Antithrombotic Effects of FK419, a Novel Nonpeptide Platelet GPIIb/IIIa Antagonist, in a Guinea Pig Photochemically Induced Middle Cerebral Artery Thrombosis Model: Comparison with Ozagrel and Argatroban

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ABSTRACT
Platelet activation and subsequent aggregation play a key role in the pathogenesis of ischemic brain damage. Recent studies revealed that enhanced platelet activation is also observed after ischemia, suggesting that secondary thrombus formation might participate in the development of cerebral infarction. The binding of platelet glycoprotein GPIIb/IIIa (integrin αIIbβ3) to fibrinogen is the final common pathway in platelet aggregation. Therefore, GPIIb/IIIa antagonists might be useful in acute ischemic stroke as well as in the secondary prevention of ischemic stroke. In the present study, we evaluated the effect of three compounds, FK419 ((S)-2-acetylamino-3-[((R)-(1-[3-(piperidin-4-yl) propionyl] piperidin-3-ylcarbonyl) amino] propionic acid trihydrate), a novel nonpeptide GPIIb/IIIa antagonist, ozagrel, a selective thromboxane A2 synthase inhibitor, and argatroban, a thrombin inhibitor, on middle cerebral artery (MCA) patency and ischemic brain damage using photochemically induced MCA thrombosis model in guinea pigs. FK419, ozagrel, or argatroban was administered 5 min after the termination of photoirradiation. FK419 dose-dependently improved MCA patency by decreasing the total occlusion time, time to continuous recirculation, and the number of cyclic flow reductions, at doses that inhibited ADP-induced platelet aggregation ex vivo. In contrast, ozagrel only improved total occlusion time, and argatroban showed no improvement in MCA patency. FK419 also reduced ischemic brain damage in a dose-dependent fashion, whereas ozagrel and argatroban did not. Finally, FK419 ameliorated neurological deficits, whereas ozagrel and argatroban did not. These results indicate that FK419, a GPIIb/IIIa antagonist, ameliorates ischemic brain damage by improving MCA patency after occlusion and that FK419 is a promising candidate for the treatment of acute ischemic stroke.

Thrombotic cardiovascular disease involves a complex set of interactions of many factors, including platelet aggregation, the coagulation cascade, and vascular-wall constituents. Platelet activation is enhanced after ischemic stroke (van Kooten et al., 1994; Grau et al., 1998; Zeller et al., 1999), leading to secondary thrombus formation and further expansion of the cerebral infarction (Figols et al., 1987; Heye and Cervós-Navarro, 1996). Furthermore, prolonged antiplatelet therapy can successfully prevent secondary vascular events after ischemic stroke (Antiplatelet Trialists’ Collaboration, 1994). Recently, two major trials of aspirin in acute ischemic stroke revealed that early aspirin use produces a small but definite benefit (CAST Collaborative Group, 1997; International Stroke Trial Collaborative Group, 1997; Chen et al., 2000). Thus, antiplatelet therapies show promise in treating both acute and secondary ischemic stroke. The antiplatelet activity of aspirin is limited, however, because it inhibits only a single pathway of platelet activation. In addition, aspirin reduces prostaglandin I2 production in the endothelium, which may lead to decreases in cerebral blood flow (Bednar and Gross, 1999). Although this unfavorable effect is not shown by ozagrel, a selective thromboxane A2 (TXA2) synthase inhibitor, its antiplatelet activity is also limited because it only inhibits a single activation pathway.

After platelet activation is triggered by a variety of agonists, a number of events are induced, such as shape change...
and a conformational change in platelet glycoprotein GPIIb/IIIa (integrin α₃β₃), which is abundant on platelets and megakaryocytes. Antagonism of GPIIb/IIIa is an attractive antiplatelet strategy because fibrinogen binding to activated GPIIb/IIIa is the final common step in platelet aggregation (Pytela et al., 1986), and GPIIb/IIIa antagonists suppress platelet aggregation induced by all known agonist stimuli (Cook et al., 1994; Collar et al., 1995). Since a wide variety of platelet activation pathways contribute to thrombus formation, a GPIIb/IIIa antagonist should provide more efficacious antithrombotic therapy than commonly available agents.

