Results in 95 Hemorrhagic Stroke Patients Included in CLASS, a Controlled Trial of Clomethiazole Versus Placebo in Acute Stroke Patients

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Background and Purpose—Clomethiazole is a neuroprotective drug that enhances γ-aminobutyrate type A (GABA_A) receptor activity. Its efficacy and safety were tested in the CLomethiazole Acute Stroke Study (CLASS). The protocol allowed a CT scan to be done after randomization but within 7 days of stroke onset to minimize delays before start of treatment. Ninety-five of the 1360 patients randomized were diagnosed as having intracranial hemorrhage rather than ischemic stroke. Safety results for clomethiazole compared with placebo in this group are reported.

Methods—The study included patients with a clinical diagnosis of acute hemispheric cerebral infarction. Treatment was a 24-hour intravenous infusion of 75 mg/kg clomethiazole or placebo. Patients with intracranial hemorrhage discovered on a postrandomization CT were withdrawn from study treatment if treatment was ongoing, and all patients were followed up to 90 days.

Results—Ninety-four patients received treatment, 47 in each group. The hemorrhage was classified as intracerebral in 89 patients (94%). Mortality at 90 days was 19.1% in the clomethiazole group and 23.4% in the placebo group. Sedation was the most common adverse event, occurring at a higher incidence in clomethiazole-treated patients (clomethiazole 53%, placebo 17%), followed by rhinitis and coughing. The incidence and pattern of serious adverse events was similar between the treatment groups. The percentage of patients reaching relative functional independence on the Barthel Index (score ≥60) at 90 days was 59.6% in the clomethiazole group and 53.2% in the placebo group.

Conclusions—Clomethiazole appears safe to administer to hemorrhagic stroke patients compared with placebo. These results would obviate the need for a CT scan before therapy is initiated in acute stroke. The safety of clomethiazole in hemorrhagic stroke patients will be further evaluated in a prospective study that is under way in North America. (Stroke. 2000;31:82-85.)

Key Words: cerebral ischemia ■ clinical trials ■ clomethiazole ■ hemorrhage ■ neuroprotection
plasma sampling were made at baseline and at the end of the study. Patients with CT evidence of infarction from treatment if treatment was ongoing. All patients were followed up to 90 days. Patients who died were scored as those that resulted in death, hospitalization, or permanent or significant disability or that were life threatening or required medical or surgical intervention. Information on all SAEs was collected up to 7 days after randomization, and data on those SAEs that were believed to be related to treatment were collected for 90 days during the first half of the study recruitment period. The protocol was then amended owing to regulatory requirements, and all data on SAEs were collected up to day 90. Functional and neurological outcomes were assessed with the Barthel Index and the SSS, respectively, at 7, 30, 60, and 90 days. The primary end point was the percentage of patients scoring ≥60 on the Barthel Index (relative functional independence) at 90 days.

### Results

#### Recruitment and Baseline Characteristics

Ninety-five (7%) of the 1360 patients randomized to CLASS were classified as having intracranial hemorrhage. One patient randomized to the clomethiazole group did not receive treatment because an intracerebral hemorrhage was found on the CT scan before treatment could be started. Therefore, 94 patients were included in the analysis of all patients treated (47 in each treatment group). All but 1 of these patients (in the clomethiazole group) were randomized before the results of the CT scans were known.

The hemorrhage was classified as intracerebral in 89 patients (94%). Of the remaining patients, 2 had subdural hematomas, 1 had subarachnoid hemorrhage, and 1 had mixed intracerebral and subarachnoid hemorrhage in the clomethiazole group, and 1 patient in the placebo group had mixed intracerebral and subarachnoid hemorrhage.

The mean age of patients classified as having an intracranial hemorrhage was 73.6 ± 11.2 years compared with 71.2 ± 11.2 years for the ischemic stroke patients (n = 1254), and these patients had slightly worse scores on the SSS-58 scale (hemor-rhagic: median 26 points, interquartile range 17 to 33; ischemic: median 28 points, interquartile range 19 to 38).

The demographic and baseline characteristics of patients in the 2 treatment groups were reasonably well balanced for age and

### Subjects and Methods

The study was performed in accordance with the Declaration of Helsinki, and the protocol was approved by the local ethics committees. All patients or their relatives gave informed consent. A full description of the study design, inclusion and exclusion criteria, treatment regimen, assessments, statistical methods, and study group descriptions of the study design, inclusion and exclusion criteria, and hemorrhagic transformation (as judged by the investigator) were not classified as having intracranial hemorrhage.

Assessments of body temperature, ECG, laboratory tests, and plasma sampling were made at baseline and at the end of the infusion. Patients were assessed at baseline and regularly during the infusion for adverse events, blood pressure, and level of sedation. Sedation was assessed by use of a sedation scale used in a previous dose-escalation trial. Serious adverse events (SAEs) were defined as those that resulted in death, hospitalization, or permanent or significant disability or that were life threatening or required medical or surgical intervention. Information on all SAEs was collected up to 7 days after randomization, and data on those SAEs that were believed to be related to treatment were collected for 90 days during the first half of the study recruitment period. The protocol was then amended owing to regulatory requirements, and all data on SAEs were collected up to day 90. Functional and neurological outcomes were assessed with the Barthel Index and the SSS, respectively, at 7, 30, 60, and 90 days. The primary end point was the percentage of patients scoring ≥60 on the Barthel Index (relative functional independence) at 90 days.

