Double-blind, randomized, vehicle-controlled study of high-dose tirilazad mesylate in women with aneurysmal subarachnoid hemorrhage. Part I. A cooperative study in Europe, Australia, New Zealand, and South Africa

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Object. Findings from previous multicenter clinical trials have suggested that tirilazad mesylate, a synthetic non-hormonal 21-aminosteroid, might be effective in preventing delayed cerebral ischemia following subarachnoid hemorrhage (SAH). This beneficial effect, however, was greater in males than females, possibly because of gender-related pharmacokinetic differences. The authors sought to assess the effects of administering a larger dose of tirilazad in women with SAH.

Methods. To test the efficacy of a higher tirilazad mesylate dose in female patients, a prospective randomized, double-blind, vehicle-controlled trial was conducted at 56 neurosurgical centers in Europe, Australia, New Zealand, and South Africa. Eight hundred nineteen patients were randomly assigned to receive either 15 mg/kg/day of tirilazad mesylate or a placebo containing the citrate vehicle. The two groups were similar in prognostic factors for delayed cerebral ischemia and overall outcome. High-dose tirilazad appeared to be well tolerated because no differences in the incidence of untoward medical events were noted between the two groups. Medical and surgical interventions were no different in the two treatment groups except for hyperdynamic therapy (intentional hypervolemia, induced hypertension, and/or hemodilution), which was more often used in the placebo-treated group to counteract symptomatic vasospasm (24% of patients given placebo compared with 18% of patients given tirilazad, p = 0.02).

Mortality rates and overall outcome, assessed using the Glasgow Outcome Scale at 3 months post-SAH, were not different between the two groups, despite a significantly lower incidence of delayed cerebral ischemia in patients given tirilazad. Post hoc subgroup analysis by neurological grade also did not reveal significant differences in outcome, although a trend toward a lower mortality rate favoring the study drug was present in patients with neurological Grade IV and V at admission (32% compared with 37%). Symptomatic vasospasm occurred in 33.7% of the placebo-treated patients as opposed to 24.8% of the patients who were given tirilazad (p = 0.005). The severity of symptomatic vasospasm was also attenuated by administration of the study drug (severe symptomatic vasospasm was reported in 11% of the placebo-treated patients compared with 6% of patients in the tirilazad-treated group (p = 0.008). Clinical cerebral infarction from vasospasm was also reduced from 13% in the vehicle-treated group to 8% in the tirilazad-treated group (p < 0.04).

Conclusions. The authors conclude that high-dose tirilazad mesylate is well tolerated in women with aneurysmal SAH. Although a significant reduction in the incidence of symptomatic vasospasm was observed in the treatment group, the primary end point (mortality rate at 3 months post-SAH) was not affected by the study drug. The use of other potentially effective rescue therapies (that is, hypervolemia, hemodilution, and induced hypertension) to counteract vasospasm may have been responsible for these contrasting observations between the two groups.

Key Words • subarachnoid hemorrhage • cerebral vasospasm • tirilazad mesylate • prognosis • intracranial aneurysm

Tirilazad mesylate is well tolerated and, in one report, it was suggested to be effective in reducing the incidence of symptomatic vasospasm and improving outcome. However, when the results were analyzed by gender, it was found that the beneficial effect of tirilazad was much greater in males than in females. Detailed pharmacokinetic studies have shown that gender dramatically affects the pharmacokinetics of tirilazad.
and U-89678, a first-order metabolite with activity comparable to that of tirilazad.\textsuperscript{5} Specifically, for the same dose, plasma concentrations of both tirilazad and U-89678 are reduced substantially in females compared with males. Thus, it has been suggested that these pharmacokinetic findings might provide an explanation for gender differences observed in the patient response to tirilazad. To test the hypothesis that higher doses (15 mg/kg/day) of tirilazad mesylate are required to prevent vasospasm and improve outcome in women with SAH, two parallel, multicenter, randomized, double-blind, vehicle-controlled clinical trials were organized. In this report we describe the findings from the trial conducted in North America\textsuperscript{19} and the findings from the trial conducted in Europe, Australia, New Zealand, and South Africa. A second report covering the findings from the trial conducted in Europe, Australia, New Zealand, and South Africa. A second report covering

