Aptiganel Hydrochloride in Acute Ischemic Stroke
A Randomized Controlled Trial

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Ischemic stroke is the third leading cause of death in the United States. Epidemiological studies indicate that as many as 730,000 strokes occur annually in the United States,1 of which between 73% and 86% are ischemic.2 Up to half of all stroke survivors are disabled, a third of them seriously enough to require assistance in daily activities.3 However, to date, the thrombolytic agent tissue plasminogen activator is the only therapy approved in the United States and Canada for the treatment of acute ischemic stroke. The limitations of tissue plasminogen activator are well-known. It must be administered within 3 hours of symptom onset, it increases the risk of brain hemorrhage, and only patients in whom cerebral hemorrhage has been definitively excluded are eligible for treatment.4 The approval of tissue plasminogen activator for use in North America has provided impetus for a change in how stroke is perceived both by the general public and among health care professionals. Acute stroke is now widely viewed as a medical emergency. There is a theoretic window of opportunity for minimizing the disabil-

Context Tissue plasminogen activator is the only thrombolytic agent approved in the United States for treatment of acute ischemic stroke, and has limitations. Aptiganel hydrochloride is a novel and selective ligand for the ion-channel site of the N-methyl-D-aspartate receptor-channel complex and a promising neuroprotective agent in animal models of focal brain ischemia.

Objective To determine whether aptiganel improves the clinical outcome for acute ischemic stroke patients.


Participants A total of 628 patients with hemispheric ischemic stroke (50.3% male; mean age, 71.5 years).

Interventions Patients were randomly assigned within 6 hours of stroke to receive 1 of 3 treatment regimens: high-dose aptiganel (5-mg bolus followed by 0.75 mg/h for 12 hours; n=214); low-dose aptiganel (3-mg bolus followed by 0.5 mg/h for 12 hours; n=200); or placebo (n=214).

Main Outcome Measures The primary efficacy end point was the Modified Rankin Scale score at 90 days after stroke onset. Secondary end points included mortality and change in National Institutes of Health (NIH) Stroke Scale score at 7 days after stroke.

Results The trial was suspended by the sponsor and the independent data and safety monitoring board because of both a lack of efficacy and a potential imbalance in mortality. There was no improvement in outcome for either aptiganel (low-dose or high-dose) group compared with the placebo group at 90 days (median Modified Rankin Scale score for all 3 treatment groups=3; P=.31). At 7 days, placebo-treated patients exhibited slightly greater neurological improvement on the NIH Stroke Scale than high-dose aptiganel patients (mean improvement for placebo group, −0.8 points vs for high-dose aptiganel, 0.9 points; P=.04). The mortality rate at 120 days in patients treated with high-dose aptiganel was higher than that in patients who received placebo (26.3% vs 19.2%; P=.06). Mortality in the low-dose aptiganel group was 22.5% (P=.39 vs placebo).

Conclusions Aptiganel was not efficacious in patients with acute ischemic stroke at either of the tested doses, and may be harmful. The larger proportion of patients with favorable outcomes and lower mortality rate in the placebo group suggest that glutamate blockade with aptiganel may have detrimental effects in an undifferentiated population of stroke patients.

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For editorial comment see p 2718.
Aptiganel hydrochloride (N-[1-naphthyl]-N-methyl-guanidine hydrochloride) is a selective ligand for the ion-channel site of the N-methyl-D-aspartate subtype of glutamate receptor. Aptiganel, when given up to 1 hour after permanent or temporary occlusion of the middle cerebral artery in rat models of ischemic stroke, reduced the amount of brain damage between 40% and 70%. Aptiganel produced a significant improvement in neurological outcome after hypothermic circulatory arrest, and decreased contusion volume and hemispheric swelling after traumatic brain injury in animal models. Aptiganel was efficacious in animal studies at a minimum plasma concentration of approximately 10 ng/mL under steady state and non-steady-state conditions. The half life of aptiganel in humans is 4 hours, and the mean clearance is 18 mL/min per kilogram. It is 88%-protein bound and is metabolized by the liver with primary excretion via the feces.

