A Phase I proof-of-concept and safety trial of sildenafil to treat cerebral vasospasm following subarachnoid hemorrhage

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OBJECTIVE Studies show that phosphodiesterase-V (PDE-V) inhibition reduces cerebral vasospasm (CVS) and improves outcomes after experimental subarachnoid hemorrhage (SAH). This study was performed to investigate the safety and effect of sildenafil (an FDA-approved PDE-V inhibitor) on angiographic CVS in SAH patients.

METHODS A 2-phase, prospective, nonrandomized, human trial was implemented. Subarachnoid hemorrhage patients underwent angiography on Day 7 to assess for CVS. Those with CVS were given 10 mg of intravenous sildenafil in the first phase of the study and 30 mg in the second phase. In both, angiography was repeated 30 minutes after infusion. Safety was assessed by monitoring neurological examination findings and vital signs and for the development of adverse reactions. For angiographic assessment, in a blinded fashion, pre- and post-sildenafil images were graded as “improvement” or “no improvement” in CVS. Unblinded measurements were made between pre- and post-sildenafil angiograms.

RESULTS Twelve patients received sildenafil; 5 patients received 10 mg and 7 received 30 mg. There were no adverse reactions. There was no adverse effect on heart rate or intracranial pressure. Sildenafil resulted in a transient decline in mean arterial pressure, an average of 17% with a return to baseline in an average of 18 minutes. Eight patients (67%) were found to have a positive angiographic response to sildenafil, 3 (60%) in the low-dose group and 5 (71%) in the high-dose group. The largest degree of vessel dilation was an average of 0.8 mm (range 0–2.1 mm). This corresponded to an average percentage increase in vessel diameter of 62% (range 0%–200%).

CONCLUSIONS The results from this Phase I safety and proof-of-concept trial assessing the use of intravenous sildenafil in patients with CVS show that sildenafil is safe and well tolerated in the setting of SAH. Furthermore, the angiographic data suggest that sildenafil has a positive impact on human CVS.

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KEY WORDS subarachnoid hemorrhage; aneurysm; delayed cerebral ischemia; cerebral vasospasm; vascular disorders

Aneurysmal subarachnoid hemorrhage (SAH) is a significant health care problem with high morbidity and mortality; up to 70% of patients will die or be permanently disabled.33 Prognosis is dependent on a number of factors such as age, presenting neurological status, and development of delayed cerebral ischemia (DCI).4,6,74 Occurring in 30%–40% of patients, DCI is the most common and potentially treatable contributor to outcome.5,57,78

Though the mechanisms underlying DCI are multifactorial, the processes considered most responsible are delayed cerebrovascular vasospasm (CVS), cerebrovascular autoregulatory dysfunction, and cortical spreading ischemia.6,47 Unfortunately, to date few therapies have proven effective for the prevention and treatment of DCI.4,82 A significant predictor of developing DCI is angiographic CVS of intracranial vessels.6,74,77 Approximately
60%–70% of patients will have CVS on digital subtraction angiography (DSA). In those patients, 50% will develop DCI. With this strong correlation, it is recommended that CVS be used as an initial outcome measure when assessing potential treatments for DCI. However, as research continues to elucidate the multifactorial nature of DCI, future interventions will need to target not only CVS, but other contributors to DCI as well.

We hypothesize that one such therapeutic target is phosphodiesterase-V (PDE-V) inhibition. PDE-V is the regulatory enzyme of the endothelial nitric oxide synthase→nitric oxide→cyclic guanosine monophosphate (eNOS-NO-cGMP) pathway. Decreased functionality of this pathway following SAH has been linked to the pathophysiology of DCI including CVS. Studies investigating the eNOS-NO-cGMP pathway have shown that inhibition of PDE-V has substantial beneficial effects. In animal SAH studies, PDE-V inhibition (mainly via administration of sildenafil, an FDA-approved selective PDE-V inhibitor) acutely reverses SAH-induced CVS, reduces neuronal cell death, restores impaired autoregulatory mechanisms, and improves neurological outcomes. In SAH patients, sildenafil has been shown to improve transcranial Doppler flow velocities. Beyond this, there are data suggesting that sildenafil beneficially affects additional contributors of brain injury after SAH. In studies of SAH in animals, sildenafil has shown to reduce plasma levels of endothelin-1, limit platelet induced microthrombosis, and promote cerebral angiogenesis in hypoxic areas.

