Effect of Cisternal Papaverine on Cerebral Blood Flow in Patients with Subarachnoid Hemorrhage

—Three Case Reports—

Hirofumi OYAMA, Masahiro NIWA, Yoshihisa KIDA, Takayuki TANAKA,
Kazuo YOSHIDA, Takanori IWAKOSHI, Ryuji KITAMURA,
Satoshi MAEZAWA, and Tatsuya KOBAYASHI

Department of Neurosurgery, Komaki City Hospital, Komaki, Aichi

Abstract

Three patients presenting with subarachnoid hemorrhage due to aneurysmal rupture underwent cerebral blood flow (CBF) measurements before and after cisternal injection of papaverine hydrochloride. One patient showed prominent increases in CBF in the frontal lobe and basal ganglia after injection of papaverine, but paradoxical decreases in the parietal lobe and corona radiata. The other two patients had poor CBF response. Dense clotting in the basal cisterns may have prevented diffusion of the agent so that only the proximal trunks of the internal carotid, anterior cerebral, and middle cerebral arteries were dilated in the former case. The dilation of proximal trunks of cerebral arteries might steal blood flow from the parietal lobe and corona radiata, where the intraparenchymal arteries were maximally dilated and cerebrovascular reserve capacity was poor.

Key words: cerebral blood flow, papaverine, subarachnoid hemorrhage

Introduction

Papaverine dilates the cerebral vessels by antagonizing the production of cyclic adenosine monophosphate and is used to improve the cerebral circulation. Intra-arterial or cisternal papaverine infusion for the clinical treatment of cerebral vasospasm after subarachnoid hemorrhage (SAH) has not always been effective.^{8,10)}

We describe the use of cisternal injection of papaverine in three patients with cerebral vasospasm after SAH and the results of cerebral blood flow (CBF) measurements to investigate the effectiveness of the treatment.¹¹⁾

Method

CBF was measured with xenon-enhanced computed tomography (CT) by the Kety-Schmidt method according to Fick, using an AZ-721 xenon gas rebreathing system (Anzai Sogyo Co., Ltd., Tokyo) and a Somatom plus CT system (Siemens, Erlangen, Ger-

many) with a matrix size of 256×256 and slice thickness of 5 mm.¹²⁾ The intra-arterial concentration of xenon was estimated from the end-tidal concentration, and the intra-parenchymal concentration of xenon was estimated by calculating the increase in CT Hounsfield number during the inhalation of xenon gas. Regional CBF was calculated by the method of least squares from the time-density curve of intra-arterial and intra-parenchymal concentrations of xenon. CT scans were taken every minute during 3 minutes of inhalation and 5 minutes of exhaustion at the levels of the basal ganglia and corona radiata. After the CBF values of each pixel were calculated, the mean hemispheric and lobular CBF were determined at the levels of the basal ganglia and corona radiata.

Papaverine hydrochloride (40 mg) in physiological saline (2 ml) was injected via a cisternal drainage tube placed around the carotid cistern. The CBF study was performed twice, before and 20 minutes after the cisternal injection of papaverine.

Received March 25, 1996; Accepted September 14, 1996

Author's present address: H. Oyama, M.D., Department of Neurosurgery, Chukyo Hospital, Nagoya, Japan.

Table 1 Hemispheric and regional CBF before and after cisternal injection of papaverine

