Nimodipine Improves Outcome when Given after Complete Cerebral Ischemia in Primates

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Twenty-seven pigtailed monkeys (Macaca nemestrina) were subjected to 17 min of complete cerebral ischemia followed by 96 h of intensive care treatment. Fourteen of the monkeys were assigned randomly to the treatment group and received nimodipine 10 µg·kg⁻¹·min⁻¹ for 10 h. Six monkeys (three treated) failed to meet preestablished protocol criteria and were excluded. The remaining treated and untreated monkeys were well matched for age, sex, and other physiologic variables. Neurologic outcome at 96 h postischemia was significantly better in the nimodipine-treated monkeys than in the controls. Eight of the 11 treated animals had an apparent normal level of consciousness; four of these had no detectable neurologic deficits and a fifth had only a slight motor apraxia. Only two of the 10 untreated animals had an apparent normal level of consciousness, and all had major neurologic deficits. Histopathologic examination showed variable ischemic neuronal change and infarction to involve gray matter in distal arterial perfusion zones. Significant white matter changes were not observed. A histopathologic scoring system yielded a significantly better mean score for the treated group than for the untreated group, and there was significant correlation between neurologic function and histopathologic findings. The authors conclude that nimodipine improves the neurologic outcome when given after an episode of complete cerebral ischemia in primates, and they recommend controlled clinical trials in patients resuscitated after cardiac arrest. (Key words: Brain: ischemia. Heart: cardiac arrest. Ions: calcium. Pharmacology: nimodipine.)

Approximately 40% of patients who are resuscitated effectively after cardiac arrest never regain consciousness and they die in the hospital, while an estimated 20% survive and have severe brain damage. Extensive research during the last two decades has been directed toward efforts to improve this dismal outcome; however, results have been disappointing, and no effective therapy has been established. The hoped-for benefit of barbiturate therapy has failed to materialize, as early promising results in two animal studies could not be reproduced, while a trial in patients failed to demonstrate any benefit.

During the last few years, interest has focused on calcium entry blockers for treating both cerebral and cardiac ischemia. With possible beneficial effects for both organs, calcium entry blockers might be of benefit in treating patients after cardiac arrest. Improved neurologic outcome after simulated cardiac arrest indeed has been reported in cats and dogs when treated with the calcium entry blocker nimodipine before the ischemic event. One possible mechanism is that nimodipine improves postischemic cerebral blood flow (CBF), which otherwise is decreased greatly for a prolonged period (down to 20% of control for at least 6 h in dogs), despite an adequate arterial blood pressure. This so-called delayed postischemic hyperperfusion state has been suggested to be responsible for a substantial degree of the ultimate neurologic damage.

Pretreatment may be appropriate in the animal laboratory, but it is usually not applicable to the management of cardiac arrest in patients, with the possible exception of controlled arrest during cardiopulmonary bypass. In dogs, when nimodipine was given only after the ischemic event, it increased the postischemic CBF to the same magnitude as was observed in dogs treated prior to ischemia. However, the neurologic outcome was intermediate, with results that were numerically better than those for untreated dogs and worse than for dogs treated with nimodipine prior to the ischemia, but

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not significantly different from either group. These outcome results were obtained in a relatively crude model of cardiac arrest and were considered sufficiently promising to justify additional studies in a more sophisticated animal model. Accordingly, we studied the effects of nimodipine given 5 min after 17 min of complete selective cerebral ischemia in primates, followed by 96 h of intensive care treatment. Improved neurologic outcome was observed in animals treated with nimodipine and should provide the justification needed for controlled clinical trials.

