Inhibition of Factor IX(a) Is Protective in a Rat Model of Thromboembolic Stroke

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Background and Purpose—Although used clinically to prevent stroke, there are few examples of anticoagulant investigations in the treatment of acute thromboembolic stroke in animal models. The treatment of thromboembolic stroke in experimental models has been investigated almost exclusively around the use of tissue plasminogen activator (tPA). In this study, using a rat thromboembolic stroke model, we investigated the use of an inhibitory anti–factor IX(a) monoclonal antibody (SB 249417) for the treatment of thromboembolic stroke and compared its efficacy to that of tPA.

Methods—Stroke was initiated by delivering 6 clots into the internal carotid artery. After 2, 4, or 6 hours, rats received either intravenous vehicle, 10.0 mg/kg tPA, or 1.0, 2.0, or 3.0 mg/kg SB 249417. At 24 hours after stroke, infarct volumes and neurological deficits were assessed.

Results—Treatment with tPA 2, 4, or 6 hours after stroke reduced infarct volumes by 35% ($P$ NS), 45%, and 39%, respectively. tPA treatment did not improve neurological deficits at any time point. Treatment with SB 249417 (3.0 mg/kg) 2, 4, or 6 hours after stroke reduced infarct volumes by 44%, 50%, and 13% ($P$ NS), respectively. Neurological deficits were reduced by 49%, 42%, and 13% ($P$ NS), respectively. Neither mortality nor hemorrhage was affected by either treatment.

Conclusions—The data indicate that the inhibition of factor IX(a) within 4 hours of thromboembolic stroke produced a more favorable outcome than tPA. When treatment was initiated 6 hours after stroke, the benefits of factor IX(a) inhibition were lost, whereas tPA continued to suppress lesion development, albeit without a corresponding improvement in functional improvements. This study suggests that cerebral ischemia and the resultant perfusion deficit are exacerbated by the activation of blood coagulation and that anticoagulants like SB 249417 may find utility in the treatment of ischemic stroke. (Stroke. 2002;33:578-585.)

Key Words: anticoagulants • factor IX • ischemia • thromboembolism • tissue plasminogen activator • rats

A
cute ischemic stroke is precipitated by thromboembolization or in situ thrombosis. Approximately 80% of ischemic stroke patients within 8 hours of stroke onset have evidence of an occlusive thrombus.1-3 Treatment options for ischemic stroke are currently limited to the lytic agent tissue plasminogen activator (tPA).4 Unfortunately, the inclusion criteria for tPA therapy are severely limited, restricting its use to within 3 hours of stroke onset and to <2.0% of ischemic stroke patients.5-7

An alternative approach to acute stroke treatment has been the use of antithrombotic agents. To date, heparin and heparinoids administered 24 to 48 hours after stroke have been thoroughly evaluated and have failed to provide neuroprotective benefits.8,9 Although efficacious in stroke prevention,10,11 antiplatelet agents have yet to demonstrate significant protection under acute stroke circumstances.8,12 In contrast, the defibrinogenating agent ancrd administered within 3 hours of stroke onset significantly improved outcomes, demonstrating efficacy comparable to that of tPA.13 The efficacy of ancrd demonstrated that a strategy aimed at suppressing thrombosis could attenuate the injury produced by ischemic stroke in humans.

The thrombolytic and antithrombotic approaches to stroke intervention have been characterized differently in preclinical stroke models. The lytic approach, represented predominantly by tPA, has been extensively characterized in animal models of thromboembolic stroke.14-19 Data gleaned from these preclinical thromboembolic stroke studies demonstrate that tPA is able to promote reperfusion and improve outcome, and, depending on the models and their attributes, it exhibits therapeutic efficacy within a time window of 3 to 6 hours.

In contrast, antithrombotic agents have been characterized in preclinical models of mechanical cerebral ischemia and reperfusion and thrombotic stroke. In murine models of
ischemia and reperfusion, inhibition of platelet function via α_{IIb}/β_{IIIa} antagonism or the inhibition of the factor IX–dependent coagulation pathway resulted in a significant reduction in infarct development. In similar rat models of ischemia and reperfusion or thrombotic stroke, inhibition of the coagulation factors Xa and thrombin with the low-molecular-weight heparin enoxaparin or the direct thrombin inhibitor argatroban also resulted in significantly reduced brain injury.

