Intra-Arterial Nitroprusside Treatment of Acute Experimental Vasospasm

LEONARD F. HIRSH, M.D.

SUMMARY The effect of intra-arterial sodium nitroprusside infusions on acute experimental basilar artery spasm was studied in dogs. Vasospasm produced by subarachnoid hemorrhage at normal intracranial pressure was partially relieved by nitroprusside. When given by the intra-arterial route, 15 times the recommended maximum intravenous dose can be infused without significant hypotension or elevation in intracranial pressure.

Although many treatments for cerebral vasospasm have been proposed, none has achieved general acceptance. Treatment with sodium nitroprusside has seemed promising but its use has been limited by the severe hypotension produced by intravenous infusion, necessitating simultaneous administration of another vaso-active drug. During treatment of a patient with ergot poisoning, the author made the serendipitous discovery that the intra-arterial use of nitroprusside appeared to have less effect on systemic blood pressure than intravenous administration, and yet the arterial vasodilatory response was maintained. Because of this, the effect of nitroprusside delivered directly into the vertebral artery on acute experimental basilar artery spasm following subarachnoid hemorrhage was studied in dogs.

Materials and Methods

Ten mongrel dogs, weighing 22 to 27 kg, were initially anesthetized with Innovar-Vet, 2 cc subcutaneously followed by 2 cc intramuscularly. An intravenous line for 5% dextrose in water was established in one forepaw, and further anesthesia was achieved with 60 mg increments of intravenous sodium pentobarbital. Sodium pentobarbital was needed during the nitroprusside trials in only one animal (dog #10). A cuffed endotracheal tube was inserted. Systemic mean arterial blood pressure (MAP) was recorded with a heparinized transducer connected to a polyethylene line placed in the inferior aorta through the left femoral artery. The right temporalis muscle was elevated from the cranium with the Bovie coagulator. A ½ inch burr hole was placed in the right parietal region, the hole tapped, the dura incised in a cruciate fashion, and a subarachnoid bolt with a Luer-lock connector threaded into the hole. Intracranial pressure (ICP) was recorded with a transducer. The suboccipital region and the posterior arch of Cl were exposed with the Bovie coagulator.

MAP and ICP were displayed on a strip chart recorder running at 0.25 mm per second. For angiography retrograde catheterization of the left vertebral artery was performed through the right femoral artery under fluoroscopic control. The dog was continuously ventilated with a mechanical volume respirator. The dog was then placed prone and a control angiogram was done demonstrating the basilar artery. The cisterna magna was tapped with a 20 gauge spinal needle, 2 cc of spinal fluid were removed, and 2 cc of fresh arterial blood were injected slowly while monitoring the ICP to produce no elevation. After 26.1 ± 1.3 minutes, during which the dog's feet were elevated 30°, angiography was repeated to demonstrate the presence or absence of basilar artery spasm (D₁: diameter basilar artery after hemorrhage, percentage of control).

An infusion of 5% dextrose in water was begun at 3.82 cc per minute (dogs 1 through 8) or at 7.64 cc per minute (dogs 9 and 10) through the vertebral artery catheter for 7.15 ± 0.28 minutes followed by angiography to evaluate the basilar artery diameter (D₂: percentage of control). Three picture angiograms were performed in each animal with 10 cc of iothalamate meglumin (Conray).

An infusion of 50 mg of sodium nitroprusside in 500 cc of 5% dextrose in water was then given for 7.69 ± 0.35 minutes at 382 µgm per minute in 8 dogs.
Followed by repeat angiography (D₁). In dogs 1 through 5 angiography was repeated after 15 minutes (D₁), and 30 minutes (D₂) to demonstrate return of vasospasm. If spasm returned, a second treatment with nitroprusside at 382 μg/min per minute was given in dogs 3 and 4 to show repeated drug effect (D₃). In dog 5 repeat nitroprusside infusion was given at 764 μg/min per minute (D₄), in dog 6 at 1530 μg/min per minute (D₉), and in dog 9 at 3060 μg/min per minute (D₀; 100 mg/500 cc D./W).

