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Abstract

OKY-1581, a thromboxane A2 (TXA2) synthetase inhibitor, was administered to cats with normal and constricted basilar arteries. At a dose of 60mg/kg (i.v.), both normal and constricted vessels dilated, and the mean arterial blood pressure (MABP) fell from 55 to 75 mmHg. If MABP remained constant, vessel diameter did not change. Subarachnoid hemorrhage (SAH) was simulated by intracisternal injection of autologous arterial blood. Regional cerebral blood flow (rCBF) was assessed by the heat clearance and H2 clearance methods. The two methods presented similar response profiles. rCBF responses to intravenous OKY-1581 fell into 3 categories: A) no change in rCBF, B) decrease in rCBF related to MABP and C) increase in rCBF in the presence of hypotension. Types A and B were observed in 3 out of 10 control cats and 4 out of 14 SAH-induced cats, with Type C responses in the remainder. There was no significant difference between the groups. While the results do not support a major role for TXA2 in cerebral vasospasm pathogenesis, OKY-1581 may still be useful in the treatment of cerebral vasospasm, as it improves distal and deep circulation and inhibits platelet aggregation.

KEYWORDS: cerebral vasospasm, thromboxane A_2, OKY-1581

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PROSTACYCLIN AND THROMBOXANE IN CEREBRAL VASOSPASM II : EFFECTS OF THROMBOXANE SYNTHETASE INHIBITOR (OKY-1581) ON EXPERIMENTALLY-INDUCED CEREBRAL VASOSPASM

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Abstract. OKY-1581, a thromboxane A_2 (TXA_2) synthetase inhibitor, was administered to cats with normal and constricted basilar arteries. At a dose of 60mg/kg (i.v.), both normal and constricted vessels dilated, and the mean arterial blood pressure (MABP) fell from 55 to 75 mmHg. If MABP remained constant, vessel diameter did not change. Subarachnoid hemorrhage (SAH) was simulated by intracisternal injection of autologous arterial blood. Regional cerebral blood flow (rCBF) was assessed by the heat clearance and H_2 clearance methods. The two methods presented similar response profiles. rCBF responses to intravenous OKY-1581 fell into 3 categories : A) no change in rCBF, B) decrease in rCBF related to MABP and C) increase in rCBF in the presence of hypotension. Types A and B were observed in 3 out of 10 control cats and 4 out of 14 SAH-induced cats, with Type C responses in the remainder. There was no significant difference between the groups. While the results do not support a major role for TXA_2 in cerebral vasospasm pathogenesis, OKY-1581 may still be useful in the treatment of cerebral vasospasm, as it improves distal and deep circulation and inhibits platelet aggregation.

Key words : cerebral vasospasm, thromboxane A_2, OKY-1581

Cerebral vasospasm following aneurysmal rupture and subarachnoid hemorrhage (SAH) often leads to cerebral ischemia. The etiology of this vasospasm is not well understood. Recently prostacyclin (PGI_2) and thromboxane A_2(TXA_2) have been implicated in the control of arterial tone in cerebral (1, 2) as well as peripheral circulation (3, 4). PGI_2, generated in the endothelium of the vessel wall, inhibits the aggregation of blood platelets and dilates the cerebral arteries (5-8). The actions of TXA_2, released from platelets, oppose those of PGI_2 (1, 9, 10). A balance between the synthesis of PGI_2 and TXA_2 may be important in maintaining normal cerebral circulation (11). If an imbalance occurs, resulting in TXA_2 predominance, it is thought that ischemic cerebrovascular disease will ensue (11).

Severe morphological alterations, including endothelial cell damage and adherent platelets, have been found at autopsy in patients who suffered from post-

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SAH cerebral vasospasm(12-14). Vasospasm is probably caused by decreased PGI_2 synthesis in the damaged vessel wall or the resulting predominance of TXA_2 (15, 16). If this hypothesis is true, correction of the imbalance between TXA_2 and PGI_2 would be useful in the treatment of vasospasm. In the first part of this study(8) it was seen that exogenously added PGI_2 was not effective in reversing an induced spasm. Thus, it is of interest to clarify the role of TXA_2 in cerebral vasospasm. In this, the second part of the study, OKY-1581 (sodium (E)-3-[4-(3-pyridylmethyl) phenyl]-2-methyl-2-propeonate), (17-19) a thromboxane synthetase inhibitor, was used to selectively reduce the amount of TXA_2 and thus improve the imbalance.