	Side	Control* (baseline)	Case 1		Case 2		Case 3	
			Baseline	Papaverine	Baseline	Papaverine	Baseline	Papaverine
Hemispheric CBF								
level of basal ganglia	rt	57.5 ± 14.6	39.1	51.9	55	52.1	50.3	49.1
	lt	56.0 ± 13.5	37.6	45.3	50.3	46.8	61.6	54.6
level of corona radiata	rt	56.0 ± 13.3	33.9	25.1	47.4	46	46.7	39.1
	lt	55.3 ± 11.3	32.2	29.1	41.9	43.2	52.9	45.9
Regional CBF								
frontal lobe	rt	54.0 ± 13.5	32.2	61.4	43.3	40	54	43.1
	lt	52.5 ± 12.0	28.1	62.9	40.6	44.9	59	51.8
temporal lobe	rt	54.1 ± 15.3	36.4	40.4	51.4	50.1	49.7	53.3
	lt	51.8 ± 14.4	36	31.4	44.6	38.7	66.1	56.9
occipital lobe	rt	50.4 ± 13.5	42	50.3	47	42.4	57.3	52.6
	lt	50.6 ± 16.8	42.2	48.3	50.1	44.7	62.3	53
parietal lobe	rt	62.5 ± 14.7	36.1	29.6	53.1	52.3	55.2	46.6
	lt	58.5 ± 12.5	35.8	33.8	50.2	50.7	60.9	52.2
basal ganglia and thalamus	rt	66.9 ± 18.4	43	54.3	76.8	68.2	45	47
	lt	67.0 ± 16.9	41.4	48.6	61	49.3	59.8	57.9
corona radiata	rt	42.5 ± 45.7	25.7	20	35.5	32.6	34.7	27.1
	lt	31.8 ± 7.5	26.7	20.4	32.5	36.4	36.1	27.6

All values are ml/100 g/min. *The mean CBF and its SD of 25 normal individuals are presented as the age-matched control values.

Case Reports

In Case 1, CBF increased prominently in the frontal lobe and basal ganglia after injection of papaverine, but the response was poor in the other lobes and CBF decreased especially in the parietal lobe and corona radiata (Table 1). In Cases 2 and 3, CBF response was poor. In all cases, the consciousness level did not change after the injection. The details of the cases are presented as follows.

Case 1: A 59-year-old male suffered sudden onset of severe headache (Hunt and Kosnik grade II). CT showed SAH. Neck clipping of an anterior communicating artery aneurysm was performed on the same day. Effective cisternal drainage was achieved from the left carotid cistern. CT showed the SAH in the basal cistern had decreased moderately except for the ambient cistern by the next day. Three days after the operation, he developed right hemiparesis and became comatose. The CBF study 5 days after the operation showed generally low baseline CBF. After injection of papaverine, CBF increased prominently in the frontal lobe, but the response was poor in the other lobes and actually decreased in the parietal lobe and corona radiata (Fig. 1). Although moderate-sized cerebral infarction appeared in the left frontal base 10 days after the operation, he recovered consciousness gradually. Hydrocephalus was treated with ventriculoperitoneal shunting and he returned to his previous work.

Case 2: A 42-year-old female suffered sudden onset

of severe headache (Hunt and Kosnik grade II). CT showed SAH. Neck clipping of an anterior communicating artery aneurysm was performed on the same day. Her SAH increased because of intraoperative aneurysmal rupture. CT showed the basal cistern was almost packed with clot the next day. Effective cisternal drainage was achieved from the left carotid cistern. She did not open her eyes spontaneously but could obey verbal orders. The CBF study 7 days after the operation showed slightly low baseline CBF. After injection of papaverine, the CBF did not change significantly (Fig. 2). She became comatose on the next day. Cerebral infarction appeared in the left frontal lobe and basal ganglia 12 days after the operation and extended to the left temporal and parietal lobes on the following day. She died 15 days after the onset.

Case 3: A 74-year-old female suffered sudden onset of severe headache and loss of consciousness. She was comatose on admission, but was able to nod later (Hunt and Kosnik grade IV). CT showed thick SAH which was prominent in the right sylvian cistern. Neck clipping of an aneurysm at the bifurcation of the right internal carotid and posterior communicating arteries was performed on the same day. Effective cisternal drainage was achieved from the right carotid cistern. She remained comatose after the operation, and developed left hemiparesis and diabetes insipidus. Hemorrhagic infarction was verified in the right frontal lobe 3 days after the operation. Dense SAH centering around the right sylvian cistern still remained even on the 6th postoperative

Fig. 1 Case 1. CT scans on admission (left column) and xenon-enhanced CT scans 5 days later (center column) showing baseline CBF was generally low. After injection of papaverine (right column), CBF increased prominently in the frontal lobe, but the response was poor in the other lobes and actually decreased in the parietal lobe and corona radiata. upper row: at the basal ganglia level, lower row: at the corona radiata level.

day, although the basal cistern was not packed with clot. The CBF study on the same day showed slightly low baseline CBF, which did not change significantly after the injection of papaverine (Fig. 3). Her neurological condition did not recover even after the ventriculoperitoneal shunting and she died 3 months after the onset.

