

## Opiate-Antagonist Reversal of Neurological Deficits —Experimental and Clinical Studies—

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**Abstract:** The proximal left  $M_1$  and the common trunk of  $A_2$  were clipped in 12 adult dogs. Naloxone was injected after placing the clips onto 6 dogs. Neither the systemic blood pressure nor the local cerebral blood flow were influenced by naloxone. In another group of 6 dogs with chronic right hemiplegia, naloxone proved passably effective in improving the hemiplegia. Eight patients with neurological deficits of various etiologies were administered levallorphan. The improvement in motor performance and/or elevation of mental activity was observed more or less in all but 2 of the patients. It was considered that the effect of opiate antagonists is based partially on the facilitation of synaptic transmission exaggerated by the arousal response.

**Key Words:** *opiate antagonist, naloxone, levallorphan, arousal response, sensory evoked potential (SEP)*

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### INTRODUCTION

In 1981, Baskin and Hosobuchi<sup>2</sup> first reported on three patients with neurological deficits of brain ischemia. Two of them showed transient but significant improvement in the deficits after intravenous (iv) injections of a small amount (0.4 mg) of naloxone, an opiate antagonist. Their report prompted many experimental and clinical studies of opiate antagonists on brain ischemia. Some studies<sup>2 3 5 12 16 21 22 24 26-28 32</sup> indicate negative data; others<sup>6 8 14 20 23</sup> indicate positive data.

In the present study, the effect of naloxone

on an ischemic model of dogs and cats, and the efficacy of levallorphan, an opiate antagonist available in Japan, were examined in 8 patients with various neurological deficits.

### MATERIALS AND METHODS

#### *Animal Experiments*

In acute experiments, 12 adult dogs were anesthetized with a 10 mg/kg intramuscular (im) ketamine injection, followed by artificial ventilation with  $N_2O$  and  $O_2$ , and immobilized by suxamethonium chloride. The proximal portion of the left  $M_1$ , and the common trunk of  $A_2$  were clipped through a transorbital approach on the left side. The blood pressure was continuously monitored through a catheter in the femoral artery, and

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$\text{PaO}_2$  and  $\text{PaCO}_2$  were periodically measured. The clips were kept on the arteries for two hours, and then removed for the following two hours. The experiment was completed in 4 hours after the clips were applied. Naloxone (2 mg/kg) was bolus injected through the femoral vein 45 minutes after placing the clips, followed by drop infusion at a constant rate of 2 mg/kg/hour in 6 dogs. In the other 6 dogs, used as controls, naloxone was not administered. A wide frontotemporal craniotomy of the left side was performed before the clipping, and sequential changes in the local cerebral blood flow (ICBF) were measured by the  $\text{H}_2$  clearance method every 30 minutes in three different cerebral cortical areas: the area fed only by the anterior cerebral artery, that fed by the middle cerebral artery and that fed by both of the arteries. The average sensory evoked potentials (SEP) of the left (ischemic) sensorimotor cortex were recorded with a SANEI Signal Processor 7T08. In chronic experiments,  $M_1$  of the left side and the common trunk of  $A_2$  were left clipped in the other 6 dogs. The efficacy of naloxone (10 mg/kg, iv) or levallorphan tartrate (5 mg/kg) on the neurological deficits was examined 1–5 days after the clipping.

In three adult cats, a right parietal craniotomy was performed with the dura opened under anesthesia as had been done with the dogs. SEPs of the right sensorimotor cortex responsive to contralateral median nerve stimulation were recorded. A small-diameter catheter was stereotactically passed into the lateral ventricle near Monro's foramen in order to introduce morphine-HCl. The influence of the intraventricular injections of morphine (1, 2 mg) and intravenous naloxone (25 mg) was examined.

#### *Clinical Studies*

Four male and 4 female patients between 39 and 78 years old with neurological disorders of various etiologies were included in the present study. Two cases (Cases 1, 8) were classified as symptomatic angospasm,

3 (Cases 4, 5, 6) as stroke, one (Case 2) as accidental obstruction of the proximal  $M_1$ , one (Case 3) as brain edema after a tumor removal, and one (Case 7) as contusional hematoma. Computed tomographical (CT) examinations demonstrated low-density areas in all these patients. Levallorphan tartrate, as naloxone is not available for clinical use in Japan, was injected intravenously in a bolus of 1 or 2 mg. The interval between the onset of the neurological deficit and the injection of the drug varied from 2 to 61 days. In 2 patients, 1 mg and then 2 mg of the drug were injected, and in the others a physiological saline solution was used as a placebo. The efficacy of the drug on various neurological deficits and/or mental status of the patients was confirmed by more than three examiners. The condition of the patients was recorded with 16 mm movies. In Cases 1, 2, 7 and 8, SEPs from the scalp on the affected side responsive to contralateral median nerve stimulation were recorded. A topographical analysis of electroencephalograms was also done before and after the administration of levallorphan in Case 8.

## RESULTS

#### *Animal Experiments*

There was no definite trend in changes of the systemic blood pressure responsive to the naloxone injection. In 2 of the 6 dogs, no change was observed at all; 2 showed a slight and transient elevation of the blood pressure upon receiving the bolus injection, and in the other 2, an elevation by 20–30 mmHg lasting about 10 minutes was observed. The sequential changes in the ICBF of the 6 dogs receiving naloxone as well as the other 6 dogs not receiving naloxone (control) in the cortical area of the anterior cerebral arterial territory are shown in Fig. 1A. The ICBF decreased to 20 ml/100 g/min immediately after the clipping and remained at that level until the clips were removed. The removal of the clips was fol-

