Effect of Selective Inhibitor of Thromboxane A2 Synthetase on Experimental Cerebral Vasospasm

TOYOKAZU FUKUMORI, M.D., EIICHI TANI, M.D., YUKIO MAEDA, M.D., AND ATSUHIKO SUKENAGA, M.D.

SUMMARY Experimental cerebral vasospasm was induced in the canine basilar artery by an intracisternal injection of fresh autogenous arterial blood. Delayed vasospasm was defined as a reduction to less than 75% of the caliber of control basilar artery 5 days after the intracisternal blood injection. A selective inhibitor of thromboxane A2 synthetase, sodium(E)-3-[4-(3-pyridylmethyl)phenyl]-2-methyl-2-propenoate, was infused intravenously for 1 or 2 hrs at 50 μg/kg/min in normal animals and in animals exhibiting vasospasm. Angiographic evidence of cerebral vasospasm was not reversed. Mean regional cerebral blood flow was not significantly increased in normal and spastic animals, but a mean difference of regional cerebral blood flow was significantly increased only in vasospastic animals. Mean arterial blood pressure and pulse rate were not seriously changed in normal and spastic animals. Another selective thromboxane A2 synthetase inhibitor, (E)-3-[4-(1-imidazolylmethyl)phenyl]-2-propenoic acid hydrochloride monohydrate, showed a similar effect on the caliber of the basilar artery, regional cerebral blood flow, blood pressure, and pulse rate, in vasospastic animals. Venous blood was taken from the internal jugular vein, and the mean platelet aggregation rate induced by 10 μg/ml of collagen was inhibited by the infusion of either selective inhibitor at 50 μg/kg/min for 2 hrs. However, mean platelet aggregation rates in vasospastic animals before and after treatment with either selective inhibitor were not significantly different to those in normal animals.

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WHEN ARTERIAL RUPTURE occurs, prostacyclin (PGI2) synthesis may be reduced at the site of rupture, and platelets, which generate thromboxane A2 (TXA2), adhere to the site of damage. PG12 formation in the canine basilar artery is significantly decreased in delayed cerebral vasospasm, and a continuous intravenous infusion of sodium(E)-3-[4-(3-pyridylmethyl)phenyl]-2-methyl-2-propenoate (OKY-1581) at the rate of 4 gm/50 ml/24 hrs until sacrifice 4 days after induction of subarachnoid hemorrhage (SAH) abolishes almost completely the occurrence of delayed cerebral vasospasm. PG12 functions as a potent relaxing action on cerebral arteries, and the contractile effect of TXA2 appears to be more pronounced on cerebral blood vessels compared to peripheral arteries. Consequently, it may be postulated that delayed cerebral vasospasm could arise from a disproportionate synthesis of TXA2. The present study uses pyridine and imidazole derivatives of a selective inhibitor of TXA2 synthetase; OKY-1581 and (E)-3-[4-(1-imidazolylmethyl)phenyl]-2-propenoic acid hydrochloride monohydrate (OKY-046), and examines their effects on delayed cerebral vasospasm and regional cerebral blood flow.

Materials and Methods

Production of Delayed Cerebral Vasospasm

Experimental cerebral vasospasm was produced by a transorbital administration of 8 to 12 ml of fresh autogenous arterial blood into the chiasmatic cistern of mongrel dogs, weighing from 10 to 17 kg, before intravenous infusion of OKY-1581 or OKY-046, as reported previously. Transfemoral vertebral angiography was carried out before and 5 days after the intracisternal blood injection and also at the end of intravenous infusion of OKY-1581 or OKY-046 for 2 hrs. The diameter of the basilar artery was measured on magnifying angiogram to examine occurrence of vasospasm and effect of OKY-1581 or OKY-046 infusion, and its true diameter was calculated from magnification rate. Delayed cerebral vasospasm was defined as a reduction to less than 75% of the caliber of the control basilar artery 5 days after the intracisternal blood injection, and its occurrence was 72.6% in the present model.

