Treatment With the Competitive NMDA Antagonist GPI 3000 Does Not Improve Outcome After Cardiac Arrest in Dogs

Mark A. Helfaer, MD; Rebecca N. Ichord, MD; Lee J. Martin, PhD; Patricia D. Hurn, PhD; Alejandro Castro, BA; Richard J. Traystman, PhD

Background and Purpose—We previously showed that treatment with a competitive N-methyl-D-aspartate (NMDA) receptor antagonist GPI-3000 (GPI) improved short-term physiological recovery after incomplete global cerebral ischemia complicated by dense acidosis. We tested the hypothesis that GPI administered after resuscitation from cardiac arrest would improve a more long-term recovery as measured by neurobehavioral assessment and neuropathology 4 days after resuscitation.

Methods—Anesthetized dogs were subjected to 7 minutes of cardiac arrest followed by vest cardiopulmonary resuscitation. Neurobehavioral outcomes were scored daily on a score ranging from 0 (normal) to 500 (worst). On the fourth day, the animals were killed, and neuropathology was evaluated in a blinded manner in the hippocampus and the neocortex by hematoxylin and eosin staining and by determination of percentage of injured neurons. Three groups of animals were treated in a randomized, blinded protocol with either saline (SAL), low-dose GPI (5 mg/kg followed by 1 mg/kg per hour for 2 hours), or high-dose GPI (25 mg/kg, followed by 5 mg/kg per hour for 2 hours).

Results—The mortality rate was higher in animals receiving GPI than in saline-treated control animals (4 of 15 deaths in SAL, 6 of 15 in the low-dose GPI group, and 9 of 18 in the high-dose GPI group). Neurobehavioral scores were depressed in GPI-treated animals compared with saline-treated control animals in a dose-dependent manner, with 96-hour scores of essentially normal (9 ± 2) in saline-treated animals compared with those animals with significant impairment (181 ± 47) treated with high-dose GPI. Neuropathological damage in the neocortex was most severe in GPI-treated animals, with the percentage of injured neurons dependent on the dose: 8.3% ± 2.7% SAL, 13.2% ± 6.4% low-dose GPI, and 39.4% ± 10.1%, high-dose GPI. CA1 neuronal damage was severe regardless of treatment.

Conclusions—Contrary to results seen in experimental global and focal cerebral ischemia, in which NMDA receptor antagonism may improve responses to injury, receptor antagonism with GPI does not improve brain outcome after cardiac arrest and resuscitation in the dog. Behavioral and histological outcomes both were worsened by GPI treatment at two doses, and mortality was higher relative to saline control treatment. We speculate that systemic drug effects, as well as potential neurotoxicity of the drug under ischemic conditions, may be responsible for the deleterious outcomes observed in our cardiac arrest model. (Stroke. 1998;29:824-829.)

Key Words: cardiopulmonary resuscitation ■ cerebral ischemia ■ glutamates ■ hippocampus ■ N-methyl-D-aspartate receptor ■ neocortex

Multiple mechanisms of cerebral ischemia and reperfusion injury have been proposed, but one consistent finding is the rise in interstitial glutamate concentration associated with cerebral ischemia.¹⁻³ Excessive activation of NMDA receptors under conditions of energy substrate depletion leads to neuronal death.⁴⁻⁵ Treatment of focal ischemia with a noncompetitive NMDA receptor antagonist such as MK-801 can reduce neuronal injury, albeit with significant adverse effects.⁶⁻⁷ Although non-NMDA (glutamate) receptor antagonists have been efficacious in global cerebral isch-
reduces infarction volume after transient focal ischemia. We have also shown that treatment with this agent during or after severe incomplete global cerebral ischemia complicated by intense acidosis ameliorates secondary deterioration of cerebral blood flow and high-energy phosphates during early reperfusion.

However, the importance of NMDA receptor–mediated mechanisms of injury in the brain after cardiac arrest is unclear. Therefore, we examined the effect of GPI on neurological and histological outcomes from cardiac arrest (7 minutes) followed by resuscitation and 96 hours of recovery.