In dogs 6, 7, and 8 the infusion rate of nitroprusside was increased from 382 μg/min per minute to 764 μg/min per minute (D₄), 1530 μg/min per minute (D₉), and 3820 μg/min per minute (D₀) to demonstrate a dose related relaxation of spasm and the minimal change in MAP.

In dog 9, 100 mg of nitroprusside in 500 cc of 5% dextrose in water was infused after the control runs at a rate of 1530 μg/min per minute (D₉). In dog 10, 150 mg of nitroprusside in 500 cc at 2292 μg/min per minute in dog 10 (97 μg/kg/min) increased the basilar diameter (D₉) as did an infusion of 150 mg nitroprusside in 500 cc at 2292 μg/min per minute in dog 10 (97 μg/kg/min) (D₀). An average MAP drop for both dogs of 44 mm Hg was noted.

### Results

In the table the experimental sequence is shown in graphic form. Following the subarachnoid hemorrhage at normal ICP, the basilar artery diameter decreased to 66.4 ± 2.1% of its control after 26.1 ± 1.3 minutes.

In dogs 1 through 8 the infusion of 5% dextrose in water at 3.82 cc per minute did not significantly change the basilar diameter (average diameter D₉ dogs 1 through 8, 64.8 ± 2.3%). In dogs 9 and 10 the same infusion at 7.64 cc per minute did not change basilar artery diameter. The average duration of these infusions was 7.15 ± 0.28 minutes. The average control MAP was 103.9 ± 5.2 mm Hg.

In dogs 1 through 8 sodium nitroprusside (50 mg in 500 cc D./W) at 382 μg/min per minute (average 15 μg/kg/min) significantly increased the basilar artery diameter to an average diameter (D₉) of 86.8 ± 4.8% of control (p < 0.001), with a resulting average MAP of 80.6 ± 7 mm Hg.

In dogs 1 through 8 sodium nitroprusside (50 mg in 500 cc D./W) at 382 μg/min per minute (average 15 μg/kg/min) significantly increased the basilar artery diameter to an average diameter (D₉) of 86.8 ± 4.8% of control (p < 0.001), with a resulting average MAP of 80.6 ± 7 mm Hg.

In dogs 6 and 8 sequential increases in the diameter of the basilar artery were recorded as the infusion rate of nitroprusside (50 mg in 500 cc D./W) was increased from 382 to 764 (D₄), 1530 (D₉), and 3820 (D₀) μg/min per minute (average respectively of 30, 61, 153 μg/kg/min). A sequential decline in MAP was also noted, the average decline during maximum nitroprusside infusion for these 3 dogs being 36 mm Hg. The average infusion time for these runs was 7.1 minutes.

In dog 9 an infusion of 100 mg nitroprusside in 500 cc D./W at 1530 μg/min per minute (66.4 μg/kg/min) increased the basilar diameter (D₉) as did an infusion of 150 mg nitroprusside in 500 cc at 2292 μg/min per minute in dog 10 (97 μg/kg/min) (D₀). An average MAP drop for both dogs of 44 mm Hg was noted.

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### Table: Experimental Sequence

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Mean 66.4 ± 10.9 64.8 ± 80.6 ± 86.8

SE = Standard error of mean.

### Levels of Significance, 2 tailed

- D₁ vs. D₂
- D₃ vs. D₉
- D₄ vs. Max D₉-D₁

Followed by repeat angiography (D₀). In dogs 1 through 5 angiography was repeated after 15 minutes (D₁), and 30 minutes (D₂) to demonstrate return of vasospasm. If spasm returned, a second treatment with nitroprusside at 382 μg/min per minute was given in dogs 3 and 4 to show repeated drug effect (D₃). In dog 5 repeat nitroprusside infusion was given at 764 μg/min per minute (D₄), in dog 6 at 1530 μg/min per minute (D₉), and in dog 9 at 3060 μg/min per minute (D₀; 100 mg/500 cc D./W).

