Cerebral vasospasm following aneurysmal subarachnoid hemorrhage (SAH) continues to affect adversely patients harboring ruptured intracranial aneurysms. Contemporary methods of prevention and treatment remain unsatisfactory. The study by Vajkoczy and colleagues reported in this issue presents an important contribution to the management of cerebral vasospasm and provides impetus for future investigation.

Since its original isolation from cultured porcine aortic endothelial cells, endothelin 1 (ET1) has emerged as a central focus in basic vascular biology and clinical medicine. As a consequence of its inherent properties to produce potent and prolonged vasoconstriction, ET1 has been postulated to be a critical mediator in the pathogenesis of cerebral vasospasm. The authors succinctly summarized the possible role of ET1 in vasospasm. Indeed, the role of ET1 appears to be complex. Local cerebrospinal fluid (CSF) and systemic levels of ET1 may be increased in absolute or relative terms (that is, in the setting of abnormal reduced levels of endothelium-derived vasorelaxative factors such as nitric oxide). Changes in the expression of ET1 receptors (particularly ETa receptors) have also been demonstrated. Additionally, sensitivity to ET1 may be altered, further contributing to perturbations favoring vascular constriction. Endothelin 1 is also known to have pleiotropic effects, serving as a mitogen and proinflammatory factor and stimulating other pathways known to play a role in vasospasm such as transactivation of tyrosine kinase receptor pathways.

Vajkoczy, et al., conducted a Phase IIa, multicenter, randomized, double-blind placebo-controlled trial in which they examined the selective ETa antagonist clazosentan in patients with severe aneurysmal SAH. The primary aims of their study were to evaluate the safety and tolerability of clazosentan in patients with aneurysmal SAH and to determine whether this agent could reduce the incidence and/or severity of angiographic vasospasm. Secondarily, the investigators endeavored to evaluate the effect of clazosentan on computerized tomography (CT)–documented ischemic lesions and possible cardiopulmonary hemodynamic effects. Finally, in an exploratory objective, they aimed to assess the effect of this agent on the reversal of angiographic vasospasm.

The authors’ inclusion criteria were clearly outlined. Patients undergoing endovascular treatment of ruptured aneurysms were excluded. These patients presently constitute a significant proportion of all patients undergoing treatment for ruptured aneurysms. Treatment was initiated after surgery, although the rationale for this delay is not clearly detailed. The investigators chose patients at high risk for vasospasm, those with a thick subarachnoid clot, which is understandable for minimizing the number of patients required for meaningful analyses. This also excluded a significant proportion of patients harboring ruptured intracranial aneurysms.

A randomized, double-blind Part A was conducted as well as an open-label Part B for patients with established vasospasm. The authors are to be commended for the excellent design of their study. Their analyses are well conducted and include intent-to-treat and conservative analyses.

Thirty-two patients were retained in the intent-to-treat analysis and 19 patients entered Part B. In Part A, clazosentan treatment markedly reduced the incidence and severity of angiographic vasospasm. In Part B, clazosentan treatment was successful in the reversal of established angiographic vasospasm in 50% of assessable patients who initially received placebo. In patients who initially received clazosentan an escalated dose of clazosentan therapy proved ineffective in altering established vasospasm. Although not statistically significant, there was a trend for the reduced incidence of new infarctions detected by CT scans in the clazosentan group when compared with the placebo group. Importantly, clazosentan proved to be safe and well tolerated, and was devoid of significant side effects, such as systemic hypotension, which have plagued other previously investigated agents.

A limitation of this study is the paucity of clinical data included. The authors chose concrete and easily ascertainable end points as surrogates for clinical outcome. Angiographic evidence of vasospasm is a concrete end point that is frequently seen, particularly in high-risk populations. As the authors discuss, however, many patients with angiographic evidence of vasospasm do not experience symptoms and the effects of this agent on symptomatic vasospasm await further investigation. The incidence of CT-evident ischemic lesions is another concrete end point. As recently demonstrat-
ed by Juvela and colleagues, ischemic lesions do correlate with poor outcome. The authors did not include immediate postoperative control CT scans (that is, those obtained before the period of vasospasm onset). Such studies may have eliminated the confounding variable of surgery-related ischemic lesions. Perhaps some of the “lacunar infarctions” witnessed in the clazosentan group were due to intraoperative events, rather than vasospasm, in which case the margin of difference would have been larger between treatment and placebo groups.

Considerable data have accrued supporting the efficacy of ET antagonists in the prevention and/or treatment of cerebral vasospasm. Nonselective ET<sub>α</sub> receptor antagonists have demonstrated efficacy, although a major clinical trial failed to corroborate the findings of experimental studies. Vajkoczy, et al., discuss the roles of the ET<sub>α</sub> and ET<sub>β</sub> receptors in their current paper, and they outline the rationale for the use of a selective ET<sub>α</sub> antagonist in the present study. Furthermore, they postulate that in the original clinical trial of an ET antagonist treatment may have failed because a nonselective agent was used. Perhaps this is true; however, this is not the entire explanation. Nonselective antagonists have shown efficacy in other cardiovascular disorders such as primary pulmonary hypertension. Moreover, selective ET<sub>β</sub> receptor antagonists have proved to be effective in the treatment of experimental cerebral vasospasm. The fact that clazosentan was both safe and effective in the treatment of cerebral vasospasm may be ascribed to the careful design and conduct of the trial, the theoretical advantages of selective ET<sub>α</sub>, receptor antagonism, the inherent properties of this agent (such as CSF penetration and favorable pharmacokinetics), or combinations thereof. Whatever the reason, it is pleasant to witness an agent experimentally shown to have potential for efficacy prove to be successful clinically, at least in a preliminary study, without being associated with significant side effects including systemic hypotension.

This is a rare and welcome event. Clazosentan needs to be investigated for the treatment of cerebral vasospasm following aneurysmal SAH in a large clinical trial. Such a trial is about to be launched and will include a significant number of participating centers in North America and Europe. This trial includes administration of the agent as soon as possible (before surgery) and the examination of its use in additional patient populations such as patients undergoing endovascular therapy. Furthermore, salvage therapy for reversal of established vasospasm with intravenous and/or intraarterial clazosentan (which should also be devoid of systemic side effects including hypotension) should be investigated in another trial.

The final solution to vasospasm likely will not involve a single “silver bullet” agent but, instead, a multimodal approach aimed at different critical elements in the pathogenesis of vasospasm. Perhaps ultra-early securing of the aneurysm followed by aggressive, early clot disruption will be important initial steps in the prevention of vasospasm. Promising minimally invasive techniques, such as percutaneous intraspinal navigation, may allow atraumatic negotiation of the entire subarachnoid cisternal system with delivery of controlled-release thrombolytics that will reduce or eliminate the burden of the subarachnoid clot (the critical substrate for development of vasospasm). It is likely that immediate administration of an ET antagonist in combination with a vascular antiinflammatory agent to attenuate two critical pathways in vasospasm pathogenesis will also be reasonable.

Although the understanding and treatment of cerebral vasospasm has evolved since 1990, it remains unsatisfactory. Drake’s concluding remarks from the International Vasospasm meeting that year remain pertinent today, “I would caution that vasospasm is still around, it is still alive and living in every neurosurgical unit. Hence, my plea that our scientists not faller or lose interest in the search for a final understanding and solution.” The present work by Vajkoczy and colleagues is an important step in the quest for a final solution for cerebral vasospasm.

References


Editorial