MATERIALS AND METHODS

Subjects and surgical procedures. Thirty-nine adult cats, weighting 2.5 to 4.5kg each, were used. Intramuscular ketamine hydrochloride (2-0-chlorophenyl-2-methylaminocyclohexane hydrochloride) (20mg/kg) was used as an anesthetic. The head was immobilized in a stereotaxic instrument. After endotracheal intubation, the cats were paralyzed with intramuscular succinylcholine chloride (1 to 2 mg/kg), repeated if neccessary, and maintained on a respirator (Igarashi Model B_2, Japan). Catheters were situated in the femoral artery for measurement of mean arterial blood pressure (MABP), and in the femoral vein for intravenous administration. MABP was recorded continuously with a pressure monitor (Statham SP-1405, USA), and blood gases were frequently checked. Arterial blood gas was maintained within the following ranges : pH 7.30 to 7.40, and pCO_2 32 to 40 mmHg. The basilar artery was exposed transclivally as described previously(8).

Measurement of vascular diameter. Basilar arterial constriction was produced by topical application of a lysed erythrocyte solution(20). Normal and constricted basilar arteries were observed directly through an operative microscope. After administration of OKY-1581 (60 mg/kg), serial photographs of the vessels were taken at 2.5X magnification, using a camera (35 mm Olympus OM1, Japan) attached to the microscope. Color slides were projected onto a screen with a slide projector, and vessel diameter was calculated in terms of pre-treatment width. The basilar arteries were kept in physiological saline or the lysed erythrocyte solution to maintain a constant diameter when not under investigation. OKY-1581, dissolved in 2 ml of physiological saline, was injected intravenously over a 1 min. period, 30 min. after the lysed erythrocyte solution was applied to the basilar artery, when maximal spasm was obtained.

Brain stem regional cerebral blood flow (rCBF) determinations : rCBF changes were assessed in 10 control cats and in 14 cats with experimental SAH. SAH was simulated by injection of 3 to 4 ml of fresh autologous arterial blood into the cisterna magna after removal of an equal volume of CSF. The removed CSF was mixed with two volumes of fresh arterial blood and was incubated at 37.0 ℃ for 3 days. The basilar artery and a part of the pontine region were exposed transclivally 3 days after the intracisternal injection of blood. Heat clearance was recorded (Shincorder CTE-202, Japan) before and after intravenous administrations of OKY-1581 (15 mg/kg, 30 mg/kg, and 60 mg/kg), using a double needle type element (MT Giken, WN-151, Japan). The interval between administration of increasing dosages was about 2 h. Thermister probes were inserted about 5 mm into the brain stem, along the basilar artery, so as not to injure arteries and veins. In the SAH group, after insertion of the probe, a prolonged spasm was produced by topical application of the blood-CSF mixture. CO_2 (8%) in air also was administered to all cats, and the responses were recorded.

rCBF determinations were performed in 4 normal cats and 5 cats with experimental SAH by the heat clearance method and the hydrogen clearance method simultaneously, both before and after treatments with OKY-1581 (30 mg/kg and 60 mg/kg). Two platinum electrodes were inserted 1.5 mm deep into different portions of the pons; one of the two electrodes was inserted 3.5 mm deep in two of the normal cats. The Ag/AgCl reference electrode was positioned in the parafemoral subcutaneous tissue. When rCBF was observed by the heat clearance method increased above the baseline level, 10 % H_2 in air was administered for 2.5 min. The H_2 clearance curve was recorded with a PH_2 monitor (Tokai Irika, PHG-300, Japan). Approximately two hours after the H_2 clearance curve returned to the baseline, the second control rCBF was measured.

RESULTS

Effect of OKY-1581 on basilar artery diameter. The basilar artery was exposed transclivally with an operative microscope in 15 cats. The artery was bathed with physiological saline which was gently aspirated before photographing. The diameter of the nomal basilar artery was regarded as 100 % . OKY-1581 (60 mg/kg) was injected, and MABP began to decrease within 20 sec. It fell 55 to 75 mmHg within 60 to 90 sec, gradually returned to within 10 to 15 mmHg of the baseline in 10 to 15 min, and recovered to baseline values within 60 min. In 2 cats, MABP gradually returned to the baseline in 13 min. The response to OKY-1581 in cats with constricted arteries was similar.

