The Effect of a New Calcium Antagonist, TA3090 (Clentiazem), on Experimental Transient Focal Cerebral Ischemia in Cats

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Background and Purpose: TA3090 (Clentiazem) has been shown to have cerebrovascular protective properties in three experimental studies. An in vivo investigation was undertaken to determine its effects on pial arteries and cerebral blood flow and its therapeutic value in transient focal cerebral ischemia.

Methods: This experiment was divided into two protocols. In the first, 200 or 400 µg/kg per hour TA3090 was administered continuously for 3 hours in cats without ischemic insult (n=6 for each group). The effects on pial arteries and cerebral blood flow were estimated. In the second protocol, 400 µg/kg per hour TA3090 (treated group, n=14) or physiological saline (control group, n=10) was administered 5 minutes before 1 hour of middle cerebral artery occlusion in cats. The effects on the pial arteries and cerebral blood flow were observed continuously, followed by autoradiography for a quantitative measurement of cerebral blood flow 5 hours after middle cerebral artery recirculation. The volumes of the cerebral edema and infarct were estimated by planimetry from cerebral preparations made for histological examination.

Results: Pial arteries dilated by up to approximately 10% in the 400-µg group and 3% in the 200-µg group 30 minutes after administration of TA3090. Increases in cerebral blood flow of about 10% in the 400-µg group and 2% in the 200-µg group were demonstrated with laser Doppler flowmetry. In the second protocol, dilatation of pial arteries was significantly smaller during and after the ischemic insult in the treated group compared with the control group (p<0.01). Cerebral blood flow decreased less significantly during ischemia (p<0.01 at the end of ischemia) and increased less significantly after ischemia (p<0.01 at the end) in the treated group compared with the control group. Autoradiography showed a more remarkable increase in cerebral blood flow due to luxury perfusion in the cerebral cortex, which was mainly perfused by the middle cerebral artery on the affected side in the control group (p<0.01). Cerebral blood flow in the cerebral cortex, thalamus, and caudate nucleus on the contralateral side of the treated group increased by about 20% more than that of the control group (p<0.05). Cerebral edema and infarction were much smaller in the treated group than in the control group (p<0.01).

Conclusions: 1) TA3090 dilates pial arteries and increases cerebral blood flow in normal brain regions in a dose–response fashion; 2) in ischemic regions compared with those in untreated animals, TA3090 results in a lesser reduction of cerebral blood flow during ischemia and in a lesser degree of hyperemia during reperfusion; 3) TA3090 is associated with less pial artery dilatation during ischemia, presumably due to improved collateral flow; and 4) the improved hemodynamic state with TA3090 is associated with significant reduction of cerebral edema and infarct size. (Stroke 1993;24:872–879)

Key Words • calcium antagonists • cerebral blood flow • cerebral ischemia • cats

A potent new calcium antagonist of the benzothiazepine type that is chemically related to diltiazem hydrochloride, TA3090, has been developed. In vitro studies have documented the calcium antagonistic properties of TA3090 as a selective inhibitor of the calcium-induced contraction of depolarized canine basilar, coronary, and mesenteric arteries;1,2;.

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See Editorial Comment, page 879

Studies have also demonstrated the drug's selectivity for rabbit cerebral arteries, which surpasses those of diltiazem and nifedipine. Furthermore, experimental studies have shown a beneficial effect of TA3090 on the reduction of infarct size in a rabbit model of middle cerebral artery (MCA) occlusion.

The effect of TA3090 on the cerebral pial arteries and its beneficial effect on cerebral damage in transient focal ischemia were studied because it may be possible to prolong the temporary clipping time during neurosurgery and obtain beneficial effects in the treatment of an extremely acute stage of cerebral infarction or a late angiospasm after subarachnoid hemorrhage.
Materials and Methods

