Ineffectiveness of Dexamethasone for Treatment of Experimental Cerebral Infarction
BY MYOUNG C. LEE, M.D., ANGELINE R. MASTRI, M.D., ARTHUR G. WALTZ, M.D., AND RUTH B. LOEWENSON, PH.D.

Abstract:
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Ischemic cerebral edema occurring with cerebral infarction may cause increases of intracranial pressure and neurological deficits or death. Certain other types of cerebral edema are influenced by adrenal glucocorticoids; there is conflicting evidence about effects on ischemic edema, largely due to differences in experimental models and dosages. Therefore, dexamethasone in large doses was studied in 15 cats with experimental cerebral ischemia and infarction produced by tranorbital occlusion of one middle cerebral artery (MCA). Five cats received dexamethasone, 4 mg per kilogram intramuscularly, twice daily for two weeks before and two weeks after MCA occlusion; five received dexamethasone for two weeks after occlusion; and five received no dexamethasone. There were no apparent differences among the three groups in the neurological deficits resulting from MCA occlusion, and no statistically significant differences in the sizes of cerebral infarcts. Dexamethasone is ineffective for the treatment of experimental cerebral ischemia produced by MCA occlusion.

Additional Key Words: middle cerebral artery occlusion cerebral edema cerebral ischemia

Cerebral ischemia and infarction are accompanied by cerebral edema, which is transient but can give rise to intracranial pressure gradients and presumably contribute to neurological deficits. Adrenal glucocorticoids retard or prevent the development of certain types of cerebral edema; therefore, steroids, particularly dexamethasone, have been used in attempts to influence cerebral edema caused by ischemia. The results have been variable.

In animal models of cerebral ischemia or hypoxia, dexamethasone has been ineffective in rats made hypoxic after occlusion of one carotid artery, in rats with microemboli injected into one carotid artery, and in squirrel monkeys with one middle cerebral artery (MCA) occluded. Methylprednisolone has been ineffective in cats with one MCA occluded. Each of these studies has been criticized, with respect to the characteristics of the experimental model, the type or dose of steroid used, or the duration of ischemia.

In gerbils with unilateral carotid artery occlusion, dexamethasone was found to be effective in one study but ineffective in another. Unfortunately, the gerbil may not provide a suitable model for experimental cerebral ischemia and infarction, because of the anatomical pattern of the cerebral circulatory system, the relatively small amount of white matter in the brain, and the unusual water balance of the animal that requires it to ingest very little exogenous water.

Pretreatment with dexamethasone has been found to be effective in preventing or delaying the development of ischemic cerebral edema in cats studied two hours after MCA occlusion; however, similar studies have not been done at later times after occlusion, when edema may be more pronounced. Systematic investigations of the therapeutic usefulness of dexamethasone in humans with strokes have been conflicting, but there is no convincing evidence of detectable benefit.

In the present study, the influences of dexamethasone on the neurological deficits and the cerebral infarcts resulting from acute ischemia were investigated. An experimental model approximating the clinical situation of strokes in humans was used, and treated animals received large doses of dexamethasone either after or both before and after the onset of ischemia.

Methods
Fifteen unselected adult cats were used. Each cat was anesthetized with phencyclidine hydrochloride, 1 mg per kilogram injected intramuscularly, and sodium pentobarbital, 25 mg per kilogram injected intraperitoneally. The left MCA was approached tranorbitaly and occluded by bipolar coagulation.

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This investigation was supported in part by Research Grant No. NS-3364 from the National Institutes of Health, Public Health Service.

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Five cats received dexamethasone, 4 mg per kilogram injected intramuscularly, twice daily for two weeks before and two weeks after MCA occlusion. Five cats received the drug in the same dosage for two weeks beginning 20 to 30 minutes after the coagulation of the MCA. Five cats received no dexamethasone. All cats were given the same preoperative and postoperative care; food and water were available but no parenteral fluids were administered.