In the nomal basilar artery, OKY-1581 produced moderate dilation of the vessel, which began within 2.5 to 3.5 min. and reached its maximum within 6.5 to 9 min. Increased diameter was maintained for over 30 min. Normal vessels increased in diameter earlier than spastic vessels. Furthermore, a fall in MABP did not elicit as strong a dilation in the constricted arteries. The response lagged a few minutes behind the maximum change in MABP. The average maximum

TABLE 1. CHANGES IN THE DIAMETER OF NORMAL BASILAR ARTERIES AFTER INTRAVENOUS ADMINISTRATION OF OKY-1581

cat	Percent diameter after administration of OKY-1581 (60 mg/kg)
No. 1	126
No. 2	121
No. 3	118
No. 4	131
No. 5	128
No. 6	141
Average	127.5 ± 7.4*

* $p < 0.005$ The original diameter of the vessel was regarded as 100 %

TABLE 2. CHANGES IN THE DIAMETER OF CONSTRICTED BASILAR ARTERIES AFTER INTRAVENOUS ADMINISTRATION OF OKY-1581

Cat	Percent diameter after administration of	
	Lysed erythrocyte solution	OKY-1581 (60 mg/kg)
No. 1	68.8	78.0
No. 2	75.3	81.2
No. 3	55.2	76.7
No. 4	75.8	81.8
No. 5	80.4	83.9
No. 6	65.5	67.6
No. 7	66.3	92.0
No. 8	62.2	86.5
No. 9	76.1	89.1
Average	69.5 ± 7.6 %*	81.9 ± 6.9 %**,*

* $p < 0.005$ Against control; ** $p < 0.005$ Against control; * $p < 0.005$ Against lysed erythrocyte treated arteries

The original diameter of normal basilar artery was regarded as 100 %.

dilation was 127.5 ± 7.4 % in 6 control cats (Table 1). The basilar artery was constricted by a topical application of the lysed erythrocyte solution to an average diameter of 69.5 ± 7.6 % (n=9) (Table 2). OKY-1581 (60 mg/kg) produced mild dilation of the vessel. The vessel diameter began to dilate within 3 to 4 min and showed maximum dilation within 6 to 10 min, returning to the pre-treatment diameter within 60 min. Dilatory action lagged 5 to 8 min behind the hypotensive effect. The average maximum dilation in the 9 treated cats was 81.9 ± 6.9 % (n=9) (Table 2). Simultaneously, branches of the basilar artery were observed. OKY-1581 dilated the constricted branches eariler than the constricted basilar artery and seemed to have a greater dilatational effect on the branches.

Brain stem rCBF as determined by the heat clearance method. The cats were prepared as controls. MABP remained at the baseline level after an intravenous infusion of 15 mg/kg OKY-1581. If MABP did not fall, rCBF held steady. A higher dose of OKY-1581 (30 mg/kg) resulted in a fall in MABP. The maximum reduction of MABP, achieved at 75 sec, varied from 30 to 40 mmHg. A dose of 60 mg/kg resulted in deep and more sustained hypotension (see above).

There were three types of rCBF (Fig. 1) : Type A (1 cat) consisted of those which did not change; Type B (2 cats) rCBF varied according to the change in arterial blood pressure, and Type C (7 cats) rCBF increased despite systemic hypotension. In one of the Type B cats, rCBF began to decrease within 30 sec, then began to increase within 2 min, and recovered to the baseline level within 5 min. The rCBF of the other Type B cat decreased within 30 sec, reached the lowest level within 2 min, and maintained a low level for over 30 min. In the Type C group, 5 cats had transient decreases in rCBF for 45 sec to 2.5 min,before the

