Limiting ischemic spinal cord injury using a free radical scavenger 21-aminosteroid and/or cerebrospinal fluid drainage

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Traumatic spinal cord injury occurs in two phases: biomechanical injury, followed by ischemia and reperfusion injury. Biomechanical injury to the spinal cord, preceded or followed by various pharmaceutical manipulations or interventions, has been studied, but the ischemia/reperfusion aspect of spinal cord injury isolated from the biomechanical injury has not been previously evaluated. In the current study, ischemia to the lumbar spinal cord was induced in albino rabbits via infrarenal aortic occlusion, and two interventions were analyzed: the use of U74006F (Tirilazad mesylate), a 21-aminosteroid, and cerebrospinal fluid (CSF) drainage. These treatment modalities were tested alone or in combination.

In Phase 1 of this study, the rabbits received 1.0 mg/kg of Tirilazad or an equal volume of vehicle (controls) prior to the actual occlusion, three doses of Tirilazad (1 mg/kg each) during the occlusion, then several doses after the occlusion. Of the Tirilazad-treated animals, 30% became paraplegic while 70% of the control animals became paraplegic. Phase 2 involved the same doses of Tirilazad as in Phase 1 and, in addition, CSF pressure monitoring and drainage were performed. The paraplegia rate was 79% in the control animals, 36% in the group receiving Tirilazad alone, 25% in the group with CSF drainage alone, and 20% in the Tirilazad plus CSF drainage group. This rate also correlated with changes noted in CSF pressure; both Tirilazad administration alone and CSF drainage alone induced a decrease in CSF pressure and the two combined produced a further decrease. There was marked improvement in the perfusion pressure when using Tirilazad alone, CSF drainage alone, and Tirilazad therapy in combination with CSF drainage, with the last group producing the largest increase. This change in CSF pressure and perfusion pressure correlated with improved functional neurological outcome. Pathological examination revealed that Tirilazad therapy reduced the extensive and diffuse neuronal, glial, and endothelial damage to (in its most severe form) a more patchy focal region of damage in the gray matter. Cerebrospinal fluid drainage resulted in pyknosis of some motor neurons, and some eosinophilia. The combination of CSF drainage and Tirilazad administration resulted in the least abnormality, with either normal or near-normal spinal cords.

It is concluded that Tirilazad administration decreased CSF pressure during spinal cord ischemia and reperfusion and, like CSF drainage, increased and improved the perfusion pressure to the spinal cord, decreased spinal cord damage, and improved functional outcome. These effects may be related to the role that Tirilazad has on free radical scavenging during ischemia and reperfusion, and it is possible that Tirilazad therapy alone or in combination with CSF drainage is an effective adjunct to other neural protective measures in spinal cord injury.

Key Words • spinal cord injury • spinal cord ischemia • free radical scavenger • 21-aminosteroid • cerebrospinal fluid drainage

Mechanical injury to the spinal cord usually does not result in complete anatomical transection, but often a complete functional loss occurs. Moreover, spinal cord function frequently appears to worsen after injury. The concept of secondary injury, including ischemia, has evolved to explain this phenomenon. Ischemia is related to major systemic reduction of blood flow, local loss of autoregulation in the injured segment of spinal cord, and marked reduction in microcirculatory flow in both gray and white matter. Following delayed ischemia, reperfusion often causes injury. The present study was undertaken to isolate the role of ischemia in spinal cord injury, because little can be
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done to reverse direct mechanical injury during trauma. In the usual blunt-trauma model of spinal cord injury, damage secondary to mechanical injury cannot readily be separated from damage secondary to delayed ischemic injury and probable reperfusion injury. In this experimental system, spinal cord injury can be studied in terms of spinal cord ischemia without the superimposed injury occurring from mechanical trauma. Intra-aortic balloon occlusion was used to study the ischemic component in isolation. The purpose of the study was to test the effect of two modalities, alone or combined, in improving the neurological outcome of ischemic spinal cord injury: 1) a free radical scavenger, 21-aminosteroid (Tirilazad mesylate*); and 2) cerebrospinal fluid (CSF) drainage.

