Stroke Associated With Sympathomimetics Contained in Over-the-Counter Cough and Cold Drugs

Carlos Cantu, MD, MSc; Antonio Arauz, MD, MSc; Luis M. Murillo-Bonilla, MD; Mario López, MD; Fernando Barinagarrementeria, MD

Background and Purpose—Phenylpropanolamine (PPA) and pseudoephedrine are sympathomimetics contained in over-the-counter cold preparations. A case-control study linked PPA use with hemorrhagic stroke in women. Twenty-two patients with stroke associated with use of these drugs are described.

Methods—In a consecutive stroke registry since 1988, 22 patients had stroke associated with over-the-counter sympathomimetics. Sympathomimetic dosage and type, time interval until stroke onset, and neuroimaging findings are described.

Results—Ten male and 12 female patients were included. Intracerebral hemorrhage occurred in 17 patients, subarachnoid hemorrhage in 4, and ischemic stroke in 1. Stroke was associated with PPA use in 16 patients (dose 75 to 675 mg), with pseudoephedrine in 4 (dose 60 to 300 mg), and with others administered by the nasal route in 2 (oxymetazoline and phenylephrine). Stroke occurred after a single dose in 17 patients and after daily use during several days in 5. The interval between drug exposure and clinical onset varied from 30 minutes to 24 hours. Stroke occurred after recommended doses of PPA (50 to 75 mg) in 32% and pseudoephedrine (60 mg) in 50% of patients. Eight patients had acute hypertension at stroke onset. Cerebral angiography was normal in 8 cases and showed diffuse vasospasm or beading in 10 patients.

Conclusions—Stroke related to over-the-counter sympathomimetics was associated with acute hypertension and/or vasospasm or angiitis mechanisms, most related to the use of PPA; however, stroke also occurred with the use of other sympathomimetics, particularly pseudoephedrine. Although stroke complications occurred when doses were used that were higher than recommended doses, apparently there is also a stroke risk when these agents are taken properly. (Stroke. 2003;34:1667-1673.)

Key Words: phenylpropanolamine stroke sympathomimetics

Phenylpropanolamine (PPA) and ephedrine are sympathomimetic amines structurally similar to amphetamines. PPA and pseudoephedrine are contained in many over-the-counter cough and cold preparations. Pseudoephedrine is also a bronchodilator and nasal vasoconstrictor, and it is generally harmless when used in recommended doses. Since 1979, many case reports have described the occurrence of intracranial hemorrhage after the ingestion of PPA or other synthetic sympathomimetics. In a controlled trial, Korn et al found that PPA contained in appetite suppressants, and perhaps in cough and cold preparations, represents an independent risk factor for hemorrhagic stroke. The first 2 cases of PPA-related hemorrhagic stroke in our hospital were described >10 years ago. Since then, information on the intake of sympathomimetic agents is systematically obtained in all patients with stroke. The objective of this study was to describe the clinical, neuroimaging, and prognostic findings in 22 patients with stroke associated with the use of over-the-counter sympathomimetics.
because it was not considered necessary by the primary care neurologist (n=2).

The information regarding doses and type of sympathomimetic agent was obtained prospectively. In each patient, the interval between exposure and stroke onset was determined. Exposure to an over-the-counter cough and cold preparation was considered when the patient had used the product within 24 hours before the stroke onset. Information regarding blood pressure (BP) on admission was obtained retrospectively from the medical records. In addition, the neuroradiological findings, particularly angiographic findings, were evaluated. The outcome was assessed at discharge and classified according to the modified Rankin Scale.22 Stroke was considered to be related to over-the-counter cough and cold sympathomimetic agents when 2 conditions were fulfilled: (1) a close relationship existed between drug ingestion and stroke development, as described above; and (2) other known causes of stroke were excluded by appropriate diagnostic tests, as previously reported in our stroke clinic in young patients with stroke.23,24

Results

Of the 22 patients, 21 had a hemorrhagic stroke (95%), and only 1 had an ischemic stroke (5%). Sixteen of the 21 hemorrhagic strokes were intracerebral (76%), 4 were subarachnoid (19%), and 1 included both types of hemorrhage. Table 1 shows the details of each patient. Figures 1 to 3 illustrate the neuroimaging findings of representative cases. Ten patients were male (mean age, 33.5 years; range, 17 to 57 years), and 12 were female (mean age, 43.7 years; range, 19 to 78 years). Seventeen patients (77%) were aged <50 years. Traditional vascular risk factors were uncommon (alcohol use in 4 cases, tobacco use in 2, and systemic hypertension in 2). One cerebrovascular event occurred from a suicide attempt. Only 1 had a prior history of substance abuse (sniffing of glue and other solvents). Structural brain lesions associated with hemorrhagic stroke (arteriovenous malformation, tumor, or aneurysm) were excluded in these 22 patients.