Antithrombotic agents have rarely been assessed in models of embolic stroke. Whether antithrombotic agents could consistently mitigate the consequences of embolic stroke and whether the degree of protection could be comparable to a lytic agent were the subjects of this study. In this report, using a novel rat thromboembolic stroke model, we investigated the use of a humanized anti–factor IX(a) monoclonal antibody (SB 249417) in the acute treatment of thromboembolic stroke and compared its efficacy with that of tPA.

**Materials and Methods**

**SB 249417**

SB 249417 is a fully humanized inhibitory anti–factor IX(a) monoclonal antibody. The antibody specifically interferes with both factor IX activation and factor IXa activity toward its substrate factor X. SB 249417 does not cross-react with or inhibit the activity of other clotting enzymes. The antibody binds with a K_{d} of 20 nmol/L and recognizes an epitope in the FIX γ-carboxyglutamic acid (Gla) domain.

**Factor IX Activity Assay**

Rats (naive or subject to thromboembolic stroke) were dosed with SB 249417, and plasma was collected at 0.25, 1, 4, 6, and 24 hours after treatment. Samples were diluted 1:10 in TBSA (50.0 mmol/L Tris [pH 7.5], 100 mmol/L NaCl, 0.1 mg/mL bovine serum albumin) and then combined with an equal volume of factor IX–deficient plasma (American Diagnostica Inc). The combined plasmas were added to an equal volume of cephalin/ellagic acid reagent (Dade Behring) and incubated for 3 minutes at 37°C. Clotting was initiated by the addition of CaCl_2 to a final concentration of 5 to 10 mmol/L. Clotting times were measured either in a fibrometer (BBL) or in an automated clotting device (MLA). Factor IX activity was determined from a standard curve generated from normal rat plasma.

**Dosing**

Intravenous dosing was initiated 2, 4, or 6 hours after embolus into the rat caudal vein. The volume of the infusions was approximately 1.0 mL and was infused over 30 minutes. The vehicle was sterile saline. An alternative vehicle, nonspecific human IgG (3.0 mg/kg IV bolus), was used. Six of the sections (clots) were collected into a PE50 catheter in a separate petri dish containing deionized water. The clot was incubated in the deionized water for 5 minutes at room temperature. At the end of this treatment (osmotic shock), the clot was placed into a solution of isotonic saline containing 1.0 mg/mL rat albumin and dissected into 1.5-mm sections. The mean clot size was 1.5 ±0.1 mm. Six of the sections (clots) were collected into a PES50 catheter in a volume of 60 μL. These 6 clots aligned end to end in the catheter were then prepared for embolization/injection into the rat. The interval between this final step and embolization was <15 minutes.

**Surgery and Embolization**

Care and use of laboratory animals followed National Institutes of Health guidelines and were approved by the institutional animal care and use committee at SmithKline Beecham Pharmaceuticals. Male Sprague-Dawley rats weighing 350 to 400 g were initially anesthetized with 5% isoflurane, which was followed by a maintenance dose of 2% isoflurane in medical O_2. Body temperature was maintained between 37°C and 38°C. Under aseptic conditions, a cervical midline incision was made, exposing the right common carotid artery (CCA) and its branches, the internal carotid artery (ICA), external carotid artery (ECA), and pterygopalatine artery (PA). A 0.4-mm stenosis was created on the CCA proximal to the carotid.
bifurcation. This was performed by tying a blunt 27-gauge needle against the CCA with suture, followed by removal of the needle. This resulted in an approximately 60% reduction in the diameter of CCA at the point of the stenosis. (2) The PA was clamped with a 10-mm microaneurysm clamp. (3) The CCA was clamped with a 10-mm clamp between the stenosis and the carotid bifurcation. (4) The CCA was similarly clamped between the carotid bifurcation and the PA. (5) The PE50 catheter containing the 6 sized clots was introduced approximately 5 mm into the previously cut ECA and tied in place with suture. (6) The ICA clamp was removed. (7) The 6 emboli were flushed into the ICA over a period of approximately 5 seconds. (8) The CCA clamp was removed. (9) Precisely 15 seconds after the removal of the CCA clamp, the PA clamp was removed, and the rat was left in this condition for 15 minutes. (10) During this period, the catheter was removed from the ECA stump and tied off on an unperturbed portion of ECA close to the bifurcation. (11) At the end of the 15-minute period, the CCA stenosis was removed, and the incision was closed.