### Clinical Material and Methods

#### Patient Population

Patients included in this study were selected from all female patients with SAH admitted to 56 neurosurgical centers in Europe, Australia, New Zealand, and South Africa (see Appendix for center names, locations, and participants in the study). The study’s protocol and consent form were approved by each participating center’s institutional review board. Entry criteria included: 1) female patients 18 years of age or older; 2) SAH confirmed by computed tomography (CT) scan or lumbar puncture; 3) a saccular aneurysm demonstrated angiographically or confirmed at surgery; and 4) therapy initiated within 48 hours of SAH. Patients assigned to any World Federation of Neurosurgical Societies (WFNS) neurological grade\textsuperscript{1} were eligible.

Patients were excluded if they had a fusiform, traumatic, or mycotic aneurysm; a severe comitant medical, neurological, or psychiatric illness; or a serious cardiovascular complication (severe or recent [< 6 months] uncontrolled hypertension, any Q-wave myocardial infarction, serious cardiac arrhythmia, or congestive heart failure). Other exclusion criteria included patients during pregnancy or puerperium and those receiving therapy with corticosteroid medications or calcium antagonists other than nimodipine prior to randomization.

#### Treatment Plan

After initial screening had been performed and informed consent obtained from patients or their representatives, the eligible patients were randomly assigned to receive either citrate vehicle or tirilazad at a dose of 15 mg/kg per day. All preparations were mixed by a pharmacist in identical volumes to maintain blinding for both patients and investigators. Randomization was stratified by center to achieve a balance in the frequency of administration of other therapies. The study drug was administered intravenously every 6 hours from entry up to Day 10 post-SAH (Day 0 = calendar day of SAH). All patients were treated with intravenously administered nimodipine (2 mg/hour) for 14 days following SAH. At the discretion of the operating surgeon, a course of oral nimodipine (60 mg every 4 hours) could be continued until Day 21 following SAH. Induced hypertension, intentional hypervolemia, and/or hemodilution therapy (triple-H therapy) for prophylaxis or treatment of symptomatic vasospasm were allowed as necessary. Balloon or pharmacological angioplasty was also allowed if deemed appropriate, but like “rescue” triple-H therapy was considered an endpoint. Other experimental therapies for vasospasm were prohibited, as was treatment with steroid medications or calcium antagonists during the period of study drug administration. The timing of surgery was selected by the operating surgeon.

#### Study End Points

The primary hypothesis of the study was that tirilazad improves overall clinical outcome in patients with aneurysmal SAH. Outcome measures of the study included the following: the primary end point consisted of the mortality rate at 91 days postdosing; major end points included the patients’ Glasgow Outcome Scale (GOS)\textsuperscript{13} scores at 3 months post-SAH or diagnosis of clinical (symptomatic) vasospasm during treatment; other end points included use of triple-H therapy, neurological worsening from vasospasm, occurrence of cerebral infarction during the treatment period, use of angioplasty, and clinical safety endpoints.

Symptomatic (clinical) vasospasm was declared by the investigator as having occurred: 1) in the presence of neurological worsening and 2) by use of clinical judgment. Neurological worsening was defined as a two-or-more point decline in the daily modified Glasgow Coma Scale (mGCS) score\textsuperscript{14} (both sides were rated on the motor score, not just the better side) or a two-or-more point increase in motor score according to the National Institutes of Health Stroke Scale.\textsuperscript{20} To be counted the change had to last for a minimum of 8 hours.

