Tirilazad Mesylate Does Not Improve Early Cerebral Metabolic Recovery Following Compression Ischemia in Dogs

Mark A. Helfaer, MD; Jeffrey R. Kirsch, MD; Patricia D. Hurn, PhD; Kathleen K. Blizzard, BS; Raymond C. Kochler, PhD; and Richard J. Traystman, PhD

Background and Purpose: Tirilazad mesylate (U74006F) has been reported to improve recovery following cerebral ischemia. We conducted a randomized blinded study to determine if the drug would improve immediate metabolic recovery after complete cerebral compression ischemia.

Methods: Mongrel dogs were anesthetized with pentobarbital and fentanyl and treated with either vehicle (citrate buffer, n=8) or tirilazad (1.5 mg/kg i.v. plus 0.18 mg/kg/hr, n=8). Normothermic complete cerebral compression ischemia was produced for 12 minutes by lateral ventricular fluid infusion to raise intracranial pressure above systolic arterial pressure. Cerebral high-energy phosphate concentrations and intracellular pH were measured by phosphorus magnetic resonance spectroscopy. Cerebral blood flow was measured with radiolabeled microspheres, and oxygen consumption was calculated from sagittal sinus blood samples. Somatosensory evoked potentials were measured throughout the experiment.

Results: During ischemia, both groups demonstrated complete loss of high-energy phosphates and a fall in intracellular pH (vehicle, 5.76±0.23; tirilazad, 5.79±0.26; mean±SEM). At 180 minutes of reperfusion, there were no differences between groups in recovery of intracellular pH (vehicle, 6.89±0.07; tirilazad, 6.88±0.18), phosphocreatine concentration (vehicle, 89±16%; tirilazad, 94±24% of baseline value), oxygen consumption (vehicle, 2.6±0.2 ml/min/100 g; tirilazad, 1.8±0.5 ml/min/100 g), or somatosensory evoked potential amplitude (vehicle, 11±6%; tirilazad, 7±4% of baseline value). Forebrain blood flow fell below baseline levels at 180 minutes of reperfusion in the tirilazad-treated animals but not in the vehicle-treated dogs (vehicle, 28±4 ml/min/100 g; tirilazad, 18±5 ml/min/100 g).

Conclusions: We conclude that tirilazad pretreatment does not improve immediate metabolic recovery 3 hours following 12 minutes of normothermic complete ischemia produced by cerebral compression.

KEY WORDS • cerebral blood flow • cerebral ischemia • evoked potentials, somatosensory • nuclear magnetic resonance • dogs

The mechanism of brain injury from ischemia and reperfusion is multifactorial. Oxygen radicals, which have been demonstrated to be produced during reperfusion after global ischemia in newborn piglets, are reactive species that may produce direct tissue injury. In addition, tissue injury initiated by oxygen radical mechanisms may be propagated by the process of membrane lipid peroxidation. Tirilazad mesylate (U74006F; 21-[4-2(2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-1-piperazinyl]-16a-methyl-pregna-1,4,9(11)-triene-3,20-dione; monomethane sulfonate) is a potent inhibitor of lipid peroxidation and a weak free radical scavenger and therefore may be expected to improve metabolic recovery from transient global ischemia.

Although treatment with tirilazad improves neurological recovery from transient complete global ischemia in dogs, the mechanism for protection has not been clearly elucidated. Following transient incomplete ischemia, others have found an improved rate of recovery of high-energy phosphates in rats treated with tirilazad. We have demonstrated similar results in hyperglycemic dogs subjected to incomplete ischemia. An earlier study in cats with near-complete ischemia showed improved cerebral blood flow (CBF) recovery that may have been in part secondary to amelioration of arterial hypotension by tirilazad. However, there is no support for improved recovery of CBF or cerebral oxygen consumption (CMRO2) following cardiac arrest in tirilazad-treated dogs.