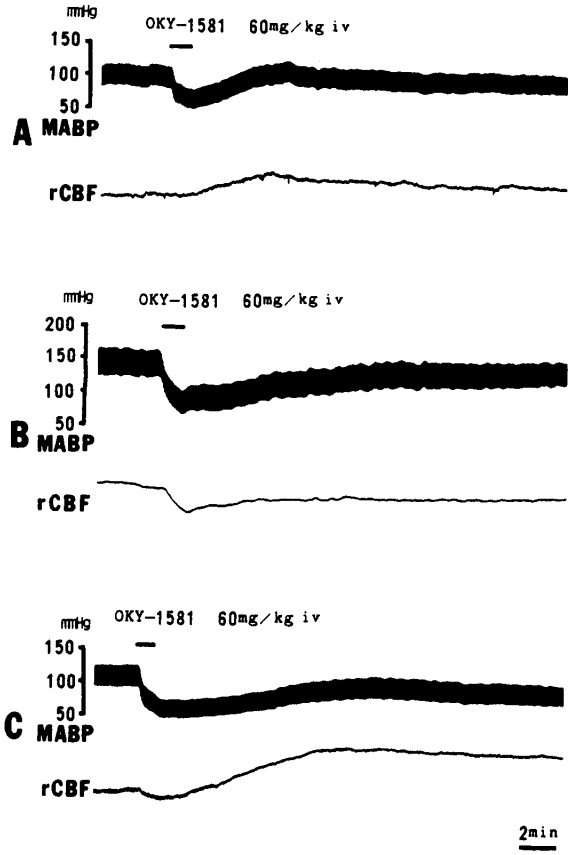

Fig. 1. rCBF after the intravenous administration of OKY-1581 (60 mg/kg) to 10 nomal cats. rCBF : regional cerebral blood frow, MABP : mean arterial blood pressure. Figures are from representative cats.

rCBF increased. The elevated flow continued for over 30 min. rCBF in the other two cats increased from the onset. The rCBF response patterns for individual cats were the same at both OKY-1581 dosages. rCBF showed a transient increase during the inhalation of 8 % CO_2 in all cats studied.

The relationship between the doses administered and the degree of MABP decrease in the SAH group was similar to that in the control group : a decrease in MABP resulted in the same 3 types of rCBF (Fig. 2). There were 2, 2 and 10 cats of Types A, B and C, respectively. One of the Type B cats showed a transient decrease, and the other showed a continued fall in rCBF, similar to the changes in the control group. Five Type C cats presented an initial transient decrease in rCBF, and the others a continuous increase for over 30 min. In this SAH model, and in the control, most of the cats (71 % and 70 %) demonstrated a sustained increase in rCBF. The response to inhalation of 8 % CO_2 was similar to that in control cats.

H_2 clearance method determinations of rCBF. The clearance curve was analyzed 45 sec following the cessation of hydrogen gas inhalation. After calculating $T_1/_2$

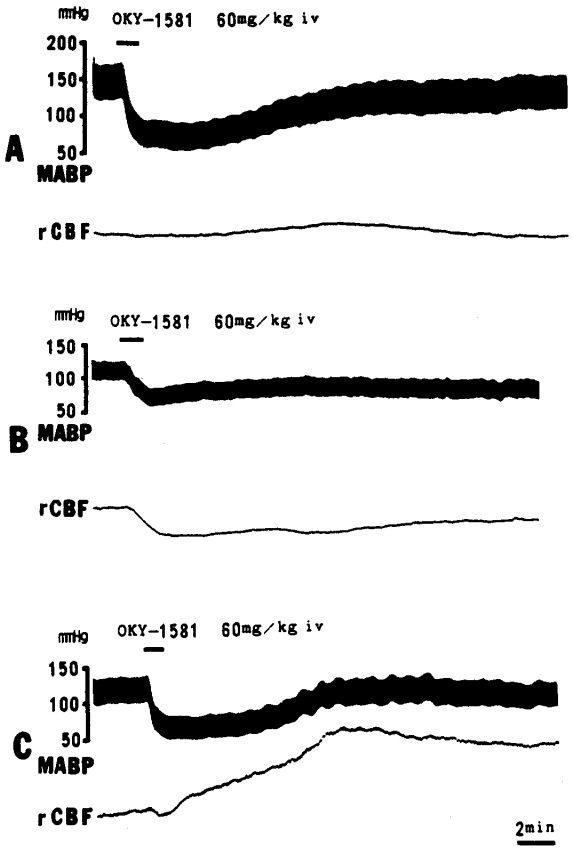

Fig. 2. rCBF after the intravenous administration of OKY-1581 (60 mg/kg) to 14 cats with experimental SAH. There were no significant differences from the control group (Fig. 1).

from the two minute initial clearance (21, 22), rCBF was calculated with the formula:

$$rCBF = \lambda \frac{0.693}{T_{1/2}} \text{ ml/100g/min. (23),}$$

where λ (tissue : blood partition coefficient for hydrogen) = 1 (24).

