Megadose corticosteroid therapy following experimental traumatic spinal injury

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Corticosteroids are frequently used in the treatment of spinal trauma, although neither experimental nor clinical evidence to support their use is persuasive. Recently there have been claims that extremely high doses ("megadoses") of corticosteroids (equivalent to 15 to 30 mg/kg of methylprednisolone) improve neurological recovery compared to results with traditional steroid doses. The authors have compared the effect of megadose dexamethasone and methylprednisolone therapy to that of saline treatment following traumatic cervical spinal injury in the cat. During 6 weeks postinjury, neurological recovery did not differ significantly in corticosteroid-treated and saline-treated animals. Moreover, histopathological changes in the spinal cord were similar in methylprednisolone- and saline-treated cats. Corticosteroid-treated animals had a higher mortality rate than did control animals, with the predominant cause of death being neurogenic pulmonary edema. It is concluded that megadose corticosteroid treatment does not improve neurological recovery in this experimental model of spinal injury, and is associated with increased mortality.

KEY WORDS • megadose corticosteroid therapy • dexamethasone • methylprednisolone • spinal cord injury

Corticosteroids are routinely and widely used in the treatment of spinal cord injury, despite the fact that they have never been demonstrated to be effective in human spinal trauma. Rather, institution of steroid therapy has been based on theoretical justifications for use of these agents (for instance, their effects on lysosomal membranes, tissue edema, and lipid peroxidation), and on experimental reports showing beneficial effects in some animal injury models. However, the theoretical bases for treatment are of uncertain relevance since the pathophysiological mechanisms underlying acute spinal cord injury are not well understood. Moreover, the experimental literature supporting the use of corticosteroids for spinal cord injury is controversial; although many investigators have shown beneficial actions for corticosteroids in certain models, others have failed to demonstrate significant improvement of neurological recovery.

These conflicting experimental reports have resulted in the utilization of ever-increasing steroid doses. Most recently, it has been suggested that even high-dose corticosteroid therapy may be insufficient. Based in part on experimental work showing that so-called "megadose" methylprednisolone (15 to 30 mg/kg) significantly inhibits lipid peroxide formation and enhances (Na⁺ + K⁺)-ATPase activity, several investigators have utilized methylprednisolone doses in this range and have reported improvement in either physiological variables or functional recovery. In contrast, another group has found no beneficial effect for "megadose" dexamethasone administered at a dose of 20 mg/kg. Some of these inter-laboratory differences may be due to differences in experimental design, such as choice of species, injury method, steroid preparation, or treatment dose schedule.

To address some of these questions, we have examined the effects of megadose therapy with either dexamethasone or methylprednisolone following traumatic spinal injury in the cat, a species previously used to show the beneficial effects of megadose methylprednisolone.

Materials and Methods

Specific pathogen-free (SPF) cats,* each weighing 3.0 ± 0.25 kg, were used. After induction of anesthesia with intravenous sodium pentobarbital (25 mg/kg), the

* Specific pathogen-free cats obtained from Liberty Labs, Liberty Corner, New Jersey.
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animals were intubated, paralyzed with gallamine triethiodide (4 mg/kg/hr), and artificially ventilated with a Harvard respirator.† Arterial blood gas values were maintained in the normal range through use of intravenous sodium bicarbonate and respirator adjustments. Temperature was maintained at 38°C with a feedback thermoregulating unit.§ Blood pressure was continuously recorded through a femoral artery catheter connected to a pressure transducer and physiograph.¶ A catheter in the femoral vein permitted infusion of drugs.

After the animal’s head was fixed in a Kopf stereotaxic unit, a ligature was placed through the supraspinous ligament between T-2 and T-3 to stabilize the cervical vertebrae in a horizontal plane. Under sterile conditions, a laminectomy was performed to expose the C-7 spinal segment. With the dura intact, the spinal cord was traumatized using a modification of the Allen method in which a 20-gm weight was dropped a distance of 40 cm (Group 1, 11 cats) or 30 cm (Group 2, 21 cats) through a guide tube onto a 10-sq mm impact plate. The injury variables (800 gm-cm in Group 1 or 600 gm-cm in Group 2) were chosen from pilot and earlier studies showing that these forces produced moderate to severe spastic quadriaparesis in untreated control animals at 6 weeks following injury. Treatment with physiological saline was initiated 1 hour after injury in four animals in Group 1 and in 11 animals in Group 2. Corticosteroid therapy was also begun at 1 hour following injury: seven animals in Group 1 received dexamethasone and 10 animals in Group 2 received methylprednisolone sodium succinate. Methylprednisolone, given intramuscularly except as indicated, was administered three times a day in the following doses: Day 1 (trauma day), 30 mg/kg total dose (15 mg/kg intravenously, and two intramuscular injections of 7.5 mg/kg each); Day 2, 15 mg/kg; Day 3, 15 mg/kg; Day 4, 12 mg/kg; Day 5, 9 mg/kg; Day 6, 7.5 mg/kg; Day 7, 6 mg/kg; Day 8, 4.5 mg/kg; and Day 9, 3.0 mg/kg. Dexamethasone was administered as a 2-mg/kg bolus followed by 2 mg/kg/hr over 6 hours for a total of 14 mg/kg.