Surgical Preparation

Experiments with TA3090 (Tanabe Seiyaku Co., Ltd., Osaka, Japan) were performed in adult cats of either sex (2.5–3.5 kg body weight) that were not subjected to fasting. In all animals, blood glucose was measured (Glucoster, Miles Inc.) soon after anesthesia was induced. Although the glucose levels were approximately 300 mg/dL, they were corrected to 100–120 mg/dL by the intravenous administration of regular insulin before the start of the experiment. Anesthesia was induced by intravenous administration of thiopental (30 mg/kg), and immobilization was obtained by administration of 60 μg/kg pancuronium bromide (Myoblock, Sankyo Inc., Tokyo). The cats were intubated and ventilated with a 3:1 mixture of N2O and O2 using a Harvard ventilator. Anesthesia was maintained with 0.5–1.0% halothane, and expired gas was monitored continuously with a gas monitor (model M1025A, Hewlett-Packard). Both femoral arteries and veins were cannulated with polyvinyl chloride (PVC) catheters for drug administration, continuous blood pressure recording (TP400T transducer and RM6200G electromanometer, Nihon Kohden, Tokyo), and frequent arterial blood gas sampling (ABL 330, Radiometer, Copenhagen). In many animals, metabolic acidosis was demonstrated, and blood pH was corrected at approximately 7.4 with intravenous infusion of sodium bicarbonate solution before the start of the experiment. The cranial temperature was maintained at 37°C with a sensor-controlled heating pad (model TK43, Asahi Denshi, Inc., Tokyo). PaO2 was maintained at approximately 100 mm Hg, PaCO2 at approximately 30 mm Hg, and blood pH at approximately 7.4; an electrocardiogram was also recorded continuously. Fluid balance of the cats was monitored by measuring the serum osmopressure (Finske Osmometer, Needham Heights, Mass.) and water intake and urine outflow.

The operative procedure was performed with the animal in the sphinx position, with the head fixed in a stereotactic holder (Narishige, Tokyo). After a longitudinal skin incision was made and the temporal muscle removed, a cranial window was made with a hand-driven trephine in the left parietal region over the ectosylvian gyrus. The dura was coagulated with a bipolar coagulator, and the window was covered with a sheet of glass and sealed with acrylic glue (Histoacryl, B. Brown, Inc., Melsungen, FRG). At the other side of the parietal region, a small trephination was made, and a small PVC catheter was inserted to record the intracranial pressure (ICP) continuously.

The left middle cerebral artery (MCA) was exposed through the transorbital approach after excentration of the orbit and enlargement of the optic foramen toward the superior orbital fissure with a dental drill. The dura mater was opened, and the arachnoid membrane was incised to expose the main trunk of the MCA for temporary clipping. A microsurgical clip (Zen clip, Ohwa, Inc., Tokyo) was used for the temporary clipping.

Assessment of Pial Arterial Diameter Changes

The diameters of the pial arteries were observed through the cranial window. A Nikon intravitral micro-scope and videotape recorder were used for the continuous observation and assessment of changes in caliber. The images of pial arteries in the cranial window were recorded on tape and analyzed later using a three-channel videoangiometer (model C316, Hamamatsu Photonics, Hamamatsu, Japan) and a multichannel recorder (WT645G, Nihon Kohden, Inc., Tokyo). To determine the preservation of the CO2 reactivity of the pial arteries, 2% bicarbonate gas was inspired for 2 minutes, followed by the confirmation of pial artery dilatation before the start of the experiment in each cat.

Measurement of Cerebral Blood Flow

A laser Doppler flowmeter (LDF) (model AIF21, Advance, Inc., Tokyo) was set on the window for continuous measurement of blood flow. At the end of the experiment in protocol 2, the regional cerebral blood flow (rCBF) was determined according to the method of Sakurada et al.5 A 250-μCi dose of [14C]iodoantipyrine dissolved in Ringer’s solution was administered intravenously for 1 minute by means of a ramp infusion (pump model 22, Harvard Apparatus South Natick, Mass.). At the end of the infusion, a tourniquet was placed around the cat’s neck and inflated during the intravenous injection of 10 mL of a saturated potassium solution to immediately stop the cerebral blood circulation. After removal of the skull bone and dura mater, the brain was lifted at its frontal part to dissect the brain stem and connecting nerves. The cerebellum was separated by incision, and the brain was carefully removed from the remaining skull, avoiding pressure on the cortex.