In dogs 6, 7, and 8 the infusion rate of nitroprusside was increased from 382 μg/min per minute to 764 μg/min per minute (D₄), 1530 μg/min per minute (D₉), and 3820 μg/min per minute (D₀) to demonstrate a dose related relaxation of spasm and the minimal change in MAP.

In dog 9, 100 mg of nitroprusside in 500 cc of 5% dextrose in water was infused after the control runs at a rate of 1530 μg/min per minute (D₉). In dog 10, 150 mg of nitroprusside in 500 cc at 2292 μg/min per minute in dog 10 (97 μg/kg/min) (D₀). An average MAP drop for both dogs of 44 mm Hg was noted.
Considering the maximum level initial nitroprusside infusion for all 10 dogs, the basilar diameter increased to 90.9 ± 2.7% of control, significantly greater than the pre-drug infusion diameter, $D_0$ ($p < 0.001$).

After 15 minutes ($D_{15}$) delay following the last nitroprusside treatment, all dogs but one showed recurrent narrowing of the basilar artery to an average diameter 73.5 ± 2.8% of control. Dog 7 did not show any change in the artery diameter.

After 30 minutes ($D_{30}$) of delay following the last nitroprusside treatment, all dogs showed recurrent basilar arterial spasm (average diameter 71.1 ± 3.2% of control). $D_{30}$ diameters were significantly smaller than the maximum diameters achieved with nitroprusside at the 0.001% level.

A second infusion of nitroprusside (50 mg in 500 cc $D_2/W$) was given in dogs 3 and 4 at 382 $\mu$g per minute ($D_5$), at 764 $\mu$g per minute in dog 5 ($D_6$), and at 1530 $\mu$g per minute in dog 6 ($D_{10}$). All animals had basilar artery enlargement, the average increase in diameter in these 4 animals from the prettrial diameter was ($D_6$) 21%. In dog 9 a second infusion of nitroprusside (100 mg in 500 cc $D_5/W$) at 3060 $\mu$g per minute (133 $\mu$g/kg/min) produced a diameter increase of 35% ($D_{11}$).

Considering the maximum level initial nitroprusside infusions for all dogs, the basilar diameter increased an average of 26.1 ± 3.3% from the pre-drug diameter ($D_0$) of 64.8 ± 2.6%. During these maximum level infusions the maximum average drop in MAP was 30 ± 5.4 mm Hg.

During all the 5% dextrose in water or nitroprusside infusions, the ICP remained normal, rising less than 5 mm Hg above its control normal level.

Pathologic examination of the brain and cervical spinal cord revealed basilar cisternal blood collections without gross parenchymal damage. The figure illustrates the basilar artery changes seen in dog 9.

**Discussion**

Even though sodium nitroprusside has been used intravenously both experimentally and clinically for the treatment of cerebral vasospasm, this agent has not

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**Figure**

Dog #9: a: Control, b: Post subarachnoid hemorrhage, c: $D_5/W$, d: Nitroprusside 1530 $\mu$g/min, e: 15 minute delay, f: 30 minute delay, g: Nitroprusside 3060 $\mu$g/min.
been administered by the arterial route for this purpose. The acute experimental cerebral vasospasm produced by subarachnoid hemorrhage in this study was clearly improved by the intra-arterial infusion of sodium nitroprusside. The degree of basilar artery spasm ($D_s$: 66.4 ± 2.1% of control) following subarachnoid blood injection is similar to that reported by Kuwayama et al. when using a similar model. The average increase in basilar diameter following the initial nitroprusside infusion was 26%. Other authors have reported increases in diameter of 28% with intravenous nitroprusside administered for treatment of experimental vasospasm.

The prior infusion of 5% dextrose in water indicates that the vehicle for nitroprusside infusion was not responsible for the dilatation. Continuous volume ventilation of these animals removed the possibility that changes in blood carbon dioxide concentration may have been responsible for the variations in basilar artery diameter. Continuous ICP monitoring demonstrated that intracranial hypertension was not a factor in this experiment.