Sildenafil has been extensively studied and proven safe in both healthy and cardiovascularly ill patients. However, to date there have been no studies in humans providing rigorous data on the safety of sildenafil in the setting of SAH. The primary objective of this study is to assess the safety of intravenous sildenafil in patients with SAH-induced CVS. Second, as a proof-of-concept, we looked to determine the ability of sildenafil to reverse CVS.

Methods

Study Design and Patient Population

A Phase I prospective, nonrandomized human trial with intravenous sildenafil using a dose escalation scheme (10 mg or 30 mg) was implemented (Fig. 1). Figure 2 shows the timeline for patient enrollment and study completion. The protocol was reviewed and approved by the study institution’s human research protection office. The US Food and Drug Administration granted an exemption from investigational new drug regulations. The trial was monitored by an independent Data Safety Monitoring Board (DSMB), led by a senior neurosurgeon with expertise in SAH management and clinical trials.

Patients admitted within 72 hours of an aneurysmal SAH were recruited from September 2011 through May 2013. Screening criteria included 1) age ≥ 21 years, 2) surgical or endovascular repair of the ruptured aneurysm, 3) modified Fisher Grade I to IV hemorrhage on initial CT imaging, and 4) CVS on DSA. Exclusion criteria were 1) pregnancy, 2) SAH secondary to traumatic or mycotic aneurysm, 3) preictal sildenafil therapy, 4) contraindications to sildenafil therapy: use of nitrates and patients with left ventricular outflow obstruction, and 5) insufficient CVS on screening DSA.

Study Interventions

Per our established clinical protocol for SAH man-
The duration of hypotension was also recorded as time to return to within 10% of baseline MAP. An adverse event related to hypotension was defined as either a decline in MAP < 70 mm Hg or a decline in MAP that resulted in worsened neurological examination findings. As a comparison with sildenafil’s effect on MAP, we analyzed the impact of nimodipine by measuring patients’ prenimodipine and 1-hour postnimodipine MAP. Elevated ICP was considered as pressure > 25 mm Hg for longer than 5 minutes. Further adverse events (those previously associated with sildenafil), for which patients were monitored, included priapism, visible flushing, and visual disturbances. After the procedure, monitoring of the patients continued in the NNICU with continuous vital sign monitoring and hourly neurological checks. Complete neurological and physical examinations were completed immediately prior to DSA, 1 hour post-sildenafil, and 12 hours post-sildenafil by a study physician.

Radiological CVS Assessment

At the time of the screening DSA, images were evaluated by one of the 3 neuroradiologists (D.T.C., C.P.D., and C.J.M.), and vasospasm was quantified as follows: comparing the screening angiogram to the admission angiogram, CVS in the internal carotid, basilar, middle, anterior, and posterior cerebral arteries was defined based on percent reduction in caliber size as none, mild (< 50% narrowing), moderate (50%–70% narrowing), and severe (> 70% narrowing). For each patient the most significant percent reduction of caliber size in any single vessel was the recorded degree of CVS. Vessel measurements were made using software on the Axiom Artis unit (Siemens Healthcare).

Postprocedural analyses of DSA images to determine whether patients showed any evidence of response to sildenafil were completed by 2 authors (C.P.D. and C.W.W.). In a blinded fashion, reviewers labeled images as “admission,” “pre-sildenafil,” and “post-sildenafil.” After labeling, images were compared and subjectively graded as “improvement” or “no improvement” in vasospasm.

A quantitative analysis of images was carried out to determine the magnitude of response. Unblinded measurements of vessel diameter were made on the admission, pre-sildenafil, and post-sildenafil DSA images. Measurements were made in millimeters at the highest degree of stenosis in each of the supraclinoidal segment of the internal carotid artery (ICA), A1 and A2 segments of the anterior cerebral artery, the M1 and M2 segments of the

Study Start

September 2011

PHASE I

Interim Analysis

PHASE II

Study Completion

May 2012

November 2012

May 2013

FIG. 2. Timeline for patient enrollment and study completion.
middle cerebral artery (MCA), the basilar artery, and posterior cerebral arteries. The petrous ICA or the cervical vertebral artery was used as a reference to correct for magnification. Change in stenosis was calculated in millimeters and by percent change from pre-sildenafil baseline measurements. For each patient the largest improvement in any single vessel was the recorded response.