Measurement of Regional Cerebral Blood Flow

Mongrel dogs were sedated with intramuscular ketamine hydrochloride (10 mg/kg), and anesthesia was then induced with an intravenous pentobarbital sodium (15 mg/kg) and maintained with a nitrous oxide-oxygen mixture (70%-30%) delivered by an Acoma AR-300 intermittent positive pressure ventilator (Acoma Industrial Co., Inc., Tokyo, Japan) in open circuit. Muscular relaxation was provided with an intravenous half-hourly administration of pancuronium bromide (0.08 mg/kg). Body temperature was kept close to 37°C with a heating blanket, and arterial blood pressure was continuously monitored with a Statham P-23-Db strain gauge transducer (Statham Laboratories, Inc., Hato Rey, Puerto Rico) connected to a cannula in the femoral artery. Arterial CO2 tension (PaCO2) was monitored by a Corning pH/blood gas 165 (Corning Glass Works, Corning, NY, U. S. A.) and kept at the desired levels throughout the experiments by adjusting the respiratory pump or by adding CO2 to the inspired gas.

The animal was fitted into a stereotaxic frame, and one or two occipital drill holes were made in the skull. One or two UHF-100 platinum electrodes (Unique
Medical Co., Ltd., Tokyo, Japan), 0.3 mm in diameter, were inserted through the drill holes into the lumen of the occipital lobe, 2.5 mm in length, and then the drill holes were filled with 2% Bacto-Agar (Difco Laboratories Inc., Detroit, Michigan, U. S. A.). The electrodes were connected to a PHG-201 UHMeter (Unique Medical Co., Ltd.) and measured regional cerebral blood flow (rCBF) by the hydrogen clearance technique. To permit full polarization and stabilization of the electrodes, the first measurement of rCBF was not made until a period of 45 min had elapsed from the initial electrode placement. Mean arterial blood pressure (MABP), pulse rate (PR), arterial blood gases and pH were examined during each measurement of rCBF.

After a resting rCBF was measured in normal or spastic animal, OKY-1581 or OKY-046 was dissolved in a cold saline and infused intravenously at 20 or 50 
\[ \text{\( \mu \text{g/kg/min} \) for 1 and 2 hrs with a Harvard apparatus infusion/withdrawal pump model 932 (Harvard Apparatus Co., Inc., Millis, MA, U. S. A.). During the infusion, the infusion syringe was cooled by an ice bath. A cold saline infused at the same rate for 2 hrs had no effect on rCBF, MABP, and PR. OKY-1581 and OKY-046 were kindly supplied by Ono Pharmaceutical Co., Ltd., Osaka, Japan.}

Platelet Aggregation Studies

Venous blood was taken from the internal jugular vein of 10 normal and 10 spastic animals before and after OKY-1581 or OKY-046 infusions at 50 
\[ \text{\( \mu \text{g/kg/min} \) for 1 or 2 hrs in normal animals. The caliber of basilar artery is measured at 50 
\[ \text{\( \mu \text{g/kg/min} \) for 1 or 2 hrs in 5 normal and 5 spastic animals, and 10 
\[ \text{\( \mu \text{g/kg/min} \) for 1 or 2 hrs in 5 normal and 5 spastic animals. The values of caliper of the basilar artery and rCBF in spastic animals are compared with those in normal animals.}

Statistical Analysis

The mean values of caliber of basilar artery and rCBF before and after OKY-1581 or OKY-046 infusions were analyzed by two-tailed t-test for uncorrelated pairs, but since rCBF, MABP, and PR were variable from animal to animal, their responsiveness to OKY-1581 or OKY-046 infusion is probably best expressed by their mean difference. The mean differences of caliber of basilar artery (\( \Delta \text{C} \)), rCBF (\( \Delta \text{rCBF} \)), MABP (\( \Delta \text{MABP} \)), and PR (\( \Delta \text{PR} \)) at the end of OKY-1581 or OKY-046 infusion were analyzed by two-tailed t-test for correlated pairs.