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In the present study, we produced 12 minutes of complete global ischemia by producing intracranial hypertension (compression ischemia) in anesthetized dogs while maintaining normal epidural temperature. This model is not associated with arterial hypotension during
reperfusion and permits ischemia to be produced remotely while the concentration of high-energy phosphates and the intracellular pH are measured semicontinuously by phosphorus-31 magnetic resonance spectroscopy (MRS). We tested the hypothesis that treatment with tirilazad mesylate would be associated with improved rates of recovery of high-energy phosphate concentrations and somatosensory evoked potential (SEP) amplitudes. We measured CBF and CMRO₂ to determine if the improved recovery of high-energy phosphates or intracellular pH could be accounted for by improved recovery of these variables.

Materials and Methods

The experimental methods have been described in detail, and the protocol was approved by the institutional animal care review board. Briefly, 16 dogs were anesthetized with intravenous fentanyl (50 μg/kg) and pentobarbital (6 mg/kg plus 3 mg/kg/hr). Systemic arterial and venous catheters were placed for measurements of pressure and infusions of fluid and drugs. A catheter was advanced from the femoral artery into the left cardiac ventricle for injection of radiolabeled microspheres. The temporalis muscles were surgically resected from the skull, and the bony ridge on the superior cranial surface was thinned with a drill. A superior sagittal sinus catheter was placed via a midline skull burr hole near the junction of the coronal sutures. The left lateral cerebral ventricle was cannulated through another burr hole with a Silastic ventricular drain catheter (Cordis, Miami, Fla.) for infusion of warmed mock cerebrospinal fluid (CSF) and measurement of intracranial pressure (ICP). Brain temperature was determined via a thermistor placed in the epidural space and maintained by whole-body heating with a water blanket. Fiberglass insulation was placed over the exposed skull to minimize heat loss.

Arterial and sagittal sinus blood samples were analyzed for Po₂, PCO₂, and pH with a Radiometer ABL electrode system (Copenhagen, Denmark). Oxygen content was measured with a CO-Oximeter (282, Instrumentation Laboratories, Lexington, Mass.). The CBF was measured by the radiolabeled microsphere technique, with 16±0.5-μm-diameter microspheres (Dupont-NEN Products, Boston, Mass.). For each CBF measurement, approximately 2×10⁶ microspheres (gadolinium-153, indium-114m, tin-113, ruthenium-103, niobium-95, and scandium-46) were injected into the left ventricular catheter. Arterial reference blood samples were withdrawn from an axillary artery at a rate of 4.94 ml/min during the injection and for 2 minutes after the injection. The CBF was calculated by the reference sample technique. CMRO₂ was calculated by multiplying the arterial–sagittal sinus O₂ content difference by blood flow to the cerebral hemispheres.

The MRS spectra were obtained using a Phospho Energistics 250-80 spectrometer (Otsuka Electronics, Colorado Springs, Colo.) with a 1.89-T horizontal superconducting magnet (25.4-cm bore, Oxford Instruments, Oxford, England). An inductively coupled, double tuned, two-turn copper surface coil 3.5 cm in diameter was placed directly over the skull. After shimming the magnetic field on the water proton peak, the phosphorus spectra were obtained at 32.5 MHz. Pulses of 75-μsec duration and 100 W were delivered to the coil at 4-second intervals. Fourier transforms of the free-induction decay were performed after exponential weighting (20 Hz). The broad peak from relatively immobile phosphates was reduced by standard line-broadening techniques (50 Hz). Spectral areas for β-adenosine triphosphate (β-ATP), phosphocreatine, and inorganic phosphate (Pᵢ) were analyzed by planimetry and expressed as a percentage of the respective area in the control spectra for each dog. Intracellular pH (pHᵢ) was calculated as 6.77+log[(α−3.29)/(5.68−α)], where α is the chemical shift (in parts per million) of Pᵢ relative to phosphocreatine. An external standard (dimethyl [2-oxopropyl]phosphonate) placed over the coil served as a marker for spectral position when the phosphocreatine peak disappeared. The precision of the pHᵢ measurements was approximately 0.06–0.10 pH units in the vicinity of the pKᵢ for Pᵢ of 6.75 and 0.1–0.2 pH units in the pHᵢ range of 5.0–6.0. The intracellular bicarbonate concentration ([HCO₃⁻]) was calculated as previously described from the Henderson-Hasselbalch equation using a pKᵢ of 6.12, pHᵢ as measured by MRS, and sagittal sinus PCO₂ with a solubility coefficient of 0.0314 mM/mm Hg. Intracellular PCO₂ was assumed to be approximately equal to sagittal sinus PCO₂ during the control period and reperfusion.