The diagnosis of vasospasm was clinically based, using the following criteria: 1) classic symptoms of vasospasm (onset occurring from Day 4–14 post-SAH; worsening of headache, stiff neck, and/or the presence of low-grade fever; insidious onset of confusion, disorientation, and/or

### Table 1

**Clinical characteristics of patients with SAH at admission and prognostic factors**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vehicle Group</th>
<th>Tirilazad Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age (years)</td>
<td>54</td>
<td>53</td>
<td>0.05</td>
</tr>
<tr>
<td>Time to admission (h)</td>
<td>7.1</td>
<td>7.0</td>
<td>0.97</td>
</tr>
<tr>
<td>Preexisting hypertension</td>
<td>27%</td>
<td>30%</td>
<td>0.28</td>
</tr>
<tr>
<td>Number of preexisting medical conditions</td>
<td>2.2</td>
<td>2.3</td>
<td>0.26</td>
</tr>
<tr>
<td>Admission blood pressure (mm Hg)</td>
<td>140/75</td>
<td>139/75</td>
<td>0.33/0.93</td>
</tr>
<tr>
<td>Posterior circulation aneurysms</td>
<td>10%</td>
<td>14%</td>
<td>0.09</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>43%</td>
<td>46%</td>
<td>0.39</td>
</tr>
<tr>
<td>Intracerebral hemorrhage</td>
<td>27%</td>
<td>30%</td>
<td>0.49</td>
</tr>
<tr>
<td>Thickness of clot</td>
<td>71%</td>
<td>67%</td>
<td>0.34</td>
</tr>
<tr>
<td>Admission WFNS grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>30%</td>
<td>30%</td>
<td>0.99</td>
</tr>
<tr>
<td>II</td>
<td>29%</td>
<td>31%</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>11%</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>11%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>19%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>mGCS score</td>
<td>11.0</td>
<td>11.2</td>
<td>0.58</td>
</tr>
</tbody>
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TABLE 2
Medical and surgical management of patients with SAH

<table>
<thead>
<tr>
<th>Management</th>
<th>Vehicle Group</th>
<th>Tirilazad Group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>triple-H therapy, prophylactic (total)</td>
<td>60%</td>
<td>59%</td>
<td>0.66</td>
</tr>
<tr>
<td>hypervolemia</td>
<td>50%</td>
<td>48%</td>
<td>0.57</td>
</tr>
<tr>
<td>hypertension</td>
<td>24%</td>
<td>26%</td>
<td>0.33</td>
</tr>
<tr>
<td>hemodilution</td>
<td>43%</td>
<td>40%</td>
<td>0.37</td>
</tr>
<tr>
<td>study drug terminated (serious medical event)</td>
<td>0.7%</td>
<td>2%</td>
<td>0.12</td>
</tr>
<tr>
<td>surgery to clip aneurysm performed</td>
<td>87%</td>
<td>86%</td>
<td>0.53</td>
</tr>
<tr>
<td>time from SAH to 1st surgery</td>
<td>26.7</td>
<td>28.5</td>
<td>0.96</td>
</tr>
<tr>
<td>to clip aneurysm (median hrs)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Statistical Analysis

To meet intent-to-treat criteria, a patient had to be randomized and receive at least one dose of study drug. We refer to these patients as “dosed patients.” All patients who were randomized, whether they received the drug or not, are known as “randomized patients.” An intent-to-treat analysis was defined as an end-point analysis that did not delete any patient or any data from any patient, except in situations in which there were multiple values for a given time point.

For analysis of categorical demographic and efficacy end points, including the crude mortality rate at 3 months, a chi-square analysis was used to test for treatment effect. For continuous baseline and efficacy end points, a one-way analysis of variance was used to test for treatment effect.

RESULTS

From November 1994 through March 1996, 819 patients (414 in the placebo-treated group and 405 in the high-dose tirilazad–treated group) with aneurysmal SAH were enrolled in the trial. Two patients (both in the vehicle-treated group) did not receive any study medication and were therefore excluded from the present analysis.

Recognized prognostic factors for outcome after aneurysmal SAH, such as patient age, preexisting medical conditions, location of the ruptured aneurysm, presence of intraventricular and/or intraparenchymal hemorrhage, thickness of the blood clot on a CT scan, and admission neurological condition were not significantly different in the two study groups (Table 1). Basic medical and surgical management also was not different in the two groups (Table 2). Surgery to clip the ruptured aneurysm was performed in 87% of patients in the placebo-treated group and in 86% of the patients in the tirilazad-treated group. The median time from SAH to surgery was 26.7 hours in the placebo-treated group and 28.5 hours in patients receiving tirilazad.

