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Effect of Cisternal Administration of Nicardipine Hydrochloride on Cerebral Vasospasm — A Preliminary Report —

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ABSTRACT

In six subarachnoid hemorrhage (SAH) cases due to aneurysmal rupture, effects of cisternal administration of Nicardipine hydrochloride (nicardipine) on vasospasm were studied. Nicardipine is one of calcium antagonists. All aneurysms were clipped within 48 hr after the onset of SAH with ventricular and cisternal drainages. Subarachnoid clot was removed as much as possible. Nicardipine or mixture of nicardipine and urokinase was administered through cisternal drainage once a day for 10 days postoperatively. The dose of nicardipine was 2 mg or 4 mg, and that of urokinase was 6,000 units or 24,000 units. On the 7th day after the onset of SAH, angiograms were performed before and 30 min after the cisternal administration of nicardipine. Then the diameters of each arteries were compared in order to estimate the vasodilative effects of nicardipine angiographically. In this study nicardipine was considered to have some prophylactic effect on vasospasm because vasospasm was not observed either angiographically or clinically in 2 out of 3 severe SAH cases on CT.

There are many therapeutic or prophylactic regimens for cerebral vasospasm after subarachnoid hemorrhage (SAH)[13]. Recently some newly developed calcium antagonists have been utilized clinically or experimentally for cerebral vasospasm after SAH. In some reports, however, the vasodilative effects of them are quite questionable[5,6,9,16,18,20].

In this report, nicardipine hydrochloride (nicardipine), a derivative of 1,4-dyhydropyridine, which is one of the calcium antagonists, was administered into the basal cisterns of SAH patients through cisternal drainage which was inserted on the surgery of ruptured cerebral aneurysm, and the vasodilative effects of this drug were investigated.

MATERIALS AND METHODS

This investigation was made with six patients of both sexes, one male and five females, aged between 34 and 64 years. CT of these all patients showed SAH due to aneurysmal rupture. The locations of aneurysms were internal carotid artery in 4 cases, middle cerebral artery in one case and anterior communicating artery in one case. Preoperative grading of clinical condition after Hunt and Kosnik[11] were under 3 in all cases. The classification of SAH on CT after Fisher et al[7] showed group 2 in 2 cases, group 3 in 3 cases and group 4 in one case. All patients underwent the clipping of the aneurysm within 48 hr after SAH attack. A ventricular drainage into the anterior horn of the lateral ventricle and a cisternal drainage into the basal cistern were also inserted in the operative side

Table 1. Summary of cases

Case	Age	Sex	Aneurysmal Site	Operation Day after SAH	*1 Grade at Operation	Hemiparesis at Operation	*2 CT GRade	*3 Spasm	*4 Consciousness at Spasm	Hemiparesis at Spasm	Hemiparesis at Discharge	*5 Outcome 3M after Discharge
1. S.A.	60	F	R.ICPC	1	2	—	3	—	0	—	—	good recovery
2. K.H.	50	M	R.MCA	0	3	—	4	diffuse severe	100	+	+	moderate disabled
3. S.K.	64	F	R.ICPC	0	3	+	3	diffuse severe	10	+	+	severely disabled
4. E.S.	36	F	Acom	1	1	—	2	—	0	—	—	good recovery
5. Y.Y.	59	F	L-ICPC	1	2	—	2	periph-eral	0	—	—	good recovery
6. Y.S.	43	F	L-ICPC	0	3	—	3	—	0	—	—	good recovery

*1: Hunt and Kosnik (1974) *2: Fisher et al (1980) *3: Koike et al (1982)
*4: Japanese coma scale *5: Glasgow outcome scale

on the surgery. The subarachnoid blood and clot were removed as much as possible. In some cases external decompression was added (Table 1).

Nicardipine was scheduled as to be administered through the cisternal drainage for 10 days as a rule from the first postoperative day. In cases 5 and 6 the cisternal drainages were slipped out spontaneously on 9th and 6th postoperative days respectively, so further administration of the drugs was impossible in these cases.

Urokinase was administered simultaneously in 5 cases in order to melt the subarachnoid clot. The items were followings, i.e. 2 mg of nicardipine alone in case 1, 2 mg of nicardipine and 6,000 units of urokinase in cases 2, 3 and 4, and 4 mg of nicardipine and 24,000 units of urokinase in cases 5 and 6 (Table 2).

