Monosialoganglioside in Subarachnoid Hemorrhage

I. Papo, MD; A. Benedetti, MD†; A. Carteri, MD; G.A. Merli, MD; S. Mingrino, MD; and R. Bruno, MD

We studied 119 patients with disturbance of consciousness following subarachnoid hemorrhage, due mostly to verified aneurysm rupture, admitted to five Italian neurosurgical departments over 18 months. Level of consciousness as assessed by score on the Glasgow Coma Scale ranged from 8 to 14 before the beginning of treatment; level of consciousness was assessed again 7, 14, and 21 days later. Patients were randomly allocated to treatment with monosialoganglioside or placebo according to a double-blind experimental design. The two treatment groups were homogeneous at entry with regard to the main clinical parameters. Both groups improved, but the rate and degree of improvement were greater in the monosialoganglioside-treated group. The difference was significant on days 14 (p=0.04) and 21 (p=0.02). Our results seem to confirm the hypothesis that monosialoganglioside reduces brain edema and provides nonspecific neuronal membrane protection. (Stroke 1991;22:22-26)

S ubarachnoid or intracerebral hemorrhage due to aneurysm rupture may lead to disturbance of consciousness of different degrees and with multiple mechanisms and is often associated with increased intracranial pressure and reduced cerebral perfusion pressure.1-4 Parenchymal hypoperfusion produces hypoxia with tissue acidosis, alteration of the lactate/pyruvate ratio, and, consequently, further membrane alterations. In this way, a vicious cycle is initiated, producing further cellular membrane damage. The severity and duration of the disturbance of consciousness is closely related to the level of hypoxia and, hence, to the impairment of cellular function.

Monosialoganglioside (GM1) is a natural component of neuronal membranes and plays an important role in neuronal transmission. Animal experiments have investigated the therapeutic effect of GM1 on the ionic and enzymatic equilibrium of neuronal cells and its effect on plasma membranes and the damaged blood-brain barrier.5-9 In addition, the role of GM1 in protecting nerve cell membranes against toxic metabolites such as glutamate has been demonstrated.7,8,10-12 Some clinical trials have confirmed this hypothesis, demonstrating the effectiveness of GM1 in patients suffering from acute stroke13 and its sequelae.14,15

The aim of our study was to assess the therapeutic effect of GM1 on the time course of disturbances of consciousness, mostly involving a diffuse neuronal impairment of the type mentioned above, after subarachnoid hemorrhage (SAH).

Subjects and Methods

We recruited 137 consecutive patients with well-documented SAH admitted to five Italian neurological departments from December 1986 to May 1988. Detailed inclusion criteria were established, and a study protocol was developed and followed.

The study was carried out according to a double-blind, randomized, placebo-controlled design. A randomization list was prepared by an independent statistical group for each department, and no person involved in the trial (including physicians and the monitoring group) had access to the code until the data set was frozen. The treatment solutions were identical in appearance and pH. Only adults with clear evidence of SAH were included, and only patients with a Glasgow Coma Scale (GCS) score of 8-14 were randomized and treated. No account was taken of the necessity for surgical intervention or the time elapsing between SAH and the initiation of treatment.

Half of the patients were given GM1 by slow intravenous infusion daily for 7 days as follows: day 1, 500 mg; day 2, 300 mg; day 3, 200 mg; and days 4-7, 100 mg. The large initial dose was given to achieve a steady state as soon as possible. The remaining

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Received March 20, 1990; accepted September 26, 1990.
patients received placebo (saline) infusions. All patients received routine treatment, both medical and surgical, as needed.

The SAH was detected by computed tomography or lumbar puncture. Angiography was performed in most patients. Sequential blood samples were taken for routine hematology and biochemistry studies to assess the safety of the drug.

The level of consciousness (as score on the GCS) was assessed, and a complete neurologic examination was performed daily during the first week and then on days 14 and 21.

Treatment efficacy was detected as changes from baseline in the GCS score and analyzed by a nonparametric method. Assessments 7, 14, and 21 days after the start of treatment were analyzed taking into account the diminishing group sizes caused by deaths and dropouts. The extended Mantel-Haenszel test was used to determine whether differences between the groups were significant. This method does not require any a priori assumption other than randomization.

To guarantee comparability of the treatment groups, the GCS scores at baseline were tested for homogeneity. To determine whether the results were consistent among departments, we performed a test for homogeneity. The term to test homogeneity was obtained by subtracting the Mantel-Haenszel statistic, which assesses treatment association, from $\chi^2_{total}$ which assesses total association. We compared mortality rates for the treatment groups using the Mantel-Haenszel test for dichotomous data.