Materials and Methods

Study Phases

Phase 1. Tirilazad was tested versus vehicle control in 10 rabbits each. A total of 40 minutes of infrarenal aortic occlusion was performed followed by strict evaluation of neurological outcome at 12, 24, 48, 72, and 96 hours after occlusion. The neurological outcome was scored according to the following scale: 0 = no movement; 1 = trace movement; 2 = sits with assistance; 3 = sits unassisted but cannot hop; 4 = weak hop; and 5 = normal hop. For some analyses, the animals' functional neurological outcome was graded as either paraplegic or nonparaplegic.

Phase 2. The rabbits were subdivided into five groups: 1) control animals with sham surgery; 2) animals that underwent CSF drainage alone; 3) animals that received Tirilazad alone; 4) animals that underwent Tirilazad treatment plus CSF drainage; and 5) control animals that underwent surgery with no aortic occlusion, but received Tirilazad alone. The functional outcome, CSF pressure, and calculated spinal cord perfusion pressure were analyzed, and the relationship between these parameters and the animals' functional neurological outcome was determined.

Experimental Design

Forty-six New Zealand albino rabbits were used in the two-phase study. The experimental setup is illustrated in Fig. 1. Eight hours before occlusion, each animal received via intraperitoneal injection either 1.0 mg/kg of Tirilazad or an equivalent volume of the vehicle (0.5 N hydrochloride solution). The rabbits were then anesthetized with 40 mg/kg of ketamine and 10 mg/kg of xylazine administered intramuscularly. To rule out a possible protective effect of ketamine or xylazine, control animals subjected to an operation alone and animals that underwent operation and balloon occlusion but no other drug therapy were compared to animals that received CSF drainage alone, Tirilazad treatment alone, or CSF drainage and Tirilazad treatment combined. The rabbits were prepared and draped in a sterile fashion and placed under a halothane hood at 1.5% volume flow rates for maintenance of the anesthesia. A heating pad prevented hypothermia. The animals were allowed to ventilate spontaneously with no attempt to adjust the anesthesia to any particular blood gas level. Intravenous access was established via an ear vein, and antibiotic agents were given preoperatively.

Operative Technique

Bilateral inguinal incisions were made to isolate both femoral arteries. A No. 20 angiocatheter was placed in one artery to monitor distal aortic pressure, and a No. 3 French vascular catheter was introduced into the contralateral artery and directed approximately to the level of the inguinal ligament. Both catheters were transduced. A celiotomy was performed to isolate the aorta at the level of the left renal artery. Five minutes prior to balloon occlusion, each animal received intravenous heparin plus either 1 mg/kg of Tirilazad or an equivalent volume of vehicle. Two additional doses of test drug or vehicle (1 mg/kg) were then given intravenously at 10 and 20 minutes after balloon occlusion.

To occlude the aorta, a No. 3 French catheter was advanced proximally within the infrarenal aorta 2 cm above the left renal artery. A vascular loop was placed via the celiotomy approximately 1 cm inferior to the left renal artery. The loop was then secured tightly with a hemostat and the celiotomy was closed. Since in the lumbar spine the cord is fed by radicular arteries branching from the aorta, such an occlusion would induce ischemia below the level of occlusion. Body temperature, heart rate, and proximal and distal aortic pressures were recorded throughout the 40-minute occlusion period.

After balloon occlusion, functional neurological out-

* Tirilazad mesylate provided by Dr. Edward Hall and the Upjohn Company, Kalamazoo, Michigan.
come alone was tested in the Phase 1 animals. In Phase 2, additional experiments were employed, in particular using CSF drainage to decrease CSF pressure. To alter and measure CSF pressure, the rabbits were turned with their shoulders upright, exposing the posterior aspect of the neck and the base of the skull. Through a posterior midline incision, a No. 24 angiocatheter was placed into the cisterna magna. Correct placement was checked by observing the waveform of the CSF pressure, in particular looking for respiratory and cardiovascular variation. Any animal a with bloody spinal tap was excluded from the study because intrathecal blood has a significant effect on measured CSF pressure. For the animals in which CSF was drained, the angiocatheter that had been placed in the cisterna magna was left open to atmospheric pressure; in addition, the pressure was transduced on a continuous basis.

