Inhibition of Factor Xa Reduces Ischemic Brain Damage After Thromboembolic Stroke in Rats

Xinkang Wang, PhD; Lin Xu, MD; Hugh Wang, PhD; Reinhard Grzanna, PhD; Yutian Zhan, MS; Robert M. Knabb, PhD; Joseph M. Luettgen, MS; Tracy A. Bozarth, MS; Robert A. Galemmo, PhD; Pancras C. Wong, PhD; Roberta Bernard, MS; Hugo Vargas, PhD; Michael Chopp, PhD; Steven M. Friedman, MD; Giora Z. Feuerstein, MD

Background and Purpose—Factor Xa (FXa) is a key coagulation protease and target for novel antithrombotic agents for prevention and treatment of diverse thromboembolic disorders. In the present study we describe the effect of a novel, potent, and selective FXa inhibitor, DPC602, on brain damage and neurobehavioral consequence in a rat thromboembolic model of stroke.

Methods—Thromboembolic stroke was induced in rats by placement of an autologous clot into the middle cerebral artery.

Results—Laser-Doppler monitoring of cerebral blood flow demonstrated that DPC602 (8 mg/kg, single IV/IP bolus pretreatment) markedly improved cerebral blood flow after thromboembolic stroke by 25% to 160% (n=6; P<0.001) at 1 to 6 hours. DPC602 demonstrated concentration- and time-dependent reductions in infarct size, with maximal effect (89% reduction; n=14; P<0.001) at the highest dose over controls. Neurological function was also significantly improved in DPC602-treated rats at days 1, 3, and 7 (n=13; P<0.01). DPC602 treatment did not cause cerebral hemorrhage, assessed by free hemoglobin in the ischemic brain tissues.

Conclusions—These data suggest that anticoagulation with a selective FXa inhibitor might ameliorate the extent of ischemic brain damage and neurological deficits after a thromboembolic event. Enhanced clot dissolution and early reperfusion may account for the cerebrovascular-protective effect of the drug. (Stroke. 2003;34:468-474.)

Key Words: anticoagulants ■ cerebral blood flow ■ cerebral ischemia ■ coagulation ■ thromboembolism

Ischemic stroke frequently results from occlusion of cerebral vessels by a thrombus generated over a ruptured atheroma, erosion of plaque intima, or thromboembolism associated with atrial fibrillation. The resultant deprivation of blood flow, and hence oxygen and glucose, in the area supplied by the occluded cerebral vessel leads to neuronal distress, which if prolonged results in neuronal cell death.

The recognition of thromboembolic events as an important cause of ischemic stroke has led to numerous trials that sought to establish efficacy of various anticoagulants, antiplatelets, and thrombolytic agents for prophylactic and treatment of strokes. The beneficial effect of early reperfusion of an occluded cerebral artery has been shown in clinical trials with tissue plasminogen activator (tPA) if patients are treated within 3 hours of symptoms. However, more recent studies with alteplase administered 3 to 5 hours or within 6 hours after the onset of stroke4 failed to show benefits while significantly increasing the risk for intracerebral hemorrhage. Thus, a very narrow “therapeutic window” exists for thrombolysis in acute ischemic stroke, which allows access to this treatment for only a minor fraction of patients (<2%).

The use of heparin in acute ischemic stroke is quite prevalent: 22% to 42% of ischemic stroke patients received heparin in one survey5 despite unproven benefits. Likewise, the role of low-molecular-weight heparin in treatment or prevention of thromboembolic stroke remains controversial.7

The most compelling case for the use of oral anticoagulants in prevention of ischemic strokes is in patients with atrial fibrillation. Five randomized, double-blind, placebo-controlled studies with warfarin in primary prevention and 3 trials in secondary prevention suggest benefits for most patients with chronic atrial fibrillation.8 In noncardiac patients, warfarin has not proven to be superior to aspirin in prevention of stroke, as reported in the Warfarin-Aspirin Recurrent Stroke Study.9 In addition, chronic treatment with warfarin requires careful management of patients, including monitoring of international normalized ratio, dietary restrictions, drug interactions, and bleeding.10 Thus, while treatment with the anticoagulant warfarin in certain high-risk patients has been beneficial in prevention of thromboembolic stroke, warfarin treatment has many limitations.
In the present study we describe the efficacy of a novel, potent, and highly selective factor Xa (FXa) inhibitor, DPC602, to improve cerebral perfusion, salvage ischemic brain tissue, and improve functional outcome in a rat thromboembolic stroke model.

