Selective Serotonin Reuptake Inhibitors and Risk of Hemorrhagic Stroke

Jordan Kharofa, BS; Padmini Sekar, MS; Mary Haverbusch, RN, BSN; Charles Moomaw, PhD; Matthew Flaherty, MD; Brett Kissela, MD; Joseph Broderick, MD; Daniel Woo, MD, MS

Background and Purpose—Selective serotonin reuptake inhibitors (SSRI) are widely prescribed. Several reports have observed an increased bleeding risk associated with SSRI use, which is hypothesized to be secondary to their antiplatelet effect.

Methods—We tested the hypothesis that SSRIs increase the risk for or potentiate the risk of hemorrhagic stroke associated with antiplatelets and anticoagulants.

Results—In multivariate analysis, we found no increased risk associated with SSRI use for intracerebral hemorrhage (odds ratio=1.1, 95% CI: 0.7 to 1.8; \( P=0.63 \)) or subarachnoid hemorrhage (odds ratio=0.6, 95% CI: 0.4 to 1.0; \( P=0.054 \)). In addition, potentiation of risk with warfarin or antiplatelets was not observed.

Conclusions—Further studies with larger populations would be needed to exclude a small increase in intracranial hemorrhage risk with SSRI use. (Stroke. 2007;38:000-000.)

Key Words: hemorrhage ■ SSRI ■ stroke

Approximately 99,000 hemorrhagic strokes occur each year in the United States, accounting for 10% to 15% of all strokes. Known risk factors for hemorrhagic stroke include increasing age, prior ischemic stroke, hypertension, smoking, and treatment with antiplatelet and antiplatelet medications. Between 1988 and 2002, 67.6 million new patients were started on the selective serotonin reuptake inhibitors (SSRI) fluoxetine, paroxetine, and sertraline. Thus, a potential effect of SSRIs on bleeding risk is of major significance.

Serotonin is released by platelets at the site of vascular injury to promote clot formation. When the endothelial layer is damaged, platelets come in contact with subendothelial collagen, which leads to release of intracellular serotonin granules that promote clot formation. Platelets contain a serotonin reuptake transporter that is similar to that in the brain. It has been demonstrated that SSRIs inhibit this transporter in platelets. One study demonstrated an 83% decrease in platelet serotonin concentrations after 2 weeks of therapeutic paroxetine administration. We tested the hypothesis that SSRIs increase the risk for hemorrhagic stroke and potentiate the risk associated with antiplatelet and anticoagulant drugs.

Methods

As part of our Genetic and Environmental Risk Factors for Hemorrhagic Stroke study (NS36695), cases of intracerebral (ICH) and subarachnoid hemorrhage (SAH) were identified in the Greater Cincinnati region from May 1997 to August 2001 and from July 2002 to October 2005 through retrospective screening of all area emergency rooms and discharge ICD-9 codes and prospective screening of neurosurgery admissions at the busiest hospitals. Patients were approached for enrollment in a genetic sampling and interview arm. Subjects who agreed were matched by age, race, and gender to population-based controls by random digit dialing. All medications taken 2 weeks before index date were recorded. The index date for cases was the date of onset; for controls it was 1 to 2 weeks before the interview, to avoid recall bias. SSRIs used for the current analysis included citalopram, escitalopram, fluoxetine, paroxetine, and sertraline. Classification of antiplatelet drugs included aspirin, clopidogrel, and dipyridamole. Because of the small number of subjects on both nonaspirin antiplatelet drugs and SSRIs (5 patients), the analysis was limited to aspirin alone.

Statistical Analysis

The data were managed and analyzed using SAS version 9.1 (SAS Institute). Univariate and multivariable analysis for the association of independent variables with stroke was achieved using a conditional logistic modeling approach (PROC LOGISTIC). The multivariable analysis used a backward elimination procedure for risk factors with significance levels of \( P<0.10 \). Interaction terms of SSRI with and without aspirin or warfarin use were included into secondary models.

Results

During the study period, 2441 patients with ICH and 894 patients with SAH were identified, of which 500 ICH (20%) and 416 SAH (46.5%) cases were enrolled in the case-control study. Comparison of interviewed and noninterviewed patients found that interviewed patients were younger for both SAH (50.9 versus 57.7 years) and ICH (65 versus 70.2 years). After adjustment for age, there was no significant difference in the prevalence of hypertension, diabetes, heavy alcohol usage, and smoking.

Received April 17, 2007; accepted April 27, 2007.

From the Department of Neurology, University of Cincinnati, Ohio.
Correspondence to Daniel Woo, MD, Department of Neurology, University of Cincinnati, 231 Albert Sabin Way, Cincinnati, OH 45267-0525. E-mail: Daniel.woo@uc.edu

© 2007 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.107.491472
A growing number of case reports attribute bleeding events to SSRI use. Sites of bleeding include genitourinary, respiratory, and gastrointestinal systems. Two population-based cohort studies found SSRI users were more likely to be hospitalized for gastrointestinal bleeding than nonusers. Both studies found that the bleeding risk of aspirin was potentiated by SSRI treatment.

