Intravenous Nitroglycerin in Experimental Cerebral Vasospasm. A Preliminary Report

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SUMMARY Cerebral arteriospasm is a common complication of subarachnoid hemorrhage and is responsible for much of the brain damage which accompanies it. No pharmacologic agent has been found which regularly alleviates arteriospasm. We have evaluated the effect of continuous intravenous nitroglycerin infusion on the diameter of the basilar artery in dogs with cerebral vasospasm experimentally induced by subarachnoid blood injection. In 6 consecutive dogs, 10 minutes after beginning intravenous nitroglycerin at 100 µg/min and at other times during 120 minutes of infusion, the diameter of the basilar artery had increased from 75 ± 2% of control value to 114 ± 2% of control value (p = 0.001). In all 6 dogs, the basilar artery diameter during infusion was greater than the control value prior to creating subarachnoid hemorrhage. Intravenous nitroglycerin caused only a moderate (8%) decrease in blood pressure. Further investigation of the effects of nitroglycerin on cerebral vasospasm is warranted.

SINCE THE FIRST angiographic demonstration of cerebral arteriospasm following subarachnoid hemorrhage from a ruptured saccular aneurysm in 1951, neurologists and neurosurgeons have considered vasospasm to be a major cause of ischemic infarction and to increase the morbidity and mortality of subarachnoid hemorrhage. In 50 consecutive cases of subarachnoid hemorrhage from ruptured saccular aneurysm studied by Fisher et al., 25 (50%) developed severe vasospasm accompanied by neurological deficits directly attributable to ischemic infarction. There is no universally accepted effective therapy for relieving such vasospasm and preventing subsequent cerebral infarction. Although direct smooth muscle relaxants such as isosorbide dinitrate, magnesium sulfate, papaverine, and nitroprusside are effective in relieving experimental cerebral vasospasm, the hypotension associated with their parenteral administration has limited their clinical usefulness. Continuous intravenous infusions of nitroglycerin have been used effectively in the setting of clinical and experimental acute myocardial infarction with only modest and easily tolerated decreases in blood pressure. In addition, nitroglycerin seems to increase collateral blood flow to the ischemic myocardium while acting as a direct coronary vasodilator. Based on this evidence, as well as evidence which suggests that nitroglycerin is also a cerebral vasodilator, we tested the effects of continuous intravenous nitroglycerin therapy on experimental cerebral arteriospasm. Our preliminary results are reported here.

Methods

Six mongrel dogs weighing 13 to 24 kg, premedicated intramuscularly with ketamine, 6-8 µg/kg, and atropine 0.1 mg, were anesthetized with pentobarbital, 15 mg/kg intravenously. No paralytic drugs were used. After tracheal intubation, the right vertebral artery was catheterized and the animals were immobilized in a stereotaxic frame in the prone position. An arterial blood gas sample was obtained prior to a control vertebral angiogram using 3 ml of Renografin-76 (Meglumine diatrizoate and sodium diatrizoate injection. E. R. Squibb & Sons, Inc., NY). Subarachnoid hemorrhage was produced by injecting 3 ml of autologous blood into the cisterna magna and tilting the dogs' heads down 15 degrees for 10 minutes. The vertebral catheter was filled with heparin, sealed, and placed under the skin of the neck. The animals were extubated and returned to their cages.

Forty-eight hours later, after re-induction of anesthesia as described above, the right femoral artery and both brachial veins were catheterized. The catheter in the right vertebral artery was reopened, the animals were again placed in the stereotaxic frame, and were mechanically ventilated with a Harvard respirator (Model 607, Harvard Apparatus, Millis, MA). For the next hour arterial blood gases were monitored and the respirator was adjusted to obtain a PCO2 value similar to that at the time of the control angiogram. The femoral catheter was connected to a pressure transducer (Model T23AC, Statham Laboratories, Inc., Hato Rey, Puerto Rico). The mean arterial blood pressure was recorded with a Grass Polygraph (Model 7WC16PA, Grass Instruments Co., Quincy, MA). A normal saline infusion of 1 cc/min was begun via the right brachial vein and continued for the duration of the experiment. The left brachial vein catheter was connected to a syringe attached to a Harvard infusion pump (Model 918). After 1 hour of saline infusion an angiogram was obtained to confirm the presence of spasm of the basilar...
NITROGLYCERIN INVASOSPASM/Kistler et al.