### Table 1. Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Clomethiazole (n=48)</th>
<th>Placebo (n=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean±SD</td>
<td>73.3±8.5</td>
<td>74.0±9.8</td>
</tr>
<tr>
<td>Weight, kg, mean±SD</td>
<td>70.4±14.4</td>
<td>68.0±14.8</td>
</tr>
<tr>
<td>Height, cm, mean±SD</td>
<td>167.6±10.3</td>
<td>165.9±7.9</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>21 (44)</td>
<td>22 (47)</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>6 (13)</td>
<td>4 (9)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>5 (10)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>20 (42)</td>
<td>16 (34)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>3 (6)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>4 (8)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Angina, n (%)</td>
<td>8 (17)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Cardiac failure, n (%)</td>
<td>4 (8)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Previous stroke, n (%)</td>
<td>3 (6)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Previous TIA, n (%)</td>
<td>4 (8)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Baseline blood pressure, mm Hg, mean±SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>169.9±24.9</td>
<td>163.2±24.4</td>
</tr>
<tr>
<td>Diastolic</td>
<td>93.0±15.1</td>
<td>91.6±14.4</td>
</tr>
<tr>
<td>Median baseline SSS-58 score (interquartile range)</td>
<td>27.5 (17–34)</td>
<td>26 (16–32)</td>
</tr>
<tr>
<td>Randomized to stratum 0–6 h, n (%)</td>
<td>35 (73)</td>
<td>24 (51)</td>
</tr>
<tr>
<td>Time since onset, h, mean±SD</td>
<td>5.6±2.8</td>
<td>6.7±3.1</td>
</tr>
</tbody>
</table>

**Values are n (%).**
severity on the SSS-58 scale. Mean time since onset of symptoms was 1 hour shorter in the clomethiazole group, and there were some differences in the medical history (Table 1). Mean blood pressure was slightly higher in the clomethiazole group (Table 1).

Dose Administered
The mean dose administered in the clomethiazole group was 58.1 mg/kg compared with 62.4 mg/kg for the placebo group. The latter was calculated from the volume administered. There were 15 withdrawals (32%) from each treatment group. The main reason for withdrawal was diagnosis of hemorrhage during the 24-hour treatment period, which was a protocol-specified criterion for withdrawal. This occurred in 10 clomethiazole patients (21%) and 12 placebo patients (20%). The second most common reason for withdrawal was the occurrence of adverse events, which occurred in 4 clomethiazole patients (9%) and 3 placebo patients (6%). All of these adverse events were related to reduced consciousness, eg, sedation or coma.

Safety
Mortality at 90 days was slightly lower for patients treated with clomethiazole than for those treated with placebo (clomethiazole 19.1%, placebo 23.4%), but the difference between groups was not statistically significant (OR 0.78, 95% CI 0.29 to 2.09; P = 0.57, 2.94). At the 95 cutpoint, the difference between the groups was 14.9 percentage units to the advantage of clomethiazole. On the SSS-48 scale, the median absolute change from baseline to last rating was 16 points for clomethiazole patients and 13 points for placebo patients.

Discussion
Stroke patients with a diagnosis of intracranial hemorrhage are usually excluded from clinical trials of putative acute stroke therapies. This was also done in CLASS if a prerandomization CT scan was performed, but a prerandomization scan was not a requirement. As a result, 7% of the patients randomized had intracranial hemorrhage. This is the first report of the safety and tolerability of a neuroprotective drug compared with placebo in patients with acute hemorrhagic stroke.

The patients included in the study were slightly older and scored only 2 points worse on the SSS than the ischemic stroke group. Correspondingly, the 90-day mortality rate of 23.4% in the placebo group was similar to that for patients with ischemic stroke who received placebo (19.4%).10 The 30-day mortality rate of 15% in the hemorrhagic stroke group is relatively low compared with most series of these patients, in whom the mortality rate at 1 month ranges from 35% to 50%.15-17 Similarly, functional outcome in this study was relatively good, with 53% of hemorrhagic patients who were treated with placebo reaching relative functional independence at 90 days, in contrast to a figure of 25% reported in previous series after 4 months of follow up.17 It is likely that the better outcome in the present study is due to a large extent to the exclusion of patients with reduced consciousness and symptoms of brain stem stroke.17

Sedation was the most common adverse event produced by clomethiazole, but the incidence of some respiratory adverse events was also increased. The pattern and incidence of adverse events was very similar to that reported for all patients.10 Clomethiazole also produced a mild lowering of systolic blood pressure during treatment compared with placebo. The mean difference between the treatment groups for the change from baseline to the minimum value at any time during treatment was 7 mm Hg (SE 3.3; P = 0.105) for systolic and 0 mm Hg (SE 2.6) for diastolic blood pressure. There were no differences between the treatment groups for mean laboratory test values, including coagulation tests, or mean ECG times.

Functional and Neurological Outcomes
The outcome on the Barthel Index at 90 days is shown in the Figure. Twenty-eight (59.6%) of 47 clomethiazole-treated patients and 25 (53.2%) of 47 placebo patients scored ≥60 on the Barthel Index, an absolute difference of 6.4% (OR 1.3, 95% CI 0.57 to 2.94). At the ≥95 cutpoint, the difference between the groups was 14.9 percentage units to the advantage of clomethiazole.
much larger study is required to test the efficacy of clomethiazole in hemorrhagic stroke.

We conclude that clomethiazole appears safe to administer to hemorrhagic stroke patients, and in contrast to thrombolytics, it should not be necessary to obtain the results of a CT scan before clomethiazole treatment for acute stroke is begun. The safety of the drug is being further studied in a prospective study that is under way in North America in which the volume of hemorrhage is also being measured.19

Acknowledgment
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References
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