Safety of Intraventricular Sodium Nitroprusside and Thiosulfate for the Treatment of Cerebral Vasospasm in the Intensive Care Unit Setting

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Background and Purpose—We have recently reported the safety of intraventricular sodium nitroprusside for the treatment of cerebral ischemia from vasospasm. Treatments have been accompanied previously by cerebral angiography to gauge treatment effect on established vasospasm. We presently report the safe coadministration of intraventricular sodium nitroprusside and thiosulfate in 10 patients with secured ruptured cerebral aneurysms in the intensive care unit, without the use of cerebral angiography for vasospasm treatment.

Methods—Patients were considered eligible for treatment on the basis of subarachnoid hemorrhage grade or manifestation of cerebral vasospasm by either transcranial Doppler ultrasonography (TCD) or neurological examination criteria. The route of administration was intraventricular, by way of ventriculostomy. Two separate protocols differing in dosage frequency were used, depending on the presence or absence of a new neurological deficit. Response to treatment was measured by TCD and neurological criteria.

Results—Good outcome was observed in 7 of 8 vasospasm patients presenting with clinical subarachnoid hemorrhage grade ≥3. Four patients demonstrated reversal of well-defined neurological deficits (hemiparesis, paraparesis) in the setting of treatment. Seven patients demonstrated a decrease in TCD velocities within 1 hour of treatment. Two patients died: 1 from intractable vasospasm despite maximal medical management and angioplasty and 1 from pulmonary causes. One episode of hypotension occurred in the setting of a high dose of medication. This responded promptly to medical management. Prolonged intracranial hypertension did not occur; modest elevations of both intracranial pressure and mean arterial blood pressure were observed when nausea and vomiting were associated with treatment, which occurred commonly in awake subjects.

Conclusions—Intraventricular sodium nitroprusside with thiosulfate may be safely administered in the intensive care unit setting without the requirement of cerebral angiography to guide the effects of therapy. (Stroke. 2002;33:486-492.)

Key Words: cerebral ischemia ■ injections, intraventricular ■ nitroprusside ■ thiosulfates ■ vasospasm

We have recently reported the safety of intraventricular sodium nitroprusside (SNP) for the treatment of cerebral ischemia from vasospasm. Treatments have been accompanied previously by cerebral angiography to gauge treatment effect on established vasospasm. We presently report the safe coadministration of intraventricular (intrathecal) SNP and thiosulfate (ITSNP/T) in 10 patients with secured ruptured cerebral aneurysms in the intensive care unit, without the use of cerebral angiography for vasospasm treatment.

Subjects and Methods

Patient Selection

Patients were initially selected for treatment according to previously established criteria of clinical or radiographic subarachnoid hemorrhage (SAH) grade 3, ruptured cerebral aneurysm definitively identified and secured by either microvascular or endovascular means, absence of hepatic or renal failure, absence of large or unequivocal cerebral infarction by CT, and absence of hypotension. The study population consisted of 10 patients (4 men, 6 women) with a mean age of 52.3 years (range, 39 to 68 years). Patients or their families gave informed consent for participation in this study. The study was approved by the Institutional Review Board of Thomas Jefferson University, Philadelphia, Pa, and was performed under Investigator Investigational New Drug 52-307 (Dr Thomas), US Food and Drug Administration.

Route of Administration and Dosage

Patients received pretreatment for nausea in the form of ondansetron HCI (Glaxo-Wellcome, Inc) 32.0 mg IV push and dexamethasone 10.0 mg IV push 15 minutes before treatment. Powdered SNP and sodium thiosulfate were steriley reconstituted in normal saline for final concentrations of 4.0 mg/mL (0.4% solution) and 10.0 mg/mL (1% solution), respectively. Meticulous photoprotection and sterile technique were observed for all aspects of delivery of the medication as well as its formulation. No formulation was stored for >12 hours. Medication was delivered intraventricularly in all cases by way of ventriculostomy attached to a microinfusion pump (type AS-50, Baxter Healthcare). Correct ventricular
catheter placement was verified by CT scan in most cases at some point during the course of intensive care treatment.