Thrombin is a central bioregulator of coagulation and is therefore a key target in the therapeutic prevention of thromboembolic disorder. Thrombin catalyzes the conversion of fibrinogen to fibrin and activates fibrin-stabilizing factor XIII and clotting factors that are necessary for prothrombin transformation. Thrombin is also a potent activator of a variety of cell events, including platelet aggregation, secretion and formation of TXA₂, and contraction of smooth muscle. Thrombin plays an important role in arterial thrombosis, and specific thrombin inhibitors, hirudin and argatroban, prevent reocclusion of canine coronary artery (Fitzgerald and Fitzgerald, 1989) and reduce the formation of microthrombi and ischemic lesions (Kawai et al., 1996). Argatroban is approved in the United States and Canada for both prophylaxis and treatment of thrombosis in patients with heparin-induced thrombocytopenia, and in Japan and Korea for treatment of various thrombotic disorders.

Photochemically induced thrombosis models are widely used to examine the effects of antithrombotic agents (Umemura et al., 1993; Nishiyama et al., 1994; Kaku et al., 1998). In these models, a photochemical reaction between rose bengal and transcutaneous light irradiation leads to endothelial injury followed by platelet adhesion, aggregation, and formation of an occlusive platelet-rich thrombus at the irradiated site (Saniahiadi et al., 1995). Particularly in the thrombotic middle cerebral artery (MCA) occlusion model in guinea pigs, spontaneous reperfusion and repeated cyclic flow reductions (CFRs), which are caused by the periodic generation of occlusive platelet thrombi, are observed after occlusion (Kawano et al., 1998). Furthermore, the extent of brain damage is related to CFRs and total patency time (Kawano et al., 1998, 1999).

Recently, FK419 ((S)-2-acetylamino-3-[(R)-1-[3-(piperidin-4-yl)propionyl]piperidin-3-ylcarbonyl]amino)propionic acid trihydrate; Fig. 1), a novel nonpeptide GPIIb/IIIa antagonist, has been discovered in our laboratories. FK419 is a selective GPIIb/IIIa antagonist that inhibits platelet aggregation in human, dogs, and guinea pigs, with weak activity in prolongation of bleeding time in dogs. In this report, we compared the efficacy of FK419, ozagrel, and argatroban in the guinea pig MCA thrombosis model.

FK419

Fig. 1. Chemical structure of FK419.
Concentration of TXB$_2$ was measured by an enzyme immunoassay kit (RPN220; Amersham Biosciences UK, Ltd., Little Chalfont, Buckinghamshire, UK) after extraction of TXB$_2$ (Ample Prep C2; Amersham Biosciences UK, Ltd.).

Coagulation Time ex Vivo. Sixty minutes after initiation of argatroban administration, animals were anesthetized with ether, and their blood was drawn from the abdominal aorta into a plastic tube containing 3.8% sodium citrate. PPP was prepared and coagulation times were measured as described above.

Photochemically Induced MCA Occlusion Model. The left MCA was photochemically occluded according to the method of Kawano et al. (1998). Briefly, animals were anesthetized with isoflurane (2% for induction, 1% for maintenance) in a mixture of air and 30% O$_2$. A catheter for the administration of drugs or rose bengal was inserted into the left jugular vein. After a left temporal incision, the temporal muscle was removed by an electric cauterizer. A subtemporal craniotomy was performed using a dental drill under an operational microscope to open a 6-mm-diameter oval bony window. The main trunk of the MCA was observed without cutting the dura mater. The head of a 3-mm-diameter optic fiber mounted on a micro manipulator was placed on the MCA segment proximal to the olfactory tract for photoirradiation. A pulsed Doppler flow probe (HHP-20; Crystal Biotech, Northboro, MA) connected to a pulsed Doppler flowmeter (PD-20; Crystal Biotech) was placed on the distal part of the MCA to measure blood flow until the end of drug administration. Photoirradiation was conducted using a xenon lamp (L2859–03; Hamamatsu Photonics, Hamamatsu, Japan) with a heat-absorption filter and a green filter. When a stable baseline blood flow was obtained, rose bengal infusion (20 mg/kg for 6 min) and photoirradiation with green light (wavelength 540 nm, intensity 32 nW/m$^2$) was performed immediately before the end of photoirradiation. Arterial blood pressure and heart rate were recorded until the end of drug administration. Arterial blood (210 µl) was collected immediately before and 1 and 3 h after photoirradiation to analyze blood gases, hematocrit, total hemoglobin, and blood glucose (ABL18; Radiometer Medical A/S, Copenhagen, Denmark). Temporal muscle temperature was monitored as an index of brain temperature.