Results

Effect of OKY-1581 or OKY-046 on Caliber of Basilar Artery

The mean value of calibers of 5 normal basilar arteries was not significantly changed by OKY-1581 infusion at 50 
\[ \text{\( \mu \text{g/kg/min} \) for 2 hrs (table 1). Figure 1 demonstrated \( \Delta \text{C} \) in each of normal animals treated with OKY-1581, and its mean value was not significant (table 2). Fifteen animals which showed less than 75% of the caliper of control basilar artery 5 days after the intracisternal blood injection, were used as spastic animals. The mean value of calibrers of 5 spastic basilar arteries at the end of OKY-1581 infusion at 20 or 50 
\[ \text{\( \mu \text{g/kg/min} \) for 2 hrs was not significantly changed (table 1). Figure 1 showed \( \Delta \text{C} \) in each of spastic arteries treated with OKY-1581 or OKY-046, and their mean values also were not significant (table 2). Thus, the angiographic cerebral vasospasm was not significantly reversed by OKY-1581 or OKY-046 infusion for 2 hrs.

Effect of OKY-1581 or OKY-046 on Cerebral Hemodynamics

The mean values of rCBF, MABP, and PR in 5 normal animals at 30.4 ± 2.5 torr of PaCO\(_2\) were 48.9 ± 4.8 ml/100 gr/min, 117 ± 8 mm Hg, and 120 ± 12 beats/min, respectively. The mean rCBF during OKY-1581 infusion at 50 
\[ \text{\( \mu \text{g/kg/min} \) in normal animals was increased with the lapse of time, but the mean rCBF at the end of OKY-1581 infusion for 1 or 2 hrs was not significantly increased (table 1). Figure 1 showed \( \Delta \text{rCBF} \), \( \Delta \text{MABP} \), and \( \Delta \text{PR} \) in each of normal animals

### Table 1: Mean Values of Caliber of Basilar Artery (BA) and rCBF in Normal and Spastic Animals before and after OKY-1581 or OKY-046 Infusion

<table>
<thead>
<tr>
<th>Animal</th>
<th>OKY-1581 Infusion</th>
<th>Caliber of BA (mm)</th>
<th>rCBF (ml/100 gr/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>5</td>
<td>0.8 ± 0.2</td>
<td>41.8 ± 9.7</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.8 ± 0.2*</td>
<td>35.3 ± 9.2*</td>
</tr>
<tr>
<td>Spasm</td>
<td>5</td>
<td>0.8 ± 0.2</td>
<td>41.8 ± 9.7</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>0.8 ± 0.2*</td>
<td>35.3 ± 9.2*</td>
</tr>
<tr>
<td></td>
<td>2 hrs</td>
<td>0.8 ± 0.2</td>
<td>41.8 ± 9.7</td>
</tr>
<tr>
<td></td>
<td>2 hrs</td>
<td>0.8 ± 0.2*</td>
<td>35.3 ± 9.2*</td>
</tr>
</tbody>
</table>
treated with OKY-1581, and their mean values were not significant (table 2).

The mean values of rCBF at 30.4 ± 2.3 torr of PaCO₂ in each 5 spastic animals were 27.5 ± 9.1 ml/100 gr/min before OKY-1581 infusion at 20 μg/kg/min, 35.3 ± 9.2 ml/100 gr/min before OKY-1581 infusion at 50 μg/kg/min, and 27.6 ± 8.0 ml/100 gr/min before OKY-046 infusion at 50 μg/kg/min, and significantly decreased as compared to that in 5 normal animals (table 1). The mean rCBF during OKY-1581 infusion at 20 or 50 μg/kg/min or OKY-046 infusion at 50 μg/kg/min in spastic animals was increased with the lapse of time, except for the mean rCBF at the end of OKY-1581 infusion at 20 μg/kg/min for 1 hr, but the mean rCBF at the end of OKY-1581 infusion at 20 or 50 μg/kg/min or OKY-046 infusion at 50 μg/kg/min for 1 or 2 hrs was not significantly changed as compared to those before OKY-1581 or OKY-046 infusion (table 1). Figure 1 exhibited ΔrCBF, ΔMABP, and ΔPR in each of spastic animals treated with OKY-1581 or OKY-046. The mean values of ΔrCBF in spastic animals were not significant at the end of OKY-1581 infusion at 20 μg/kg/min for 1 or 2 hrs, but significantly increased by OKY-1581 or OKY-046 infusion at 50 μg/kg/min for 1 or 2 hrs, as shown in table 2. The mean values of ΔMABP and ΔPR in spastic animals treated with OKY-1581 or OKY-046 were not significant, except for significant decrease of mean ΔMABP at the end of OKY-1581 infusion at 50 μg/kg/min for 2 hrs and significant increase of mean ΔPR at the end of OKY-1581 infusion at 50 μg/kg/min for 1 hr (table 2), both of which, however, were not seriously changed.