**Methods**

**Study Subjects and Preischemic Preparation**

Twenty-seven unmedicated pigtailed monkeys (Macaca nemestrina) of either sex, weighing 3.3 to 7.2 kg, were studied. The protocol was approved by the institutional Animal Care Committee. The monkeys uniformly were fed but received only water *ad libitum* the last 24 h before the experiment. They initially were anesthetized with halothane 0.5% and nitrous oxide 66% in oxygen. Succinylcholine 7 mg·kg⁻¹ was given im to facilitate endotracheal intubation with a cuffed wire–spiral reinforced tube, and ventilation was controlled with a Harvard® pump. Muscle relaxation was maintained with pancuronium 0.1 mg·kg⁻¹ iv initially, followed by doses of 0.02 mg/kg as needed. Through a peripheral iv catheter, all monkeys received 50–75 ml 5% dextrose in 0.45% saline preischemia. Catheters were placed in the abdominal aorta via the femoral artery for blood sampling and pressure monitoring and in the inferior vena cava via the femoral vein for drug infusions. The EEG (bifrontal) and ECG were monitored by percutaneous needle electrodes. Body temperature was measured with a rectal thermistor and maintained close to 36.8° C throughout the experiment with the use of heating pads and heat lamps when needed. End-tidal CO₂ was monitored with a Beckman LB-2® infrared analyzer, and arterial blood gases were determined by electrodes (Instrumentation Laboratories) at 37° C. Arterial blood gases and hematocrit were measured immediately preischemia and frequently postischemia. Serum electrolytes and blood glucose were determined preischemia and 24 h postischemia. A collapsed inflatable tourniquet that would be used to produce ischemia was placed around the neck. Halothane was discontinued for 4–5 min before ischemia was induced.

**Ischemic Period**

Complete cerebral ischemia was produced by a method previously described by Bleyaert et al.⁴ and Gisvold et al.⁶ Rapid induction of hypotension (within 1 min) was induced by trimethaphan, 20–40 mg iv, to a mean arterial pressure (MAP) of approximately 50 mmHg. At this MAP the neck cuff was inflated abruptly to 1,500 mmHg for an ischemic period lasting exactly 17 min. The inhaled gas was changed to 100% O₂ at the beginning of ischemia. A tendency to hypertension usually lasting the first 5 min of ischemia was counteracted by the use of trimethaphan and positive end-expiratory pressure (PEEP) to maintain MAP at 50–80 mmHg. After exactly 14 min of ischemia, a norepinephrine drip was started at 0.4 μg·kg⁻¹·min⁻¹ and adjusted as needed to maintain MAP at 80 mmHg just before cuff deflation. Immediately after deflation, MAP always decreased abruptly but was restored rapidly to a MAP of 80–110 mmHg by adjusting the rate at which norepinephrine was infused.

Completeness of cerebral ischemia was assured by the absence of cerebral blood flow monitored with ¹³³Xe. Immediately after inflation of the cuff, ¹³³Xe was added to the inspired oxygen at a concentration of 3 mCl/l O₂. Lead collimated scintillation detectors with 1½ X ½ inch NaI crystals recessed 1 inch behind a ½ inch opening were placed over the lower abdomen and on each side of the head. The detector over the abdomen gave a reading of >10,000 cpm during the ischemic period, while any increase in radioactivity above the background level detected by the detectors over the head was interpreted as failure to achieve complete cerebral ischemia.

**Postischemic Treatment**

Five minutes postischemia, the monkeys received either nimodipine 10 μg·kg⁻¹ iv as a bolus given over a 2-min period, followed by an infusion of 1 μg·kg⁻¹·min⁻¹ for 10 h or similar volumes of a placebo‡‡ according to a randomized list. All personnel were blinded as to the treatment groups except for one technician (WG). The animals were studied in groups of four to six per week. Optimal life support was given for 96 h postischemia; the monkeys were at all times attended by a minimum of two technicians and a physician.

