Dose Escalation Study of the NMDA Glycine-Site Antagonist Licostinel in Acute Ischemic Stroke

Gregory W. Albers, MD; Wayne M. Clark, MD; Richard P. Atkinson, MD; Kenneth Madden, MD; Joann L. Data, MD, PhD; M. J. Whitehouse, MD for the Licostinel Acute Stroke Study Group

Background and Purpose—Licostinel (ACEA 1021; 5-nitro-6,7-dichloro-2,3-quinoxalinedione), a competitive antagonist of glycine at the N-methyl-D-aspartate (NMDA) receptor, is an effective neuroprotective agent in animal models of cerebral ischemia. The purpose of this study was to assess the safety, tolerability, and pharmacokinetics of licostinel in patients with acute stroke.

Methods—In this 5-center dose escalation trial, patients were enrolled within 48 hours of an ischemic stroke and treated with ascending doses of a short infusion of licostinel or a placebo. Adverse effects were assessed with clinical and laboratory measurements, and patient outcome was determined with the National Institutes of Health Stroke Scale.

Results—Sixty-four patients (44 treated with escalating doses of licostinel and 20 who received placebo) were treated. Lower doses of licostinel (0.03 to 0.60 mg/kg) were not associated with any significant adverse effects. Higher doses of licostinel (1.2 to 3.0 mg/kg) were associated with a variety of mild-to-moderate adverse effects including neurological and gastrointestinal complaints. No major psychotomimetic effects or significant safety concerns occurred. At the higher dose levels, peak plasma concentrations of licostinel were substantially higher than those required for neuroprotection in animal stroke models. A similar improvement in National Institutes of Health Stroke Scale scores over time was seen in both the placebo group and the licostinel-treated patients.

Conclusions—A short infusion of licostinel in doses up to 3.0 mg/kg is safe and tolerable in acute stroke patients. Licostinel may be a safer and better tolerated neuroprotective agent than many of the previously evaluated NMDA antagonists. (Stroke. 1999;30:508-513.)

Key Words: cerebral infarction ■ neuroprotection ■ stroke management ■ stroke, acute

Excessive activation of the N-methyl-D-aspartate (NMDA) subclass of glutamate receptors appears to be a key mediator of brain injury during acute ischemic stroke. Overactivation of NMDA receptors during ischemic stroke leads to a toxic influx of cations through the NMDA receptor–associated ion channel. NMDA receptors can be antagonized at a variety of sites; noncompetitive antagonists can bind to the ion channel that is associated with the NMDA receptor, whereas other agents compete directly with excitatory amino acids for binding to the glutamate recognition site. Unfortunately, clinical studies in human stroke patients have demonstrated that pharmacological antagonism of either of these sites may result in a characteristic adverse effect profile that includes hallucinations, confusion, agitation, and cardiovascular instability. Additional safety concerns regarding some NMDA antagonists include the observation of vacuolization of neuronal cytoplasm in specific cortical regions in rats. Although the significance of these vacuoles is unclear, they are considered to be potentially neurotoxic. Enthusiasm for the use of NMDA antagonists as cerebral protective agents has been dampened by these safety issues. Safety concerns have led to termination of the clinical development of several NMDA antagonists after phase II trials in stroke patients. A large phase III trial was conducted with the competitive NMDA antagonist selfotel with dosages lower than required to achieve plasma concentrations comparable to the levels required for optimal neuroprotection in animal stroke models. This large clinical trial was terminated prematurely because of an apparent lack of clinical efficacy.

