The effect of nimodipine on intracranial pressure

Volume-pressure studies in a primate model

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Nimodipine was administered by intravenous infusion to six male baboons before, during, and after 6 hours of middle cerebral artery occlusion. Intracranial pressure (ICP) and systemic blood pressure were monitored continuously. An epidural balloon was inflated at regular intervals at three levels of arterial CO₂ tension (25, 35, and 50 mm Hg) before and after the administration of nimodipine, and volume-pressure curves were generated. In every case, curves generated after intravenous nimodipine infusion were lower and shifted more to the right than the same set of curves generated before nimodipine administration, regardless of the baseline ICP. The reduction in ICP following nimodipine infusion was not due to a reduction in mean arterial blood pressure and was statistically significant at all three levels of pCO₂ (p < 0.01). These results suggest that, in the presence of elevated ICP due to cerebral infarction, there is no increased risk of exacerbating intracranial hypertension with the addition of nimodipine.

KEY WORDS • nimodipine • intracranial pressure • calcium channel blocker • baboon

Nimodipine, a calcium channel blocker, has been shown to increase cerebral blood flow (CBF), particularly in areas of the brain where the blood-brain barrier has been disrupted. Increased CBF in these regions could potentially lead to deleterious increases of intracranial pressure (ICP), particularly in a patient with extensive swelling from stroke or a mass lesion. For this reason, investigators have cautioned against using calcium antagonists in acute stroke patients.

This laboratory investigation was undertaken to define the effects of nimodipine administration on ICP in a primate stroke model. Volume-pressure curves were generated by inflating an epidural balloon at intervals before, during, and after stroke in six animals to mimic the clinical situation in a patient with a stroke or other intracranial mass lesion. Curves were obtained before and after an intravenous injection of nimodipine at each data collection interval for 54 hours following temporary middle cerebral artery (MCA) occlusion.

Materials and Methods

Experimental Model

Six male baboons (Papio anubis) were used for the experiment. All were exempted from one of two other MCA stroke studies due to protocol violations. The animals were sedated with a 3-cc intramuscular injection of a 9:1 ketamine:acepromazine mixture. An intravenous cannula was inserted, and lactated Ringer’s solution was administered in a 500-cc bolus followed by a constant infusion of 70 cc/hr. Pancuronium bromide (Pavulon, 4 mg) and thiopental sodium (Penthal, 100 mg) were given intravenously, and the animal was intubated. An arterial cannula was inserted in the femoral artery for continuous recording of blood pressure. Paralysis and sedation were maintained with intravenous infusion of pancuronium bromide, 1 mg/hr, and thiopental sodium, 60 mg/30 min. The animals were mechanically ventilated with an oxygen:air mixture (30%:70%). Frequent arterial blood gas determin-
TABLE 1
Summary of experimental protocol*

<table>
<thead>
<tr>
<th>Time</th>
<th>Manipulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>volume-pressure curves generated; nimodipine infusion (50 µg/kg over 50 min), followed by additional volume-pressure curves</td>
</tr>
<tr>
<td>0 hr</td>
<td>MCA occ via transorbital approach</td>
</tr>
<tr>
<td>1 hr: 1 hr postocc</td>
<td>volume-pressure curves generated before &amp; after nimodipine infusion (50 µg/kg over 50 min)</td>
</tr>
<tr>
<td>6 hrs: 6 hrs postocc</td>
<td>MCA RPF; clip removed after 6 hrs of total occlusion</td>
</tr>
<tr>
<td>10 hrs: 4 hrs post-RPF</td>
<td>volume-pressure curves generated before &amp; after nimodipine infusion (50 µg/kg over 50 min)</td>
</tr>
<tr>
<td>14 hrs: 8 hrs post-RPF</td>
<td>termination</td>
</tr>
<tr>
<td>22 hrs: 16 hrs post-RPF</td>
<td></td>
</tr>
<tr>
<td>30 hrs: 24 hrs post-RPF</td>
<td></td>
</tr>
<tr>
<td>38 hrs: 32 hrs post-RPF</td>
<td></td>
</tr>
<tr>
<td>46 hrs: 40 hrs post-RPF</td>
<td></td>
</tr>
<tr>
<td>54 hrs: 48 hrs post-RPF</td>
<td></td>
</tr>
</tbody>
</table>

* Experiments were conducted with the baboons under continuous anesthesia and sedation maintained with pancuronium bromide 1 mg/hr and thiopental sodium 60 mg/30 min. Volume-pressure curves were generated in each instance at pCO2 levels of 25, 35, and 50 mm Hg. MCA = middle cerebral artery; occ = occlusion; RPF = reperfusion.