The brains were immersed in liquid isopentylhydrocupreine, chilled to −70°C, and stored in a freezer at −20°C until sectioning. Coronal sections 20 μm thick were cut on a cryostat (model OTF/AS, Bright, Inc.) at −20°C for autoradiography and dried immediately on a heating plate at 60°C to prevent diffusion of the lipophilic tram.

Tissue samples were taken from both occipital lobes to determine the [14C]iodoantipyrine concentration per gram of wet weight and were compared with the neighboring autoradiograms (autocalibration). These tissue probes were digested in hyamine hydrase (Protosol, New England Nuclear, Boston, Mass.) and suspended with scintillation fluid (Quick Scint No. 402). Thereafter, radioactivity was measured with a scintillation counter (model LS7500, Beckman). Autoradiography was performed by exposing the dried brain sections to Kodak NMB film for 2 weeks. The rCBF was measured by the autoradiographic method. Calculations were performed according to Sakurada et al,5 using a tissue–blood partition coefficient of 0.8 for [14C]iodoantipyrine. A microcomputer imaging device (Imaging Research, Ontario, Canada) was used for the densitometry and calculation.

Histopathologic Methods

Histological examination was performed to see the pathological changes in the brain at the time of autoradiography (6 hours after the start of the experiment). The 10-μm-thick cryostat coronal sections obtained between sections for autoradiography were used for morphological studies to estimate the localization of blood flow and to histologically examine the ischemic
area. The coronal sections were fixed in an ascending alcohol chain and stained with hematoxylin and eosin and Luxol fast blue. In this experiment, areas with cerebral edema were judged to correspond to the areas of the decreased intensity of stain and estimated by densitometry with a microcomputer imaging device. Areas with pyknotic cells were considered to be areas of cerebral infarction and were delineated meticulously on the section by an examiner unaware of the animal’s history. Three sections (cut at the temporal tips, optic chiasm, and mamillary bodies) were picked up, and their pathological areas and hemispheric spaces were examined. The coronal section at the optic chiasm was usually through the center of the window. The volumes of the cerebral edema and infarct were expressed as the ratio of the sum total of the pathological areas to the sum total of hemispheres in the three slices of the brain.

**Statistical Analysis**

Values of a given parameter in the various experimental groups were compared with the other groups using the Mann-Whitney U test. Calculations were performed on an Apple Macintosh computer using the STAT VIEW II program.

**Experimental Protocols**

Protocol 1: Effects of intravenous TA3090 on pial arteries and cerebral blood flow changes. Twelve adult cats were used for this experimental protocol. A dose of 200 or 400 µg/kg per hour TA3090 was administered for 3 hours (n=6 cats for each dose group). Caliber changes in the pial arteries, rCBF (measured by LDF), ICP, mean arterial blood pressure (MAP), and heart rate were recorded continuously.

Protocol 2: Effects of intravenous TA3090 on 1-hour focal cerebral ischemia. Thirty-six adult cats were used in this experimental protocol. In 20 cats, the continuous intravenous administration of 400 µg/kg per hour TA3090 was started 5 minutes before MCA occlusion and continued to the end of the experiment. As a control, 16 cats that underwent same surgical procedures were used; continuous intravenous infusion of the same volume of physiological saline was performed in the same manner as with the TA3090 group. Occlusion time of the MCA was 1 hour, and survival time after recirculation of the MCA was 5 hours.

Upon occlusion of the MCA, cessation of pial artery pulsation and a marked slowing of pial venous blood flow were confirmed through the window. A marked drop in blood flow in the LDF was observed whenever adequate ischemia occurred in the area of the MCA. If these findings were not observed even after recapping, the animal was excluded from the study because of inadequate ischemia.

A total of 14 cats in the TA3090 group and 10 cats in the control group could be evaluated effectively.

**Results**

There were no significant changes in arterial PaCO₂, PaO₂, hematocrit, serum potassium, serum sodium, or pH in any of the groups during experimental periods.

**Protocol 1**

The ICP increased 10% after 45 minutes compared with the resting value and remained at the 7.5% level 90 minutes after the administration of 400 µg/kg per hour TA3090 (p<0.01). The MAP in the group given this dosage decreased significantly at the first stage, 30 minutes after the administration was started (p<0.05), but improved to an insignificant level 60 minutes later (Figure 1).

