Clomethiazole Acute Stroke Study in Ischemic Stroke (CLASS-I)
Final Results

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Background and Purpose—A previous trial (the Clomethiazole Acute Stroke Study) generated the hypothesis that clomethiazole is effective in patients with a major ischemic stroke (total anterior circulation syndrome), and this was tested in the present study.

Methods—A total of 1198 patients with major ischemic stroke and a combination of limb weakness, higher cortical dysfunction, and visual field deficits were randomly assigned to clomethiazole (68 mg/kg IV over 24 hours) or placebo. The study drug was initiated within 12 hours of symptom onset. Functional outcome and neurological recovery were assessed at days 7, 30, and 90, with the proportion of patients with a Barthel Index ≥60 at last follow-up as the primary outcome measure.

Results—The patients were randomly assigned equally, and the two treatment groups were well matched for baseline characteristics, including stroke severity (mean National Institutes of Health Stroke Scale score 16.9 ± 5.2). Ninety-six percent were classified as total anterior circulation syndrome. The proportion of patients reaching a Barthel Index score of ≥60 was 42% in the clomethiazole-treated group and 46% in the placebo-treated group (odds ratio, 0.81; 95% CI, 0.62 to 1.05; \(P = 0.11\)). There was no evidence of efficacy on any secondary outcome variables (modified Rankin Score, National Institutes of Health Stroke Scale, Scandinavian Stroke Scale, and 30-day CT infarct volumes) compared with placebo. Subgroup analysis showed a similar lack of treatment effect in patients treated early (<6 hours) and in those treated later (6 to 12 hours). Somnolence was an expected pharmacological effect of clomethiazole, and this occurred during treatment as an adverse event in half of the patients randomly assigned to study drug.

Conclusions—The target population was selected, and sufficient drug was given to produce the expected pharmacological effect in the brain. Clomethiazole does not improve outcome in patients with major ischemic stroke. (Stroke. 2002;33:122-129.)

Key Words: antithrombotic therapy ■ clomethiazole ■ GABA ■ neuroprotection ■ stroke

Stoke is the third leading cause of death and the leading cause of disability in most developed countries. In the United States, ~750,000 strokes occur every year, but the only approved treatment for acute ischemic stroke, intravenous recombinant tissue plasminogen activator (rt-PA), must be given within 3 hours to carefully selected patients. A minority of patients are treated with rt-PA, partly because of concerns over safety and the short time administration window of 3 hours after stroke onset. Therefore, a need exists for novel stroke treatments that might confer benefit with less risk or a longer time window for initiation. Compounds that appear to limit the histopathological and behavioral sequelae of ischemia are called neuroprotectants. Clomethiazole is a neuroprotectant that enhances \(\gamma\)-aminobutyric acid (GABA\(_A\)) receptor activity and is effective in multiple animal stroke models. Enhancement of GABA\(_A\) receptor activity will cause hyperpolarization of neuronal membranes to prevent the excitotoxic effects of glutamate, including ligand and voltage-gated calcium influx. Clomethiazole reduces ischemia-induced cerebral damage and clinically relevant behavioral abnormalities in rodents and primates at plasma concentrations of 3.5 to 19 \(\mu\)mol/L.

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See Editorial Comment, page 128
TABLE 1. Major Inclusion and Exclusion Criteria for CLASS-I

Inclusion criteria
1. Age 18 to 90 years and no preexisting functional handicap
2. Clinical diagnosis of acute ischemic stroke with higher cortical dysfunction plus homonymous visual field defect plus limb weakness
3. NIHSS score ≥3 for the sum of arm, leg, and hand strength items (5, 6, and 12)
4. Stroke onset within 12 hours of treatment
5. Fully conscious (slight drowsiness acceptable)

