Reversible Segmental Cerebral Arterial Vasospasm and Cerebral Infarction

Possible Association With Excessive Use of Sumatriptan and Midrin

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Objective: To describe a patient who developed reversible segmental cerebral arterial vasospasm and cerebral infarction while taking excessive amounts of sumatriptan succinate and a combination drug (Midrin) consisting of isometheptene mucate, 65 mg, dichloralphenazine, 100 mg, and acetaminophen, 325 mg.

Design: Case report.

Setting: Tertiary care center.

Patient: A 43-year-old man who developed a left occipital infarct after taking a total of 23 sumatriptan succinate tablets (25-mg per tablet) and 32 Midrin tablets during a 7-day period and who on digital subtraction angiography was shown to have segmental cerebral arterial narrowing in multiple vessels. An extensive evaluation for other possible risk factors for cerebral infarction was unrevealing.

Main Outcome and Results: Discontinuation of sumatriptan and Midrin regimens and administration of nicardipine hydrochloride led to nearly total resolution of the angiographic findings, and the patient had no recurrent strokes.

Conclusions: One should consider the diagnosis of drug-induced vasospasm in patients with cerebral infarction and a history of excessive use of sumatriptan and Midrin. The initial angiographic abnormalities may resemble those found in patients with primary angiitis of the central nervous system.

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blood cells, and nonreactive results from cerebrospinal fluid VDRL. Computed tomography and magnetic resonance imaging of the head performed on day 17 showed a 2.5×2.5-cm, left occipitoparietal infarct without hemorrhage or mass effect (Figure 1, D). The patient was transferred to our care. A 3-vessel digital subtraction angiogram on day 20 (8 days following the fixed visual field defect) showed segmental narrowing of small- to medium-sized arteries in the anterior and posterior circulation bilaterally (Figure 1, A-C). A repeated cerebrospinal fluid analysis the same day showed protein levels of 95 mg/dL; a glucose level of 3.8 mmol/L (68 mg/dL); red blood cells, 39×10⁶/L, and white blood cells, 12×10⁶/L. Cerebrospinal fluid cultures were negative for organisms. Results of transesophageal echocardiography and electrocardiography were normal. Results of a complete blood cell count, routine blood chemistry tests, chest x-ray, and urinalysis were normal. The results of the following additional tests showed no abnormalities: serum rapid plasma reagin, antinuclear antibody, rheumatoid factor, antiphospholipid antibody screen, and antithrombin III. Factor V Leiden mutation was not detected by DNA polymerase chain reaction. The patient was treated with oral nicardipine hydrochloride and aspirin (325 mg/d). An angiogram repeated on day 59 showed nearly complete resolution of the abnormalities previously seen (Figure 2). The patient remains free of headaches and has had nearly complete resolution of his hemianopia.

**COMMENT**

Sumatriptan, administered either intravenously or orally, has been associated with angina pectoris, myocardial infarction, and ventricular arrhythmias in patients both with and without underlying coronary atherosclerosis.4-7 Our patient had angiographic evidence of reversible segmental cerebral arterial vasospasm analogous to the vasospasm seen on coronary angiography. There are pharmacological reasons to think sumatriptan caused vasospasm in our patient. Sumatriptan is an agonist with affinity for 5-HT1B (serotonin), 5-HT1D, and contractile 5-HT1–like receptors. It induces vasospasm in isolated nonhuman8-9 and human10 basilar artery preparations. In a recent review, Parsons11 concluded that there are contractile serotonin receptors in large pre- and postcircle of Willis vessels and relaxation receptors in small resistance pial arterioles.

### Table: Patients With Ischemic Stroke Associated With Sumatriptan Use

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Head CT</th>
<th>Head MRI</th>
<th>Angiography</th>
<th>Cardiac Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/46</td>
<td>Initially showed left thalmic low attenuation; follow-up results normal</td>
<td>NR</td>
<td>NR</td>
<td>Normal ECG findings</td>
</tr>
<tr>
<td>2/F/25</td>
<td>Normal</td>
<td>NR</td>
<td>Left frontoparietal infarct and superior sagittal sinus thrombosis</td>
<td>NR</td>
</tr>
<tr>
<td>3/F/22</td>
<td>NR</td>
<td>Left cerebellar infarct</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>4/M/39</td>
<td>Left occipital infarct</td>
<td>NR</td>
<td>Diffuse segmental arterial narrowing that reverted to normal on repeated study</td>
<td>NR</td>
</tr>
<tr>
<td>5/M/43‡</td>
<td>NR</td>
<td>Left occipital infarct</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Sumatriptan was given as sumatriptan succinate.

†CT indicates computed tomography; MRI, magnetic resonance imaging; NR, not reported; and ECG, echocardiogram.

‡Present case.
We cannot entirely exclude the possibility that our patient had idiopathic reversible cerebral arterial vasospasm like the patients described by Call and colleagues, and that the use of sumatriptan and Midrin was incidental. However, the angiographic features of our patient differed from those described by Call et al., whose patients had vasospasm predominantly involving arteries around the circle of Willis. The luminal irregularities seen in our patient were more diffusely distributed. Midrin use was a possible contributing cause of vasospasm in our patient. Midrin contains isometheptene mucate (65 mg per tablet), a sympathomimetic agent implicated as the cause of segmental vasospasm in a postpartum woman who ingested 10 tablets of Midrin in 1 week.

Our patient had angiographic findings similar to those seen in primary angiitis of the central nervous system. A meningocortical biopsy was not done because we had an alternative explanation for our patient's angiographic abnormalities and because he had no clinical or serologic evidence of systemic vasculitis. In one study of 30 consecutively referred patients, conventional cerebral angiography had less than 30% specificity for primary angiitis of the central nervous system. The magnetic resonance imaging scan of our patient's head showed only the single infarction. Multiple infarcts are commonly seen on magnetic resonance imaging scans in patients with primary angiitis of the central nervous system.

The combined use of sumatriptan and Midrin should be considered among the nearly 30 conditions that can resemble primary angiitis of the central nervous system. One should consider the diagnosis of drug-induced vasospasm in patients with cerebral infarction and a history of excessive sumatriptan and/or Midrin use. It might be appropriate to consider the establishment of a registry to determine the incidence of ischemic stroke in users of sumatriptan and to investigate whether the coadministration of Midrin predisposes to ischemic stroke. Nicardipine is efficacious in vasospasm induced by subarachnoid hemorrhage. Nicardipine may also be useful in patients like ours who have drug-induced cerebral vasospasm.

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REFERENCES