The SEPs were generated with foreleg stimulation at a rate of 5.9 per second and recorded from the skull electrode placed near the somatosensory cortex with a reference needle electrode in the snout. Signal averaging of 128 responses was performed with the Med-80 ( Nicolet Instrument Corp., Madison, Wis.), and replicate waves were recorded to ensure reproducibility. Amplitude of the primary cortical wave was measured from the peak of the first positive wave to the peak of the first negative wave. The peripheral nerve was stimulated only during limited periods of data collection.

Muscle paralysis was achieved with 0.1 mg/kg i.v. pancuronium bromide. Control measurements were obtained for CBF, CMRO₂, two 16-minute MRS spectra (256 free-induction decays), and replicate SEP recordings. One of two treatments was administered in a blinded randomized fashion. Experimental dogs (n=8) received tirilazad as an intravenous bolus of 1.5 mg/kg over 15 minutes, then as an infusion of 0.18 mg/kg/hr. This dose of tirilazad, with or without a subsequent infusion, is the dose that other investigators have reported as efficacious in ameliorating neurological injury following cerebral ischemia. Control animals (n=8) received an equivalent volume of the citrate buffer vehicle at the same infusion rate (1 ml/kg over 15 minutes followed by 0.12 ml/kg/hr). After 5 minutes of infusion, the second MRS measurements were made. Ischemia was then produced by infusing warmed mock CSF into the lateral ventricle via an insulated reservoir pressurized to 250 mm Hg above baseline systolic arterial blood pressure. The initial high reservoir pressure was required to assure that systolic arterial blood pressure did not exceed ICP during the accompanying Cushing response. Controlled hemorrhage through a large-bore arterial catheter was initiated at the onset of ICP elevation to blunt this response. After approximately 2 minutes, mean arterial blood pressure stabilized and ICP was lowered to 75 mm Hg above systolic arterial blood pressure. The collected blood was reinfused during the subsequent ischemic period. Reperfu-
The MRS spectra and SEPs were obtained throughout ischemia and the first 15 minutes of reperfusion in both groups (Table 1). Sagittal sinus PCO₂ fell transiently during the period associated with hyperemia at 8 minutes of reperfusion. Arterial glucose levels were elevated during early reperfusion. Mean arterial blood pressure was not different from the control value by 8 minutes of reperfusion and remained unchanged throughout reperfusion (Table 2). Epidural brain temperature remained well within the physiological range during the control period, ischemia, and reperfusion.

There were no differences between groups in regional or whole-brain CBF over the course of the experiment. Regional hyperemia was evident in both groups at 8 minutes of reperfusion (Table 3). Postischemic forebrain blood flow at 180 minutes fell significantly below the control level in the tirilazad-treated group but not in the vehicle-treated group (Figure 1). Hyperemia in the brain stem was greater than that in the forebrain, as has been described in other models of ischemia.18,19 The CMRO₂ was not different between groups. In both groups, CMRO₂ decreased below the control value at 30 minutes of reperfusion but was not significantly depressed thereafter (Figure 1). The ratio of CBF to CMRO₂ was similar in the two groups during the control period (9.6±0.8 in the vehicle-treated group versus 10.2±0.8 in the tirilazad-treated group) and was not different from control levels by 60 minutes of reperfusion in both groups (at 180 minutes, 10.6±1.4 in the vehicle-treated group and 11.4±0.6 in the tirilazad-treated group).

During ischemia pH fell sharply, to 5.76±0.23 in the vehicle-treated group and to 5.79±0.26 in the tirilazad-treated group. There was no difference between groups in the rate of recovery of pH, or calculated [HCO₃⁻], during early reperfusion or in the steady-state recovery of pH, or [HCO₃⁻], (Figure 2). Concentrations of both

### Results

Arterial pH, PaCO₂, Pao₂, and hemoglobin concentration remained within the normal physiological ranges during ischemia and reperfusion in both groups (Table 1). Sagittal sinus PCO₂ fell transiently during the period associated with hyperemia at 8 minutes of reperfusion. Arterial glucose levels were elevated during early reperfusion. Mean arterial blood pressure was not different from the control value by 8 minutes of reperfusion and remained unchanged throughout reperfusion (Table 2). Epidural brain temperature remained well within the physiological range during the control period, ischemia, and reperfusion.