### Table 2

Mean Values of ΔC, ΔrCBF, ΔMABP, and ΔPR at the End of OKY-1581 or OKY-046 Infusion in Normal and Spastic Animals

<table>
<thead>
<tr>
<th>Animal</th>
<th>n</th>
<th>OKY-1581 (μg/kg/min)</th>
<th>ΔC (mm)</th>
<th>ΔrCBF (ml/100 gr/min)</th>
<th>ΔMABP (mm Hg)</th>
<th>ΔPR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>5</td>
<td>50 1 hr</td>
<td>1.2±0.5ns</td>
<td>-1.3±2.3ns</td>
<td>0.8±3.8ns</td>
<td>-2.6±3.4ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 hrs</td>
<td>0±0ns</td>
<td>4.1±3.9ns</td>
<td>-0.6±4.1ns</td>
<td>2.4±6.4ns</td>
</tr>
<tr>
<td>Spasm</td>
<td>5</td>
<td>20 1 hr</td>
<td>-0.2±2.5ns</td>
<td>2.8±5.2ns</td>
<td>0.6±5.8ns</td>
<td>-1.0±7.5ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 hrs</td>
<td>0±0ns</td>
<td>3.4±2.7ns</td>
<td>-0.8±2.6ns</td>
<td>1.0±7.5ns</td>
</tr>
<tr>
<td>Spasm</td>
<td>5</td>
<td>50 1 hr</td>
<td>3.3±2.3*</td>
<td>-2.4±2.4*</td>
<td>3.6±2.5*</td>
<td>3.0±3.0ns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 hrs</td>
<td>0.1±0.1ns</td>
<td>6.5±2.0*</td>
<td>-3.0±1.9*</td>
<td>3.0±3.0ns</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Animal</th>
<th>n</th>
<th>OKY-046 (μg/kg/min)</th>
<th>ΔC (mm)</th>
<th>ΔrCBF (ml/100 gr/min)</th>
<th>ΔMABP (mm Hg)</th>
<th>ΔPR (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasm</td>
<td>5</td>
<td>50 1 hr</td>
<td>3.5±1.9f</td>
<td>-2.7±3.4f</td>
<td>-2.6±8.5f</td>
<td>-1.6±5.6f</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 hrs</td>
<td>0±0ns</td>
<td>4.5±2.6f</td>
<td>-2.7±3.1f</td>
<td>-1.6±5.6f</td>
</tr>
</tbody>
</table>

Statistical analysis is examined by two-tailed t-test for correlated pairs.
NS: not significant, * = p < 0.05, † = p < 0.025, ‡ = p < 0.005
and 63.0 ± 28.0 and 61.9 ± 42.4% in normal and spastic animals treated with OKY-046, respectively (table 3). Representative tracings of platelet aggregation induced by 10 µg/ml of collagen in spastic animal before and at the end of OKY-1581 or OKY-046 infusion at 50 µg/kg/min for 2 hrs are shown in figure 2.