The values obtained from the 4 control cats are shown in Table 3A. The average of the untreated control flow was 32.1 ± 9.3 ml/100g/min. (n=8) (Fig. 3). The average rCBF after the administration of OKY-1581 (30 mg/kg) was 39.9 ± 11.5 ml/100g/min. (n=8), an increase of 24.3 % ($P<0.005$). Two hours later, the control rCBF was measured again, and averaged slightly less than before (30.2 ± 8.4 ml/100g/min. (n=6)). The rCBF measured after a higher dose of OKY-1581 (60 mg/kg) averaged 41.9 ± 8.1 ml/100g/min. (n=6). This represents a 38.7 % increase ($P<0.025$) over the second control measurement.

The rCBF in 5 cats with experimental SAH was markedly decreased in comparison to the control group. (Fig. 4). The rCBF in 3 out of 10 measurements

TABLE 3-A, rCBF IN THE PONTINE REGION IN NORMAL CATS DETERMINED BY THE H_2 CLEARANCE METHOD AFTER THE ADMINISTRATION OF OKY-1581

Control Cats	1st control	OKY-1581 (30 mg/kg)	2nd control	OKY-1581 (60 mg/kg)
No. 8C	37.5	40.8		ml/100g/min.
	14.1*	21.7*		
No. 12C	43.9	57.8	43.3	46.2
	21.7*	25.7*	19.8*	25.7*
No. 13C	36.1	46.2	30.7	43.9
	31.5	40.8	25.2	38.5
No. 14C	40.8	51.3	38.5	49.5
	31.5	34.7	23.5	47.8
Average	32.1 ± 9.3	39.9 ± 11.5	30.2 ± 8.4	41.9 ± 8.1
Relative value	100 %	124.3 %	100 %	138.7 %
p <		0.005*		0.025**

* Against 1st control, ** Against 2nd control
This table shows the rCBF in the region 1.5 mm from the surface.
(* rCBF in the region 3.5 mm from the surface)

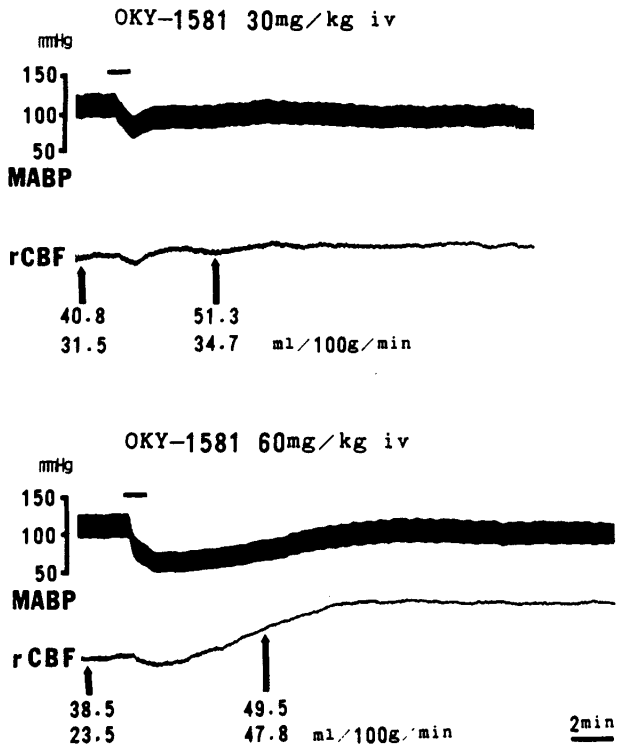

Fig. 3. One control case (Cat No. 14C) before and after the administration of OKY-1581. rCBF was measured at 2 different points in the pontine region by the H_2 clearance method before and after the administration of OKY-1581 (30 mg/kg and 60 mg/kg). The first control rCBF was 40.8 and 31.5 ml/100g/min., and the rCBF after the administration of OKY-1581 (30 mg/kg) was 51.3 and 34.7 ml/100g/min., respectively (upper graph). The second control rCBF was 38.5 and 23.5 ml/100g/min., and the rCBF after the infusion of OKY-1581 (60 mg/kg) was 49.5 and 47.8 ml/100g/min., respectively (lower graph).