Materials and Methods

Focal Brain Ischemia

Rats were housed and cared for in accordance with the Guide for the Care and Use of Laboratory Animals (Department of Health, Education, and Welfare [Department of Health and Human Services] publication No. NIH 85-23, revised 1996, Office of Science and Health Reports, Division of Research Resources [DRR]/National Institutes of Health, Bethesda, Md). Procedures involving the use of laboratory animals were approved by our Institutional Animal Care and Use Committee.

Male Sprague-Dawley rats (aged 20 weeks; weight, 340 to 450 g) were used for the present study. Rats were anesthetized with either pentobarbital (50 mg/kg IP) or gas inhalation composed of 30% oxygen (0.3 L/min) and 70% nitrous oxide (0.7 L/min) mixture. The gas was passed through an isoflurane vaporizer set to deliver 3% to 4% isoflurane for initial anesthesia induction and 1.5% to 2% during surgery.

To induce focal embolic stroke, a thrombus was prepared and inserted into the internal common carotid artery approximately 1 to 2 mm from the middle cerebral artery (MCA), as described in detail previously. No clot was injected in sham-operated animals.

Drug Administration

DPC602 [(4-methoxyphenyl)- and (2-aminomethyl) phenyl pyrazole] was developed as a potent and selective inhibitor of FXa, with a Ki of 2.5 nM for rat FXa. DPC602 or saline was administered to rats intravenously and intraperitoneally (50% each). A dose of 8 mg/kg DPC602 (1.5 mg/mL in saline) was used in all the studies except for the dose-dependent study, as specified in the figure legends. The compound was administered immediately before MCA occlusion (MCAO) in all the studies, except in the therapeutic window study in which animals were dosed at 60 minutes after MCAO, as specified in Figure 3.

Physiological Measurements

Regional cerebral blood flow (CBF) was measured with a laser-Doppler perfusion monitor (Moor Instruments Inc). Under anesthesia, a small incision was made at the midpoint between the right orbit and the external auditory canal. The temporalis muscle was retracted, and the underlying fascia was cleared. A small area of skull approximately 1 mm posterior and 5 mm lateral to the bregma in the ipsilateral hemisphere was thinned to allow placement of the laser-Doppler probe. CBF was monitored before and after MCAO in the animals treated with 8 mg/kg DPC602 or vehicle.

The arterial blood pressure and heart rate were measured with the use of an MP100 Workstation and analyzed with the use of AcqKnowledge software (BIOPAC Systems, Inc) according to the manufacturer’s specification. Femoral arterial blood samples were analyzed for pH, oxygen (PO2), and carbon dioxide (PCO2) by direct collection through polyethylene tubing (PE-50) into an i-STAT G3+ cartridge and processed with a portable clinical analyzer (Abbott Laboratories).

Measurement of Infarct Volume

Infarct volume was measured with the use of 2,3,5-triphenyltetrazolium chloride (TTC)–stained brain slices (24 hours after MCAO) as described previously.

Immunohistochemical Analysis

The MCA was dissected from rats (n = 5) 6 hours after MCAO. Cryostat sections were processed for immunohistochemical analysis as described previously. The primary antibodies used in the present study include rabbit anti-human tPA (Corning Biochem, Inc), sheep anti-human thrombin IgG (Enzyme Research Laboratories), and goat anti-human P-selectin (C-20) (Santa Cruz Biotechnology, Inc). Clots (n = 3) prepared ex vivo but not introduced into the MCA served as additional controls to detect the presence of the markers in the clot before insertion into the MCA.

Neurological Deficits and Rotarod Test

Neurological deficits were examined at days 1, 3, and 7 after MCAO or sham operation with the use of a 5-point scale adapted and modified from Zhang et al, as follows: no neurological deficit, 0 points; right Horner’s syndrome, failure to extend left forelimb, hindlimb, turning to left and circling to left, each 1 point. The Accelerating Speed Treadmill (Stoelting) was used for the rotarod test. Four trials were allowed at each session, and the mean values were collected for group data analysis.

Tail Transection Bleeding Test

The tail of anesthetized rats (1 and 6 hours after dosing of DPC602 or saline; n = 6) was cut at 5 mm from the tip with a disposable surgical blade. Rats were placed on a 37°C heating pad, and the bleeding time was assessed with the use of a filter paper every 30 seconds up to 60 minutes.