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**Table 2. Mean Arterial Blood Pressure, Intracranial Pressure, and Epidural Temperature During Control Period and 180 Minutes of Reperfusion in Dogs**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
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<th>30</th>
<th>60</th>
<th>120</th>
<th>180</th>
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<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
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<td>Intracranial pressure (mm Hg)</td>
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<td>24±3</td>
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<td></td>
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<td>28±11</td>
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<td>Epidural temperature (°C)</td>
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<td>37.9±0.4</td>
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Values are mean±SEM; n=8 for both groups.

* p<0.05 different from control.

**Discussion**

We tested the hypothesis that tirilazad treatment would improve acute metabolic recovery from complete cerebral compression ischemia. If lipid peroxidation results in enough membrane damage to impair electrical activity and oxidative metabolism, then tirilazad, a potent inhibitor of lipid peroxidation, would be predicted to improve recovery of SEP amplitude and of metabolism following ischemia and reperfusion. Twelve minutes of ICP-induced complete global cerebral ischemia caused complete loss of SEP amplitude, loss of high-energy phosphates, and a severe decrease in pH. In this model of normothermic, normoglycemic compression ischemia, preadministration and continuous infusion of tirilazad had no impact on recovery of CBF, CMRO₂, SEP amplitude, pH, or high-energy phosphates during 3 hours of reperfusion.

One explanation for the lack of benefit from tirilazad on immediate cerebral recovery is that membrane lipid peroxidation may be quantitatively significant only after several hours of reperfusion, beyond the time window of

**Table 3. Regional Brain Blood Flow During Control Period and 180 Minutes of Reperfusion in Dogs**

<table>
<thead>
<tr>
<th>Region</th>
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<th>180</th>
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<tr>
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<td>Tirilazad</td>
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<td>Brain stem</td>
<td>Vehicle</td>
<td>27±2</td>
<td>188±34*</td>
<td>53±12†</td>
<td>22±3</td>
<td>25±3</td>
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<td>Tirilazad</td>
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<td>46±4</td>
<td>22±4</td>
<td>22±6</td>
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<tr>
<td>Forebrain</td>
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<td>111±18*</td>
<td>48±7†</td>
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<tr>
<td></td>
<td>Tirilazad</td>
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<td>113±25*</td>
<td>49±5</td>
<td>28±6</td>
<td>24±8</td>
</tr>
<tr>
<td>Posterior fossa</td>
<td>Vehicle</td>
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<td>182±29*</td>
<td>72±14*</td>
<td>33±4</td>
<td>32±4</td>
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<tr>
<td></td>
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<td>221±57*</td>
<td>68±10†</td>
<td>36±6</td>
<td>32±9</td>
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<td>Thalamus</td>
<td>Vehicle</td>
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<td>174±34*</td>
<td>70±7*</td>
<td>33±6</td>
<td>26±7</td>
</tr>
<tr>
<td></td>
<td>Tirilazad</td>
<td>30±3</td>
<td>179±36*</td>
<td>90±26†</td>
<td>37±10</td>
<td>34±7</td>
</tr>
</tbody>
</table>

Values are mean±SEM ml/min/100 g; n=8 for each group.

†p<0.05 different from control.

* p<0.01 different from control by Newman-Keuls test analyzed excluding hyperemic point.

β-ATP and phosphocreatine were depleted in all dogs by the end of ischemia. There was no difference between groups in the rate of recovery of high-energy phosphates during early reperfusion or in the steadystate recovery values (Figure 3). Recovery of high-energy phosphates at 180 minutes of reperfusion occurred in most dogs. However, in three dogs (two treated with tirilazad and one with vehicle) there was an initial recovery of β-ATP and phosphocreatine concentrations, followed by a secondary deterioration until there was no evidence of a signal. Forebrain blood flow also progressively decreased in these three animals by 180 minutes of reperfusion.