The rationale for the studies performed on Group 1 animals was based on earlier investigations from our laboratory showing that high-dose (2.5 mg/kg) dexamethasone therapy was ineffective in a traumatic 600 gm-cm cervical spinal injury. Use of the higher injury variables (800 gm-cm) in these animals was an attempt to maximize potential differences between control and treatment animals; however, this study was aborted early because of the extremely high mortality rate in dexamethasone-treated animals (five of the seven animals died). In Group 2, injury variables previously employed in our laboratory were used, and methylprednisolone was administered instead of dexamethasone to enable comparisons with other published studies.

Following treatment, the catheters were removed, and the animals were given 600,000 units of Bicillin (procaine penicillin G) intramuscularly, then placed in a temperature-controlled cage. After the animals' temperatures were stabilized at normal levels, they were returned to their home cages. Neurological function was evaluated weekly by a neurologist who was unaware of each animal’s treatment group. A modification of the five-point ordinal scale originally developed by Tarlov[10] was used to score forelimb and hindlimb function as follows: 0 = absence of voluntary movement; 1 = spontaneous movement but inability to support weight; 2 = ability to support weight but unable to walk; 3 = ability to walk but with marked spasticity and/or ataxia; 4 = ability to run but with mild spasticity or ataxia; and 5 = normal motor function. A total functional neurological score was obtained by adding the hindlimb and forelimb scores.

At 6 weeks postinjury the animals were killed with sodium pentobarbital. Spinal cords were removed and fixed in glutaraldehyde for 7 days. Spinal cord segments from the C-5 to T-2 level were sliced in cross sections at 2-mm intervals, allowing careful measurement of the cranio-caudal extent of lesions present. The cross-sectional slices were then dehydrated in graded alcohols, embedded in paraffin, and cut in 5-μ sections with a rotary microtome. Sections were stained with hematoxylin and eosin and Luxol-fast blue, and studied with a light microscope. The area of demyelination at the injury site was measured using an ocular micrometer. The total volume of injury was calculated using the formula $V = L \times X \times Y$, where $V$ is the volume, $L$ is the craniocaudal extent of injury, and $X$ and $Y$ are the sides of the rectangle approximated by the cross-sectional area of injury (Fig. 1). The volume of injury (in cu mm) was assigned a score of 1 to 5, as shown in Table 1.

A complete necropsy was performed on all animals that died before the end of the 6-week follow-up period. Gross and histopathological examinations of tissues from these cats were performed to identify pathological changes and the cause of death.

### TABLE 1

<table>
<thead>
<tr>
<th>Score</th>
<th>Injury Volume (cu mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81-100</td>
</tr>
<tr>
<td>2</td>
<td>61-80</td>
</tr>
<tr>
<td>3</td>
<td>41-60</td>
</tr>
<tr>
<td>4</td>
<td>21-40</td>
</tr>
<tr>
<td>5</td>
<td>0-20</td>
</tr>
</tbody>
</table>

† Harvard respirator manufactured by Harvard Apparatus Co., Inc., 150 Dover Road, Millis, Massachusetts.
‡ Feedback thermoregulating unit manufactured by Yellow Springs Instrument Co., P.O. Box 279, Yellow Springs, Ohio.
§ Pressure transducer and physiograph manufactured by Narco Bio-Systems, 7651 Airport Boulevard, Houston, Texas.
¶ Kopf stereotaxic unit manufactured by David Kopf Instruments, 7324 Elmo Street, Tujunga, California.
TABLE 2
Histopathological scores for saline- and methylprednisolone-treated cats*

<table>
<thead>
<tr>
<th>Histopathological Score</th>
<th>Saline-Treated Cats</th>
<th>Methylprednisolone-Treated Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>total cats</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>

* For a description of scoring system see Table 1.

