Anticonvulsant Lamotrigine Administered on Reperfusion Fails To Improve Experimental Stroke Outcomes

Richard J. Traystman, PhD; Judith A. Klaus, RN; A. Courtney DeVries, PhD; Amanda B. Shaivitz, BS; Patricia D. Hurn, PhD

Background and Purpose—Recent results suggest that selective inhibitors of presynaptic neuronal ion channels can diminish glutamate release during cerebral ischemia and modulate excitotoxic cell death. The aim of the present study was to evaluate lamotrigine (LTG), an antiepileptic that inhibits presynaptic sodium and voltage-sensitive calcium channels, as a potential stroke resuscitation agent in the rat. Three dosages of LTG were examined for effect on infarction volume and sensorimotor behavioral recovery after middle cerebral artery (MCA) occlusion.

Methods—Halothane-anesthetized male Wistar rats were subjected to 2 hours of MCA occlusion by the intraluminal occlusion technique. Physiological variables were controlled, and ipsilateral cortical perfusion was monitored by laser Doppler flowmetry throughout ischemia. At onset of reperfusion, rats received intravenous LTG 5, 10, or 20 mg/kg or PBS (n=9 to 11 per group) during 15 minutes. Behavioral assessment was completed at 3 and 7 days after stroke, and the brain was harvested for histology (triphenyltetrazolium chloride staining).

Results—Values are mean±SE. Cortical infarction volumes were unchanged in LTG-treated animals: 14±6% of contralateral cortex at 5 mg/kg LTG, 17±7% at 10 mg/kg, and 30±6% at 20 mg/kg, versus saline-treated cohorts (12±3%; P=0.19; n=9). Caudate-putamen infarction injury was also unchanged (37±11% of contralateral caudate-putamen at 5 mg/kg LTG, 44±8% at 10 mg/kg, and 65±9% at 20 mg/kg versus saline (38±11%; P=0.18). Total infarction was not different among groups (P=0.15). Consistent with histology, behavioral outcomes were unimproved by treatment.

Conclusions—Histological damage and behavioral recovery at 7 days after MCA occlusion was not altered by LTG treatment over the dosage range used in the present study. (Stroke. 2001;32:783-787.)

Key Words: anticonvulsant ■ cerebral ischemia, focal ■ cerebral ischemia, transient ■ stroke, experimental ■ stroke, ischemic ■ triazine

Glutamate excitotoxicity is a well-established mechanism of cell death in experimental and clinical stroke and cerebral ischemia. Available data indicate that postsynaptic N-methyl-D-aspartate receptor antagonists may have a suboptimal profile of therapeutic versus adverse effects in stroke therapy.1–3 Therefore, novel antiglutamatergic therapies are needed. An alternative pharmacological approach is to depress neuronal release of glutamate through inhibition of presynaptic ion channels. Voltage-sensitive calcium and sodium channels are important controllers of excitatory neurotransmitter release in neurons. Recent results suggest that selective inhibitors of these channels can diminish extracellular glutamate concentration during cerebral ischemia and potentially modulate an important source of excitotoxic cell death.4–6

The antiepileptic drug lamotrigine (LTG) is a phenyltriazine derivative that acts by stabilizing voltage-sensitive sodium channels in a usage-dependent manner, preventing glutamate and aspartate release and reversibly blocking excitatory neurotransmission7–8 (for review, see Tauboll and Gjerstad9). In addition, LTG also inhibits calcium currents in corticostriatal and hippocampal neurons, which suggests action at high voltage, release-coupled calcium channels.10–12 LTG has been used as a neuroprotective agent in several models of global4,8,13,14 and permanent focal cerebral ischemia,15 with varying degrees of efficacy. Most of these studies used pretreatment or intraschismic drug administration, and the therapeutic utility and timing of LTG in stroke resuscitation remains unclear. Because the agent has not been evaluated in reversible focal stroke, it is not known whether LTG is efficacious when administered after ischemia and once perfusion has been restored. We hypothesized that if it is the dampening of intraschismic glutamate release that is critical to stroke outcome, then LTG administered even immediately on reperfusion would be too delayed to salvage tissue from infarction. Alternatively, a secondary and delayed rise in extracellular glutamate concentration has been characterized in transient ischemia that may represent a second window for

Received July 25, 2000; final revision received December 1, 2000; accepted December 5, 2000.