Assessment of Hemorrhagic Transformation by Brain Hemoglobin Levels

Rats (n = 12) were dosed with DPC602 or saline before MCAO or sham operation. After 24 hours, rats were anesthetized with ketamine and xylazine and then subjected to complete transcardial perfusion with saline to remove all remaining intravascular blood. Blood content in the brain was quantified following a previously described method with the use of a plasma hemoglobin assay kit (Sigma). Hemoglobin levels in the contralateral hemisphere were subtracted from the ipsilateral hemisphere to minimize potential variability of retained blood.

Pharmacokinetic Studies With DPC602

Rats were dosed with DPC602, and 500-μL blood samples were collected in a sodium citrate tube at 1 minute, 1 hour, and 6 hours after dosing (n = 5). Total plasma levels of DPC602 were measured by high-performance liquid chromatography (Hewlett-Packard Series 1100). Rat plasma (0.1 mL) was denatured with acetonitrile (0.4 mL) and centrifuged at 2000 g for 20 minutes. Supernatants were decanted into 12 × 75-mm glass tubes and evaporated at 45°C under a stream of nitrogen. Samples were dried and redissolved in 45% acetonitrile/55% 0.2% ammonium formate, pH 4. For high-performance liquid chromatography separation, 0.02 mL was injected over a Zorbax RX-C8, 4.6 × 250-mm, 5-μm pore size column with a 45% acetonitrile/55% 0.2% ammonium formate, pH 4, mobile phase at a rate of 1 mL/min. Absorbance at 280 nm was recorded. Peak area was proportional to DPC602 plasma concentration. Sample concentrations of DPC602 were calculated from a standard established in rat plasma spiked with 0 to 50 μmol/L DPC602.

Prothrombin Time and Activated Partial Thromboplastin Time

Rats were dosed with 8 mg/kg DPC602 or saline, and 1-mL blood samples were collected in a sodium citrate tube at 1 and 6 hours after dosing (n = 4). Prothrombin time (PT) was assayed by a Sysmex CA6000 coagulation analyzer (Dade-Behring) on a 50-μL platelet-poor plasma sample, and coagulation was initiated by adding 100 μL of thromboplastin C Plus reagent (Dade-Behring). For the activated partial thromboplastin time (APTT) measurement, 50 μL of sample was placed into a sample cup and incubated at 37°C for 1 minute; 50 μL of APTT reagent (Sigma) was added and incubated at 37°C for 2 minutes. Thereafter, 50 μL of CaCl2, was added and incubated at 37°C to start clot formation.

Downloaded from http://stroke.ahajournals.org/ by guest on May 1, 2016
TABLE 1. Plasma Concentration of DPC602 in Rats and its Effect on Peripheral Bleeding

<table>
<thead>
<tr>
<th>Time After Dosing</th>
<th>Plasma Levels, μmol/L</th>
<th>Tail Bleeding Time, min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline</td>
<td>DPC602</td>
</tr>
<tr>
<td>15 min</td>
<td>18.0±2.6</td>
<td>ND</td>
</tr>
<tr>
<td>60 min</td>
<td>13.7±0.9</td>
<td>7.4±0.5</td>
</tr>
<tr>
<td>6 h</td>
<td>2.9±0.3</td>
<td>8.8±0.8</td>
</tr>
</tbody>
</table>

Rats were dosed with 8 mg/kg DPC602, and blood samples were collected at the times indicated after dosing; total plasma levels of DPC602 were measured (n=5) as described in Materials and Methods. Ki=2.5 nmol/L for rat FXa. Plasma protein binding=96% for SN602. Tail bleeding time (min) was measured at 60 minutes and 6 hours after dosing (n=6) as described in Materials and Methods. ND indicates experiments not done.

Statistical Analysis
All data are presented as mean±SE for the indicated number of rats. Statistical comparisons were made by ANOVA (Fisher’s protected least squares difference), and values were considered to be significant when P<0.05.

Results
Plasma Levels of DPC602 and Effect on Bleeding Test
Table 1 shows that free plasma compound concentration reached 288-, 219-, and 46-fold of the Ki at 15 minutes, 1 hour, and 6 hours, respectively, after dosing. The same dose significantly increased tail bleeding time at 4.2- and 1.8-fold increases over control (P<0.05; n=6) at 1 and 6 hours, respectively (Table 1). Thus, this dosing regimen of DPC602 conveyed clear anticoagulant capacity throughout at least 6 hours after MCA embolization.