Dosage of Sympathomimetics and Interval Until Stroke

Sixteen patients received PPA, 4 pseudoephedrine, 1 phenylephrine, and 1 oxymetazoline. The last 2 agents were used by the nasal route. Doses of PPA fluctuated between 50 and 675 mg. Three patients were given a single recommended dose of PPA (50 to 75 mg), 6 received a single double dose (150 to 185 mg), and 4 were given a single excessive dose of PPA (450 to 675 mg). Three other patients received PPA daily during several days before stroke: 2 in recommended doses (75 mg BID) and 1 in double doses (150 mg BID). PPA contained in the cough/cold preparations was usually combined with 1 or more additional drugs, ordinarily an antihistamine: chlorpheniramine in 7 patients, brompheniramine in 6, and dextromethorphan plus guaifenesin in 2.

The doses of pseudoephedrine fluctuated between 60 and 300 mg. One patient was given a single regular dose, 2 received a single but excessive dose, and 1 took recommended doses of pseudoephedrine daily during 1 week. In regard to sympathomimetics used by the nasal route, 1 patient received regular doses of oxymetazoline using a nasal spray during 1 week, and 1 had a prior history of systemic hypertension and had been using nasal phenylephrine TID during 4 months.

The interval between the exposure to the sympathomimetic and stroke onset was 30 minutes to 3 hours in 8 patients, 3 to 6 hours in 5 patients, and 6 to 24 hours in 9 patients.

Stroke Features and Clinical Outcome

The most common location for intracerebral hemorrhage was lobar in 8 patients, usually involving the frontal lobe. Additional locations included putaminal/capsular in 5 patients, thalamic in 2, and caudate in 2. Intraventricular extension occurred in 7 patients. The only ischemic stroke involved the vertebrobasilar distribution; initially the patient developed “top of basilar artery” symptoms, and subsequently right occipital and thalamic infarctions were documented.

High BP was common during admission (90% of patients). Persistent and uncontrolled hypertension (systolic BP >180 mm Hg and/or diastolic BP >110 mm Hg) was documented in 8 cases, including 3 patients using a single low dose of the sympathomimetic drug. Both patients with hypertension history took antihypertensive treatment regularly. They developed a severe hypertensive crisis (BP ≥220/110 mm Hg): one of them took regular daily doses of pseudoephedrine during the previous week, and the other received daily nasal phenylephrine as a decongestant during 4 months. No information about whether the 6 other patients who developed acute hypertension had previously documented labile hypertension was available. However, a pheochromocytoma was diagnosed in 1 patient 2 years later.

Cerebral angiography was normal in 8 patients and showed “vasculitis-like” abnormalities in 10 patients (45%). These features included widespread segmental narrowing and beading, usually in both the carotid and vertebrobasilar territories. Cerebral vascular abnormalities were observed at the main stem of the basal arteries, major branches, or small arteries (Figures 1 to 3). There was no clinical or laboratory evidence of other disorders that explained the “vasculitic” changes seen on cerebral arteriography. These patients usually had spontaneous clinical improvement without using immunosuppressive agents. Moreover, in 4 patients with follow-up DSA, complete resolution of the arterial abnormalities was documented. At discharge, the clinical outcome was total recovery in 11 patients, mild disability in 7, moderate disability in 2, and death in 2 patients.

Discussion

This study found that 22 of 2500 consecutive stroke patients in a neurological reference center had a stroke after using an over-the-counter cough and cold sympathomimetic drug. These were implicated in 2.5% of the patients with intracerebral hemorrhage and in 8.1% of the cases with nonaneurysmal SAH in our stroke registry. Although most were related to PPA, stroke can also occur with the use of other sympathomimetics, particularly pseudoephedrine. We found 39 cases reported in the literature: 31 associated with the use of PPA2–10,19–21,25–40; 4 with pseudoephedrine, ephedrine, and ephedra alkaloid derivatives16,41–43; 2 with phentermine44,45; and 2 with sympathomimetics used by the nasal route (oxymetazoline and fenoxazoline).46,47

