Gavestinel Does Not Improve Outcome After Acute Intracerebral Hemorrhage
An Analysis From the GAIN International and GAIN Americas Studies

E. Clarke Haley Jr, MD; John L.P. Thompson, PhD; Bruce Levin, PhD; Stephen Davis, MD; Kennedy R. Lees, MD; John G. Pittman, MS; Janet T. DeRosa, MPH; Paul Ordronneau, PhD; Devin L. Brown, MD; Ralph L. Sacco, MD; for the GAIN Americas and GAIN International Investigators*

Background and Purpose—Glycine Antagonist in Neuroprotection (GAIN) International and GAIN Americas trials were prospectively designed, randomized, placebo-controlled trials of gavestinel, a glycine-site antagonist and putative neuroprotectant drug administered within 6 hours of suspected ischemic or hemorrhagic stroke. Both trials reported that gavestinel was ineffective in ischemic stroke. This analysis reports the results in those with primary intracerebral hemorrhage.

Methods—The primary hypothesis was that gavestinel treatment did not alter outcome, measured at 3 months by the Barthel Index (BI), from acute intracerebral hemorrhage, based on pooled results from both trials. The BI scores were divided into 3 groups: 95 to 100 (independent), 60 to 90 (assisted independence), and 0 to 55 (dependent) or dead.

Results—In total, 3450 patients were randomized in GAIN International (N=11005) and GAIN Americas (N=1646). Of these, 571 were ultimately identified to have spontaneous intracerebral hematoma on baseline head computerized tomography scan. The difference in distribution of trichotomized BI scores at 3 months between gavestinel and placebo was not statistically significant (P=0.09). Serious adverse events were reported at similar rates in the 2 treatment groups.

Conclusions—These observations from the combined GAIN International and GAIN Americas trials suggest that gavestinel is not of substantial benefit or harm to patients with primary intracerebral hemorrhage. These findings are similar to results previously reported in patients with ischemic stroke. *(Stroke. 2005;36:1006-1010.)*

Key Words: hemorrhage ▪ neuroprotection ▪ stroke

One of the major potential advantages of a successful neuroprotectant drug for acute stroke would be its relative safety compared with thrombolytic therapy. In fact, the ideal neuroprotectant drug should be safe enough that it could be administered to patients with suspected acute stroke, either ischemic or hemorrhagic, before neuroimaging, thereby expediting treatment during the critical time window when the biochemical events leading to infarction are in progress and potentially modifiable. Moreover, some investigators have suggested that treatment with neuroprotective drugs early in the course of primary intracerebral hemorrhage might lessen the damage related to the hemorrhage and improve outcome.1,2

Such a strategy was used in the design of 2 large multicenter randomized, placebo-controlled clinical trials of gavestinel, a specific antagonist at the glycine site of the N-methyl-D-aspartate receptor, for acute stroke. The details of the design and results of each of these trials, GAIN International3 and GAIN Americas,4 have been published previously. In both trials, patients with intracerebral hemorrhage were eligible for inclusion, although the primary analysis was performed only on those patients who did not have hemorrhagic stroke on a baseline head computerized tomography scan obtained either before or within 12 hours of the initial dose of study medication. Preliminary experience in human trials with gavestinel treatment of intracranial hemorrhage was sparse.5,6 This report focuses on the safety and potential efficacy of gavestinel in a much larger pooled population of patients in GAIN International and GAIN Americas who had hemorrhagic stroke.

Patients and Methods

This study was prospectively designed to test the safety and preliminary efficacy of gavestinel in acute primary intracerebral hemorrhage. The primary null hypothesis to be tested was that gavestinel treatment did not alter outcome from acute intracranial hemorrhage when begun within 6 hours of the onset of symptoms. This hypothesis was a secondary hypothesis of each of the main trials. Another secondary hypothesis was that serious adverse events were not more frequent with gavestinel treatment than with placebo. It was recognized that neither Glycine Antagonist in Neuroprotection

Received February 15, 2005; accepted February 17, 2005.

**The GAIN Americas and GAIN International Investigators are listed in the Appendices to References 3 and 4.

Correspondence to E. Clarke Haley Jr, MD, Box 800394, Department of Neurology, University of Virginia Health System, Charlottesville, VA 22901.

E-mail ech@virginia.edu

© 2005 American Heart Association, Inc.