Paralysis and controlled ventilation were maintained for the initial 24 h, with 100% O₂ for the first 2 h and N₂O 50% in oxygen thereafter until extubation. N₂O, which has been shown to have no effect on outcome in this model,¹⁷ provided analgesia and sedation during immobilization in an attempt to avoid a previously reported severe hypertensive reaction¹⁸ and to blunt

‡‡ The solvent for nimodipine was used as the placebo. This contained per deciliter: ethanol 15 g, polyethylene glycol 15 g, sodium citrate 0.2 g, and citric acid 0.08 g.
TABLE 1. Neurologic Deficit Score (Maximum deficit = 500 points, normal = 0 points)

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Score</th>
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<tbody>
<tr>
<td>I.</td>
<td>Level of consciousness (0–200 points)</td>
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<tr>
<td></td>
<td>normal 0, clouded 30, stupor 60–120, coma 200</td>
<td></td>
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<tr>
<td>II.</td>
<td>Respiration (0–60 points)</td>
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<tr>
<td></td>
<td>normal 0, abnormal 20–40, ventilator dependent 60</td>
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<tr>
<td>III.</td>
<td>Cranial nerve function (0–80 points)</td>
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<tr>
<td></td>
<td>normal 0, moderately abnormal 4, severely abnormal 8, for each of 10 reflexes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>pupal size, light reflex, eye position, eyelid reflex, corneal reflex, ciliary reflex, ocular reflex, auditory response, gag reflex, carinal cough reflex</td>
<td></td>
</tr>
<tr>
<td>IV.</td>
<td>Motor and sensory function (0–80 points)</td>
<td></td>
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<tr>
<td></td>
<td>Grasp: normal 0, abnormal 10, pathologic grasp reflex 20</td>
<td></td>
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<td></td>
<td>Response to pain: quick appropriate response in all limbs 0, sluggish response in all limbs 10, inappropriate response in one or more limbs 20</td>
<td></td>
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<tr>
<td></td>
<td>Body position: normal 0, mild opisthotonus 10, severe opisthotonus 20</td>
<td></td>
</tr>
<tr>
<td>V.</td>
<td>Behavior (0–80 points)</td>
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<tr>
<td></td>
<td>Walking: normal 0, ataxic walk 10, unable to walk 20</td>
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<td></td>
<td>Feeding: normal 0, ataxic feeding 10, unable to feed 20</td>
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<td></td>
<td>Chewing: normal 0, unable to chew 10</td>
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<td></td>
<td>Sitting: normal 0, sits with support 3, unable to sit 10</td>
<td></td>
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<tr>
<td></td>
<td>Standing: normal 0, stands with support 5, unable to stand 10</td>
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<td></td>
<td>Self cleaning: normal 0, unable to groom 10</td>
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<td></td>
<td>0 points = normal 500 points = brain death</td>
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Any increase in CBF and metabolism results from the stress of immobilization.17, 18 $P_{aCO_2}$ was maintained at 25–30 mmHg and $P_{aO_2}$ above 100 mmHg by increasing $F_{aO_2}$. A minimum of 2–3 cmH$_2$O PEEP was maintained. Respiratory care included tracheal suctioning when needed, intermittent deep lung inflations (sighing), chest physiotherapy, and turning the monkeys from side to side every 4 h. At 24 h postischemia, the residual effects of the muscle relaxant, pancuronium, were reversed with atropine, 0.25 mg, and neostigmine, 0.5 mg iv. Controlled ventilation was terminated and their tracheas extubated if spontaneous ventilation was deemed adequate as judged by the presence of carinal and pharyngeal reflexes and maintenance of a $P_{aCO_2} < 35$ mmHg.