Medication was delivered according to 1 of 2 protocols defined by the clinical circumstances. Protocols differed in dose and in dose frequency. Specifically, an “acute” high-dosage rescue protocol (1.0 mL of ITSNP/T over 1 to 2 minutes, repeated every 5 minutes to a total of 10 mL and preceded each time by the withdrawal of 5 to 10 mL of cerebrospinal fluid [CSF]; n = 6) was used for patients with new or aggravated neurological deficits attributable to vasospasm or with acute elevation of transcranial Doppler ultrasonography (TCD) velocities, whereas a “chronic” low-dosage protocol (2.0 mL of ITSNP/T over 60 minutes, preceded by withdrawal of 5 to 10 mL of CSF; n = 10) was used for prophylaxis (subsequent to use of the acute protocol in 6 of 10 cases).

The indications for ventriculostomy included Glasgow Coma Scale score <8, hydrocephalus, interval increase in ventricular size by CT, and intraventricular hemorrhage. The ventriculostomy catheter was simultaneously used for intracranial pressure (ICP) monitoring during treatment. This was achieved by brief interruptions of the 1-hour infusion at 15-minute intervals. Arterial blood pressure monitoring was performed in the usual fashion with the use of a radial artery catheter; in 9 patients a Swan-Ganz intracardiac catheter was used for intensive hemodynamic monitoring during administration of hypertensive, hypervolemic, hemodilutional (HHH) therapy. All patients received intravascular volume expansion with colloid and crystalloid and oral nimodipine. All patients with one exception also received phenylephrine HCl to raise mean arterial blood pressure. Cerebral angiography was performed only for those patients demonstrating neurological deficit or TCD elevation refractory to ITSNP/T for 2 hours.

Three patients received cerebral angioplasty at some point during the course of treatment. Patient 2 (Table 1) underwent 2 angioplasty procedures in the setting of a suboptimal ventricular catheter position (Figure 2B). Patients 6 and 7 underwent cerebral angioplasty after demonstrating vasospasm that was refractory to ITSNP/T treatment over 2 hours. All 3 of these patients demonstrated poor CSF access because of either ventricular effacement or ventriculostomy catheter malposition (Figures 2A, 2B, 5A). Patient 2 demonstrated a steep decline in mean TCD values (from 230 to 179 cm/s) in the setting of angioplasty because of either ventricular effacement or ventriculostomy catheter malposition (Figures 2A, 2B, 5A). Patient 2 demonstrated a steep decline in mean TCD values (from 230 to 179 cm/s) in the setting of ITSNP/T treatment after the ventriculostomy malposition was detected by CT and corrected following the second angioplasty.

### Results

With a single exception (patient 6), all patients showed some degree of positive response to ITSNP/T. Four patients demonstrated unequivocal reversal of serious neurological deficits (hemiparesis and paraplegia) in the setting of treatment, ie, within 1 hour. Seven patients demonstrated a downward change in mean middle cerebral artery (MCA) TCD velocities within 1 hour of treatment (Table 1). Although cerebral angiography was not used as a means to gauge response to treatment, it was performed in 4 cases in which insufficient treatment effect was observed: in 3 of these cases angioplasty was performed for refractory vasospasm, and in 1 case angiography demonstrated significantly reduced cerebral circulation time despite the absence of a significant change in
TCD velocities (Figure 1A). Figures 2, 3, and 4 discuss the courses of patients 2, 4, and 5, respectively.

One episode of brief arterial hypotension occurred, which responded rapidly to discontinuation of the infusion and increased fluid and pressor administration. No incidence of prolonged intracranial hypertension was observed. The majority of patients (6 of 10) experienced nausea and vomiting with treatment; this effect was blunted by pretreatment with ondansetron and dexamethasone and in most cases was brief, rarely lasting beyond the period (1 hour) of treatment. A brief (1 to 2 minutes) rise in ICP was noted in conjunction with vomiting and was not associated with a deterioration of neurological function.

Two patients (patients 6 and 7; Table 1) died: 1 from intractable vasospasm despite cerebral angioplasty (Figure 5) and 1 from pulmonary complications (severe pneumonia and acute respiratory distress syndrome with pneumothorax).

Outcome was determined at 12 to 23 months after SAH by Glasgow Outcome Scale (GOS) and modified Rankin Scale disability score. Among survivors, all except 1 (patient 8, who did not develop delayed neurological deficit and was discharged home) were discharged to rehabilitation facilities after acute hospitalization. Seven of 8 surviving patients had good recovery (87.5% of survivors, 70% of all patients treated), and 1 patient had a moderate to severe disability.