From the Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, School of Medicine, Baltimore, Md.

Correspondence to Richard J. Traystman, PhD, Distinguished University Research Professor Vice Chairman, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins Medical Institutions, Blalock 1408, 600 N Wolfe St, Baltimore, MD 21287. E-mail rtraystm@jhmi.edu

© 2001 American Heart Association, Inc.

Stroke is available at http://www.strokeaha.org

783
antiglutamatergic intervention.\textsuperscript{16,17} The aim of the present study was to evaluate 7-day behavioral recovery and infarction volume when LTG is administered on recirculation after middle cerebral artery (MCA) occlusion.

**Subjects and Methods**

All methods are as previously published.\textsuperscript{18–20} Male Wistar rats (200 to 325 g, Harlan) were randomized into treatment groups, and subsequently received baseline behavioral testing, MCA occlusion (MCAO), and functional assessment during a 7-day recovery period. All behavioral and histological evaluations were conducted by an investigator blinded to animal treatment assignment. The present study was conducted in accordance with the National Institutes of Health guidelines for the care and use of animals in research. All protocols were approved by the Animal Care and Use Committee of the Johns Hopkins University.

Behavioral testing to establish baseline parameters was conducted 1 to 3 days before MCAO. In brief, behavioral tests were conducted in a quiet room, during the light phase (between 1 and 3 PM EST). Between trials, testing apparatus was cleaned with a 75% alcohol solution. All trials were scored by the same experimentally uninformed observer.

**Locomotor Balance and Coordination**

Rats were placed at the center of a wooden bridge or pole that was suspended approximately 60 cm above a foam pillow. Animals were tested in random order by use of a 2-cm-wide bridge or a 2-cm-diameter pole. Latency to fall from the bridge or pole in seconds was recorded. Animals that did not fall received a score of 120 s.

**Strength and Agility**

Rats were placed in the middle of a mesh screen maintained at a 45° angle, facing downward. Time for each rat to complete a 90° turn was recorded. In addition, ability to turn in a narrow alley was measured as a measure of coordinated muscle movement and agility. Animals were tested in a 12-cm-wide blind alley, with each animal placed to face the back wall. Time to turn around and face the open end of the alley was recorded. Last, forelimb strength and grasping ability was evaluated by suspending the rats by their forelimbs on a wire. The wire was stretched between 2 posts at a height of 50 cm over a foam pillow. Time in seconds until the animal fell was recorded. A score of zero was assigned to animals that did not grasp the wire or that fell immediately. The trial lasted a maximum of 90 s.

On the day of surgery, each animal was anesthetized with 1% to 1.5% halothane delivered by means of face mask in oxygen-enriched air. A femoral artery and venous catheter were placed for arterial blood pressure and arterial blood gases, and for infusion of drug and fluids. Rectal and temporalis muscle temperatures were controlled at 36°C to 38°C with heat lamps. Cortical perfusion by laser Doppler flowmetry (LDF; model MBF3D, Moor Instruments Ltd) was measured as previously described, with probe placement at 6 mm lateral and 2 mm posterior to bregma. Focal cerebral ischemia was accomplished using the intraluminal filament model (4-0 nylon monofilament suture) of proximal MCAO as previously described.\textsuperscript{18,19} The right common carotid artery was exposed through a midline skin incision and ligated. Two of these animals were excluded due to ineffective occlusion. Two of these animals were excluded due to ineffective occlusion. The external carotid artery was ligated, the occipital branch was cauterized, and the pterygopalatine artery was ligated. An occluding filament was advanced through the common carotid artery until the LDF signal displayed an abrupt and significant reduction, confirming ongoing ischemia, and then the filament was secured in place. Rats that did not demonstrate a significant reduction in LDF signal (≤45% of baseline values) were excluded from study. Ischemic LDF was determined over 5-minute periods at 5, 15, 30, 60, 90, 105, and 120 minutes after MCAO, and the suture was withdrawn, with prompt restoration of blood flow. LTG 5, 10, or 20 mg/kg or PBS vehicle was infused through the femoral venous catheter during 15 minutes (infusion rate, 6 mL/h) beginning at the onset of reperfusion as the occluding filament was removed. Arterial blood pressure and LDF were recorded continuously during vehicle or drug infusion. Arterial blood gases were again measured at the end of the drug infusion, and then all instrumentation was removed. The animal was allowed to recover and was evaluated for behavioral deficits at 3 and 7 days of reperfusion. On day 7, the brain was harvested under deep halothane anesthesia. Tissue was sliced into seven 2-mm-thick coronal sections for 2,3,5-triphenyltetrazolium chloride staining and quantification through standard photography and digital planimetry (SigmaScan Pro, Jandel). The infarcted area was numerically integrated across each section and over the entire ischemic hemisphere. Infarct volume was measured separately in the cortex and caudate-putamen and expressed as volume percentage of the contralateral structure. Ipsilateral total infarction was also measured and expressed as a percentage of the contralateral structures (sum of contralateral cortex and caudate putamen).