MAP was maintained at 80–120 mmHg the first 24 h postischemia. This required a norepinephrine infusion during the first hours postischemia. Trimethaphan (3–15 $\mu$g·kg$^{-1}$·min$^{-1}$) later was used as needed to avoid hypertension. Five percent dextrose in 0.45% NaCl was infused at 5 ml·kg$^{-1}$·h$^{-1}$ for the first 24 h and continued thereafter until the monkeys could take enough fluids per os. Potassium chloride 10–20 mMq·h$^{-1}$ was added to the iv fluids, with the amount adjusted according to the K$^+$ content of the urine. The maintenance iv infusion was increased or lactated Ringer’s solution was given if necessary to compensate for excessive urine losses, while furosemide 1 mg iv was given if urine output was below 1 ml·kg$^{-1}$·h$^{-1}$ in any 4-h period. Diazepam 0.1 mg·kg$^{-1}$ iv was given if necessary to treat seizures during the first 48 h postischemia. Gentamicin 1 mg·kg$^{-1}$ iv was given every 8 h during the first 2 days. Benzathine penicillin, 300,000 units, and procaine penicillin, 300,000 units im, were given daily. Arterial and central venous catheters usually were removed at 24 h postischemia to allow the monkeys to move freely. When their condition permitted, the monkeys were moved to padded open pens, and when they were judged to be near normal, they were returned to their cages. In all animals, age estimates based primarily upon dentition were made by a veterinarian who was unaware of the treatment groups.

EXCLUSIONS

Animals that did not meet all preestablished protocol criteria were excluded from data analysis before the final 96-h evaluation. The decision to exclude animals was made by a blinded observer (JDM) who was unaware of treatment groups and of the hemodynamic response to the drug or placebo injection. Exclusion was based upon strict criteria: Age > 10 years old; a preischemic blood glucose > 180 mg/dl;§§; evidence of incomplete ischemia; severe infections or severe cardiopulmonary complications such as pulmonary edema resulting in a postischemic $P_{aCO_2} < 60$ mmHg and/or $P_{aCO_2} > 45$ mmHg; failure to achieve an immediate postischemic MAP of >80 mmHg (within 3 min after cuff deflation); thereafter an MAP < 70 mmHg for more than 60 min or of <50 mmHg at any point or an MAP > 130 mmHg for more than 1 h.

EVALUATION OF NEUROLOGIC FUNCTION POSTISCHEMIA

Neurologic function was evaluated at 26, 48, 72, and 96 h postischemia by the same blinded observer (JDM). The neurologic examination and scoring method, modified from that previously described, is presented in table 1. A neurologic deficit score from 0 to 500 points was determined from level of consciousness, respiration, cranial nerve function, motor and sensory function, and behavior. The results are expressed as percent normal neurologic function, where 100% is normal and 0% is apparent brain death.

HISTOPATHOLOGIC EVALUATION

After the final clinical evaluation, the monkeys were reanesthetized with im ketamine 3–5 mg/kg, and a left thoracotomy was performed. They then were killed by infusing 500 ml 4% buffered paraformaldehyde into the left ventricle at a pressure of 100 mmHg, with the descending thoracic aorta cross-clamped and the right atrium opened. One hour later, the brains were removed and placed in buffered paraformaldehyde. All brains

§§ As determined by Chemstrip bG®, Bio-dynamics, Indianapolis, Indiana.
were fixed for 4 weeks prior to gross and microscopic examinations by a neuropathologist (BWS) who was blind as to treatment groups. Coronal whole-mount paraffin-embedded microsections were cut at 6 μm and were stained by the hematoxylin and eosin method. Representative sections of cerebral cortex, basal ganglia, thalamus, midbrain, pons, medulla, and cerebellum were read and graded according to the type and extent of histopathology as previously described. The latter included infarction, ischemic nerve cell changes, and edema. The severity of injury was assessed on a five-point scale: normal, 0; minimal, 1; moderate, 2; severe, 3; maximal, 4. The points then were multiplied by a weighting factor (infarction, 4X; ischemic nerve cell change, 2X; edema, 1X) to obtain a score for each of 19 anatomic regions. Total neuropathologic scores then were computed for each animal.