Effects of DPC602 on Physiological Parameters
The effects of DPC602 on heart rate, arterial blood pressure, pH, blood oxygen (PO2), and carbon dioxide (PCO2) were evaluated in rats after sham operation or MCAO. All the respiratory and cardiovascular parameters remained within baseline values in both saline- and DPC602-treated rats (Table 2).

TABLE 2. Physiological Conditions in the Presence or Absence of DPC602 After MCA Occlusion

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MCAO</th>
<th>HR, min⁻¹ (n=8)</th>
<th>MABP, mm Hg (n=8)</th>
<th>PO2, mm Hg (n=10)</th>
<th>PO2, mm Hg (n=10)</th>
<th>pH (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>Before</td>
<td>309±9</td>
<td>90±4</td>
<td>42±3</td>
<td>131±6</td>
<td>7.29</td>
</tr>
<tr>
<td></td>
<td>15 min</td>
<td>325±15</td>
<td>85±7</td>
<td>47±4</td>
<td>133±11</td>
<td>7.23</td>
</tr>
<tr>
<td></td>
<td>6 h</td>
<td>334±29</td>
<td>101±5</td>
<td>44±4</td>
<td>134±7</td>
<td>7.33</td>
</tr>
<tr>
<td>DPC602</td>
<td>Before</td>
<td>309±8</td>
<td>90±3</td>
<td>43±2</td>
<td>134±6</td>
<td>7.31</td>
</tr>
<tr>
<td></td>
<td>15 min</td>
<td>297±5</td>
<td>80±3</td>
<td>46±3</td>
<td>127±9</td>
<td>7.22</td>
</tr>
<tr>
<td></td>
<td>6 h</td>
<td>308±20</td>
<td>92±2</td>
<td>42±3</td>
<td>133±10</td>
<td>7.28</td>
</tr>
</tbody>
</table>

DPC602 (8 mg/kg) or saline was administrated before MCAO. Physiological data were measured 15 minutes before, or 15 minutes and 6 hours after MCAO. No statistical difference was observed between DPC602 and saline treatment.

HR indicates heart rate; MABP, mean artery blood pressure.

Figure 1. Effect of DPC602 on the change of regional CBF after MCAO. Rats were dosed with 8 mg/kg DPC602 (n=10) or saline (n=10) before MCAO. Regional CBF was continuously monitored before (Pre), immediately after (time 0), and at 1, 2, 4, 6, and 24 hours after MCAO. *P<0.05, **P<0.01 compared with time 0 in the same group. DPC602 Elevates Regional CBF After MCAO
A rapid decrease in the relative regional CBF in the ipsilateral cortex was measured after MCAO (34% CBF remaining relative to the pre-MCAO baseline; n=10; P<0.001). Reduced CBF was sustained for at least 6 hours, yet slow and partial recovery was noted over 24 hours after MCAO (76% of baseline) (Figure 1). Rats dosed with 8 mg/kg DPC602 (n=10) had an accelerated recovery in CBF after MCAO, showing 35%, 50%, 65%, 78%, 91%, and 101% CBF relative to the pre-MCAO baseline at 0, 1, 2, 4, 6, and 24 hours after MCAO, respectively (Figure 1).

Immunohistochemical Analysis of tPA, P-selectin, and Thrombin Expression in Clot
To investigate the potential mechanisms responsible for the accelerated CBF recovery in DPC602-treated rats, we examined the expression of tPA (the molecule directly involved in the clot resolution), P-selectin (a marker for activated platelets), and thrombin (the downstream protease activated by FXa) in the occluding clot (n=5). The tPA immunoreactivity was strong in clots of rats treated with DPC602 (Figure 2). Similarly, tPA immunoreactivity was strong at the edge section of the clot in vehicle-treated rats, while only a weak
basal level of tPA was noted in the mid-clot sections (Figure 2). It was also noted that tPA was strongly induced in the vessel wall of clot-obstructed vessels regardless of the presence or absence of DPC602 (Figure 2, indicated with arrows). In contrast, tPA immunoreactivity was not detected in normal, nonoccluded vessels (Figure 2, inset). A similar distribution pattern was observed for P-selectin in clots of DPC602- or vehicle-treated rats except that P-selectin expression was not detected in the vessel wall (Figure 2). Thrombin (the downstream product of FXa) immunoreactivity was relatively weak in the clots of animals treated with DPC602, while it was strong in saline-treated animals, especially at the edges of the clots, where active thrombogenic surface might prevail.