Each cat was examined for the presence of neurological deficits at the time of recovery from anesthesia and at regular intervals subsequently. Neurological deficits were graded from 0 to 4 as follows: 0: no deficits; 1: minimal impairment of placing or stepping reactions on the side opposite MCA occlusion, deviation of the head, or circling; 2: minimal weakness or lack of use of one or both limbs opposite the lesion; 3: moderate weakness or lack of use of one or both limbs opposite the lesion; 4: no use of the limbs opposite the lesion.

Two weeks after MCA occlusion, each cat was killed by the intravenous injection of a saturated solution of potassium chloride. The brain was removed, fixed in 10% formalin, and imbedded in paraffin. Coronal sections were stained with hematoxylin and eosin. Sections near the tips of both limbs were examined independently by two investigators, without knowledge of which cats had received dexamethasone, and ranked in order of the sizes of the infarcts. The Mann-Whitney "U" test for rank order was used to assess differences in the sizes of the infarcts among the three groups.16

Results

There were no apparent differences among the three groups in neurological deficits (table 1), sizes of the cerebral infarcts (table 2), or histological appearance of the infarcts. As in previous studies of this experimental model of cerebral ischemia,14 the neurological deficits were remarkably uniform, reflecting involvement of the internal capsule; but the sizes of the infarcts varied considerably, ranging from small lesions in and near the basal ganglia to massive involvement throughout the region of distribution of the MCA. The "U" test showed no significant differences in the sizes of the infarcts among the three groups. The Spearman rank correlation coefficient for the rankings of the two investigators was 0.88, which was significantly different from zero (P < 0.01).15

Discussion

Ischemic cerebral edema developing after experimental MCA occlusion in cats has been shown to be transient, reaching a maximum two days after MCA occlusion.1 In the present study, measurements of water content of cerebral tissue were not made, so that the therapeutic usefulness of dexamethasone could be determined by estimates of the severity of the neurological deficits and the sizes of the cerebral infarcts. These are only indirect measures of ischemic cerebral edema, but they are meaningful when therapeutic effectiveness is under consideration. Even if dexamethasone were shown to retard or prevent the development of ischemic cerebral edema, the usefulness of the drug would depend on the outcome of ischemia as measured by neurological deficits and sizes of infarcts.

In experimental models of cerebral ischemia and infarction, survival is not an adequate criterion for determining the effectiveness of a therapeutic agent. In cats, death after surgical procedures for MCA occlusion may occur for a number of reasons, such as pneumonitis or electrolyte imbalance. Postoperative deaths occur as frequently after sham operations as after MCA occlusions, and (in Minnesota) postoperative deaths are much more common in late winter and early spring. Thus, we have not used survival as a criterion for studies of therapy of experimental cerebral ischemia, and data obtained from cats that were prepared for the present study but did not survive to the end of the experiment were not included in the analysis.

### Table 1

<table>
<thead>
<tr>
<th>Neurological Deficits (Graded 0 to 4)</th>
<th>Days after occlusion</th>
<th>Difference</th>
<th>Mean difference</th>
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<tr>
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<td>Group</td>
<td>Animal</td>
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<td>No dexamethasone</td>
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<td>Dexamethasone before and after occlusion</td>
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<td>Dexamethasone after occlusion</td>
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*Stroke, Vol. 5, March-April 1974*
not survive the first few days after occlusion were not included in the analysis. In smaller animals also, survival may depend on factors unrelated to cerebral ischemia, such as surgical shock, which may be influenced by the systemic effects of adrenal glucocorticoids. Before an agent can be considered effective for the treatment of cerebral ischemia it must be shown to have a direct effect on the lesion in the brain, not merely on survival.

Although there is now abundant evidence that dexamethasone has little or no specific, direct influence on cerebral ischemia, the drug still is used frequently for the treatment of acute strokes in humans. Anecdotal reports are used to support claims for therapeutic effectiveness and lack of complications, but intensive care or other therapeutic measures actually may be responsible for improvements in clinical status attributed to dexamethasone. General care with support of vital functions is still the most effective treatment for acute cerebral ischemia; certainly, in experimental models in animals, dexamethasone appears to be of no therapeutic benefit.

Acknowledgments
Technical assistance was provided by Carlos Verdeja, and Kay Daltas.

References
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Stroke. 1974;5:216-218
doi: 10.1161/01.STR.5.2.216

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