Neurological Deficit Score

The neurological deficit scoring system was similar to that described previously by Barone et al. After embolization (2, 4, or 6 hours), animals were assigned scores according to the following deficit scoring criteria: no neurological deficit; forelimb paralysis, partial; hindlimb sensorimotor deficit; ipsilateral circling; ipsilateral 3; immobile; convulsions; ipsilateral 3; neglect; righting response 3; immobile 3. Scores were tallied for each animal, and rats receiving a score of ≥3 were randomized for inclusion in the study.

Infarct Analysis

Twenty-four hours after embolization, rats were anesthetized and killed. The brain was removed, and 7 transverse (coronal) cerebral sections were taken every 2.0 mm from the frontal cerebral pole. The sections were incubated in 1.0% 2,3,5-triphenyltetrazolium chloride (TTC) for 20 minutes, followed by formalin fixation. The stained cerebral sections were photographed, and hemispheric swelling and infarct volumes were quantified with the use of an image analysis system (Image Pro-Plus, Media Cybernetics), as previously described. All quantification was blinded (ie, compiled by an operator unaware of treatment groups).

Histology

In a subset of rats, 24 hours after embolization, brains were collected (see above), washed in ice-cold saline, and fixed in 10% formalin (4°C) for 24 hours. After fixation, brains were stored in 70% ethanol before standard histological processing. Sections were stained with hematoxylin and eosin-phloxine.

Intracerebral Hemorrhage Assay

Intracerebral hemorrhage was assessed as described previously. In rats subjected to thromboembolic stroke, forebrains were removed 24 hours after stroke, homogenized, sonicated, and centrifuged. The supernatant was collected and assayed for hemoglobin with the use of a commercially available hemoglobin detection kit (Sigma). Under these assay conditions, a blood volume increase of 0.5% to 1.0% in the forebrain extract was detectable. The assay end point is the generation of cyanomethemoglobin, which is detectable at an optical density of 540 nm (OD540).

Statistical Methods

Infarct volumes and neurological deficits are presented as mean±SEM. Statistical analyses were by 1-way ANOVA followed by Duncan’s post hoc comparison of the means (Statistica 6.0, Statsoft).

Figure 2. Dose-related and temporal effects of SB 249417 on factor IX activity in naive or rats subjected to thromboembolic stroke. A, Dose-related effects of SB 249417 (IV bolus) on factor IX activity in naive rats. Plasma samples were collected 1 hour after SB 249417 infusion. B, Effects of SB 249417 (3.0 mg/kg IV bolus) on factor IX activity in rats subjected to thromboembolic stroke.

Results

Factor IX Activity

The anti–factor IX (a) monoclonal antibody (SB 249417) dose-dependently inhibited factor IX activity when administered intravenously in a naive rat (Figure 2A). The dose range of SB 249417 at 1.0, 2.0, and 3.0 mg/kg (IV bolus) inhibited factor IX activity by 26±28%, 67±10%, and 87±6%, respectively. On the basis of these results, this full dose range was selected for the initial stroke studies. A bolus dose of 3.0 mg/kg had been shown previously to be an effective antithrombotic dose in rat models of arterial and venous thrombosis without a bleeding liability. The pharmacodynamic effects of a bolus 3.0-mg/kg dose of SB 249417 lasted between 4 and 6 hours in rats with thromboembolic stroke, with peak factor IX inhibition (85±6%) at 1 hour after dosing comparable to that observed in naive animals (Figure 2B). In rat safety pharmacology studies, the antibody did not affect cardiovascular or hemodynamic indices such as heart rate or blood pressure, nor were there any drug-related changes in body temperature or respiratory function (not shown).