All values are reported as mean ± SEM unless otherwise indicated. Data from the pole and wire were not normally distributed; therefore, data were transformed \( \log_{10}(Y + 1) \) before analysis. Transformation was not successful at normalizing the data from the alley, inclined screen, and bridge. Thus, these data were analyzed by Kruskal-Wallis 1-way ANOVA on ranks. If no significant difference occurred between the experimental groups on any of the test days, groups were collapsed and Kruskal-Wallis 1-way ANOVA on ranks was conducted across time with post hoc comparisons conducted by use of the method of Dunn. Data points >3 SDs from the mean were removed before analysis (alley, \( n = 3 \)). Physiological parameters and LDF were subjected to 2-way ANOVA and post hoc Newman-Keuls test. Differences in infarction volumes, mean ischemic LDF, and plasma hormone levels were determined by 1-way ANOVA. If significant differences were found, a post hoc Newman-Keuls test was applied. Criterion for statistical significance was \( P < 0.05 \).

**Results**

Mortality was defined as death of any animal that received experimental treatment and entered the 7-day recovery period. These losses included 7 animals in the saline-treated group and 7, 10, and 5 in the groups treated with LTG 5, 10, and 20 mg/kg, respectively. Final numbers of subjects per treatment group were saline-treated, \( n = 9 \); LTG 5 mg/kg, \( n = 10 \); LTG 10 mg/kg, \( n = 11 \); and LTG 20 mg/kg, \( n = 10 \).

Physiological data are summarized in Table 1. Arterial blood pressure and blood gases were similar among groups during MCAO and early reperfusion. Furthermore, LTG administration did not alter temperature, arterial blood gases, or arterial blood pressure in the reperfusing animals at any of the 3 doses (Table 1). The ipsilateral LDF signal during MCAO decreased rapidly to approximately 25% of baseline values and remained depressed in each animal throughout occlusion. On reperfusion, LDF returned to near baseline by 30 minutes. No difference existed in LDF among treatment groups during MCAO occlusion or early reperfusion. Infusion of saline or LTG did not alter recovery of the LDF signal. Five animals were excluded from study because of inadequate reduction of the intraschismic LDF signal, which suggested ineffective occlusion. Two of these animals were saline treated, and 1 animal per group was excluded from the LTG 5, 10, and 20 mg/kg groups.