Baseline SEP amplitudes were not different between groups (vehicle, 43±11 μV versus tirilazad, 53±15 μV). As in our previous study,17 SEPs became isoelectric within 2 minutes in all dogs during ischemia. Five of eight (63%) in each group showed no recovery of SEP by the end of reperfusion. Overall, the recovery of SEP amplitude was similar between groups (vehicle, 11±6% versus tirilazad, 7±4% of control values).
our observations. Following global ischemia, the brain concentration of thiobarbituric acid–reactive material begins to increase at 2 hours of reperfusion but is considerably greater at 8 hours. Additional evidence comes from the finding that membrane function as measured by ion flux recovers quickly during reperfu-

FIGURE 1. Plots of mean±SEM forebrain blood flow (top panel) and cerebral metabolic rate for oxygen (bottom panel) for vehicle-treated (○) and tirilazad-treated (△) dogs; n=8 in each group. *p≤0.05 different from control for both groups; +p≤0.05 different from control for tirilazad-treated animals.

FIGURE 2. Plots of mean±SEM intracellular pH (top panel) and intracellular bicarbonate concentration (bottom panel) for vehicle-treated (○) and tirilazad-treated (△) dogs; n=8 in each group. There are no significant differences between groups.

FIGURE 3. Plots of mean±SEM concentrations of β-adenosine triphosphate (BETA ATP, top panel) and phosphocreatine (middle panel) concentrations and phosphocreatine–inorganic phosphate ratio (PCR/Pi, bottom panel) for vehicle-treated (○) and tirilazad-treated (△) dogs; n=8 in each group. There are no significant differences between groups.

It is possible that the drug was given at an inadequate dose and/or time to allow penetration into the brain. However, we believe that this is unlikely because the dose used was similar to that used by other investigators who demonstrated a salutary effect in the face of neurological injury. Nevertheless, we cannot exclude the possibility that there is significant lipid peroxidation during early reperfusion and that mechanisms other than lipid peroxidation predominate in limiting metab-

Reports of therapeutic efficacy for tirilazad have been mixed. In rats, tirilazad does not improve neurological outcome but is associated with amelioration of neuronal damage in the neocortex and improved rate of recovery of high-energy phosphates following transient ischemia.
Our laboratory also demonstrated an improved rate of recovery of pH and SEPs following transient normoglycemic incomplete global ischemia in dogs. This was a model of incomplete ischemia (unlike the present study) and therefore might afford an environment of improved drug delivery to damaged tissues. Moreover, following hyperglycemic incomplete ischemia, which would be expected to accentuate lipid peroxidation, tilazad treatment is associated with improved recovery of high-energy phosphates and SEPs. In dogs, tilazad administration either before or after an episode of complete global ischemia results in improved neurological outcome without apparent improvement in short-term benefit in CBF or CMRO2. Our data are consistent with the observation that tilazad treatment does not improve recovery of CBF or CMRO2 following transient normoglycemic complete compression global ischemia.

Our study of elevated ICP may be associated with more mechanical injury during ischemia than is found in the model of Perkins and colleagues because we used higher levels of ICP during the first 2 minutes of ischemia (350 mm Hg) and during the subsequent 10 minutes of ischemia (175 mm Hg). Greater ventricular distention may cause some traumatic injury, particularly to periventricular white matter tracts subserving SEP conduction. It is possible that the degree of membrane dysfunction in this case may be too severe to be ameliorated by inhibitors of lipid peroxidation. With 12 minutes of compression ischemia at an initial ICP of 200 mm Hg and a subsequent ICP of 20-50 mm Hg above diastolic arterial blood pressure, SEP amplitude was 41±4% of control. This value is higher than the present value of 11±6% in the vehicle-treated group but is comparable to the 32±4% recovery seen in pigs after 10 minutes of aortic occlusion and the 26±14% to 61±16% recovery (depending on treatment) seen in dogs after 8 minutes of cardiac arrest and 6 minutes of cardiopulmonary resuscitation. Others have demonstrated that the cerebral metabolic deterioration from cerebral ischemia is accentuated by impact injury. Therefore, there may be a significant component of mechanical distention in addition to ischemia in the present study. Another consideration is that rectal temperature was controlled in the previous studies but brain temperature was not monitored. It is possible that brain temperature may have decreased during ischemia or the initial period of reperfusion. Hypothermia during early reperfusion results in modest improvement in subsequent SEP amplitude and may contribute to the greater SEP recovery seen in earlier studies.