More than 85% of the patients in both groups received the planned dosage (Table 3). Death (10% in the placebo-treated and 8% in the tirilazad-treated group) was the main reason for discontinuation of the planned treatment. The number of patients whose treatment was interrupted because of medical events (serious or nonserious) was not statistically different between the two groups.

Three-Month Outcome

Glasgow Outcome Scale scores were available for 99% of patients at 3 months. Ten individuals (three in the high-dose tirilazad–treated group and seven in the placebo-treated group) were lost to follow-up review. There were no statistically significant differences in the proportion of patients with favorable outcome, defined as the combined categories of good recovery or moderate disability (Table 4). Fifty-two percent of patients receiving high-dose tirilazad were able to return to their previous employment compared with 50% of patients treated with vehicle (not statistically significant). Primary or contributing causes of
the two groups. However, a trend toward a lower incidence of mortality favoring the study drug was present in patients with WFNS Grades IV and V (32% compared with 37%; not statistically significant).

Vasospasm and Neurological Worsening

The incidence of symptomatic vasospasm was significantly lower in the tirilazad-treated group (25% compared with 34% in the vehicle-treated group, p = 0.005). The need for triple-H therapy to treat ischemic symptoms (Table 6) was 24% in the vehicle-treated group and 18% in the tirilazad-treated group (p = 0.02). Cerebral infarction secondary to vasospasm (vehicle-treated group 13%, tirilazad-treated group 8%; p = 0.04), severe vasospasm (vehicle-treated group 11%, tirilazad-treated group 6%; p = 0.008), and mean highest MCA velocity (vehicle-treated group 133 cm/second, tirilazad-treated group 6%; p = 0.04), severe vasospasm (vehicle-treated group 11%, tirilazad-treated group 8%; p = 0.04, severe vasospasm (vehicle-treated group 11%, tirilazad-treated group 6%; p = 0.008), and mean highest MCA velocity (vehicle-treated group 133 cm/second, tirilazad-treated group 6%; p = 0.008, and mean highest MCA velocity (vehicle-treated group 133 cm/second, tirilazad-treated group 6%; p = 0.008, and mean highest MCA velocity (vehicle-treated group 133 cm/second, tirilazad-treated group 6%; p = 0.008) were also significantly lower in patients given tirilazad. The use of angioplasty to reverse vasospasm did not differ between the two groups.

Worsening of neurological status from any cause during the study period occurred with similar frequency in both groups. The main causes (primary or contributing) of this worsening are summarized in Table 7.

Drug Safety

Tirilazad at a dose of 15 mg/kg/day was well tolerated by patients in this study. Infusion site disorders at the injection site were observed in 8.9% of patients receiving tirilazad and in 10.2% of those given placebo. Treatment was interrupted in two patients, both in the vehicle-treated group, and discontinued in eight patients (four in the vehicle-treated group and four in the tirilazad-treated group) because of injection site reactions. Administration of vehicle had to be discontinued because of elevated levels of liver enzymes in one of the vehicle-treated patients; this did not occur in the tirilazad-treated patients. No significant differences were registered between the two groups in vital signs, electrocardiographic findings, or any other laboratory parameters, including elevations in creatine kinase. Serious or life-threatening medical events were reported with equal frequency in both groups.

Discussion

Study Rationale

Preclinical and clinical studies of tirilazad mesylate have demonstrated promising effects. Tirilazad exerts its action through free-radical scavenging, a chemical antioxidant effect, and a physicochemical interaction with the cell membrane that decreases membrane fluidity (membrane stabilization). These effects are paralleled in animal models of SAH by a decrease in enzymatic and nonenzymatic lipid peroxidation, and result in improvement in cerebral microvascular blood flow, reduction of secondary opening of the blood-brain barrier and associated vasogenic edema, and reduction of delayed cerebral vasospasm. Tirilazad has also been shown to be neuroprotective in several models of focal cerebral ischemia. The results of earlier trials suggest that, in the clinical setting, tirilazad prevents vasospasm and improves prognosis following aneurysmal SAH.