Exclusion criteria
1. Diagnosis other than ischemic stroke (eg, intracranial hemorrhage or tumor)
2. Severe respiratory, hepatic, or renal disorders
3. Systolic blood pressure <100 mm Hg
4. Seizure at stroke onset (exclude Todd’s paralysis)
5. Treatment with thrombolytic agents, corticosteroids (for cerebral edema), experimental or empirical treatments for stroke, or sedative drugs (if residual sedation suspected)
6. Aggressive antihypertensive therapy (eg, nipride or >30 mg parenteral labetalol between stroke onset and randomization)
7. Breast-feeding or pregnant women and women of child-bearing potential lacking a negative pregnancy test

The efficacy and safety of 75 mg/kg clomethiazole administered within 12 hours of stroke onset was evaluated in a large placebo-controlled study in Europe and Canada, the Clomethiazole Acute Stroke Study (CLASS). The study failed to show a significant benefit overall when comparing the proportion of patients scoring ≥60 on the Barthel Index (BI). However, an apparent benefit of clomethiazole was seen in a post hoc analysis of a subgroup of patients having a clinical syndrome of major stroke: total anterior circulation syndrome (TACS). The proportion achieving BI ≥60 was 40.8% of clomethiazole-treated patients compared with 29.8% of placebo-treated patients. Clomethiazole was well tolerated: Sedation was the most common adverse event, found in about half of all the clomethiazole-treated patients compared with 10% of placebo-treated patients. The subgroup analysis from CLASS generated a second trial (Clomethiazole Acute Stroke Study in Ischemic Stroke, CLASS-I) designed to test the hypothesis that clomethiazole administered within 12 hours of stroke onset is effective in patients with major acute ischemic stroke. In this article, we report of the results of CLASS-I.

Methods

Overall Study Design
The CLASS-I study was a randomized, double-blind, multinational (United States and Canada), multicenter, placebo-controlled investigation of the efficacy and safety of clomethiazole started within 12 hours of symptom onset. Full details of the study design have been reported elsewhere. Patients were recruited from 139 US and 14 Canadian centers involved in the study. The protocol and informed consent were approved by human subject protection committees at each site before study initiation. Informed consent was obtained before patient inclusion. A total of 1200 patients were planned for random assignment. The primary outcome measure was the proportion of patients scoring ≥60 on the BI at the end of follow-up. A BI score of 60 was chosen as the cutoff point because this measure of patient function predicts at least assisted independence in activities of daily living and the ability to avoid institutional care. Secondary outcome variables include the modified Rankin Scale, CT infarction volume, and neurological recovery measured on two stroke scales, the National Institutes of Health Stroke Scale (NIHSS) and the Scandinavian Stroke Scale (SSS). The inclusion and exclusion criteria for CLASS-I are shown in Table 1. Patients were included if they had signs of a major stroke defined as a combination of limb weakness plus higher cortical dysfunction (eg, aphasia or neglect) and homonymous visual field defect. This definition differed slightly from the TACS specification for practical reasons. Before study entry, all patients underwent a CT brain scan to identify intracranial hemorrhage, tumor, or other excluded conditions. Random assignment was stratified for age (18 to 66, 67 to 74, 75 to 80, and 81 to 90 years), NIHSS score (0 to 5, 6 to 10, 11 to 20, and 21 to 42), and time (<6 or 6 to 12 hours) after symptom onset by means of a telephone-based interactive voice response system. For patients with unknown onset time, the time when they were last known to be without symptoms was used.

Treatment
The starting dose of clomethiazole was 68 mg/kg, given as a 15-minute loading infusion of 6 mg/kg followed by a 2-stage maintenance infusion: 31 mg/kg infused over 7.75 hours (4 mg/kg per hour) followed by 31 mg/kg infused over 16 hours (1.9 mg/kg per hour). This dosage regimen was designed to produce plasma concentrations of 10 µmol/L or above in a large proportion of patients, based on pilot studies and the frequency of dose interruptions caused by sedation seen in the CLASS trial. The placebo group received an equivalent volume of 0.9% saline. Clomethiazole and placebo were supplied in identical bottles to keep the treatment assignment blinded. Blood samples were drawn at 3 different occasions in all patients for a population pharmacokinetic analysis. Patients were evaluated at regular intervals during the infusion for sedation with the following scale: 1, fully awake; 2, drowsy but answers when spoken to; 3, answers slowly when spoken to; 4, reacts when spoken to but does not answer; 5, reacts only to painful stimuli; and 6, does not react to painful stimuli. Excessive sedation (score ≥4) led to an interruption of the infusion that was then restarted at half the previous rate when the sedation abated (sedation score ≤3). The infusion was not restarted if the sedation had not abated within 2 hours after the interruption. The total duration of drug administration was 24 hours, including any dose interruptions.