Pharmacological agents that can prevent cation influx through the NMDA channel without causing significant adverse effects have been sought. In 1987, it was discovered that NMDA receptor activation requires glycine to bind to the NMDA receptor. Antagonists of the glycine binding site have...
neuroprotective effects in animal stroke models similar to those of other NMDA antagonists but appear to have a more favorable safety profile.\textsuperscript{5–10} One glycine site antagonist, GV 150526, was well tolerated in phase II studies and is currently being evaluated in acute stroke patients in a phase III efficacy trial.\textsuperscript{11}

Licostinel (ACEA 1021) is a potent and selective antagonist of the glycine site on the NMDA receptor.\textsuperscript{12} Preclinical testing of licostinel in several experimental ischemic stroke models has documented substantial neuroprotective effects, no evidence of cerebral vacuolization, and minimal effects on cerebral blood flow or metabolism.\textsuperscript{13,14} Recent studies with a testing of licostinel in several experimental ischemic stroke models has documented substantial neuroprotective effects, no evidence of cerebral vacuolization, and minimal effects on cerebral blood flow or metabolism.\textsuperscript{13,14} Recent studies with a short infusion of licostinel indicate that the minimum effective steady-state plasma concentration for neuroprotection in a rat reperfusion middle cerebral artery occlusion model is 2.0 $\mu$g/mL.\textsuperscript{15} Studies of licostinel in healthy volunteers demonstrated that short infusions of $\geq 2.0$ mg/kg for 15 minutes, associated with plasma levels of 30.8±5.3 $\mu$g/mL, were well tolerated, without evidence of any significant neurological, psychiatric, cardiovascular, or laboratory abnormalities.\textsuperscript{16}

The purpose of this study was to evaluate the safety, tolerance, and pharmacokinetics of increasing doses of licostinel in patients who had an acute ischemic stroke. An additional objective was to determine the maximal-tolerated dose of licostinel administered as a short intravenous infusion.

Subjects and Methods

This study was a 5-center dose escalation and safety trial. The protocol was approved by the institutional review committees at all sites, and informed consent was obtained for all patients. Patients between 18 and 80 years of age who could be treated within 48 hours of onset of an acute ischemic stroke were eligible. Patients were required to be alert or drowsy and have a neurological deficit severe enough to score $\geq 3$ points on the NIH Stroke Scale. A head CT or MRI with findings compatible with an acute ischemic stroke was required before drug administration. Cardiovascular stability (pulse 50 to 100 bpm and blood pressure 100/60 to 200/115 mm Hg), as well as a negative pregnancy test (in premenopausal or nonsurgically sterile females) were required. Patients with neurological symptoms considered to localize to the vertebrobasilar arterial system were excluded. Other exclusion criteria included seizure within the past 4 weeks; a significant bleeding disorder or gastrointestinal bleed within the past 2 weeks; morbid obesity or cachexia; significant laboratory abnormalities (white blood count; hematocrit; or creatinine, sodium, potassium, glucose, or oxygen saturation measurements); infective endocarditis; recent myocardial infarction; unstable angina; compensated heart failure; fever (temperature $>38.5^\circ$C); or significant immunologic, hepatic, or renal dysfunction. In addition, patients with a concurrent major affective disorder, substance abuse, moderate-to-severe dementia, or major surgery within the past week were excluded. Medication exclusions included thrombolytic agents, ketamines, opioids, dextromethorphan derivatives, psychotomimetics, or barbiturates.

Before study drug administration, all patients underwent a complete medical and neurological history and examination, which included the NIH Stroke Scale. During study drug administration, patients were closely monitored by study personnel and had continuous cardiac telemetry. Oxygen saturation was monitored intermittently for 48 hours. During drug administration, patients remained at bed rest. Additional medical treatments such as administration of antiplatelet and anticoagulant agents were allowed. Neurological examinations that included the NIH Stroke Scale were performed 1 hour, 4 hours, 8 hours, 12 hours, 24 hours, 48 hours, 1 week, and 1 month after drug administration. Blood and urine samples were obtained for determination of licostinel plasma levels as well as for routine laboratory studies at specified time intervals. Patients were seen for a follow-up evaluation at 7 days. All adverse events whether they were felt to be related to study drug or not were recorded.