Table 2. Administration of drugs and its duration

Case	Age	Sex	Dose of Nicardipine (mg)	Dose of Urokinase (units)	Duration of Administration (days)
1. S.A.	60	F	2	—	10
2. K.H.	50	M	2	6,000	10
3. S.K.	64	F	2	6,000	10
4. E.S.	36	F	2	6,000	10
5. Y.Y.	59	F	4	24,000	9
6. Y.S.	43	F	4	24,000	5

The drugs, which were dissolved with the 5-10 ml of saline, were administered gradually for one min manually with pumping method through the cisternal drainage, then the drainage was clipped for 2 hr.

Cerebral angiography was performed on 7th day after SAH attack in all cases in order to estimate the condition of clipping and to examine the occurrence of cerebral vasospasm. In the 5 cases the drugs were administered in the same manner described above during the angiography. The angiography was repeated 30 min after the drug administration, then the vasodilative effects of cisternal administration of nicardipine were examined.

Table 3. Angiographical classification of vasospasm

Diffuse	: narrowing over 2 cm in length in the proximal part
Severe:	reduction of diameter by more than 50%
Mild:	reduction of diameter by 25% to 50%
Peripheral	: narrowing over 2cm in length in the distal part
Local	: single localized narrowing
Multi local	: multiple localized narrowing

(Koike et al)

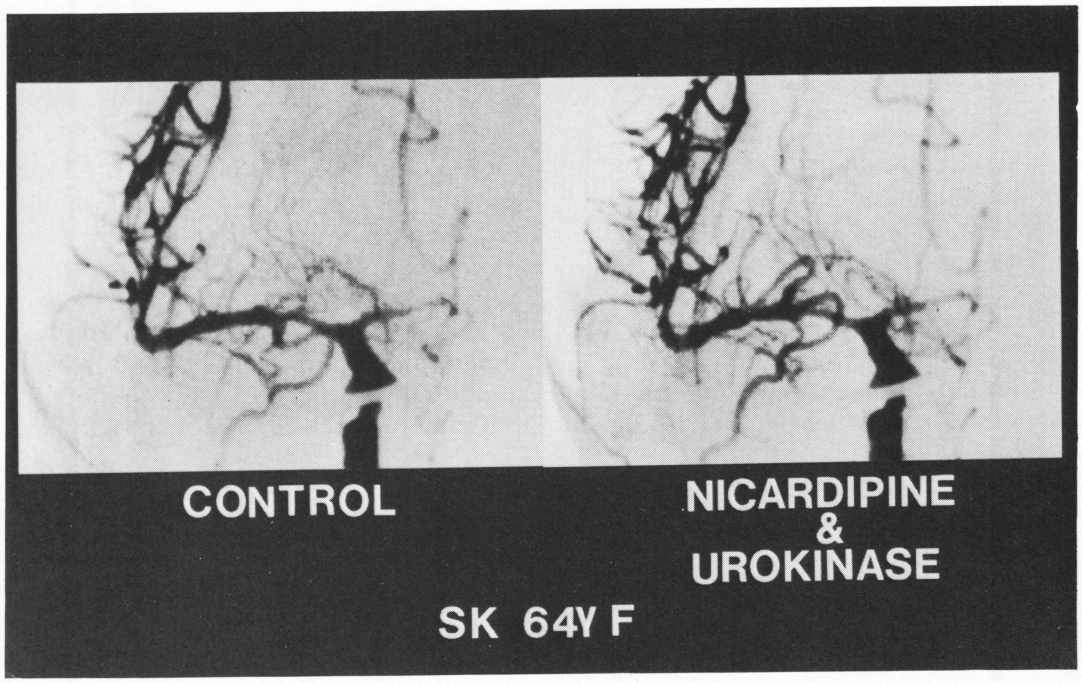

Fig. 1. Right carotid angiograms of case 3 Left: before cisternal administration of drugs Right: 30 minutes after cisternal administration nicardipine and urokinase Note that there is no difference in the diameters of arteries before and after the cisternal administration of nicardipine.

Table 4. Vessel diameter before and after administration of drugs

		Case									
		1		2		3		4		5	
		pre (mm)	post (mm)	pre (mm)	post (mm)	pre (mm)	post (mm)	pre (mm)	post (mm)	pre (mm)	post (mm)
VESSELS	C_1	4.7	4.7	4.8	4.8	5.0	5.0	3.2	3.2	5.0	5.0
	A_1	2.2	2.2	*1.8	1.8	*1.2	1.2	2.0	2.0	3.5	3.5
	M_1	2.7	2.7	*1.8	1.8	*1.2	1.2	2.5	2.5	3.0	3.0
	A_2	1.2	1.2	*2.0	2.0	1.4	1.8	1.0	1.0	*0.7	0.7
	M_2	1.3	1.3	*0.7	0.7	*0.8	0.8	2.5	2.8	*1.1	*1.1
Nicardipine (mg)		2		2		2		2		4	
Urokinase (units)		* *		6,000		6,000		6,000		24,000	
Type of spasm		—		diffuse severe		diffuse severe		—		peripheral	

pre: before cisternal administration of drugs
post: after cisternal administration of drugs
*spasm