Safety studies indicate that aptiganel is relatively well tolerated in healthy human volunteers and acute stroke patients (who received study medication within 24 hours of stroke onset). Adverse effects include increases in heart rate and blood pressure and neurological disturbances, such as blurred vision, nystagmus, numbness, dizziness, and sedation with increasing doses. In preliminary studies, it was determined that the maximum tolerable dose in humans was a 5-mg bolus infused over 3 to 5 minutes followed by a 12-hour, constant-rate, maintenance infusion of 0.75 mg/h.

The present study was designed to compare the efficacy and safety of 2 doses of aptiganel with placebo in patients with acute ischemic stroke. The 2 dosing regimens were designed to produce steady-state plasma concentrations of aptiganel of approximately 5 and 10 ng/mL.

**METHODS**

An international, double-blind, placebo-controlled, randomized study was undertaken to determine whether either of the 2 doses of aptiganel, administered as a bolus over 3 to 5 minutes and a 12-hour maintenance infusion within 6 hours of ischemic stroke onset, would significantly improve objective stroke outcome measures (reflecting neurological impairment, handicap, disability, and quality of life) compared with placebo, without increasing mortality. A phase 2 dose comparison trial was nested within a phase 3 trial. Patients were enrolled between July 15, 1996, and September 29, 1997.

The primary efficacy end point for the Phase 2 portion of the trial was the change in the National Institutes of Health (NIH) Stroke Scale score at discharge or at 7 (±2) days after stroke (for those still hospitalized) compared with baseline. The primary efficacy end point for the phase 3 portion of the trial was the Modified Rankin Scale score at 90 (±7) days after stroke.

Secondary efficacy end points were (1) the NIH Stroke Scale score difference between baseline and discharge or 7 (±2) days, between baseline and 30 (±5) days, and between baseline and 90 (±7) days; (2) Barthel Index score at 30 (±5) days and 90 (±7) days; (3) the Scandinavian Stroke Scale score at hospital discharge or 7 (±2) days, at 30 (±5) days, and at 90 (±7) days; (4) the Modified Rankin Scale score at 30 (±5) days; and (5) mortality over the follow-up period of 90 (±7) days. Mortality was reevaluated at 120 days after stroke. All scales were administered by a blinded rater who was not involved in patients’ acute treatment and observation periods.

This trial was conducted according to Food and Drug Administration regulations and guidelines, which also encompass principles established by the Declaration of Helsinki. Written informed consent was obtained from each patient or legal representative prior to participation. Telephone consent was allowed if approved by the clinical investigator’s institutional review board. All centers had a country-specific consent form that complied with the Declaration of Helsinki. This trial was conducted in 156 centers in the United States, Australia, Canada, South Africa, England, and Scotland. Local institutional review boards or ethics committees approved the consent form and protocol at all centers.

An independent data and safety monitoring board was commissioned by Boehringer Ingelheim Pharmaceuticals Inc to monitor overall patient safety. The committee was composed of 7 members, including 1 biostatistician with expertise in stroke and 6 physicians with expertise in acute stroke or emergency medicine. The members were not otherwise involved in the conduct of the study. The data and safety monitoring board met on 6 separate occasions to review the safety results including listings and summaries of adverse experiences, abnormal results of laboratory tests, vital signs, and electrocardiograms in a blinded fashion. Reports to the data and safety monitoring board were prepared by an independent statistician at a contract research organization not otherwise involved in the conduct of the trial.

Trial medication was administered as an intravenous bolus followed by a 12-hour maintenance infusion. The 3 treatment groups were (1) patients who received high-dose aptiganel (5.0-mg bolus) followed by 0.75 mg of aptiganel per hour for a total of 14.0 mg; (2) patients who received low-dose aptiganel (3.0-mg bolus) followed by 0.5 mg of aptiganel per hour for a total of 9.0 mg; and (3) patients who received placebo for both the bolus and maintenance infusion.
Inclusion Criteria
Study drug could be initiated within 6 hours of the onset of ischemic stroke signs and symptoms. If the patient woke from sleep with the deficit, the time of onset was considered as the last time he/she was observed to be normal (ie, prior to bedtime). Patients were included if their symptoms were present for more than 30 minutes, were not rapidly improving, and were distinguishable from other etiologies, such as syncope, seizure, migraine, or hypoglycemia. Patients were required to be older than 16 years.