**Statistical Analysis**
All statistical analyses were completed using SAS (version 9.3, SAS Institute Inc.). Comparisons of continuous patient data pre- and post-sildenafil used a paired t-test, whereas comparisons made across low-dose and high-dose groups used a 2-sample t-test. Categorical variables across groups were compared using Fisher’s exact t-test. For statistical tests, significance was defined as p < 0.05.

**Results**

**Patient Population**
Twenty-four patients provided consent for the study, and 12 were excluded for not undergoing repeat DSA (n = 2) or having insufficient degree of angiographic vasospasm (n = 10). Twelve patients received sildenafil; 5 (42%) were in the low-dose (10 mg) group and 7 (58%) were in the high-dose (30 mg) group. Demographic data are provided in Table 1. Most patients (66%) were in Hunt and Hess Grade III or IV, and 92% of patients had modified Fisher Grade III or IV SAH.

**Safety and Tolerability**
There were no adverse pulmonary or neurological events. All patients accessible for subjective assessment tolerated the doses without complaint of worsening headache, flushing, or visual changes. All neurological examination findings remained stable. One patient showed improvement after infusion, with resolution of a pronator drift.

Data regarding blood pressure, ICP, and heart rate can be found in Table 2. (With the following data, averages are given with standard deviations in parentheses.) Ten of 12 patients (83%) developed hypotension following sildenafil, with greatest decline in MAP an average of 17% (SD 9%) below baseline. The change was transient in all cases, with return to baseline occurring by an average of 18 (SD 15) minutes. The magnitude of this decline was not significantly different from that seen in patients following nimodipine, which was an average of 11% (SD 6). There were no differences in the degree of hypotension between low- and high-dose groups, and return to baseline MAP occurred by 16 and 20 minutes, respectively (differences all nonsignificant). No patient had a hypotension-related adverse event.

There was no significant change between pre- and post-sildenafil ICP or heart rate. No patient had elevated ICP within the 24-hour period following sildenafil therapy.

**Angiographic CVS**
Individual angiographic data for patients are shown in Table 3. Of the 12 patients completing the study, 1 (8%) had mild, 6 (50%) moderate, and 5 (42%) severe CVS on pre-sildenafil DSA. Angiography occurred on average at posthemorrhage Day 7 (range Days 5–10). Eight (67%) were found to have a positive angiographic response to sildenafil [3 (60%) in the low-dose group and 5 (71%) in the high-dose group [difference in response rate not significant]]. No patient was found to have worsening CVS following sildenafil infusion. Examples of angiographic improvement are seen in Figs. 3 and 4.

The largest degree of vessel dilation, across all patients (both low- and high-dose groups), was an average of 0.8 mm (range 0–2.1 mm). This corresponded to an average percentage increase in vessel diameter of 62% (range 0%–200%). When considering only patients identified as angiographic responders, the average dilation was 1.1 mm in the low-dose group and 1.2 mm in the high-dose group.

**Discussion**
The data from this Phase I clinical trial investigating the use of sildenafil for the treatment of angiographic CVS

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**Table 1. Patient demographics and admitting characteristics**

<table>
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<th>Variable</th>
<th>Value</th>
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<td>Mean age in yrs (range)</td>
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<td>Sex</td>
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<tr>
<td>Male</td>
<td>6 (50)</td>
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<td>Female</td>
<td>6 (50)</td>
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<td>V</td>
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<td>Hydrocephalus on admission</td>
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<table>
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<td>IV</td>
<td>5 (42)</td>
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ACoA = anterior communicating artery; OphA = ophthalmic artery; PCoA = posterior communicating artery; PICA = posterior inferior cerebellar artery.

* Values are number of patients (%) unless stated otherwise.
provide the first evidence that sildenafil in the setting of aneurysmal SAH is both safe and well tolerated. This is the first study to demonstrate in a rigorous fashion that sildenafil has a beneficial effect on CVS in humans.