Autoregulation can be altered because of subarachnoid hemorrhage and the infusion of nitroprusside. Although cerebral autoregulation was not directly tested in these experiments it seems unlikely that the observed basilar artery dilatation was a response to the decreased systemic MAP during the nitroprusside infusion. Examination of the maximum diameter change for each dog (Max $D_s$) and the maximum MAP drop (Max $\Delta$ MAP) reveals no clear correlation. Dog 10 demonstrated the largest drop in MAP and yet had next to the smallest change in basilar artery diameter. MAP did not change in dog 1 and yet the basilar artery diameter increased significantly.

The vascular dilatation produced by intra-arterial nitroprusside is dose related, as demonstrated by dogs 6 and 8. Large drug doses may be necessary for treatment of acute cerebral vasospasm, but appear well tolerated when given by the intra-arterial route. The maximum nitroprusside infusion employed was 153 $\mu$g/kg/min. With this large dose, other vasopressor drugs were not required to maintain adequate MAP. The average maximum drop in MAP in these experiments was 30 mm Hg. In contrast, others have reported that vasopressors may be required with the intravenous use of nitroprusside, when the infusion rate is as low as 4.31 $\mu$g/kg/min in dogs or 3 $\mu$g/kg/min in humans. The cause of this differential effect on blood pressure depending on the route of nitroprusside administration is presently unknown.

The return of acute cerebral vasospasm after 15 or 30 minutes following completion of the nitroprusside infusion suggests that the vasodilatation is secondary to the drug infusion and not to the spontaneous resolution of acute spasm. It also indicates that the effect of intra-arterial nitroprusside is transient, and to obtain a sustained vascular response a continuous drug infusion would be required. The vasodilatation produced by a second trial of intra-arterial nitroprusside (dogs 3, 4, 5, 6, 9) following the return of arterial acute spasm demonstrates that the effect of intra-arterial nitroprusside is not lost suggesting that tachyphylaxis to sodium nitroprusside does not occur within this short time frame.

Nitroprusside has been shown not to affect cerebral blood flow when given intravenously even when cerebral perfusion pressure drops to 30 mm Hg. This study shows that adequate cerebral perfusion pressures are maintained even with high doses of intra-arterial nitroprusside. Titration of intra-arterial nitroprusside to keep cerebral perfusion pressure above this minimum level while at the same time relieving the acute vasospasm should result in an increase in cerebral blood flow. Cerebral blood flow has also been reported to rise in normal animals following a direct intra-arterial injection of sodium nitroprusside.

Although ICP has been reported to rise during intravenous nitroprusside infusion, no significant elevation of ICP occurred during this study. In the clinical setting of a subarachnoid hemorrhage ICP may be elevated and intracranial compliance may be limited, so that a further rise in ICP produced by intra-arterial nitroprusside could be significant. If sodium nitroprusside is used clinically for the treatment of acute vasospasm, continuous monitoring of ICP and MAP is necessary. Cerebral vascular autoregulation may be lost following subarachnoid hemorrhage and nitroprusside itself may affect cerebral autoregulation, so every effort should be made to prevent significant changes in MAP which could lead to cerebral ischemia or increased ICP.

Prolonged infusions of nitroprusside can lead to cyanide toxicity, although this has seldom been a clinical problem. A maximum nitroprusside infusion of 1.5 mg/kg, or a 10 minute infusion of the maximum dose used in this study (153 $\mu$g/kg/min), is considered safe. With adjunctive thiosulfate, higher dose levels may be possible. Rarely, nitroprusside may lower the platelet count. With these precautions in mind, the intra-arterial use of nitroprusside to treat acute cerebral vasospasm might allow larger doses of this agent to be delivered more directly to the affected cerebral blood vessels without the need for the simultaneous administration of a vasopressor agent which could produce cardiac arrhythmias and complicate the treatment regimen.

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