Do Endothelin-Receptor Antagonists Prevent Delayed Neurological Deficits and Poor Outcomes After Aneurysmal Subarachnoid Hemorrhage?
A Meta-Analysis

Andreas Kramer, MSc, FRCPC, MD; Jeffrey Fletcher, MD

Background and Purpose—Delayed ischemic neurological deficits (DINDs) contribute to poor outcomes after aneurysmal subarachnoid hemorrhage (SAH). Endothelin-1 is an important mediator involved in the development of vasospasm.

Methods—We performed a systematic review and meta-analysis of randomized controlled trials assessing the use of endothelin-receptor antagonists (ETRAs) in patients with SAH.

Results—Three studies met eligibility criteria, enrolling 867 patients. ETRAs significantly reduced the occurrence of DINDs (OR 0.68 [0.49 to 0.95]) and radiographic vasospasm (OR 0.31 [0.19 to 0.49]), but did not have any impact on mortality (OR 1.09 [0.69 to 1.72]) or poor neurological outcomes (OR 0.87 [0.63 to 1.20]). Any benefit of ETRAs may have been partially offset by adverse effects, including hypotension (OR 2.39 [1.37 to 4.17]) and pulmonary complications (OR 2.12 [1.51 to 2.98]).

Conclusions—Although ETRAs reduce radiographic vasospasm and DINDs, there is currently no evidence that they improve outcomes. (Stroke. 2009;40:3403-3406.)

Key Words: neurocrictal care ■ SAH ■ subarachnoid hemorrhage ■ vasospasm ■ endothelin

Delayed ischemic neurological deficits (DINDs) occur in 20% to 30% of patients with aneurysmal subarachnoid hemorrhage (SAH) and contribute to morbidity and mortality. Endothelin-1 concentrations are increased in the cerebrospinal fluid and blood of patients with SAH, particularly when vasospasm develops.1 Thus, there has been increasing interest in the use of endothelin-receptor antagonists (ETRAs) to prevent vasospasm.

Methods
Without language restrictions, we systematically searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (1950 to the present), using the strategy described in Appendix 1. We also searched the references of selected papers, the proceedings of the International Stroke Conference (2007 to 2009), and Google Scholar. Registered clinical trials were sought at http://www.who.int/trialsearch/

Studies were included if patients had SAH attributable to a ruptured aneurysm, treatment was randomly assigned, and an ETRA was compared with a control group. Our primary outcome was the development of DINDs, which we considered synonymous with the term “delayed neurological deficits” (DNDS). Secondary outcomes included angiographic vasospasm, drug-related complications, death, and poor neurological outcome. Poor outcome was defined as a Glasgow Outcome Scale (GOS) categorization of “severe disability” or worse.

Abstracts were screened by both investigators, initially looking for all studies in which ETRAs were administered to patients with SAH. Selected articles were then independently reviewed and eligibility criteria applied.

Data were extracted in duplicate using a standardized form. RCTs were critically appraised using the Jadad scale, which scores studies’ description of randomization (2 points), blinding (2 points), and attrition information (1 point).2 We also assessed whether manuscripts adequately reported concealment of treatment allocation. Disagreements were resolved by consensus.

We planned a priori to use fixed effects models for our summary measures in the absence of significant heterogeneity, which was evaluated using the I² statistic (I²<50%) and Q test (P<0.10).

Results
Of 291 records, 3 were original RCTs.3–5 Agreement between reviewers in study selection was perfect. 867 patients were enrolled in the 3 studies, which are described in Table 1. Two trials, involving 447 patients, used the ET-A antagonist clazosentan.3–4 The third randomized 420 patients to receive either placebo or a mixed ET-A/B antagonist (TAK-044).5

The development of DINDs was reported in only 1 RCT.3 However, we considered the definition used by
Shaw and colleagues (DNDs) to be sufficiently similar to combine results.5 In the study by Macdonald and colleagues,4 patients were not given the treatment they were randomized to receive.3 Thus, the primary outcome was based on 829/867 patients, of which 520 received ETRAs and 309 placebo. Use of ETRAs resulted in a significant reduction in DINDs/DNDs (OR 0.68 [0.49 to 0.95]; P<0.02), with a number needed to treat (NNT) of 9 (Figure). There was no significant heterogeneity. However, when using only cases of DNDs categorized by Shaw and colleagues as “definite,” the cumulative result was no longer statistically significant.

Only 2 studies systematically assessed all patients for angiographic vasospasm.3–4 Compared with 113 placebo-treated patients, the 328 treated with ETRAs were dramatically less likely to develop vasospasm (OR 0.31 [0.19 to