Statistical Analysis. Values are expressed as the mean ± S.E.M. All data from in vivo studies except for neurological deficits were evaluated by one-way analysis of variance (ANOVA) followed by Dunnett’s multiple comparison test. Kruskal-Wallis test followed by Dunnett’s multiple comparison test were used for neurological deficits. A $P$ value less than 0.05 was considered significant.

Results

Inhibition of Platelet Aggregation in Vitro. FK419 dose-dependently inhibited ADP- and collagen-induced platelet aggregation in vitro. IC$_{50}$ values for inhibition of ADP and collagen were 380 ± 28 and 920 ± 32 nM, respectively. In

<table>
<thead>
<tr>
<th>Dose (mg/kg + mg/kg/h for 3 h)</th>
<th>Platelet Aggregation (%)</th>
<th>TXB$_2$ Production</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 min</td>
<td>60 min</td>
</tr>
<tr>
<td>Control</td>
<td>64.9 ± 4.4 (0.0)</td>
<td>55.2 ± 1.4 (0.0)</td>
</tr>
<tr>
<td>0.03 + 0.1</td>
<td>37.1 ± 4.8 (42.8)</td>
<td>34.5 ± 2.8 (37.5)</td>
</tr>
<tr>
<td>0.06 + 0.2</td>
<td>10.9 ± 4.2 (83.2)</td>
<td>13.3 ± 7.9 (75.9)</td>
</tr>
<tr>
<td>0.12 + 0.4</td>
<td>0.0 ± 0.0 (100.0)</td>
<td>0.1 ± 0.1 (99.8)</td>
</tr>
</tbody>
</table>

* $P < 0.05$, ** $P < 0.01$ versus control (one-way ANOVA followed by Dunnett’s multiple comparison test).
There were no significant changes in MCA blood damage. (Fig. 5).

ment (Fig. 5).

ment in MCA patency was observed with argatroban treat-

and time to first reperfusion (Fig. 4). Similarly, no improve-

effects on number of CFRs, time to continuous reperfusion,

occlusion time at all doses tested, there were no significant

reperfusion. Although ozagrel significantly shortened total

served spontaneous reperfusion after the primary occlusion

5 min after photoirradiation in all groups (Fig. 2). We ob-

not statistically different among the groups.

treatment, argatroban actually tended to aggravate brain
damage (Fig. 7, B and C). FK419 treatment (0.03 mg/kg +
0.1 mg/kg/h and above) tended to improve total neurologic score
(Fig. 8). Significant improvement of forelimb paralysis was
observed at 0.06 mg/kg bolus + 0.2 mg/kg/h infusion for 3 h.

treated animals sustained consistent cortical and subcortical
lesions (Fig. 6A). FK419 reduced the lesioned area in a dose-
dependent fashion (Figs. 6B and 7A), with significance in total area (cerebral cortex + striatum) and cerebral cortex at
0.03 mg/kg + 0.1 mg/kg/h and higher. Percentage reductions
in ischemic brain damage in total and cerebral cortex were as
follows: 0.009 mg/kg + 0.03 mg/kg/h, 19 and 18%; 0.03 mg/kg
+ 0.1 mg/kg/h, 32 and 36%; 0.06 mg/kg + 0.2 mg/kg/h, 47 and
42%. In contrast, ozagrel did not significantly reduce brain
damage, and argatroban actually tended to aggravate brain
damage (Fig. 7, B and C). FK419 treatment (0.03 mg/kg +
0.1 mg/kg/h and above) tended to improve total neurologic score
(Fig. 8). Significant improvement of forelimb paralysis was
observed at 0.06 mg/kg bolus + 0.2 mg/kg/h infusion for 3 h.

Fig. 2. Typical recording and quantitative analysis of MCA blood flow. MCA blood flow was quantified during drug administration. Drugs or saline were administered 5 min after the end of photoradiation for 3 h. Time to MCA occlusion was approximately 5 min and not statistically different among the groups.

contrast, ozagrel and argatroban did not inhibit ADP- and
collagen-induced aggregation at concentrations up to 100
µM.

Prolongation of Coagulation Time in Vitro. Argatro-
ban concentration-dependently prolonged PT and APTT with
2-fold prolongation concentrations of 810 ± 44 and 1300 ± 60
nM, respectively. In contrast, FK419 or ozagrel had no effect
on PT or APTT at concentrations up to 100 µM.

