensory evoked potentials). Within the craniotomy the dura mater and arachnoid were reflected, and a laser-Doppler flow probe (Perimed, Stockholm, Sweden) was secured just above the surface of the brain for monitoring local cortical microvascular perfusion. The electroencephalogram (EEG) was recorded from stainless steel screws implanted to secure the suture of the laser-Doppler probe, and the total EEG power spectrum was computed between 1 and 16 Hz from a fast Fourier transform of the EEG signal over 10-second epochs (Laboratory Technologies Corp., Wilmington, Mass.). The EEG power values represent an average of six consecutive epochs. The animal was then rotated 45°, and the left common carotid artery was exposed. A transit-time flow probe (Transonic Systems Inc., Ithaca, N.Y.) was placed on the artery for the measurement of common carotid artery blood flow, and an adjustable clamp was fitted around the artery just proximal to the carotid bifurcation for introducing a controlled eccentric stenosis. Following acquisition of basal (prestenotic) measurements, the artery beneath the clamp was rolled between the thumb and forefinger to denude the endothelium (confirmed histologically by Dr. R.K. Clark, SmithKline Beecham Pharmaceuticals), and the clamp was tightened to reduce carotid blood flow to approximately 25% of the basal value. This procedure represents a high-grade stenosis (approximately 95% reduction in cross-sectional area) in the damaged carotid artery. Sham-operated dogs (n=4) were prepared and monitored similarly; however, stenosis was not applied to the common carotid artery nor was the endothelium denuded.

The experimental animals were divided into vehicle, SK&F 106760, aspirin, and aspirin+SK&F 106760 groups. In the vehicle group (n=7), saline was administered during the observation period following the third consecutive reduction in carotid blood flow. All parameters were monitored for 1 hour following saline or drug administration, at which time samples for nuclear magnetic resonance (NMR) spectroscopy were obtained (see below) and the dog was killed. The protocol for the SK&F 106760 (n=8) and aspirin (n=9) groups was similar to that for the vehicle group; however, these dogs received 1 mg/kg i.v. SK&F 106760 or 5 mg/kg i.v. aspirin, respectively. Aspirin (10 mg/ml) was dissolved in a 10% ethanol/250 mM Tris solution. In the aspirin+SK&F 106760 group (n=5) all animals received aspirin as in the aspirin group. However, if cyclic carotid blood flow reductions persisted after aspirin treatment, the thrombus was mechanically dislodged and 1 mg/kg i.v. SK&F 106760 was administered. If aspirin abolished the cyclic carotid blood flow reductions in this group, then the stenosis was tightened to reduce carotid blood flow an additional 50%. If cyclic reductions in carotid blood flow reappeared, the effects of SK&F 106760 were evaluated again. In all cases, SK&F 106760 and aspirin were administered as an intravenous bolus.

Animals were included in the experimental groups if they met the following criteria: 1) poststenosis thrombogenesis caused a reduction in carotid blood flow and a concomitant decrease in total EEG power; 2) mechanical disruption (shaking loose) of the occlusive thrombus resulted in recovery of carotid blood flow, cortical perfusion, and EEG power; and 3) the thrombogenic process was cyclic, occurring at least three times following mechanical disruption of the thrombus. Approximately 80% of the dogs prepared fulfilled the inclusion criteria.
In the sham-operated group and some dogs in the vehicle and SK&F 106760 groups, cortical gray matter samples 1 cm in diameter were collected from the cortical perfusion monitoring site at the end of the 1-hour observation period by a tissue-suction sampling technique into liquid nitrogen and stored at -70°C for further processing. Perchloric acid extraction of the frozen brain samples was carried out according to the method of Evanochko et al. After neutralization with KHCO3, the extract was passed through a Chelex-100 column and the eluate was lyophilized and stored at -70°C until analysis. For phosphorus-31 NMR spectroscopy, the lyophilized powder was dissolved in 1.8 ml of 40% D2O. For proton NMR spectroscopy, the lyophilized powder was dissolved in 100% D2O containing 1 mM sodium 3-trimethylsilyl-propionate-2,2,3,3-d4 as the internal standard.

All phosphorus-31 NMR spectra were recorded at 37°C in a Gx-400 (9.4 T) spectrometer (JEOL USA, Inc., Peabody, Mass.) operating at 161.92 MHz for phosphorus using a 10-mm 1H[31P] probe built by Cryomagnetics, Inc., Oak Ridge, Tenn. Five hundred transients were collected with a 10,000-Hz spectral window, a 90° pulse width, and a 24-second pulse delay for fully relaxed spectra. All proton NMR spectra were recorded at 37°C in a GX-500 (11.75 T) spectrometer (JEOL) operating at 500.00 MHz for proton. Forty-eight transients were collected with a 5,291 Hz spectral window, a 90° pulse width, and a 10-second pulse delay. Peak areas were calculated for quantitative analysis of adenosine triphosphate (ATP), phosphocreatine (PCr), and lactate in each sample.