### Table 1. Characteristics of the Three Randomized Controlled Trials Involving the Use of ETRAs in Patients With SAH

<table>
<thead>
<tr>
<th>Study</th>
<th>Enrollment (ETRA/Placebo)</th>
<th>Grade</th>
<th>Treatment</th>
<th>Drug (Time of Initiation)</th>
<th>Dose (n)</th>
<th>Duration</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macdonald</td>
<td>413 (317/96)</td>
<td>WFNS 1–4</td>
<td>45% clipped percent coiled n/a</td>
<td>Clazosentan (within 56 hours)</td>
<td>1 mg/hr (108) 5 mg/hr (111) 15 mg/hr (98)</td>
<td>14 days</td>
<td>Moderate-severe angiographic vasospasm (&gt;33% narrowing) on day 9±2</td>
<td>DIND† (within 14 days) DI (at 6 weeks) Rescue therapy‡ (within 14 days) Extended GOS (at 12 weeks) Adverse events</td>
</tr>
<tr>
<td>Vajkoczy</td>
<td>34 (15/17)</td>
<td>HH 3–4</td>
<td>100% clipped</td>
<td>Clazosentan (within 48 hours)</td>
<td>0.2 mg/kg/hr</td>
<td>14 days</td>
<td>Moderate-severe angiographic vasospasm (&gt;33% narrowing) on day 8±1</td>
<td>DI (at 14 days) Adverse events</td>
</tr>
<tr>
<td>Shaw</td>
<td>420 (207/213)</td>
<td>WFNS 2–4</td>
<td>75% clipped</td>
<td>TAK-044 (time n/a)</td>
<td>≤50 mg three times per day</td>
<td>10 days</td>
<td>DND* (classified as “definite” or “probable”) within 3 months</td>
<td>DND (within 10 days) DI (within 3 months) GOS (at 3 months) Adverse events</td>
</tr>
</tbody>
</table>

**Di** indicates delayed infarction; **DIND**, delayed ischemic neurological deficit; **DND**, delayed neurological deficit; **ETRA**, endothelin receptor antagonist; **GOS**, Glasgow Outcome Scale; **HH**, Hunt-Hess grade; **SAH**, subarachnoid hemorrhage; **WFNS**, World Federation of Neurological Surgeons grade.

*Defined as definite if “clinical features confirmed with CT, MRI, postmortem” and probable if “clinical evidence without confirmation by CT, MRI, postmortem.”
†Defined as neurological deterioration (decline ≥2 in GCS or increase ≥2 in NIHSS) with radiographic vasospasm or abnormal transcranial Doppler (Lindegaard ratio ≥3, mean MCA, or ACA velocity >200 cm/sec or increase >50 cm/sec in 24 hours).
‡Defined as need for hemodynamic therapy or angioplasty in presence of radiographic vasospasm or abnormal transcranial Doppler.

Hypotension, pulmonary complications, anemia.

**Figure.** Efficacy of endothelin receptor antagonists in the prevention of delayed ischemic neurological deficits (above) and radiographic vasospasm (below).
Table 2. Critical Appraisal of Randomized Controlled Trials Involving Endothelin-Receptor Antagonists in Patients With Aneurysmal Subarachnoid Hemorrhage

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Sponsor</th>
<th>Jadad Score</th>
<th>Intention-to-Treat Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macdonald</td>
<td>Multi-center North America &amp; Europe</td>
<td>Acetelion</td>
<td>4</td>
<td>Adequate</td>
</tr>
<tr>
<td>Vajkoczy</td>
<td>Multi-center Germany</td>
<td>Acetelion</td>
<td>5*</td>
<td>Adequate</td>
</tr>
<tr>
<td>Shaw</td>
<td>Multi-center Europe</td>
<td>Takeda</td>
<td>4</td>
<td>Not clear</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pharmaceutical</td>
<td>2</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Score upgraded after correspondence with author.
†Data provided for intention-to-treat mortality analysis, but not for other outcomes.

Discussion

Our findings are as follows: First, ETRAs greatly reduce the incidence of radiographic vasospasm. Second, ETRAs significantly reduce the risk of DINDs, a finding that none of the individual trials could previously demonstrate. Third, ETRAs have potentially important adverse effects, including hypotension and pulmonary complications. Fourth, there is currently no evidence that ETRAs improve neurological outcomes. Finally, the observed efficacy and deleterious effects were consistent for both drugs studied, regardless of ET-A receptor selectivity.

Because vasospasm is widely considered to be responsible for DINDs, interventions aimed at ameliorating arterial narrowing have a strong therapeutic rationale. However, additional factors, such as small vessel vasospasm, cortical spreading depression, and thrombosis could also play important roles. The lack of impact of ETRAs on such factors could, in part, explain the discrepancy between their impressive effects on large vessel vasospasm compared with the lack of outcome benefit. Reductions in vasospasm, without any improvement in outcomes, have also been observed with other drugs, including tirilazad and nicardipine.

The multifaceted complexity of caring for critically ill patients makes it difficult to demonstrate the efficacy of any 1 intervention. Assuming that 30% of patients have a poor outcome, even with 867 patients in 3 RCTs, there was still only 35% power to detect a 5% absolute risk reduction.

The adverse effects of ETRAs could neutralize some of their benefit. Hypotension is an undesirable complication in the setting of cerebral ischemia, and occurred 2 to 4 times more often with ETRAs than with placebo. Similarly, pulmonary complications have been associated with worse outcomes after SAH. Even patients treated with the lowest dose of clazosentan were 10 times more likely to develop pulmonary edema. Although fluid retention is thought to be primarily attributable to the renal effects of ET-B blockade, it also appears to occur with highly selective ET-A antagonists. The mechanisms whereby ETRAs might increase the occurrence of pneumonia or acute lung injury (ALI) remain largely unknown. Paradoxically, ETRAs have been suggested as a potential therapy for ALI, because they may accelerate alveolar fluid clearance.

This meta-analysis has several limitations. Although the cumulative number of patients was moderate, the results are based on only 3 studies. Various doses of 2 different drugs were used, 1 of which was a nonselective ETRA. It remains possible that reporting bias could have hindered publication of additional (negative) trials.

Conclusions

ETRAs prevent both radiographic vasospasm and DINDs, but current evidence does not indicate that they improve outcomes. Further evaluation seems justified, but future studies should incorporate well-planned strategies to address the adverse effects of ETRAs to maximize the chance of demonstrating benefit.

Disclosures

None.

References


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