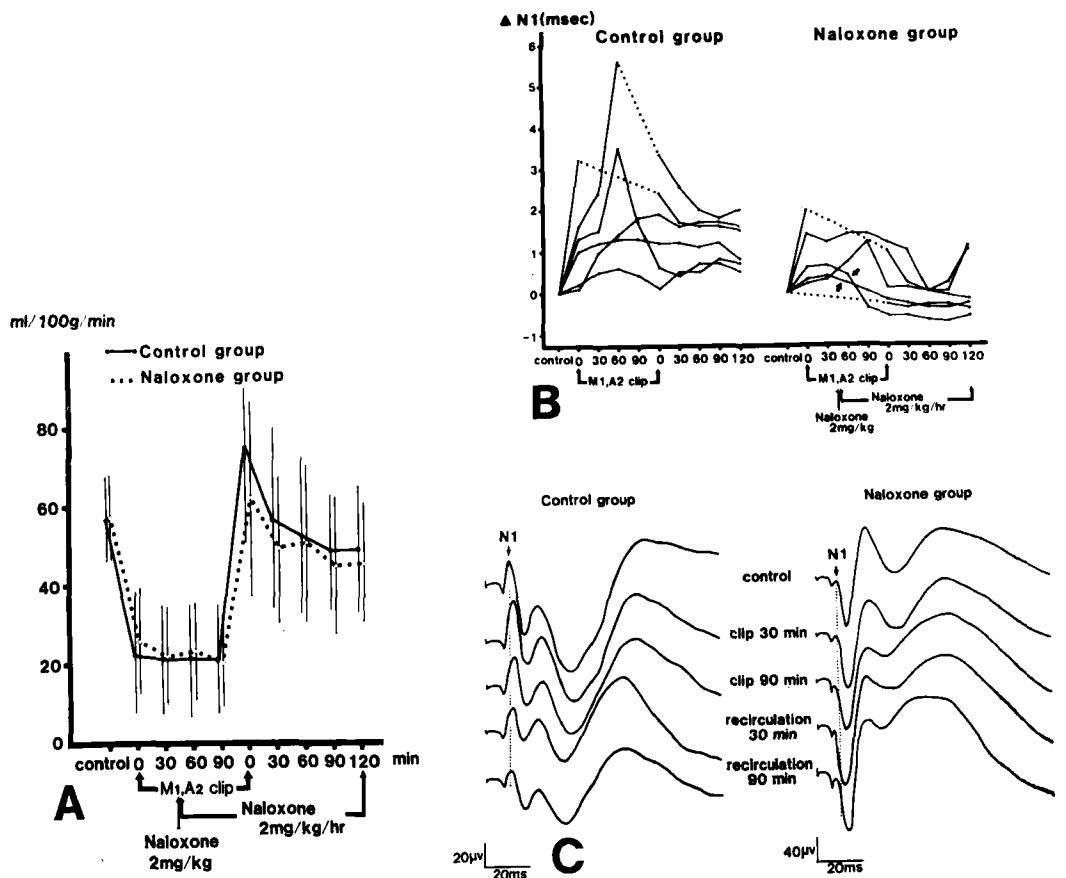


Fig. 1: A. Sequential changes in the cortical ICBF in dogs. There were no significant differences between the naloxone injected group (.....) and control group (—). B. Sequential changes in  $\Delta N_1$  (time difference in the  $N_1$  peak latency before and after clipping) of SEPs responsive to contralateral median nerve stimulation. The dotted line shows the period during which SEPs had disappeared. The  $N_1$  latency in the naloxone group returned to near the original level about an hour after circulation was restored, but not in the control group. Arrows indicate the two dogs whose  $N_1$  latencies were shortened even in the ischemic period. C. An example of sequential changes in the  $N_1$  latencies in both groups.

lowed by a hyperperfusion and then a return to the base level within an hour. No significant difference in the ICBF was found between the naloxone group and the control group. The same results were obtained from the cortical area fed by  $M_1$  as those from the area fed by both  $M_1$  and  $A_2$ . The changes in the peak latency of the first negative wave ( $N_1$ ) are shown in Fig. 1B and C. Even while the clipping continued, the

latency was shortened in 2 of the 6 dogs after the naloxone administration (arrows in Fig. 1B). In the other 2 dogs, the  $N_1$  latencies were not shortened by naloxone. In the remaining 2 animals,  $N_1$  disappeared while they were being clipped. There was a tendency for the  $N_1$  latency to be reversed soon after the circulation was recommenced in the naloxone group. In contrast, the latency never recovered by the end of the experiment

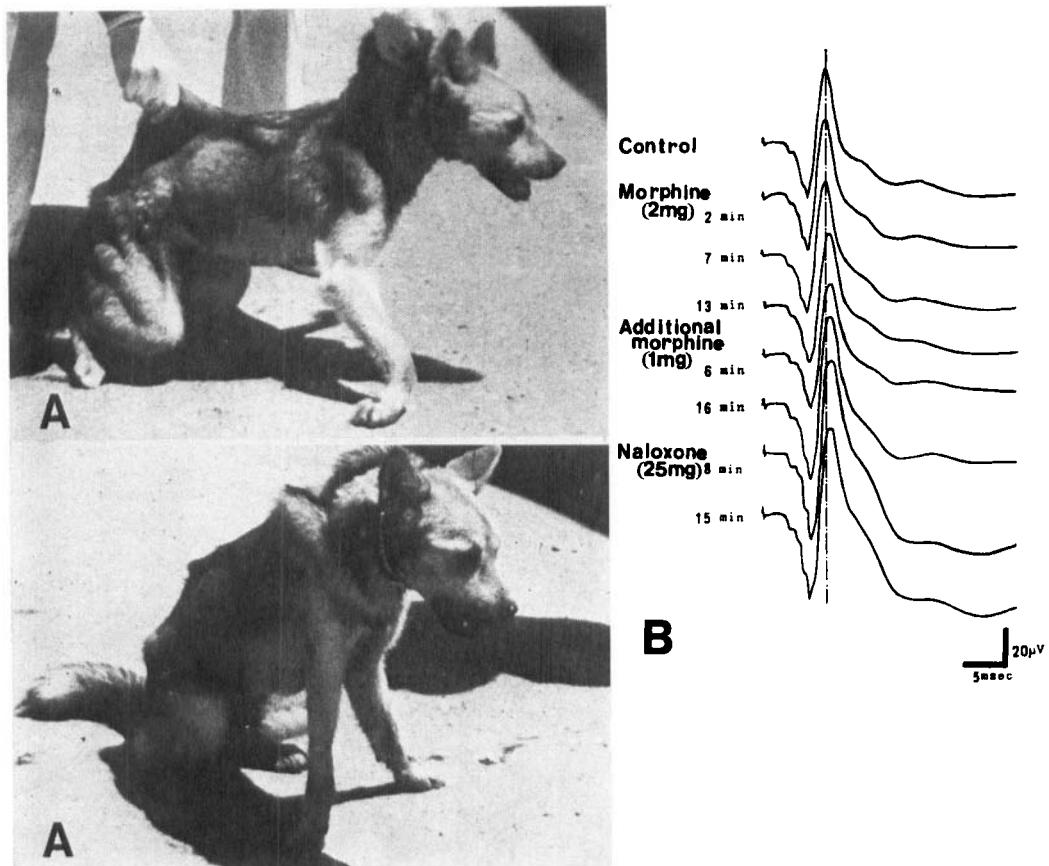


Fig. 2: A. Effect of naloxone (10 mg/kg, iv) on hemiplegia produced by applying clips to the left M<sub>1</sub> and common trunk of A<sub>2</sub>. The dog could stand up after naloxone, but with a different posture from the normal in that the leg was not bent. The bottom photograph shows the extension of the forefoot. The upper photograph shows the dog before receiving naloxone. B. Effect of intraventricular morphine and intravenous naloxone injections on SEPs in cats. Morphine significantly prolonged the N<sub>1</sub> peak latency. Naloxone (25 mg) did not reverse the prolonged latency.

in the control group even after the circulation was restored.

In the chronic experiments, all of the 6 dogs developed nearly complete hemiplegia. Naloxone (10 mg/kg) or levallorphan (5 mg/kg) incompletely reversed the hemiplegia, especially of the forefoot (Fig. 2A). The effect of the drugs was not dramatic. Increased muscle tone was observed. The dogs extended their legs stiffly straight to maintain a standing posture, not taking the normal slightly-flexed position of the limbs.

The peak latency of the first predominant

negative wave of SEP in the cats was prolonged by a few milliseconds after the intraventricular morphine injection. However, this prolongation was not reversed by a 25 mg naloxone injection intravenously (Fig. 2B).

#### *Clinical Results (Table 1)*

Case 1: K.H.

A 57-year-old female suddenly developed severe occipitalgia on May 1, 1984, and was diagnosed as a subarachnoid hemorrhage. A

Table 1: Patients to Whom Levallophan, an Opiate Antagonist, Was Given

Case No	Initials	Age/ Sex	Original disease	CT or angiographic findings/Neurological deficits	Days* after onset	Dosage (iv) of Levallophan	Notable neurological changes
1	K.H.	57/F	aneurysm (1t MCA)	Angiospasm LDA (1t temporal) rt hemiparesis aphasia	13 days	2 mg	Motor function (arm) improved, aphasia improved
2	M.I.	40/M	AVM (1t frontoparietal)	MCA obstruction, LDA (1t fronto-temporoparietal) rt hemiparesis aphasia	23 days	1 mg	writing faster (with 1t hand), rt hemiparesis improved (especially lower limb)
3	M.T.	39/M	Postoperative edema (1t parietal tumor)	LDA (1t white matter) rt hemiparesis	38 days	2 mg	Same as above
4	S.K.	70/F	Stroke	LDA (1t fronto-temporoparietal) rt hemiparesis mutism, akinesthesia	23 days	1 mg	Slight improvement of motor function (rt upper limb)? irritable sensation
5	M.K.	78/F	stroke (1t)	LDA (1t internal capsule and basal ganglia)	2 days	1 mg	Awaking response (open eyes, moving non-hemiplegic limbs incessantly), withdrawal response of hemiplegic (right) upper limb
6	M.S.	73/F	stroke (1t)	LDA (1t anterior thalamus, 1t temporal) rt hemiplegia, aphasia	10 days	1 mg	Gazing and watching the examiner's movement
7	T.S.	49/M	aneurysm (AcomA, ACA) AVM (1rt)	LDA (1t anterior thalamus, 1t temporal) rt hemiplegia, aphasia	7 days	1 mg	No change at all
8	H.I.	62/M	angiopasm, junctional dilatation (rt IC-PC)	LDA (1t white matter) rt hemiplegia	61 days	2 mg	No change at all

\*: The period between the appearance of neurological deficits and the administration of levallophan.