PPA use is associated largely with the occurrence of intracranial hemorrhage21,26,27 and only occasionally with
development of an ischemic stroke. Only 1 of the 16 patients in our series had an ischemic stroke, and only 2 cases are described in 31 previous reports. Table 2 compares several features of the PPA-related cases in this series with other previously described patients and with the cases described by Kernan et al. The latter authors showed that the use of appetite suppressants containing PPA by young women was associated with an increased risk of hemorrhagic stroke. Because no male subject reported the use of appetite suppressants containing PPA, the authors could not determine
whether men were at increased risk for hemorrhage under such condition. The study of Kernan et al did not establish cold remedies as risk factors for hemorrhagic stroke. However, this study suggests that an additional association exists between this disorder and the first application of PPA contained in cough or cold preparations only among female patients. Although the stroke risk is more obvious when PPA is used as a chronic appetite suppressor, 15 of 16 cases in our series were related to PPA used as a cold remedy. Additionally, the fact that >40% of the cases included in the present series were men suggests that they are also susceptible to vascular damage secondary to PPA use. Men probably require higher doses of PPA to develop adverse cerebrovascular effects. Male patients in our series (n=7) and in previous series (n=9) revealed that 14 (87.5%) used a dose ≥150 mg. In fact, Kernan et al21 reported that the risk of hemorrhage is greater when a dose >75 mg is used. Approximately 50% of the cases previously reported had daily doses ≥150 mg (Table 2). In our study 81% of the patients also had daily doses ≥150 mg, usually as an attempt to improve cold symptoms faster. Moreover, some patients have taken an overdose as a deliberate suicide attempt.8-26 Conversely, it should be noted that some cerebrovascular events are associated with a single low dose of PPA, probably in an idiosyncratic manner.3,8,9,31,33-37,39

The interval between the use of the sympathomimetic and stroke onset was variable, in most cases ≤6 hours (60% to 70%), but in 25% to 35% the interval lasted <1 hour. This finding emphasizes the apparent relationship between drug ingestion and stroke development. Cerebral hemorrhages were largely parenchymal in the present series (80%) and in the reported cases (60%). Kernan et al21 primarily found cases of SAH (61%). Perhaps this is because of the study design used by these last authors, in which the use of PPA was prospectively and carefully investigated in every case of cerebral hemorrhage, either intracerebral or subarachnoid.

Figure 1. Case 4. MRI, coronal view, depicts a left putaminal hemorrhage with mild intraventricular hemorrhage (top). Cerebral angiography, lateral view of left carotid artery, shows segmental narrowing and occlusion of small arteries (arrows) of the left middle cerebral artery.

Figure 2. Case 6. CT scan (left top) shows a small hemorrhage in fronto-orbital region. Cerebral angiography reveals widespread segmental narrowing and beading in carotid territories (black arrows). Right top, lateral view of left carotid angiogram; left bottom, left oblique view of right carotid angiogram; right bottom, left oblique view of left carotid angiogram.

Figure 3. Case 7. CT scan (left bottom) shows left caudate hemorrhage with intraventricular rupture. Cerebral angiography on admission (top) shows narrowing (arrows) of main trunks of right middle cerebral artery and anterior cerebral artery (left top), left middle cerebral artery and anterior cerebral artery (middle top), and basilar artery and posterior cerebral arteries (right top). A complete resolution of the arterial abnormalities was documented in a follow-up cerebral angiography (bottom).
Several mechanisms by which PPA causes cerebrovascular complications have been proposed: the development of hypertensive crisis, as occurred in 31% of our cases and as a consequence of a direct vasoconstrictive action of the drugs, or the development of angiitis, as documented in 55% of the patients who underwent angiography in our study. In the only case assigned to a histopathological examination, Glick et al described a young woman with angiographic and biopsy findings of necrotizing vasculitis of small arteries and veins caused by the PPA contained in her diet pills. Four months later, DSA showed resolution of the vascular lesions. In the present series, in 4 patients with follow-up DSA, complete resolution of the arterial abnormalities was also documented.

In several countries the use of PPA has been reduced almost completely, but information on the use of other common sympathomimetics, administered by both oral and nasal routes, is limited. Pseudoephedrine has seldom caused adverse effects because it is a very weak sympathomimetic amine. However, the relationship between pseudoephedrine and stroke was evident in 4 patients in our series, including 2 cases caused by the ingestion of recommended doses. There are only 2 other cases described in the literature: one after the ingestion of a single regular dose and another after an excessive dose in a suicide attempt. This last patient and 1 patient included in our series showed angiographic changes similar to those observed with PPA. Recently, Dowd et al described 4 cases of ischemic colitis ascribed to pseudoephedrine use. Now that pseudoephedrine is preferred to PPA in cold preparations, one must be aware of the potential cerebrovascular damage that this sympathomimetic can cause.