The perfusion pressure was calculated by finding the difference between CSF pressure and mean arterial blood pressure (MABP) measured distal to the occlusion. The MABP gives a rough approximation of the arterial pressure below the level of the occlusion, and can be determined from a separate catheter placed in the contralateral artery to the balloon-containing catheter, as mentioned previously. The CSF pressure was measured as described above at the same level in the supine animal as the MABP. The difference between MABP and CSF pressure yields a perfusion pressure, and this calculated perfusion pressure was used as a relative measurement to approximate perfusion pressure at the spinal cord. The amount of CSF drained was not kept at a constant but was allowed to equilibrate with the atmospheric pressure, the amount usually being only a few cubic centimeters. The pressure was therefore zeroed, in a sense, at the start of the experiment in the CSF drainage groups and the volume drained was not directly measured.

In both Phase 1 and Phase 2, the hemostatic vessel loop was removed after 40 minutes and the No. 3 French catheter was then withdrawn. Each animal received 1.0 mg/kg of Tirilazad or vehicle intravenously at 2 hours after occlusion and then every 6 hours until a total of 38 hours had passed since the occlusion. Neurological assessment was performed on all animals at 12, 24, 48, 72, and 96 hours after occlusion.

Pathological Analysis

Pathological evaluation was carried out in 14 spinal cords. Entire spinal columns were removed immediately after the animals had been sacrificed, and total laminectomies were performed to allow optimum penetration of the fixative to the spinal cord. A 10% phosphate-buffered formalin solution was used as a fixative for at least 10 days. The spinal cords with nerve roots including dorsal root ganglia were removed from the spinal columns and representative specimens were obtained from the thoracic, lumbar, and sacral spinal cords, including the cauda equina. Paraffin-embedded specimens were processed in the standard fashion and stained with hematoxylin and eosin (H & E). Specimens obtained from the upper thoracic cord were treated as controls to differentiate early ischemic changes from nonspecific postmortem changes.

Pathological analysis included extent of neuronal damage, intensity and character of the inflammatory response, changes in blood vessels, and changes in white matter. For the purpose of analysis, a simplified scale of neuronal damage was introduced: Grade 0, extensive generalized neuronal loss; Grade 1, extensive neuronal loss with focal changes at different levels; Grade 2, focal neuronal loss; Grade 3, eosinophilia and/or pyknosis; and Grade 4, normal.

Results

Effect of Tirilazad Administration

The results of Phase 1 are illustrated in Fig. 2. In the animals receiving Tirilazad, a significant percentage were nonparaplegic and, when scored as described above, showed far better neurological function than vehicle-treated control animals. All of these animals were tested unanesthetized during evaluation at 96 hours after the 40-minute occlusion. Evaluations were not performed past the 96-hour period in this experiment.

Figure 3 summarizes the functional neurological outcome observed at both 48 hours and 96 hours postocclusion in the Phase 2 animals. Neurological outcome is expressed as a percent paraplegia rate. Tirilazad administration alone showed no deleterious neurological effects on the animals, whether or not they underwent occlusion.

Tirilazad Administration Plus CSF Drainage

To evaluate one possible mechanism of protection produced by the test drug, CSF pressure and perfusion pressure (measured just prior to removal of the hemostatic vessel loop 40 minutes after occlusion) were analyzed (Fig. 4). All treated animals showed a significant decrease in CSF pressure compared to control animals, which translated into an increase in calculated perfusion pressure (Table 1). Tirilazad administration and CSF drainage together produced the largest drop in CSF pressure, resulting in an even larger increase in perfusion pressure.
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To more fully analyze the beneficial effects of Tirilazad treatment and/or CSF drainage, the functional neurological outcome relative to CSF pressure and calculated perfusion pressure of all experimental and control animals was then evaluated (Table 2). These results enabled us to correlate a specific change in CSF pressure and calculated perfusion pressure with a functional neurological outcome (Fig. 5). Comparisons relative to paraplegia versus nonparaplegia were made for all groups of experimental animals, not just the treatment groups or the control group. The group of nonparaplegic animals showed a drop in CSF pressure and a resultant increase in the calculated perfusion pressure; the paraplegic animals did not show the same magnitude of change.