The pial arteries dilated gradually after the start of TA3090 administration and reached maximum value 40 minutes later; the diameter eventually decreased slightly, but the arteries remained in a dilated state (8±3% in the 400 µg/kg per hour group, p<0.01; 3±2.5% in the 200 µg/kg per hour group) (Figure 2).

The CBF measured by LDF through the cranial window increased to 10% and remained in such a state until the end of the experiment, although the CBF increased to 12% transiently 2 hours after the administration of 400 µg/kg per hour TA3090. This increase in CBF was significantly higher than that in the 200-µg-dose group (Figure 3).

**Protocol 2**

Changes in intracranial pressure and mean arterial blood pressure. Although MABP was significantly lower

![Figure 1. Graph showing changes in intracranial pressure (ICP) and mean arterial pressure (MAP), measured continuously. ICP increased about 10% more (*) and MAP decreased to about -10% lower than resting value (●) 30 minutes after the start of 400 µg/kg per hour i.v. TA3090. In the 200-µg group, the ICP increase was about 5% in the first stage but only 1% later.](image)

![Figure 2. Graph showing changes in pial arterial diameter. Arteries dilated by 10% 30 minutes after administration of 400 µg/kg per hour TA3090 (●). In the 200-µg group, dilatation was about 5% (●). Ninety minutes later, the values were 8% and 2%, respectively, and remained there until the end of the experiment.](image)
Regional cerebral blood flow measured by autoradiography. There were remarkable differences in rCBF between the control group and the TA3090 group 5 hours after reperfusion of the MCA (Table 2). In the control group, the rCBF in the suprasylvian gyrus, ectosylvian gyrus, sylvian gyrus, and head of the caudate nucleus of the affected side increased markedly and reached a level three times greater than that in the contralateral side in six animals in the control group. The differences in the rCBF in the corpus callosum, internal capsule, thalamus, and hippocampus between the affected and unaffected sides were not statistically significant. On the other hand, although the rCBF in the ectosylvian gyrus and the head of the caudate nucleus in the TA3090 group increased more significantly (p<0.01) in the affected side than in the contralateral side, the increase in rCBF was not as remarkable compared with that in the control group. Furthermore, as in the control group, the rCBF in the other areas was almost the same as that in the contralateral side. The continuous administration of TA3090 resulted in an approximately 20% increase in rCBF over that of the control group in the cerebral cortex, caudate nucleus, and thalamus of the nonaffected side (Figure 6).

**Histopathologic findings.** The extent of cerebral edema and infarction was determined from histological findings. In the control group, cerebral edema was approximately 47.4±7.8% (mean±SE) of the hemisphere, and cerebral infarct was 41.9±5.9%. In the TA3090 group, cerebral edema was 25.5±4.3% and cerebral infarct 18.4±3.1%. The extent of both cerebral edema and infarction was significantly larger in the control group than in the TA3090 group (p<0.01) (Figure 7).

**Discussion**

**Calcium Antagonistic Activities of TA3090**

The recently synthesized 1,5-benzoazepine derivative TA3090 has potent and long-lasting antihypertensive and vasodilatory actions. Although diltiazem (another 1,5-benzoazepine derivative) is an effective calcium antagonist, the calcium antagonistic activity of TA3090 is more potent and exhibits a higher degree of cerebrovascular selectivity against agonist- and potassium-induced contractions than that of diltiazem. Moreover, the concentration of TA3090 required to affect the cerebral vasculature is much lower than that required to depress the action of the heart, and the concentration is achieved at doses that do not significantly lower arterial blood pressure in rabbits. In this experiment with cats, the action of TA3090 on the heart...
and arterial blood pressure was much weaker than that for cerebral arterial diameter changes.