Discussion

OKY-1581 and OKY-046 are selective inhibitors of TXA₂ synthetase.\textsuperscript{10-16} The concentrations of OKY-1581 and OKY-046 to induce 50% inhibition (ID\textsubscript{50}) for TXA₂ synthesis in rabbit platelets are 3 × 10^{-9} and 1.1 × 10^{-8} M, respectively.\textsuperscript{10,16} In addition, the molecular weights and the half lives are 275 and 10 min in OKY-1581 and 282.73 and 1.1 hrs in OKY-046, respectively.\textsuperscript{10,16} Consequently, the concentrations of OKY-1581 and OKY-046 at the end of infusion at 50 µg/kg/min for 2 hrs may theoretically be 3.3 × 10^{-3} and 1.4 × 10^{-4} M, respectively, which may be enough to inhibit TXA₂ synthesis nearly completely.\textsuperscript{16} An intravenous infusion of OKY-1581 at 10 to 1000 µg/kg/min for 1 hr in anesthetized baboons decreases thromboxane B₂ (TXB₂: the breakdown product of TXA₂) plasma level and increases 6-keto prostaglandin F\textsubscript{1α} (6-keto PGF\textsubscript{1α}, the breakdown product of PGI\textsubscript{2}) level in most animals.\textsuperscript{17} An oral administration of OKY-1581 in humans and monkeys shows a dose-dependent inhibition of serum TXB₂.\textsuperscript{14,15} Nevertheless, the intravenous OKY-1581 at 50 µg/kg/min for 2 hrs did not change significantly the caliber of normal canine basilar artery, and in addition, the intravenous infusion of OKY-1581 or OKY-046 at 50 µg/kg/min for 2 hrs failed to reverse the angiographic vasospasm in dogs.

Serum concentrations of TXB₂, prostaglandin E\textsubscript{2}, and prostaglandin F are reportedly changed from 126 ± 66, 3 ± 4, 10 ± 8 ng/ml to 5 ± 1, 70 ± 18, 63 ± 2 nm/g at 2 hrs after a subcutaneous administration of 100 mg of OKY-1581 in rabbit, respectively.\textsuperscript{11} Wong and Cheung\textsuperscript{18} show that 3 thromboxane synthetase inhibitors: 1-octyl-imidazole, 9,11-iminoepoxyprosta-5,13-dienoic acid, and 9,11-azo prosta-5,13-dienoic acid, decrease TXB₂ formation with a concurrent increase in prostaglandin F\textsubscript{2α} (PGF\textsubscript{2α}), prostaglandin E\textsubscript{2} (PGE\textsubscript{2}), and prostaglandin D\textsubscript{2} (PGD\textsubscript{2}), with PGE\textsubscript{2} being the major product, in human platelets.

![Figure 2. Representative tracings of platelet aggregation of spastic animal induced by 10 µg/ml of collagen before and after OKY-1581 or OKY-046 infusion at 50 µg/kg/min for 2 hrs.](image-url)
changes may occur after OKY-046 infusion. Since experimental cerebral vasoconstriction is produced by PGF$_2\alpha$,\textsuperscript{19-21} and PGE$_2$,\textsuperscript{19, 21} the non-significant change of the caliber of normal basilar artery at the end of OKY-1581 infusion at 50 µg/kg/min for 2 hrs might be due to an increased formation of PGF$_2\alpha$ and PGE$_2$ in platelet, and the failure to reverse the angiographic vasospasm with OKY-1581 or OKY-046 infusion might be due to an increased formation of PGF$_2\alpha$ and PGE$_2$ in platelet and increased PGE$_2$ formation in spastic artery.\textsuperscript{2} However, an intracarotid infusion of PGF$_2\alpha$ or PGE$_2$ is reported to reduce CBF.\textsuperscript{22, 23}

The reduced rCBF in spastic animals is similar to that in clinical cases, in which CBF falls after recent SAH, particularly in patients with severe vasospasm.\textsuperscript{24-30} The reduced CBF in SAH could be also due to cerebral edema, intracranial hematoma, increased intracranial pressure, and hydrocephalus, in addition to vasospasm. The mean rCBF in normal and spastic animals was not significantly changed by OKY-1581 or OKY-046 infusion, but the mean ΔrCBF in spastic animals was significantly increased by OKY-1581 infusion at 50 µg/kg/min for 1 (p < 0.05) or 2 hrs (p < 0.005) or by OKY-046 infusion at 50 µg/kg/min for 1 or 2 hrs (p < 0.025), despite no reversal of angiographic vasospasm. The fact that there were no serious influences of OKY-1581 or OKY-046 on MABP and PR is in agreement with data on OKY compounds in animals.\textsuperscript{13, 14} Thus, the significant increase of ΔrCBF in spastic animals by OKY-1581 or OKY-046 may not be due to the change of caliber of large extraparenchymal vessels, MABP, or PR, but to an acceleration of microvascular circulation. However, the mean ΔrCBF in normal animals was not significantly increased by OKY-1581 infusion at 50 µg/kg/min for 1 or 2 hrs.