Table 1 Diameter of Basilar Artery and Changes in Blood Pressure During Continuous Intravenous Nitroglycerin Infusion (100 µg/min)

<table>
<thead>
<tr>
<th>Dog #</th>
<th>D'</th>
<th>D''</th>
<th>ΔD</th>
<th>Dose (µg/kg/min)</th>
<th>MAP</th>
<th>MAP''</th>
<th>ΔMAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>75%</td>
<td>117%</td>
<td>42%</td>
<td>7.69</td>
<td>105 mmHg</td>
<td>99 mmHg</td>
<td>6%</td>
</tr>
<tr>
<td>2</td>
<td>82%</td>
<td>119%</td>
<td>37%</td>
<td>6.9</td>
<td>125 mmHg</td>
<td>109 mmHg</td>
<td>13%</td>
</tr>
<tr>
<td>3</td>
<td>77%</td>
<td>113%</td>
<td>36%</td>
<td>5.41</td>
<td>130 mmHg</td>
<td>118 mmHg</td>
<td>9%</td>
</tr>
<tr>
<td>4</td>
<td>75%</td>
<td>106%</td>
<td>31%</td>
<td>5.41</td>
<td>130 mmHg</td>
<td>124 mmHg</td>
<td>5%</td>
</tr>
<tr>
<td>5</td>
<td>69%</td>
<td>112%</td>
<td>43%</td>
<td>4.17</td>
<td>135 mmHg</td>
<td>125 mmHg</td>
<td>7%</td>
</tr>
<tr>
<td>6</td>
<td>73%</td>
<td>119%</td>
<td>46%</td>
<td>7.04</td>
<td>145 mmHg</td>
<td>130 mmHg</td>
<td>10%</td>
</tr>
</tbody>
</table>

Mean ± SEM 75% ± 2 114% ± 2 39% ± 2 6 ± 1 128 ± 5 117 ± 5 8% ± 1

Student's t 14.12 6.95 17.47 6.94

Level of significance (2 tail) p < 0.001  p < 0.001  p < 0.001  p < 0.001

artery. Subsequently, an intravenous bolus of 300 µg of nitroglycerin was injected to test for reactivity to the drug. One minute later, after the blood pressure had returned to within 90% of the control value, the continuous intravenous infusion of nitroglycerin was begun. The infusion rate was set at 100 µg/min and was continued for 120 minutes. Angiograms were taken during this period and for 1 hour after discontinuing the nitroglycerin infusion, while still maintaining the saline infusion. All angiograms were taken by injecting 3 ml of Renografin-76 through the right vertebral artery catheter. A constant x-ray tube-head-film distance was carefully maintained. The diameter of the basilar artery, as seen on the angiogram, was measured by 2 different observers using a measuring magnifier with a metric scale engraved at 0.1 mm intervals (Bausch & Lomb, Boston, MA).

At the completion of the experiment the animals were sacrificed. Their brains were then examined neuropathologically to determine the location of the subarachnoid hemorrhage as well as to establish the presence of any areas of infarction or intracerebral hemorrhage.

The significance of changes in blood pressure and arterial diameter was assessed by the Student t-test.

Results

The effects of continuous intravenous infusion of nitroglycerin at 100 µg/min on the diameter of the basilar artery and on mean arterial blood pressure in six dogs is seen in table 1. All diameters are expressed as percent of the control diameter of the basilar artery before subarachnoid hemorrhage.

Forty-eight hours after the induction of subarachnoid hemorrhage all animals had spasm of the basilar artery which reduced the diameter of that vessel to a mean value of 75% of control (table 1 and figs. 1, 2 and 3). The data were remarkably homogeneous for each of the 6 dogs. During nitroglycerin infusion, the diameter of the basilar artery increased promptly and dramatically to values greater than control (p < 0.001). Throughout the 120 minutes of infusion the artery remained dilated, yet 10 minutes after discontinuing nitroglycerin the diameter decreased to slightly less than control values (fig. 2). Sixty minutes after nitroglycerin was stopped, basilar arterial diameter had decreased to values only slightly above those recorded 48 hours after subarachnoid hemorrhage (figs. 2, 3). A modest but definite decrease in mean arterial pressure was noted during the infusion which returned promptly to control value after nitroglycerin was discontinued (table 1). With the use of the respirator, arterial PCO₂, pH and PO₂ remained stable throughout the entire experiment. The PCO₂ measured at the time of each arteriogram varied no more than 5 mm Hg. Neuropathological examination of each brain showed subarachnoid blood around the
basilar artery. There was no evidence of cerebral hemorrhage or infarction.