TABLE 3
Comparison of neurological grades in methylprednisolone- and saline-treated cats*

<table>
<thead>
<tr>
<th>Weeks After Injury</th>
<th>Methylprednisolone-Treated Cats</th>
<th>Saline-Treated Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fore-limb</td>
<td>Hind-limb</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>2.5</td>
</tr>
</tbody>
</table>

* The scores are median values for eight saline-treated and six methylprednisolone-treated cats. Scoring is according to a modification of the Tarlov system: for a description see text.

Blood pressure changes between groups were analyzed with repeated-measurement analysis of variance (ANOVA). Neurological and pathological scores were compared using the Mann-Whitney rank sum test. Correlations between neurological and pathological scores were evaluated using the Spearman rank correlation test. Fisher’s exact probability test was used to compare survival rates between groups. A p value of less than 0.05 was considered statistically significant.

Results

The spinal cords displayed typical traumatic lesions after the standardized trauma: many were cavitated and all showed degrees of gliosis, demyelination, and axonal reaction. Remaining myelin was concentrated at the periphery of the cord. Minimal cellular reaction was observed (Fig. 1). Histopathological scores did not differ significantly between methylprednisolone-treated and control animals (Table 2) (Mann-Whitney rank sum test: \( p > 0.05 \)).

Trauma caused a transient increase in mean arterial blood pressure (MABP), followed by a gradual decline over the next 60 minutes from 129 ± 6 mm Hg to 87 ± 7 mm Hg (mean ± standard error of the mean). Although treatment with methylprednisolone caused a slight decrease in MABP within 30 minutes after injection (Fig. 2), there were no significant differences between the treatment and control groups at any time during the 4-hour monitoring period (repeated-measurement ANOVA: \( F = 0.14; p > 0.05 \)).

Neurological function was not significantly different between animals treated with methylprednisolone and control animals treated with saline (Fig. 3) at any time during the 6-week follow-up period (Table 3) (Mann-Whitney rank sum test: \( p > 0.05 \)).

In both studies, the mortality rate was higher in corticosteroid-treated than in control animals (72% versus 0% in Group 1, and 40% versus 28% in Group 2, respectively; Table 4). These differences were not sig-
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TABLE 4
Comparison of mortality rates in corticosteroid- and saline-treated cats*

<table>
<thead>
<tr>
<th>No. of Cats</th>
<th>Treatment</th>
<th>Died No.</th>
<th>Died %</th>
<th>Survived No.</th>
<th>Survived %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>saline</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>dexamethasone</td>
<td>5</td>
<td>72</td>
<td>2</td>
<td>28</td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>saline</td>
<td>3</td>
<td>28</td>
<td>8</td>
<td>72</td>
</tr>
<tr>
<td>10</td>
<td>methylprednisolone</td>
<td>4</td>
<td>40</td>
<td>6</td>
<td>60</td>
</tr>
</tbody>
</table>

* For a description of groups see text.

ificant (p = 0.07), possibly due to the small number of animals in each group.

All of the deaths in the two studies occurred 2 to 5 days after trauma. The principal gross pathological observation was the development of pulmonary edema, with wet heavy pulmonary parenchyma, mediastinal edema, and pleural effusion of copious amounts of serosanguineous fluid. Pulmonary histopathological changes were consistent with the gross findings, and included alveolar capillary congestion, dilated lacteal vessels, and protein and fibrin aggregates within alveolar spaces (Fig. 4).

Discussion

The present findings demonstrate that megadose corticosteroid therapy fails to reduce either the neurological dysfunction or the histopathological changes produced by traumatic cervical spinal cord injury in the cat. Two independent studies were performed. The first evaluated the effect of dexamethasone (14 mg/kg, administered intravenously over 6 hours) in a severe cervical injury model (800 gm-cm) (Group 1). This study was aborted prematurely because of the very high mortality rate of the dexamethasone-treated animals (five of seven animals died). The second study (Group 2) utilized a somewhat less severe injury model (600 gm-cm) and employed methylprednisolone at doses previously shown to be effective in in vivo and in vitro studies.19,26,35 The rationale for the changes in methodology in Group 2 resulted in part from the excessive mortality rate in Group 1 and in part from a desire to make the model similar to that used for studies investigating the therapeutic effects of naloxone13 and thyrotropin-releasing hormone (TRH).15 Use of methylprednisolone rather than dexamethasone in this study was necessitated by the question of potentially different rates of entry into the central nervous system by the two steroid preparations, as well as the previous reports of the beneficial effects of methylprednisolone after spinal injury in the cat.5,26,35 As in the dexamethasone study, however, methylprednisolone treatment was associated with a trend toward higher mortality, and failed to improve neurological function or to reduce histopathological changes. Although the mortality rates associated with megadose corticosteroid therapy (72% and 40%, respectively, for Groups 1 and 2) just failed to reach significance as compared to those for saline-treated control animals (p = 0.07), they are significantly higher than those of animals treated with naloxone (12%, p < 0.05)13 or TRH (0%, p < 0.05)15 in other

