GM1 Ganglioside Therapy in Acute Ischemic Stroke

To the Editor:

The results of the study by Argentino et al. are in broad agreement with those of our earlier investigation, which they did not quote although ours was the first, long-term, double-blind trial of the ganglioside GM1 in acute stroke. However, unlike these authors, we were unable to find a significant change in neurologic score at any time between the control and treated groups. This may reflect a slight difference in treatment regimens (we treated our patients daily with GM1 [100 mg] intramuscularly for 28 days as opposed to intravenously for 15 days) and in the inclusion of our study population of patients with intracerebral hemorrhage, hemorrhagic infarction, or computed tomographic evidence of previous asymptomatic stroke. The remaining demographic characteristics are similar for the two studies, as far as they can be assessed.

On the other hand, we agree with Argentino et al. in finding no difference in disability scores between the two groups at any stage during the follow-up period (in our case 180 days, compared to their 120 days). Surprisingly, although the authors found a good concordance between the neurologic scores and the disability index, statistical significance was found only for the former. This implies a borderline result at best.

What is important in the evaluation of the efficacy of a putative protective or restorative medication in acute stroke is not the neurologic score but the disability index; not the Medical Research Council grading of weakness but the effective recovery of useful function. These decide the length of hospital stay and whether the patient will again be able to function in society. We respectfully submit, therefore, that there is no evidence for the efficacy of GM1 following acute stroke from either our prior study or from the current report, and that its prolonged administration as advocated by Argentino et al. will not change this fact.

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References


The following is in response:

To the Editor:

The statistically significant difference between GM1-treated and placebo-treated patients that we found did not refer to the mean values of neurologic scores, which were similar among the groups, as clearly depicted in our Tables 4 and 5, but to the degree of neurologic improvement, as obtained by subtracting the Canadian Neurological Scale score at entry from the scores on days 1–15, 21, and 120, respectively. However, it is not clear what these differences in degree of neurologic improvement could mean in terms of functional recovery.

We completely agree with Hoffbrand and colleagues that the success of a stroke treatment depends more on whether the patient is able to return home to useful function than on the results of his neurologic examination. On the other hand, the activities of daily living scales are demanding and could not be used for stroke patients in the acute phase because performance is often limited by factors that are not dependent on their neurologic deficit. Furthermore, taking into account functional scales for long-term follow-up, we cannot know how much of their recovery is due to rehabilitation. In this context, it is interesting, rather than surprising, that we found a good correlation between mean neurologic global scores and the disability index, neither of which was statistically significant, confirming the functional value of the Canadian Neurological Scale score.

Nevertheless, we think that no available parameters for evaluation of functional outcome in stroke patients, whether based on neurologic or disability scales, are sufficient. At present, one way to overcome this handicap could be to define more homogeneous and comparable subgroups of patients by stratifying them according to prognostic parameters such as age, severity of neurologic status at admission, and interval time between onset of symptoms and treatment. We think that only multicenter studies, capable of larger enrollment of a continuous series of patients, could help to reach this goal.

Our study only partially fulfilled these criteria; for instance, the time interval of 12 hours between stroke onset and treatment, although shorter than that of previous studies, was well over the so-called “therapeutic window.” Moreover, our data are hardly comparable with those of previous studies due to significant differences in the study design, such as treatment not started in the acute phase, too small a sample size, and different outcome measures.

We therefore believe that the results we obtained need to be further tested in a larger population of 800 patients, stratified according to sex, age, and Canadian Neurological Scale score at entry, and who are treated within 5 hours of stroke and for a longer period (21 days). Our Early Stroke Treatment trial will have the enrollment of the established number of patients, and we think that at the end of 1990 we will be able to provide our definitive results.

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References

Acute Stroke and Circadian Rhythm

To the Editor:

To date, little has been known about periodicity in the time of stroke onset. In a recent paper, however, Marler et al. studied the relationship between time of day and onset of ischemic stroke and compared their results with those of six previous studies.