A single IV dose of licostinel (CoCensys, Inc) or vehicle control (placebo) was administered for 15 to 30 minutes at a rate of 4 mL/min. Six sequential dose groups were evaluated: 0.03, 0.15, 0.60, 1.2, 2.0, and 3.0 mg/kg. The study design called for 9 patients to be enrolled in each dose group (6 active and 3 control). Because of an increased incidence of adverse effects noted in dose groups 5 and 6, an additional 9 patients were enrolled in dose group 6 (3.0 mg/kg). After completion of the second set of patients in dose group 6, the sponsor and investigators decided to conclude the study.

Results

Sixty-nine patients were randomized and entered into the study. Five patients were withdrawn before receiving study medication (in 3 patients, abnormal laboratory values became available before dosing; family members withdrew consent from 1 patient; and in another, the investigational product was improperly mixed and precipitated during drug preparation). Sixty-three of the 64 enrolled patients who received study drug completed the entire infusion (1 licostinel-treated patient discontinued the infusion because of injection site pain). Twenty patients received the vehicle control (placebo), and 44 patients were treated with increasing doses of licostinel. The baseline characteristics of the study population are summarized in Table 1. No significant differences between the placebo- and licostinel-treated groups were noted, although the licostinel patients were slightly older and had a lower baseline NIH Stroke Scale score.

A variety of adverse effects were reported by patients in both the licostinel and the placebo groups. In general, the frequency and severity of adverse effects were similar in drug-treated and control patients in dose groups 1 through 3. Patients assigned to active treatment in dose groups 4 through 6 had a higher frequency of adverse effects, which typically involved neurological or gastrointestinal complaints (Figure 1). All adverse events were classified by the investigators as to whether they were mild, moderate, or severe, as well as whether they were unrelated, unlikely to be, possibly, probably, or definitely related to study drug. Most adverse events

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=20)</td>
</tr>
<tr>
<td>Age (mean), y (range)</td>
</tr>
<tr>
<td>Sex, % male</td>
</tr>
<tr>
<td>Race, % white</td>
</tr>
<tr>
<td>Previous stroke, %</td>
</tr>
<tr>
<td>Previous TIA, %</td>
</tr>
<tr>
<td>Hypertension, %</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
</tr>
<tr>
<td>Cardiac disease,* %</td>
</tr>
<tr>
<td>NIH stroke scale, mean value</td>
</tr>
<tr>
<td>Time to treatment, mean h after stroke onset</td>
</tr>
</tbody>
</table>

*Includes myocardial infarction, atrial fibrillation, and congestive heart failure.
in all treatment groups were considered to be mild and unlikely to be related or unrelated to study drug. The most frequent adverse events that were considered to have a possible, probable, or definite relationship to study drug are listed in Table 2. Among these adverse effects, certain neurological, gastrointestinal, and injection site complaints were seen more often in licostinel-treated patients than placebo controls. In addition, bradycardia was noted in 3 licostinel patients and in 1 control patient. Other than injection site complaints, these adverse events occurred more often in the high-dose licostinel groups (groups 4 to 6) than in the low-dose groups (groups 1 to 3).

A variety of transient central nervous system symptoms accounted for the most frequent adverse effects. Approximately one half of the patients in dose groups 4 to 6 experienced neurological symptoms. Four licostinel-treated patients experienced episodes of agitation; 3 of these were mild and did not require treatment, and 1 was moderate in severity and was treated with diphenhydramine hydrochloride (Benadryl). Four licostinel-treated patients reported mild dizziness, which typically began within the first few minutes after the infusion was completed. Dizzy feelings resolved within 2 hours and were not associated with decreases in blood pressure. Four licostinel patients became somnolent (1 became sleepy during the infusion, 2 became somnolent shortly after the infusion, and 1 had onset 12 hours after the infusion). All patients recovered completely without intervention within 8 hours. Two patients (one each in dose groups 5 and 6) noted transient memory disturbances. One licostinel-treated patient (dose group 4) developed mild visual hallucinations 5 minutes after the start of the infusion. The patient described seeing unusual laserlike lights that he knew were not real. These hallucinations occurred intermittently for ≈1 hour and were not bothersome to the patient. This patient also reported transient drowsiness, nausea, and dizziness during the same time period. His maximum plasma concentration of licostinel (18 μg/mL) was no higher than expected for his dose group.