Assessments
Patients were assessed at admission for demographic and baseline characteristics that included medical and cerebrovascular history, ECG, characteristics of the present stroke, and stroke severity according to the NIHSS and SSS. Stroke type was classified by the Oxfordshire scheme for clinical stroke syndrome at baseline and at day 7 by the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) investigators scheme for etiologic inference. Patients were assessed at days 7, 30, and 90 for functional outcome on the BI and modified Rankin scale (not day 7), and for neurological recovery on the NIHSS and SSS. The BI was also assessed by telephone at day 60. All efficacy measurements were to be made by an assessor who was not involved during the administration of the study drug to maintain blinding of treatment assignment in view of the expected adverse events with clomethiazole. CT scans were obtained at baseline, at 24 hours, and at 30 days after treatment. Findings of acute or old ischemic lesions, appearance and size of hemorrhage, and presence of edema were evaluated locally by the treating physicians. Infarction volumes were determined from the 30-day scans within a central laboratory that lacked access to clinical history (blinded readings).

Sample Size and Statistical Analysis
The planned sample size of 1200 randomly assigned patients was based on the data obtained in CLASS. For patients with major
ischemic stroke, we assumed a placebo response rate of 30% to 35% and hypothesized a 9% difference between the placebo and clomethiazole groups. Also, we postulated a 2-sided overall α=0.05, a power ≥80%, and some compensation for patient attrition.19 The analysis of efficacy data included all randomly assigned patients who received study drug and had at least 1 posttreatment assessment of efficacy. The analysis of safety data included all patients who received any quantity of study drug. The last available observation was used for patients dropping out for reasons other than death before day 90. Patients who died during the study were assigned the worst score on the efficacy scales in the analysis. The analysis of the primary outcome measure compared treatment by means of a Mantel-Haenszel test for general association, stratified for randomization categories. The size of the between–treatment group differences was estimated by odds ratios and associated confidence intervals. Secondary analyses of the BI were performed on the noncategorized score as well as other categorizations of the scores. Analyses of the modified Rankin scale compared treatment groups with regard to the proportion of patients scoring 2 at most and the distribution of noncategorized scores. Change scores from baseline on the two stroke scales (NIHSS and SSS) and the lesion volume at 30 days were also analyzed. The analysis of mortality rates compared the total population was rated as TACS; with the TOAST system, by discharge 32% were rated as probable or possible large-vessel atherothrombotic, 38% cardioembolic, and 4% small-vessel atherothrombotic. Consistent with other large trials, 25% were rated “other” or “incomplete.” Forty-four percent of the patients were randomly assigned within 6 hours in both treatment groups. The patients randomly assigned within 6 hours from symptom onset showed baseline demographics similar to those randomly assigned later, and the treatment groups were also well balanced. The baseline severity was an NIHSS score of 17.2±5.3 (n=513) for patients randomly assigned within 6 hours and 16.6±5.2

### Results

**Patient Characteristics**

In total, 1198 patients were randomly assigned into the study, 599 into each treatment group. Treatment was never started in 27 patients: 12 in the clomethiazole group and 15 in the placebo group. In addition, 2 patients (1 per group) provided no efficacy data but were included in the safety analysis. The full analysis data set defined in accordance with international guidelines used in the efficacy analysis therefore included 586 clomethiazole-treated and 583 placebo-treated patients. The treatment groups were well balanced on all baseline demographic variables, portions of which are presented in Table 2 for all randomly assigned patients. The severities of presenting strokes were equivalent and moderately severe, showing an NIHSS score of 16.9±5.2 (mean±SD). The total SSS was 21.8±11.0 (n=1196), also moderately severe. The presenting characteristics of the patients are shown in Table 3: With the Oxfordshire classification system used, 96% of the total population was rated as TACS; with the TOAST