LDA: Low-density area.

Effective: Any kind of objective improvement, nevertheless remarkable or less remarkable, was detected.

Equivocal: Objective improvement was very slight with predominant subjective effect (Case 3); Determination of effectiveness remained some equivocation (Case 5).

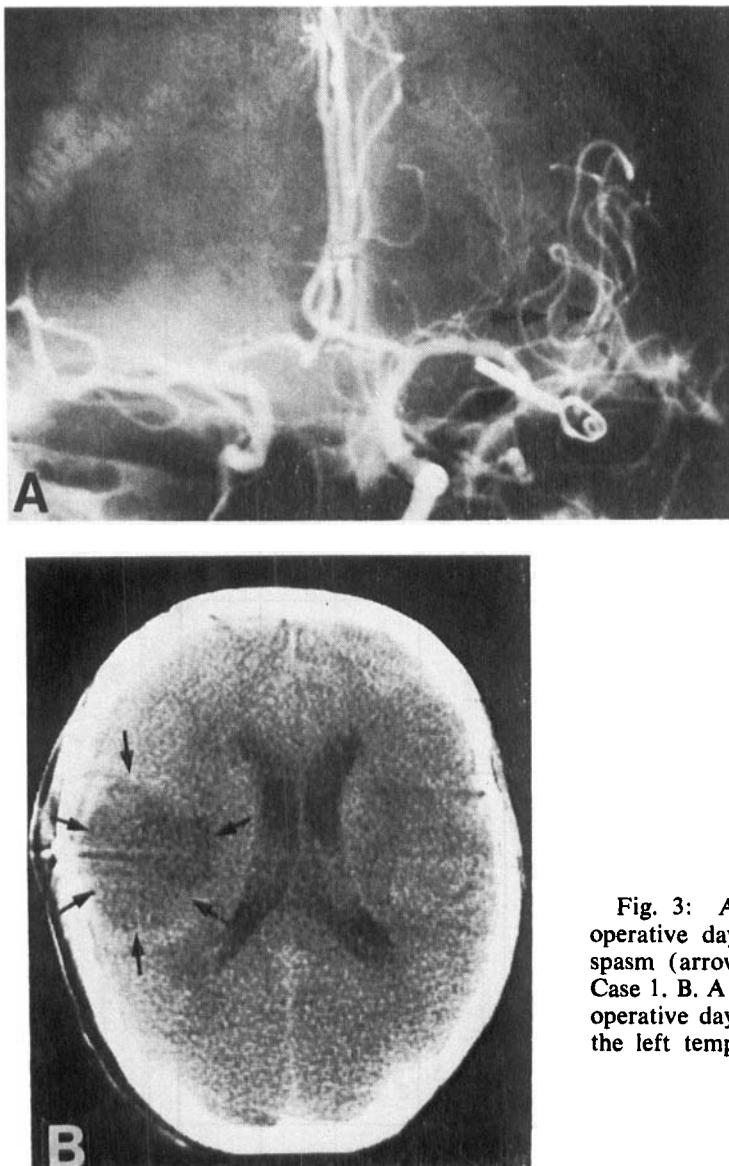


Fig. 3: A. Left CAG on the 10th post-operative day, demonstrating diffuse angiospasm (arrows) distal to the M<sub>1</sub> portion in Case 1. B. A plain CT scan on the 14th post-operative day revealed a low-density area in the left temporal region.

carotid angiography disclosed an aneurysm of the left middle cerebral artery. She was transferred to our neurosurgical clinic the following day. No neurological abnormalities were found except for moderate nuchal rigidity. Neck clipping was performed on the day of admission. The postoperative course was uneventful until May 10, when the left carotid angiography (CAG) was done. A diffuse angiospasm distal to the M<sub>1</sub> portion was demonstrated (Fig. 3A). The patient's

condition gradually deteriorated. Right hemiparesis, sensory and motor aphasia became apparent following a few days. She could only move her forearm on the right side. A plain CT scan on the 14th postoperative day revealed a low-density area in the left temporal region (Fig. 3B). Levallorphan (2 mg) was administered (iv) 13 days (May 25) after the appearance of hemiparesis and aphasia. She was able to raise her right arm more promptly than before 5 minutes after

the injection. A motor performance of the lower limb did not seem to be effective. The aphasia slightly improved as the motor effect became apparent. She could only say a single word such as "pencil" or "watch." These effects were transient continuing only for about 10 minutes. An injection of saline failed to show any neurological change. SEPs were recorded before and after levallorphan, but no reliable record was obtained because of artifacts.

#### Case 2: M.I.

A 40-year-old male was admitted on January 11, 1984. He had had an episode of unconsciousness associated with right hemiparesis in February, 1980. The hemiparesis improved in a few months, but he developed frequent attacks of Jacksonian-type convulsions. An angiography on admission demonstrated an arteriovenous malformation (AVM) mainly fed by the ante-

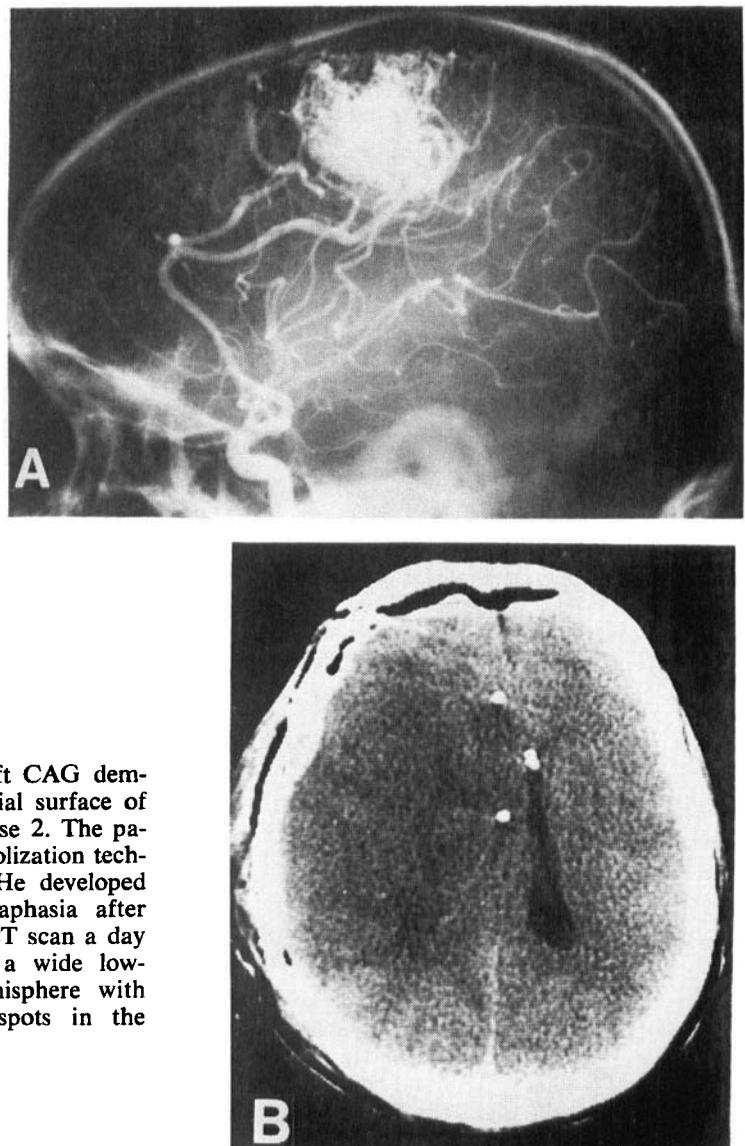


Fig. 4: A. Preoperative left CAG demonstrates an AVM in the medial surface of the frontoparietal region in Case 2. The patient was treated with the embolization technique using silicone spheres. He developed right hemiplegia and motor aphasia after the embolization. B. A plain CT scan a day after the embolization. Note a wide low-density area in the left hemisphere with severe brain edema. White spots in the brain are silicone spheres.

