Title: NEUROLOGIC OUTCOME FOLLOWING REGIONAL CEREBRAL ISCHEMIA WITH MEHOHEXITAL, MIDAZOLAM, AND ETOMIDATE

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Introduction Barbiturates have been reported to provide cerebral protection during ischemia due to their ability to depress cerebral metabolism [1]. Since etomidate produces similar changes in cerebral blood flow and metabolism [2], and because of its anticonvulsant properties, etomidate might be expected to provide similar neuronal protection from ischemia[3]. Benzodiazepines also depress cerebral metabolism and have been shown to prolong survival in the hypoxic mouse model[4]. Here we have compared the cerebral protectant effects of methohexital, midazolam and etomidate to each other and to nitrous oxide using a model of regional cerebral ischemia in the rat.

Methods Male Sprague-Dawley rats weighing 350-450 g were anesthetized, intubated and ventilated with isoflurane in 30% oxygen. Catheters were inserted in femoral arteries and veins for blood pressure monitoring and drug infusions and the right subclavian vein for blood withdrawal. The right common carotid artery was isolated and a loose ligature placed around it for later clamping. Screw electrodes were placed on the skull for EEG recording. At the completion of surgery the wounds were infiltrated with 0.5% bupivacaine. Rectal temperature was maintained at 37°C and vecuronium was administered as needed to maintain paralysis. Isoflurane was discontinued and each animal received a loading dose of the test drug followed by a maintenance infusion at the following doses (mg/kg/min): methohexital (low dose = 0.01, high dose = 0.1), midazolam (low dose = 0.02, high dose = 0.2) or etomidate (low dose = 0.02, high dose = 0.2). Ischemia was produced by maintaining FiO_2 = 30% with mean blood pressure of 30 mmHg. At the end of ischemia the carotid artery was unclamped and the blood slowly reinfused. Each animal received only one dose of test drug and level of ischemia. Arterial PCO_2 was adjusted to 35-45 mmHg by altering ventilation and normal pH was maintained during hypotensive and reinfusion periods with a bicarbonate infusion as necessary. The catheters were then removed and incisions closed. Control rats were maintained on 70% N_2O/30% O_2 during the ischemia challenge. Neurological deficits were initially evaluated 3 hours after recovery and repeated for 3 days. Scores were rated from 0 to 5 as follows: 0 = normal, 1 = paw adduction or abnormal posturing, 2 = circling or rolling behavior marked by motor rigidity or weakness, 3 = stimulated seizure activity, 4 = unstimulated seizure activity, 5 = death associated with stroke.

Results All animals lived for at least 3 hours after recovery from hypotension. Rats that died showed progressive signs of severe stroke including abnormal paw positioning during handling, circling and rolling behavior followed by stimulation-induced and non-stimulated seizures. EEG demonstrated depression during hypotension with return of activity after reinfusion of blood. Differences among treatment groups are shown in the table. Ventilation with N_2O alone resulted in greater mortality and increased neurologic deficit scores compared to methohexital, midazolam and etomidate. Higher doses of each drug resulted in increased deficit scores. Etomidate produced higher neurologic deficit than midazolam or methohexital but this effect did not reach significance. With the more severe ischemic challenge neurologic deficit scores and mortality rates were similar to N_2O treated animals.

Discussion The model used in this study produces unilateral cerebral ischemia due to carotid ligation and hypotension. N_2O produced significantly greater incidence of death and higher deficit scores compared to methohexital, midazolam, and etomidate. The higher neurologic deficit seen with high vs low doses of each test drug may be explained by a greater cardiovascular and respiratory depression that may counterbalance cerebral protectant effects of these drugs. Current additional studies are investigating the possible difference in cerebral protection with etomidate versus midazolam and methohexital.

References

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3. Wauquier A, et al: Anti-Hypoxic effects of etomidate, thiopental and methohexital. Arch Int Pharmacodyn 249:330-334, 1981
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Mortality Rates and Stroke Deficit Scores Following Regional Cerebral Ischemia

Drug/ Dose	Mortality	Deficit Score	N
70% N_2O	67%	4.3	6
Methohexital			
low	0%*	1.4*	8
high	20%*	1.8*	10
Midazolam			
low	10%*	1.4*	10
high	20%*	2.1*	10
Etomidate			
low	25%*	2.0*	8
high	60%	3.5	10

* = P<.05 compared to N_2O