Pathological Findings

Fourteen spinal cords were evaluated microscopically. In this group of rabbits, three animals had undergone sham operation, three had received vehicle only (controls), three had received Tirilazad only, three had undergone CSF drainage only, and two animals had been treated with Tirilazad administration and CSF drainage. The animals that underwent sham operation remained neurologically intact (neurological outcome score 5). Among the three animals in the occlusion control group, the average final outcome score was 2.5. The animals in groups with either Tirilazad alone or CSF drainage alone had fairly good preservation of

![Graph showing neurological outcomes](image)

**FIG. 3.** Bar graph showing neurological outcomes in Phase 2 of the study. Results are expressed as a percent paraplegia rate and were obtained at 48 and 96 hours after infrarenal aortic occlusion. Statistical significance (asterisks) was noted in all of the experimental groups when compared with the control group (p < 0.05). U74006F = Tirilazad mesylate; CSF = cerebrospinal fluid drainage.

| TABLE 1 |
| Change in CSF pressure and perfusion pressure after Tirilazad therapy and/or CSF drainage* |
| --- | --- | --- |
| Animal Group | Change in CSF Pressure | Perfusion Pressure |
| control | +2.8 ± 0.6 | 5.6 ± 1.0 |
| Tirilazad | -2.0 ± 0.4† | 9.0 ± 0.8‡ |
| CSF drainage | -0.8 ± 0.8† | 9.2 ± 1.1† |
| CSF drainage + Tirilazad | -2.3 ± 0.9† | 11.1 ± 1.2† |
| Tirilazad (sham operation) | -0.2 ± 0.4† | 42.6 ± 1.2§ |

* Means are expressed ± standard error of the mean. For description of animal groups see text. CSF = cerebrospinal fluid. Statistical significance compared to control rabbits (analysis of variance): † = p < 0.05; ‡ = p = 0.08.

§ Excluded from statistical analysis.

<p>| TABLE 2 |
| Change in CSF pressure and perfusion pressure according to neurological outcome* |</p>
<table>
<thead>
<tr>
<th>Neurological Outcome Group</th>
<th>Change in CSF Pressure</th>
<th>Perfusion Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>paraplegic</td>
<td>1.4 ± 1.4</td>
<td>6.2 ± 1.2</td>
</tr>
<tr>
<td>nonparaplegic</td>
<td>-1.0 ± 0.5</td>
<td>17.8 ± 3.4†</td>
</tr>
</tbody>
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* Means are expressed ± standard error of the means. CSF = cerebrospinal fluid.

† Statistical significance compared to paraplegic group: p < 0.05, Student's t-test.

![Graph showing changes in CSF pressure and perfusion pressure](image)

**FIG. 4.** Bar graphs demonstrating changes in cerebrospinal fluid (CSF) pressure (left) and calculated perfusion pressure (right) in Tirilazad mesylate (U74006F)-treated animals, animals undergoing CSF drainage (CSF), and animals receiving the combined treatment. Analysis of variance revealed significance (p < 0.05, asterisks) in all comparisons except when comparing the calculated perfusion pressure in Tirilazad-treated versus control animals (p = 0.08, cross). Vertical bars indicate standard error of the mean.

function, with an average final outcome score of 3.7 in each group. A consistently better result was achieved in animals that received both Tirilazad and CSF drainage, with an average end result of 4.

These clinical results correlated well with changes observed in the pathological specimens (Fig. 6). The most severe microscopic changes were observed in the control group animals and were characterized by extensive and diffuse neuronal loss, white matter edema, capillary endothelial swelling, and proliferation (Fig. 6A). The spinal cords were normal in the sham group (Fig. 6B). The spinal cords in the Tirilazad group without CSF drainage differed dramatically from those in the vehicle control group: in the former, only occasional focal damage to the gray matter and more limited mononuclear inflammatory cell reaction was seen (Fig. 6C). In the animals that underwent CSF drainage, only eosinophilia and pyknosis of some motor neurons were found (Fig. 6D); one area of focal neuronal loss was observed in one animal. The Tirilazad treatment plus CSF drainage group showed the best results, with either normal or near-normal cords. Additional important information in this subgroup of 14 animals was obtained from continuous CSF pressure monitoring. The animals treated with either Tirilazad therapy or CSF drainage had markedly lower CSF pressures than control group animals, with mean endpoint pressures of 4.7, 1.7, and 11 torr, respectively (standard error of the mean < 10%).

Discussion

The results of this study suggest that Tirilazad administration and/or CSF drainage lower CSF pressure and improve the perfusion pressure to the spinal cord. These changes correlate with an improvement in functional neurological outcome. This correlation was studied in an experimental model that analyzed the ischemic component of injury in isolation from mechanical injury to the spinal cord. This is important for it is thought that in the ischemic and possibly the reperfusion phases of spinal cord injury, there is ongoing biochemical and metabolic destruction of the spinal cord and that frequently this secondary injury may be the foremost component contributing to the final functional neurological outcome. In addition, ischemia may be the only phase of injury at present in which medical intervention might prevent further spinal cord damage.