Platelet Aggregation, Production of TXB2, and Coag-
ulation Time ex Vivo. FK419 dose-dependently and consist-
ently inhibited ADP-induced platelet aggregation at each
time point and at all doses tested (Table 1). Platelet aggrega-
tion was inhibited around 50% at 0.03 mg/kg + 0.1 mg/
kg/h. Almost complete inhibition was achieved at a dose of
0.12 mg/kg + 0.4 mg/kg/h. In another experiment, FK419 at
doses of 0.009 mg/kg + 0.03 mg/kg/h showed approximately
only 10% inhibition of ADP- and collagen-induced platelet
aggregation (data not shown). Ozagrel did not inhibit platelet
aggregation induced by ADP or collagen but did significantly
reduce TXB2 production at a dose of 30 mg/kg bolus + 100
mg/kg/h infusion for 1 h (Table 2). Argatroban significantly
prolonged APTT and PT (about 8-fold at 18 mg/kg + 60
mg/kg/h).

Antithrombotic Effect of FK419, Ozagrel, and Ar-
gatroban. MCA blood flow decreased to zero approximately
5 min after photoradiation in all groups (Fig. 2). We ob-
served spontaneous reperfusion after the primary occlusion
and subsequent periods of reperfusion and reocclusion
(CFRs; Fig. 2), regardless of the treatment group. After re-
peated CFRs, MCAs were completely reperfused. FK419
dose-dependently reduced the number of CFRs, with signifi-
cance at 0.03 mg/kg + 0.1 mg/kg/h (Fig. 3). FK419 also
significantly shortened total occlusion time and the time to
continuous reperfusion at the same dose. Although not sig-
nificant, FK419 treatment also decreased the time to first
reperfusion. Although ozagrel significantly shortened total
occlusion time at all doses tested, there were no significant
effects on number of CFRs, time to continuous reperfusion,
and time to first reperfusion (Fig. 4). Similarly, no improve-
ment in MCA patency was observed with argatroban treat-
ment (Fig. 5).

Effects of FK419, Ozagrel, and Argatroban on Isch-
emic Brain Damage. There were no significant changes in
physiological parameters measured at any time points in
FK419-treated animals (Table 3).

TTC staining of brain sections revealed that vehicle-

Discussion

The final step in platelet aggregate formation is mediated
by GPIIb/IIa. We have recently discovered FK419, a novel
nonpeptide GPIIb/IIIa antagonist, which is a broad inhibitor
of platelet aggregation, regardless of the agonist used to
induce aggregation, with weak activity in prolongation of
bleeding time in dogs (Mihara et al., unpublished observa-
tions). Furthermore, FK419 does not affect agonist-directed
intracellular calcium mobilization in platelets (Honda et al.,
unpublished observations), suggesting that it does not di-
rectly alter platelet activation but elicits antiaggregatory
effects via GPIIb/IIIa antagonism. The ability of FK419 to
inhibit converging platelet aggregation pathways is a major
advantage compared with other clinically available anti-

Fig. 3. Antithrombotic effect of FK419. A, number of CFRs; B, total
occlusion time; C, time to continuous reperfusion; and D, time to first
reperfusion were evaluated using MCA blood flow. FK419 was adminis-
tered 5 min after the end of photoradiation for 3 h. Each column
represents the mean ± S.E.M. of 10 to 11 animals. *, P < 0.05; **, P <
0.01 versus control (one-way ANOVA followed by Dunnett’s multiple
comparison test).
Each column represents the mean ± S.E.M. of 9 to 10 animals. *, P < 0.05 versus control (one-way ANOVA followed by Dunnett’s multiple comparison test).

<table>
<thead>
<tr>
<th>TABLE 3</th>
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<tbody>
<tr>
<td>Physiological variables before and after FK419 treatment in photochemically induced MCA occlusion model</td>
</tr>
</tbody>
</table>

FK419 was administered 5 min after the end of photoradiation. Values in parentheses represent bolus (mg/kg) and 3-h infusion (mg/kg/h) dosages. Values are expressed as the mean ± S.E.M. of five animals.

