Aminophylline plus nitroprusside and dopamine for treatment of cerebral vasospasm

A preliminary report

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Cerebral vasospasm following subarachnoid hemorrhage continues to elude effective treatment. Volume expansion is very helpful at times, but cannot be relied on. The authors have combined elements of two vasospasm regimens that could have additive effects. After a trial of volume expansion, aminophylline, dopamine, and nitroprusside were used in combination in each of five patients. All had documented vasospasm and all improved markedly.

Key Words: aneurysm · cerebral vasospasm · dopamine · aminophylline · nitroprusside · volume expansion
Combined therapy for cerebral vasospasm

TABLE 1
Clinical summary in five patients with cerebral vasospasm

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Aneurysm Location*</th>
<th>Days Treated</th>
<th>Neurological Grade† At Start of Regimen</th>
<th>Neurological Grade† At End of Regimen</th>
<th>Residual Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25, M</td>
<td>PCoA</td>
<td>3</td>
<td>IV</td>
<td>III</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>43, F</td>
<td>basilar tip</td>
<td>2</td>
<td>IV</td>
<td>II</td>
<td>minimal quadriparesis</td>
</tr>
<tr>
<td>3</td>
<td>57, F</td>
<td>basilar tip</td>
<td>2</td>
<td>IV</td>
<td>II</td>
<td>minimal lower extremity weakness</td>
</tr>
<tr>
<td>4</td>
<td>45, M</td>
<td>ACoA</td>
<td>1</td>
<td>III</td>
<td>IV</td>
<td>moderate aphasia; moderate hemiparesis</td>
</tr>
<tr>
<td>5</td>
<td>52, M</td>
<td>ACoA</td>
<td>4</td>
<td>IV</td>
<td>II</td>
<td>mild rt leg weakness; mild aphasia</td>
</tr>
</tbody>
</table>

* PCoA = posterior communicating artery; ACoA = anterior communicating artery.
† Grade according to Hunt and Hess.4

with Amicar (aminocaproic acid), 2 gm/hr intravenously, and most received low doses of phenobarbital for sedation. One patient was treated with kanamycin and reserpine immediately after admission in an attempt to prevent vasospasm.

Aminophylline was started with a 500-mg loading dose and then administered at 1 mg/kg/hr by constant infusion. The level of aminophylline in the blood was tested regularly to avoid toxic accumulation of the drug. Dopamine was begun at a dose of 1 to 5 µg/kg/min, and slowly titrated until the blood pressure began to rise. The dopamine infusion was not raised above 15 µg/kg/min, to avoid vasoconstriction. Once a minimal increase in blood pressure was seen secondary to the dopamine infusion, nitroprusside was administered at 1 µg/kg/min. The dopamine and nitroprusside doses were then titrated to maintain the patient's blood pressure at a predetermined level. In all patients, we maintained the mean arterial blood pressure at approximately 110 to 120 mm Hg, a level that had been achieved during the period of volume expansion.

Of the five patients with this regimen (Table 1), all had severe neurological deficits and a decreased level of consciousness at the start of treatment. They had not improved during the 6-hour trial of volume loading but did improve with the regimen. Diuresis induced by the treatment was a problem in all of them, but it was closely observed and responded well. The improvements shown by these patients were substantial; they progressed to a higher grade of neurological status, with a substantial increase in motor performance. A short description of the cases follows.

Case Reports

Case 1

Our first patient was a 25-year-old man who collapsed after complaining of a severe headache. On initial examination in the emergency room he was easily aroused but lethargic, and showed no focal neurological deficit (Hunt and Hess Grade III). Marked neck stiffness was present, and a CT scan showed diffuse subarachnoid blood. He was admitted to the intensive care unit and treated with Amicar, kanamycin, and reserpine.12 Over several hours he deteriorated to Hunt and Hess Grade IV, being un-responsive except for purposeful movement in reaction to deep pain. An angiogram demonstrated a left posterior communicating artery aneurysm with severe spasm in the left carotid and middle and anterior distribution. Volume loading as described previously was carried out and when no improvement was seen in 6 hours, the triple-drug regimen was begun.