In evaluating the safety of sildenafil in this patient population, our primary concern was that it would induce unacceptable hypotension. We have seen from other promising trials that hypotension is a potential confounder affecting patient outcomes.\textsuperscript{48,49,51} We have shown that at both a low dose (10 mg) and a high dose (30 mg), the blood pressure profile is acceptable without evidence of a prolonged adverse effect. While there was a decline in MAP by an average of 17\%, this was transient with a rapid return to baseline within an average of 18 minutes (Table 2). There was no evidence that this response was dose dependent. When comparing the mild hypotension after sildenafil to that encountered after nimodipine, we found no significant difference between the 2 drugs (Table 2). Furthermore, the hypotension seen after nimodipine developed 1 hour following ingestion, whereas with sildenafil all patients had returned to baseline within 1 hour. Other encouraging data suggesting the safety of sildenafil in the SAH patients are the lack of an adverse impact on ICP and/or cardiopulmonary status. Furthermore, previously described issues surrounding its tolerability (flushing, headaches, visual decline, and etc.) were not encountered.

Angiographically, 62\% of patients demonstrated a positive response. There was no significant variance related to dose. Though the degree of vessel dilation was modest in absolute magnitude (average improvement of 0.8 mm; 62\% increase in vessel diameter), when comparing this intravenously dosed medication to reported response rates for intraarterial papaverine and verapamil (response rates of 67\%–98\%; vessel diameter increases of 26\%–44\%),\textsuperscript{16,43,54} our observed response to sildenafil was quite promising. It should be noted that the angiographic effects reported here were focal areas of dilation in specific vasospastic vessels (Figs. 3 and 4); the response was not necessarily a global

<table>
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<tr>
<th>Case No.</th>
<th>Sildenafil Dose (mg)</th>
<th>Maximum Drop in MAP (% from baseline)</th>
<th>Time to Return to Baseline MAP (mins)</th>
<th>Drop in MAP Post-Nimodipine (% from baseline)</th>
<th>Pre-Sildenafil ICP (mm Hg)</th>
<th>Post-Sildenafil ICP (mm Hg)</th>
<th>Pre-Sildenafil Heart Rate (bpm)</th>
<th>Post-Sildenafil Heart Rate (bpm)</th>
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**TABLE 3. Angiographic data**

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<tr>
<th>Case No.</th>
<th>Vasospasm Grade</th>
<th>Sildenafil Dose (mg)</th>
<th>Improve Post-Sildenafil</th>
<th>Maximum Dilatation (mm)</th>
<th>Maximum Dilatation (%)</th>
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<tr>
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<td>Moderate</td>
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NR = nonresponder.
improvement in the degree of vasospasm. Therefore, we are not claiming that our results prove that sildenafil “reverses” CVS, but we do believe our findings demonstrate a “proof-of-concept” that sildenafil is acting in positive way on the pathophysiology of cerebral vasospasm.

Sildenafil as Treatment for DCI

The vasodilatory effect seen with sildenafil has been primarily attributed to its modulation of the eNOS-NO-cGMP pathway. It has long been understood that a significant component of the development of SAH-induced CVS has been the dysfunction of the eNOS-NO-cGMP pathway, and numerous interventions designed to upregulate this pathway have been shown to improve CVS in preclinical and, at times, clinical studies. The majority of these interventions have targeted the upstream elements of this molecular cascade (eNOS and NO). Results from these upstream therapeutic approaches, however, have been disappointing due to a lack of specific and effective eNOS agonists as well as a myriad of difficulties associated with NO-directed therapies including the short half-life of available NO donors and the substantial systemic side effects such agents often induce. As a result, many investigators have begun to target the downstream element of the eNOS-NO-cGMP pathway by administering PDE-V inhibitors like sildenafil as a means for inhibiting SAH-induced CVS and DCI.

In animal studies, PDE-V inhibition attenuates or acutely reverses SAH-induced CVS, and sildenafil-induced neuronal cell death, and improves post-SAH neurological outcome. PDE-V inhibition has also been shown to augment autoregulatory vasodilatation in humans without SAH and, in a rat model of SAH, restore impaired autoregulatory mechanisms. More recently in SAH patients, sildenafil has been shown to have a positive effect on transcranial Doppler flow velocities in refractory CVS.