### Table 2. Demographic and Baseline Characteristics of Patients in the Study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Clomethiazole (n=599)</th>
<th>Placebo (n=599)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y mean±SD</strong></td>
<td>72.1±11.9</td>
<td>71.7±12.2</td>
</tr>
<tr>
<td><strong>Sex, male (%)</strong></td>
<td>280 (47)</td>
<td>283 (47)</td>
</tr>
<tr>
<td><strong>Weight, kg mean±SD</strong></td>
<td>74.9±18.3</td>
<td>74.2±16.6</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>511 (85)</td>
<td>499 (83)</td>
</tr>
<tr>
<td>Black</td>
<td>63 (11)</td>
<td>66 (11)</td>
</tr>
<tr>
<td>Asian</td>
<td>14 (2)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>9 (2)</td>
<td>12 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (0)</td>
<td>7 (1)</td>
</tr>
<tr>
<td><strong>Smoker, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>150 (25)</td>
<td>142 (24)</td>
</tr>
<tr>
<td>Hypertension (current)</td>
<td>458 (76)</td>
<td>434 (72)</td>
</tr>
<tr>
<td>Myocardial infarction (past)</td>
<td>97 (16)</td>
<td>98 (16)</td>
</tr>
<tr>
<td>Atrial fibrillation (past or current)</td>
<td>220 (37)</td>
<td>192 (32)</td>
</tr>
<tr>
<td><strong>Previous stroke</strong></td>
<td>115 (19)</td>
<td>130 (22)</td>
</tr>
<tr>
<td>Transient ischemic attacks</td>
<td>88 (15)</td>
<td>124 (19)</td>
</tr>
<tr>
<td>NIHSS score, mean±SD</td>
<td>16.9±5.2</td>
<td>16.9±5.2</td>
</tr>
<tr>
<td><strong>Baseline SSS, mean±SD</strong></td>
<td>21.8±10.7</td>
<td>21.8±11.2</td>
</tr>
</tbody>
</table>

### Table 3. Characteristics of Presenting Stroke (All Patients Randomized)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Clomethiazole (n=599)</th>
<th>Placebo (n=599)</th>
<th>Total (n=1198)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary continence</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continent</td>
<td>310 52</td>
<td>332 55</td>
<td>642 54</td>
</tr>
<tr>
<td>Incontinent</td>
<td>100 17</td>
<td>79 13</td>
<td>179 15</td>
</tr>
<tr>
<td>Catheterized</td>
<td>189 32</td>
<td>187 31</td>
<td>376 31</td>
</tr>
<tr>
<td>High cortical dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphasia</td>
<td>378 63</td>
<td>374 62</td>
<td>752 63</td>
</tr>
<tr>
<td>Neglect</td>
<td>478 80</td>
<td>474 79</td>
<td>952 79</td>
</tr>
<tr>
<td>Dyscalculia</td>
<td>153 26</td>
<td>138 23</td>
<td>291 24</td>
</tr>
<tr>
<td>Apraxia</td>
<td>172 29</td>
<td>162 27</td>
<td>334 28</td>
</tr>
<tr>
<td>Other</td>
<td>127 21</td>
<td>126 21</td>
<td>253 21</td>
</tr>
</tbody>
</table>
| Total anterior circulation syndrome | 577 96     | 577 96          | 1154 96
(n=658) for those randomly assigned later. The earlier-presenting patients were on average 3 years older (mean age, 73.6±11.1 years) than the patients presenting 6 to 12 hours after symptom onset (70.6±12.6 years). These differences may be chance distributions, but greater severity in patients randomly assigned within 6 hours was also noted in the CLASS. Baseline hemodynamic and metabolic variables, including temperatures, were identical between the groups. Antithrombotic therapy, including anticoagulation and antiplatelet therapy, was equivalent as well.

