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Title: BARBITURATES FOR FOCAL CEREBRAL ISCHEMIA IN CATS

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Introduction. While barbiturate has been shown to reduce infarction following focal cerebral ischemia in animal models,¹ the specific mechanism of its action remains unknown. Direct effects of barbiturate that may be involved in the protective effect include: reduced cerebral metabolic oxygen requirement, membrane stabilization, free-radical scavenging, and anesthesia. To determine whether reduction of brain edema is the mechanism by which barbiturates exert their protective effect, we examined the effect of barbiturates on cerebral ischemia produced by unilateral transorbital middle cerebral artery (MCA) occlusion in cats.

Methods. Thirty-nine cats (2 to 4 kg) were anesthetized with halothane in 100% oxygen. Monitoring included continuous measurement of systemic arterial pressure, end-tidal CO₂, intracranial pressure (ICP), and EEG, and intermittent determinations of arterial blood gases and hematocrit. There were four groups. The controls, Group I (n=5), received a sham operation and no barbiturate. Groups II (n=14), III (n=11), and IV (n=9) underwent MCA occlusion, with Group II receiving no barbiturates, Group III receiving pentobarbital (30 mg/kg) 30 minutes before operation, and Group IV receiving both the preoperative pentobarbital and another 30 mg/kg in divided doses over the 24 hours following operation. Each animal was ventilated until it was able to breathe spontaneously and maintain normal gas exchange. Intensive nursing care and monitoring were continued until 72 hours after operation, at which time the cats were given intravenous Evans blue dye (2%) and sacrificed. The brains were removed; and water, sodium (Na⁺), and potassium (K⁺) contents and specific gravity were measured in tissue samples from selected areas of both hemispheres: basal ganglia, subcortical white matter, Evans blue-dyed white matter, and cortical gray matter. The brains were formalinized and then dissected to determine the size of the infarct induced by MCA occlusion.

Results. The mortality rate for the 72-hour postoperative period was 50% for Group II, 62% for Group III, and 37.5% for Group IV. In Groups III and IV, 56% of the animals had an ICP greater than 15 mm Hg, but the upper range was 90 mm Hg in Group III and only 40 mm Hg in Group IV. The variation in infarct sizes among Groups II, III, and IV was nonsignificant: (the percent of the hemisphere affected was 8.3 ± 1.5, 9.0 ± 2.4, and 4.9 ± 1.1, respectively. The water content in the selected areas of the nonischemic (unoperated) hemisphere was similar in all four groups. In the ischemic hemisphere, the water content was significantly higher in the MCA-occluded groups (II, III, and IV) than in the control group and did not differ between the groups treated with barbiturates (III and IV) and the untreated group (II). The Na⁺ content (Table) was increased above the levels of the control group in both hemispheres in the MCA-occluded groups. This rise appeared to be moderated by preoperative barbiturate treatment (Group III), but the addition of postoperative barbiturate (Group IV) produced an even greater rise in Na⁺ levels. With the increases in Na⁺ content, there were concomitant decreases in K⁺.

Na⁺ contents (dry wt): % increase over controls.

| Group | Hemisphere | Basal ganglia | White matter | Gray matter |
|-------|-------------|---------------|--------------|-------------|
| II | ischemic | 187±47 | 200±60 | 157±30 |
| | nonischemic | 24±14 | 81±38 | 17±17 |
| III | ischemic | 121±62 | 71±28* | 138±38 |
| | nonischemic | 4±12 | 26±16 | 4±5 |
| IV | ischemic | 265±48 | 308±63 | 191±21 |
| | nonischemic | 91±40 | 68±27 | 31±8 |

*P < 0.05

Serum levels of barbiturate measured in Groups III and IV were, respectively: 22 and 18 µg/ml at 1 hr post-infusion; 18 and 16 at resumption of EEG, 15 and 18 at extubation, and (Group IV only) 23 at hr 24, 16 at hr 48, and 6 at hr 72.

Discussion. Barbiturates have been shown to decrease cerebral blood flow, cerebral metabolic rate, and ICP, and to reduce infarct size following permanent MCA occlusion.¹ Although the differences in infarct size and mortality among the MCA-occluded groups were not significant, our results suggest that infusion of barbiturates before and for 24 hours after MCA occlusion does reduce the infarct size and improve survival. Since treatment with barbiturates failed to diminish the water content of the ischemic hemispheres, it must be through other mechanisms that barbiturates exert their effect. Our measurements of Na⁺ and K⁺ corroborate previously reported reduction of K⁺ efflux from ischemic cells,² indicating stabilization of extracellular-intracellular electrolyte flux. The increase in Na⁺ in Group IV may indicate that large doses of barbiturate disrupt the integrity of the cell membranes. Although barbiturates have been used to control intracranial hypertension in head injury,³ they failed to prevent rises in ICP in our ischemic model. In special circumstances (such as during clip ligation of intracranial aneurysms), barbiturate given before or at the time of major cerebral artery occlusion and continued postoperatively may mitigate the effects of focal infarction. In view of the significant cardiorespiratory depressant action of barbiturates, careful monitoring and supportive care are mandatory.

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References.

- Hoff JT, Smith AL, Hankinson HL, et al: Barbiturate protection from cerebral infarction in primates. *Stroke* 6:28-33, 1975
- Astrup J, Nordstrom CH, Rehncrona S: Rate of rise in extracellular potassium in the ischemic rat brain and the effect of preischemic metabolic rate, Cerebral Function, Metabolism, and Circulation. Edited by Ingvar DH, Lassen N. Copenhagen, Munksgaard, 1977, pp 376-377
- Rockoff M, Marshall L, Shapiro HM: High-dose barbiturate therapy in humans: A clinical review of 60 patients. *Ann Neurol* 6:194-199, 1979
- Hoff JT, Pitts LH, Spetzler R, et al: Barbiturates for protection from cerebral ischemia in aneurysm surgery, Cerebral Function, Metabolism, and Circulation. Edited by Ingvar DH, Lassen N. Copenhagen, Munksgaard, 1977, pp 158-159