**Microvascular Observations**

In protocol 1, the pial arteries dilated more significantly \((p < 0.01)\) in animals that received 400 \(\mu\)g/kg per hour TA3090 than in those receiving 200 \(\mu\)g/kg per hour. This result suggests that TA3090 gives rise to a dose-dependent dilatation of the pial arteries like that of nimodipine. In this experiment, pial arterial dilatation in the treated group appeared to correlate with decrease of MABP and increase of ICP secondary to TA3090 infusion. However, the degree of the pial dilatation was out of proportion to the MABP decrease, and the rCBF also increased despite the blood pressure change. These results indicate that TA3090 dilates the pial arteries and increases the rCBF not as a simple result of autoregulatory reaction but with its pharmacologically positive action.

Pial arteries dilated remarkably during 1-hour MCA occlusion because of an autoregulatory reaction and returned to a state of 30–40% dilatation after MCA recirculation. Vasodilation of the pial arteries in cats receiving continuous intravenous administration of TA3090 was not as prominent as that in control cats during and after MCA occlusion, probably because of collateral circulation from arteries that were not occluded due to the action of TA3090. Although vasocon-

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**Table 2. Regional Cerebral Blood Flow (ml/100g/min) 5 Hours After Middle Cerebral Artery Reperfusion in Cats**

<table>
<thead>
<tr>
<th>Structure</th>
<th>Control group</th>
<th>TA3090 group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipsilateral</td>
<td>Contralateral</td>
</tr>
<tr>
<td>Cortex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marginal gyrus</td>
<td>60.4±5.8</td>
<td>62.3±5.8</td>
</tr>
<tr>
<td>Suprasylvian gyrus</td>
<td>226.6±19.5</td>
<td>74.6±6.1</td>
</tr>
<tr>
<td>Ectosylvian gyrus</td>
<td>232.2±20.4</td>
<td>75.6±5.4</td>
</tr>
<tr>
<td>Sylvian gyrus</td>
<td>183.4±14.4</td>
<td>78.2±5.3</td>
</tr>
<tr>
<td>White matter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corpus callosum</td>
<td>26.6±2.6</td>
<td>25.3±2.6</td>
</tr>
<tr>
<td>Internal capsule</td>
<td>25.8±2.8</td>
<td>26.3±2.6</td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medial</td>
<td>66.6±4.0</td>
<td>68.3±4.6</td>
</tr>
<tr>
<td>Lateral</td>
<td>72.0±8.0</td>
<td>69.8±4.9</td>
</tr>
<tr>
<td>Caudate nucleus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>226.9±26.3</td>
<td>78.4±7.4</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>51.5±2.2</td>
<td>50.7±4.2</td>
</tr>
</tbody>
</table>

Values are mean±SD in milliliters per 100 grams per minute. *\(p<0.05\), †\(p<0.01\).

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**Figure 4.** Graph showing pial arterial diameter changes. Arteries dilated by 65% soon after middle cerebral artery (MCA) occlusion and returned to 30% 2 hours later; they redilated by 50% at the end of experiment in the control group (△). In the TA3090 group (○), they dilated by 30% during MCA occlusion and remained at a state of 25% dilatation after MCA recirculation.

**Figure 5.** Graph showing changes in cerebral blood flow (CBF) before, during, and after middle cerebral artery (MCA) occlusion (measured by laser Doppler flowmetry). In the control group (△), CBF decreased to −90% at the time of occlusion and then returned to −80%. Soon after MCA recirculation and at the end of the experiment, a 40% hyperperfused state was recorded. In the TA3090-treated group (○), CBF dropped to −90% at the time of MCA occlusion and then recovered gradually to −60% at the end of occlusion. After MCA recirculation, CBF increased to a 20% hyperperfused state and then remained at a 10% increased state.
striction of pial arteries around severely ischemic areas
during MCA occlusion has been previously described,14-17 pial arteries in this experiment dilated in both the control and the treated groups. Pial arterial dilatation in animals treated with TA3090 was not as prominent as that in the control group during and after MCA occlusion. This action on the pial arteries was much different from findings with nimodipine,18 in which the pial arteries remained remarkably dilated even after MCA recirculation. This indicates that nimodipine may reduce the threshold of blood-brain barrier breakthrough more prominently than has been previously reported.19

Regional Cerebral Blood Flow

Cortical blood flow was measured continuously with LDF in the present study. Although many laboratories use LDF to assess blood flow within the central nervous system, this method has not always been valid for the measurement of central nervous system blood flow.20-23 However, LDF enables accurate measurement of changes in rCBF due to induction of focal cerebral ischemia.24 In the present study, there was a large discrepancy between the rCBF measured quantitatively by autoradiography and that estimated from changes in blood flow measured continuously by LDF. This discrepancy could have resulted from the decreased estimation of cortical surface blood flow because LDF was performed through a cover glass over the cranial window.