Materials and Methods

This study is in compliance with the guidelines of the National Institutes of Health for care and handling of animals and was approved by our institutional animal care and use committee. Fifty-one preconditioned 8- to 15-kg mongrel dogs were anesthetized with 12.5 mg/kg thiopental and 0.2 mg/kg pancuronium, intubated, and paralyzed. Fifty-one preconditioned 8- to 15-kg mongrel dogs were anesthetized with 12.5 mg/kg thiopental and 0.2 mg/kg pancuronium, intubated, and monitored through capnography (model 78356A capnograph, Hewlett-Packard) to maintain end-tidal CO2 concentration between 35 and 40 mm Hg. One gram ampicillin, 1 g cefazolin, and 2 mg/kg gentamicin were administered intramuscularly. Stent graft procedures were used to place two 0.07-in (OD) Tygon catheters (Norton Performance Plastics) in the femoral vein and artery. These were tunneled to emerge between the shoulders to prevent removal during mechanical ventilation. Temperature was measured with a thermometer placed in the mid esophagus, and maintained between 37.8°C and 38.4°C with the use of a heating lamp and warming blanket. Arterial blood gases were adjusted to maintain Pao2 between 100 and 150 mm Hg and Paco2 between 35 and 40 mm Hg. Five minutes before the start of the arrest, 0.8 mg of epinephrine and 1 mEq/kg of sodium bicarbonate were administered intravenously. Beginning 7 minutes after initiation of cardiac arrest, vest chest compressions were initiated at 60 times per minute and maintained a diastolic blood pressure of 60 mm Hg. Five compressions were linked to one ventilation. After 1.5 minutes of CPR, 100 J was delivered (Life Pack, Physiocontrol Corp) via previously placed chest pads (R2 Peds Pads, R2 Medical Systems Inc). If there was no ROSC, repeat shocks were instituted. If two repeat shocks failed to resuscitate the animal, additional doses of epinephrine were administered every minute of continued CPR. Shocks were repeated every minute. If ROSC was not established within 7 minutes, the animal was excluded from the study.

The time to ROSC was defined as the time from initiation of cardiac arrest to the time when mean PaO2 equaled 60 mm Hg. On ROSC, treatment was administered in a randomized investigator-blinded fashion: (1) intravenous saline (40 mL/kg over 15 minutes, then 3 mL/kg per hour for 2 hours); SAL, (2) low-dose GPI (5 mg/kg in a comparable amount of saline over 15 minutes then 1 mg/kg per hour for 2 hours); and (3) high-dose GPI (25 mg/kg in a comparable amount of saline over 15 minutes then 5 mg/kg per hour for 2 hours). These dosages were chosen on the basis of our previous study. The animals then remained intubated until they had a cough and gag and were able to breathe spontaneously. They were physiologically monitored and supported to maintain normal vital signs for 4 days.

The animals underwent daily neurobehavorial scoring with use of the rating scale developed by Safar and colleagues to evaluate recovery in dogs after CPR. Neurological examination and neurobehavioral scoring were carried out at 24, 48, 72, and 96 hours after ROSC by a single examiner who was blinded to treatment group and the details of the surgery and resuscitation. The scores ranged from a normal score of 0 for no deficit to the worst score of 500 for a maximal deficit. Animals with neurobehavioral scores of 5 to 10 had normal consciousness and gait abnormalities that were minimal to none. Animals with scores 100 to 200 had normal consciousness but were apathetic and had mild to moderate tone and gait abnormalities. Animals with scores 200 to 300 were somnolent or stuporous and had severe motor abnormalities (tone and movement) but intact brain stem reflexes. Animals with scores >300 were deeply depressed or comatose, had severe motor deficits, and in some cases had brain stem reflex deficits. The recovering animals that demonstrated marked stereotypical motor behaviors, such as tonic limb extensor paroxysms, running movements, neck extensor dystonias, and oral-lingual dyskinesias, also underwent concurrent EEG recordings (Grass Instruments, models 6 to 6ES 825B). Four scalp needle electrodes were placed to record two bipolar channels (right and left, frontal and occipital) and ECG with use of a Grass electroencephalograph at a sensitivity of 7 μV/mm.

On the fourth day, the dogs that survived a 4-day recovery period were used to determine neuropathological scores. The dogs were deeply anesthetized with sodium pentobarbital and then perfused (20 minutes) intra-aortically with cold (4°C) 4% paraformaldehyde prepared in 0.1 mol/L phosphate buffer (pH 7.4). Neurodegeneration was assessed in 10-μm sections stained with hematoxylin and eosin. Profile counting was used to estimate ischemic neuronal damage in septal hippocampus (striatum pyramidale of CA1) and motor cortex (layers II and II) of vehicle- and drug-treated animals. Neuropathological scores were determined by an observer unaware of treatment. In each microscopic field, the fraction of neurons with ischemic cytopathology (ie, the percentage of neuronal damage) was determined in each animal. The criteria for ischemic cytopathology were an eosinophilic cytoplasm, cytoplasmatic vacuolation, perikaryal shrinkage, and nuclear pyknosis.

