The Treatment of Brain Ischemia With Vasopressor Drugs

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Abstract: Vasopressor drugs were administered to 13 patients soon after the development of focal brain ischemia even though there was no significant decrease in their blood pressure. The neurological function of five patients improved following an increase of their blood pressure to levels of 150 to 170/85 to 100 mm Hg. Focal brain dysfunction recurred whenever the blood pressure was allowed to fall to the initial level during the immediate postinsult period. Significant recovery was maintained in three of these five patients; neurological function in these three did not deteriorate when the blood pressure was allowed to fall to levels of 90/60, 100/70 and 120/80, respectively, after the immediate postischemic period. The critical blood pressure level required for improvement of brain function during the ischemic episode was not lowered by simultaneous treatment with low-molecular-weight dextran, hyperosmotic agents, dexamethasone and aminophylline in case 1 or by treatment with papaverine in case 3.

ADDITIONAL KEY WORDS brain circulation cerebrovascular disease norepinephrine brain infarction transient ischemic attacks stroke

Denny-Brown1 was probably the first to note that improvement of neurological function following a brain ischemic episode is often associated with a rise in blood pressure. Regional cerebral blood flow measurements have shown that a slight increase in aortic blood pressure will produce an increase in blood flow in the involved brain region following a transient ischemic episode while it has no effect upon blood flow in brain regions where vasomotor autoregulation has not been disturbed.2 A few patients with focal brain ischemia have been treated successfully with vasopressor drugs.3-5 Some of these patients required a blood pressure during the immediate postinsult period which was greater than their normal blood pressure.

This is a report of 13 patients who were treated with vasopressor drugs shortly after the development of focal brain ischemia. The ischemic insult was not associated with a decrease in blood pressure.

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Methods

Consecutive, nonhypertensive patients who developed focal brain ischemia without a change in their blood pressure and who were evaluated by one of the authors within four hours of onset were treated with a vasopressor drug infusion. The blood pressure was raised to 150 to 170/85 to 100 mm Hg for at least three hours. The infusion was discontinued if no improvement in brain function occurred. If neurological improvement did not occur after 30 minutes of vasopressor drug therapy, the patients were also treated with low-molecular-weight dextran (500 ml over a three-hour period, then 500 ml every 12 hours) and dexamethasone (6 mg every six hours).

If brain function had improved during vasopressor treatment, the vasopressor drug infusion was then slowed in order to allow a decrease in the blood pressure. The blood pressure needed for preservation of brain function was then determined by repeatedly raising the blood pressure and allowing it to fall. Hyperosmotic glucose and mannitol, low-molecular-weight dextran, aminophylline, and dexamethasone were given to one patient who had improved with vasopressor drug treatment to see if these agents would lower the blood pressure level needed for preservation of brain function during the first few
hours after their administration. The effect of papaverine upon the blood pressure needed for preservation of brain function was observed in another patient. A double-blind evaluation of the neurological function was performed in cases 1, 4 and 5.

Results
Five of these 13 patients had improvement of brain function during the immediate post-ischemic period whenever the blood pressure was raised to approximately 150 to 170/85 to 100 mm Hg with vasopressor drug therapy. None of these patients had a blood pressure above 140/80 prior to the ischemic episode. Brain function deteriorated during this period whenever the blood pressure was allowed to fall by decreasing the drug infusion rate. The vasopressor infusion was increased within a few minutes after the development of brain dysfunction whenever possible. Relapses did not occur while the blood pressure was elevated. Complete recovery occurred in case 1. The blood pressure level needed for preservation of brain function during the first nine hours following ischemia was not reduced by the concomitant administration of low-molecular-weight dextran, hyperosmotic glucose and mannitol, aminophylline, and dexamethasone in this patient. Minimal residual dysfunction persisted in case 2. Mild residual dysfunction was present in cases 3 and 4. Deterioration did not occur in these four cases when the vasopressor drugs were discontinued after seven to 24 hours of treatment, even though the blood pressures fell to 100/70, 90/60, 125/60 and 120/80, respectively. The effective blood pressure during the immediate postischemic period was not lowered by the concomitant administration of low-molecular-weight dextran, hyperosmotic glucose and mannitol, aminophylline, and dexamethasone in this patient. Minimal residual dysfunction persisted in case 2. Mild residual dysfunction was present in cases 3 and 4. Deterioration did not occur in these four cases when the vasopressor drugs were discontinued after seven to 24 hours of treatment, even though the blood pressures fell to 100/70, 90/60, 125/60 and 120/80, respectively. The effective blood pressure during the immediate postischemic period was not lowered by the concomitant administration of low-molecular-weight dextran, hyperosmotic glucose and mannitol, aminophylline, and dexamethasone in this patient.