Thromboxane B2 (TXB2) generation was determined in canine serum by incubating approximately 5 ml whole blood in a glass tube for 45 minutes, then centrifuging at 2,000g for 10 minutes. Serum was removed and stored at -70°C until assayed. The TXB2 levels were measured by a specific and sensitive radioimmunoassay (Advanced Magnetics, Inc., Cambridge, Mass.). There was no significant cross-reactivity of the TXB2 antibody with other prostaglandins. The sensitivity of the radioimmunoassay was 4 pg TXB2/tube, and the 50% intercept on the standard curve was 25 pg/tube. The TXB2 levels were expressed as nanograms per milliliter of serum.

The time course and dose-related effects of SK&F 106760 on ex vivo platelet aggregation investigated in naïve dogs (as above) anesthetized with 35 mg/kg i.v. pentobarbital. All animals were intubated and prepared for intravenous drug administration, blood collection, and continuous monitoring of arterial blood pressure. Citrated blood samples (5 ml) were collected periodically for up to 2 hours following the bolus administration of 0.1–3.0 mg/kg i.v. SK&F 106760. At each time, platelet-rich plasma was prepared and mean±SEM platelet aggregation response to 10 μM adenosine diphosphate (ADP) was determined as described previously.15

Multiple comparisons with control (usually poststenosis) values were evaluated by applying Bonferroni's inequality to the two-tailed paired t test.16 The significance of differences among group means was determined by performing a one-way analysis of variance followed by adjusted t tests with probability values corrected by the Bonferroni method. Quantal responses were arranged in 2×2 contingency tables and analyzed by using Fisher's exact test. All summary values were expressed as mean±SEM, and differences were considered significant at p≤0.05.

Results

In pentobarbital-anesthetized dogs, the intravenous administration of SK&F 106760 caused a dose-related inhibition of ex vivo platelet aggregation elicited by 10 μM ADP (Figure 2). The 0.1 mg/kg dose of SK&F 106760 caused only marginal and transient inhibition of platelet aggregation. However, SK&F 106760 caused complete inhibition of platelet aggregation at 0.3, 1.0, and 3.0 mg/kg. The antiplatelet effect was reversible, and the time course was dose-related. Based on these results, the 1 mg/kg dose of SK&F 106760 was chosen for further study in the canine model of extracranial carotid artery thrombosis. This was the lowest bolus dose tested that caused a near-complete blockade of ex vivo platelet aggregation for 1 hour.

High-grade carotid stenosis in the canine model of extracranial carotid artery thrombosis caused a gradual reduction in carotid blood flow, cortical perfusion, and EEG in all dogs (Figure 3). Mechanical disruption of the thrombus resulted in recovery of the carotid blood flow, cortical perfusion, and EEG. This thrombogenic process was cyclic, with reductions in carotid blood flow and EEG occurring after each mechanical disruption. In vehicle-treated animals, complete occlusion of the common carotid artery occurred when the thrombus was not dislodged following the third cycle (Figure 3A). This resulted in a prolonged reduction in carotid blood flow, cortical perfusion, and EEG power. Occasionally during the 1-hour observation period the common carotid artery would spontaneously reperfuse and reocclude (Figure 3A). However, in no case was there evidence of recovery in the EEG. The results obtained from the
vehicle group are summarized in Figure 4. At the end of 1 hour, cortical levels of ATP and PCr were reduced 81% and 86%, respectively, and the lactate concentration was increased 358% in the vehicle group compared with the sham-operated group (Figure 5).

In similarly prepared dogs, the administration of 1 mg/kg i.v. SK&F 106760 immediately aborted the thrombogenic process and prevented occlusion of the carotid artery (Figure 3B). Consequently, blood flow and EEG power improved significantly throughout the 1-hour observation period (Figure 4). At the end of the observation period cortical levels of ATP, PCr, and lactate in the SK&F 106760 group did not differ from those in sham-operated animals (Figure 5) but were significantly better than those in the vehicle group. Stenosis of the common carotid artery in the SK&F 106760 group reduced carotid blood flow to 26.1±2.2% of the basal value, not significantly different from that observed in the vehicle group (25.8±2.2%). It is noteworthy that unusual bleeding from surgical sites or otherwise was not observed in the SK&F 106760 group.