In addition, 3 animals served as nonischemic control animals to evaluate the effects of GPI (25 mg/kg) on the neurobehavior and neuropathology in the absence of cardiac arrest. All 3 animals demonstrated temporary neurobehavioral effects that resolved between 48 and 72 hours. No obvious injury or inflammatory changes were identified in any brain region by light microscopy.

Data are presented as mean ± SEM. Statistical analysis was performed with CRUNCH (Crunch Software Inc), using multiple ANOVA (with repeated measures) with the Newman-Keuls test to evaluate differences with P set at ≤ .05. Mortality was analyzed with the nonparametric Kruskal-Wallis test.

Results

Three animals could not be resuscitated and were excluded from randomization and treatment. Of those randomized, the mortality rate was greater among GPI-treated animals than saline-treated ones and correlated with drug dose. Mortality in saline-treated dogs was 4 of 15 and occurred 2 ± 0.6 days after arrest. The low-dose GPI group mortality was 6 of 15 and occurred 1 ± 0.3 days after arrest. The high-dose GPI group suffered a mortality rate of 9 of 18 and occurred 1.4 ± 0.3 days after arrest. Of the survivors, there were no differences among the three groups related to resuscitation events (Table 1).

In all three groups, neurobehavioral scores improved from 24 to 96 hours of recovery (Fig 1). However, neurobehavioral scores in high-dose GPI were poor (181 ± 47) compared with those in animals treated with saline (9 ± 2) or from the low-dose GPI group (70 ± 29). Seizures were not observed in the three groups related to resuscitation events.
any animals. In some cases, GPI-treated animals manifested stereotyped motor behaviors that were not associated with epileptiform discharges on EEG. Postoperative vital signs were similar in the three groups (Table 2), but heart rate was initially elevated in the high-dose GPI group, which resolved on day 2 after extubation. Likewise, arterial blood gases and hemoglobin levels were similar in the three groups (Table 3). PaO₂ was higher on the first postoperative day in the high-dose GPI animals, because of the need for prolonged intubation and ventilation in these animals.

Hippocampal injury (Fig 2) was severe in all groups (84.6%±7.8% for saline-treated control animals, 93.7%±2.8% for the low-dose GPI group, and 94.8%±0.8% for the high-dose GPI group). Cortical neuronal damage correlated with GPI dose (8.3±2.7% for saline-treated animals, 13.2±6.4% for low-dose GPI, and 39.4±10.1% for high-dose GPI, Fig 2).

**Table 1. Resuscitation Parameters**

<table>
<thead>
<tr>
<th>Group</th>
<th>Mortality Rate</th>
<th>Day of Mortality</th>
<th>Number of Shocks</th>
<th>Number of Epi Doses</th>
<th>ROSC (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>4 of 15</td>
<td>2.0±0.6</td>
<td>2.1±1.6</td>
<td>3.0±1.4</td>
<td>9.6±1.6</td>
</tr>
<tr>
<td>Low-dose GPI</td>
<td>6 of 15</td>
<td>1.0±0.0</td>
<td>2.5±0.7</td>
<td>1.0±0.0</td>
<td>8.9±0.2</td>
</tr>
<tr>
<td>High-dose GPI</td>
<td>9 of 18*</td>
<td>1.4±0.3</td>
<td>2.7±0.3</td>
<td>3.3±0.9</td>
<td>9.4±0.4</td>
</tr>
</tbody>
</table>

EPI indicates epinephrine.
*Different from saline control group.

**Figure 1.** Behavioral scores improve over time in all groups. Scores ranged from normal (0) to 500 (most severely injured). Open circles represent saline-treated control animals, squares represent animals receiving low-dose GPI, and triangles represent animals receiving the high dose of GPI. The filled symbols represent animals receiving low-dose GPI, and triangles represent animals receiving high-dose GPI. The filled symbols represent animals receiving high-dose GPI. The filled symbols represent animals receiving low-dose GPI. The filled symbols represent animals receiving high-dose GPI. At 24 hours, the animals receiving saline had scores better than those receiving the low-dose GPI. At 48, 72, and 96 hours, the scores of the animals receiving high-dose GPI were worse than those of animals receiving low-dose GPI.