Histological damage at 7 days after stroke was not altered by LTG treatment. Cortical and caudate-putamen infarction volumes were also unchanged by LTG- versus saline-treated cohorts at any dosage level (\( P = 0.19 \) and \( P = 0.18 \), respectively, for cortex and caudate-putamen analysis; Figure). Total infarction volume was not different among groups: \( 16 \pm 4\% \), \( 18 \pm 7\% \), \( 22 \pm 7\% \), and \( 35 \pm 6\% \) of contralateral...
MCAO-induced deficits in sensorimotor function were readily apparent in all animals. Poststroke function was generally characterized by depression of locomotor activity and prolonged latency in performing tasks. When behavioral recovery was compared among all treatment groups, performance of sensorimotor tasks at 3 and 7 days after MCAO was not improved by LTG treatment. The only difference among groups in any of the behavioral variables was a somewhat longer latency to fall when suspended from a wire on postocclusion day 7 in the LTG 20 mg/kg-treated animals ($P = 0.03$). At 7 days after occlusion, latency to drop from the wire was $22.6 \pm 9.1$, $25.8 \pm 8.6$, $32.2 \pm 5.6$, and $49.8 \pm 10.8$ in saline-treated and LTG 5, 10, and 20 mg/kg groups, respectively. Because few differences occurred among the saline- or drug-treatment groups at any dosage level, we evaluated the data from all animals treated with MCAO to better understand temporal poststroke recovery. When sensorimotor testing was summarized in aggregate across all treatment groups, significant MCAO-induced deficits in sensorimotor tests were apparent at 3 and 7 days (Table 2). Latency to fall when suspended from a wire was significantly longer on days 3 and 7 post-MCAO as compared with baseline performance ($P = 0.01$), and latency to fall from the pole was significantly longer on day 7 ($P = 0.02$) compared with baseline. No significant differences existed across test days in latency to turn in the alley or on the inclined screen ($P = 0.07$ and $P = 0.08$, respectively). A separate cohort of sham-operated, experimentally unmanipulated female rats was tested in the same series of sensorimotor tasks to determine whether repeated testing altered behavior. No significant change was seen in task performance across trials in any of the sensorimotor tests. Therefore, MCAO-induced behavioral changes are unlikely to be artifacts of repeated testing.

**Discussion**

The main finding of the present study is that LTG administered immediately on reperfusion did not improve tissue or functional outcome in the present model of experimental stroke. We evaluated infarction volume at 7 days to observe drug effects on the maturing lesion when acute cerebral edema has resolved. Behavioral assessment paralleled these histological findings; given that sensorimotor function was not improved by LTG at any dosage level.

We used a full dose-response protocol in the present study, with 3 intravenous dosages of LTG: 5, 10, and 20 mg/kg. The

**TABLE 1. Physiological Data**

<table>
<thead>
<tr>
<th></th>
<th>Lamotrigine, mg/kg</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Saline</td>
<td>5</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>90±3</td>
<td>98±3</td>
<td>88±3</td>
<td>90±2</td>
</tr>
<tr>
<td>Ischemia</td>
<td>90±3</td>
<td>93±5</td>
<td>85±2</td>
<td>94±4</td>
</tr>
<tr>
<td>Reperfusion</td>
<td>90±3</td>
<td>95±5</td>
<td>89±3</td>
<td>86±4</td>
</tr>
<tr>
<td>PaCO₂, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>56±3</td>
<td>53±2</td>
<td>52±2</td>
<td>48±2*</td>
</tr>
<tr>
<td>Ischemia</td>
<td>47±3</td>
<td>47±2</td>
<td>48±1</td>
<td>46±2</td>
</tr>
<tr>
<td>Reperfusion</td>
<td>52±2</td>
<td>51±3</td>
<td>52±3</td>
<td>50±3</td>
</tr>
<tr>
<td>pH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>7.32±.01</td>
<td>7.33±.01</td>
<td>7.32±.02</td>
<td>7.36±.01</td>
</tr>
<tr>
<td>Ischemia</td>
<td>7.35±.02</td>
<td>7.39±.02</td>
<td>7.40±.01</td>
<td>7.38±.01</td>
</tr>
<tr>
<td>Reperfusion</td>
<td>7.34±.01</td>
<td>7.35±.01</td>
<td>7.34±.01</td>
<td>7.31±.02</td>
</tr>
<tr>
<td>Temperature °C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>36.9±.02</td>
<td>36.7±.2</td>
<td>36.9±.2</td>
<td>36.7±.2</td>
</tr>
<tr>
<td>Ischemia</td>
<td>37.4±.2</td>
<td>37.4±.3</td>
<td>37.5±.2</td>
<td>37.5±.2</td>
</tr>
<tr>
<td>Reperfusion</td>
<td>37.1±.3</td>
<td>37.4±.3</td>
<td>37.0±.3</td>
<td>37.1±.3</td>
</tr>
</tbody>
</table>

Mean±SE for baseline, at 60 minutes of MCAO, and at 30 minutes of reperfusion. Temperature indicates temporal muscle temperature.

For saline group, n=9; LTG 5 mg/kg, n=10; LTG 10 mg/kg, n=11; and LTG 20 mg/kg, n=10.

* P<0.05 from saline.