Case Reports
CASE 1
A 54-year-old man had a transient episode of right hemiparesis of 30 minutes' duration. Another episode developed two hours later while he was in the emergency room. There was no change in his blood pressure (125/80 mm Hg); this was measured before and after the development of brain ischemia. He remained alert but had paralysis of his right upper extremity with moderate paresis of right leg and right lower face. An intravenous infusion of levarterenol bitartrate (Levophed) was begun 20 minutes after the onset at a rate which increased the blood pressure to 170/100. Normal brain function returned within a few minutes. Levarterenol was immediately discontinued, and the blood pressure was allowed to fall to 120/75. Right hemiparesis with right arm paralysis recurred within five minutes. The levarterenol infusion was started again, and normal brain function returned within two minutes after the blood pressure reached 160/100. Normal brain function returned within a few minutes. Levarterenol was immediately discontinued, and the blood pressure was allowed to fall to 120/75. Right hemiparesis with right arm paralysis recurred within five minutes. The levarterenol infusion was started again, and normal brain function returned within two minutes after the blood pressure reached 160/100. The blood pressure was maintained at 160/100 with a levarterenol infusion. A bolus of 50 ml of 50% glucose and 50 ml of 20% mannitol was given. Low-molecular-weight dextran (500 ml) was infused over a 15-minute period. The central venous pressure remained at 8 cm H₂O. Ten milligrams of dexamethasone were administered intravenously. Right upper extremity paralysis and right lower extremity paresis developed within a few minutes each of the five occasions that the infusion rate of levarterenol was decreased with a resultant fall in blood pressure below 160/100 during the next two hours. An additional 500 ml of dextran had been administered over these two hours.

Five hundred milligrams of aminophylline was then infused over a 15-minute period. The levarterenol infusion rate was decreased on two additional occasions, and right arm paralysis returned within a few minutes after the blood pressure was allowed to fall below 160/100. A levarterenol infusion was continued for six additional hours. The infusion was then discontinued, and cerebral function remained normal with
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A blood pressure of 100/70. It was necessary to restore intravascular volume with isotonic saline while the levarterenol infusion was being discontinued, since the vasopressor drug and an osmotic diuretic had produced a mild volume deficit. A left carotid arteriogram, performed 12 hours later, did not reveal any extracranial or intracranial vascular abnormality. The cause of the ischemia could not be determined. A source for an embolus was not detected, and no additional ischemic episodes occurred over a six-month period.

CASE 2
A 49-year-old woman had received prosthetic aortic and mitral valves one month before she suddenly developed a left hemiplegia without any significant change in her blood pressure (85/55 mm Hg). Her previous blood pressure recordings were usually 90/60 with a range from 85/60 to 116/70. Three hours later, she still had paralysis of the distal left upper and lower extremities with a decreased sensation for pin prick, touch and proprioception on the left side. Cerebrospinal fluid findings were normal except for 26 red blood cells; xanthochromia was not present. A neosynephrine infusion was then begun at a rate which increased the blood pressure to 120/70. Left leg motor function recovered, but there was no improvement in the left arm or left face after 15 minutes of treatment. The infusion was discontinued, and the leg was again paralyzed within five minutes (BP 85/70). The blood pressure was then increased to 160/80; left leg function returned and some movements of the left fingers were first observed, but left facial paralysis remained. The infusion was slowed on two additional occasions and the blood pressure was allowed to fall with a resultant marked increase in left-sided dysfunction. The left leg strength recovered within a few minutes after the blood pressure was increased. Then the blood pressure was maintained at 140/80 for eight hours with a constant levarterenol infusion. Left hand function began to recover and some left facial movements could be made. The infusion was continued for 24 hours, at which time there was only a mild left-sided neurological deficit. Neurological deterioration did not occur when the blood pressure level was allowed to fall to 90/60. Five days later an electroencephalogram revealed a right frontal-temporal delta focus, and there was increased radioactivity in this region on the brain scan. An embolus was presumed to be the cause of the ischemia and infarction.