rior cerebral artery in the median surface of the left frontoparietal region (Fig. 4A). A neurological examination revealed a slight hemiparesis of the right side with no other abnormalities. An embolization of the AVM using silicone spheres was performed on March 27, after a large frontotemporal

craniotomy with the most proximal portion of  $M_1$  being clipped temporarily. The AVM was successfully obliterated, but the patient developed complete motor aphasia and right hemiplegia. A CT scan a day after the embolization revealed a wide low-density area with severe brain edema (Fig. 4B); there-

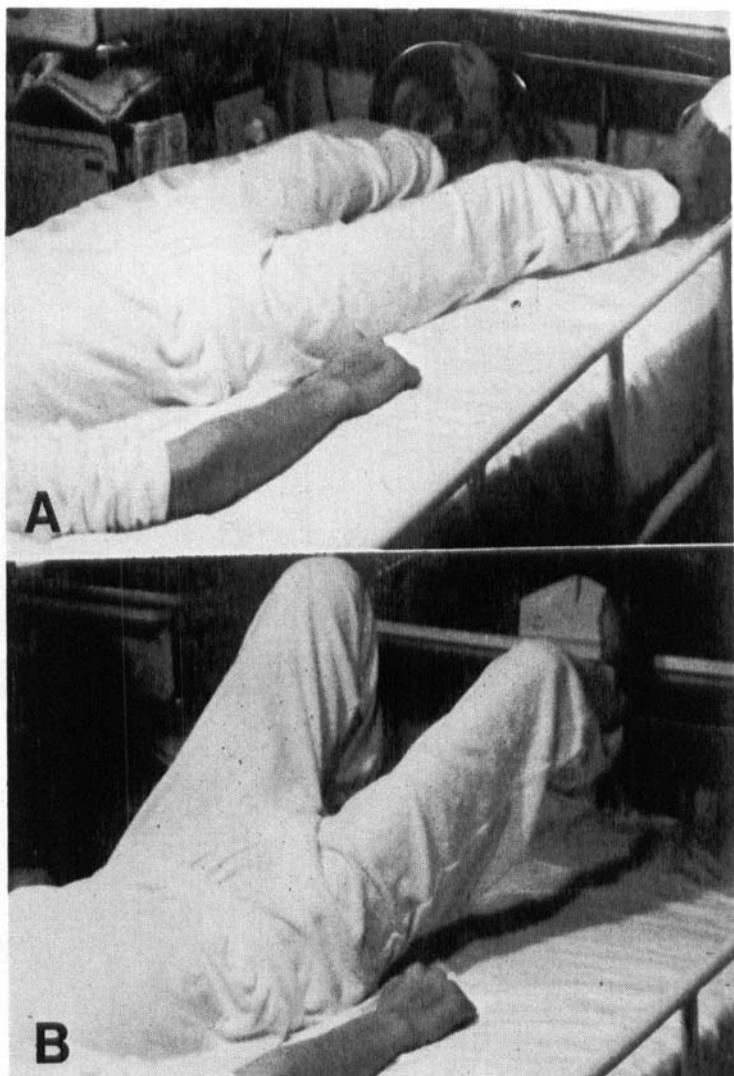


Fig. 5: Effect of levallorphan (1 mg) in Case 2. A: The patient was hardly able to flex his right knee by himself before levallorphan. B. He was able to flex his right knee, raise the lower limb and hold it in a position from 7 to 20 minutes after the injection. The effect on the motor performance of the upper limb was very slight.

fore, external decompression was done on the same day. One of the spheres was found to have obliterated the proximal middle cerebral artery. The right hemiplegia had shown a tendency to improve gradually when levallorphan (1 mg) was injected on April 20 (23rd postoperative day). He was able to write with his non-hemiplegic left hand significantly faster than before after the levallorphan injection. Neither motor aphasia, right and left disorientation, finger agnosia nor acalculia improved. He could not flex his right knee by himself before levallorphan. The motor function of his right leg definitely improved 7 minutes after the injection of the drug, which lasted 20 minutes (Fig. 5). The effect on the motor performance of the upper limb was slight, with the finger movement being slightly improved. Levallorphan was tried again on May 4 (38th postoperative day), with 2 mg of the drug. The efficacy was the same as the previous time, although the effects appeared 2 minutes after the injection. No definite change in the SEP patterns was detected by the drug injection.

### Case 3: M.T.

A 39-year-old male first had an attack of the right hemiconvulsion in May, 1984. The attacks gradually became associated with the transient postictal palsy. A left parietal tumor was demonstrated on a CT scan, and he was transferred to our clinic on July 27. A neurological examination revealed slight motor and sensory disturbances of the lower right limb. The CT scan demonstrated a round enhanced mass in the left parietal region. A wide frontotemporoparietal craniotomy was performed on August 21, and the tumor was subtotally removed. The skull was left removed. A histological diagnosis indicated glioblastoma multiforme. The patient developed a slight hemiparesis of the right side postoperatively. The hemiparesis became nearly a complete hemiplegia after a hemiconvulsion which attacked him on the 5th postoperative day. The hemiplegia, how-

ever, tended to improve slowly after the attack. A postoperative CT scan on September 5 (15th postoperative day) demonstrated a diffuse low-density area of the white matter (Fig. 6A). Levallorphan (1 mg) was administered on September 19. He was able to raise his right arm slightly higher than before 2 minutes after the injection (Fig. 6B). The effect lasted for about 10 minutes, but was considered equivocal. The muscle tone was ascertained to be elevated in the upper right limb. The patient vehemently complained of a very irritable sensation, and said it was very difficult to suppress his emotion, driving him to do something after the injection. He, therefore, refused a reexamination.

### Case 4: S.K.

A 70-year-old female began to develop progressive right hemiparesis on July 28, 1982. She was admitted 2 days later. On admission, she was in a state of drowsiness, mutism and akinetic. There was a nearly complete hemiplegia of the right side. The patient took an extensive posture in the upper limb, but a withdrawal movement in the lower limb on painful stimuli. A CT scan on admission demonstrated a wide low-density area in the left frontotemporoparietal region, associated with mild brain edema (Fig. 7A). An angiography was not done. Levallorphan (1 mg) was injected on the day of admission. She spontaneously began to keep both eyes open 2 minutes after the injection. She moved the nonhemiplegic upper left and lower limbs incessantly, trying to wear her clothes neatly at the same time. She grasped the examiner's hand with her left (non-hemiplegia) hand in response to an order, but it did not seem that she understood the examiner's words because she did not obey any other orders. On painful stimuli of the upper right limb, a withdrawal movement was seen with a prompt flexing of the wrist and elbow joints. The lower right limb showed a withdrawal movement in response to a weaker pain than before the injection.