Discussion

Cisternal injection of papaverine is reported to influence the cerebral hemodynamics in patients with vasospasm due to aneurysmal rupture.⁽¹⁾ Arterial dilatation started within 30 minutes of the initial injection and an 85% increase in diameter was seen at 60 minutes, which continued for at least 90 minutes. However, CBF response to the cisternal injection of papaverine was seen in only our Case 1 who had hypoperfusion. The response was poor in Cases 2 and 3 who had slight hypoperfusion despite their

poor neurological conditions.^{2,9)} Arteries with marked vasospasm are believed to respond more to papaverine than those with less vasospasm.⁽¹¹⁾

CBF increased prominently in the frontal lobe and basal ganglia of Case 1 after injection of papaverine but CBF did not consistently increase in other sites. The basal cisterns were filled with dense clot especially in the ambient cistern, which may have obstructed the diffusion of the drug. Vasodilatation is observed only in the internal carotid artery or proximal trunks of the anterior and middle cerebral arteries where papaverine can make direct contact, but not in the distal branches beyond A₃ or M₃.⁽¹¹⁾

Case 1 also showed a paradoxical decrease in CBF in the parietal lobes and corona radiata in contrast to the markedly increased CBF in the frontal lobe and basal ganglia. The low perfusion pressure due to cerebral vasospasm causes compensatory vasodilatation of intraparenchymal arteries, which appear to have poor cerebrovascular reserve capacity.⁽⁷⁾ When

Fig. 2 Case 2. CT (left column) and xenon-enhanced CT scans (center column) 7 days after the onset showing baseline CBF was slightly decreased. After injection of papaverine (right column), CBF did not change significantly. upper row: at the basal ganglia level, lower row: at the corona radiata level.

papaverine is injected into the cistern, the dilation of the proximal trunks of the cerebral arteries might steal the blood flow from these maximally dilated intraparenchymal arteries. Such inequitable redistribution of CBF is also observed in other loading tests using induced hypertension or acetazolamide when autoregulation is impaired.^{1,4,7} In addition, papaverine might cause dose-dependent increases in both the regional CBF and the intracranial pressure.⁶ The combination of increased intracranial pressure and subsequent decreased cerebral perfusion pressure seems to be dangerous.⁵

These complex effects may explain why the clinical results of intracisternal papaverine infusion are not clear.^{8,10} Previously, intracisternal papaverine achieved improvement of paresis or consciousness level in almost half of patients but no effect in the others, besides the complication of intracerebral hemorrhage in two patients.¹¹ In our Cases 1 and 2,

the gradually deteriorating consciousness level and cerebral infarction indicated the progression of symptomatic vasospasm. The consciousness level did not change significantly after injection of papaverine because of poor diffusion of the drug, with subsequent inequitable redistribution of CBF due to vasoreactivity to the agent. Case 3 remained almost comatose from the onset due to the initial SAH. The influence of papaverine on the consciousness level was obscure. Certainly the prognosis for patients with symptomatic vasospasm is better when the CBF is over 30 ml/100 g/min.^{3,13,14} However, the use of cisternal papaverine to increase CBF should be considered carefully because of the problems of steal phenomenon and increased intracranial pressure. In addition, CBF and clinical response to this treatment is inconsistent.

Fig. 3 Case 3. CT (left column) and xenon-enhanced CT scans (center column) 6 days after the onset showing baseline CBF was slightly decreased. After injection of papaverine (right column), CBF did not change significantly. upper row: at the basal ganglia level, lower row: at the corona radiata level.