**Statistical Evaluation**

The significance of postischemic differences in neurologic function between the two groups was evaluated by the two-tailed Mann-Whitney rank sum test. Histopathologic scores were evaluated by both unpaired Student’s t test and the rank sum test. Correlation between the neurologic function rank and histopathology rank was assessed by determining the Spearman rank correlation coefficient. Any differences in physiologic variables were determined by unpaired Student’s t test. A probability of less than 0.05 was regarded as significant. All mean values are reported with the standard error of the mean.

**Results**

Eleven treated and 10 untreated monkeys fulfilled all protocol criteria and therefore were included in the final analysis.

**Exclusions**

Three treated and three untreated monkeys were excluded prior to the final 96-h evaluation. Two treated and one untreated monkey developed severe cardiopulmonary complications during the initial 72 h, with pulmonary edema and hypoxia. One treated monkey had incomplete ischemia; one untreated monkey inadvertently received 500 ml 5% dextrose in 0.45% saline prior to ischemia, with a resulting blood glucose of 357 mg/dl; and one untreated monkey was judged to be older than 15 years.

**Study Group Match**

The treated versus untreated groups were well matched for approximate age (3.3 ± 0.3 yr vs. 4.0 ± 0.8 yr, respectively), body weight (5.1 ± 0.3 kg vs. 5.1 ± 0.3 kg), and sex (eight males and three females vs. eight males and two females, respectively).

**Physiologic Variables (Table 2)**

There were no significant differences between treated and untreated monkeys in blood gases, MAP, temperature, blood glucose, or electrolytes when measured preischemia or postischemia, except for a higher K+ in treated monkeys 24 h postischemia. K+ tended to be higher in this group preischemia, and there were no significant differences between preischemic and posts ischemic values. MAP returned to 80 mmHg at 90 ± 16 s versus 73 ± 16 s postischemia in treated versus untreated monkeys, respectively (NS). With the bolus injection of nimodipine or placebo, about 50% of the animals became transiently hypotensive, followed by immediate recovery in response to norepinephrine. Although blind to treatment, it was assumed by those caring for the animals
that the hypotension was due to nimodipine. At the end of the study, it was learned that this clinical sign was a reliable indicator of the treatment group in 19 of 21 monkeys. There were no significant differences in total dosage or duration of trimethaphan or norepinephrine infusions between the two groups. Heart rate was significantly greater in treated than in untreated monkeys during drug infusion (first 10 h postischemia), while the hematocrit was less in treated than in untreated monkeys 16–24 h postischemia.

**Completeness of Ischemia**

$^{133}$Xe was detected in the brain of one monkey during the ischemic period, and it was excluded. In all other monkeys ischemia was complete; $^{133}$Xe could not be detected during ischemia, while a sharp increase in brain radioactivity occurred within seconds after tourniquet deflation.

**EEG Return Postischemia**

The EEG became isoelectric at $11 \pm 1$ s versus $15 \pm 3$ s (mean ± SE) for treated and untreated monkeys, respectively (NS). There was also no significant difference in the timing of EEG return or in the pattern of EEG activity in the treated and untreated groups. A burst-suppression pattern appeared at $45 \pm 5$ min versus $45 \pm 6$ min, and a continuous activity pattern returned at $80 \pm 10$ min versus $102 \pm 12$ min in the treated versus the untreated groups.

**Seizure Activity Postischemia**

One nimodipine-treated and two untreated monkeys had seizure activity at some point during the initial 48-h postischemic period and were treated with diazepam. They were ranked as numbers 8 (nimodipine treated—receiving a total dose of 3.5 mg diazepam 40–46 h postischemia), 16 (0.5 mg diazepam 26 h postischemia), and 20 (3 mg diazepam 23–24 h postischemia) at the time of final neurologic evaluation (more than 48 h after the last dose of diazepam had been given).