Over the past few years tirilazad mesylate has undergone extensive clinical investigation. Three double-blind, randomized, vehicle-controlled clinical trials, in which the effects of this drug were investigated in 2154 patients with aneurysmal SAH, have been completed and reported. The largest of those studies (1015 dosed patients) was conducted at 41 neurosurgical centers in Europe, Australia, and New Zealand. The results of that study demonstrated that tirilazad has a positive effect on SAH, including a significant increase in patient survival; also more patients were able to return to their previous occupation (55% in the tirilazad-treated group as opposed to 37% in the control group, p = 0.007). When the results of this trial were analyzed by gender, however, the positive effects of tirilazad were seen essentially only in male patients. A second major trial (897 patients of both sexes) was conducted at 55 neurosurgical centers in the United States and Canada, but no evidence of improved survival was demonstrated for the tirilazad group.

Table 4

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vehicle Group (%)</th>
<th>Tirilazad Group (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOS good recovery</td>
<td>53%</td>
<td>55%</td>
<td>0.72</td>
</tr>
<tr>
<td>moderate disability</td>
<td>16%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>severe disability</td>
<td>12%</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>vegetative state</td>
<td>1%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>dead</td>
<td>18%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>favorable outcome</td>
<td>69%</td>
<td>68%</td>
<td>0.85</td>
</tr>
<tr>
<td>Kaplan-Meier (mortality at 91 postdosing)</td>
<td>0.81</td>
<td>0.83</td>
<td>0.72</td>
</tr>
</tbody>
</table>

Table 5

<table>
<thead>
<tr>
<th>Cause of Death/Disability</th>
<th>Vehicle Group (%)</th>
<th>Tirilazad Group (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>direct effect of SAH</td>
<td>27</td>
<td>26</td>
<td>0.93</td>
</tr>
<tr>
<td>vasospasm</td>
<td>18</td>
<td>13</td>
<td>0.09</td>
</tr>
<tr>
<td>ischemia due to other causes</td>
<td>3</td>
<td>4</td>
<td>0.53</td>
</tr>
<tr>
<td>rebleeding</td>
<td>6</td>
<td>7</td>
<td>0.70</td>
</tr>
<tr>
<td>hydrocephalus</td>
<td>10</td>
<td>7</td>
<td>0.09</td>
</tr>
<tr>
<td>surgical complications</td>
<td>8</td>
<td>7</td>
<td>0.77</td>
</tr>
<tr>
<td>medical complications</td>
<td>12</td>
<td>12</td>
<td>0.94</td>
</tr>
<tr>
<td>medical therapy complications</td>
<td>1</td>
<td>&lt;1</td>
<td>0.43</td>
</tr>
<tr>
<td>other</td>
<td>8</td>
<td>6</td>
<td>0.38</td>
</tr>
<tr>
<td>unknown</td>
<td>5</td>
<td>4</td>
<td>0.46</td>
</tr>
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</table>
The observation that tirilazad was more effective in men than in women was unexpected and inconsistent with the experimental preclinical studies in which the drug was found to be equally effective in male and female animal models of SAH. Detailed pharmacological studies have now shown that both gender and use of anticonvulsant medication (phenytoin and/or phenobarbital) can affect the pharmacokinetics of tirilazad and its active metabolites. Plasma concentrations are substantially reduced in women compared with men and in patients taking anticonvulsant medications. The gender differences observed in the efficacy of the drug, combined with inferences made from these gender differences in pharmacokinetics, led to the decision that testing of higher doses in female patients was warranted and, hence, to the present study.

**Significance of This Study**

The present trial was conducted to investigate the effects of high-dose tirilazad in women who have suffered aneurysmal SAH and showed a significant, absolute reduction of 9% in the incidence of clinical vasospasm in the treatment group. A decrease in the highest mean MCA velocity seen on TCD ultrasonography (123 cm/second compared with 133 cm/second, p = 0.04), a lower incidence of severe clinical vasospasm (6% compared with 12%, p = 0.008), and significantly less cerebral infarction due to vasospasm (8% compared with 13%, p = 0.04) were also observed in the tirilazad-treated group. However, this significant reduction in symptomatic vasospasm was not reflected in an improvement in overall outcome. The rate of favorable outcome at 3 months was similar in both groups.