### Results

The five neurosurgical departments recruited 137 patients. Eighteen were excluded from the analysis because of major protocol violations: two had a predominantly parenchymal hemorrhagic component, 14 had GCS scores outside the required range, and two did not attend the follow-up. Table 1 shows the contribution of each department after exclusion.

The clinical parameters and prognostic factors were evenly distributed between the groups (Table 2), and no significant heterogeneity was detected.

Angiography demonstrated aneurysms in 92 patients, 90 in the anterior circulation and two in the posterior. Four-vessel examination failed to reveal a source of bleeding in seven patients. In the remaining 20, angiography was incomplete or omitted because of clinical deterioration (Table 3). Of the 119 patients, 78 (39 in the GM1-treated group and 39 in the placebo-treated group) underwent surgery during or immediately before the follow-up period (21 days). Twenty-five patients (11 randomized to the GM1-treated group and 14 randomized to the placebo-treated group) died during the 21 days of observation, and three were lost to follow-up because of transfer to another institution (Table 4). Consequently, analysis was performed on 113 patients at 7 days, on 101 at 14 days, and on 91 at 21 days.
The difference in GCS score between the groups was not significant on day 7 (p=0.39) but it was on both days 14 (p=0.04) and 21 (p=0.02) (Table 5). As an estimate of the overall treatment effect, a weighted average of the mean treatment differences for all five departments was calculated using weights consistent with those of the Mantel-Haenszel test. These differences were 1.32 and 1.29, respectively, on days 14 and 21 (Table 5, Figure 1). Results of the treatment×department heterogeneity test were not significant at any time (Table 5). There was no significant difference in mortality rates between the groups (11 of 60 [18.3%] in the GM1-treated group and 14 of 59 [23.7%] in the placebo-treated group).

One patient receiving an antiepileptic drug (in the GM1-treated group) developed a diffuse erythema. No differences were observed between the groups in terms of laboratory data, complications, and new or adverse events (Table 6).

**Discussion**

The results of this double-blind trial show a significant improvement in the level of consciousness as measured by score on the GCS for patients treated with GM1 compared with placebo. A comparable amount of improvement has been considered clinically relevant in similar studies of naloxone20 and nimodipine21 in patients with SAH.

Improvement in the level of consciousness in our patients given GM1 was most evident 1 and 2 weeks after the end of treatment, indicating that the pharmacologic effect of the drug induces a more rapid and, probably, more complete functional recovery in subjects with diffuse reversible neuronal impairment.

Based on the decline in mean GCS score in the placebo-treated group from day 7 to day 14 and the continuous increase in mean GCS score in the GM1-treated group, it is possible that GM1 prevents or moderates vasospasm in some patients.

By means of cytotoxic substances such as arachidonic acid and prostaglandins, SAH can cause many different complications, including vasospasm and both cytotoxic and vasogenic cerebral edema. These complications are often associated with a reduction in cerebral perfusion pressure, and the resulting hypoxia appears to be responsible for disturbances of consciousness, particularly their duration and severity.

Substantial experimental data show that GM1 protects cell membranes from injury.5–8,22 It is known that exogenous GM1 is incorporated into cell membranes and becomes pharmacologically active in protecting the membrane from endogenous and exogenous toxic insults. It also has been demonstrated that GM1 has a particular affinity for "incorporation" into neuronal tissue at the locus of injury.12,23–25 GM1 can stimulate the activity of Na,K-ATPase and adenylcyclase.9,24–26 Karpik and Mahadik25 also suggest that GM1 protects the membrane from hydrolysis, phospholipase activation, and the toxic effect of free radicals. In addition, GM1 reduces membrane permeability to water, in agreement with data obtained with negatively charged phospholipids.27 GM1 also neutralizes the toxic effect of glutamate on the membrane and diminishes the efflux of intracellular K+ and the influx of Ca2+.8,27

According to Karpik and Mahadik,25 GM1 limits cerebral edema by modulating free radical concentration, lipid hydrolysis, phospholipase activation, or membrane injury caused by arachidonic acid. From the pathophysiologic and morphologic standpoints, the most relevant effect of GM1 is the reduction of edema, both cytotoxic and vasogenic. This phenom-

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**Table 5. Comparisons of Treatment Groups on Days 7, 14, and 21 in Study of GM1 in Subarachnoid Hemorrhage**