Fig. 1. Artist’s sketch depicting temporary occlusion of the middle cerebral artery (arrow) and the location of the epidural balloon catheter and intracranial pressure monitor.

French Foley catheter was inserted into the epidural space (Fig. 1). This 10-cc balloon catheter was connected to a Harvard infusion pump for inflation and deflation. The right MCA was exposed via the transorbital route, and a temporary vascular clip was applied at its origin from the internal carotid artery. After 6 hours of MCA occlusion, the clip was removed, the orbital cavity was filled with cranial resin, and the incision was closed. Anesthesia was maintained with intravenous pancuronium bromide, 1 mg/hr, and thiopental sodium, 60 mg/30 min. Each animal received Cefadyl (cephapirin), 1 gm intravenously every 12 hours.

Before temporary MCA occlusion, initial volume pressure curves were generated. These studies were performed at three separate end-tidal pCO2 levels: 25, 35, and 50 mm Hg, verified by a real-time capnometer correlated with arterial blood gases. The balloon catheter in the epidural space was gradually inflated (maximum inflation 10 cc or an ICP of 120 torr). The ICP and mean arterial blood pressure (MABP) were continuously recorded on a channel polygraph recorder. To create volume-pressure curves, the ICP was determined at each milliliter of balloon inflation.

After the initial baseline studies, a loading dose of nimodipine (50 µg/kg) was administered intravenously over 50 minutes. After administration of the loading dose, volume-pressure curves were repeated at the same three end-tidal pCO2 levels. Repeat volume-pressure curves, with and without nimodipine, were generated at 1 and 6 hours after MCA occlusion, at 4 hours after removal of the MCA clip, and then at 8-hour intervals for 48 hours after reperfusion (Table 1). In most cases,...
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Results

All animals demonstrated an increase in CBF after the administration of nimodipine as measured by stable-xenon CT studies (Fig. 2). Mean CBF values were 65.0 ± 13 cc/100 gm/min (± standard error of the mean) at baseline and 84.5 ± 9 cc/100 gm/min after nimodipine infusion (an average increase of 30%). The infusion of nimodipine, 50 µg/kg over 50 minutes, reduced the MABP from 94.5 ± 15 to 82.1 ± 18 mm Hg (13%), a reduction that persisted beyond the first 15 minutes of the infusion in only 23% of the infusions.

All animals developed a stroke in the right MCA distribution, and the ICP increased progressively over the 54 hours of the study. The average ICP at pCO2 35 mm Hg was 6.1 torr at the initiation of the study and 24.2 torr at the conclusion of the study. At autopsy, all of the brains had MCA infarctions similar to those described with this technique in other primate models of temporary MCA occlusion.10-13

In every case, the volume-pressure curves generated at the lowest level of pCO2 (25 mm Hg) were lower (mean 26.4 ± 2.3 mm Hg) than the curves generated at a pCO2 of 35 mm Hg (mean 34.6 ± 3.7 mm Hg), which in turn were lower than the curves generated at a pCO2 of 50 mm Hg (mean 51.2 ± 2.7 mm Hg). This relationship held whether no drug, saline, placebo (nimodipine carrier), or nimodipine was administered before generating the volume-pressure curves. Furthermore, this relationship held irrespective of the baseline ICP.

In addition, curves generated after nimodipine administration were lower, and they were shifted more to the right than the same set of curves generated before nimodipine administration. This relationship held regardless of the order in which the three curves were obtained or the amount of cerebral swelling present (as indicated by the increase in ICP during the evolution of the stroke, Fig. 3). This reduction in ICP was statistically significant at every data collection interval at all three levels of pCO2 (p < 0.02), except three times at pCO2 25 mm Hg (Table 2). This effect was not seen with the infusion of normal saline or with the infusion of nimodipine carrier. The r value (the numerical value that describes the percentage of correlation between the raw data points for each curve and the respective curve of best fit) was statistically significant (p < 0.05) for every curve generated.

The MABP was not markedly different before and after the administration of nimodipine. In almost every

Fig. 2. Results of stable-xenon computerized tomography studies of cerebral blood flow (CBF) before (left) and after (right) administration of nimodipine (1 µg/kg/min). The mean increase in CBF in all animals was 30%.
case, there was a transient reduction in MABP (average 13%, range 10% to 18%) when the infusion was initiated; however, this infrequently (23% of the infusions) persisted longer than 15 minutes. Cerebral perfusion pressure was the same or higher after the addition of nimodipine compared to CPP before the administration of nimodipine at 80% of the data collection intervals (Fig. 4). At no time did the administration of nimodipine in the dose given cause marked systemic hypotension or dramatically impair CPP.