In the autoradiographic study, the rCBF in the cortex and basal ganglia of the hemisphere contralateral to that with MCA occlusion increased more significantly in the treated group than in the control group. On the other hand, the rCBF in the affected area of the hemisphere with MCA occlusion increased remarkably 5 hours after recirculation of the MCA in the control group because of postischemic hyperperfusion25-27; this phenomenon confirms Lassen’s concept of “luxury perfusion.”28 In the cats treated with TA3090, postischemic hyperperfusion was not so prominent as in the control group. Moreover, the fact that rCBF during recirculation was lower in the TA3090-treated group than in the control group may be secondary to the decreased blood pressure in the former group, although this difference reached statistical significance only at 2 hours after recirculation.

These LDF and autoradiographic findings indicate that TA3090 augments the rCBF with its vasodilatory effect in the contralateral hemisphere and also increases rCBF during MCA occlusion in the ischemic hemisphere, as shown in another potent Ca2+ channel blocker, nimodipine.17,29,30

Histopathologic Findings

Although transorbital occlusion is a well-established technique generally considered to be one of the least

![Figure 6](http://stroke.ahajournals.org/)

**Figure 6.** Autoradiography showed a remarkable increase in the regional cerebral blood flow (CBF) of the middle cerebral artery areas of the cerebral cortex and caudate nucleus in the control group (top panel). In the TA3090-treated group the increase in CBF was slight, although CBF values of the contralateral cerebral cortex, caudate nucleus, and thalamus increased 20% more compared with those of the control group (bottom panel).

![Figure 7](http://stroke.ahajournals.org/)

**Figure 7.** Bar graph showing areas of cerebral edema and infarction (as mean±SE % of hemisphere). Cerebral edema and infarction were 47.4±7.8% and 41.9±5.9%, respectively, in the control group, and 25.5±4.3% and 18.4±3.4%, respectively, in the TA3090-treated group. The extent of cerebral edema and infarction was significantly smaller in the control group (*p<0.01*).
traumatic methods for the production of focal ischemia in cats, there is great variability in the density of ischemia, depending on the actual location of the vessel clip and the individual efficacy of collateral vascularization. To obtain consistently meaningful results, it is therefore necessary to precisely confirm remarkable blood flow disturbances in the ischemic brain. In the present study, cessation of pial arterial pulsation and a marked slowing of pial venous blood flow were confirmed through the window; when the MCA was clamped, the prominent decrease of blood flow was checked by LDF.

In this study the pathological area was estimated 5 hours after the ischemic insult. The earliest ischemic cytological alterations involving neurons, neuromasts, and astrocytes can be demonstrated convincingly 2½ hours after arterial occlusion in paraffin-embedded sections stained with hematoxylin and eosin. Although it is difficult to estimate the area of cerebral edema and infarction precisely at an early stage (such as 5 hours after cerebral ischemic insult), these areas can be calculated objectively from cerebral preparations with a microcomputer imaging analyzer, which can distinguish ischemic areas from normal areas by measuring contrast differences in objects.

TA3090 pre-treatment significantly decreased pathological areas evoked by 1-hour MCA occlusion in our study. The reduction in pathology in these areas can probably be attributed to the ability of TA3090 to antagonize the vasoconstriction that must occur in the ischemic area and adjacent vascular systems. Pretreatment with TA3090 was reported to reduce infarct size significantly in rabbits with permanent MCA occlusion. Although the brain might be compromised to a greater degree by reperfusion injury in transient ischemia, pre-treatment with TA3090 decreased the size of pathological areas by enhancing the level of blood flow during the ischemic interval. The possibility that TA3090 has a direct effect on neuronal metabolism is controversial, and whether the drug has an additional cellular protective function has yet to be investigated.

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