RESULTS

Vasospasm was classified into 5 groups after Koike et al[15] (Table 3). In two cases (cases 2 and 3), diffuse severe spasm was observed on 7th day after SAH attack. Their consciousness was disturbed and hemiparesis were noted. In one case (case 5) peripheral spasm was noted by angiography. The outcomes after Glasgow outcome scale 3 months after the discharge, showed good recovery except the 2 cases of hemiparesis (cases 2 and 3). It was noted, however, that vasospasm was not found in 2 cases (case 1 and 6) out of 3 cases of Fisher's group 3 on CT which were thought to be sure to occur vasospasm (Table 1).

The immediate effects of nicardipine were studied by comparing the arterial diameters obtained by angiograms before and after the cisternal administration of the drugs during the angiography. The diameters of arteries were measured in anteroposterior view by a pair of slide calipers on the angiographic films direct-

ly. The measurement points of C1, M1 and A1 portions were 5 mm distant from the internal carotid artery bifurcation respectively. Those of M2 and A2 portions were 10 mm distant from the trifurcation of the middle cerebral artery or anterior communicating artery respectively. When vasospasm was noted at the measuring vessel, the diameter of spastic portion was measured. Consequently vasodilative effects of nicardipine were observed little at the A2 (case 3) and the M2 (case 4) portions which did not show vasospasm. The vasodilative effects to spastic vessels were not observed at all (Fig. 1, Table 4).

In all cases the side effects due to cisternal drug administration were not observed.

DISCUSSION

The vasodilative effect of calcium antagonists has been well known and considered to be effective to vasospasm of the cerebral arteries after subarachnoid hemorrhage (SAH) as well[1,2]. In the experimental studies, calcium antagonists were applied to isolated spastic arteries[3,14,19], to spastic arteries directly *in vivo*[3,10], or administered intravenously[17], intra-arterially[8,12] and intrathecally[8], in whichever cases vasospasm was reported to be improved. But according to more recent experimental studies, Varsos et al[20] reported that intravenous bolus injection of nifedipine failed to reverse the vasoconstriction, and Espinosa et al[5,6], Nosko et al[18] and Krueger et al[16] reported that oral administration of nimodipine was not useful in the prophylaxis of vasospasm after SAH.

In the clinical studies, Allen et al[1] reported that oral administration of nimodipine had some prophylactic effects to vasospasm. Auer et al[2] reported that intraoperative local application of nimodipine to the cerebral arteries made them dilated in 100% cases on the surgery of ruptured aneurysm. They also tried topical cisternal administration of nimodipine after aneurysmal clipping through the cisternal drainage, which dilated the normal and even the spastic arteries in 70% cases. When nimodipine was injected to the carotid arteries of the cerebral vasospasm patients after SAH, on the other hand, Grotenhuis et al[9] described the intracarotid application of nimodipine was not effective angiographically.

So far as nicardipine, Handa et al[10] reported the marked vasodilative effects when it was applied directly to the experimentally induced vasospasm of the cat basilar artery.

In this study, nicardipine was administered into the basal cistern directly through the cisternal drainage which was inserted on the aneurysmal surgery. But the administration of nicardipine failed to prove the vasodilative effects especially to the spastic arteries angiographically. the concentration of nicardipine was 0.2—0.4 mg/ml which was 20—40 times as high as was used experimentally by Handa et al[10]. That concentration was considered to be sufficient to dilate arteries although the drug was diluted with cerebrospinal fluid. To detect the direct action of this drug, angiography on the drug administration was done two times with 30 min interval. The vasodilative effect of this drug was reported to continue from one min till 2 hr after its direct application to the arteries experimentally[10], so this 30 min interval of angiography was considered to be adequate in this study. The reasons why the vasodilative effects of nicardipine could not be observed in this study were suspected as follows. First, the arteries had already dilated as much as they could, as the drug had been applied before angiography during the postoperative period. Second the drug might not be able to contact the arteries because of the blood clot in the subarachnoid space or the adhesion of the arachnoid membrane.

From the view points of clinical course, however, it was a very impressive finding that cerebral vasospasm could not be observed at all in two cases of Fisher's group 3 on CT in whom the cerebral vasospasm was surely thought to occurr[7]. This fact suggested that the cisternal administration of nicardipine had some prophylactic effects to the occurrence of cerebral vasospasm.

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