Our results are in accordance with 2 prior reports which assessed intracranial bleeding risk associated with SSRIs. A nested case-control study in a cohort of antidepressant users found no association between SSRI use and intracranial hemorrhage. Although no increased risk of hemorrhage was observed, the study identified only 65 cases of hemorrhage of which 7 were exposed to SSRIs. Another nested case-control study based on information from a patient registry concluded that SSRI exposure was not a risk factor for ICH. The present study includes a larger number of SSRI-exposed cases of hemorrhagic stroke (n=71) and controls and a more comprehensive list of relevant risk factors. Our results strengthen the argument that SSRI use does not lead to an increased risk of hemorrhagic stroke. After an ischemic stroke, many patients experience depression and are frequently placed on an SSRI along with antiplatelet or anticoagulant drugs, and our findings provide reassurance that no major increase in hemorrhage risk is expected.

A limitation is that our study had 81% power to detect an OR of 1.6 or greater and a smaller risk may not have been detected. Although our interviewed cases were similar to noninterviewed cases, they were slightly younger. Thus, our study may miss an increased risk of hemorrhagic stroke with SSRI use among an older population.

Further study is needed to determine whether SSRI use increases the risk of hemorrhage among patients with a prior ischemic stroke or has a small effect on risk.

### Discussion

We did not find an increased risk of hemorrhagic stroke or its subtypes with SSRI use, nor did we find evidence that SSRIs potentiate the bleeding risk conferred by warfarin or aspirin. These results are important given the widespread use of SSRIs, the prior reports of systemic bleeding complications, and the specific use of SSRI for poststroke depression.

### Table. All Hemorrhagic Strokes: Univariate and Multivariate Risks

<table>
<thead>
<tr>
<th>Variables</th>
<th>No.</th>
<th>Controls, n (%)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>71 (7.8)</td>
<td>158 (8.9)</td>
<td>0.9 (0.6–1.2)</td>
<td>0.300</td>
<td>0.8 (0.5–1.2)</td>
<td>0.254</td>
</tr>
<tr>
<td>Frequent alcohol</td>
<td>84 (9.2)</td>
<td>92 (5.2)</td>
<td>1.9 (1.4–2.6)</td>
<td>&lt;0.001</td>
<td>1.7 (1.2–2.5)</td>
<td>0.003</td>
</tr>
<tr>
<td>Warfarin</td>
<td>77 (8.4)</td>
<td>43 (2.4)</td>
<td>4.1 (2.7–6.3)</td>
<td>&lt;0.001</td>
<td>3.2 (2.0–5.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart disease</td>
<td>208 (22.7)</td>
<td>270 (15.2)</td>
<td>1.6 (1.3–2.0)</td>
<td>&lt;0.001</td>
<td>1.4 (1.1–1.8)</td>
<td>0.011</td>
</tr>
<tr>
<td>History of ischemic stroke</td>
<td>60 (6.7)</td>
<td>30 (1.7)</td>
<td>4.5 (2.8–7.2)</td>
<td>&lt;0.001</td>
<td>3.7 (2.1–6.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>27.5 (6.6)</td>
<td>28.5 (6.6)</td>
<td>0.98 (0.96–0.99)</td>
<td>&lt;0.001</td>
<td>0.97 (0.96–0.99)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treated hypertension</td>
<td>326 (35.6)</td>
<td>634 (35.7)</td>
<td>1.3 (1.1–1.6)</td>
<td>0.004</td>
<td>1.4 (1.1–1.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Untreated hypertension</td>
<td>200 (21.8)</td>
<td>135 (7.6)</td>
<td>3.9 (3.0–5.0)</td>
<td>&lt;0.001</td>
<td>3.5 (2.6–4.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia with statin</td>
<td>125 (13.7)</td>
<td>328 (18.5)</td>
<td>0.6 (0.5–0.8)</td>
<td>&lt;0.001</td>
<td>0.5 (0.4–0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypercholesterolemia with nonstatin</td>
<td>10 (1.1)</td>
<td>25 (1.4)</td>
<td>0.6 (0.3–1.4)</td>
<td>0.234</td>
<td>0.4 (0.1–0.9)</td>
<td>0.036</td>
</tr>
<tr>
<td>Current smoker</td>
<td>362 (39.5)</td>
<td>433 (24.4)</td>
<td>2.2 (1.8–2.7)</td>
<td>&lt;0.001</td>
<td>1.8 (1.4–2.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Former smoker</td>
<td>249 (27.2)</td>
<td>627 (35.3)</td>
<td>0.9 (0.7–1.1)</td>
<td>0.224</td>
<td>0.9 (0.7–1.1)</td>
<td>0.240</td>
</tr>
<tr>
<td>Less than high school education</td>
<td>218 (23.8)</td>
<td>193 (10.9)</td>
<td>3.2 (2.5–4.1)</td>
<td>&lt;0.001</td>
<td>2.7 (2.1–3.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High school education</td>
<td>352 (38.4)</td>
<td>612 (34.5)</td>
<td>1.7 (1.4–2.0)</td>
<td>&lt;0.001</td>
<td>1.5 (1.2–1.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Disclosures

None.

References

Selective Serotonin Reuptake Inhibitors and Risk of Hemorrhagic Stroke
Jordan Kharofa, Padmini Sekar, Mary Haverbusch, Charles Moomaw, Matthew Flaherty, Brett Kissela, Joseph Broderick and Daniel Woo

Stroke. published online September 27, 2007;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2007/09/27/STROKEAHA.107.491472.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/