Stroke is available at http://www.strokeaha.org doi: 10.1161/01.STR.0000163053.77982.8d
Institutes of Health Stroke Scale [NIHSS] scores categorized as 2 to 5, age (75 or younger or older than 75 years) and stroke severity (National Institute of Neurological Disorders and Stroke rtPA Stroke Trial12 was calculated. Adverse events, both serious (eg, life-threatening, resulting in death, or prolonging hospitalization) and nonserious, were recorded in a contemporaneous fashion. Routine blood work obtained at baseline and at the end of treatment was sent to a central laboratory to screen for hematological, renal, and hepatic dysfunction. The safety of participants in the trial was overseen by an independent Safety and Efficacy Data Monitoring Committee (see Appendix 1).

Statistical Analysis
In each GAIN trial, the test of the primary null hypothesis used the extended Mantel–Haenszel $\chi^2$ test (1 degree of freedom), stratified by baseline stroke severity and age group, to combine the evidence from the 6 strata. This took account of the stratified randomization, which minimizes any confounding arising from age and NIHSS differences between strata. In the current analysis, the same approach was prespecified for the test of the primary null hypothesis. The data from the 12 strata (6 from each trial) were combined in a similarly stratified analysis using the extended Mantel–Haenszel procedure; $P<0.05$ (2-sided) was considered statistically significant.

This procedure assumes that the odds ratios for treatment in the 2 trials are the same (the intracerebral hemorrhage rates in each may differ). A likelihood ratio test was used to test this assumption. A significant difference (ie, $P<0.05$) would indicate a treatment by trial interaction and that an analysis that combined the data from the 2 trials would be inappropriate. A stratified Cox proportional hazards model compared survival over 3 months in the 2 trials. Both results indicated that the data could be combined ($P=0.18$, for the primary analysis and $P=0.29$, for survival).
TABLE 1. Baseline Characteristics of Patients With Intracerebral Hematoma in GAIN Americas and GAIN International*

<table>
<thead>
<tr>
<th></th>
<th>Gavestinel</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>280</td>
<td>284</td>
</tr>
<tr>
<td>Age, mean±SD</td>
<td>67.5±12.0</td>
<td>68.5±12.2</td>
</tr>
<tr>
<td>Proportion male, No. (%)</td>
<td>165 (58.9)</td>
<td>173 (60.9)</td>
</tr>
<tr>
<td>Proportion white, No. (%)</td>
<td>222 (79.3)</td>
<td>229 (80.6)</td>
</tr>
<tr>
<td>Baseline blood pressure:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic, mm Hg (mean±SD)</td>
<td>172.0±27.4</td>
<td>169.9±26.8</td>
</tr>
<tr>
<td>Diastolic, mm Hg (mean±SD)</td>
<td>92.8±16.4</td>
<td>92.3±16.5</td>
</tr>
<tr>
<td>Baseline NIHSS score, median (interquartile range)</td>
<td>15.0 (9.0–18.0)</td>
<td>13.0 (9.0–18.0)</td>
</tr>
<tr>
<td>Time from onset to treatment, min (median, interquartile range)</td>
<td>278.0 (235.0–330.0)</td>
<td>290.0 (240.0–330.0)</td>
</tr>
<tr>
<td>Intraventricular extension, No. (%)</td>
<td>79 (28.2)</td>
<td>75 (26.4)</td>
</tr>
</tbody>
</table>

*None of the differences between gavestinel and placebo groups is statistically significant at P<0.05 2-sided. All comparisons take stratification into account. A 2-way analysis of variance for treatment group by stratum was used for age and baseline blood pressure, a stratified Wilcoxon test for baseline NIHSS score and time from onset to treatment, and a Mantel–Haenszel test across strata for proportion male, proportion white, and hemorrhage characteristics.

All comparisons of baseline characteristics in gavestinel versus placebo groups take stratification into account. A 2-way analysis of variance for treatment group by stratum was used for continuous variables, a stratified Wilcoxon rank-sum test for ordinal measures, and a Mantel–Haenszel test across strata for categorical variables.

Results

From March 1998, through October 1999, 3450 patients were randomized in GAIN International (N=1804) and GAIN Americas (N=1646). Of these, 572 were judged by the Image Adjudication Committee to have hemorrhagic stroke on the baseline head computerized tomography scan (Figure 1). One was not located intracerebrally, leaving 571 actual intracerebral hemorrhages. Two patients did not receive treatment and were excluded from the analysis. Additionally, 5 patients (3 gavestinel and 2 placebo) were excluded because they had received tissue plasminogen activator before randomization. One patient randomized to gavestinel instead received placebo, whereas 2 patients randomized to placebo received gavestinel. For the primary efficacy analysis, which used intent-to-treat principles, there were 280 patients assigned gavestinel versus 284 patients assigned placebo. The safety analyses included all randomized and treated patients according to the drug they actually received: 284 gavestinel patients versus 285 placebo patients. Seven patients were missing 3-month BI scores. Earlier post-treatment assessments were carried forward for 6 of these (4 gavestinel and 2 placebo). One gavestinel patient was completely lost to follow-up and was imputed to have the lowest possible BI score.