**Discussion**

Sublingual nitroglycerin has long been regarded as a safe and effective vasodilator. Recently it has been given intravenously and intra-arterially in clinical and experimental acute myocardial infarction. Evidence from these studies suggests that it improved collateral flow to the ischemic myocardium. Despite the increasing use of intravenous nitroglycerin in patients with cardiac disease little is known about its effect on the cerebral circulation. Poletti et al. applied nitroglycerin in dogs topically to branches of the middle cerebral artery put into spasm by subarachnoid blood and they found nitroglycerin to be a potent cerebral vasodilator. Low and Gilboe, using an isolated preparation of canine brain, showed a decrease in peripheral resistance of the cerebral circulation after intra-carotid injection of nitroglycerin. They also suggested that nitroglycerin was a potent cerebral vasodilator.

We began studying the effect of intravenous nitroglycerin on cerebral blood vessels and cerebral circulation for two reasons: First, there is no proven effective therapy for cerebral vasospasm. Nitroglycerin as a vasodilator has only mild hypotensive properties and may increase collateral flow to ischemic tissues. Second, although it is now being widely used as a vasodilator in patients with cardiac disease, little is known about its effect on cerebral blood vessels and cerebral circulation.

Our preliminary studies were designed to evaluate the effects of continuous intravenous nitroglycerin infusion on experimentally induced cerebral vasospasm. Six consecutive dogs were studied 48 hours after subarachnoid hemorrhage to eliminate confusion with the transient spasm lasting less than 3 hours which is seen after acute injection of blood into the subarachnoid space. Each animal served as its own control. Because a continuous saline infusion was maintained before, during, and after the study, the only variable was the nitroglycerin infusion. The cerebrovascular response to nitroglycerin was prompt, dramatic and almost identical in all 6 dogs resulting in a mean increase in basilar artery diameter of 39% ($p < 0.001$). This therapeutic effect was accomplished with a decrease in mean arterial pressure of only 8%.

Because of the results of our animal work we have begun to study the effects of nitroglycerin in patients with cerebral vasospasm. Initially we have only used it when more traditional therapy to increase cerebral perfusion has failed to stop progressive neurological deterioration. We cannot, as yet, recommend nitroglycerin for human use in cerebral vasospasm. We believe, however, that further investigation of its effect on cerebral hemodynamics in vasospasm and stroke is needed.

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Serial Measurement of Cerebral Blood Flow Using External Counting of Microspheres

T. A. MCALDEN, PH.D.

SUMMARY Described is a modified method of measuring organ blood flow which combines the serial injection of a standard dose of microspheres and the external counting of their gamma activity when they are distributed to the tissues. The method produces similar results to measurements of grey matter blood flow by the clearance of $^{133}$Xenon.

USE OF EXTERNAL counting of the clearance of a radioactive inert gas such as $^{133}$Xenon to measure blood flow is widespread. However, the technique involves certain assumptions which may not be correct when comparing a control to an experimental measurement. In the study of cerebral blood flow the use of the $^{133}$Xenon technique has recently been criticized. The main arguments used were that the extracerebral tissues were not excluded from the counting field, the capillary permeability for xenon may alter and the analysis of the clearance curve is often not as straightforward as a simple biexponential curve. The radio-labelled microsphere technique was proposed as a viable alternative. However, this microsphere technique has certain drawbacks. The number of flow determinations is limited by the number of differently labelled microspheres available. The alterations in flow may not be monitored as an experiment proceeds, and the addition of an isotope, such as $^{95}$Nb, with a large amount of backscatter into low keV ranges, will render inaccurate counting of low keV isotopes ($^{141}$Ce). In addition, it is possible that serial lodging of spheres in the tissue may alter flow. The present study has resolved some of these disadvantages by external counting of standard injections of microspheres with a single radiolabel.

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