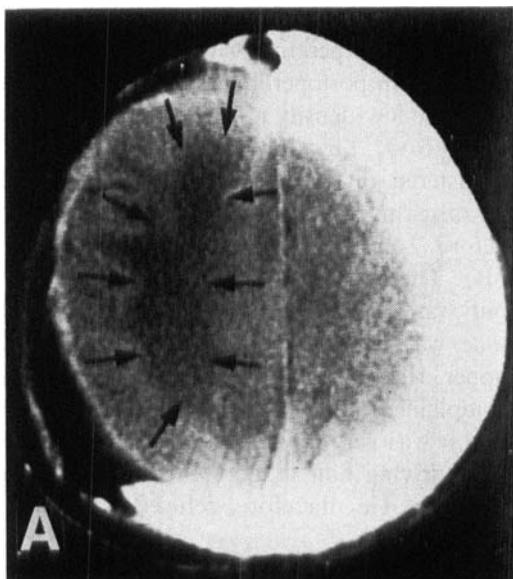
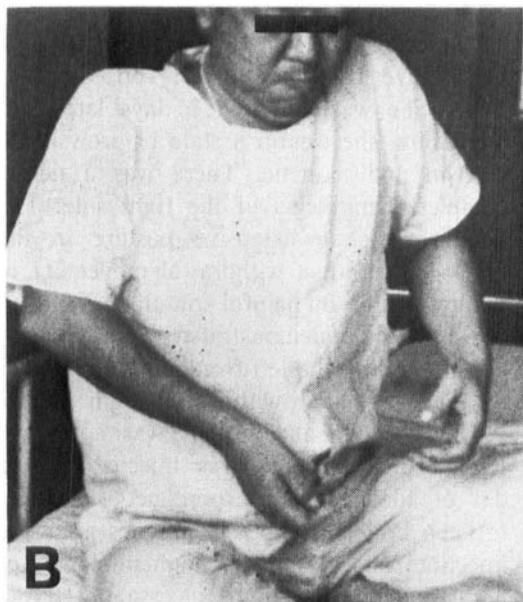


Fig. 6: A. A plain CT scan on the 15th postoperative day, demonstrating a diffuse low-density area in the white matter of the left side in Case 3. B. Levallophan (1 mg) was injected. He could raise his right arm slightly higher after the injection (right side) than before (left side). Muscle tone of the limb increased after naloxone in this case.



These effects continued for about 10 minutes, and then returned to the previous state. One hour after the first injection, 2 mg of levallophan was again administered with the same effect. A placebo (saline) injection showed no effect.

#### Case 5: M.K.

A 78-year-old female developed right hemiparesis on July 29, 1984, but completely recovered in a few hours. However, gradually increasing motor disturbances of the upper right and lower limbs again appeared

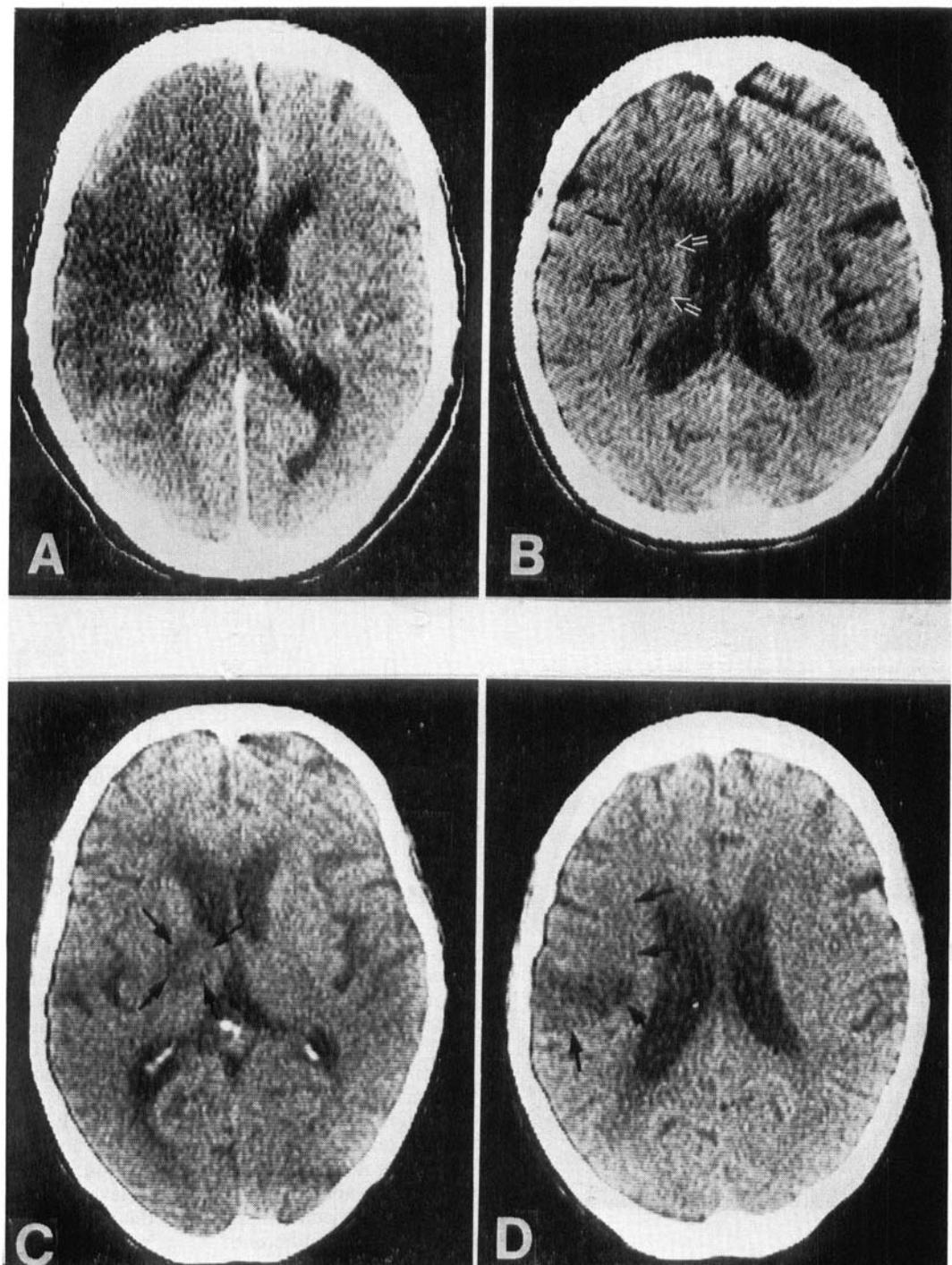


Fig. 7: CT scans at admission of Case 4 (A), Case 5 (B) and Case 6 (C, D). They all demonstrated low-density areas of various sizes and locations.

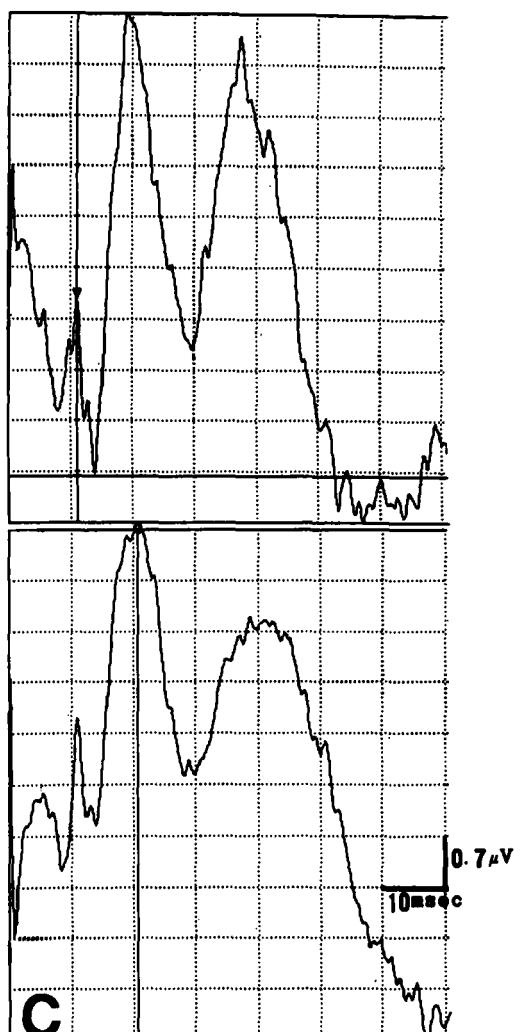
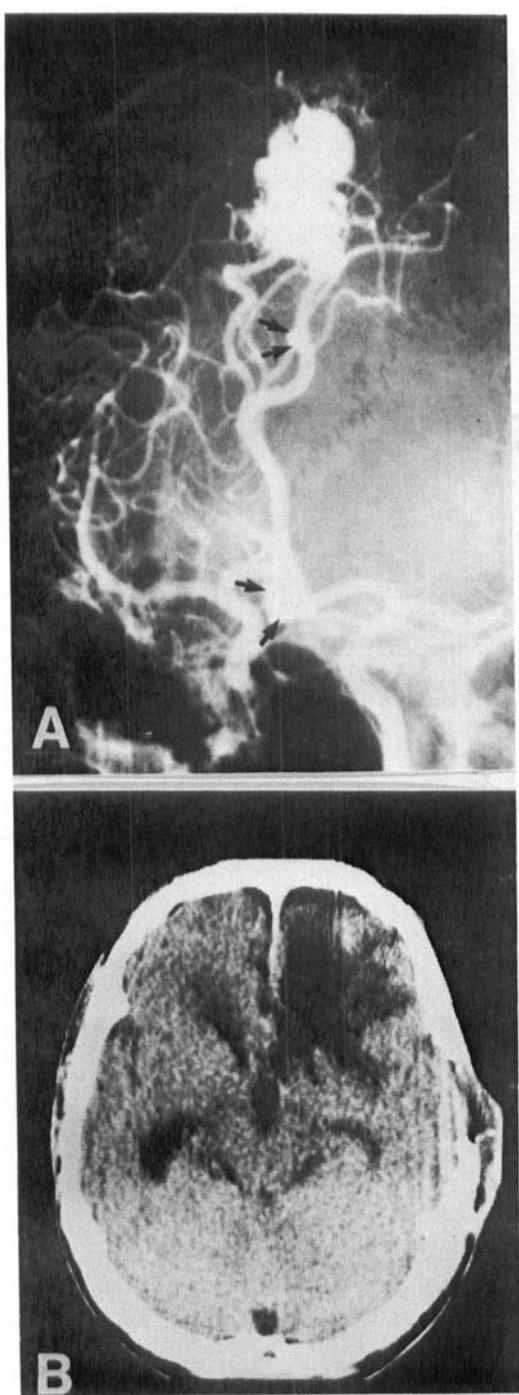