Within a few hours the patient began to improve, and within 12 hours he was moving spontaneously, following commands, and answering simple questions (Hunt and Hess Grade III). Attempts to taper the medications resulted in clear-cut deterioration in his level of consciousness. After 2½ days he was successfully weaned from the medications. His aneurysm was clipped uneventfully 1 week later, and he was ultimately discharged neurologically intact. Although we were skeptical, this patient's dramatic response led us to treat four subsequent patients with the triple-drug therapy.

Case 2

This 43-year-old woman with an SAH documented by lumbar puncture was found to have a large basilar tip aneurysm on angiography. Initially, she was noted to be lethargic but showed no focal deficit (Hunt and Hess Grade III). Five days after the hemorrhage she became less responsive and was quadriparetic, with the legs showing only a trace of movement in reaction to painful stimuli (Hunt and Hess Grade IV). When 6 hours of volume replacement failed to produce improvement, the triple-drug regimen was begun. Within a few hours she was able to lift her legs voluntarily off the bed. Ultimately, she displayed only a minimal quadriparesis, which would increase with each effort to taper the drugs (Hunt and Hess Grade III). After 48 hours the drugs were discontinued without deleterious effect on her neurological status. This aneurysm was deemed unclippable by the surgeon, and the patient was discharged home in good condition and remains well to date.

Case 3

This 57-year-old woman had a basilar tip aneurysm demonstrated angiographically and was awaiting sur-
surgery. She was neurologically intact except for some lethargy, but 5 days after rupture of the aneurysm developed a severe paraparesis (% strength). She was stuporous, but on stimulation could be aroused to follow simple commands (Hunt and Hess Grade IV). Her arms were also weak at %. Angiography showed vasospasm in the basilar artery and posterior cerebral arteries. After 6 hours of volume loading without improvement, we began our regimen. A few hours later she was able to raise her legs off the bed and dorsiflex her feet. She reached % strength in both the lower and the upper extremities, then regressed to % strength with tapering of the dose. When we raised the dose she improved, and after 2 days she retained her strength when the regimen was tapered. This aneurysm was not clipped due to its intimate association with perforating arteries as seen on repeat angiography.

Case 4

This 45-year-old man presented with an abrupt severe headache and resultant lethargy (Hunt and Hess Grade III). Lumbar puncture yielded bloody cerebrospinal fluid, and a CT scan demonstrated blood in the interhemispheric fissure. On angiography, an anterior communicating artery aneurysm filled.

Six days after hemorrhage he gradually developed a right hemiparesis and aphasia (Hunt and Hess Grade IV). Volume loading resulted in no change in neurological status. An angiogram demonstrated diffuse vasospasm in the left carotid system. After the usual 6 hours of volume loading, we began the triple-drug therapy. His speech improved within a few hours. Subsequently, the right hemiparesis improved but the leg remained profoundly weak. The regimen was discontinued at 24 hours when he developed pulmonary complications that proved to be due to a pulmonary embolus. He maintained the neurological improvement but died from the pulmonary embolism before the aneurysm could be clipped.

Case 5

This 52-year-old man presented with progressive visual loss in the left eye. By CT scan and angiography he was found to have a large anterior communicating artery aneurysm with resultant left optic nerve compression. There was no history of SAH. At surgery, the neck of the aneurysm could not be clipped, but it was ligated. The aneurysm was collapsed by needling and a small amount of blood was spilled into the subarachnoid space. Postoperatively, the patient did well for 4 days. He then developed progressive lethargy, weakness of the right leg, and a receptive aphasia (Hunt and Hess Grade IV). Angiography demonstrated severe vasospasm in the anterior communicating and left carotid arteries near the aneurysm, which did not fill. He was given 12 hours of volume loading without improvement. The triple-drug regimen was then started, and within 2 hours he became more responsive and was following simple commands. Within 6 hours the plegic right leg moved visibly on command, and within 6 more hours antigravity strength was achieved (Hunt and Hess Grade III). He had % strength both proximally and distally. As noted in the previous cases, the initial attempts to decrease the medications were met with frank neurological deterioration. Ultimately, the regimen was successfully discontinued. It is of note that the patient’s receptive speech disturbance was unchanged throughout. He continued to improve and was discharged from the hospital.