TCD velocities (Figure 1A). Figures 2, 3, and 4 discuss the courses of patients 2, 4, and 5, respectively.

Figure 1. A, Patient 1. A 42-year-old man presented with ruptured left internal carotid artery (LICA) aneurysm. Microsurgical clip ligation was complicated by elevated ICP for several days postoperatively. Ventricular catheter placement was initially suboptimal with poor CSF access and required correction. The patient responded clinically to ITSNP/T by improved neurological examination (right hemiparesis and dysphasia). Because TCD velocities remained unchanged, however, cerebral angiography was performed. LICA injection before and after ITSNP/T demonstrated no significant change in the caliber of large-conductance vessels but a significant decrease in cerebral circulation time, implying increased cerebral blood flow through collateral microcirculation. Multiple retreatments were required as vasospasm resolved (see Table 1) (from Stroke. 2000;31:1195–1196, by permission). B, Shown 3 months after SAH, the patient made a full neurological recovery.

Figure 2. A, Patient 2. A 39-year-old woman presented with left MCA aneurysm rupture. Microsurgical repair and clip ligation were performed. Delayed ischemic neurological deficit was right hemiparesis and speech dysfunction. B, Initial ventricular catheter placement. The perforations of the catheter are in parenchyma. Two angioplasty procedures were performed for vasospasm. C, After repositioning on SAH day 7, a profound drop in ipsilateral TCD velocities with clinical improvement in the setting of treatment was observed. Multiple retreatments were required as vasospasm resolved (see Table 1). The patient made a full neurological recovery and subsequently had elective clip ligation of a contralateral unruptured aneurysm.
having completely recovered from paraplegia but with significant remaining short-term memory deficit (Table 2). Both patients who died had presented with clinical SAH grade 4. Altogether, 7 of 8 patients (87.5%) presenting with clinical SAH grade ≥3 and with cerebral vasospasm demonstrated good outcome as measured by GOS and modified Rankin Scale disability score; 100% of treated survivors were independently ambulatory and independent in activities of daily living at last follow-up (May 2001), and 3 of 6 patients (50%) who were working at the time of ictus had returned to work.

Discussion
The concept of adventitial administration of nitric oxide donors for the alleviation of cerebral ischemia due to vasospasm was first tested in the clinical setting in 1997. Recently we published initial clinical results of intrathecal SNP, demonstrating its safe use in a total of 24 patients in various clinical situations. Since initial clinical results also suggested efficacy, a prospective therapeutic trial was planned. During preliminary investigations of prophylactic administration of ITSNP/T, we observed its safety in a total of 24 patients in the intensive care unit setting without the use of cerebral angiography or the need for any other displacement of the patient. This report describes a subset of SAH patients treated in the intensive care unit with ITSNP/T, many of whom were initially excluded from early ITSNP/T treatment because of SAH-related cerebral swelling but received the medication after ICP was controlled and vasospasm was diagnosed.

This study corroborates earlier impressions regarding the safe limits of intraventricular SNP administration, specifically, the safe administration of 4.0 mg within a 5-minute period. We observed no untoward effect of repeatedly administering this amount to an apparent cumulative dose of 40 mg. These data should be considered in the context of the possible withdrawal of some active medication during every CSF aspiration preceding a new injection.

This study also supports the safety of administration of ITSNP/T in the intensive care unit, without cerebral angiography or neurophysiological monitoring. This is a clear advantage over angiographically guided treatment and results from greater certainty regarding dosage. Hemodynamic and ICP monitoring, however, remain essential elements of this treatment paradigm because of the risks of arterial hypotension and intracranial hypertension.

The efficacy of this treatment with regard to treatment and prevention of cerebral ischemia from vasospasm remains theoretical in light of the limited nature of the study but is suggested by some of the clinical results in this study that appeared to be responses to treatment. The proportion of good outcomes in this group (87.5% of patients presenting with clinical SAH grade ≥3 and vasospasm) is also noted because it represents patients historically at substantial risk of permanent neurological morbidity. These findings echo character-
istics of ITSNP-treated patients that we have reported previously.1,7