**Discussion**

The major findings of this study are that competitive NMDA receptor antagonism after 7 minutes of cardiac arrest and resuscitation in dogs impairs neurobehavioral and neuro-pathological outcomes compared with those in saline-treated animals. Furthermore, the deleterious effects of the administration of this agent (GPI 3000) on mortality are strongly dose dependent. Surprisingly, these results differ from those obtained with focal and incomplete global cerebral ischemias and suggest that systemic effects of NMDA receptor antagonists may influence recovery.

We chose the present experimental cardiac arrest model in a large animal for its clinical applicability, its low overall mortality rate, its reproducible neocortical and hippocampal pathology, and the lack of dependence on cardiopulmonary bypass procedures. Because the arrest time is short, neurobehavioral deficits are mild and typically short-lived. In addition, because excitatory amino acid release occurs early in ischemia, inhibition of these mechanisms should be instituted in short-duration ischemias. This model is advantageous in that both beneficial (or in the case of GPI-treated groups, deleterious) outcomes can be measured.

NMDA blockade with GPI depressed recovery after cardiac arrest. The increased mortality rates associated with GPI treatment may result in part from effects outside the central nervous system. NMDA receptors have been identified in the lung, but the effects of blockade of these lung receptors on resuscitation after cardiac arrest are not known. Similarly, NMDA receptor blockade with ketamine in the myocardium causes diminution of contractile force, the spontaneous rate of contraction, and the transsarcolemmal calcium currents. The widespread physiological consequences of cardiac arrest and

**Table 2. Postoperative Vital Signs**

<table>
<thead>
<tr>
<th>Postoperative Day</th>
<th>Group</th>
<th>Heart Rate (beats/min)</th>
<th>Mean PaO₂ (mm Hg)</th>
<th>Respiratory Rate (breaths/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Saline</td>
<td>84±7</td>
<td>88±3</td>
<td>40±8</td>
</tr>
<tr>
<td></td>
<td>Low-dose GPI</td>
<td>88±5</td>
<td>92±3</td>
<td>40±10</td>
</tr>
<tr>
<td></td>
<td>High-dose GPI</td>
<td>110±7*</td>
<td>95±3</td>
<td>27±10</td>
</tr>
<tr>
<td>2</td>
<td>Saline</td>
<td>93±9</td>
<td>91±5</td>
<td>44±12</td>
</tr>
<tr>
<td></td>
<td>Low-dose GPI</td>
<td>78±10</td>
<td>92±7</td>
<td>26±6</td>
</tr>
<tr>
<td></td>
<td>High-dose GPI</td>
<td>91±11</td>
<td>84±5</td>
<td>29±6</td>
</tr>
<tr>
<td>3</td>
<td>Saline</td>
<td>59±7</td>
<td>82±2</td>
<td>32±6</td>
</tr>
<tr>
<td></td>
<td>Low-dose GPI</td>
<td>84±1</td>
<td>87±1</td>
<td>. .</td>
</tr>
<tr>
<td></td>
<td>High-dose GPI</td>
<td>96±13</td>
<td>91±4</td>
<td>18±4*</td>
</tr>
</tbody>
</table>

*Different from saline control group.
resuscitation\textsuperscript{23} in concert with the potential for cardiopulmonary dysfunction from NMDA receptor blockade are a potential explanation for a higher mortality rate in GPI-treated animals.

NMDA antagonism has been evaluated in the setting of cardiac arrest. Using a model of normothermic ventricular fibrillation cardiac arrest with a 96-hour recovery, Sterz and colleagues\textsuperscript{26} evaluated the efficacy of the noncompetitive NMDA receptor antagonist MK-801. In this global cerebral ischemia model, no improvement was demonstrated in neurobehavioral or neuropathological outcome with MK-801 treatment. The authors concluded that their results do not negate the hypothesis that neuronal hyperexcitability mediated by excitatory amino acids causes neuronal injury in the face of global cerebral ischemia. They interpreted their negative result to emphasize the existence of multiple mechanisms mediating secondary brain injury. Using GPI, we have demonstrated improvements in acute bioenergetics and neurophysiological recovery associated with a severe model of incomplete global cerebral ischemia.\textsuperscript{12} In that study, the administration of GPI (25 mg/kg bolus followed by 5 mg/kg per hour) after 30 minutes of global cerebral ischemia resulted in improvement in high-energy phosphates in the brain. Since we demonstrated that NMDA receptors may have a role in the neuropathophysiology associated with this cerebral injury,\textsuperscript{12} we were prompted to evaluate this agent in a more clinically applicable model and to evaluate chronic outcomes. In the present study, we found the unexpected result that this agent worsened outcome compared with saline. The dramatically different results compared with our previous study\textsuperscript{12} are due to differences in the methods used to produce cerebral ischemia, the acute versus chronic recovery period during which observations were made, and the use of histological and neurobehavioral outcomes in the present study. In our early observations of GPI efficacy,\textsuperscript{12} we used global cerebral ischemia induced by reversible intracranial hypertension, which results in few adverse systemic effects. The ischemic insult is limited to the cerebral vascular bed in that model. In contrast, cardiac arrest results in both cerebral and systemic low-flow conditions and likely affects numerous noncerebral factors that alter cell injury mechanisms. Furthermore, our previous evaluation of the efficacy of GPI was determined over only the first 3 hours of reperfusion in the anesthetized dog and used hemodynamic and bioenergetic measures of brain outcomes. The present findings reflect a longer observation period (96 versus 3 hours) that likely allowed initial injury maturation reflected by loss of neuronal viability and depressed functional recovery in the awake animal.