CASE 3
A 76-year-old man developed a myocardial infarction and had a pacemaker implanted because of complete heart block. Three weeks after the operation, he developed aphasia; this was followed by right hemiplegia and hemianopia 15 minutes later. The patient remained alert, but did not improve. The cerebrospinal fluid examination was normal. The blood pressure was unchanged (110/70). A levarterenol bitartrate infusion was begun one hour later, and the blood pressure was increased to 160/90. Right arm and leg strength improved within 20 minutes. Expressive dysphasia persisted, but marked improvement occurred in receptive language ability and the right visual field deficit. Over the next two hours, left cerebral dysfunction became more severe on each of the seven occasions that the levarterenol infusion was discontinued. Improvement recurred each time the infusion was started again. Five hundred milligrams of papaverine hydrochloride were then given intravenously over a 30-minute period. The same blood pressure level, maintained by levarterenol, was needed before and after its administration. Levarterenol was discontinued 24 hours later without an exacerbation of neurological dysfunction even though the blood pressure decreased to 125/60. Dysarthria, expressive dysphasia, and mild right hemiparesis remained. The patient continued to improve until five days later when he developed a perforated duodenal ulcer. Peritonitis, bronchopneumonia, and pulmonary edema caused his death two days later. Postmortem examination of the brain revealed an ischemic, necrotic 2-cm infarction in the left basal ganglia-internal capsule region.

CASE 4
A 65-year-old man had a previous cerebral infarction with persistent right supranuclear facial weakness and right arm paresis without dysphasia for three years. While in the hospital for an evaluation of a peripheral neuropathy, he suddenly developed a severe receptive and expressive dysphasia and a right hemianopia without a significant change in his blood pressure (140/80). Levarterenol was administered to maintain his blood pressure between 160/90 and 170/90. Rapid improvement of the receptive dysphasia occurred while a right extinction hemianopia and expressive dysphasia persisted. The blood pressure was then allowed to fall to 140/85; a dense hemianopia and receptive dysphasia recurred. The blood pressure was again raised and improvement of left cerebral function occurred within a few minutes. After 24 hours of levarterenol infusion, he was able to tolerate blood pressures of 120/80 without neurological deterioration. Residual deficit from this ischemic episode was limited to a moderate expressive dysphasia at discharge one week after onset.

CASE 5
A 75-year-old man developed a left hemiparesis which recovered 24 hours later. Two weeks later
he developed left hemiplegia, left hemianopia, and loss of proprioception on the left without a change in his blood pressure (130/75). He was given hypertonie glucose and low-molecular-weight dextran. Thirty minutes later, his blood pressure was raised to 170/100 with levarterenol infusion; left-sided strength became almost normal while the left homonymous hemianopia and left proprioceptive deficit persisted. A decrease in his blood pressure was allowed on five occasions over the next two hours; left hemiplegia recurred within minutes after the blood pressure fell below 160 each time and quickly resolved when the blood pressure was then rapidly increased. After seven hours of treatment, left motor function remained near normal with a blood pressure of 150/80 without the need for vasopressor treatment. Low-molecular-weight dextran and corticosteroid drugs were administered. Ten hours later, left hemiplegia had again developed without a change in blood pressure (130/80), but physicians were not contacted. Two hours later his blood pressure was again raised, but no significant improvement occurred after one hour of treatment. Vasopressor drug therapy was discontinued. Occlusion of the right internal carotid artery was demonstrated one hour later by arteriography. The patient gradually deteriorated over the next few days and died of brain herniation. A postmortem examination was not performed.

Discussion

Three previous reports have described the reversal of focal brain ischemia with vasopressor drugs. 

A temporary beneficial effect of vasopressor drugs was demonstrated in five of the 13 patients in this report. Significant recovery was maintained in three of the five after this treatment was discontinued. These patients needed a higher blood pressure for preservation of function in a focal brain region during the immediate postinsult period than that which was required before the insult. The elevated blood pressure was no longer needed after several hours of vasopressor drug treatment. This suggests that there was either a transient physiological disturbance or a structural change in the vessels in the ischemic region which recovered during the vasopressor treatment period. One possible explanation would be a reversal of endothelial and perivascular astrocytic edema. 