A significant increase in cerebral blood volume in Grade III and IV patients with severe diffuse vasospasm suggests that cerebral vasospasm consists of constriction of the large extraparenchymal vessels accompanied by massive dilatation of intraparenchymal vessels.\textsuperscript{32} Ettinger shows an increased coagulability in patients with SAH.\textsuperscript{33} An endothelial damage is a prominent feature and observed to extend back into sizable arterial branches in 119 autopsy cases with cerebral infarction following ruptured aneurysm,\textsuperscript{34} and Crompton\textsuperscript{35} further notes that arteries with endothelial damage are not thrombosed but associated with cerebral infarction. However, fibrin-platelet emboli formed on damaged vascular endothelium are not easily distinguishable in histological preparations. Thus, vasospasm could be not necessarily the only factor contributing to the morbidity and mortality of SAH, but rather set the stage for events which further decrease brain perfusion to lead clotting or/and platelet aggregation in the parenchymal microvasculature. OKY-1581 and OKY-046 block platelet aggregation induced by arachidonic acid or collagen in rabbits and humans,\textsuperscript{10-16} and prevent experimental thrombosis induced by arachidonic acid and AgNO$_3$.\textsuperscript{10, 14} The mean platelet aggregation rates and the mean percent inhibitions of platelet aggregation in spastic animals by OKY-1581 or OKY-046 infusion at 50 µg/kg/min for 2 hrs were not significant as compared to those in normal animals. However, OKY-1581 or OKY-046 infusion at 50 µg/kg/min increased ΔrCBF significantly only in spastic animals. Suzuki et al\textsuperscript{36} report that only 2 of 9 patients with vasospasm show mild signs of cerebral ischemia by an oral administration of trapidil, an antagonist and selective synthesis inhibitor of TXA$_2$.

Patients with SAH show an increase of PGF$_2\alpha$, and PGE$_2$ in cerebrospinal fluid,\textsuperscript{16-19} suggesting that arachidonic acid metabolites are synthesized as a result of SAH. Gaudet and Levine\textsuperscript{40} report, in gerbils subjected to unilateral carotid occlusion, that PGE$_2$ and PGF$_2\alpha$ levels are elevated in both hemispheres and 6-keto PGF$_1\alpha$ is only slightly increased, particularly PGF$_2\alpha$ level remaining elevated at 6 hrs after occlusion. Shohami et al\textsuperscript{41} report, in rats subjected to severe incomplete cerebral ischemia, that PGE$_2$ in the brain tissue accumulates during the first 5 min of ischemia and its level declines at 15 min and that TXB$_2$ in the brain tissue remains high during the whole time course of experiment. The effect of PGE$_2$ on the caliber of canine cerebral arteries is variable.\textsuperscript{42} The increased synthesis of PGF$_2\alpha$, PGE$_2$, or TXA$_2$ in the ischemic brain tissue may constrict the local blood vessels,\textsuperscript{19-21} diminish the local brain blood flow,\textsuperscript{22, 23} but actually the parenchymal vessels dilate\textsuperscript{24-30} and CBF decreases\textsuperscript{24, 34} in vasospasm. In addition, PGE$_2$, and PGD$_2$ antagonize human platelet aggregation.\textsuperscript{24-25} Similar prostaglandin products may be produced in the ischemic brain tissue in vasospasm, but the local microcirculation in vasospasm could be inexplicable only on the basis of the disturbed prostaglandin metabolism. However, it is shown that treatment with indomethacin prior to incomplete cerebral ischemia reduces the levels of PGE$_2$ and TXB$_2$ in rat ischemic brain tissue and accelerates EEG recovery after reperfusion, suggesting that indomethacin improves the post-ischemic reflow.\textsuperscript{41} Thus, the increased TXA$_2$ production which may occur in the ischemic brain tissue in vasospasm, may diminish by the treatment with OKY compounds, thereby ameliorating the local microcirculation.

References

EXPERIMENTAL CEREBRAL VASOSPASM/Fukumori et al


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