Exclusion Criteria
Patients with computed tomographic (CT) evidence of hemorrhage, brainstem stroke, primary or metastatic brain tumors (every effort was to be made to obtain a baseline CT scan prior to study randomization) were excluded. If a CT scan could not be performed at the time of entry, the investigator was to have rendered a clinical diagnosis of ischemic stroke and a CT scan was required before the end of the 12-hour infusion. Other exclusion criteria included severe mental deficit, severe neurological disorder (dementia, multi-infarct dementia, advanced multiple sclerosis, which would interfere with the assessment of the patient’s ability for independent functioning), mild symptoms (NIH score of <6), severe obtundation (defined as a score ≥2 on the NIH level of consciousness subcategory), sustained hypertension (defined during the baseline period by 2 readings occurring 30 minutes apart with a systolic blood pressure ≥200 mm Hg or diastolic blood pressure ≥110 mm Hg); and/or a clinical diagnosis of malignant hypertensive crisis accompanied by other signs or symptoms of cardiac, renal, hepatic, or intracranial involvement, such as hypertensive encephalopathy (eg, nausea, vomiting, obtundation, etc) or end-organ disease (eg, papilledema, retinal hemorrhage, hematuria, or congestive heart failure), sustained hypotension (defined by a systolic blood pressure ≤90 mm Hg or a diastolic blood pressure ≤50 mm Hg), clinically significant hypoglycemia (eg, serum glucose ≤40 mg/dL [≤2.2 mmol/L]).

Quinidine may inhibit the metabolism of aptiganel and increase serum blood concentrations to toxic levels, therefore its use was restricted. Use of other concomitant medications approved by the Food and Drug Administration was permitted, including intravenous heparin, aspirin, ticlopidine, and warfarin. Use of investigational drugs was prohibited (including all fibrinolytic and thrombolytic agents, such as tissue plasminogen activator, which was not yet approved at the time the study was designed) and low-molecular-weight heparins.

Eligible, consenting patients were randomized equally to either low-dose or high-dose aptiganel or matching placebo. A negative pregnancy test was required for all women of child-bearing potential before study medication was administered. Patients were treated in a variety of inpatient hospital units; however, the majority were treated in specialized units in experienced stroke centers. Stroke subtype was assigned using the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria.19

After administration of study medication, patients were carefully monitored for safety, neurological function, and functional disability for 12 hours after infusion. At the end of the observational period (24 hours from start of study medication), patients were examined by an investigator and a 12-lead electrocardiogram and clinical laboratories were performed. A second CT scan was to be performed before discharge to verify the diagnosis of ischemic stroke.

All adverse events were reported throughout the 90 (±7) days of patient care. Adverse events considered to be a part of the initial acute stroke process were not recorded unless these events worsened or if they required treatment after administration of study medication. Routine physical examinations, electrocardiogram, and hematologic tests (blood chemistries) were performed at baseline, during the observation period, at day 7 (±2) or discharge, day 30 (±5), and day 90 (±7).

Phase 2 Analysis
The planned phase 2 analysis (interim analysis of the first 300 patients in the trial) evaluated the change in the NIH Stroke Scale score between baseline and hospital discharge or 7 (±2) days after stroke for those still hospitalized. Clinical response was analyzed using the Jonckheere-Terpstra test, which extends the Wilcoxon rank-sum test to more than 2 ordered populations (ie, high-dose aptiganel, low-dose aptiganel, or placebo). The hypothesis test was 1-sided, with a significance level of .05. The analysis rules specified that the trial could be terminated early only if continuation was futile. There was no circumstance that would have called for terminating the trial early because of a conclusion that the phase 2 trial successfully demonstrated the efficacy and safety of aptiganel, thus no α was expended in the interim analyses. Because the phase 2 study was nested within a phase 3 study, the trial continued to recruit patients while the interim phase 2 analysis was conducted. Patient recruitment was halted subsequent to the completion and review of this analysis. The time required to complete the phase 2 analysis was about 3 months. Within this period, data were verified and forwarded for double entry, programs were written for data display, data were analyzed, and an initial report compiled. At the time of termination, 628 patients had been enrolled.

Phase 3 Analysis
Efficacy analyses were performed on the data set that included all patients treated with the study drug who had at least 1 follow-up assessment. The phase 3 model for primary analyses evaluated treatment effects in pairwise comparisons with placebo using the rank–sum–test procedures for long-term functional outcome. The principal statistical hypothesis was whether aptiganel at either the high or low dose would improve patient outcome. The null hy-
change was prespecified as the threshold. The median baseline NIH Stroke Scale score was the classification rule was established and documented prior to the unblinding of treatment assignment.