Discussion

The history of vasospasm treatment has been characterized by a series of enthusiastic early reports of successful drug therapy, most of which have proved disappointing in broader clinical usage. In our experience, each of the widely used regimens has worked with some patients. We initially tried this triple-drug regimen because of its theoretical appeal; however, we have continued to use it because of the consistent clinical response. This experience leads us to believe that the regimen has real value and merits a wider and more formal evaluation.

In principle, these drugs could have synergistic action. Although complete pharmacological mechanisms remain to be defined, there are certain facts which are clear. Aminophylline relaxes smooth muscle via cyclic adenosine monophosphate (AMP) release. Dopamine increases blood pressure by acting as a cardiac stimulant and promotes perfusion of the cerebrovascular bed. Nitroprusside has a distinct relaxant effect on vascular smooth muscle. We do not know whether this combination regimen acts directly by opening spastic arteries or treats some biochemically responsive related disorder. However, each of our patients showed a clear clinical response within a few hours. The neurological improvement was clearly dose-dependent.

In practice, the aminophylline and dopamine doses varied little in each patient. The nitroprusside dosage was manipulated frequently, through a range from barely running to 4 μg/kg/min. Thiocyanate levels were monitored throughout.

The regimen was not without problems. Three of the five patients showed evidence of central nervous system stimulation with irritability and hyperexcitability. These effects were seen within a few hours of beginning the drugs, but were not difficult to control. They disappeared when the regimen was tapered. A second side effect, more difficult to manage, was the massive diuresis elicited by this drug combination. The diuresis varied from 150 cc to 1000 cc of urine output per hour. All three of these drug agents may have diuretic properties, and the combination was dramatic at times. We carefully replaced volume losses with crystalloid and colloid to maintain the
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desired hemodynamic parameters in order to promote cerebral perfusion and avoid hypovolemia. We must stress that this regimen requires intensive nursing care. Swan-Ganz monitoring was essential in preventing cardiovascular or pulmonary complications in the face of massive volume replacement. Because of the problems with diuresis, we tapered the drugs as soon as the patients' clinical condition permitted. No other complications of this rather complex drug regimen were seen. We had anticipated cardiac irritability and possible arrhythmias, but none were encountered.

We have used this regimen in two subsequent patients. One patient, who suffered from a long-standing seizure disorder, had a grand mal seizure 2 hours after the regimen was begun. She suffered no ill effects from the seizure, but the regimen was discontinued. The other patient had a longer-standing (1 week) vascular spasm from a right internal carotid artery aneurysm. She had been responsive only to pain, and had a left hemiparesis. The regimen was begun and she improved to a level where she responded to commands, with improved strength in the left side. Because of the length of time after onset of the deficit we are not certain of the regimen's role in this case.

We are reporting our brief experience with this triple-drug regimen because of the surprisingly good results, in the hope that other clinical investigators will be encouraged to try it. This is the best record of treatment in our personal experience with vasospasm. We have seen only sporadic cases of improvement with any other available treatment regimens, even though we have used each several times. Could there be another explanation for these patients' improvement? This is always possible in an uncontrolled trial. It is unlikely that we simply ran across seven patients who were going to improve. Nor do we think that the volume loading could be responsible because we try this regimen in vasospasm patients, in the same manner over long periods, and only a few improve. The fact that tapering the three-drug regimen often worsened the deficit, with improvement when the dosage was again increased, is strong evidence that our treatment was responsible. One could speculate that the diuresis which is so marked may be a clue, either as a sign of the biochemical action or as an aid in washing out some toxic factor. Admittedly, the number of patients is small, the mechanism of drug interactions poorly understood, and the regimen difficult to manage clinically. Taking into consideration the above limitations, our preliminary experience indicates that the regimen has promise and merits further investigation.

References


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