Table 1 outlines the baseline characteristics of the patients in each treatment group. There was an approximate balance in the age, race, sex, and time from onset of symptoms to initiation of treatment. There were similar proportions of patients who had small versus large hematomas and intraventricular extension of the hemorrhage. Despite the stratified randomization, the gavestinel group had a median 2 point higher baseline NIHSS score than placebo patients did. None of the differences in baseline characteristics was statistically significant.

Mortality was not significantly different between the 2 groups (stratified Wald test z score=−0.878, P=0.380; relative hazard ratio=0.843, 95% confidence interval=0.575 to 1.235). In the efficacy population, 51 of 280 (18%) gavestinel-treated patients died within 3 months compared with 58 of 284 (20%) placebo patients. In the safety population (n=569), 54 of 284 (19%) gavestinel patients died compared with 59 of 285 (21%) placebo patients.

Figure 2 shows the distribution of BI scores at 3 months in the 2 treatment groups divided into the prespecified cutoffs for independence, assisted independence, and dependence or death. Overall, the difference in distribution of 3-month BI scores favored gavestinel but did not reach statistical significance (P=0.128). Analyses of the secondary outcomes, including the modified Rankin Scale and NIH Stroke Scale, failed to disclose any statistically significant differences (Appendix 2).

The proportion of patients who reported serious adverse events was similar in both groups (Table 2). There were no important differences between the groups in the incidence of nonserious adverse events, except that the proportion of patients with elevated bilirubin (a known side effect of gavestinel) was 14% in the gavestinel group compared with 5% in the placebo group. All bilirubin elevations were transient.

![Figure 2](http://stroke.ahajournals.org/)

**Figure 2.** Distributions of BI scores and mortality at 3 months. Differences in outcome were not statistically significant (extended Mantel–Haenszel χ² test).

*Subcategory percentages do not add to 100% due to rounding.
Michael Gent, DSc, McMaster University, Hamilton, Ontario, Canada; MD, University of Cincinnati Medical Center, Cincinnati, Ohio; MD, FACR, University of Cincinnati, Cincinnati, Ohio; Antonio Carolei, MD, Aquila, Italy; Stephen Davis, MD, Melbourne, Australia; Hans-Christoph Diener, MD, Essen, Germany; Markku Kaste, MD, Helsinki, Finland; Jean-Marie Orgogozo, MD, Bordeaux, France; John Whitehead, PhD, Reading, UK.

GAIN International Steering Committee: Kennedy Lees, MD (chair), Glasgow, UK; Kjell Asplund, MD, Umea, Sweden; Antonio Carolei, MD, Aquila, Italy; Stephen Davis, MD, Melbourne, Australia; Hans-Christoph Diener, MD, Essen, Germany; Markku Kaste, MD, Helsinki, Finland; Jean-Marie Orgogozo, MD, Bordeaux, France; John Whitehead, PhD, Reading, UK.

GAIN Americas Steering Committee: Ralph Sacco, MD, (chair), New York, NY; Stephen Phillips, MD, Halifax, Canada; Clarke Haley, MD, Charlottesville, Va; John Thompson, PhD, New York, NY; Bruce Levin, PhD, New York, NY; nonvoting members: Paul Ordonez, PhD and Rose Snipes, MD, Glaxo Wellcome, Inc, Research Triangle Park, NC.

Acknowledgments

The authors gratefully acknowledge the contributions of the patients who participated in these studies and their families, without whose efforts this work would not have been possible. This work has been presented, in part, at the 4th World Stroke Congress, Melbourne, Australia; November, 2000. This study was funded by GlaxoSmithKline, Inc. (formerly Glaxo Wellcome, Inc.). Dr. Haley was employed by the University of Virginia Health System, which received financial support from Glaxo Wellcome, Inc. to fund the activities of the Coordinating and Data Management Center and Statistical Analysis Center for GAIN Americas. Drs. Thompson, Levin, and Sacco, Mr. Pittman, and Ms. DeRosa were employed by Columbia University, which received financial support from Glaxo Wellcome, Inc. to fund the activities of the Coordinating and Data Management Center and Statistical Analysis Center for GAIN Americas. Dr. Ordonez is an employee of GlaxoSmithKline.

References


Gavestinel Does Not Improve Outcome After Acute Intracerebral Hemorrhage: An Analysis From the GAIN International and GAIN Americas Studies

for the GAIN Americas and GAIN International Investigators

*Stroke*. 2005;36:1006-1010; originally published online April 14, 2005;
doi: 10.1161/01.STR.0000163053.77982.8d

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 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/36/5/1006

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/