**Secondary End Points.** Results were compared by using the Kruskal-Wallis test as an initial test of whether there were differences among treatments. Pairwise comparisons between individual doses and placebo were made using the Wilcoxon rank-sum test when the initial test achieved statistical significance (P<.05). The 95% confidence intervals for the differences between the treatments were to be calculated for each end point.

**Safety Assessments.** Crude and hazard rates, severity, and the casual relationship of the adverse events were calculated. Mortality rates at 30 (±7) days were compared using the Fisher exact test. In addition, deaths were evaluated by using the log-rank test for censored data. Both analyses were done at a nominal alpha level of .05. The laboratory values were analyzed for clinically relevant changes.

Hypotheses about the effect of other variables on outcome were explored using proportional odds regression procedures and linear models analysis of covariance procedures. Hypotheses were tested using the likelihood ratio test. Odds ratios were estimated by maximum likelihood and computations were based on logistic models (SAS Institute Inc, Cary, NC). Hypotheses were also tested using F tests derived from general linear model analyses. Putative prognostic factors included severity of stroke (by pretreatment NIH Stroke Scale), elapsed time between onset of symptoms and start of treatment (0-3 hours, 3-6 hours), age, history of stroke, and type of stroke (TOAST classification, progressive stroke).

**Sample Size.** In consideration of the 2 comparisons between treatment and control (high-dose aptiganel vs placebo and low-dose aptiganel vs placebo), the significance level of each comparison was .0272 to achieve a studywise level of significance of .05. Adjustment for multiple comparisons using Dunnett procedure resulted in a shift in the z score required for significance from 1.96 to 2.21, which increased the sample size per group by 20%. Sample size was increased a further 5% to account for patients who were not expected to have a measurable response because of early loss to follow-up or misdiagnoses, such as hemorrhagic strokes. Under the assumption that a median Modified Rankin Scale score of 3.0 would have been seen in the placebo group at day 90 (±7) and an improvement of 1 point in median score would have been seen with aptiganel treatment, a sample size of at least 300 patients per treatment group was required to reject the null hypothesis with 80% statistical power at a 2-sided significance level of .05 by using the 2-sample Wilcoxon test. Thus, with 300 patients in 3 treatment groups, 900 patients were to be treated and included in the primary analysis.

**RESULTS**

**Phase 2 Analysis**

Table 1 reports NIH scores at baseline and day 7 by treatment group. The prespecified Jonckheere-Terpstra test for a dose-response trend was not significant (P = .41). However, slightly greater improvement occurred in placebo-treated patients compared with patients who received either dose of aptiganel. In addition, while 4 patients (3.1%) died in the placebo group during the first 7 days, there were 10 deaths with low-dose aptiganel and 12 deaths with high-dose aptiganel (8.6% and 9.9%, respectively). The difference in mortality rates between placebo and active treatment, combining the 2 doses, is statistically significant (χ²=4.99;
group, and 56 (26.3%) in the high-dose aptiganel group \((P=.03)\). Based on the results of the phase 2 interim analysis, the trial was terminated early.

**Phase 3 Analysis**
A total of 628 patients (the planned enrollment was 900) were randomized and received study medication or placebo. Aptiganel was administered to 414 patients with acute stroke and placebo was administered to 214 patients. Of these 628 patients, 619 patients had efficacy measurements and are included in the analysis. Six hundred twenty-seven patients are included in the survival analysis; 1 patient left the hospital against medical advice on day 4 and was lost to follow-up. A summary of the subject disposition is presented in Figure 1.

**Phase 3 Efficacy**
Primary Outcome Analyses. As shown in Table 2, patient demographics and baseline characteristics were similar for the 3 treatment groups. The efficacy analyses were performed on all patients treated with the study drug or placebo who had at least 1 follow-up assessment (Table 3). There was no improvement in outcome for either aptiganel group when compared with placebo at 90 days based on the Modified Rankin Scale \((P=.31)\). There were no differences between the 3 treatment groups at 90 days after stratification for baseline severity (baseline NIH Stroke Scale score of \(<12 vs \geq 12\)). Among the 57 patients enrolled with an intracerebral hemorrhage, the death rate was 26% in the placebo group, 33.3% in the low-dose group, and 36.4% in the high-dose group \((P>.06)\).