Finally, some anecdotal case reports on the cerebrovascular complications of chronic nasal sprays have been published, including 2 patients with brain infarction, apparently secondary to chronic use of the nasal decongestants oxymetazoline and fenoxazoline, and another case of retinal artery occlusion associated with the excessive use of nasal spray containing oxymetazoline. The vascular damage in these cases was ascribed to arterial occlusions, in contrast to oral sympathomimetic-related complications, which are predominantly hemorrhages. We describe 2 patients with cerebrovascular complications associated with the application of nasal decongestants. One patient had a SAH after several daily applications.

### TABLE 2. Comparison of the Clinical and Neuroimaging Features of Phenylpropanolamine-Related Cerebrovascular Complications

<table>
<thead>
<tr>
<th>Feature</th>
<th>Current Cases</th>
<th>Case Reports</th>
<th>Kernan et al Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, M/F</strong></td>
<td>n=16</td>
<td>n=31</td>
<td>n=27</td>
</tr>
<tr>
<td>Age, mean±SD (y)</td>
<td>39.5±16.4</td>
<td>31.4±13.7</td>
<td>37.2±8.4</td>
</tr>
<tr>
<td>Doses, %</td>
<td>(n=29)</td>
<td>(n=30)</td>
<td>(n=30)</td>
</tr>
<tr>
<td>12–75 mg</td>
<td>3 (18.7)</td>
<td>12 (41.4)</td>
<td>20 (74.1)</td>
</tr>
<tr>
<td>76–149 mg</td>
<td>0 (0)</td>
<td>3 (10.3)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td>150–300 mg</td>
<td>8 (50.0)</td>
<td>6 (20.4)</td>
<td>5 (18.5)</td>
</tr>
<tr>
<td>&gt;300 mg</td>
<td>5 (31.3)</td>
<td>8 (27.6)</td>
<td>1 (3.7)</td>
</tr>
<tr>
<td><strong>Reason for using PPA, %</strong></td>
<td>(n=30)</td>
<td>(n=30)</td>
<td>(n=30)</td>
</tr>
<tr>
<td>Appetite suppressant</td>
<td>0 (0)</td>
<td>15 (50.0)</td>
<td>21 (77.8)</td>
</tr>
<tr>
<td>Cough/cold remedy</td>
<td>15 (93.7)</td>
<td>10 (33.3)</td>
<td>6 (22.2)</td>
</tr>
<tr>
<td>Suicide attempt and psychostimulant</td>
<td>1 (6.3)†</td>
<td>5 (16.7)‡</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Interval between drug intake and stroke onset, %</strong></td>
<td>(n=30)</td>
<td>(n=30)</td>
<td>(n=30)</td>
</tr>
<tr>
<td>30 min–1 h</td>
<td>5 (31.2)</td>
<td>11 (36.7)</td>
<td>day the drug was consumed</td>
</tr>
<tr>
<td>1–3 h</td>
<td>2 (12.5)</td>
<td>10 (33.3)</td>
<td></td>
</tr>
<tr>
<td>3–6 h</td>
<td>4 (25.0)</td>
<td>1 (3.3)</td>
<td></td>
</tr>
<tr>
<td>6–24 h</td>
<td>5 (31.2)</td>
<td>8 (26.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke type, %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICH</td>
<td>11 (68.7)</td>
<td>21 (67.7)</td>
<td>9 (33.3)</td>
</tr>
<tr>
<td>SAH</td>
<td>3 (18.7)</td>
<td>5 (16.1)</td>
<td>18 (66.7)</td>
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<tr>
<td>ICH+SAH</td>
<td>1 (6.2)</td>
<td>3 (9.7)</td>
<td>...</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>1 (6.2)</td>
<td>2 (6.4)</td>
<td>...</td>
</tr>
<tr>
<td>Cerebral angiography</td>
<td>(n=13)</td>
<td>(n=18)</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>4 (30.8)</td>
<td>8 (37.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Vasculitis like-abnormalities</td>
<td>9 (69.2)</td>
<td>10 (62.5)</td>
<td></td>
</tr>
</tbody>
</table>

*Feature not determined in the remaining cases.
†Suicide attempt.
‡Suicide attempt (n=2); psychostimulant (n=3).
ICH indicates intracerebral hemorrhage; SAH, subarachnoid hemorrhage; NA, not available.
of oxymetazoline, and the other developed a combination of SAH, tempo-occipital hemorrhage, and contralateral occipital infarction. This patient was hypertensive and was receiving daily applications of phenylephrine during several months because of an allergic rhinitis. Although the stroke may have been caused by the high BP, the distribution of the vascular lesions suggests that the nasal sympathomimetic played a role in the cerebrovascular episode.