Upregulation of presynaptic excitatory amino acid transporters has been demonstrated to increase within 5 minutes of bilateral common carotid occlusion. This upregulation transports the excess excitatory amino acids that are

### Table 3. Postoperative Laboratory Values

<table>
<thead>
<tr>
<th>Postoperative Day</th>
<th>Group</th>
<th>pH</th>
<th>Pco\textsubscript{2} (mm Hg)</th>
<th>P0\textsubscript{2} (mm Hg)</th>
<th>Hemoglobin (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Saline</td>
<td>7.40±0.05</td>
<td>31.1±1.0</td>
<td>116±14</td>
<td>11.5±0.6</td>
</tr>
<tr>
<td></td>
<td>Low-dose GPI</td>
<td>7.38±0.01</td>
<td>28.2±0.9</td>
<td>138±32</td>
<td>10.9±32</td>
</tr>
<tr>
<td></td>
<td>High-dose GPI</td>
<td>7.38±0.02</td>
<td>30.4±1.8</td>
<td>250±36*</td>
<td>11.7±0.7</td>
</tr>
<tr>
<td>2</td>
<td>Saline</td>
<td>7.42±0.02</td>
<td>32.9±2.2</td>
<td>112±16</td>
<td>13.8±0.9</td>
</tr>
<tr>
<td></td>
<td>Low-dose GPI</td>
<td>7.38±0.03</td>
<td>27.6±1.6</td>
<td>88±1</td>
<td>11.9±0.9</td>
</tr>
<tr>
<td></td>
<td>High-dose GPI</td>
<td>7.38±0.01</td>
<td>32.8±1.8</td>
<td>131±34</td>
<td>15.9±5.9</td>
</tr>
<tr>
<td>3</td>
<td>Saline</td>
<td>7.41±0.01</td>
<td>33.7±2.5</td>
<td>97±3</td>
<td>13.3±1.4</td>
</tr>
<tr>
<td></td>
<td>Low-dose GPI</td>
<td>7.38±0.01</td>
<td>32.0±0.10</td>
<td>94±0.1</td>
<td>14.0±0.1</td>
</tr>
<tr>
<td></td>
<td>High-dose GPI</td>
<td>7.41±0.03</td>
<td>31.3±1.9</td>
<td>100±8</td>
<td>11.1±0.7</td>
</tr>
</tbody>
</table>

*Different from saline control group.

![Figure 2. Neocortex damage is dependent on GPI dose.](http://stroke.ahajournals.org/)

HIPPOCAMPUS
CORTEX

Figure 2. Neocortex damage is dependent on GPI dose. Hippocampal and neocortex neuronal dropout percentages are represented by open circles and open squares, respectively. Filled symbols represent the mean and SEM. There are no differences between the three treatment groups in terms of hippocampal neuronal dropout. The dose-response relationship with neocortex neuronal dropout percentages follows a linear regression model with $r^2=.99$. 
released into the extracellular space from the intracellular space in response to ischemia. This upregulation has a biphasic time course, with partial return to control levels at 1 hour of reperfusion followed by a second increase at 48 hours only to fall to control levels within 7 days.27 In addition, it is likely that glutamate receptor desensitization occurs after exposure to elevated neurotransmitters during or after ischemia,27 an effect that could be altered by the administration of a glutamate receptor antagonist. Others28,29 have shown that NMDA receptor–blockade alters receptor density and may thereby affect receptor activity after the antagonist is no longer present. The balance of excitatory and inhibitory amino acids shifting between the intra- and extracellular compartments has been shown to modulate neuronal injury associated with cerebral injury.2

In this more prolonged setting, it is conceivable that administration of GPI causes the balance of amino acid binding and transporting to lead to the deleterious effects seen in the present study.