Of theoretical importance is the impact of this treatment at the level of the microcirculation, as suggested by the case illustration (Figure 1A). In this case the impact of treatment on the larger-caliber conductance vessels appears to be minimal, while the decreased cerebral circulation time indicates improved cerebral blood flow by way of the microcirculation. A similar argument for the importance of microcirculatory effects might pertain to the failure of cerebral angioplasty to alleviate neurological deficit in some patients (Figure 5). The non-vasospasm-specific dilation of collateral blood vessels is a theoretical mechanism of this treatment that remains to be proven by formal measurements of cerebral blood flow. Limited studies of this nature have been performed by other investigators.9

Additionally with regard to efficacy, the apparent failure of treatment for the patient illustrated in Figure 5 (patient 6)

TABLE 2. Outcome of Patients With Vasospasm Treated With ITSNP/T

<table>
<thead>
<tr>
<th>Pt No.</th>
<th>Hunt/Hess Grade (at Time of Surgery)</th>
<th>Follow-Up, mo</th>
<th>Modified Rankin Scale Score</th>
<th>GOS Score</th>
<th>Pt Progress Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>23</td>
<td>0</td>
<td>Good</td>
<td>Better</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>27</td>
<td>0</td>
<td>Good</td>
<td>Better</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>19</td>
<td>0</td>
<td>Good</td>
<td>Better</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>17</td>
<td>3</td>
<td>Moderate-severe (short-term memory deficit)</td>
<td>Better</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>19</td>
<td>0</td>
<td>Good</td>
<td>Better</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>...</td>
<td>5</td>
<td>Dead</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>...</td>
<td>5</td>
<td>Dead</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>15</td>
<td>0</td>
<td>Good</td>
<td>Better</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>13</td>
<td>2</td>
<td>Good (mild upper extremity weakness, short-term memory deficit)</td>
<td>Better</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>14</td>
<td>2</td>
<td>Good (L hemiparesis, short-term memory deficit)</td>
<td>Better</td>
</tr>
</tbody>
</table>

Pt indicates patient; L, left.
deserves consideration. Two points are especially relevant in this case: (1) severe vasospasm was established in this patient before medication was administered, and (2) CSF access was limited because near-total ventricular effacement had occurred secondary to intracranial hypertension. Other considerations possibly related to treatment failure but not thought to be relevant in this patient’s case are inadequate photoprotection of the compound throughout the delivery apparatus, inaccurate ventriculostomy placement (of note, this was problematic in 3 patients in the present report), inadequate CSF circulation for the distribution of ITSNP, and a high volume of SAH (both because of CSF circulation impairment and because of the theoretical “hemoglobin sink” effect of the subarachnoid blood in absorbing the nitric oxide molecule, which binds avidly to the heme group\(^\text{10-13}\)).

### Rationale for Coadministration of SNP and Sodium Thiosulfate

Because the metabolism of SNP liberates cyanide ion,\(^\text{14}\) prolonged administration of SNP may precipitate a toxic accumulation of cyanide. Because cyanide is a normal product of energy metabolism, the mechanisms for its removal are usually abundant in body tissues. These include rhodanase, an enzyme that facilitates the conversion of cyanide and thiosulfate to thiocyanate. Thiosulfate is also abundant in many body tissues but is theoretically susceptible to depletion under conditions of very high rhodanase activity.\(^\text{14}\) The resulting compound, thiocyanate, is then eliminated by the kidney. The strategy of coadministration of thiosulfate with SNP, which has been reported for systemic (intravascular) SNP treatment,\(^\text{15}\) is to avoid depletion of the substrate for rhodanase and therefore to minimize the possibility of cyanide toxicity. This rationale acknowledges that the dosage of SNP used for alleviation of acute cerebral ischemia (up to 42 mg in 1 hour) may significantly exceed the dosage used for systemic administration, when it is taken into consideration that the intrathecal space is much smaller in volume than the intravascular space.

### Conclusions

These observations support the conclusion that ITSNP/T may be administered in the intensive care unit setting with an acceptable margin of safety. The proportion of symptomatic vasospasm patients having good neurological outcome suggests that the treatment may be efficacious and is in agreement with earlier published reports.\(^\text{1,7}\) Dorsch and King,\(^\text{8}\) in an analysis of >1000 patients, found the historical frequency of good outcome in patients having vasospasm to be 44% compared with the higher incidence of good outcome (70%) in SAH patients not having vasospasm. These results suggest that ITSNP/T should be subjected to a systematic prospective analysis of prophylactic treatment to examine its possible impact on the incidence of delayed cerebral ischemia after aneurysmal SAH.

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### References