<table>
<thead>
<tr>
<th>Item</th>
<th>Timing</th>
<th>Control</th>
<th>FK419</th>
</tr>
</thead>
<tbody>
<tr>
<td>%Change in mean blood pressure</td>
<td>Before</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
</tr>
<tr>
<td></td>
<td>1 h</td>
<td>5.5 ± 4.7</td>
<td>6.4 ± 7.6</td>
</tr>
<tr>
<td></td>
<td>3 h</td>
<td>8.8 ± 5.0</td>
<td>−0.5 ± 2.2</td>
</tr>
<tr>
<td>pH</td>
<td>Before</td>
<td>7.317 ± 0.017</td>
<td>7.326 ± 0.015</td>
</tr>
<tr>
<td></td>
<td>1 h</td>
<td>7.380 ± 0.022</td>
<td>7.357 ± 0.008</td>
</tr>
<tr>
<td></td>
<td>3 h</td>
<td>7.391 ± 0.027</td>
<td>7.383 ± 0.006</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>Before</td>
<td>40.4 ± 0.7</td>
<td>41.1 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>1 h</td>
<td>37.4 ± 0.9</td>
<td>38.1 ± 0.8</td>
</tr>
<tr>
<td></td>
<td>3 h</td>
<td>34.8 ± 0.7</td>
<td>35.0 ± 0.4</td>
</tr>
<tr>
<td>Total hemoglobin (g/dl)</td>
<td>Before</td>
<td>13.1 ± 0.2</td>
<td>13.4 ± 0.3</td>
</tr>
<tr>
<td></td>
<td>1 h</td>
<td>12.2 ± 0.3</td>
<td>12.4 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>3 h</td>
<td>11.3 ± 0.3</td>
<td>11.3 ± 0.1</td>
</tr>
<tr>
<td>Blood glucose (mg/dl)</td>
<td>Before</td>
<td>183 ± 20</td>
<td>187 ± 21</td>
</tr>
<tr>
<td></td>
<td>1 h</td>
<td>144 ± 10</td>
<td>144 ± 7</td>
</tr>
<tr>
<td></td>
<td>3 h</td>
<td>151 ± 15</td>
<td>151 ± 7</td>
</tr>
<tr>
<td>Temporal muscle temperature (°C)</td>
<td>Before</td>
<td>36.2 ± 0.1</td>
<td>36.4 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>1 h</td>
<td>36.3 ± 0.1</td>
<td>36.5 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>3 h</td>
<td>36.7 ± 0.1</td>
<td>36.8 ± 0.1</td>
</tr>
</tbody>
</table>

Thrombotic compounds, such as aspirin and ozagrel, that only inhibit a single pathway and thus show limited efficacy.

We chose to use a photothrombotic occlusion model to determine the in vivo efficacy of FK419. This model provides a robust and reproducible platform in which the extent of brain damage reportedly correlates well with number of CFRs and total MCA occlusion time (Kawano et al., 1998, 1999). Consistent with these reports, we observed spontaneous reperfusion and continuous CFRs after MCA occlusion. CFRs are putatively caused by periodic acute occlusive platelet thrombi, and similar phenomena have been reported in various species (Nishiyama et al., 1994; Kaku et al., 1998; Kawano et al., 2000), including humans (Folts et al., 1982).

In the current studies, the parameters of MCA blood flow were somewhat variable in three experiments, especially the time to first reperfusion and number of CFRs. Individual analysis revealed that total occlusion time was relatively well correlated with brain damage. However, the correlation was not high enough to draw definitive conclusions for predicting brain damage. Therefore, other parameters might also contribute to the brain damage. Further studies are needed to clarify the relationship of MCA blood flow and the final outcome of brain infarction in this model. Despite these ca-
veats, as the total occlusion time and brain damage were relatively consistent in three experiments, it is reasonable to assume that comparison of the efficacies of three drugs is justified.

FK419 dose-dependently inhibited ADP-induced platelet aggregation ex vivo in guinea pigs, and we set three doses of almost no inhibition, about 50%, and 80% inhibition of platelet aggregation for evaluating its efficacy in stroke model. It was found that FK419 dose-dependently reduced the number of CFRs and improved MCA patency. Consistent with this improvement in MCA blood flow, FK419 decreased ischemic brain damage in a dose-dependent manner. These results indicate that FK419 might ameliorate the development of ischemic brain damage (not just delay the progression) by preventing secondary thrombus formation after occlusion, whereas the measurements of brain damage at later time points are needed for better understanding of the mode of action of FK419.