### Treatment Exposure

The time to treatment (mean±SD) was 7.7±2.6 hours in clomethiazole-treated patients and 7.7±2.7 hours in placebo-treated patients. The delivered dose (mean±SD) was 59.2±15.9 mg/kg in clomethiazole-treated patients, which is 87% of the target dose. A theoretical dose of 65.5 mg/kg was calculated for placebo-treated patients from the volume of vehicle infused. The main reason for the differences between the treatment groups was a higher number of dose reductions and treatment withdrawals in the clomethiazole group because of sedation. The target plasma concentrations of clomethiazole were achieved in most patients. In 91% of all plasma samples, the concentration exceeded 5 μmol/L, and population kinetic analysis gave an average concentration during the 24-hour clomethiazole infusion of 11.9±4.6 μmol/L in patients with a plasma sample taken between 22 and 26 hours after start of dosing (n=405). These concentrations were associated with sedation in the clomethiazole-treated group.

During the entire infusion, 42.8% (251 of 587) of clomethiazole-treated patients exhibited a score of 4 or more, compared with 7.2% (42 of 583) of placebo-treated patients. Generally, this sedation occurred during the maintenance phase, although 57 (10%) of the clomethiazole patients scored 4 or more during the loading phase, compared with 10 (1%) of the placebo-treated patients.

### Efficacy Analysis

There was no evidence of efficacy on any of the outcome variables. The proportion of patients with a BI score ≥60 at 90 days is shown in Table 4. The difference between the treatment groups is not statistically significant. Categorized scores at the end of follow-up are illustrated in Figure 1 for all patients and for the early (0 to 6 hours) and late (6 to 12 hours) time strata. There were no significant differences between the treatment groups for patients in either stratum. The results of an analysis adjusting for baseline covariates did not alter this conclusion. The overall results with the secondary variables Rankin, NIHSS, and SSS used were also negative for any drug effect (Table 4), and there were no significant differences between the treatment groups for the early or the late time stratum. Over the intervening time points, the odds ratios were all near unity, suggesting that there was no early drug effect that was missed by the 3-month end points. No effect was noted on the 30-day lesion volumes (Table 4). Volumetric measurements could not be obtained on 314 patients (167 clomethiazole-treated and 147 placebo-treated), primarily because of patient death.

### Table 4. Efficacy Analyses for Primary and Secondary Variables at 90 Days

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Clomethiazole (n=586)</th>
<th>Placebo (n=583)</th>
<th>Odds Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>% BI last rating ≥60</td>
<td>42</td>
<td>46</td>
<td>0.81 (0.62, 1.05)</td>
<td>0.11</td>
</tr>
<tr>
<td>% Modified Rankin Score last rating ≤2</td>
<td>26</td>
<td>26</td>
<td>0.96 (0.72, 1.28)</td>
<td></td>
</tr>
<tr>
<td>NIHSS change from baseline</td>
<td>-5.5 (-11, 17)</td>
<td>-6.0 (-10, 16)</td>
<td>N/A</td>
<td>0.68</td>
</tr>
<tr>
<td>Median (quartiles)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSS change from baseline</td>
<td>7 (-4, 20)</td>
<td>8 (-2, 21)</td>
<td>N/A</td>
<td>0.23</td>
</tr>
<tr>
<td>Median (quartiles)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infarct volume, cm³*, mean (SD)</td>
<td>62 (68)</td>
<td>61 (67)</td>
<td>N/A</td>
<td>0.67</td>
</tr>
</tbody>
</table>

N/A indicates not applicable.

*Day 30.

Figure 1. Primary outcome of the CLASS-I study. Percentages of patients in the categories death and Barthel Index score 0 to 55, 60 to 90, and 95 to 100 are shown. The 95 to 100 category is generally considered independent and near normal or normal functioning. Scores >60 are associated with functional independence. Patient with scores <60 are generally dependent on others for some or all activities of daily living. In the total CLASS-I population and in the two time strata individually, there are no statistically significant differences. CMZ, clomethiazole; pbo, placebo.
the functional measures, no differences were noted in either time stratum.