Episodes of mild-to-moderate nausea were reported by 7 patients (1 in the placebo group). Four of the 7 patients with nausea experienced vomiting. The highest incidence of nausea and vomiting was in dose group 6 (Table 2).

Injection site complaints were slightly more common in licostinel-treated patients than in the placebo group; however, these complaints did not appear to be dose related. Among the licostinel patients, injection site complaints included burning, irritation, or pain. The 2 placebo patients who complained of injection site problems experienced local edema or inflammation. The severity of the injection site reactions was rated mild in most patients; moderate severity was noted in 1

TABLE 2. Subjects With Common Adverse Effects

<table>
<thead>
<tr>
<th>Licostinel Dose Group (mg/kg)</th>
<th>Placebo</th>
<th>1 (0.03)</th>
<th>2 (0.15)</th>
<th>3 (0.6)</th>
<th>4 (1.2)</th>
<th>5 (2.0)</th>
<th>6 (3.0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=20</td>
<td>n=6</td>
<td>n=6</td>
<td>n=7</td>
<td>n=6</td>
<td>n=7</td>
<td>n=12</td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>1 (17)</td>
<td>1 (14)</td>
<td>2 (17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (17)</td>
<td></td>
<td>3 (35)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (33)</td>
<td></td>
<td>2 (17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site complaints</td>
<td>2 (10)</td>
<td>2 (33)</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>1 (14)</td>
<td>1 (8)</td>
<td></td>
</tr>
<tr>
<td>Memory impairment</td>
<td></td>
<td>1 (14)</td>
<td>1 (8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>2 (10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (5)</td>
<td></td>
<td>1 (17)</td>
<td>5 (42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>1 (17)</td>
<td>4 (33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>1 (5)</td>
<td>1 (17)</td>
<td>2 (17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are number and percent (in parentheses).
licostinel patient. This patient had the study medication
continued prematurely because of injection site pain.

Five episodes of bradycardia were reported in 4 subjects (1
placebo patient had 2 episodes of mild bradycardia). Two
licostinel patients had mild bradycardia, which began within
30 minutes of the start of the infusion and resolved within 2
hours. One patient (dose group 6) experienced severe brady-
cardia. This patient had a history of cardiac arrhythmia, heart
disease, and hypotension. Digoxin had been started 2 days
before entering the study, and the patient’s heart rate at
baseline was 57 to 58 bpm. Ten minutes after the start of the
infusion, the patient’s heart rate dropped to 45 bpm but
returned to 60 bpm by the end of the infusion. Blood pressure
values remained stable throughout the infusion.

Fifteen serious adverse events were reported in 13 patients.
Six of these events occurred in subjects in the placebo group.
Only 1 serious adverse effect was felt to be potentially related
to licostinel: a dose group 6 patient who had a baseline
sodium concentration of 135 mEq/L developed hyponatremia
(lowest sodium value 122 mEq/L, 6 days after drug infusion)
that resolved with intravenous fluid administration over 8
days. This event was considered potentially drug-related
because no alternative explanation for the hyponatremia was
discovered. Only 1 death occurred during this study. A
patient in dose group 2 died secondary to complications
related to multiple recurrent strokes; this death was consid-
ered to be unrelated to study medication.