**TABLE 2. Behavioral Data**

<table>
<thead>
<tr>
<th></th>
<th>Pre-MCAO (Baseline)</th>
<th>Post-MCAO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 3</td>
<td>Day 7</td>
</tr>
<tr>
<td>Latency to fall from a wire, s</td>
<td>8.1±1.3</td>
<td>21.3±4.3*</td>
</tr>
<tr>
<td>Latency to fall from a 2-cm square bridge, s</td>
<td>56.1±6.4</td>
<td>94.0±6.7*</td>
</tr>
<tr>
<td>Latency to fall from a pole, s</td>
<td>20.9±4.7</td>
<td>37.0±7.0</td>
</tr>
<tr>
<td>Latency to turn in alley, s</td>
<td>1.7±.02</td>
<td>5.4±2.2</td>
</tr>
<tr>
<td>Latency to turn on inclined screen, s</td>
<td>1.4±.01</td>
<td>2.7±.07</td>
</tr>
<tr>
<td>No. of arm entries</td>
<td>6.3±0.8</td>
<td>1.5±0.2*</td>
</tr>
</tbody>
</table>

Data are presented as mean±SE. *Significant difference vs baseline.
choice of dosages was based on previous studies that used parenteral rather than oral drug formulations and showed some degree of efficacy in rodent models. Early reports emphasized that LTG has a potentially narrow range of effectiveness. The agent reduced neuronal loss after cardiac arrest and infarction size after permanent MCAO in rat over a range of 8 to 20 mg/kg.\(^4,13,15\) In a previous report, intravenous LTG administration of 10 mg/kg resulted in plasma levels of 8 to 13 \(\mu\)g/mL in rat, levels that are similar to plasma levels of patients who receive LTG as an antiepileptic.\(^13\) Brain concentrations of LTG in rat rose within minutes of intravenous administration and remained elevated for \(\geq\)5 hours after dosing.\(^13\) On the basis of these data, we used a middle dosage level of 10 mg/kg. Furthermore, in our preliminary studies that assessed cardiovascular effects of LTG at 50 to 100 mg/kg, we observed undesirable blood pressure fluctuations and cardiovascular instability in rats, as have been reported previously in pig.\(^6\) Therefore, we limited our highest dosage to 20 mg/kg for treatment after MCAO.

Previous animal investigations using preischemic or intraschismic LTG administration have demonstrated reduction of tissue injury or neurological deficits in many\(^4,13–15\) but not all\(^6\) studies. Cerebroprotective effects of LTG have been credited to its inhibition of presynaptic neuronal sodium channels, thus reducing inward sodium currents and preventing excessive depolarizations. The drug also modulates potassium outward transient current, potentially inhibiting pathological excitation.\(^21\) Ischemic glutamate release is not thought to be through vesicular exocytosis, but through a reversal of electrogenic, sodium-coupled amino acid transporters. Increases in internal Na\(^+\) and external K\(^+\) during ischemia, in conjunction with membrane depolarization, prompt reversal of glutamate transporters, releasing cytosolic glutamate. LTG may stabilize glutamatergic neurons under these pathological circumstances through blockade of inward sodium and possibly calcium currents. Other potentially neuroprotective mechanisms have been identified, such as indirect inhibition of veratrine-stimulated nitric oxide synthesis and consequent increase in cGMP.\(^22\)

However, the timing of the action of LTG relative to ischemic pathophysiology is important. One explanation for the lack of efficacy in our rat focal stroke model is that the agent was supplied as a single infusion during early reperfusion. Few data are available regarding efficacy of LTG as a resuscitation agent; ie, administered during recovery from a previous ischemic insult. In experimental cardiac arrest, LTG improved selective neuronal injury within hippocampus when the agent (10 mg/kg) was administered either before or after arrest.\(^13\) Although return of EEG activity was suppressed in LTG-treated rats, CA1 pyramidal cell counts were increased relative to untreated animals.\(^13\) Larger doses of LTG (30 to 100 mg/kg) supplied hippocampal neuroprotection in gerbil with a postischemic treatment paradigm.\(^4,14\) LTG improved CA1 neuronal loss after transient forebrain ischemia in gerbil, even when administered up to 1 hour after ischemia.\(^14\) Although posts ischemic LTG was not tested, water-maze performance was improved when LTG was administered in a combination preischemic and postischemia paradigm.\(^14\)