**Neurologic Outcome**

Nimodipine significantly improved neurologic function 96 h postischemia (fig. 1) ($P < 0.05$ by Mann-Whitney rank sum test). Eight of the 11 treated monkeys had an apparent normal level of consciousness; four of these had no detectable neurologic deficits; and a fifth had only a slight motor apraxia. Two of the remaining three treated monkeys had very poor neurologic function at 96 h. Of the entire group of 21 monkeys, these were the only animals that deteriorated neurologically after 48 h. The remaining 19 either stabilized or continued to improve after 48 h. None of the untreated monkeys were normal; the best (No. 6) had a neurologic function score of 89%, was unable to stand and walk, and exhibited abnormal grooming behavior. Two of the untreated monkeys (Nos. 6 and 10) were judged to have a normal state of consciousness, while the remaining monkeys demonstrated a progressive degree of stupor. The typical untreated monkey (Nos. 13, 14, 15, 16, and 17) had an obtunded level of consciousness, maintained an opisthotonoid body position, but responded purposefully to noxious stimuli. None of the animals were ventilator dependent; only three (Nos. 11, 12, and 20) had required ventilatory support at some point between 24 and 96 h postischemia. There was no correlation between neurologic outcome and hematocrit. Rapidity of return of EEG activity postischemia was not a good indicator of ultimate neurologic outcome.²²

**Histopathologic Evaluation**

Histopathologic examination revealed a pattern of pathologic changes, characterized by primarily early ischemic neuronal change, ischemic neuronal necrosis, and infarction. Predictably, changes at all locations were most noticeable in the gray matter; white matter alter-

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²² Linear correlation analysis of the rank given for time of return of burst suppression activity with the rank given for neurologic function yielded: $Y = 0.35X + 7.1$ with $r = 0.35$ and $P > 0.05$. Correlation analysis of the rank given for return of continuous EEG activity with neurologic function rank yielded the following: $Y = 0.56X + 4.8$ with $r = 0.57$ and $P < 0.01$. 

ations consisted primarily of perivascular extravasation of fixative and were thus considered artifactual. Ischemic changes as well as infarction usually were symmetric and followed the distribution of distal arterial perfusion zones; asymmetric involvement was noted most often in the brain stem. The posterior circulation was most affected, a feature reflected in the extent to which brain stem lesions were encountered.

Supratentorial sites most severely affected included the hippocampal formation (h. 1 and 2) and the calcarine cortex; the temporoparietal regions were less involved, and the frontal and insular cortices were affected only mildly; cellular changes were most noticeable in deep cortical layers. Of basal ganglia structures, the globus pallidus was most vulnerable, representing the second most frequent overall site of symmetric infarction. The caudate nuclei and putamen showed primarily early ischemic neuronal changes. Moderate ischemic neuronal necrosis was noted in the thalami; in only two instances were infarcts observed in this location.

In the brain stem, the site most severely involved was the midbrain, the oculomotor nuclei being the structures involved most often by infarcts. This structure was followed, in decreasing order of frequency, by the medulla, substantia nigra, and the pontine nuclei. The cerebellar cortex frequently was involved by ischemic neuronal necrosis, particularly its superior portion; the dentate and roof nuclei largely were spared.

The mean histopathology score for the treated group (105 ± 14) was significantly better (P < 0.05) than for the untreated group (150 ± 15). This difference did not achieve significance with the use of the Mann Whitney rank sum test. However, there was a significant correlation (P = 0.02) between the neurologic function rank and histopathology rank (fig. 2). The latter was achieved despite an unexplained contradiction in that one treated monkey judged to be almost normal (neurologic function rank #5) had major ischemic changes (histopathology rank #18), while another untreated monkey with major neurologic deficits (neurologic function rank #19) had only minor ischemic changes (histopathology rank #4). We have no reason to suspect that this contradiction occurred as a result of either a clerical error or a switch in the brains prior to histopathologic scoring.

**Discussion**

Nimodipine treatment improved the outcome in monkeys subjected to 17 min of complete cerebral ischemia. This could not be attributed to any differences between treated and untreated monkeys other than the treatment itself. Factors such as body temperature, age, blood gases, hemodynamics, drug solvent, and glucose levels that could affect postischemic outcome were not different between the two groups. Hematocrit was significantly lower after 12 h in the treated group, but in individual animals there was no correlation between hematocrit and neurologic outcome.

