Title: EFFECTS OF NIMODIPINE ON NEUROLOGIC FUNCTION FOLLOWING COMPLETE GLOBAL ISCHEMIA IN PRIMATES

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Introduction. Persistence of severe neurologic deficits is a major complication in patients surviving cardiorespiratory arrest. Accordingly, there is continued interest in therapeutic interventions, including calcium entry blockers, which, when given in the immediate post-resuscitation period, might improve neurologic outcome. The calcium entry blocker nimodipine when given before or after complete cerebral ischemia in dogs improves post-ischemic cerebral blood flow.[1,2] Animals treated with nimodipine before the ischemic event had significantly better neurologic function 48 h post-ischemia than did the untreated group. When nimodipine was given only after ischemia, neurologic function was intermediate and not significantly different from either the untreated group or the pre-treated nimodipine group. Because these results were equivocal, the importance of the delayed hypoperfusion state and the possible clinical benefit of therapy with calcium entry blockers was considered unresolved. We therefore undertook an investigation of neurologic outcome following ischemia and nimodipine therapy in a primate model of complete global ischemia.[3,4]

Methods. Twenty-one pigtailed monkeys were anesthetized with 0.5% halothane and 66% N_2O in O_2; paralyzed with succinylcholine, intubated with a 4-4.5 mm ID cuffed wire spiral endotracheal tube and ventilated. Catheters were placed in a femoral artery and vein and a peripheral vein for maintenance fluids. Mean arterial pressure (MAP), esophageal temperature, ECG, fluid balance, and EEG were monitored continuously. Arterial blood gases, hemoglobin, glucose, and electrolytes were measured immediately prior to ischemia and at frequent intervals post-ischemia. Following discontinuation of the halothane, hypotension to 40-50 mmHg was induced with trimethaphan and a tourniquet placed around the neck, was inflated to 1500 mmHg to produce global cerebral ischemia for 17 min. During this period the monkeys were ventilated with 100% oxygen containing Xe^{133}. Scintillation probes placed over the head failed to detect any xenon, assuring the absence of cerebral blood flow. Following ischemia MAP was restored within 2 min with a norepinephrine infusion. Five minutes post-ischemia eleven monkeys received nimodipine (10 $\mu g \cdot kg^{-1}$) followed by an infusion (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) for 10 h. Ten monkeys received an equal volume of placebo. The animals were then cared for in an intensive care setting for 24 h or longer as needed. Paralysis and hyperventilation (100% O_2 for 2 h then 50% N_2O, 50% O_2) was maintained until extubation. MAP was maintained at 80-120 mmHg with norepinephrine or trimethaphan as needed. At 24 h extubation was performed when ABG and protective reflexes were adequate. Animals were continuously watched for 96 h post-ischemia. Detailed neurologic evaluations were done by a blinded observer at 26, 48, 72, and 96 h. Following the final neurologic evaluation the monkeys were killed and their brains fixed in buffered paraformaldehyde for histopathologic examination. This work is in progress and the results will be reported at the time of presentation.

Results. Monkeys were ranked from 1 to 21 according to their neurologic function at 96 h (100% function = normal, 0% function = brain death) (Figure 1). Using the Mann-Whitney rank sum test the monkeys treated with nimodipine had significantly better neurologic function than the untreated group ($p < 0.05$). Four monkeys receiving nimodipine were absolutely normal, their behavior and personalities indistinguishable from their pre-ischemic behavior; one was only mildly apraxic. None of the untreated monkeys were normal.

Discussion. From these results we conclude that nimodipine, when given after complete cerebral ischemia, can improve neurologic outcome in primates and clinical trials may now be warranted.

References.

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