FIG. 3. Effects of methylprednisolone or saline treatment in six and eight cats, respectively, on neurological recovery 6 weeks after experimental cervical spinal cord injury. Points represent the sums of forelimb and hindlimb neurological grades for individual animals; histograms represent median scores. No significant differences were observed between the groups. Grading is according to a modification of the Tarlov system: for a description see text.

FIG. 4. Photomicrograph of a specimen of lung tissue illustrating severe pulmonary edema. The alveoli are filled with an eosinophilic proteinaceous fluid. Scattered macrophages are present. H & E, x 200.
studies using an identical spinal injury model. Moreover, the mortality rates with corticosteroid therapy in the present studies are similar to the 40% rate previously reported with this model using high-dose dexamethasone. The MABP, which increased with other treatments that improve neurological recovery in this model, was not significantly affected by methylprednisolone treatment.

The principal cause of death in both groups of animals, as in previous studies with this model, appeared to be pulmonary edema. We believe the edema to be neurogenic in origin since no non-neurogenic causes were found to account for it. Death from neurogenic pulmonary edema has also been reported in humans after cervical spinal injury. Other neurological conditions associated with induction of pulmonary edema include cranial trauma, cerebral hemorrhage, epilepsy, elevated intracranial pressure, and brain tumors. The precise pathophysiological mechanisms involved are unknown, but the major hypotheses suggest a transient systemic and pulmonary hypertension and/or a loss of pulmonary capillary integrity.

An increased tendency for complications without beneficial effects has been noted in humans following high-dose corticosteroid treatment for head injury, spinal injury, or brain tumor. A recent controlled trial comparing high-dose (15 mg/kg) and low-dose methylprednisolone therapy in human spinal injury showed no beneficial effect of the high dose on neurological recovery; yet infection rates were higher and there was a trend suggesting a higher mortality rate from cardiopulmonary complications.

The lack of benefit from megadose corticosteroid therapy in this study and in the study by Eidelberg, et al., contrasts with the findings from several other laboratories. Inter-laboratory differences have been characteristic of experimental work in spinal cord injury, and may result from methodological differences between laboratories. However, most of the previous positive studies were performed in the cat, as in the present experiments, and used similar doses and dose schedules for methylprednisolone. Moreover, neither the method of injury nor the site of injury appears likely to explain the reported differences. On the other hand, the reported beneficial effects of megadose methylprednisolone and megadose dexamethasone in the rhesus monkey have been limited (although they were statistically significant). In contrast to the lack of effect of megadose corticosteroid treatment in our cat model, treatment with either naloxone or TRH has resulted in dramatically improved neurological recovery in this model. Furthermore, both naloxone and TRH therapy have proved superior to high-dose dexamethasone treatment when these therapies have been directly compared.

Although the beneficial role of megadose or high-dose corticosteroid therapy in neurological recovery remains questionable, the evidence suggesting an effect of this therapy on physiological variables appears to be much more persuasive. For example, megadose methylprednisolone therapy has been shown to significantly improve spinal cord blood flow, recovery of extracellular calcium, enhancement of spinal cord (Na⁺ + K⁺)-ATPase activity, and attenuation of lipid peroxide formation. However, in view of the present as well as earlier functional studies, such physiological actions may not relate directly to neurological recovery. Moreover, even if megadose corticosteroid therapy were associated with some improvement of neurological function, the increase in morbidity and mortality with such doses, as observed in the present and other studies, suggests caution with regard to the use of these doses for human spinal cord injury.

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References

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The experiments reported herein were conducted according to the principles set forth in the “Guide for the Care and Use of Laboratory Animals,” Institute of Laboratory Animal Resources, National Research Council DHEW Publ. No. (NIH) 78-23.

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