Fig. 8: A. Preoperative right CAG demonstrating an AVM in the right parietal region, an AcomA aneurysm (lower arrows) and a distal anterior cerebral arterial aneurysm (upper arrows) in Case 7. B. A CT scan after removal of the contusional hematoma which was caused by a previous operation of AVM removal. C. The SEP pattern on the central scalp, responsive to contralateral median nerve stimulation before (upper) and after (lower) the levallorphan (2 mg) injection, was not thought to be significantly different.

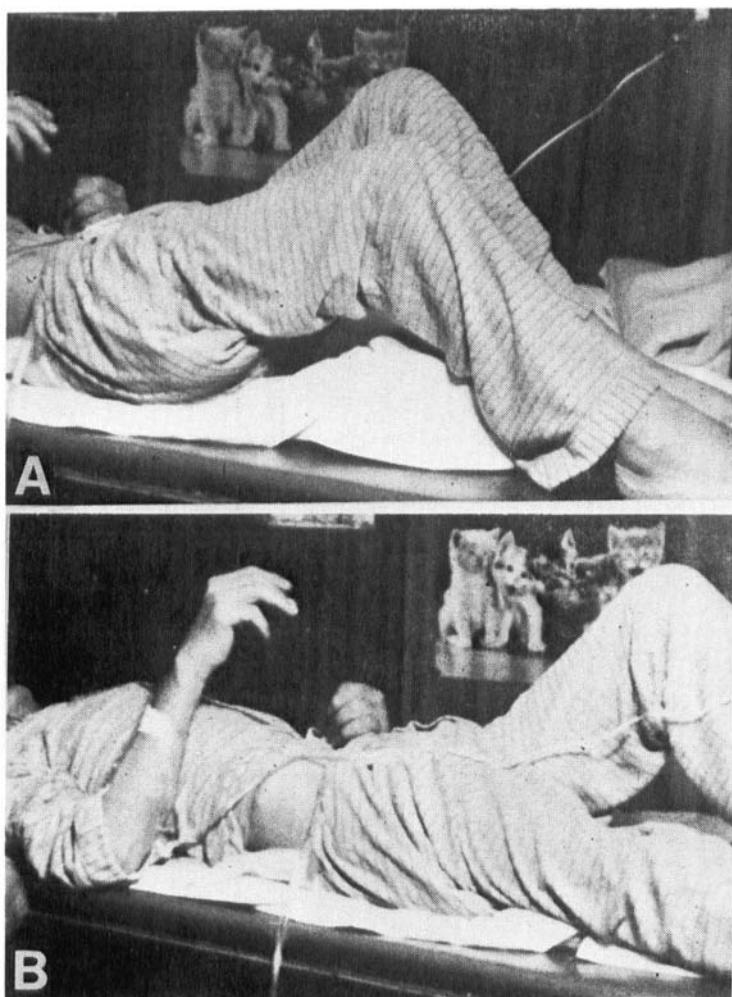


Fig. 9: Effect of levallorphan (2 mg) on the motor performance in Case 7. A. He could not flex his left knee by himself, and could not keep the flexed position before levallorphan. The picture shows the left knee passively flexed, with the flexed position being kept with the help of the right leg. B. He was able to flex his left knee by himself and hold the position without the help of the right leg after levallorphan.

the next evening. She was admitted on July 31, with a complete right hemiplegia and total aphasia. Both her eyes were closed, and she appeared akinetic. A CT scan on admission demonstrated a low-density area in the left internal capsule, probably including the upper portion of the thalamus as well as the basal ganglia (Fig.

7B). An angiography was not done. Levallorphan (1 mg) was injected on August 7. No motor effect was seen, but she spontaneously opened both eyes widely 5 minutes after the injection, and followed the examiner's movements throughout the following 10 minutes. An injection of saline one hour later did not produce such changes.

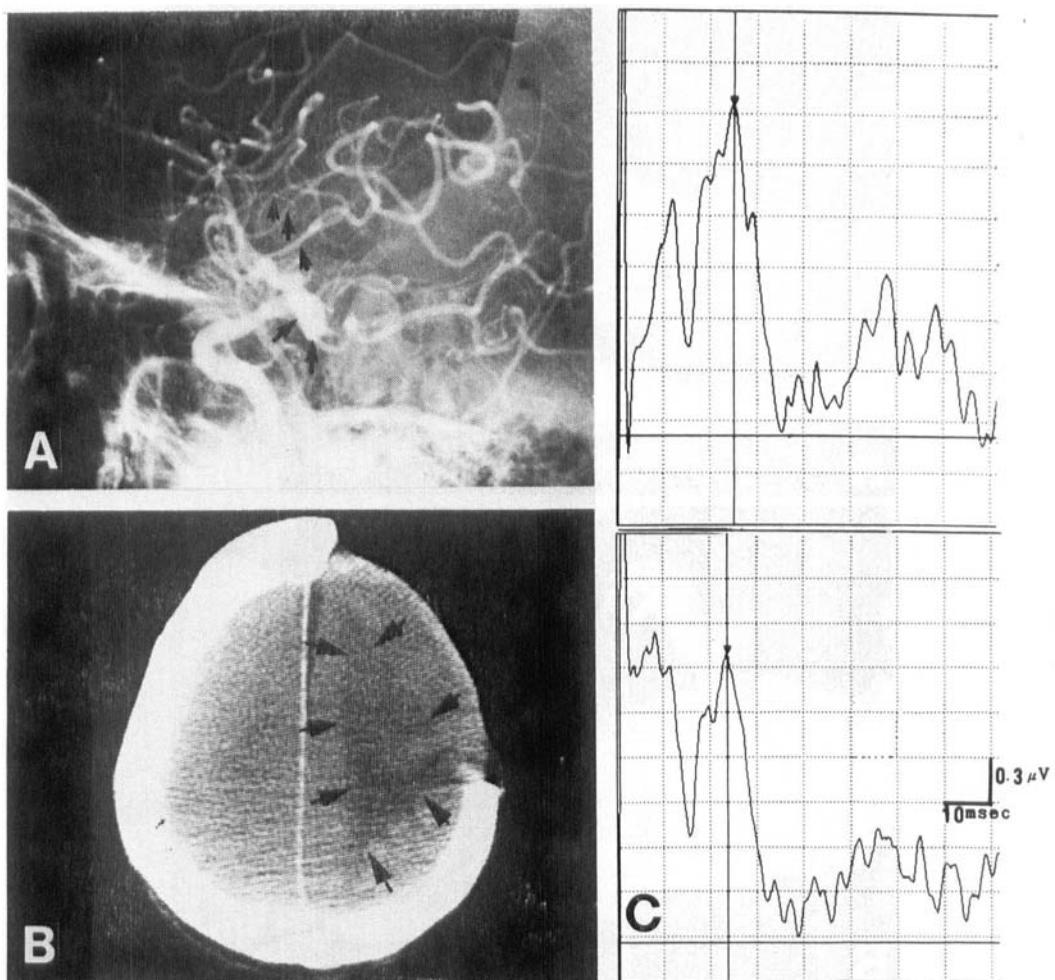


Fig. 10: A. Right CAG of Case 8 taken on the 9th postoperative day demonstrating a large junctional dilatation (lower arrows) which was completely wrapped, and angiospasm of the  $M_3$  portion (upper arrows). B. A CT scan demonstrates a wide low-density area in the right white matter. C. The SEP pattern was not seem to be significantly changed between before (upper) and after (lower) levallorphan.

