Title: EFFECT OF THE EXCITATORY AMINO ACID ANTAGONIST MK-801 ON NEUROLOGIC FUNCTION FOLLOWING COMPLETE CEREBRAL ISCHEMIA IN PRIMATES

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Introduction. Synaptic transmission mediated by excitatory amino acids (EAA; primarily L-glutamate and L-aspartate) is thought to be involved in postischemic neuronal necrosis due to depolarization and calcium entry.[1] MK-801 is a potent non-competitive antagonist of the N-methyl-D-aspartate (NMDA) class of glutamate receptors and readily crosses the blood-brain barrier. MK-801 has been shown in several experimental preparations to attenuate postischemic histopathologic injury.[1] The present study tested the hypothesis that MK-801, when administered after ischemia, would improve recovery following complete cerebral ischemia in an established primate model.

Methods. Ten pigtailed monkeys were anesthetized with halothane 0.5% in N_2O 66% and O_2, paralyzed with pancuronium, intubated, and mechanically ventilated. Catheters were placed in a femoral artery for pressure measurements and blood sampling, and in a femoral and peripheral vein for fluid and drug administration. Monkeys were hydrated with dextrose 5% in 0.45% saline solution 12 $ml \cdot kg^{-1}$ i.v. Mean arterial pressure (MAP), rectal temperature, EKG, fluid balance, and EEG were monitored continuously. Arterial blood gases (ABG), hemoglobin, glucose, and electrolytes were measured immediately prior to ischemia and at frequent intervals postischemia. Complete cerebral ischemia was produced using previously described methods.[2] Following discontinuation of halothane, hypotension to 40-50 mmHg was induced with trimethaphan, and a tourniquet placed around the neck was inflated to 1500 mmHg to produce complete cerebral ischemia of 17 min duration. During this period the monkeys were ventilated with 100% O_2 containing ^{133}Xe. Scintillation probes placed over the head failed to detect any ^{133}Xe, assuring the absence of cerebral blood flow. Following ischemia, MAP was restored to $\geq$ 80 mmHg within 2 min using a norepinephrine infusion. Five minutes postischemia five monkeys received MK-801 300 $\mu g \cdot kg^{-1}$ i.v. over 5 min followed by an infusion of 150 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 10 h. An additional five monkeys received an equivalent volume of saline placebo. The animals were then cared for in an intensive care setting for 24-48 h as their condition demanded. Plasma samples were obtained for 24 h postischemia to determine MK-801 drug levels. Paralysis and hyperventilation to $PaCO_2$ of 25-30 mmHg was maintained until 20 h postischemia (100% O_2 for 30 min postischemia, then 50% N_2O in O_2). MAP was maintained at 80-120 mmHg using a norepinephrine infusion. After 20 h of mechanical ventilation, extubation was performed when protective reflexes and ABG values were adequate (i.e. PaO_2 > 60 mmHg and $PaCO_2$ < 35 mmHg). Upon discharge from the intensive care environment, monkeys were returned to their cages. They were examined a minimum of every six hours, and if unable to feed themselves, they were hydrated. Neurologic evaluations were performed by a blinded observer at 26, 48, 72, and 96 h using the scoring scale of Steen et al.[2] Following the final neurologic evaluation, the monkeys were killed and their brains were fixed in buffered paraformaldehyde for histopathologic examination. (This work is in progress and the results will be reported at the time of the presentation.) Data analysis between groups was performed using unpaired t-tests and the Mann-Whitney rank sum test.

Results. The treatment groups were well matched for weight and preischemic and postischemic physiologic variables. Blood glucose immediately prior to ischemia was 146 $\pm$ 19 $mg \cdot dl^{-1}$ (mean $\pm$ SE) in the placebo treated group and 153 $\pm$ 9 in the MK-801 group. MK-801 treated monkeys had MK-801 mean plasma levels > 30 $ng \cdot ml^{-1}$ for the 10 h of infusion. Monkeys were ranked from 1 to 10 according to their neurologic function at 96 h (100% function = normal, 0% function = brain dead) (Fig. 1). There were no significant differences between MK-801 and placebo treated monkeys ($p = 0.53$, with placebo monkeys having the numerically better outcome).

Discussion. This study demonstrates that the EAA antagonist MK-801, when given immediately postischemia in doses sufficient to produce mean plasma drug levels in excess of 30 $ng \cdot ml^{-1}$, has no beneficial effect on neurologic outcome following complete cerebral ischemia in this primate model.

References.

1. Rothman SM, Olney JW: Excitotoxicity and the NMDA receptor. Trends in Neurosciences 7:299-302, 1987
2. Steen PA, Gisvold SE, Milde JH, Newberg LA, Scheithauer BW, Lanier WL, Michenfelder JD: Nimodipine improves outcome when given after complete cerebral ischemia in primates. Anesthesiology 62:406-414, 1985