Another confounding variable is the use of pentobarbital, which may exert a neuroprotective effect and thereby mitigate any protective effect of tilazad. However, our use of high-dose fentanyl with low-dose (6 mg/kg/hr) pentobarbital resulted in a control CMRO2 of 3.6 ml/min/100 g, which is higher than the 2.4 ml/min/100 g obtained with pentobarbital as the sole anesthetic or the 2.7 ml/min/100 g obtained with isoflurane. Thus, pentobarbital is not likely to exert protection by a mechanism involving reduced CMRO2.

In summary, we report no improvement in the rates of metabolic recovery or SEP recovery with tilazad treatment in dogs following 12 minutes of normoglycemic, normothermic, complete global cerebral compression ischemia.

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Editorial Comment

Helfaer and colleagues raise interesting questions regarding the role of tirilazad as a treatment for cerebral ischemia. They correctly interpret (with considerable caution) their convincingly negative data regarding the effects of the 21-aminosteroid tirilazad on the recovery of metabolic and neurophysiological recovery (somatosensory evoked potentials) in a dog model of severe global cerebral ischemia up to 180 minutes after reperfusion. Helfaer et al place their findings in the context of a literature that is becoming increasingly ambiguous, and with good reason. Differences in dosages, routes of administration, times of administration, species and strain, time from insult to assessment, and end point parameters, not to mention fundamental differences in the models themselves, confound the analysis of existing literature.

Positive data merit comment. Beneficial effects of tirilazad were observed most consistently using models of transient focal ischemia. Six published studies1–6 examining morphological end points report beneficial effects on infarct volume, hippocampal histology, brain edema, or electrophysiological recovery. Less encouraging results were reported recently after permanent vessel occlusion.6 Dosage regimens sufficient to ameliorate infarction in temporary models have not been consistently beneficial after permanent occlusion. Hence, it is not unreasonable to conclude in a preliminary way that the results after temporary occlusion may reflect the fact that free radicals and lipid peroxidation mechanisms predominate during reperfusion, that tissue injury tends to be less severe, and/or that drug delivery is enhanced during reperfusion and therefore more favorable for pharmacoprotection.

Similar caveats also apply to reports on the efficacy of tirilazad in models of global cerebral ischemia. In the accompanying article, Helfaer and colleagues found that tirilazad given intravenously at a dosage comparable with others showing a salutary effect on behavior and mortality failed to improve the recovery of metabolic and neurophysiological parameters (pH, phosphocreatine, oxygen consumption, somatosensory function, and cerebral blood flow) after 180 minutes of reperfusion. The same group showed that tirilazad treatment improved recovery of high-energy phosphates and somatosensory evoked potentials in models of incomplete global ischemia.7 Two other studies8,9 documented improved survival and behavior in canines after 10–12 minutes of global ischemia. Differences in efficacy between complete and incomplete ischemia are again notable, although the latter two studies were performed in models of complete ischemia. Mixed results with tirilazad were also obtained in rat and gerbil models as well.10–14 As pointed out by Helfaer et al, the periods for assessing efficacy may be critical. In this regard, it would be of interest to see in their studies a determination of the extent to which metabolic and neurophysiological recovery (or lack thereof) at 4 hours correlates with histological or neurological outcome at 7 days and whether the model can be protected by any known agents (e.g., excitatory amino acid antagonists). Minding the cautious articulations by Helfaer and colleagues, the findings underscore the growing recognition that single-drug treatments may not be sufficient to attack the evolution of this complex pathophysiologic process, particularly after very severe ischemic insults.

Especially problematic is the interpretation of negative data from experiments using a single dose of drug. This may be especially pertinent to tirilazad because access into brain may be limited after intraperitoneal administration. Hence, only a fraction of the administered dose may reach the central nervous system. For certain drugs, it is at least theoretically possible that optimum dosing regimens may differ for each model and species, again obviating comparisons between studies. Less-than-optimun dosages and timing regimens may obscure potentially important therapeutic effects. Drug concentrations in blood and brain and/or its vessels (not routinely available for tirilazad) may be useful for...
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