**Safety Analysis**

Table 5 summarizes the incidence of adverse events during treatment. There were more reports of somnolence (including sedation) and rhinitis in the clomethiazole-treated group. Treatment withdrawal occurred in 108 (18.3%) of clomethiazole-treated patients, of which 94 (16%) were caused by sedation. The corresponding figures for the placebo-treated group were 39 (6.6%) and 26 (4.4%). Pneumonias (pneumonia, pneumonia lobar, and aspiration pneumonia) were reported as serious adverse events in 10 patients in the clomethiazole group and 9 patients in the placebo group. Progressive stroke during the treatment period was reported as a serious adverse event in 19 patients in the clomethiazole group compared with 11 patients in the placebo group, which may have been influenced by the impact of the transient drug-induced sedation. The magnitude of other imbalances was slight (data not shown). Death at 90 days was similar for both treatment groups (Figure 1). The Kaplan–Meier estimates of the survival distributions for all patients valid for safety analysis (Figure 2) were not significantly different (log rank test, \( P = 0.557 \)).

The 24-hour CT scan showed edema in 58% and intracerebral hemorrhage in 8% of the patients (Table 6); there were no differences between the groups. Additional scans were obtained for deteriorations in 116 clomethiazole-treated patients and 133 placebo-treated patients. Again, the findings were similar in both groups.

**Discussion**

In this trial, the hypothesis generated from the prior trial failed confirmation. Clomethiazole did not improve functional outcome in patients with signs of major stroke, even in patients randomly assigned within 6 hours of symptom onset. Our study suggests that clomethiazole has no effect on disability, stroke deficit, or infarction volume in patients with acute major stroke.

A plethora of previous trials also failed to show neuroprotection for acute ischemic stroke. The reasons for the previous failures vary: These include lack of efficacy in preclinical testing, inadequate brain tissue concentrations of the active compound, poor patient selection criteria, inadequate outcome measures, and other trial design flaws. We addressed each of these problems before beginning our trial. Clomethiazole was shown to be neuroprotective in multiple stroke models.7,8 In the preceding dose-ranging and CLASS studies, we determined an effective drug administration scheme that yielded serum concentrations similar to those found to be neuroprotective in animal stroke models.9,10 In the present study, the plasma concentration in virtually all patients was 5 \( \mu \text{mol/L} \), which is neuroprotective in animals,11 and the average concentration exceeded this by \( 2.5 \)-fold. Furthermore, the sedation observed indicates that clomethiazole reached brain tissue in sufficient quantities to produce the expected pharmacological effect.

Patient selection for this trial was based on the results of a previous large efficacy study (CLASS). In CLASS, the TACS subgroup showed a possible beneficial effect. We hypothesized that such patients might be most likely to have salvageable brain tissue. The clinical constellation of findings we defined as major acute ischemic stroke in the present study closely resembles the TACS subgroup, and 96% of patients

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**Table 5. Adverse Events Occurring in \( \geq 5\% \) of Patients During Treatment (All Safety-Eligible Patients)**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Clomethiazole (n=587), n (%)</th>
<th>Placebo (n=584), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>297 (50.6) 74 (12.7)</td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>101 (17.2) 91 (15.6)</td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>94 (16.0) 60 (10.3)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>79 (13.5) 80 (13.7)</td>
<td></td>
</tr>
<tr>
<td>Coughing</td>
<td>45 (7.7) 34 (5.8)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>38 (6.5) 42 (7.2)</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>37 (6.3) 22 (3.8)</td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>37 (6.3) 11 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Rhonchi</td>
<td>34 (5.8) 19 (3.3)</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>30 (5.1) 16 (2.7)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>21 (3.6) 33 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>16 (2.7) 43 (7.4)</td>
<td></td>
</tr>
<tr>
<td>Bradycardia</td>
<td>15 (2.6) 29 (5.0)</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 6. CT Scan Findings (All Safety-Eligible Patients)**