There was a significant difference in the NIH Stroke Scale score for placebo vs high-dose aptiganel group \((P=.04)\), with placebo showing greater improve-
### Table 3. Outcome Measures*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Low Dose</th>
<th>High Dose</th>
<th>(P) Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Institutes of Health change score: 7-day from baseline</td>
<td>-0.8 (5.31)</td>
<td>0.1 (9.58)</td>
<td>0.9 (9.71)</td>
</tr>
<tr>
<td>30-day from baseline</td>
<td>-1.2 (11.4)</td>
<td>0.1 (12.7)</td>
<td>0.5 (12.3)</td>
</tr>
<tr>
<td>90-day from baseline</td>
<td>-0.7 (13.6)</td>
<td>0 (14.4)</td>
<td>0.7 (14.2)</td>
</tr>
<tr>
<td>Modified Rankin score, mean (SD) [median]‡ 30-day</td>
<td>3.3 (1.78) [4]</td>
<td>3.5 (1.79) [4]</td>
<td>3.6 (1.78) [4]</td>
</tr>
<tr>
<td>90-day</td>
<td>3.1 (1.93) [3]</td>
<td>3.3 (1.97) [3]</td>
<td>3.4 (1.96) [3]</td>
</tr>
<tr>
<td>Scandinavian Stroke scale§ 7-day</td>
<td>35.2 (16.7)</td>
<td>34.3 (16.9)</td>
<td>32.3 (17.4)</td>
</tr>
<tr>
<td>30-day</td>
<td>42.3 (15.2)</td>
<td>42.7 (14.9)</td>
<td>39.9 (15.5)</td>
</tr>
<tr>
<td>90-day</td>
<td>44.5 (14.8)</td>
<td>45.3 (13.9)</td>
<td>43.0 (15.0)</td>
</tr>
<tr>
<td>Barthel Index§ 30-day</td>
<td>55.9 (40.2)</td>
<td>53.0 (41.3)</td>
<td>46.6 (40.5)</td>
</tr>
<tr>
<td>90-day</td>
<td>61.2 (41.0)</td>
<td>58.4 (42.7)</td>
<td>53.7 (42.3)</td>
</tr>
</tbody>
</table>

*Values expressed as mean (SD) unless otherwise indicated. †Comparison is with placebo. ‡Lower scores reflect better outcomes. §Higher scores reflect better outcomes.

There were significant differences in the Barthel Index at 30 days; pairwise comparison of placebo with high-dose aptiganel significantly favored placebo (\(P = .01\)). The Barthel Index at day 90 showed a marginally significant difference (\(P = .05\)) between placebo and high-dose aptiganel, favoring placebo. The Modified Rankin Scale score at day 30 showed a significant negative dose response (\(P = .04\)) with the lowest score (best outcome) in the placebo group. There was also a significant difference between placebo and high-dose aptiganel (\(P = .04\)). There was no significant difference between other outcomes assessed (Table 3).

Baseline factors were evaluated to determine which features significantly predicted recovery. TABLE 4 gives the odds ratios for various factors predicting excellent recovery, defined as a Modified Rankin Scale score of 0 or 1 at 90 days (no symptoms or no significant disability). Recovery was seen in 51 (24.2%) of 211 placebo patients, 47 (23.9%) of 197 low-dose aptiganel patients, and 47 (22.3%) of 211 high-dose aptiganel patients (low-dose aptiganel vs placebo, \(P = .94\); high-dose aptiganel vs placebo, \(P = .64\)); thus treatment was not associated with improved recovery. Patients with more severe initial stroke (as evidenced by baseline NIH Stroke Scale score of \(\geq 12\)), age 73 years or older, large-artery atherosclerosis, ischemic infarct on the CT scan performed on day 7, infarct of greater than 1.5 cm in diameter on the day 7 CT scan, mass effect on baseline CT scan, or intracranial hemorrhage were less likely to recover (Table 4).

### Safety Evaluation and Adverse Events

All 628 patients who were randomized and received treatment were included in the safety analysis. TABLE 5 gives the adverse events. The investigators considered 269 (42.8%) patients to have had adverse events related to study medication. Hypertension was reported in significantly more patients in both the low-dose (\(P = .02\)) and high-dose (\(P = .002\)) aptiganel groups than in patients receiving placebo. More than twice as many patients who received high-dose aptiganel than patients who received placebo had ventricular arrhythmia (\(P = .03\)). One case in the high-dose aptiganel group was severe. There was significantly more cerebral edema in the high-dose aptiganel group than the placebo group (\(P = .003\)). Other adverse events occurring at a significantly higher rate with aptiganel treatment were somnolence, stupor, and confusion.