The improvement in outcome occurred, even though nimodipine treatment was not initiated until 5 min postischemia. We previously reported that nimodipine improved the outcome when given before 10 min of complete cerebral ischemia using a simple but crude dog model. When given postischemia in the same model, the results were equivocal; i.e., not significantly different from either controls or dogs given nimodipine preischemia. The present study in primates demonstrates that postischemic treatment does improve the outcome and that the effects of 17 min of complete ischemia are potentially reversible.

This supports the assumption that at least a part of the brain damage resulting from complete cerebral ischemia is caused by postischemic events. Certainly the distribution of ischemic lesions in our animals to the distal arterial perfusion zones is consistent with a form of incomplete ischemia that only could have occurred during the postischemic reperfusion phase. This indirectly suggests that the most vulnerable structure of the brain to complete cerebral ischemia is the cerebral vasculature per se. Accordingly, adequate reperfusion of the brain may be the critical factor in determining brain salvage following a period of complete ischemia.

It is well established in animal models that after complete cerebral ischemia, an initial brief hyperemic phase is followed by a prolonged period of delayed hypoperfusion. In dogs this lasts for more than 6 h, with cerebral blood flow often down to 20% of normal. In patients, following cardiac arrest, a low flow state has been observed in the initial 2–6 h postresuscitation, with return to normal by 24 h. It has been suggested that this hypoperfusion state might be responsible for a large part of the ultimate brain damage. Such a hypoperfusion state might be due to calcium-induced cerebral vasospasm, increased blood viscos-
ity, and platelet aggregation. Previous studies in dogs have shown that nimodipine can improve cerebral blood flow in this period, even when the drug is given only postischemia. Other deleterious reactions involving calcium might occur directly in neurons during and after ischemia. Perhaps increased levels of free intracellular calcium partly might uncouple mitochondrial oxidative phosphorylation and be involved in reactions that break down proteins and membrane phospholipids with secondary production of prostaglandins, leucotrienes, and thromboxanes, which might cause further tissue damage by vasoconstriction and platelet aggregation. Thus, many possible mechanisms may explain the beneficial effects of the calcium entry blocker nimodipine.

The selected drug dose for this study was based upon that which improved the outcome in dogs, and the rate of infusion was close to that reported to increase CBF in normal primates (2 μg·kg⁻¹·min⁻¹) and in humans with cerebrovascular disease (1 μg·kg⁻¹·min⁻¹). Nimodipine was infused for 10 h, as compared with previous studies utilizing infusions ranging from 10 min up to 2 h. The prolonged infusion was chosen because of the unknown duration of the delayed hypoperfusion state. That two of the treated monkeys deteriorated after 48 h suggests the possibility that the treatment may have been of insufficient duration in these animals. Except for a modest transient tachycardia, there were no untoward cardiovascular responses to the infusion, while the initial bolus injection caused a brief but easily controlled hypotensive response. The same was true in our canine studies. Although in vitro studies indicate that nimodipine has a much greater effect on cerebral than on peripheral vessels, the hypotension probably was due to peripheral vasodilation, with the tachycardia due to reflex sympathetic stimulation. However, no detrimental cardiovascular effects have been reported for nimodipine in either other animal or human studies. In fact, calcium entry blockers have been reported to have a beneficial effect on the heart by reducing myocardial damage during ischemia and in the reperfusion period and by reducing infarct size.