#### Case 6: M.S.

A 73-year-old female developed right hemiparesis on November 14, 1984. She was admitted on November 21, when she was found to have a right hemiplegia associated with incomplete sensory and motor aphasia. She seemed to be well oriented. A CT scan on admission revealed a round low-density area in the anterior thalamus, as well as a wide low-density area in the temporal re-

gion of the left side (Fig. 7C, D). An angiography was not attempted. Levallorphan (1 mg) was injected on the day of admission, but it did not produce any effect.

#### Case 7: T.S.

A 49-year-old male suddenly developed unconsciousness on November 4, 1984. He was admitted to our neurosurgical clinic on November 7, when he was drowsy and tetraparetic. A carotid angiogram (CAG)

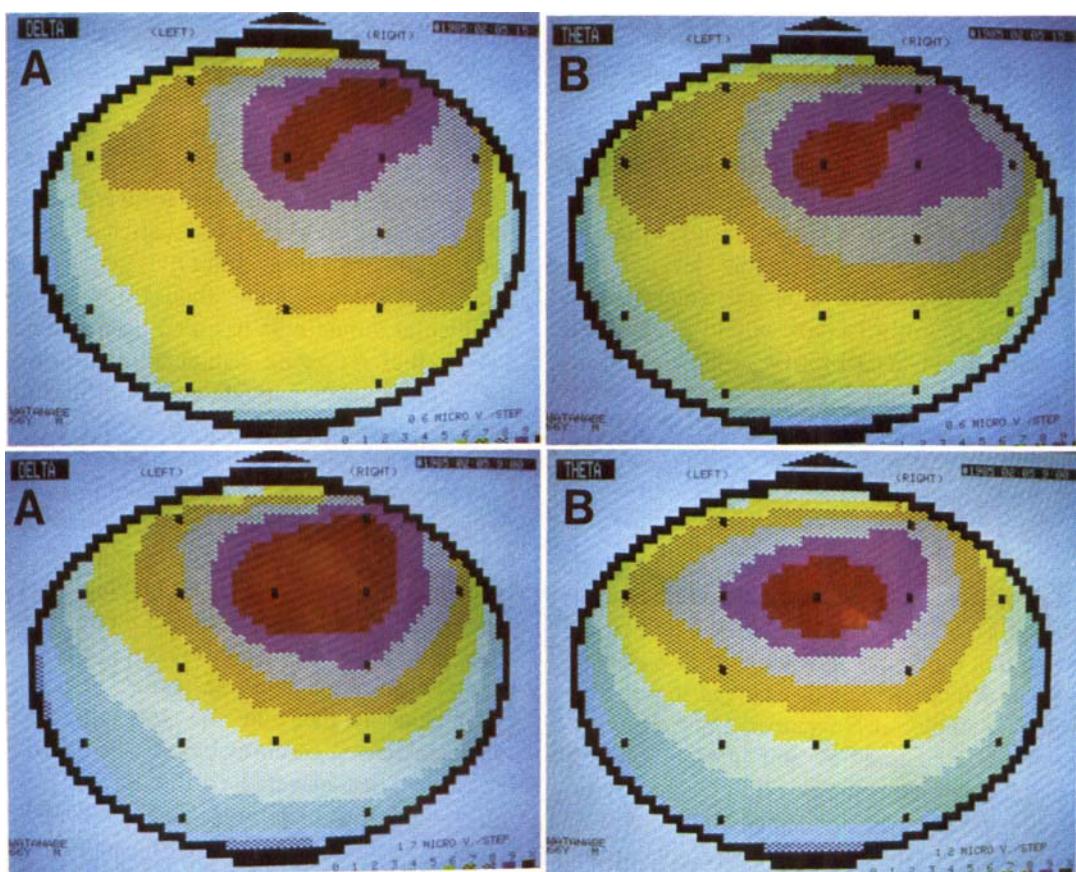


Fig. 11: A topographical distribution of  $\delta$  (A) and  $\theta$  (B) waves before (upper) and after (lower) levallorphan in Case 8. There seemed to be no notable changes in the distributions of both waves between before and after levallorphan.

revealed an AVM in the medial surface of the right parietal region, associated with aneurysms of the anterior communicating artery (AcomA) and the distal anterior cerebral artery (Fig. 8A). A CT scan on admission suggested that the unconsciousness attack was caused by an AcomA aneurysmal rupture. The aneurysm reruptured on November 20, and an emergency wide frontotemporal craniotomy was performed with a successful neck clipping. The bone flap was left removed. The consciousness level gradually improved to be alert with residual left hemiparesis. On December 13, the total removal of the AVM was performed. A post-

operative angiography revealed the disappearance of the AVM. However, CT scans showed a contusional hematoma in the right frontal lobe. He became completely hemiplegic on the left side with full consciousness after this operation. Cranioplasty as well as evacuation of the intracerebral hematoma was done on January 17, 1985. Fig. 8B shows a CT scan after the hematoma evacuation. He was alert but moderately disoriented with a nearly complete hemiplegia. Levallorphan (2 mg) was injected on January 30. Three minutes later, he was able to flex his lower left limb by himself and hold on to that position, which he could not do

before (Fig. 9). There was a slight improvement in the arm movement as well. He seemed to be slightly depressed and withdrawn during the examination. Tachycardia was seen, the pulse rate being about 100/min; all these changes lasted for about half an hour. The SEP patterns on the right parietal scalp were not significantly different between before and after the levallorphan injection (Fig. 8C). This particular patient was able to fully flex or extend his left leg by himself the next morning following injection to the surprise of his family and the medical staff. He also became active in other aspects, speaking to anyone and actively responding to orders.

#### Case 8: W.I.

A 62-year-old male was found unconscious on November 11, 1984. He became alert the following day without any neurological deficit. He was transferred to our neurological clinic on November 29. An angiography demonstrated a right internal carotid-posterior communicating (IC-PC) aneurysm. An operation was performed on the day of admission. After a right frontotemporal craniotomy, a large junctional dilatation at the posterior communicating artery was found with a lot of coagula around it. It was completely wrapped with muscles. The skull was left removed. Postoperatively, he was alert, but he gradually developed a left hemiparesis, which was accelerated after an angiography was done on December 7. The angiography showed a diffuse narrowing of the M<sub>3</sub> portion (Fig. 10A). A CT scan on January 11, 1985, demonstrated a wide low-density area in the right white matter (Fig. 10B). A complete hemiplegia continued with full consciousness. Levallorphan (2 mg) was injected on February 5, but it produced no effect on the motor performance. An electroencephalographic (EEG) examination revealed no significant change between before and after the injection. A topographical analysis of EEG did not show remarkable changes either (Fig. 11). The

SEP patterns also did not seem to be changed before and after the levallorphan injection (Fig. 10C).

