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 Patients with intracranial hemorrhage discovered on a postrandomization CT were withdrawn from study treatment if treatment was ongoing, and all patients were followed up to 90 days.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

Clomethiazole (Zendra, AstraZeneca) is a neuroprotective drug that has been shown to be effective in several animal models of cerebral ischemia. The compound enhances γ-aminobutyrate type A (GABA_A) receptor activity, and this is a plausible mechanism for its neuroprotective effect. The efficacy and safety of clomethiazole were tested in a double-blind, placebo-controlled study that recruited 1360 patients with a clinical diagnosis of acute hemispheric cerebral infarction (CLomethiazole Acute Stroke Study [CLASS]). There was no statistically significant difference between the treatment groups in functional outcome for all patients treated. However, for 545 patients classified before randomization as having total anterior circulation syndrome, the percentage who reached relative functional independence (Barthel Index score ≥60) was 40.8% for clomethiazole and 29.8% for placebo, a relative benefit of 37% (nominal P=0.008). It is widely believed that it is important to start acute stroke treatment as soon as possible after onset of the stroke. To minimize delays in the hospital, the study did not require a CT scan before randomization; however, one had to be performed within the first 7 days after randomization. This resulted in the inclusion of patients with a diagnosis of
intraocular hemorrhage. We report here on the safety of clomethiazole versus placebo in patients with intracranial hemorrhage.

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 members has been given elsewhere. In brief, 1360 patients were recruited at 85 centers in 7 European countries and Canada. Patients were included if they were aged 40 to 90 years and were conscious, with a clinical diagnosis of acute hemispheric cerebral infarction and onset of symptoms in the 12 hours before randomization. They had to score ≤40 on the sum of the Scandinavian Neurological Stroke Scale (SSS) long-term items and ≤14 for the sum of the SSS motor items of arm, hand, and leg at baseline. Patients were randomized to either clomethiazole or placebo (75 mg/kg), which was administered as a 15-minute loading infusion (8% of total dose) followed by a maintenance infusion to 24 hours. If patients became excessively sedated, the infusion was interrupted and then resumed at half the previous rate.

A CT scan was required within 7 days of stroke onset. When this was done before randomization, patients with a diagnosis of intracranial hemorrhage were excluded. Patients diagnosed with intracranial hemorrhage after a postrandomization CT scan were withdrawn from treatment if treatment was ongoing. All patients were followed up to 90 days.

Hemorrhage on the CT scan was classified as subdural hematoma, intracerebral hemorrhage, or subarachnoid hemorrhage. More than 1 category could be recorded. Patients with CT evidence of infarction 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.

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 ± 9.1 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 (hemorrhagic: 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
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. 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%). 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%. 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. 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.

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. Clomethiazole also produced a mild lowering of systolic blood pressure. This was similar to what was seen in all patients in whom it was not associated with a worse outcome. The incidence of SAEs was similar between the treatment groups, and there was no difference in mortality.

Hemorrhagic patients constituted a small subgroup of all patients randomized, and the study was not powered to detect a difference between treatment groups in functional outcome for this subgroup. There were indications of a better functional outcome in hemorrhagic stroke patients treated with clomethiazole compared with placebo, but this might be due to imbalances in severity and prognostic factors at baseline. A
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

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References

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