A serious adverse event was defined as a fatal or immediately life-threatening clinical experience, a permanently or severely disabling event, an event that required or prolonged inpatient hospitalization, a congenital anomaly, cancer, or overdose. There were a high number of serious adverse events in all treatment groups as would be expected in an elderly acute stroke population. The overall incidence of serious adverse events was 273 (43.9%) of 628 randomized patients, of whom 87 (40.7%) were in the placebo group, 84 (42.0%) were in the low-dose group, and 102 (47.7%) were in the high-dose group (placebo group vs high-dose group, \(P = .14\)). The 5 most common reported serious adverse events defined by an incidence of 2% or greater for the placebo group in descending order included cerebrovascular disorder (new stroke, 9.8%), pneumonia (4.2%), cerebral hemorrhage (2.8%), cardiac arrest (2.8%), and cardiac failure (2.3%).

Severe adverse events are shown in TABLE 6. Eighty-six patients (40.2%) in the placebo group experienced severe adverse events compared with
87 (43.5%) in the low-dose and 114 (53.3%) in the high-dose aptiganel groups (placebo group vs high-dose group, \(P = .01\)). Four (1.9%) placebo patients had severe adverse events that were considered to be related to study medication compared with 4 (2.0%) in the low-dose and 6 (2.8%) in the high-dose aptiganel groups (placebo group vs high-dose group, \(P = .52\)). Thirteen patients had study-drug infusion discontinued due to a serious adverse event: 3 (1.5%) in the placebo group, and 4 (2.0%) and 6 (2.8%) in the low-dose and high-dose aptiganel groups (\(P = .31\)). Fatal adverse events during the infusion period were seen in 2 patients who received placebo and who had cerebral hemorrhages, in 2 patients who received low-dose aptiganel (1 with cerebral edema and 1 with cerebral hemorrhage), and in 1 patient who received high-dose aptiganel, who had a myocardial infarction. There were no clinical laboratory, electrocardiographic, or vital sign abnormalities that could be clinically attributed to aptiganel.

COMMENT

The primary finding of this study is that aptiganel administered in the doses tested within 6 hours of symptom onset is not efficacious in the treatment of patients with acute ischemic stroke, and may be harmful. No significant improvement was seen in the aptiganel groups compared with placebo in any efficacy parameter; in fact some parameters indicated a significant difference favoring placebo over high-dose aptiganel. There was a trend favoring placebo in mortality rates, although the differences were not significant. Adverse events including hypertension, ventricular arrhythmia, somnolence, stupor, and cerebral edema were associated with aptiganel treatment, particularly at the higher dose. In parallel with this trial, a phase 3 trial was conducted in patients with traumatic brain injury. This trial was also terminated prematurely based on efficacy and safety data from interim analyses (the results of the aptiganel traumatic brain injury trial will be reported separately).

The value of glutamate antagonist treatment rests on the concept of incremental neuronal damage following the initial incident related to excessive extracellular concentrations of excitatory amino acids. There are several possible explanations for the failure of aptiganel treatment to improve outcomes in this study. First, the timing or method of dosing may not have been optimal. In animal models, aptiganel was effective when administered within 1 hour of stroke onset. In this trial, the vast majority of patients were treated between 3 and 6 hours after symptom onset. The compound may not be as effective in humans as in animal models, or controlled laboratory experiments may not adequately reflect the complexity of stroke with regard to risk factors, natural history, and treatment. Finally, glutamate may not play as important a role in ongoing deterioration as was hypothesized, or its role may be variable depending on specific stroke subtypes or other variables.

The theory of the ischemic penumbra itself may provide insight into the present results. The penumbra represents an intermediate zone between infarction and full metabolic function. The fate of the penumbra depends on both the degree and duration of ischemia. Secondary processes may lead to delayed death of neurons within the penumbral region. Calcium appears to have beneficial properties at moderate levels that may be present in regions of the penumbra. It is therefore possible that blocking calcium through glutamate antagonist therapy may inhibit the capacity of neuronal cells to respond to an ischemic challenge.