## DISCUSSION

Naloxone has been shown to decrease the mortality and morbidity rate after a spinal cord injury,<sup>10 11</sup> head injury,<sup>18</sup> hypotensive shock and hypovolemic shock<sup>9 17 19</sup> in experimental animals. It has also been demonstrated that naloxone significantly improves the vital signs in patients receiving electro-convulsive shock therapy.<sup>4</sup> In these reports, the authors postulated that the effect of naloxone was based on its antagonistic activity against the elevated opioid concentrations in these pathological conditions. A bolus and/or drip infusion of naloxone (1–10 mg/kg) elevated the systemic blood pressure, pulse rate and pulse pressure, and improved respiration in these studies. The improvement in the outcome was attributed to the increased cerebral blood flow (CBF) because of an elevated cardiovascular output volume and respiratory rate. In contrast to these reports, there was no consistent tendency for the systemic blood pressure to rise, and the ICBF did not significantly increase by naloxone in the present animal experiments. This discrepancy does not seem to be due to differences in the dose of naloxone administered. Although dogs were used in another study<sup>19</sup> and were injected with the same amount of naloxone as in our study, the result was different. The reason for the discrepancy is unknown, but it might be due to the difference in the experimental setup.

Levallorphan tartrate was used in our clinical study. It has a weak opiate-agonistic activity.<sup>28</sup> However, even naloxone shows agonistic effects when administered in large doses (more than 10 mg/kg).<sup>30</sup> Faden<sup>13</sup> cited Nehs' description that the efficacy of 20 mg/kg of naloxone was remarkably less than 2 mg/kg. Our present clinical study includes 6 patients with ischemic lesions, one of

whom developed brain edema after a tumor was removed and the other who underwent a hematoma evacuation. Levallophan (1, 2 mg) was a bolus injected during the period of 2 to 61 days after the appearance of neurological deficits. All of these patients had low-density areas of various sizes and locations at the time of the drug injection. All kinds of motor and/or mental changes were observed definitely or less definitely in all them. The efficacy of levallophan was transient, lasting up to 10-30 minutes after the injection. Concerning the clinical dose of opiate antagonists, Faden<sup>13</sup> indicated that 2-5 mg/kg of naloxone gave the maximum effect, and criticized the ordinal clinical dosage (0.4-1.2 mg) as being far less than necessary. He also indicated that the usual timing of the drug administration was too late. We considered 2 mg of levallophan, which has a weak opiate agonistic activity, a safe dosage to examine the drug's effect in patients. As for the timing of the injection, the administration 8 weeks after the ischemic attack reversed the hemiparesis in one patient in a study by Baskin,<sup>2</sup> and another study<sup>24</sup> has indicated the efficacy of the drug 36 days after the ischemic attack. In the present series, 2 mg of levallophan administered 47 days after the appearance of neurological deficits proved effective (Case 7). The motor performance of paretic or paralytic limbs improved transiently more or less after the drug injection in four patients (Cases 1, 2, 4, 7). In Case 3, a slight improvement in the motor performance was highly regarded as a result of the increased muscle tone. Gaines<sup>16</sup> has warned against misinterpreting the increased muscle tone after the treatment as a motor improvement. Baskin<sup>2</sup> described such increased muscle tone in one of his patients. Increased muscle strength in dogs in our experiment after naloxone was apparently considered to be the elevated muscle tone as well. Another predominant aspect of the clinical effect of levallophan in our study was the arousal response seen in Cases 3, 4 and 5. The

ability of Case 2 to write faster than before the treatment with his non-hemiplegic left hand might be interpreted as a kind of arousal response. Cutler<sup>8</sup> found such arousal response with naloxone, but also reported 2 patients with an adverse mental effect, namely, depression. In this series, only one patient (Case 7) seemed to be mentally depressed and withdrawn for about one-half hour, in spite of an improvement in the motor performance. It was peculiar that the motor function of the hemiplegic lower limb had remarkably improved and the patient became very active in speaking and moving the next morning in this case. The effect of a single bolus injection of the opiate antagonist to continue for more than one hour has never been reported. Thus, the improvement in this patient was considered to be the result of mental activation, which might have been triggered by levallophan. However, no rational explanation for this could be given.

The concentration of  $\beta$ -endorphin in the cerebrospinal fluid (CSF)<sup>2 15 32</sup> as well as the brain tissue<sup>2 22</sup> has been shown to increase after ischemic attacks in humans and animals. Hosobuchi<sup>22</sup> indicated a 40-80% increase in the ischemic hemisphere of gerbils in the acute stage. It is believed that opiates inhibit the synaptic transmission.<sup>7 23</sup> Naloxone or levallophan antagonizes the action of opiates<sup>23</sup> thus facilitating the synaptic transmission. This action of the opiate antagonist appeared to have been proven in our present acute experiments on dogs. Naloxone shortened the  $N_1$  latency even in the ischemic period while applying the clips to two dogs, and a reversal of the  $N_1$  latency to the original level was seen only in the naloxone group, not in the control group. The  $N_1$  latency of SEPs in our experimental cats was prolonged significantly by morphine, which is a representative opiate, but this prolongation was not reversed by 25 mg of naloxone. The ineffectiveness of naloxone in this experiment might be attributed to too high a dose of the drug<sup>13 30</sup> for a cat.<sup>13</sup> As much as 25 mg naloxone

might have contributed to be an opiate agonist, but the actual reason for this is uncertain. A SEP analysis responsive to contralateral median nerve stimulation was done in 4 patients (Cases 1, 2, 7, 8) in the present clinical study. Reliable records were obtained in Cases 2, 7 and 8. In all of them, no significant changes were observed, in spite of having clinical effects of the drug on Cases 2 and 7. This might be partially due to the inconsistency of the SEP patterns according to the patient's mental and physical conditions. Hence, the analysis of SEPs in the clinical cases might not be so reliable. Some reports<sup>5 12 13</sup> have indicated improved EEG or SEP patterns after a naloxone injection in humans or experimental animals, but others<sup>8 23</sup> have indicated no change. There are also conflicting results in the literature concerning the effect of naloxone on the cerebral blood flow (CBF) in the patients with cerebral ischemia and ischemic animal models. Some reports<sup>11 18 19 21 28</sup> have indicated that CBF did increase, but others have indicated that it did not.<sup>3 16 23</sup> In one of Baskin's<sup>2</sup> patients, CBF did not increase, in spite of a remarkable neurological improvement. Baskin<sup>3</sup> also found that the elevation of the systemic blood pressure and of the cardiac output volume induced by isoproterenol did not lead to an improvement in the neurological deficits. Further, Levey<sup>27</sup> indicated that CBF in the ischemic hemisphere in cats made by a middle cerebral artery obliteration did decrease by 20% after 2 mg/kg of naloxone was injected, in spite of the ischemic neurological deficits being reversed. He suggested that the neurological improvement was made by the transfer of blood from the non-functioning area to the healthy part of the brain. Levey<sup>27</sup> also found, using a nuclear magnetic resonance imaging technique, that the metabolic rate did not change in the ischemic area after 2 mg/kg of naloxone. However, in the basal ganglia, including the substantia nigra, red nucleus and periaqueductal gray, the metabolic rate had remarkably increased.

The effect of opiate antagonists may be at least partially based on their arousal activity. There are many opiate receptors in the basal ganglia and brain stem<sup>25 29</sup> to which the opiate antagonists may bind and thus modulate the mental status. Opiates have been described in relation to the mood and memory in psychiatric patients.<sup>31</sup> And as Levey<sup>26 27</sup> pointed out, an elevation of the metabolic rate in the basal ganglia and some mesencephalic nuclei may play an important role for the arousal response. On the other hand, the effect of opiate antagonists may be elicited by the improvement in the synaptic transmission in the acute ischemic stage, when the  $\beta$ -endorphin concentration has been increased. There is further the possibility that the synaptic transmission may be facilitated in the penumbra<sup>1</sup> even in the chronic stage. An improvement in the motor performance might be exaggerated by the arousal response such as seen in the present study. An elevation of the systemic blood pressure or ICBF did not seem to be indispensable to neurological improvement. Further studies are needed to clarify the mechanism of efficacy of opiate antagonists.

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