Pharmacokinetic data are summarized in Table 3. The
mean half-life of licostinel varied from 16.5 hours in dose
group 1 to 8.7 hours in group 6. Maximal plasma concentra-
tions were strongly related to dose. All patients in dose
groups 4 through 6 had maximum plasma concentrations of
≥14 μg/mL. Plasma levels obtained during and after discon-
tinuation of the infusion are shown in Figure 2 for the patients
who received licostinel in dose groups 1 to 6.

There was no evidence of systemic toxicity of licostinel on
the basis of routine laboratory studies and physical examina-
tions. Two licostinel-treated patients had moderate increases
of both BUN and creatinine (dose group 1 and 5). These
events began ≥6 days after the investigational drug was
administered and were considered unlikely to be related to
licostinel. The mean creatinine levels in all dose groups
remained within the normal range. Although 1 patient devel-
oped significant hyponatremia (see above), the group mean
sodium values remained within the normal range for all dose
groups. A moderate amount of protein in the urine was
reported in 1 licostinel-treated patient (dose group 3) who had
a urinary tract infection and a history of diabetes.

TABLE 3. Pharmacokinetic Summary (mean±SD) After Intravenous Infusion of Licostinel

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose, mg/kg</th>
<th>No.</th>
<th>Infusion time, h</th>
<th>Cmax, μg/mL</th>
<th>CL, L·h⁻¹·kg⁻¹</th>
<th>T1/2, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.03</td>
<td>6</td>
<td>0.25</td>
<td>0.59±0.16</td>
<td>0.0139±0.0095</td>
<td>16.5±1.1</td>
</tr>
<tr>
<td>2</td>
<td>0.15</td>
<td>6</td>
<td>0.25</td>
<td>2.72±1.04</td>
<td>0.0164±0.0085</td>
<td>11.1±5.3</td>
</tr>
<tr>
<td>3</td>
<td>0.60</td>
<td>7</td>
<td>0.25</td>
<td>11.09±2.57</td>
<td>0.0189±0.0079</td>
<td>10.2±1.0</td>
</tr>
<tr>
<td>4</td>
<td>1.20</td>
<td>6</td>
<td>0.25–0.50</td>
<td>22.83±9.93</td>
<td>0.0179±0.0103</td>
<td>13.2±8.1</td>
</tr>
<tr>
<td>5</td>
<td>2.00</td>
<td>6</td>
<td>0.25–0.50</td>
<td>36.06±9.37</td>
<td>0.0150±0.0063</td>
<td>10.4±2.0</td>
</tr>
<tr>
<td>6</td>
<td>3.00</td>
<td>12</td>
<td>0.25–0.50</td>
<td>46.68±10.00</td>
<td>0.0138±0.0047</td>
<td>8.7±3.2</td>
</tr>
</tbody>
</table>

Values are mean±SD unless otherwise noted. Cmax indicates maximum plasma concentration; CL, clearance; and T1/2, half-life.

Figure 2. Mean plasma concentration profile of licostinel-treated patients. In the legend, G1–6 indicates groups 1–6.
Elevated urinary protein values were associated with urinary tract infections and not considered significant by the investigators. Mean values for microscopic hematuria fluctuated during the study. The highest value at baseline was in dose group 1, and the highest mean values at the 24- and 48-hour points were in dose group 5. Significant hematuria was typically associated with urinary tract infections or indwelling catheters.

A comparison of the mean NIH Stroke Scale scores among the different dose groups is shown in Figure 3. In general, an approximate 4-point mean improvement in NIH Stroke Scale scores was noted in all groups during the month after stroke onset. An increase in the NIH Stroke Scale scores in group 2 is accounted for by the single patient who developed multiple recurrent strokes and subsequently died.