Discussion

Nimodipine, a slow channel calcium antagonist with preferential effects on central nervous system (CNS) blood vessels, has been the subject of considerable investigation in recent years. It appears to have several physiological effects that may be of benefit in the treatment of CNS ischemia and stroke. These include the ability to increase CBF selectively,\(^3,4,8,14\) to inhibit constriction of cerebral vessels in response to a number of vasoactive agents,\(^9-18\) and to block postischemic hypoperfusion.\(^6,7\) Pretreatment with nimodipine has been shown to improve neurological recovery in dogs subjected to transient complete cerebral ischemia.\(^14\) Rabbits subjected to focal cerebral ischemia had improved cortical blood flow, preservation of intracellular brain pH, and improved electroencephalographic activity following treatment with nimodipine.\(^7\) These effects were dose-dependent.\(^2,6-9,14,18\)
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TABLE 2

<table>
<thead>
<tr>
<th>Time of Measurement</th>
<th>Level of pCO2</th>
<th>25 mm Hg</th>
<th>35 mm Hg</th>
<th>50 mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td></td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0015</td>
</tr>
<tr>
<td>1 hr postocc</td>
<td></td>
<td>0.3067</td>
<td>0.0001</td>
<td>0.0025</td>
</tr>
<tr>
<td>6 hrs postocc</td>
<td></td>
<td>0.264</td>
<td>0.0001</td>
<td>0.0025</td>
</tr>
<tr>
<td>4 hrs post-RPF</td>
<td></td>
<td>0.0013</td>
<td>0.0037</td>
<td>0.0008</td>
</tr>
<tr>
<td>8 hrs post-RPF</td>
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<td>0.0026</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>16 hrs post-RPF</td>
<td></td>
<td>0.0001</td>
<td>0.0007</td>
<td>0.0001</td>
</tr>
<tr>
<td>24 hrs post-RPF</td>
<td></td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>32 hrs post-RPF</td>
<td></td>
<td>0.001</td>
<td>0.0001</td>
<td>0.0005</td>
</tr>
<tr>
<td>48 hrs post-RPF</td>
<td></td>
<td>0.1191</td>
<td>0.0002</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* Levels of statistical significance at each data collection interval (left column) for intracranial pressure (ICP) data generated at each level of pCO2 before and after the administration of nimodipine. At three points in time the differences in ICP before and after nimodipine were not statistically significant (NS). occ = occlusion; RPF = reperfusion.

In baboons, the effects of nimodipine on CBF also appear to be dose-dependent. Several investigators have determined that the optimal intravenous dose of nimodipine (that which maximally increases CBF yet preserves cerebral vasoresponsiveness and prevents systemic hypotension) appears to be between 1.0 and 2.0 µg/kg/min. We used 50 µg/kg of nimodipine as a loading dose and infused it over 50 minutes. Administering the loading dose more rapidly caused marked systemic hypotension. The rate of infusion of 1 µg/kg/min resulted in only a modest fall in mean pressure (13%), a reduction that did not persist longer than 15 minutes from the start of the infusion 77% of the time. The observed increase in CBF (30% above control values) as determined by stable-xenon CT studies at a pCO2 of 35 mm Hg is comparable to that reported by other investigators who employed similar techniques.

The effects of intravenous nimodipine on ICP have not been defined in previous studies. Harper, et al., documented increases in CBF following nimodipine administration in regions in which the blood-brain barrier had been disrupted that were nearly twice the level recorded for nimodipine-enhanced CBF without barrier defects. They postulated that the increased perfusion to regions of blood-brain barrier disruption might have therapeutic advantages and limit infarct size. Others have expressed concern that the increase in CBF observed with nimodipine may increase fluid and protein extravasation in the areas of barrier disruption and cause focal swelling with a subsequent increase in ICP. Harris, et al., noted that the metabolism of cellular energy is more susceptible to ischemic damage after nimodipine infusion. They documented an increase in permeability to calcium and potassium ions and a resultant increase in water accumulation in areas of focal ischemia in nimodipine-treated primates. Bedford, et al., measured ICP in five patients with supratentorial mass lesions after the intravenous administration of verapamil. They noted a statistically significant rise in ICP within 4 minutes after verapamil infusion (from 18 ± 3 to 29 ± 5 mm Hg; p < 0.05). It is not known whether this effect would have persisted because after the ICP rise they treated all patients rapidly with lidocaine and hyperventilation; they did not report the level of pCO2 at which these observations were made, nor whether the pCO2 levels changed during the experiments. They speculated that the increase in ICP in their patients after a 5-mg bolus injection of verapamil (a dose and rate of administration that is not equivalent to that employed in our model) was due to a reduction in cerebrovascular resistance and an increase in cerebral blood volume. The average reduction in mean blood pressure seen in their patients was 20%, a drop not significantly different from the reduction in blood pressure observed in our model (13%). The two studies also differ with respect to their time courses and the calcium antagonist tested. Bedford, et al., examined the acute effects of a bolus of verapamil on ICP while our study examined ICP after the gradual infusion of nimodipine over 50 minutes.