Neuroprotective Effect of DPC602 on Rat Brain After MCAO
To evaluate whether improved CBF in DPC602-treated rats translates into neuroprotective action, we examined dose- and time-dependent effects of DPC602 on infarct sizes 24 hours after MCAO. A dose-dependent decrease in ischemic lesion was observed, with 23% (n=8; P=0.71), 53% (n=10; P<0.05), and 89% (n=14; P<0.001) reduction by 0.08, 0.8, and 8 mg/kg DPC602, respectively (Figure 3A). The reduction of infarct size was observed in both cortical and subcortical regions. However, no significant reduction in infarct size was noted when DPC602 was administered at 60 minutes after MCAO (n=11; 24% reduction over controls; P=0.34) (Figure 3B).

Neurological score was assessed over 7 days after MCAO in rats treated with DPC602 or saline. As illustrated in Figure 4A, the overall neurological deficits were significantly less in the DPC602-treated rats (n=17) than controls (n=17) at day 1 (34% improvement; P<0.001), day 3 (33% improvement; P<0.01), and day 7 (35% improvement; P<0.01) after MCAO. Similar functional recovery was observed with rotarod test for the same groups of animals (Figure 4B). DPC602-treated rats significantly improved in rotarod running ability over vehicle treatment at day 1 (with 271% improvement; P<0.01), day 3 (170%; P<0.01), and day 7 (105%; P<0.01) after MCAO. The extent of functional recovery of DPC602-treated animals in the rotarod test was almost similar to that of sham-operated rats (n=14) (Figure 4B).
Effect of DPC602 on Intracerebral Hemorrhage

Since anticoagulants may carry bleeding liability, the effect of DPC602 on intracerebral hemorrhage was evaluated. As depicted in Figure 5, hemoglobin content was significantly increased in ischemic brain tissues compared with nonischemic brain tissues ($P < 0.05$; $n=12$). However, there was no difference between DPC602- and saline-treated rats in the amount of hemoglobin in ischemic tissues.

**Figure 3.** Concentration- and time-dependent effect of DPC602 on infarct size in the brain after MCAO. Rats were subjected to MCAO, and infarct size was measured 24 hours after ischemia with the use of TTC-stained images. A, Concentration-dependent effect of DPC602 on infarct size, $n=14$, 8, 10, and 14 for the saline and 0.08-, 0.8-, and 8-mg/kg DPC602 groups, respectively. B, Time-dependent effect of DPC602 on infarct size. Saline or DPC602 (8 mg/kg) was administered immediately before ($n=14$) or 60 minutes after ($n=11$) MCAO. $^{*}P < 0.05$, $^{***}P < 0.001$ compared with group treated with vehicle (saline).

**Figure 4.** Effect of DPC602 on neurological deficits and rotarod assay. Neurological scores and rotarod tests were evaluated at 1, 3, and 7 days after sham operation or MCAO. Saline (vehicle) or 8 mg/kg DPC602 was administered into rats immediately before MCAO. $n=14$ for the sham group and $n=17$ for 2 MCAO groups (DPC602 and vehicle). $^{*}P < 0.01$ compared with vehicle treatment.

**Figure 5.** Effect of DPC602 on intracerebral hemorrhage. A, Representative standard assay for the amount of blood in rat brain tissue. OD, absorbance at 600 nm. B, Effect of DPC602 on intracerebral hemorrhage in sham-operated or ischemic brain tissues. Rats were administrated 8 mg/kg DPC602 or saline followed by sham operation or MCAO for 24 hours. Hemispheric brain tissues ($n=12$) were dissected after transcardial perfusion. The levels of intracerebral hemorrhage in the brain tissue were measured according to the standard as shown in A; data are illustrated as ipsilateral blood levels after subtraction from contralateral volumes of the same animal. $^{*}P < 0.05$ compared with sham-operated animals.

**Effect of DPC602 on Intracerebral Hemorrhage**

Since anticoagulants may carry bleeding liability, the effect of DPC602 on intracerebral hemorrhage was evaluated. As depicted in Figure 5, hemoglobin content was significantly increased in ischemic brain tissues compared with nonischemic brain tissues ($P < 0.05$; $n=12$). However, there was no difference between DPC602- and saline-treated rats in the amount of hemoglobin in ischemic tissues.