The lack of improvement in overall prognosis in patients given tirilazad, despite a significant reduction in the incidence of symptomatic vasospasm, does have a possible explanation. No significant differences in incidences of mortality and significant adverse effects were noted between the two groups to explain these differences. The only significant difference was an imbalance in the use of rescue therapies (triple-H therapy) to counteract clinical vasospasm once it occurred. Tirilazad significantly reduced the need for hyperdynamic therapy—therapeutic triple-H treatment was used in 18% of tirilazad-treated patients as opposed to 24% of vehicle-treated patients (p = 0.02). If it is assumed that hyperdynamic therapy is, at least partly, effective in reversing the clinical manifestations of cerebral ischemia when they occur, which although never submitted to formal trial almost certainly is the case, then this could explain the lack of difference between outcome in the two groups. A similar confounding effect from hyperdynamic therapy was observed in a mul-

### Table 6

<table>
<thead>
<tr>
<th>Factor</th>
<th>Vehicle Group (%)</th>
<th>Tirilazad Group (%)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>symptomatic vasospasm</td>
<td>34</td>
<td>25</td>
<td>0.005</td>
</tr>
<tr>
<td>severe symptomatic vasospasm</td>
<td>11</td>
<td>6</td>
<td>0.008</td>
</tr>
<tr>
<td>clinical cerebral infarction from vasospasm</td>
<td>13</td>
<td>8</td>
<td>0.04</td>
</tr>
<tr>
<td>neurological worsening during treatment period</td>
<td>34</td>
<td>33</td>
<td>0.90</td>
</tr>
<tr>
<td>neurological worsening from vasospasm (primary or contributing)</td>
<td>15</td>
<td>12</td>
<td>0.12</td>
</tr>
<tr>
<td>triple-H therapy, therapeutic (total)</td>
<td>24</td>
<td>18</td>
<td>0.02</td>
</tr>
<tr>
<td>hypervolemia</td>
<td>21</td>
<td>16</td>
<td>0.07</td>
</tr>
<tr>
<td>hypertension</td>
<td>13</td>
<td>11</td>
<td>0.44</td>
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<tr>
<td>hemodilution</td>
<td>16</td>
<td>12</td>
<td>0.11</td>
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<tr>
<td>angioplasty</td>
<td>0.7</td>
<td>1</td>
<td>0.30</td>
</tr>
</tbody>
</table>

**Fig. 1.** Three-dimensional bar graph showing the incidence of symptomatic vasospasm in both the tirilazad (drug)-treated group and the vehicle-treated group from admission until Day 14 post-SAH.
ticenter trial conducted to evaluate the effects of the calcium channel blocker nicardipine in patients with SAH.9

**Alternative Benefits of Tirilazad**

The reduced need for rescue hyperdynamic therapy in patients receiving tirilazad in this study highlights a possibly important effect of this drug. Although it is believed to be generally effective in reversing the ischemia of symptomatic vasospasm, hyperdynamic treatment is by no means without risks,18,22 with occasional serious or even fatal complications and obvious limitations in preoperative patients. In addition, this type of therapy is very labor intensive and costly, requiring, as it does in most cases, management in an intensive care unit and the use of invasive hemodynamic monitoring including Swan–Ganz catheters and arterial lines. It is possible that by using tirilazad, with its impressive safety record, the resulting reduction in the need for triple-H therapy could translate into a significant cost saving, as well as safer management of patients.

**Conclusions**

In this study, administration of high-dose tirilazad was well tolerated in women with aneurysmal SAH and decreased the rate of symptomatic vasospasm. However, this beneficial effect did not result in better outcomes for the patients, probably because of concomitant administration of other effective rescue therapies in patients who did not receive tirilazad.

**Acknowledgments**

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**Appendix**

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