A more complex response profile was observed in animals receiving 5 mg/kg i.v. aspirin. In three of the nine dogs tested, aspirin administration aborted the thrombogenic process and prevented occlusion of the carotid artery (Figure 6A). In these animals, as in the SK&F
106760 group, carotid blood flow, cortical perfusion, and EEG power were improved. However, in the majority (six) of the nine animals aspirin administration failed to abort the thrombogenic process and occlusion of the common carotid artery (Figure 6B). Thus, the total incidence of carotid reocclusion in the aspirin group was significantly greater ($p<0.01$) than that observed in the SK&F 106760 group and occurred despite a rapid (<5 minutes) and profound (>94%) inhibition of serum thromboxane generation in dogs (two responders and four nonresponders) receiving aspirin (data not shown). There was no apparent relation between inhibition of thromboxane generation and the antithrombotic effects of aspirin in this model. Stenosis of the common carotid artery in the aspirin group reduced carotid blood flow to 23.1±2.7% of the basal value. Arterial blood pressure and degree of stenosis did not differ among the vehicle, aspirin, and SK&F 106760 groups.

In the aspirin+SK&F 106760 group 5 mg/kg i.v. aspirin was administered as in the aspirin group. If aspirin failed to prevent occlusion ($n=3$), the thrombus was mechanically disrupted and 1 mg/kg i.v. SK&F 106760 was administered. In these dogs, SK&F 106760 aborted the thrombogenic process, prevented occlusion and irreversible deterioration of the EEG, and promoted complete recovery of all monitored parameters over the course of the 1-hour observation period (Figure 7).
In three animals (one from the aspirin group) in which aspirin treatment prevented thrombosis the stenosis was increased by tightening the carotid clamp to reduce carotid blood flow an additional 50%, to approximately 12.5% of the basal value. This procedure caused the reappearance of cyclic reductions in blood flow that were sensitive to the antithrombotic effect of SK&F 106760 (Figure 8). In contrast, increasing the carotid stenosis did not trigger the thrombogenic process following SK&F 106760 treatment (Figure 8B). The results demonstrate the efficacy of SK&F 106760 under conditions capable of rendering dogs insensitive to the antithrombotic effects of aspirin.

Discussion

Part of the integrin superfamily of adhesive protein receptors, GP IIb/IIIa is the most abundant integrin on the platelet surface.17-18 Platelet activation by one or more platelet stimulants causes exposure of GP IIb/IIIa binding sites for adhesive proteins (e.g., fibrinogen, von Willebrand's factor, and fibronectin).17-18 The exposure of this adhesive protein binding site on GP IIb/IIIa is essential for platelet aggregation.8 Fibrinogen, the major adhesive protein required for human platelet aggregation, interacts with GP IIb/IIIa by virtue of platelet receptor recognition domains containing Arg-Gly-Asp (RGD) amino acid sequences located on the alpha chain of the molecule.19,20 The current model of platelet aggregation suggests that multiple RGD sequences on the fibrinogen alpha chain allow bridging between adjacent activated platelets via interactions with platelet membrane GP IIb/IIIa.21 Indeed, numerous peptide fragments containing the RGD sequence inhibit platelet aggregation and inhibit fibrinogen binding to GP IIb/IIIa.22

SK&F 106760 is a novel RGD mimic capable of competitively inhibiting fibrinogen binding to GP IIb/IIIa.10 In accord with this action, SK&F 106760 inhibits in vitro platelet aggregation elicited by all known endogenous agonists. The demonstrated efficacy of antiplatelet agents (e.g., aspirin and ticlopidine) in the treatment of TIA and prevention of stroke in high-risk patients5,7 led us to examine the antiplatelet and antithrombotic effects of SK&F 106760. In dogs the intravenous administration of SK&F 106760 caused a dose-related inhibition of ex vivo platelet aggregation, the duration of inhibition was dose-related, and the inhibition was completely reversible consistent with a competitive interaction of SK&F 106760 at RGD binding sites on GP IIb/IIIa.

The antithrombotic effects of SK&F 106760 were assessed in an acute canine model of extracranial carotid artery disease with high-grade stenosis. This arterial thrombosis model represents a modification of the method described by Uchida and Murao11 in which platelet aggregates and platelet-rich thrombi have been identified adhering to the lumen of stenotic carotid arteries.23 The administration of 1 mg/kg i.v. SK&F 106760 in this model immediately inhibited the cyclic reductions in carotid blood flow and prevented the formation of an occlusive thrombus. Consequently, neurophysiological (EEG), cerebral hemodynamic (cortical perfusion), and metabolic (ATP, PCr, and lactate concentrations) deterioration were not observed in the SK&F 106760 group. These results correlated well with the rapid and complete inhibition of ex vivo platelet aggregation observed following the administration of 1 mg/kg i.v. SK&F 106760. In contrast, severe reductions in EEG power, cerebral perfusion, and cortical ATP and PCr concentrations accompanied the formation of an occlusive thrombus in all vehicle-treated dogs.