<table>
<thead>
<tr>
<th>Day</th>
<th>GM1 Mean</th>
<th>SEM</th>
<th>Placebo Mean</th>
<th>SEM</th>
<th>Difference Mean</th>
<th>SEM</th>
<th>p*</th>
<th>Test</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>12.53</td>
<td>0.36</td>
<td>12.03</td>
<td>0.46</td>
<td>0.50</td>
<td>0.58</td>
<td>0.39</td>
<td>9.09</td>
<td>10</td>
<td>0.52</td>
</tr>
<tr>
<td>14</td>
<td>13.59</td>
<td>0.34</td>
<td>12.28</td>
<td>0.54</td>
<td>1.32</td>
<td>0.64</td>
<td>0.04</td>
<td>5.60</td>
<td>10</td>
<td>0.84</td>
</tr>
<tr>
<td>21</td>
<td>14.32</td>
<td>0.20</td>
<td>13.02</td>
<td>0.49</td>
<td>1.29</td>
<td>0.53</td>
<td>0.02</td>
<td>6.69</td>
<td>9</td>
<td>0.67</td>
</tr>
</tbody>
</table>

GM1, monosialoganglioside. Descriptive statistics for all five departments combined are based on weighted averages reflecting adjustment for departments through relative contributions to Mantel-Haenszel procedure. *Based on extended Mantel-Haenszel procedures.
FIGURE 1. Graphs of improvement in score on Glasgow Coma Scale (GCS) in patients with subarachnoid hemorrhage treated with monosialoganglioside (●) or placebo (○). Top: 113 patients at 7 days; center: 101 patients at 14 days; bottom: 91 patients at 21 days.

Non has been experimentally demonstrated in both traumatic and ischemic edema,24-26,27 but the mechanisms whereby GM1 plays a role in reducing the duration of functional deficit, as well as the effect of GM1 on vasospasm or other pathologic mechanisms, must still be clarified.

We believe that SAH causes diffuse hypoxic damage leading to impairment of consciousness due to multiple functional disturbances. The beneficial effect of GM1 observed in our patients was probably due to its membrane-protecting effect, resulting in a reduction in primary and secondary cell damage and brain edema. The precise mechanism of this effect is not known, but it accounts for the quicker recovery of neuronal function in GM1-treated patients. A larger trial with a longer follow-up is planned to confirm and validate the benefit of GM1 in this type of patient.

FIGURE 2. Graphs of 95% confidence intervals for treatment differences for each department individually (0, Treviso; 1, Vicenza; 2, Modena; 3, Ancona; and 4, Padova) and for all five departments combined at (top) 14 days and (bottom) 21 days after start of study of monosialoganglioside in subarachnoid hemorrhage.

Appendix 1. List of Participants
Clinical Coordinating Center: I. Papo, MD (chief), and M.A. Recchioni, MD—Ospedale Le Torrette di Ancona.
Participating centers in alphabetical order of place: G.A. Merli, MD (chief), and L. Corradini,

TABLE 6. Number of Complications and New or Adverse Events in Study of GM1 in Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Complication/event</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GM1</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>4</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>2</td>
</tr>
<tr>
<td>Headache</td>
<td>4</td>
</tr>
<tr>
<td>Nausea/vertigo</td>
<td>0</td>
</tr>
<tr>
<td>Seizures</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6</td>
</tr>
<tr>
<td>Fever</td>
<td>5</td>
</tr>
<tr>
<td>Melena</td>
<td>1</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>24</td>
</tr>
<tr>
<td>Abnormalities in laboratory tests</td>
<td>16</td>
</tr>
<tr>
<td>Diffuse erythema</td>
<td>1</td>
</tr>
</tbody>
</table>

GM1, monosialoganglioside.
MD—Ospedale Civile di Modena, Neurosurgical Department; S. Mingrino, MD (chief), and S. Ferla, MD—Ospedale Civile di Padova, Neurosurgical Department; A. Carteri, MD (chief), and D. Billeci, MD—Ospedale Civile di Treviso, Divisione di Neurochirurgia; A. Benedetti, MD (chief), L. Volpin, MD, and U. Fornezza, MD—Ospedale Civile di Vicenza, Divisione di Neurochirurgia; R. Bruno, MD, and A. Bacchieri, PhD—Clinical Research Department, FIDIA, Abano Terme.

Acknowledgments

We gratefully acknowledge the cooperation of Prof. A. Migliore and his group and Dr. G. Curatola for biochemical consulting help in preparing the manuscript.

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Key Words • gangliosides • subarachnoid hemorrhage
Monosialoganglioside in subarachnoid hemorrhage.
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doi: 10.1161/01.STR.22.1.22

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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