**Discussion**

This study demonstrates that a short infusion of licostinel, up to 3.0 mg/kg, can be safely administered to acute stroke patients with tolerable side effects. Peak plasma levels similar to or greater than those required for neuroprotection in animal stroke models were achieved in patients treated with doses of $\geq 0.15$ mg/kg. The primary goal of this study was to determine the highest well-tolerated loading dose of licostinel that can be administered to acute stroke patients. The results suggest that doses $\geq 2.0$ mg/kg are associated with only minimal toxicity. At doses of 3.0 mg/kg, adverse experiences, although not serious, were commonly encountered. Therefore, although there were no significant safety concerns even at the 3.0 mg/kg dose, we chose not to proceed to higher doses and consider 2.0 mg/kg to be the maximal, well-tolerated loading dose for acute stroke patients.

The most common adverse events attributable to licostinel were transient central nervous system and gastrointestinal complaints. Similar but frequently more severe adverse reactions have been seen with previously evaluated NMDA antagonists. Transient sedation or cognitive dysfunction is likely related to inhibition of excitatory neurotransmission. Other NMDA antagonists have often caused more dramatic agitation and hallucinations in humans at plasma levels comparable to the neuroprotective levels in animal models. Transient agitation, dizziness, somnolence, and memory impairment also occurred in the higher-dose licostinel-treated groups but were typically mild in severity. One patient suffered mild visual hallucinations, which were not bothersome and resolved rapidly.

Some NMDA antagonists have caused blood pressure changes or cardiovascular instability. Licostinel did not alter cardiovascular stability in any dose group, although 2 licostinel patients in the highest dose group developed transient bradycardia. The most bothersome adverse effects were nausea and vomiting, which were primarily restricted to the highest dose group. Emesis occurred in one third of the licostinel-treated patients in dose group 6; only 1 other licostinel-treated patient (dose group 4) had nausea or vomiting. These results, combined with the favorable safety profile reported for other glycine site NMDA antagonists, suggest that glycine site antagonists have a superior safety profile to other NMDA antagonists. In this trial, however, licostinel was typically not administered within the first few hours after stroke onset, and the adverse effect profile might differ in hyperacute stroke patients.

In this study, peak plasma concentrations that were comparable to or higher than those required for substantial neuroprotective effects in several animal stroke models were achieved in dose groups 2 to 6. Peak serum levels were achieved rapidly, but were maintained for only 1 to 2 hours, because of the rapid distribution half-life of the compound. Additional evaluation of longer infusion times, to verify that adequate plasma levels can be maintained for extended periods, will be required.

The goal of this study was to evaluate the safety of licostinel. The small sample size, single bolus dose, and long treatment window do not allow an assessment of the potential efficacy of the compound. A similar improvement in NIH stroke scores over time was seen in both the placebo and the licostinel-treated patients. Larger clinical trials, in which licostinel is administered rapidly after symptom onset, will be required to assess efficacy in stroke patients.

In summary, this preliminary study suggests that licostinel may be a safer and better-tolerated neuroprotective agent than many of the previously evaluated NMDA antagonists. Glycine site antagonists offer similar neuroprotective benefits in animal ischemia models and may be better suited for human stroke studies.
Appendix
Licostinel Acute Stroke Study Group participating centers are as follows.
Stanford Stroke Center, Palo Alto, Calif: Gregory W. Albers, MD, Principal Investigator; David Tong, MD, Midori Yenari, MD, Nanette Hock, RN, Helmi Lutsep, MD, Associate Investigators.
Oregon Health Sciences University, Portland, Ore: Wayne M. Clark, MD, Principal Investigator; Bruce Coull, MD, Maurice Hourihane, MD, Michael Wynn, OD, Joseph Quinn, MD, Kevin Jamison, MD, Associate Investigators.
Mercy General Hospital, Sacramento, Calif: Richard Atkinson, MD, Principal Investigator; John Byer, MD, Deidre Wentworth, MSN, RN, Christi DeLemos, RN, Associate Investigators.
Marshfield Clinic, Marshfield, Wis: Kenneth Madden, MD, Principal Investigator; Percy Karanjia, MD, Associate Investigator.
Cornell Medical Center–New York Hospital, New York, NY: Denise Barbut, MD, MRCP, Principal Investigator.

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