Thromboembolic Stroke Model Attributes

The thromboembolic stroke model developed for this study is a variation of a previously described rat model and is distinguished by changes in clot preparation and the surgical and embolization techniques. The parameters sought in the present thromboembolic stroke model were (1) consistently reproducible emboli with minimal exogenously added procoagulants; (2) embolic delivery of clots into the cerebral circulation; (3) >85% infarct frequency; and (4) improvement of some aspects of outcome in the model by the administration of a lytic agent (tPA). The method of emboli preparation resulted in a predictable and uniform clot structure. The formed emboli assumed a tubelike shape and were composed of erythrocytes, leukocytes, and platelets trapped...
in a fibrin mesh. The deionized water treatment (osmotic shock) of the emboli caused cells trapped in the fibrin mesh to lyse (Figure 3). If emboli were not exposed to an osmotic shock, infarct frequency fell precipitously. The number of clots embolized was optimized around the resulting infarct size, infarct frequency, and 24-hour mortality. It was determined empirically that the required emboli number could be reduced (from 12 to 6) by temporarily stenosing the CCA and reopening the PA after embolization. To reduce experimental variability, only rats with neurological deficit scores of 98% were randomized for inclusion in the study. Pretreatment scores across all treatment groups ranged from 6.4 to 6.8 and were not statistically different (P > 0.25). Only those rats surviving 24 hours were included in the final analysis of infarct volumes and neurological deficits. Arterial blood gases (pH, PCO₂, PO₂) measured 1 hour after surgery were within the normal range (not shown).

**Effects of tPA and SB 249417 on Infarct Development and Mortality**

In control animals (treated with saline), the mean lesion volume produced in this model was 328 ± 26 mm³, comprising an infarct of approximately 39% of the contralateral hemisphere. The percentage of hemispheric swelling was comparable among all treatment groups and was ≤ 5.0%. The effect of treatment with tPA or SB 249417 on lesion volume is shown in Table 1. Treatment with tPA 2, 4, or 6 hours after stroke reduced infarct volumes by 35% (P = 0.11), 45% (P = 0.04), and 39% (P = 0.01), respectively. Treatment with 1.0, 2.0, or 3.0 mg/kg SB 249417 2 hours after stroke produced a dose-related infarct reduction of 14%, 30%, and 44% (P = 0.04), respectively. When treatment was initiated 4 hours after stroke onset, doses of 2.0 and 3.0 mg/kg resulted in a significant reduction (approximately 50%; P < 0.01) in infarct volume. Treatment initiated 6 hours after stroke (3.0 mg/kg) had no effect on lesion development. Treatment with a nonspecific IgG (3.0 mg/kg) did not significantly affect lesion development in this model (not shown). The infarct distribution in this model occurred with a similar frequency in the cortical and subcortical regions of the forebrain, and the protection observed in either treatment group occurred in both. Mortality in the model ranged from 30% to 40% by 24 hours and was not improved or exacerbated by the treatments (Table 2).

**Neurological Deficits**

The effect of treatments on 10 sensorimotor deficits was assessed with the use of a 21-point deficit scoring scale, with increasing deficit reflected by an increasing score. Scores were initially assessed at either 2, 4, or 6 hours after embolization/pretreatment for the purpose of selection and randomization for the study. Scores were reassessed after treatment at 24 hours (Table 3). Treatment with tPA 2, 4, or 6 hours after stroke did not significantly improve 24-hour deficit scores compared with the vehicle score at 24 hours. Treatment with SB 249417 resulted in a significant dose-related reduction in deficit scores. In the 2-hour study, treatment with 3.0 mg/kg of SB 249417 resulted in a significant reduction in the neurological deficit score in comparison to both the vehicle 24-hour score (49% reduction; Table 3).

| Table 1. Infarct Volume Following Treatment 2, 4, or 6 Hours After Stroke |
|-----------------------------|-----------------------------|-----------------------------|
|                            | 2 h                         | 4 h                         | 6 h                         |
| Vehicle                    | 326 ± 42                    | 331 ± 29                    | 359 ± 39                    |
| tPA 10.0 mg/kg IV           | 214 ± 43                    | 180 ± 37*                   | 220 ± 31*                   |
| SB 249417                  |                             |                             |                             |
| 1.0 mg/kg IV               | 281 ± 50                    | ND                          | ND                          |
| 2.0 mg/kg IV               | 251 ± 40                    | 169 ± 32*                   | ND                          |
| 3.0 mg/kg IV               | 182 ± 43*                   | 162 ± 34*                   | 311 ± 36                    |

ND indicates not done.