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Another problem encountered in this and other acute stroke intervention studies is related to the high recovery rates in placebo-treated patients.\textsuperscript{23} In the present study, 24\% of placebo patients experienced full recovery. The most significant predictor of poor outcome is severity of initial stroke.\textsuperscript{24} In the present study, patients with an NIH Stroke Scale score of less than 12 were 7 times more likely to recover than those with a score of 12 or greater.

\begin{table}
\caption{Number of Patients With Most Common Adverse Events*}
\begin{tabular}{|l|l|l|l|l|l|}
\hline
WHO Organ Class and Preferred Term & Placebo & Aptiganel Hydrochloride & & & \\
& (n = 214) & Low Dose (n = 200) & High Dose (n = 214) & Low Dose & High Dose \\
\hline
Application site & & & & & \\
Application site reaction & 23 (10.7) & 16 (8.0) & 21 (9.8) & .34 & .75 \\
Body as a whole & & & & & \\
Fall & 23 (10.7) & 19 (9.5) & 17 (7.9) & .67 & .32 \\
Fever & 52 (24.3) & 57 (28.5) & 60 (28.0) & .33 & .38 \\
Headache & 54 (25.2) & 50 (25.0) & 43 (20.1) & .96 & .20 \\
Pain & 51 (23.8) & 48 (24.0) & 61 (28.5) & .97 & .27 \\
Cardiovascular & & & & & \\
Hypertension & 36 (16.8) & 53 (26.5) & 60 (28.0) & .02 & <.01 \\
Hypotension & 16 (7.5) & 16 (8.0) & 24 (11.2) & .84 & .18 \\
Peripheral edema & 28 (13.1) & 25 (12.5) & 26 (12.1) & .86 & .77 \\
Central and peripheral nervous system & & & & & \\
Agitation & 52 (24.3) & 54 (27.0) & 68 (31.8) & .53 & .09 \\
Confusion & 28 (13.1) & 29 (14.5) & 46 (21.5) & .68 & .02 \\
Insomnia & 32 (15.0) & 26 (13.0) & 18 (8.4) & .57 & .04 \\
Cerebral edema & 6 (2.8) & 14 (7.0) & 22 (10.3) & .05 & <.01 \\
Somnolence & 34 (15.9) & 52 (26.0) & 65 (30.4) & .01 & <.01 \\
Stupor & 11 (5.1) & 19 (9.5) & 33 (15.4) & .09 & <.01 \\
Gastrointestinal system & & & & & \\
Abdominal pain & 15 (7.0) & 20 (10.0) & 21 (9.8) & .27 & .30 \\
Constipation & 67 (31.3) & 51 (25.5) & 56 (26.2) & .19 & .24 \\
Diarrhea & 27 (12.6) & 28 (14.0) & 29 (13.6) & .68 & .77 \\
Nausea & 31 (14.5) & 45 (22.5) & 39 (18.2) & .04 & .30 \\
Vomiting & 20 (9.3) & 48 (24.0) & 40 (18.7) & <.01 & <.01 \\
Heart rate and rhythm & & & & & \\
Ventricular arrhythmia & 10 (4.7) & 8 (4.0) & 22 (10.3) & .74 & .03 \\
Bradycardia & 30 (14.0) & 11 (5.5) & 26 (12.1) & <.01 & .57 \\
Atrial fibrillation & 16 (7.5) & 18 (9.0) & 25 (11.7) & .57 & .14 \\
Tachycardia & 18 (8.4) & 22 (11.0) & 25 (11.7) & .37 & .56 \\
Musculoskeletal system & & & & & \\
Skeletal pain & 25 (11.7) & 22 (11.0) & 21 (9.8) & .83 & .53 \\
Psychiatric & & & & & \\
Depression & 40 (18.7) & 29 (14.5) & 39 (18.2) & .25 & .90 \\
Respiratory system & & & & & \\
Coughing & 17 (7.9) & 16 (8.0) & 33 (15.4) & .98 & .02 \\
Dyspnea & 18 (8.4) & 22 (11.0) & 27 (12.6) & .37 & .16 \\
Pneumonia & 34 (15.9) & 28 (14.0) & 36 (16.8) & .59 & .79 \\
Respiratory & 25 (11.7) & 24 (12.0) & 28 (13.1) & .92 & .66 \\
Skin and appendages & & & & & \\
Rash & 19 (8.9) & 23 (11.5) & 21 (9.8) & .38 & .74 \\
Skin ulceration & 26 (12.1) & 28 (14.0) & 34 (15.9) & .58 & .27 \\
Urinary system & & & & & \\
Hematuria & 15 (7.0) & 22 (11.0) & 17 (7.9) & .15 & .71 \\
Urinary incontinence & 22 (10.3) & 35 (17.5) & 32 (15.0) & .03 & .15 \\
Urinary tract infection & 57 (26.6) & 63 (31.5) & 72 (33.6) & .28 & .11 \\
Vascular (extracardiac) & & & & & \\
Cerebrovascular & 25 (11.7) & 20 (10.0) & 19 (8.9) & .58 & .34 \\
Total With Any Adverse Event & 206 (96.3) & 196 (96.0) & 213 (99.5) & .29 & .02 \\
\hline
\end{tabular}