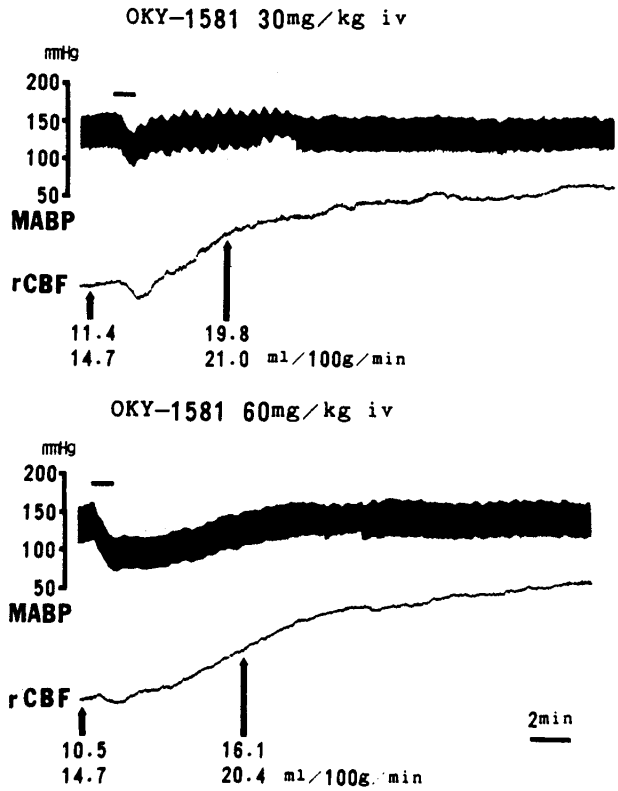

Fig. 4. One SAH case (Cat No. 12S) before and after the administration of OKY-1581. The rCBF was measured in the same manner as in the control group. The rCBF decreased much more in cats with vasospasm than in control cats. The first control rCBF was 11.4 and 14.7 ml/100g/min., and the rCBF after the administration of OKY-1581 (30 mg/kg) was 19.8 and 21.0 ml/100g/min., respectively (upper graph). Through rCBF increased after the administration of OKY-1581, it remained well below the levels in the non-constricted cases.

TABLE 3-B. rCBF IN THE PONTINE REGION IN CATS WITH SAH DETERMINED BY THE H_2 CLEARANCE METHOD AFTER THE ADMINISTRATION OF OKY-1581

Cats with SAH	1st control	OKY-1581 (30 mg/kg)	2nd control	OKY-1581 (60 mg/kg)
No. 9S	13.7	16.1	11.9	22.7 ml/100g/min.
No. 10S	16.1	14.7	17.5	21.7
No. 11S	19.3	22.4	14.7	16.9
No. 12S	11.4	19.8	10.5	16.1
	14.7	21.0	14.7	20.4
No. 13S	19.2	19.0	17.3	18.2
	11.6	11.7	11.9	14.7
Average	15.1 ± 3.0	17.8 ± 3.5	14.1 ± 2.5	18.7 ± 2.8
Relative value	100 %	117.9 %	100 %	132.6 %
$p <$		Not significant*		0.01**

* Against 1st control, ** Against 2nd control

was so low (below 10 ml/100g/min.) that it could not be calculated accurately (Table 3B). The average of the control rCBF value was 15.1 ± 3.0 ml/100g/min. (n=7). The rCBF after the administration of OKY-1581 (30 mg/kg) was 17.8 ± 3.5 ml/100g/min. (n=7), a 17.9 % increase (not significant). The control rCBF after a second measurement two hours later averaged 14.1 ± 2.5 ml/100g/min. (n=7). The average of rCBF was 18.7 ± 2.8 ml/100g/min. (n=7) after the infusion of OKY-1581 (60 mg/kg), a 32.6 % increase ($P<0.01$) over the corresponding baseline. Increases in rCBF were smaller, both absolutely and relatively, in cats with SAH than in control cats, though both groups showed definite increase in rCBF after the administration of OKY-1581.

DISCUSSION

The pathogenesis of cerebral vasospasm following intracranial aneurysmal rupture is not well understood. Recently, however, the balance between PGI_2 and TXA_2 synthesis in cerebral (1,2) and peripheral circulation (3,4) has drawn much attention, since an imbalance resulting in a relative increase in TXA_2, a powerful vasoconstrictor (1), could contribute to ischemic cerebrovascular conditions such as vasospasm (11). It has been suggested that decreased PGI_2 synthesis in the vessel wall causes this imbalance (15, 16).