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Clomethiazole (n=587)</th>
<th>Placebo (n=584)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients With</td>
<td>586</td>
<td>581</td>
</tr>
<tr>
<td>Baseline CT scan, n</td>
<td>107 (18.3)</td>
<td>124 (21.3)</td>
</tr>
<tr>
<td>Edema, n (%)</td>
<td>337 (58.1)</td>
<td>334 (58.6)</td>
</tr>
<tr>
<td>Any bleed, n (%)</td>
<td>54 (9.2)</td>
<td>50 (8.6)</td>
</tr>
<tr>
<td>Intracerebral hemorrhage, n (%)</td>
<td>48 (8.3)</td>
<td>49 (8.6)</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage, n (%)</td>
<td>8 (1.4)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Subdural hematoma, n (%)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
</tbody>
</table>

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**Figure 2. Survival analysis in the CLASS-I study.** There is no difference in mortality rates between treatment groups.
randomly assigned were classified as such. The difference is due to slightly different definitions of major acute ischemic stroke and TACS. The patients included were very similar to the TACS patients in CLASS in terms of mean age and severity. The main differences were that patients were randomly assigned into CLASS-I on average 1 hour later than into CLASS, had a higher incidence of history of hypertension, and had a lower incidence of history of angina. It seems highly unlikely that the negative results in CLASS-I could be attributed to these minor differences.

To our knowledge, prior clinical stroke trials have not targeted major ischemic stroke patients. Patients with TACS have previously been reported to have large infarctions on follow-up brain imaging, and this was observed in the present study. Data from positron emission tomography studies show that such patients can harbor large areas of minimally perfused yet viable brain tissue at the time when treatment was initiated in the present study. Furthermore, patients with major acute ischemic stroke are more likely to exhibit a middle cerebral artery occlusion and show improvement after thrombolysis as late as 6 hours after stroke onset, suggesting the preservation of viable penumbra. Nonetheless, clomethiazole had no efficacy in this group of patients in the present trial, suggesting either that the drug is ineffective or that there is less salvageable brain tissue at the time when treatment was initiated than we hypothesized.

Despite the fact that our prior studies suggested that clomethiazole would prove efficacious for major acute ischemic stroke, we doubt that this trial represents a type II error because of the large sample size and total lack of treatment effect even with early treatment. Because the trial was not designed to study patients randomly assigned very early, for example, within 4 hours of symptom onset, no conclusions can be drawn regarding effects in these patients. The incidence of favorable outcome in the placebo group (as defined by a BI ≥60) was greater in CLASS I (46%) compared with CLASS patients with TACS (29.8%). It is possible that the placebo response in CLASS TACS is a random low, but this difference may also reflect improvements in patient treatment during the last few years and differences in outcome between the North American (CLASS-I) and predominately European (CLASS) patient populations in these two clinical trials. The outcome of the placebo group in the present study is similar to that recently reported for the placebo group of PROACT-II, another study in North America that enrolled patients of similar stroke severity. The better outcome of the placebo group in CLASS I does not alter the conclusion that the drug is ineffective in patients with TACS; hence, the positive result in the TACS subgroup of CLASS must be regarded as a chance finding.

It is not known whether clomethiazole would have been efficacious if it had been combined with t-PA thrombolysis. Patients eligible for t-PA were excluded from CLASS I and randomly assigned to a small safety study (n=200) that studied the combination of t-PA and clomethiazole. The TACS subgroup in that study also appeared to benefit from clomethiazole treatment. This difference was not statistically significant and could have been a chance finding. This is supported by the lack of effect of clomethiazole in the present study. In that study, there were also fewer hemorrhages in the t-PA–plus–clomethiazole group compared with the t-PA–plus–placebo group, but the difference was not statistically significant. To determine whether thrombolysis with t-PA is a prerequisite for seeing an improved outcome with clomethiazole treatment in patients with acute ischemic stroke would require further study. The neuroprotective effects of clomethiazole, however, were not restricted to models allowing reperfusion, since it has been shown to improve outcome in a primate model of permanent focal brain ischemia.