*P < 0.05 compared with vehicle (1-way ANOVA followed by Duncan’s post hoc test) n = 20–25 rats per group.
TABLE 2. Percent Survival Following Treatment 2, 4, or 6 Hours After Stroke

<table>
<thead>
<tr>
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<th>Percent Survival</th>
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<tbody>
<tr>
<td></td>
<td>2 h</td>
</tr>
<tr>
<td>Vehicle</td>
<td>72</td>
</tr>
<tr>
<td>tPA 10.0 mg/kg IV</td>
<td>61</td>
</tr>
<tr>
<td>SB 249417</td>
<td></td>
</tr>
<tr>
<td>1.0 mg/kg IV</td>
<td>67</td>
</tr>
<tr>
<td>2.0 mg/kg IV</td>
<td>70</td>
</tr>
<tr>
<td>3.0 mg/kg IV</td>
<td>81</td>
</tr>
</tbody>
</table>

ND indicates not done.

Values in parentheses are number of rats surviving 24 hours/total number of rats embolized.

P=0.002) and the tPA 24-hour score (40% reduction; P=0.03). In the 4-hour treatment regimen, significant reductions were observed in comparison to the vehicle group at both the 2.0- (33% reduction; P=0.008) and 3.0-mg/kg (42% reduction; P=0.001) doses. No improvement in deficits occurred when treatment was initiated 6 hours after stroke. Treatment with a nonspecific IgG (3.0 mg/kg) 4 hours after stroke did not affect neurological deficit scores in this model (not shown). The improvements observed in all treatments and dosing regimens occurred principally through the regain of contralateral motor function as assessed by the forelimb and hindlimb placement tests and the contralateral circling tests. With SB 249417 treatment, a clear positive correlation developed between the reduction of infarct and deficit reduction (r=0.85, P=0.04).

Hemorrhage

Hemorrhage was assessed 24 hours after stroke before and after forebrain sectioning by gross inspection. No hemorrhage was detected in either treatment group or treatment regimen. In a separate group of animals treated 2 or 4 hours after stroke with tPA or SB 249417 (3.0 mg/kg), changes in forebrain hemoglobin content were assessed with a hemoglobin detection assay capable of detecting a 0.5% to 1.0% change in cerebral hemoglobin content. Cyanometihemoglobin levels in the vehicle, tPA, and SB 249417 (3.0 mg/kg) groups as measured by OD540 in the 2-hour study were 0.1, 0.12, and 0.11, respectively (P>0.33). The corresponding values in the 4-hour after stroke treatment groups were 0.14, 0.14, and 0.14, respectively (P>0.8). The higher OD540 values in the 4-hour data set do not reflect an increase in hemorrhage versus the 2-hour data but instead are the consequence of a change in the assay protocol that further concentrated the brain extract samples. Therefore, as observed by gross inspection, no changes indicating cerebral hemorrhage were detected.

Forebrain Histology

Forebrains from vehicle- and SB 249417–treated rats were collected 24 hours after stroke. Histological analysis demonstrated that the occlusive emboli were still present in both untreated and SB 249417–treated animals (Figure 4). No evidence of infarct- or treatment-related petechial hemorrhage or primary occlusion recanalization was detected.

Discussion

Though widely used in the clinic to prevent recurrent stroke, there are few reported examples of anticoagulant or anti-thrombotic investigations in the treatment of acute thromboembolic stroke in animal models. With the exception of a recent report,31 the treatment of thromboembolic stroke in preclinical models has been investigated almost exclusively around the use of lytic agents. In this model of severe thromboembolic stroke representing a significant treatment challenge, the administration of an anti–factor IX(a) antibody as long as 4 hours after stroke significantly reduced both infarct volumes and the associated neurological deficits. Treatment 6 hours after stroke did not improve either end point. With SB 249417 treatment, a clear correlation existed between infarct and neurological deficit reduction. The percent inhibition of factor IX activity required for efficacy in the 2-hour treatment regimen was 85±10%, whereas in the 4-hour regimen this declined to 65±10%. Whether this reduced requirement for factor IX inhibition reflects the beginning of spontaneous recanalization or some other process, such as localized factor IX consumption,32 remains to be determined. Histological and biochemical analysis of SB 249417–treated infarcted forebrains did not demonstrate evidence of either petechial or gross hemorrhage.