*Values are expressed as number (percentage) unless otherwise indicated. Most common adverse events are those with incidences of .010 or greater in any treatment group.
†Comparison is with placebo.
\end{table}
Thus, acute interventions may be most likely to demonstrate beneficial results in patients who experience a more severe initial stroke. The higher proportion of patients with improved functionality and the lower mortality rate in the placebo group suggest that glutamate blockade with aptiganel may have detrimental effects in an undifferentiated stroke population; the largest differences were seen between placebo and high-dose aptiganel. The lack of clinical improvement was associated with increases in cerebral edema; also reported with an-
tal effects in an undifferentiated stroke group suggest that glutamate block-
ade with aptiganel may have detrimen-
tal effects in an undifferentiated stroke population; the largest differences were
seen between placebo and high-dose aptiganel. The lack of clinical improvement
was associated with increases in cerebral edema; also reported with an-
tal effects in an undifferentiated stroke group suggest that glutamate block-

Author Contributions: All of the authors had full ac-
to all of the data in the study and take respons-
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Acquisition of data: Albers, Goldstein, Hall, Lesko.

Analysis and interpretation of data: Albers, Goldstein, Hall, Lesko.

Statistical expertise: Hall.

Obtained funding: Lesko.

Administrative, technical, or material support: Albers, Lesko.

Study supervision: Goldstein, Hall, Lesko.

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Role of the Sponsor: All data were collected, en-
tered, and checked, and data tables were created by an
independent contract research organization. The
contract research organization performed the
interim analysis, providing a report containing all analy-
ses requested by the data safety and monitoring board.
The final analysis was performed by a statistician em-
ployed by Boehringer Ingelheim.

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Shoquist: Michel Beaudry, MD; Saskatchewan: Re-
gina: Felix Veloso, MD.

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Table 6. Number of Patients With Severe Adverse Events∗

<table>
<thead>
<tr>
<th>WHO Organ Class and Preferred Term</th>
<th>Placebo (n = 214)</th>
<th>Aptiganel Hydrochloride Low Dose (n = 200)</th>
<th>High Dose (n = 214)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral edema</td>
<td>4 (1.9)</td>
<td>11 (5.5)</td>
<td>16 (7.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Stupor</td>
<td>4 (1.9)</td>
<td>2 (1.0)</td>
<td>13 (6.1)</td>
<td>0.46</td>
</tr>
<tr>
<td>Respiratory Phenomena</td>
<td>8 (3.7)</td>
<td>11 (5.5)</td>
<td>12 (5.6)</td>
<td>0.39</td>
</tr>
<tr>
<td>Vascular (extracardiac)</td>
<td>5 (2.3)</td>
<td>7 (3.5)</td>
<td>11 (5.1)</td>
<td>0.48</td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>18 (8.4)</td>
<td>15 (7.5)</td>
<td>15 (7.0)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Total With Any Severe Adverse Event | 86 (40.2)       | 87 (43.5)                       | 114 (53.3)      | 0.29    |

†Values are expressed as number (percentage). Serious adverse events occurring among 5% or greater in any treat-
ment group. | Comparison is with placebo.
REFERENCES


The only medicine for suffering, crime, and all other woes of mankind, is wisdom. Teach a man to read and write, and you have put into his hands the great keys of the wisdom box. But it is quite another thing to open the box.
—T. H. Huxley (1825-1895)