In conclusion, over-the-counter sympathomimetic-related stroke was associated with hypertensive crisis and/or vasculitis-like mechanisms. Most cases were related to PPA use; however, stroke can also occur with the use of other sympathomimetics, particularly pseudoephedrine. Although stroke complications occurred when doses higher than recommended doses were used, stroke also occurred even when the agents were taken properly.

References

Over-the-Counter Cold Remedies and Stroke

For decades a number of sympathomimetic drugs have been marketed as over-the-counter diet pills, decongestants, or both. During the 1980s and 1990s one of these, phenylpropanolamine (PPA), accounted for an estimated 5 billion doses annually in the United States. In humans PPA produces arousal; unlike amphetamine it does not produce euphoria. It is a recognized street drug, however, sometimes misrepresented as amphetamine (“look-alike pills”), and by mail order it has been available as a “legal stimulant.”

Complications of PPA include acute hypertension, psychosis, seizures, and stroke, especially hemorrhagic. More than 30 case reports describe intracerebral or subarachnoid hemorrhage following either recommended or excessive dosage. Proposed mechanisms include surges of hypertension, cerebral vasospasm (sometimes evident at angiography), and vasculitis (in one case evident at leptomeningeal biopsy). In 2000 Kerman and coworkers reported results of a multicenter case-control study addressing the association of PPA use and intracerebral or subarachnoid hemorrhage. Patients (n=702) and controls (n=1375) were 18 to 49 years of age. This study confirmed PPA as an independent risk factor for hemorrhagic stroke. The odds ratio was 16.58 (P=0.02) for women using appetite suppressants containing PPA and 3.13 (P=0.08) for women using cough or cold remedies containing PPA. For men there was no increased risk of hemorrhagic stroke in association with cough or cold remedies; no men reported use of appetite suppressants. The greater risk of appetite suppressants was attributed to higher dose, but strokes followed recommended as well as excessive doses, and with cough and cold remedies they were associated with first use. It was concluded on the basis of this study that PPA causes between 200 and 400 strokes annually in the United States. Later that year the FDA ordered products containing PPA to be withdrawn from the market. Ephedrine and pseudoephedrine, present in over-the-counter decongestants and bronchodilators, also have low abuse potential, yet dependence does occur. Complications include hypertensive crisis and psychosis. Ischemic and hemorrhagic strokes have occurred in ephedrine users, and intracranial hemorrhage has followed pseudoephedrine use. Ischemic and hemorrhagic strokes are also described in recreational users of “dietary supplements” containing ephedra alkaloids (“ma huang”). Case reports describe cerebral infarction and retinal artery branch occlusion in chronic intranasal abusers of sprays and drops containing phenoxazoline or oxymetazoline.

Evidence that ephedrine, pseudoephedrine, or topical intranasal agents are stroke risk factors is thus anecdotal. Moreover, in contrast to its ban on PPA-containing diet remedies, the FDA’s ban on cough or cold remedies containing PPA was based on a trend that fell short of conventional statistical significance. More convincing data on the association of stroke and cough and cold remedies would thus be welcome. In this issue of Stroke, Cantu and coworkers describe 22 patients with stroke temporally associated with use of these products. Patients were culled from a consecutive stroke registry of 2500. Ten were men aged 17 to 57 years; 12 were women aged 17 to 78 years. Twelve were younger than 40 years old. Twenty-one strokes were hemorrhagic (17 intracerebral, 4 subarachnoid). Sixteen patients used PPA, 4 pseudoephedrine, and, by nasal route, 1 phenylephrine and 1 oxymetazoline. With PPA and pseudoephedrine, strokes followed both recommended and excessive doses and either single or daily use. Acute hypertension was present in 8 of the 22 patients. Cerebral angiography was normal in 8 and showed vasospasm or beading in 10.

These patients do suggest an association between sympathomimetic cold remedies and stroke. In fact, the number of drug-associated strokes was very likely underestimated by excluding patients with aneurysmal subarachnoid hemorrhage or vascular malformation. (Among patients with cocaine-associated intracranial hemorrhage, saccular aneurysms or vascular malformations were found in nearly half who were studied angiographically. The report by Cantu et al is anecdotal, however, for controls are conspicuously lacking.

On the basis of what was at stake, the FDA justifiably banned cough and cold remedies containing PPA despite a probability value of only 0.08. Unfortunately, the ban makes it impossible, at least in the United States, to conduct a study that would definitively confirm the FDA’s wisdom. It is not too late, however, to conduct a study assessing the risk of cold remedies containing other sympathomimetic agents. The report presented by Cantu et al suggests that such an endeavor might be fruitful.

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References

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Stroke. 2003;34:1667-1672; originally published online June 5, 2003;
doi: 10.1161/01.STR.0000075293.45936.FA
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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