Vasopressor drugs and hypertension decrease the amount of infarction that occurs with middle cerebral artery ligation in experimental animals. 

Another possibility in cases with a brain embolus would be that fibrinolysis occurred during the treatment period. Since blood flow measurements were not made, it is, of course, a theoretical possibility that the vasopressor drugs may have had some other effect upon the central nervous system in these patients.

Aminophylline has been reported to increase blood flow in an ischemic brain region with a resultant improvement in neurological function. It causes vasoconstriction of normal cerebral vessels without changing either the vessels in ischemic brain or the aortic blood pressure. The administration of aminophylline to case 1 appeared to be without benefit, since it did not lower the level of blood pressure which was needed for preservation of focal brain function.

Although vasodilator substances increase blood flow to normal brain regions, it is possible that these agents will produce a steal of blood from an ischemic brain region since the ischemic region has a fixed arteriolar resistance due to maximal dilatation or structural changes. On the other hand, a possible beneficial effect with papaverine, a vasodilator drug, in the ischemic stroke patient has been reported. 

The effective blood pressure level in our case 3 was not lowered by the concomitant administration of papaverine during the immediate postinsult period.

Low-molecular-weight dextran has increased blood flow in ischemic brain regions in experimental animals and has increased the level of consciousness of patients with a recent infarction. Corticosteroid drugs have reduced cerebral dysfunction in patients with a brain infarction in one report. No definite beneficial effect with these agents or with hyperosmolar glucose and mannitol were observed in any of our patients in the first few hours of treatment. There is no proof that these agents were not beneficial in these cases, but they were not as effective as vasopressor drugs.
in maintaining focal brain function in the first five cases.

Successful treatment with vasopressor drugs suggests that it is probably unwise to decrease the blood pressure during focal cerebral ischemic attacks or ischemic infarction. Neurological deterioration due to a hypersensitivity to antihypertensive drugs has been reported in the acute ischemic stroke patient. After the immediate poststroke period, antihypertensive drugs are indicated since they appear to decrease the incidence of subsequent infarction.

Additional observations and experimental studies should be performed with vasopressor drugs to determine their indications and contraindications in patients with brain ischemia and infarction. It is important to compare the results of this treatment with control groups and patients treated with different methods. It is possible that these patients who responded would have recovered without vasopressor treatment. It is also possible that the patients who did not respond were made worse. Although vasopressor drugs appear to prevent infarction in certain cases, some authors have warned that vasopressor agents may cause edema or hemorrhage if they are administered after an infarction has already occurred. Obviously, the clinician must be able to determine with a high degree of certainty that the patient has an ischemic brain problem rather than a hemorrhage before beginning vasopressor therapy. This differentiation is sometimes difficult for even the most experienced clinician. Our studies in these cases and unpublished observations following arteriographical complications suggest that patients who respond to vasopressor treatment have had ischemia for less than three hours. Levaterenol appears to be the best drug for this purpose since it has a brief duration of action; this is important whenever an excessive amount is administered. It has both an alpha-vasoconstrictive effect and a beta-inotropic effect when low doses are used. Large doses may produce renal arteriolar vasoconstriction and increase the peripheral resistance to a point that left ventricular failure or ischemia may occur. The doses needed in the therapy of these patients (1 to 6 µg/min) did not decrease urine output. Neosynephrine, which has a primarily vasoconstrictive action, also may be used since it acts briefly. Metaraminol bitartrate (Aramine) is not recommended since it has a duration of many minutes; it also replaces endogenous catecholamines, and hypotension may occur after the drug is discontinued. Constant, meticulous observation of the rate of infusion, blood pressure, cardiac rhythm, urine output, central venous pressure, and arterial gases is essential, as is neurological examination. Vasoconstrictor drugs may produce volume depletion; therefore, whenever the vasopressor drug is decreased, it is necessary to give adequate volume replacement to prevent a decreased venous return. Dramatic responses to vasopressor drugs have always occurred within one hour after their administration in our limited experience. It is probably best to discontinue this therapy in patients who do not have any clinical improvement after several hours of treatment.

References


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