The mechanism by which factor IX(a) inhibition is protective in this thromboembolic model is speculative. The most frequently proposed benefits of an anticoagulant in acute stroke result from a protection of collateral blood flow via the prevention of blood coagulation, a process driven by ischemia-induced blood stasis and stagnant hypoxia. In animal models there is experimental evidence under the conditions of ischemia/reperfusion that blood coagulation, through its deposition of fibrin or through platelet activation, can contribute to microvascular flow perturbations.33–36 Additionally, there is evidence that polymorphonuclear influx into the cerebral ischemic territory can obstruct and retard microvascular perfusion.37–39 Currently, there is no direct evidence demonstrating the mechanism by which SB 249417 exerts its benefits. Histological analysis indicates that in treated animals at least some occlusive emboli are still present. Experiments designed to directly assess the role of SB 249417 in

TABLE 3. 24-Hour Neurological Deficit Scores Following Treatment 2, 4, or 6 Hours After Stroke

<table>
<thead>
<tr>
<th></th>
<th>Neurological Deficit Score</th>
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<tr>
<td></td>
<td>2 h</td>
</tr>
<tr>
<td>Vehicle</td>
<td>6.0±0.5</td>
</tr>
<tr>
<td>tPA 10.0 mg/kg IV</td>
<td>5.0±0.6</td>
</tr>
<tr>
<td>SB 249417</td>
<td></td>
</tr>
<tr>
<td>1.0 mg/kg IV</td>
<td>5.0±0.6</td>
</tr>
<tr>
<td>2.0 mg/kg IV</td>
<td>4.5±0.6</td>
</tr>
<tr>
<td>3.0 mg/kg IV</td>
<td>3.0±0.7*</td>
</tr>
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ND indicates not done.

*P<0.01 compared with vehicle (1-way ANOVA followed by Duncan’s post hoc test) (n=20–25 rats per group).
the protection of cerebral blood flow or on the attenuation of polymorphonuclear influx after thromboembolic stroke will be the subject of further investigations.

Nearly all tPA studies in rat thromboembolic stroke models report a treatment window of <4 hours\textsuperscript{14–16,18} despite the observation of significant recanalization on administration of tPA 4 hours after stroke.\textsuperscript{14} The only partial exception to this is a report by Sakurama et al.,\textsuperscript{19} in which treatment with tPA as long as 6 hours after stroke significantly reduced lesion development but failed to improve the neurological status of the treated animals. The model or technical distinctions responsible for the various reported treatment windows are not clear but likely reflect thromboembolic model differences in emboli preparation or surgical technique. The tPA treatment window reported in the present study, if defined solely on the basis of TTC-delineated infarct reduction, appears to be \(\geq 6\) hours. However, significant improvements in neurological deficits were not observed in any treatment regimen with tPA (Figure 5). The lack of a strong correlation between infarct and deficit reduction complicates the interpretation of the data but may reflect the presence of a diffuse tPA-related neurological injury\textsuperscript{40–42} not captured on TTC staining and gross inspection.

Given that this lack of a correlation is not a consistent feature of all rodent tPA thromboembolic stroke studies, then, like the variability reported for tPA treatment windows, it is conceivable that the correlation between infarct and deficit reduction is in part a function of the model itself. Any number of variables associated with animal preparation (eg, anesthesia and clot preparation) could combine to produce a biochemical environment within an animal subjected to thromboembolic stroke to either exacerbate or mitigate tPA-related toxicities. For example, halothane, the widely used anesthesia in rodent stroke studies, is an established inhibitor of platelet function.\textsuperscript{43} Therefore, comparing outcomes from thromboembolic studies with subtle technical distinctions is fraught with uncertainty.

This report adds to a growing body of literature indicating that selective inhibition of factor IX(a) is an effective antithrombotic strategy.\textsuperscript{21,25,28,29,44–47} The data lend additional support to the concept that ischemic injury and the resultant perfusion deficit are in part exacerbated by the activation of blood coagulation and a subsequent propagation of thrombosis.

Overall, the data collected in this thromboembolic stroke study suggest that inhibition of factor IX(a) within 4 hours of stroke onset produces a more favorable outcome than treatment with tPA. However, when therapy is initiated 6 hours after stroke, the protective benefits of SB 249417 are lost. Although tPA treatment produced a reduction in lesion volume at all time points studied, it did not significantly reduce functional deficits associated with stroke. In this rat model neither therapy resulted in hemorrhagic conversion, and therefore an assessment of the relative treatment-related hemorrhagic risk will be the subject of future investigations.

Acknowledgment

This work was supported by GlaxoSmithKline.
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Stroke. 2002;33:578-585
doi: 10.1161/hs0202.102950
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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