Title: EFFECTS OF NIMODIPINE UPON NEUROLOGIC OUTCOME FOLLOWING CARDIAC ARREST IN CATS

Authors: A Tateishi, M.D., JE Fleischer, M.D., JC Drummond, M.D., MS Scheller, M.D., MH Zornow, M.D., MR Grafe, M.D., Ph.D., HM Shapiro, M.D.

Institution: Department of Anesthesiology, University of California San Diego, La Jolla, California 92093

Introduction: Nimodipine (N), a calcium entry blocker, has been reported to improve neurologic outcome in primates when administered after complete cerebral ischemia achieved by use of a neck tourniquet and induced hypotension (1). In order to more closely simulate the clinical situation, we have examined the effects of N on neurologic outcome when administered after induced cardiac arrest and resuscitation in cats.

Methods: Forty-five colony bred cats, age 4-6 months, weighing 1.8-2.8 kg, and fasted for 16-20 h, were studied with Institutional Review Board approval. Cats were initially anesthetized with 4% halothane (H) in oxygen followed by pancuronium 0.3 mg/kg iv to facilitate tracheal intubation. Ventilation was controlled to maintain normocarbia. Anesthesia was maintained with 1-1.5% H and 70% nitrous oxide in oxygen. Esophageal temperature was servo-controlled to 37.5 C°. Cannulae were passed into the distal abdominal aorta and right atrium (RA) via the left femoral artery and vein, respectively. A guide wire introduced into the RA cannula for the later application of a fibrillating current, protruded 2-5 mm from the atrial end of cannula. Mean arterial pressure (MAP), RA pressure (RAP), electrocardiogram (ECG, lead II), electroencephalogram (EEG, fronto-occipital and bi-temporal leads), and end-tidal CO2 and H were continuously monitored. Animals received 0.9% NaCl at 4 ml/kg/h with pancuronium 0.5 mg/h. Following surgical preparation H was decreased to 0.5 % and animals were left undisturbed for 30 min. One minute after discontinuing the H, animals were subjected to a 14 min period of electrically induced cardiac arrest followed by a rigidly standardized resuscitation protocol. Resuscitation was considered successful when systolic blood pressure was maintained above 100 mmHg within four minutes of initiating CPR. Cats were randomly divided in a blinded fashion into two groups; N-treated and placebo-treated (P). In both groups, beginning at 5 min post-resuscitation (PR), cats received either N 10 μg/kg over 2 min plus 2 μg/kg/min for 10 h or the same volume of P (N solvent). Five cats in a sham group were managed in the same way as the N and P groups, however, they were not subjected to cardiac arrest. Following resuscitation or sham arrest, intensive care treatment was provided for 20-30 h, during which time sedation and paralysis were maintained with midazolam and pancuronium, respectively. MAP was maintained between 80-120 mmHg by infusion of norepinephrine (NE) or trimethaphan (TMP). The trachea was extubated after reversal of muscle relaxation if the PaCO2 was maintained below 40 mmHg. A neurologic deficit score (NDS) was determined at both 48 and 96 h PR by two observers blinded to the treatment groups (0 - normal; 100 - brain death). After the 96 h examination, animals were anesthetized, perfusion fixed with formalin, and the brains harvested for subsequent histopathological examination. A histopathologic score for each brain was determined by two observers blinded to the treatment groups. Animals were excluded from the study if they met any of the following predetermined criteria: pre-arrest plasma glucose >180 mg/dl, any perfusing heart beat >1 min into the ischemic period, and resuscitation requiring >4 min. Physiologic variables were analyzed within each treatment group using a repeated measures ANOVA and corrected paired t-tests. Inter-group comparisons were carried out with unpaired t-tests. A p value < 0.05 was considered statistically significant.

Results: Nine out of 45 cats studied were excluded prior to the 96 h examination. One cat was excluded with an elevated pre-arrest plasma glucose, four could not be resuscitated within 4 min, two were excluded due to technical difficulties, and two (one N and one P) could not be extubated. A total of 31 animals (16 N and 15 P) were entered into statistical analysis. The N and P groups were well matched for body weight, sex, pre-arrest physiological variables, time of halothane administration, and resuscitation time. MAP was significantly lower in the N-treated cats at 30 min, 1 and 8 h PR. There were also significant differences in the total doses of NE (2.0±1.9 mg N vs. 0.2±0.4 mg P) and TMP (11±17 mg N vs. 55±36 mg P) administered. Two patterns of EEG recovery were noted, one with continuous slow activity and the other with "spindle-like" sharp waves mixed with periods of suppression. There were no differences between the treatment groups in the occurrence of "spindle-like" EEG, or in the recovery time of first EEG activity (31±8 min N vs. 28±8 min P), although recovery of continuous EEG activity occurred earlier in N-treated (37±7 min) than in P-treated cats (43±6 min, $p < 0.05$). The time of EEG recovery did not correlate with the final neurologic outcome. There were no differences in NDS (see figure) or histopathology scores between the N and P groups. All sham animals had a NDS of 0 at 96 h PR. There was a significant correlation between NDS and histopathology score ($p < 0.001$).

Discussion: Our results conflict with those of Steen, et al. (1), who reported that neurologic outcome was improved by N administered to primates following 17 min of complete cerebral ischemia. Our results are complicated by the observed differences in MAP despite significant differences in vasoactive agents administered. The doses of NE and TMP administered may have acted to diminish any true differences in NDS between groups. The mean NDS for the P group (20 ± 16) was less than the expected NDS of 25-30 based on previous studies in this model. The reasons for this are unclear. However, it is clear that the lower NDS for the P group makes demonstration of a beneficial effect of N more difficult. Within the specific conditions of the present study, N does not appear to improve neurologic outcome or histopathology in cats following resuscitation from cardiac arrest.

References:

1. Steen PA, et al. Nimodipine improves outcome when given after complete cerebral ischemia in primates. Anesthesiology 62:406-414, 1985.

Neurologic Deficit Scores at 96 h PR
There was no difference between groups.