Recent research has indicated that much of the ischemic and reperfusion injury to central nervous system (CNS) elements is secondary to the production of free radicals that alter lipid membranes, inducing lipid peroxidation with further destruction of cells and ultimately cell death. This alteration occurs in the neural, vascular, and supporting cells of the CNS. Indeed, Demopoulos, et al., theorized that both regional ischemia and acute spinal cord injury are mediated via the production of free radicals that attack the cell membrane lipids in the traumatized zone.

In models that analyze blunt spinal cord injury, it has been noted that severe blunt trauma results in a progressive decrease of spinal cord blood flow in the injured segment. Initially, there is actually a short phase of hyperemia secondary to the loss of autoregulation in the microvasculature. This loss appears to peak at about 10 minutes after injury and normalize at approximately 30 minutes after injury. Normal spinal cord blood flow is approximately 15 ml/100 gm/min, with a lower limit of about 10 ml/100 gm/min. Severe blunt trauma will cause spinal cord blood flow to decrease to levels that induce irreversible damage. It has been previously shown that this decrease in spinal cord blood flow can be reversed by administering Tirilazad.

Hall and several others have proposed a sequence of events that may occur during spinal cord injury and ischemia. These researchers noted that blunt spinal cord injury results in hemorrhage at the traumatized zone and also in a significant influx of calcium into the traumatized cells. The calcium influx activates other mechanisms, including the activation of various phospholipases and the subsequent release of arachidonic acid as well as increased prostaglandin synthetase activity.

More importantly, the initial cascade of damage induces the production of free radicals and lipid per-
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![Photomicrographs of pathological specimens from rabbits undergoing various treatment modalities.](image)

**A:** Specimen from a control animal showing extensive and diffuse neuronal loss, white matter edema, capillary endothelial swelling, and proliferation.  **B:** Specimen from a rabbit that underwent Sham operation showing a normal spinal cord.  **C:** Specimen from a Tirilazad-treated animal, without cerebrospinal fluid (CSF) drainage, showing occasional focal damage to the gray matter and more limited mononuclear inflammatory cell reaction.  **D:** Specimen from a rabbit that underwent sham operation showing a red blood cell and astrocytes.  H & E. × 30.

Oxidation products that activate phospholipases, resulting in the further release of arachidonic acid. The arachidonic acid is then metabolized via prostaglandin synthetase-catalyzed reactions, producing various arachidonic acid metabolites. Many of these metabolites, including thromboxane E₂ and prostaglandin F₂α, are potent mediators of ischemia.

Iron released from hemoglobin present in damaged red blood cells at the site of trauma is a very potent catalyst for free radical production and lipid peroxidation. The arachidonic acid metabolites further promote ischemia in the gray matter, and this gray matter ischemia produces fairly significant lactic acidosis intracellularly and free radical generation, which then produces further lipid peroxidation. The oxygen-containing free radicals and lipid peroxidation products appear to be the central mediators of the ischemic damage to the traumatized tissues. Unfortunately, the lipid peroxidation products and free radicals promote further release of arachidonic acid and further production of the ischemia-promoting arachidonic acid metabolites. These metabolites also promote spread of ischemia from the gray matter into the white matter, producing demyelination and axonal damage that result in permanent neurological deficits.

**Mechanisms of Action of Tirilazad**

Tirilazad has been shown to be a very potent scavenger of free radicals and in particular an extremely potent inhibitor of lipid peroxidation. It is very effective in the reactions catalyzed by iron. Tirilazad also appears to decrease the amount of arachidonic acid released at the trauma site. This decrease may be secondary to its inhibition of the positive feedback pathway mentioned previously or may be due to a separate second mechanism. The antioxidant effect is not related to any glucocorticoid activity of this compound. Tirilazad does not have any effect on the hypothalamic-pituitary-adrenal axis and does not appear to act via the steroid receptor.

In a cat model of acute subarachnoid hemorrhage, Tirilazad treatment has shown a blunting of the rise in
intracranial pressure (ICP), suggesting that one mechanism providing CNS protection in spinal cord injury might be the effect of Tirilazad on CSF pressure.\(^{35}\) If Tirilazad administration also blunted the rise in ICP by lowering CSF pressure and thereby improving perfusion pressure, we thought that the drug may translate this improvement in perfusion to greater functional outcome.