The hypothesized mechanism through which sildenafil and other PDE-V inhibitors exert their beneficial vascular effects has been in their ability to increase intracellular cGMP levels in vascular smooth muscle cells, and, as a result, normalize vascular tone. However, there are other pathways through which PDE-V inhibition may also be acting. Endothelin-1, a potent cerebral vasoconstrictor, has been strongly implicated in early brain injury, CVS, and ultimately DCI following aneurysmal SAH. Studies evaluating endothelial function in erectile dysfunction and pulmonary hypertension have demonstrated that sildenafil substantially reduces endothelin-1 levels. The development of platelet-induced microthrombi within the microvasculature has also been implicated in DCI, and sildenafil has been shown to limit this prothrombotic cascade. Lastly, when cerebral blood flow to an area decreases to ischemic levels, sildenafil has demonstrated the ability to decrease the size of the infarct and improve outcomes by promoting angiogenesis in hypoxic areas. Each of these pathways

FIG. 3. A: The anteroposterior DSA image of a left carotid artery injection prior to sildenafil. B: The anteroposterior DSA image of the same left carotid artery following sildenafil infusion. C: A zoomed image of the pre-sildenafil angiogram, showing severe CVS of the left A1 and A2 segments of the anterior cerebral arteries (white arrows). D: Demonstrates areas of dilation in the proximal left A1 (dotted arrow) and A2 (solid arrow) segments of the anterior cerebral artery post-sildenafil.

FIG. 4. A: The lateral DSA image of a left carotid artery injection prior to sildenafil. B: Lateral DSA image of the same left carotid artery following sildenafil infusion. C: A zoomed image of the pre-sildenafil angiogram showing a focal area of stenosis in the superior M2 division of the middle cerebral artery (arrow). D: Improvement in the vasospasm is seen in the M2 segment of the MCA following sildenafil infusion. The focal area of stenosis has resolved (arrow).
represents future areas of study in determining sildenafil’s role in treating DCI.

Study Limitations

The aims of this study were to assess the safety of sildenafil in SAH patients with CVS and to determine whether sildenafil results in a positive angiographic response. With the prescribed doses (10 mg and 30 mg), we were able to achieve both goals. However, it is possible that sildenafil was under-dosed. Studies evaluating safety and efficacy in pulmonary hypertension, have determined that oral dosing up to 300 mg/day in divided doses (comparable to 150 mg/day intravenously) can be achieved safely.24,67 Our initial concern was that the systemic vasodilatation would result in an unacceptable degree of hypotension and/or an adverse impact on ICP. Since we have now demonstrated that a single infusion is well tolerated, future studies will need to increase the prescribed dosage level in combination with changing the dosing scheme to daily divided doses continuing through the vasospasm window.

Second, the relatively small number of patients included in our study precludes us from making definitive conclusions regarding sildenafil’s impact on CVS and neurological outcomes. Assessing neurological outcome was outside the scope of this Phase I trial. Also, as we have previously discussed, our angiographic analysis was a proof-of-concept, being used to demonstrate a positive physiological response in the setting of CVS. Future clinical trials will need to be randomized and adequately powered to make meaningful assessments as to the effects of sildenafil on CVS and patient outcomes.

Conclusions

The results from this Phase I safety and proof-of-concept trial assessing the use of intravenous sildenafil in patients with angiographic CVS show that sildenafil is safe and well tolerated in the setting of SAH. Furthermore, the angiographic data are the first of its kind to provide evidence that sildenafil has a positive impact on CVS. This information, along with the substantial amount of preclinical data in SAH studies and sildenafil’s proven track record in treating other pathophysologies related to vascular endothelium dysfunction, provides a strong rationale for future clinical investigations into its effectiveness in preventing and treating SAH-related DCI.

Acknowledgments

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Disclosure
Dr. Derdeyn reports that he has ownership in Pulse Therapeutics and is a consultant for MicroVention and Penumbra.

Author Contributions
Conception and design: Washington, Derdeyn, Han, Vellimana, Zipfel. Acquisition of data: Washington, Arias, Cross, Moran. Analysis and interpretation of data: Washington, Derdeyn, Dhar. Drafting the article: Washington. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Washington. Statistical analysis: Washington. Study supervision: Washington, Zipfel.

Supplemental Information
Previous Presentation
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