Although to date the only studies demonstrating the efficacy of nimodipine in improving neurologic function following complete cerebral ischemia have been done in animals, nimodipine has been used extensively in both the oral and intravenous forms to treat vasospasm following subarachnoid hemorrhage (SAH) in patients. By blocking the influx of extracellular calcium, the primary source for contraction of the large cerebral vessels, it is felt that nimodipine can reduce or alleviate the occurrence of vasospasm following SAH, thereby preventing or ameliorating any ischemic neurologic deficit. In a prospective double-blind study, oral nimodipine significantly reduced the occurrence of severe neurologic deficits from spasm without apparent side effects. When given intravenously to patients with vasospasm following SAH, 0.5–2 mg·h⁻¹ nimodipine significantly increased CBF, with improvement in CBF most pronounced in the least perfused brain regions. The increase in CBF often was associated with rapid improvement of the clinical symptoms. A larger dose of 24–48 mg·day⁻¹ nimodipine given intravenously to patients for 1 week following SAH also demonstrated its efficacy in the treatment of ischemic complications. The two noted side effects of this dose were mild hypotension and heart rate changes, which were well tolerated.

Norepinephrine was used in the present study in the same manner as it had been used in previous studies with this model. It was required both to compensate for the hypotension caused by trimethaphan given before and during ischemia and to maintain MAP in the immediate posts ischemic period. There was no significant difference in the norepinephrine required by each group posts ischemia except at the time of bolus injection.

The monkeys that were excluded from the study all had very poor neurologic outcomes. One monkey exceeded the age limit. Three experienced cardiopulmonary complications with pulmonary edema. As this occurred in both treated and untreated monkeys and previously has been described in controls in the same model, it probably was not due to the drug treatment but rather is a function of the model. Possibly “neurogenic pulmonary edema” secondary to severe intracranial pathology accounted for this complication. The remaining two monkeys possibly illustrate the detrimental effect of an increased level of cerebral glucose during hypoxia. One monkey inadvertently received a large glucose load pres ischemia, and in the other the ischemia was incomplete, thus permitting a continued supply of glucose. This has been reported to be deleterious in animal studies, probably due to brain accumulation of lactic acid. Also, in a study of cardiac arrest patients, neurologic outcome was correlated negatively with plasma glucose levels. In the monkey with incomplete ischemia, additional brain damage might have been expected due to cerebral venous stasis caused by the neck tourniquet.

The basic primate model used in this study has been used extensively in other studies of complete cerebral ischemia. It has been modified progressively to achieve a more exact duration of ischemia and less variability in circulatory and respiratory support post-ischemia. These are features that are not easy to achieve in other models of complete ischemia such as produced by ventricular fibrillation or asphyxiated cardiac arrest. In these models, a positive drug effect might be obscured by variability in factors other than cerebral ischemia. Monitoring the completeness of ischemia with Xe and the use of a blind observer for determining exclusions and neurologic evaluation were major modifications made in the present study. The merits of the model are reflected by the highly reproducible neurologic outcome in the control groups of this and previous studies.

In this regard, it should be noted that one of us (SEG) had used this model of complete cerebral ischemia in approximately 90 monkeys (including control and various treatment groups) and had never observed a monkey with apparent normal neurologic function following 16 min of ischemia (as opposed to the 17 min of ischemia used in this study). The model obviously is not identical to cardiac arrest in patients, since whole body ischemia deliberately is avoided. Instead, a controlled insult of complete cerebral ischemia is produced without the possible confounding and uncontrollable systemic effects that otherwise might occur. This permits valid evaluation of interventions specifically intended to attenuate or prevent brain damage after cardiac arrest.

We conclude that nimodipine given after complete cerebral ischemia significantly improves the neurologic outcome in primates. Apart from a possible hypotensive response to bolus injection and a slight tachycardia during continuous infusion, no potentially detrimental cardiovascular effects were apparent. Our results confirm that the hoped-for benefits suggested by pretreatment studies in cats and dogs are applicable to primates when treatment is limited to the postischemic period only. Nimodipine has been used in patients with other types of cerebral ischemia without any apparent untoward effects. We therefore believe it is now appropriate that nimodipine therapy be evaluated in well-controlled randomized studies after cardiac arrest in patients.

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