Previous work has documented neurotoxicity associated with NMDA receptor blockade (MK-801) in the brain. This toxicity is most prominent in the posterior cingulate and retrosplenial cortices and is seen on light microscopy in very high doses, with electron microscopy necessary for demonstration of the vacuolization seen at smaller doses.30 Olney et al31 suggested that NMDA receptor blockade decreases GABAergic inhibition of excitatory synaptic pathways with resulting neurotoxicity. In our study, we did not show signs of toxicity on a light microscopic evaluation with high doses of GPI in the absence of ischemia. Nevertheless, we cannot fully exclude this possibility. What is clear from our data is the potential for deleterious outcome when there is an interaction between ischemia and competitive NMDA receptor antagonism.

In this study, we have defined a chronic model of 7 minutes of cardiac arrest, 1.5 minutes of CPR followed by external defibrillation without extracorporeal resuscitation, and a 96-hour recovery that mimics the clinical situation in humans. With an acceptable mortality rate (27%), we demonstrated the utility of this chronic model in defining the neurobehavioral and neuropathological effects after saline administration. This model results in nearly complete recovery of neurobehavioral function by the 4th postoperative day, and hippocampal and neocortical neuronal damage at 84.6% ± 7.8% and 8.3% ± 2.7%, respectively. Furthermore, blockade of the NMDA receptor with GPI worsens mortality rates, neurobehavioral outcome, and neocortical neuropathology in a dose-dependent manner.

Acknowledgments

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The article by Helfaer et al reports on a pharmacological study that resulted in “negative” data (ie, the kind of data investigators usually try not to produce, as the premise of pharmacological studies is that “we try to demonstrate some usefulness of the chemical in view of proving a research hypothesis or supporting eventual clinical utility”). However, the study by Helfaer et al is, in my opinion, a very important one because publications of pharmacological studies are heavily biased toward the “good news.” Although we do not know exactly the ratio of reporting positive versus negative results with a compound (many journals/reviewers have little patience with pharmacological studies that “did not work”), it is nevertheless extremely important to report such data. The NMDA/glutamate hypothesis in neuroinjury has been an intriguing example in which early optimism (mid-1980s) ran into a perplexing stage (mid-1990s), during which expectations for positive clinical studies in stroke and neurotrauma have been difficult to realize—and, as the decade closes, may not be counted as 20th century pharmaceutical/academic achievement in drug discovery and development. Is it possible that, early on, too little has been reported on negative data for this class of agents as well as for other compounds that block the glutamate/NMDA receptor/channel complex (non-competitive antagonists)?

In this light, the demonstration by Helfaer et al (in a well-designed and well-executed study) that a compound which possesses the primary pharmacology of competitive NMDA receptor antagonists in fact worsens the outcome (histologically and functionally) of cerebral insult (ischemia and reperfusion) may call attention to the need for thorough analysis of the reasons for this detrimental effect. Although the study has not explored the mechanism of the negative results (an endeavor that needs to be undertaken), several possibilities must be entertained: (1) Is the reported data particular to the specific agent used? It would be useful to compare other competitive NMDA antagonists of diverse chemical structures in the same models. (2) Do noncompetitive antagonists behave the same way in this model (ie, is this a model/species-specific issue? Other species and models of global ischemia and reperfusion need to be used. (3) Does the compound (or the class) act on central versus peripheral target organs? The authors alluded to this possibility but have not explored it. (4) Are certain metabolites of the compound responsible for the toxic effects? Better understanding of the pharmacokinetics and pharmacodynamics of the compound need to be reviewed before broad implications are made.

These issues are important points that need to be better addressed in pharmacological studies, regardless of the compound tested. It is highly advisable that researchers design their studies up front to address these concerns. This reviewer’s opinion is that Stroke explores principles of pharmacological conduct to be recommended to scientists interested in pharmacological studies to ensure that pharmacological observations in vivo are provided with more complete insights on the issues addressed above. Such standards could be very instrumental in reducing the “noise” of apparently conflicting data that confuse pharmacological efficacy based on mechanism of action with confounding issues of metabolism, pharmacokinetics and pharmacodynamics, site of action, and species and models particularities.

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