OKY-1581, a thromboxane A_2 synthetase inhibitor, is considered to possess a vasodilating effect on extracranial vessels, because it induces dose-dependent systemic hypotension. However, the systemic blood pressure decreased so promptly after intravenous OKY-1581 administration that it is unlikely that this early hypotensive activity was due to a relative increase in PGI_2. OKY-1581 seemed to act directly on the cardiovascular system. MABP gradually recovered and was stable at 10 to 15 mmHg below the baseline for about an hour. This later hypotension may have been due to dilation of extracranial vessels caused by decreased TXA_2 synthesis. Thus, OKY-1581 seems to possess both a transient, direct action and a delayed indirect action on the extracranial vascular system. The latter effect is thought to involve the PGI_2-TXA_2 interaction.

The present study has shown that administration of OKY-1581 results in dilation of both normal and constricted basilar arteries and branches. A short period is required before the dilation begins. In contrast, papaverine hydrochloride, which is a powerful vasodilator of intracranial as well as extracranial vessels (25), produces marked dilation of cerebral vessels immediately after intravenous administration (8). Since the vasodilating effect of OKY-1581 requires a short latency and is not immediate as with papaverine hydrochloride, it is not considered to be direct. Though the delayed dilation implicates decreased TXA_2 synthesis, the sequential changes in PGI_2 and TXA_2 concentrations in vessel walls and plasm must be strictly investigated.

The small branches of normal and constricted basilar arteries tended to dilate earlier and more extensively than the trunk vessels after injection of OKY-1581.

Thus it was confirmed that OKY-1581 had a greater vasodilating action on cerebral vessels than PGI_2, and that its action is focused on small vessels (arterioles) rather than on large ones.

After an injection of OKY-1581, the rCBF increased in most cats regardless of SAH, in contrast to injections of PGI_2. The rCBF patterns observed by the heat clearance method correlated well with those obtained by the H_2 clearance method. There were no significant differences in the rCBF patterns between the normal and SAH cats. Though OKY-1581 increased rCBF in both groups, a specific action on constricted vessels was not noted. This result leads the author to believe that even if TXA_2 increases locally around the constricted vessel wall, it is not the main factor causing cerebral vasospasm.

OKY-1581 may increase rCBF by reducing the amount of TXA_2 which would lead to a relative increase in PGI_2 activity or by increasing the amount of PGI_2. As the author's previous study has shown that exogenous PGI_2 did not increase rCBF in a majority of cats (8), it is difficult to conclude that the increase in rCBF after the injection of OKY-1581 was due to the action of PGI_2. If large arterial trunks dilate markedly, as after papaverine, rCBF will increase (8). On the other hand, if dilation is weak or non-existent, as with PGI_2, rCBF will not increase. OKY-1581 dilated large vessels slightly and rCBF increased moderately to markedly. The exact mechanism of action remains to be elucidated.

Endothelial degeneration has been observed early in the course of vasospasm (12, 14). The damage is followed by platelet adhesion and aggregation which play a major role in the propagation of thrombosis (13, 26, 27). Thrombus formation may contribute to diminished blood flow, or fragments may develop into emboli which lead to distal infarctions. Though the signs and symptoms of cerebral ischemia seen in patients with SAH can be attributed to actual arterial narrowing, thrombi also may be an important factor. The effect of thrombi and emboli is greatest on small diameter vessels. OKY-1581 acts mainly on small vessels, and can inhibit platelet aggregation (6), thus increasing rCBF. Therefore, OKY-1581 produces only limited dilation of constricted large arteries, but it improves the distal circulation by preventing platelet aggregation and increasing rCBF. However, the disadvantage of lowered systemic blood pressure must be considered. If adequate peripheral circulation can be preserved, the neurological deficits associated with vasospasm might be prevented. Severe spasm of vessels continuing for over 10 h will not respond to various vasodilating agents (28). Once neurological signs and symptoms occur, it is difficult to alleviate them. Therefore, any treatment should be initiated before deficits occur. The results suggest that OKY-1581 should be used prophylactically. A clinical study is required to evaluate this treatment.

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