Variable results were obtained with 5 mg/kg i.v. aspirin in this thrombosis model. Formation of an occlusive thrombus was observed in the majority of animals treated with aspirin, and the deterioration of cerebral hemodynamic and neurophysiological parameters in this subgroup was indistinguishable from that in the vehicle group. In contrast, thrombus formation was inhibited in only three of nine dogs in the aspirin group. In these animals, changes in cerebral hemodynamic and neurophysiological parameters were similar to those observed in the SK&F 106760 group. Overall, the results obtained with aspirin in the present study were similar to results originally obtained by Uchida and Murao in a similar model of carotid thrombosis. In that study, 10 mg/kg i.v. aspirin had a slight but nonsig-
significant effect on spontaneous recurring reductions in carotid and cerebral blood flow. The results from both studies are somewhat surprising given the profound and persistent inhibition of thromboxane synthesis observed in all dogs in our aspirin group. These results suggest that thrombogenic processes in a model of extracranial carotid artery thrombosis with high-grade stenosis are largely thromboxane-independent.

Aspirin-resistant arterial thrombosis has also been reported in the Folts canine model of coronary thrombosis. These investigators demonstrated that severity of the stenosis was an important factor in determining the efficacy of aspirin treatment. In their model, tightening the coronary stenosis restored the cyclic reductions in coronary blood flow inhibited by aspirin treatment. We obtained similar results; cyclic reductions in carotid blood flow reappeared following tightening of the carotid stenosis in dogs sensitive to the antithrombotic effects of aspirin. In contrast, suddenly increasing the carotid stenosis (as might occur following rupture and dissection of an atheromatous plaque) did not elicit thrombogenesis, as evidenced by lack of blood flow reductions, in animals treated with SK&F 106760. Furthermore, SK&F 106760 treatment immediately abolished blood flow reductions elicited by tightening the carotid stenosis in dogs sensitive to the antithrombotic effects of aspirin and prevented cerebral hemodynamic and neurophysiological deterioration in animals insensitive to the antithrombotic effects of aspirin. The results again suggest that proaggregatory eicosanoids play a minor role in mediating thrombogenic processes in a model of high-grade carotid stenosis. Moreover, the results also suggest that the antithrombotic efficacy of SK&F 106760 is significantly greater than that of aspirin.

The mechanisms responsible for aspirin-resistant thrombogenesis may be related to the high-grade stenosis in this model. The enhanced shear rate in severely stenotic arteries increases platelet adhesion to the
subendothelium and accelerates platelet thrombus formation. Baumgartner has demonstrated in flowing blood (in vitro) that platelet aggregation and adherence to the subendothelium is not altered by aspirin treatment at high shear rates. These results suggest that adhesion-induced platelet activation and aggregation at high shear rates are mediated by thromboxane-independent stimuli. Regardless of the precise thrombogenic stimulus (e.g., ADP, thrombin, or collagen), it is clear that the platelet GP IIb/IIIa receptor antagonist SK&F 106760 is a more effective antithrombotic agent than aspirin in the acute canine model of extracranial carotid artery thrombosis with high-grade stenosis.

Previous approaches to the inhibition of the platelet GP IIb/IIIa receptor have employed murine monoclonal antibodies to GP IIb/IIIa. These antibodies have been shown to inhibit fibrinogen binding to platelet GP IIb/IIIa and are capable of inhibiting ex vivo platelet aggregation in human volunteers. However, issues concerning the prolonged duration of action and the development of human anti-mouse antibodies may limit the therapeutic utility of GP IIb/IIIa monoclonal antibodies. These limitations may not apply to the competitive GP IIb/IIIa antagonist SK&F 106760 given its shorter, dose-related duration of action and its doubtful antigenic potential.

Bleeding complications may also be an important caveat for the clinical application of GP IIb/IIIa antagonists. Indeed, the antiplatelet GP IIb/IIIa monoclonal antibody fragment 7E3 F(ab')2 causes mucocutaneous hemorrhagic symptoms in cynomolgus monkeys at doses needed to abolish whole blood platelet aggregation. In addition, bitistatin, an RGD-containing protein from viper venom, caused a 3.5- to 4.0-fold increase in the
template bleeding time at doses needed to prevent coronary reocclusion in a canine model of coronary thrombosis. In view of the results, it is noteworthy that no unusual bleeding was observed in any of the dogs receiving SK&F 106760. This observation is consistent with recent evidence that antithrombotic doses of some GP IIb/IIIa antagonists (including SK&F 106760) do not increase the bleeding time.

In conclusion, the platelet fibrinogen receptor (GP IIb/IIIa) antagonist SK&F 106760 is a powerful antiplatelet agent with broad antithrombotic potential. The present study suggests that treatment with an appropriate GP IIb/IIIa antagonist may stop or ameliorate TIA's and prevent cerebral infarction associated with extracranial carotid artery disease.

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