To contribute to the study of temporal onset of acute stroke in relation to circadian rhythm, we performed a prospective clinical study in 206 consecutive patients with acute cerebrovascular disease (69 with atherothrombotic infarcts, 45 with lacunar infarcts, 33 with intraparenchymal hemorrhages, 28 with cardioembolic brain infarcts, 16 with transient ischemic attacks, 13 with subarachnoid hemorrhages, one with subdural hematoma, and one with venous infarct). Brain computed tomography was performed on all patients between 72 hours and 3 weeks after the beginning of the symptoms. We compared the observed with the expected frequency of stroke onset in four 6-hour intervals, using a \( \chi^2 \) test.

The distribution of time of stroke onset was 57 during nocturnal sleep (25%) and 149 during the waking hours (75%). Atherothrombotic cerebral infarcts developed significantly during night sleep (25%) while spontaneous intraparenchymal hemorrhages usually developed in the morning with the patient awake (63.5%; \( p<0.001 \)). A significant number of patients with infarcts of cardioembolic origin were also awake when they started (\( p<0.02 \)) (Table 1). However, lacunar infarcts, transient ischemic attacks, and subarachnoid hemorrhages had a uniform pattern of distribution through the day’s 24 hours. We compared their results with those of six previous studies.

To the Editor:

We read with great interest the paper of Marler et al. in which he describes a strong morning increase in onset of ischemic stroke. These results correlate very well with our studies in viscoelasticity of whole blood made during the last 4 years. Between 1984 and 1988, we investigated the course of viscoelasticity during a 24-hour period in 423 (225 male, 198 female, median age 63) patients suffering from ischemic stroke. We included only those patients who had had ischemic stroke more than 8 weeks ago and who were without cardiac or renal decompensation or previous hemorheological treatment. Viscoelasticity of whole blood (20° C) was determined by oscillating capillary rheometer and densitometer (Fa. Paar, Graz, Austria) at 7 AM, 3 PM, and 11 PM. For statistical evaluation (Wilcoxon signed rank test), the shear rate 2/2sec for viscosity and elasticity was performed on matched pairs between 7 AM and 3 PM and between 7 AM and 11 PM. Due to the great number of smokers, a heterogeneity of viscoelasticity was expected, as reported by Dintenfass, and, in fact, we did not have a normal distribution of data.

The table shows median values and interquartile ranges (25% as well as 75%) in parentheses and their significances among the three time points. The morning values were significantly higher than those at 3 and 11 PM, which argues for an increase in morning onset of ischemic stroke.

### Table 1. Viscoelasticity of Whole Blood

<table>
<thead>
<tr>
<th>Time points</th>
<th>7 AM</th>
<th>3 PM</th>
<th>11 PM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viscosity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>16.2</td>
<td>14.9</td>
<td>15.2</td>
</tr>
<tr>
<td>Range</td>
<td>13.5-17.4</td>
<td>12.1-16.3</td>
<td>12.3-16.8</td>
</tr>
<tr>
<td><strong>Elasticity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7.3*</td>
<td>6.5</td>
<td>6.7</td>
</tr>
<tr>
<td>Range</td>
<td>5.4-8.1</td>
<td>4.4-7.5</td>
<td>4.5-7.8</td>
</tr>
</tbody>
</table>

\( p<0.01 \) by Wilcoxon signed rank test.

References


### Table 1. Circadian Rhythm and Cerebrovascular Disease

<table>
<thead>
<tr>
<th>Time of day (hr)</th>
<th>0.01-6</th>
<th>6.01-12</th>
<th>12.01-18</th>
<th>18.01-24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic disease</td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Atherosclerotic disease</td>
<td>31</td>
<td>45</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>Lacunar infarct</td>
<td>11</td>
<td>24.5</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Intraparenchymal hemorrhage</td>
<td>1</td>
<td>3</td>
<td>21</td>
<td>63.5</td>
</tr>
<tr>
<td>Cardioembolic infarct</td>
<td>5</td>
<td>18</td>
<td>11</td>
<td>39</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1</td>
<td>6</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>3</td>
<td>23</td>
<td>7</td>
<td>54</td>
</tr>
</tbody>
</table>

\( p \) values obtained by \( \chi^2 \) test.
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S Oppenheimer

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