The ability of this antioxidant, the so-called "lazaroid compound," to decrease CSF pressure has not been analyzed. When CSF pressure is lowered, the intraspinal pressure is significantly reduced, which in turn reduces ischemic damage by improving the perfusion pressure to the neural and supporting tissue.\(^{35,61,62,87}\) Results showing that CSF drainage actually induced an improvement in neurological outcome and in perfusion pressure to the injured spinal cord illustrated the possible importance of the CSF pressure effect. The combination of CSF drainage and Tirilazad treatment appeared to further reduce the CSF pressure and promote an even larger increase in the perfusion pressure, resulting in an improvement in neurological outcome.

**Tirilazad Treatment and CSF Drainage**

There was a remarkable difference in the general functional outcome and in rates of paraplegia and nonparaplegia in the animals studied. The ability of Tirilazad administration and/or CSF drainage to produce improved functional neurological outcome was quite significant, with many more animals in the experimental groups showing improvement in their functional capabilities and a much larger percentage being nonparaplegic.

The fact that both CSF drainage and Tirilazad administration showed improvement in this particular model of ischemic spinal cord injury suggests that such treatment would be useful in spinal cord injury secondary to multiple causes and not just in trauma per se. For example, Tirilazad treatment and/or CSF drainage might be used to prevent spinal cord ischemia during some component of planned surgery such as lumbar or cervical decompression in patients with lumbar or cervical stenosis. The procedure may be useful during intradural and especially intramedullary spinal cord procedures. Indeed the spinal cord protection provided by these agents may be initiated prior to the insult to the spinal cord. Using such an agent prior to the actual injury period is extremely useful because much of the ischemic and reperfusion injury to the spinal cord actually occurs soon after the initial biomechanical injury.\(^{11,12}\) Non-neurosurgical applications include using Tirilazad during the repair of abdominal aortic aneurysms or in any procedure in which blood flow in the aorta or other smaller vessels supplying the spinal cord may be temporarily reduced or stopped.

**Pathology and Tirilazad Administration Plus CSF Drainage**

Our initial investigations showed that both the functional and the physiological improvement produced by these two interventions resulted in significant alterations in the pathological specimen. When the animals underwent infraaortic balloon occlusion, marked necrosis of the spinal cord was noted throughout both the gray and white matter. All three experimental treatments (Tirilazad alone, CSF drainage alone, and Tirilazad plus CSF drainage) diminished the pathological changes. In particular, the spinal cords in animals receiving the combined treatment showed a normal or near-normal appearance with only occasional pyknosis of neurons and occasional areas of eosinophilia noted on H & E-stained specimens. A marked improvement was noted with either of the treatments used alone, although occasionally pathological specimens showed some areas of focal necrosis.

**Conclusions**

Using a model that induces spinal cord ischemia by occluding the intrarrenal aorta allowed evaluation of several possible protective interventions. This model effectively induces ischemic injury followed by reperfusion injury without a biomechanical insult to the spinal cord, thereby enabling the study of ischemic reperfusion in relative isolation from biomechanical injury. We analyzed the possible protective action of Tirilazad (a free radical scavenger, antioxidant, and lipid peroxidation inhibitor) and CSF drainage in inhibiting the damage mediated during spinal cord ischemia. Both Tirilazad administration and CSF drainage provided a significant degree of protection against neurological deficit in the spinal cord. Cerebrospinal fluid pressure rose during ischemia in untreated animals, while both Tirilazad treatment and CSF drainage reversed this rise and lowered the CSF pressure. It is likely that Tirilazad administration not only inhibits damage from ischemia by blocking the deleterious effects of free radicals and lipid peroxide metabolites, but it may also provide protection by decreasing CSF pressure. This decrease in CSF pressure results in improved perfusion pressure to the spinal cord. How spinal cord injury actually induces the decrease in intraspinal perfusion pressure has not been fully elucidated, but it appears that the ischemia- and reperfusion-dependent component of this decrease in intraspinal perfusion pressure can be significantly reversed using Tirilazad treatment or CSF drainage. We believe that Tirilazad administration and/or CSF drainage may be useful in the treatment of patients with multiple types of spinal cord injuries, including both traumatic and isolated ischemic/reperfusion injury.

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