References

- 1) Darby JM, Yonas H, Marks EC, Durham S, Snyder RW, Nemoto EM: Acute cerebral blood flow response to dopamine-induced hypertension after subarachnoid hemorrhage. *J Neurosurg* 80: 857-864, 1994
- 2) Dinh YRT, Lot G, Benrabah R, Baroudy O, Cophignon J, Seylaz J: Abnormal cerebral vasodilation in aneurysmal subarachnoid hemorrhage: Use of serial ^{133}Xe cerebral blood flow measurement plus acetazolamide to assess cerebral vasospasm. *J Neurosurg* 79: 490-493, 1993
- 3) Fukuda T, Hasue M, Ko M, Hasegawa K, Nakamura T, Miwa T: [Time-related changes in the cerebral blood flow in subarachnoid hemorrhage due to ruptured cerebral aneurysm]. *No Shinkei Geka* 20: 339-347, 1992 (Jpn)
- 4) Handa Y, Hayashi M, Takeuchi H, Kubota T, Kobayashi H, Kawano H: Time course of the impairment of cerebral autoregulation during chronic cerebral vasospasm after subarachnoid hemorrhage in primates. *J Neurosurg* 76: 493-501, 1992
- 5) McAuliffe W, Townsend M, Eskridge JM, Newell DW, Grady MS, Winn HR: Intracranial pressure changes induced during papaverine infusion for treatment of vasospasm. *J Neurosurg* 83: 430-434, 1995
- 6) Murata S, Kikkawa K, Nagao T: Cerebral vasodilating and spasmolytic actions of a new Ca-antagonist, Cletiazem (TA-3090), in anesthetized animals. *J Cardiovasc Pharmacol* 19: 790-797, 1992
- 7) Nakagawara J, Wada K, Takeda T, Usami S, Hashimoto I, Shimazaki M, Tanaka C, Nakamura J, Suematsu K: [Prediction of cerebral ischemia due to cerebral vasospasm in SAH using SPECT and ^{123}I -IMP with acetazolamide test]. *Surgery for Cerebral Stroke* 17: 301-307, 1989 (Jpn)

- 8) Oda Y, Konishi T, Okumura T, Kang Y, Kikuchi H, Kamijyo Y: [Treatment of vasospasm after ruptured cerebral aneurysms by 'Pellet-Cisternal-Drain: PCD' containing sustained-release vasodilators]. *No Shinkei Geka* 16: 965-970, 1988 (Jpn)
- 9) Ohta H: Postoperative luxury perfusion syndrome in patients with severe subarachnoid hemorrhage treated by early aneurysmal clipping. *Neurol Med Chir (Tokyo)* 30: 16-23, 1990
- 10) Okumura T, Oda Y, Arimitsu T, Mori K: [Sustained-release pellet of vasodilators: Basic experiment]. *No Shinkei Geka* 12: 1265-1271, 1984 (Jpn)
- 11) Segawa H, Saito I, Okada T, Nagayama I, Kitamura K, Takakura K, Sano K: [Efficacy of intracisternal papaverine on symptomatic vasospasm]. *No Shinkei Geka* 14: 847-854, 1986 (Jpn)
- 12) Suzuki R, Nambu K: [Theory of xenon-CT], in Suzuki R, Segawa H (eds): [Clinical CBF Measurement by Xenon-CT]. Tokyo, Neuron, 1993, pp 11-29 (Jpn)
- 13) Touho H, Karasawa J, Ohnishi H, Shishido H, Yamada K, Shibamoto K: Evaluation of therapeutically induced hypertension in patients with delayed cerebral vasospasm by xenon-enhanced computed tomography. *Neurol Med Chir (Tokyo)* 32: 671-678, 1992
- 14) Touho H, Ueda H: Disturbance of autoregulation in patients with ruptured intracranial aneurysms: Mechanism of cortical and motor dysfunction. *Surg Neurol* 42: 57-64, 1994

Address reprint requests to: H. Oyama, M.D., Department of Neurosurgery, Chukyo Hospital, 1-1-10 Sanjo, Minami-ku, Nagoya 457, Japan.