**Effect of DPC602 on PT and APTT**

A significant increase in PT was observed only acutely (1 hour) but not 6 hours after dosing of 8 mg/kg DPC602 (Figure 6). No significant effect of DPC602 on the APTT was noted either 1 or 6 hours after dosing.

**Discussion**

FXa plays a critical role in the coagulation cascade by generation of thrombin, the ultimate serine protease that generates fibrin from fibrinogen. In the present study we demonstrated that a potent and selective FXa inhibitor enhances dissolution of a clot dislodged in the MCA, thereby reducing infarct size and improving neurological outcome. The better adaptation of the DPC602-treated rats to the accelerating rotarod running may reflect not only improvement of motor function but also improvement of learning and adaptation to new challenges. It is noteworthy that partial spontaneous resolution of the clot was also evidenced in vehicle-treated rats, yet the kinetics of this endogenous process was insufficient to salvage brain tissue. The efficacy
of the FXa inhibitor in clot resolution and stroke outcome suggests that in the presence of the FXa inhibitor the prothrombotic action on the occluding clot surface has been diminished.

The marked tPA immunoreactivity at the edge of clots (in both DPC602- and vehicle-treated animals) may suggest a key role of this fibrinolytic factor in clot resolution. It has been previously demonstrated that administration of tPA after MCAO by a fibrin-rich clot (similar to the clot used in this study) enhances reperfusion.\(^1\)\(^4\)\(^5\) In the present study we demonstrate the de novo induction of tPA in the MCA vessel wall occluded with a thrombus. These data extend previous reports in which tPA expression was limited to the endothelium of small vessels (such as bronchial and pulmonary vessels, particularly under inflammatory conditions) but not large arteries or veins.\(^16\) We also have shown for the first time that the occluding clot is actively thrombogenic, as evidenced by immunoreactive P-selectin (a marker of activated platelets) and the presence of thrombin in the clot. The interpretation of the prothrombotic nature of the occluding clot must be made with caution since no quantification of these parameters was completed.

While pretreatment of rats with DPC602 demonstrated significant improvement in infarct size and functional outcome after ischemic brain injury, the therapeutic window appears to be narrow because much of the neuroprotection was lost when treatment was delayed beyond 60 minutes after MCAO. These data may suggest that the anticoagulant must be present before the thromboembolic event. However, one may speculate that prolongation of the therapeutic window for the anticoagulant might be achieved by the combination of an anticoagulant with antiplatelet agents or triple therapy in combination with fibrinolytic agents.

While we have obtained evidence in support for a thrombus-directed mechanism for enhanced CBF by the FXa inhibitor, we cannot exclude other possible sites for DPC602 actions. It has been previously shown that in response to occlusion of the MCA, fibrin deposition in brain parenchymal microvessels can be found as early as 4 hours after MCAO.\(^13\) Furthermore, fibrin and platelet deposition in the parenchymal vessels has also been described in a baboon model of transient cerebral ischemia.\(^17\) These data suggest that anticoagulant may also act downstream of the occluding thrombus to improve tissue perfusion by inhibition of microvessel thrombosis in addition to reduction of thrombus mass.

Since anticoagulants may carry risk of bleeding, it was important to evaluate whether the treatment with DPC602 could result in hemorrhagic transformation. As the data show, no increase in tissue hemoglobin was found DPC602-treated rats, suggesting no intracerebral bleeding at the dosing regimen. However, DPC602 administered at the highest dose extended bleeding time (both 60 minutes and 6 hours after dosing) and PT at 60 minutes, suggesting possible bleeding liabilities.

In conclusion, our present study demonstrated that a potent and selective FXa inhibitor at an anticoagulant dose provides induced neuroprotection in an experimental model of thromboembolic stroke. Accelerated thrombolysis of the clot and possibly downstream inhibition of microvascular thrombosis may act in concert to alleviate brain injury and improve functional outcome after thromboembolic stroke.

References


Inhibition of Factor Xa Reduces Ischemic Brain Damage After Thromboembolic Stroke in Rats

Xinkang Wang, Lin Xu, Hugh Wang, Reinhard Grzanna, Yutian Zhan, Robert M. Knabb, Joseph M. Luettgen, Tracy A. Bozarth, Robert A. Galemmo, Pancras C. Wong, Roberta Bernard, Hugo Vargas, Michael Chopp, Steven M. Friedman and Giora Z. Feuerstein

Stroke. 2003;34:468-474; originally published online January 16, 2003; doi: 10.1161/01.STR.0000049765.81774.A3

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/34/2/468