Appendix

An appendix listing the contributors to the CLASS-I study can be found online at http://www.strokeaha.org.

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Editorial Comment

Clomethiazole: An Unsuccessful Bachelor, but Perhaps a Prosperous Married Man?

The investigators of this study are to be congratulated.1 They have generated a potentially important hypothesis from a post-hoc subgroup analysis of a previous similar clinical trial, designed an appropriate and adequately powered new trial to examine the a priori hypothesis, executed the new trial according to protocol, and analyzed and reported it accordingly. Although we share their disappointment that the hypothesis was not confirmed, we have learned from their scientific rigor, and may yet learn from the negative result.

Previous clinical trials of neuroprotective drugs have frequently been flawed by studying heterogeneous groups of stroke patients, often many hours after stroke onset, with inadequate doses of study drug, inappropriate outcome measures, and too few patients to reliably identify or exclude a modest, but important, treatment effect. However, because the CLASS-I trial,1 and its predecessor (CLASS)2 were not flawed as such, we are now in the unusual position of being able to reliably conclude that one of the putative neuroprotective agents for stroke, clomethiazole, when administered alone, in a dose of 68 mg/kg within the first 12 hours of ischemic stroke, is most unlikely to be effective.

How can this be so, given the plausible mechanism of neuroprotective action of clomethiazole, and its consistently favorable effects on ischemia-induced brain damage in animal models?

It is possible that we do not understand the pathophysiology, or have developed invalid animal models, of acute ischemic stroke. However, I think the main reason for this negative result is that the study drug failed to reach the ischemic penumbra, and certainly not in sufficient dose. The authors argue that “the sedation observed indicates that clomethiazole reached brain tissue in sufficient quantities to produce the expected pharmacologic effect,” and furthermore, “the neuroprotective effects of clomethiazole . . . are not restricted to models allowing reperfusion.” However, I would argue that the occurrence of sedative adverse effects merely indicates that the drug is getting into the normal working brain (and sedating it) and not necessarily into the ischemic brain (the target), and any neuroprotective effects of clomethiazole in models without reperfusion are unlikely unless the clomethiazole is administered before the ischemic event, rather than after it (as is the case in human models). I also remain to be convinced that a high enough dose of clomethiazole was perfusing the brain soon enough in pa-
tients in the active treatment group. The authors state that “plasma concentrations in virtually all patients were equal to or greater than 5 μmol/L, which is neuroprotective in animals, and the average concentration exceeded this by approximately 2.5-fold.” However, the plasma samples were taken between 22 and 26 hours after the start of dosing, so it is not known if the plasma concentrations of clomethiazole within the first few critical hours were as high 3.9 to 19 μmol/L (the concentrations shown to be effective in animal models).

Whatever the reasons may be for this negative result, the CLASS and CLASS-I trials are sound and the results reliable—clomethiazole is unlikely to be effective when administered on its own. However, they do not necessarily mean that clomethiazole should be discarded as a potentially effective neuroprotective drug. It may be quite effective when it is delivered to ischemic but surviving brain (ie, the ischemic penumbra), for example when administered together with, or soon after, an effective fibrinolytic agent (with or without an antiplatelet agent, and even another type of neuroprotective drug).3

The foresight of the CLASS-I investigators to begin a small safety study of the combination of tissue plasminogen activator and clomethiazole is to be commended, and it is hoped that they, and others, will be encouraged to continue to plan and undertake large randomized trials of combination thrombolytic/neuroprotective drugs that have the statistical power to identify important treatment effects.

In pharmacology school, combination drug therapy is usually discouraged, for fear of adverse interactions, but in the school of life, it is often said that a good woman brings out the best in a man. Perhaps tissue plasminogen activator will be clomethiazole’s bride.

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