Our data indicate that the low dosages that are tolerated without hemodynamic sequelae in rat (5 to 20 mg/kg) do not provide protection in either cortex or striatum when given during reperfusion. These results are consistent with those of Smith and Meldrum\(^17\) in that delayed LTG administration during permanent MCAO by 2 hours was ineffective in reducing damage. A likely explanation is that the therapeutic window for antiglutamatergic neuroprotection is defined by the period of anoxic depolarization and peak excitatory neurotransmitter release, typically within the first 1 to 2 hours of focal cerebral ischemia in rat.\(^23\) If secondary increases in extracellular glutamate concentration occur during the first reperfusion hours after ischemic stroke,\(^16,17\) modulation of neuronal sodium channels by LTG at this time does not alter the ultimate progress of tissue damage. A less likely explanation is that LTG has dose-dependent adverse effects that obscure its antiglutamatergic potential during reperfusion. In humans, common side effects are predominately neurological (eg, ataxia and visual disturbances) and dermatologic (for review, see Matsuo\(^24\)). Adverse neurological effects such as loss of locomotor coordination have also been reported in rats but at higher doses than used in the present study.\(^15\)

As we reported previously,\(^20\) the present model of transient MCAO is characterized by altered performance of some, but not all, sensorimotor tasks during the first week of recovery. Non-drug-treated, sham-operated rats did not show deficits or improvements in performance despite repeated task performance over days. Therefore, we think it is unlikely that selective recovery or loss of motoric behavior is related to learning or skill acquisition. Instead, a depression of locomotor activity is present, as reflected in the increased latency to fall from the square bridge and pole after MCAO. Stroked animals spent less time exploring the entire length of the bridge and pole and were therefore less likely to misstep and fall. Latency to fall from the wire also increased dramatically after MCAO and may be due to an abnormal grasp reflex in the forelimbs after damage to the frontal cortex. Abnormal grasp reflexes have been reported in humans with cortical damage.\(^25\) Similar alterations in sensorimotor performance on the bridge, pole, wire, and elevated plus maze, in addition to an increased latency to turn on an inclined screen, have been previously reported in male rats\(^20\) and mice\(^26\) subjected to MCAO. LTG did not improve this latency to perform tasks, and dosing at 20 mg/kg resulted in even more prolonged latency to drop from the wire. This result suggests that LTG did not ameliorate and might at high dosage levels enhance depressed cortical function after experimental stroke.

All animals were randomly assigned to treatment group, and surgery was performed by a single investigator (J.K.). Previous studies with the intraluminal filament MCAO technique in our laboratory resulted in premature death rates in placebo or vehicle-treated rats of 0% to 33% with a 22-hour recovery endpoint.\(^17,18,27,28\) Premature deaths in the present study with a 7-day recovery endpoint were 33% in the high-dosage LTG group and ranged from 41% to 48% in the other groups. The relative underrepresentation of premature deaths in high-dosage LTG was not statistically significant. The increase in premature deaths over 7 days versus 1-day survival in our previous studies probably was due not only to
stroke maturation and action of late-phase inflammatory injury mechanisms, but also to multiple systemic and environmental factors pertinent to convalescence from large cerebral infarction. No pattern was observed for time of death among the treatment groups or in vehicle-treated animals. Furthermore, cause of death was not rigorously studied by full-body autopsy in all animals. Similar premature death rates have been reported in other MCAO studies that evaluated histological and behavioral damage 4 to 7 days after injury.29–31

In conclusion, LTG administered immediately on reperfusion over a range of dosages did not improve tissue or functional outcome from transient focal cerebral ischemia in rat. We conclude that efficacy of the agent may be limited to experimental or clinical settings in which preischemic or intraischemic LTG administration is feasible.

Acknowledgments
The present study was supported by NIH grant NS-20020 and Glaxo Wellcome, Inc.

References
Anticonvulsant Lamotrigine Administered on Reperfusion Fails To Improve Experimental Stroke Outcomes
Richard J. Traystman, Judith A. Klaus, A. Courtney DeVries, Amanda B. Shaivitz and Patricia D. Hurn

Stroke. 2001;32:783-787
doi: 10.1161/01.STR.32.3.783

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/32/3/783

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/