Title: EFFECT OF AN EXCITATORY AMINO ACID ANTAGONIST (MK-801) ON NEUROLOGIC OUTCOME IN A CANINE MODEL OF COMPLETE CEREBRAL ISCHEMIA

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Introduction. Complete cerebral ischemia in both experimental animals and humans results in a selective pattern of neuronal degeneration. Recent evidence has suggested that the pattern of post-ischemic neuronal degeneration is caused in part by regional differences in the activity of the excitatory amino acid transmitters (i.e., the excitotoxic mechanism of neurotoxicity).[1] This hypothesis proposes that ischemia produces elevations in extracellular excitatory amino acids, such as L-glutamate and L-aspartate. These amino acids then act to stimulate specific membrane receptors on post synaptic neurons. Prolonged stimulation of these excitatory receptors results in neuronal death. Of the excitatory receptors, the N-methyl-D-aspartate (NMDA) receptor is the best characterized. High concentrations of this excitatory receptor are found in areas of the brain that are most vulnerable to ischemia (hippocampus, crebral cortex, and striatum).

Current evidence suggests that administration of NMDA receptor antagonists result in neuronal sparing in a setting of cerebral ischemia.[2] MK-801, a potent, selective, and lipid soluble NMDA receptor antagonist, has repeatedly improved post ischemic neuronal survival in the hippocampus. Whether this improved survival is associated with improved neurological outcome is unknown. The present study examined the effect of systemically administered MK-801 on neurological outcome in a canine model of complete cerebral ischemia.

Methods. Complete cerebral ischemia was produced in 26 dogs by simultaneous crossclamping of the thoracic venae cavae and aorta for 11 min duration.[3] Five minutes following global ischemia, an i.v. bolus of either MK-801 150 $\mu g \cdot kg^{-1}$ or an equivalent volume of placebo was administered. Thereafter an 8 h infusion of either MK-801 75 $\mu g \cdot kg^{-1} \cdot h^{-1}$ or an equivalent volume of placebo was given. The treatment was randomized with all participants blinded to the selected treatment. Blood samples for determination of plasma MK-801 concentrations were taken from all dogs at the end of the infusion and at 1, 2, 4, 8, and 24 h post-ischemia. After 6-7 h the dogs were weaned from the ventilator and placed on room air. At approximately 8 h post-ischemia, the animals were extubated assuming adequate blood gases. Animals were excluded from the study if they had a pre ischemia blood glucose > 150 $mg \cdot dl^{-1}$, a MAP < 60 mmHg within 1 min post-ischemia, a $PaCO_2$ > 45 mmHg or a PaO_2 < 55 mmHg while spontaneously ventilating with room air. The animals were scored neurologically by a blinded observer at 24, 48, and 72 h post-ischemia. Using a scale of 1 to 4, animals were graded as 1 = normal, 2 = animals could stand but were ataxic and/or blind, 3 = animals could not stand, and 4 = dead. After final neurological scoring at 72 h, the dogs were killed and the brains were harvested and stored in buffered 4% paraformaldehyde. Histopathologic analysis of the hippocampus was subsequently performed by a neuropathologist. Physiological variables were compared using repeated-measures ANOVA with Dunnett's test. The Mann-Whitney rank sum test was used to compare neurologic outcome between groups. A Spearman rank correlation coefficient was used to assess correlation between histopathologic and neurologic outcome.

Results. Eight dogs were excluded from the study because of failure to meet protocol criteria. Of the remaining 18 dogs, 9 were given MK-801 and 9 placebo. Mean plasma MK-801 concentrations were 20-30 $ng \cdot ml^{-1}$. Physiological variables were well matched between groups. All the MK-801 treated animals were grade 3 (comatose) at 24 h; 6 of these improved dramatically to grades 1 or 2 at 48 h. At 72 h post-ischemia, 5 MK-801 treated animals were normal as were 3 of the placebo treated animals. There was no significant difference between groups ($p > 0.5$) in either the neurologic or histopathologic outcome. There was, however, a significant ($p < 0.01$) correlation ($r_s = 0.61$) between histopathologic and neurologic outcome. None of the animals studied had a normal hippocampal histopathologic outcome.

Discussion. MK-801 improved neither neurologic nor histopathologic outcome in this model of complete cerebral ischemia, although the plasma drug levels in this study were comparable to those in animal studies that have demonstrated neuronal sparing.[4] MK-801 exerted a potent sedative effect that lasted nearly 48 h, which underscored the importance of waiting at least 72 h before assignment of a final neurologic outcome score. MK-801 did not appear to be a respiratory depressant, nor did it have appreciable hemodynamic side effects at the dose used in the present study. Though the neurologic outcome scoring system used in this study did not directly assess hippocampal function, a correlation between hippocampal histopathologic and neurologic outcome was found.

References.

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