In addition to preventing CFRs, FK419 tended to decrease the time to first reperfusion, suggesting that FK419 might possess thrombolytic activity, in addition to its antiaggregatory activity, and that this thrombolytic effect against a primary thrombus, in part, contributed to its improvement on MCA patency. Thrombolytic activity of GPIIb/IIIa antagonists have been reported in coronal and femoral arteries (Mousa et al., 1994; Gold et al., 1997; Domanovits et al., 1998), the mechanism of which is supposed to be related to platelet disaggregation (Mousa et al., 1994) and inhibition of plasminogen activator inhibitor-1 secretion (Tsao et al., 1997). Although further studies are needed to clarify the thrombolytic effect of FK419, such activity may provide additional benefits in the treatment of acute ischemic stroke.

To elucidate the potential of FK419 as an agent for acute ischemic stroke, we compared the efficacy of FK419 with ozagrel, a clinically used TXA2 inhibitor, and argatroban, a thrombin inhibitor, in the same MCA thrombosis model. In contrast to FK419, ozagrel did not inhibit platelet aggregation ex vivo, consistent with previous results (Kawano et al., 1999). Lack of inhibition of platelet aggregation ex vivo with
ozagrel is explained by prostaglandin endoperoxide accumulation, which can directly stimulate TXA2 receptor on platelets (Mayeux et al., 1988) due to inhibition of TXA2 synthase. Accumulated prostaglandin endoperoxide, however, is rapidly converted to prostaglandin I2 (PGI2), a potent antiaggregatory and vasodilatory factor, by PGL2 synthase in the presence of blood vessels (Kuzuya et al., 1986). Thus, inhibition of TXA2 synthase by ozagrel might lead to suppressing platelet aggregation in vivo. TXB2 generation is almost completely suppressed at clinical doses of ozagrel (Uyama et al., 1985). In our hands, ozagrel significantly inhibited TXB2 production at 30 mg/kg + 100 mg/kg/h, which was insufficient to significantly inhibit TXB2 production ex vivo, suggesting that ozagrel might exert its antithrombotic effect in vivo stronger than ex vivo, since in an in vivo situation, inhibition of TXA2 synthase might lead to PGL2 generation as stated above. Consistent with the results of MCA blood flow, ozagrel did not significantly ameliorate ischemic brain damage.

Under similar experimental conditions, argatroban scarcely affected MCA blood flow and did not reduce infarct size, despite the fact that the same dose of argatroban prolonged coagulation parameters. In fact, although this compound is currently in clinical use, the effect of argatroban on cerebral infarction in humans is almost completely suppressed at clinical doses of ozagrel (Uyama et al., 1985; Kawano et al., 1999; Abumiya et al., 1998). In our hands, argatroban did not ameliorate brain damage (Hirata et al., 1993). The dose of argatroban examined in the present study was high enough to prolong the coagulation parameters; therefore, coagulation cascade may not play a central role in guinea pig arterial thrombosis induced by endothelial damage.

Although direct evidence of the presence of CFRs in human cerebral arteries has not been reported yet, CFRs may be present in the acute stage of stroke, since thrombosis after thrombolytic therapy has been observed in human cerebral arteries (von Kummer et al., 1995; Wallace et al., 1997). Therefore, inhibition of CFRs and improvement of brain circulation by GPIIIa antagonists are expected to prevent development of cerebral infarction in humans.

In conclusion, FK419 effectively improved MCA blood flow and ameliorated ischemic brain damage, whereas ozagrel and argatroban was minimally effective, suggesting that GPIIIa antagonists would be an attractive intervention for the treatment of acute ischemic stroke. We also found that FK419 was effective even if administered after the onset of ischemia, in contrast to previous work where pretreatment of GPIIIa antagonists ameliorated ischemic brain damage by improving brain circulation (Kaku et al., 1997, 1998; Choudhri et al., 1998; Kawano et al., 1999; Abumiya et al., 2000). Given that platelet-rich thrombi are a major factor in the failure of successful thrombolysis with recombinant tissue-plasminogen activator (Collen and Lijnen, 1991), FK419 may offer even better therapeutic benefits for recombinant tissue-plasminogen activator-resistant thrombi. Thus, although further studies are needed to define the therapeutic potential of FK419, we propose that FK419, a novel GPIIIa antagonist, shows promise as a therapy for acute ischemic stroke.

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References


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