The reported increase in ICP (whether due to global increases in CBF or to focal mechanisms) could result in reduced blood flow to the regions of ischemia, conceivably allowing the ischemic process to extend and thus expanding the size and extent of the cerebral infarction. The risk would presumably be greatest in patients with swelling from infarction, tumor, or an
intracranial hemorrhage. This question of increased ICP with calcium antagonist therapy has particular current interest, given that several clinical studies are underway to evaluate the efficacy of calcium antagonists in stroke patients.

Our findings that nimodipine reduces ICP even in the presence of blood-brain barrier disruption from a stroke, with or without an additional mass effect and regardless of the level of pCO₂, appear to contradict earlier fears. Our studies performed before and after focal blood-brain barrier disruption demonstrated that, in the presence of elevated ICP due to stroke, nimodipine did not increase ICP further. Despite the addition of an epidural mass to raise ICP even higher, nimodipine at no time elevated ICP but rather shifted all volume-pressure curves down and to the right. The reduction in ICP with nimodipine was statistically significant (p < 0.01) and was not observed when placebo or saline was substituted for the nimodipine infusion. The rise in ICP within minutes of calcium antagonist infusion, as reported by Bedford, et al., was not observed by us — a difference that could be due to the pharmacological differences in the calcium antagonists employed in the two models.

The mechanism by which nimodipine increases CBF yet reduces ICP is elusive. It is not likely that this is caused by the drop in mean systemic blood pressure that was observed with each nimodipine infusion for two reasons: 1) a drop in mean blood pressure of 13% (on average) should have little or no effect on CPP or ICP if autoregulatory mechanisms remain intact; and 2) the reduction in mean blood pressure was rarely sustained during the infusions (typical duration 15 minutes), yet the reduction in ICP was consistent and reproducible up to 60 minutes postinfusion. Our data demonstrate that the effect of nimodipine on ICP outlasted its effect on systemic blood pressure and preserved or improved CPP in the majority of cases.

McCalden, et al., demonstrated that a nimodipine infusion of 1 μg/kg/min in baboons increased CBF 20% above control levels, had little effect on mean systemic blood pressure, and significantly reduced the mean cerebrovascular resistance (p < 0.05). This decrease in cerebrovascular resistance may be due to vasodilatation of cerebral vessels and/or inhibition of vascular constriction. Calcium antagonists appear to inhibit the final common pathway of cerebrovascular reactivity initiated by calcium ions.

Several investigators have reported that nimodipine interferes with the normal responses of the cerebral vessels to alterations in arterial CO₂ tension. Calculations have revealed that nimodipine markedly attenuates the normal cerebrovascular responses to both hyper- and hypocapnia. Cerebral blood flow does not increase as much per mm Hg increase in arterial CO₂ tension after nimodipine infusion nor does it fall as much per mm Hg reduction in pCO₂ as expected (not statistically significant) compared to control animals not treated with nimodipine. This reduction in the responsiveness of the cerebrovasculature to CO₂ caused by nimodipine does not explain the reduction in ICP observed at every measured time at all three levels of pCO₂ studied (25, 35, and 50 mm Hg). We suspect that the reduction in ICP with the administration of nimodipine at the dose given (1 μg/kg/min, a dose known to increase CBF while maintaining arterial blood pressure) must be due to a reduction in total cerebral blood volume. Other mechanisms to explain a reduction in ICP (holding mean blood pressure relatively constant), such as a reduction in cerebrospinal fluid or interstitial or intracellular fluid volumes, are unlikely because the reduction in ICP occurred too rapidly after the infusion of nimodipine. While our findings are contradictory to those reported by Bedford, et al., we believe a reduction in cerebral blood volume is the most likely explanation of our results.

To clarify the mechanism of action of nimodipine, further studies that simultaneously measure CBF, ICP, and cerebral blood volume should be pursued. Based on our present observations, however, we conclude that in the presence of elevated ICP from cerebral infarction there is no increased risk of exacerbating intracranial hypertension with the addition of nimodipine.

References

10. Selman WR, Spetzler RF, Roessmann UR, et al: Barbi-
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