Effect of Methylprednisolone on Experimental Cerebral Infarction in the Mongolian Gerbil

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Abstract:
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In a double-blind study, the effect of high doses of methylprednisolone on the cerebral edema induced by cerebral infarction was evaluated in 76 Mongolian gerbils. The incidence of experimentally induced cerebral infarction following carotid artery ligation is high in these animals because they lack a posterior communicating artery. One hour after the left common carotid artery had been ligated, 34 animals were given 30 mg per kilogram of the adrenocorticosteroid and the dose was repeated 24 and 48 hours later. Thirty-four animals were given normal saline on the same treatment schedule. Eight animals with sham operations were not treated. The animals were observed for ten days for signs of stroke. Surviving animals were killed on the tenth day and all brains were examined macroscopically and microscopically. Stroke developed in 41% of all animals; 31% died within ten days. Of the steroid-treated animals, stroke developed in 38% and 26% died. Of the saline-treated animals, stroke developed in 44% and 35.5% died. The differences were not significant by chi square analysis and the authors concluded that large doses of methylprednisolone given one hour after carotid ligation failed to prevent or influence the course of experimental stroke.

Additional Key Words
stroke cerebral edema carotid ligation

The effects of dexamethasone on cerebral ischemia caused by cerebral infarction have been studied in several experimental models, including cats,1 squirrel monkeys,2 rats,3 and gerbils,4 and in patients with stroke.7 The results of these studies vary, some indicating that dexamethasone is effective in reducing mortality,3,7 others stating that it has no significant effect on morbidity or mortality,1,2,6,8 and one suggesting that it does not prevent infarction but does decrease resultant mortality.4 This variation in results could have been related to differences in dosage, treatment schedule, time lag between insult and initial treatment, and model used. Several authors have recommended that further trials with high doses of steroids be done.4,7

Because the conflicting results above occurred when dexamethasone was used, we believed that a study of the effects of high doses of methylprednisolone on cerebral ischemia might be of value. We chose the highest dose reported for clinical use,4 and attempted to duplicate, in gerbils, the clinical conditions of stroke treatment.

The gerbil is a particularly good model for studies of cerebral ischemia. It lacks a blood vessel corresponding to the posterior communicating artery and thus has an incomplete circle of Willis.10,11 This absence of a route for collateral circulation accounts for the high incidence of ipsilateral cerebral infarction that can be produced in gerbils by unilateral common carotid artery ligation. The incidence of infarction ranges from 33% in gerbils 9 to 23 days old4 to 84% in adult gerbils.3 The infarction is fatal in 37% to 65% of gerbils.

Methods
Seventy-seven young adult gerbils, weighing 40 to 65 gm, were anesthetized with intraperitoneal sodium pentobarbital (60 mg per kilogram). One animal died after induction of anesthesia. In the remainder, a left ventral cervical incision was made. In eight, the left carotid artery was isolated but not ligated. In 68, the left common carotid artery was doubly ligated and transected. The skin was closed with steel clips, and each animal was then given an intraperitoneal injection of 1% Trypan blue (0.7 cc).

Thirty-four animals with carotid ligation were treated with intraperitoneal methylprednisolone sodium succinate (Solu-Medrol,* 30 mg per kilogram), the first dose being given one hour after ligation and the dose then repeated 24 and 48 hours later.

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Supported in part by USPHS Grants NS 06655 and NS 11101, and a grant from the Upjohn Company.

*Supplied through the courtesy of the Upjohn Company.

Kalamazoo, Michigan.
and again 48 hours later. Thirty-four animals with carotid ligation were treated with the same dosage of normal saline on the same schedule. The eight animals in which a sham operation had been done were not treated.

Animals were evaluated in a double-blind study for morbidity and mortality. They were observed every eight hours for the first three days and then daily for the next seven days. A decrease in alertness and movements, circling behavior, and limb splaying were considered signs of cerebral infarction. The time of death was recorded.

Surviving animals were killed ten days after operation. All brains were removed, fixed in formalin, and photographed. Whole specimens and sections were examined microscopically. Sections (90 μ thick) were made of blue-stained areas and examined microscopically.

Results
The nine gerbils undergoing sham operations survived for the full ten study days. Three had ptosis lasting from six to nine days, but none had operative sequelae when killed and none had evidence of infarction at necropsy.

Twenty-eight of the 68 animals with unilateral carotid ligation showed clinical and pathological signs of infarction (41% morbidity). Twenty-one of the 28 infarcted animals died (75% mortality from infarction). The average interval between ligation and death was 22 hours; range was from five to 36 hours. This interval was not significantly different in the saline-treated and the steroid-treated animals. Neurological signs seen in the animals with infarction were not different between the two treatment groups.

Of the 34 methylprednisolone-treated gerbils, 13 had infarction (38% morbidity) and nine died (26% mortality).

Of the 34 saline-treated animals, 15 had infarction (44% morbidity) and 12 died (35.5% mortality). By chi square analysis, the difference in mortality between the two treatment groups was not significant. A comparison of mortality data only from animals sustaining infarction again showed no significant differences: nine of the 13 steroid-treated animals died (69%) and 12 of the 15 saline-treated animals died (80%).

Discussion
In studies similar to this one, i.e., using Mongolian gerbils and producing cerebral infarction by carotid ligation, the highest survival rates reported occurred when steroids were first given immediately after ligation. However, since this timing is impractical for clinical situations, we delayed the first dose for one hour after surgical ligation. Our findings support those of Kahn, who found that dexamethasone “neither improved nor worsened the natural course of infarction” when first given one hour after carotid occlusion. Kahn’s dose of dexamethasone (0.5 mg per kilogram per day) was much lower than our dose of methylprednisolone. Even when given immediately after occlusion or as premedication for two weeks before occlusion, dexamethasone at high doses failed to alter the number of infarctions or the deaths from infarction in squirrel monkeys and cats. In rats with carotid ligation followed by anoxic exposure, a high dosage of dexamethasone given just after ligation and just after anoxic exposure failed to prevent cerebral infarction.

The steroid dosage used in this study was the highest therapeutic dosage reported in humans, i.e., 30 mg per kilogram per day. It was essentially equivalent to the dosage of dexamethasone used by Harrison and Russell (5 mg per kilogram per day) which resulted in a reduction in mortality from 60% to 20% in a similar gerbil study. The difference in our results and theirs may have been related to the fact that they administered dexamethasone to their animals immediately after operation, an impractical procedure in most clinical situations.

Of the two clinical studies relevant to this discussion, one indicated that dexamethasone (16 mg per day for ten days started within 48 hours of infarction) was effective in improving the course of stroke if the stroke had been severe. The other study indicated that dexamethasone (12 mg per day for ten days started within 48 hours of infarction) failed to improve clinical response.

At present it appears unlikely that massive steroid therapy, given at least one hour postinsult or later, significantly improves morbidity or mortality in experimental stroke.

Acknowledgments
We wish to thank Dr. William Bullock for his assistance in animal pathology.

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Stroke. 1974;5:444-446
doi: 10.1161/01.STR.5.4.444

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1974 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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