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, dichloralphenazone, 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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We describe a patient who experienced a posterior cerebral artery territory infarction while taking an excess of sumatriptan succinate and a combination drug (Midrin) consisting of isometheptene mucate, dichloralphenazone, and acetaminophen and who was found on serial digital subtraction angiography to have reversible segmental arterial vasospasm. Four patients with cerebral infarction in association with sumatriptan use have been described previously (Table).[1-3] However, 1 of these patients had an underlying sagittal sinus thrombosis. In none of these cases was cerebral angiography reported. The importance of differentiating this condition from granulomatous angiitis of the central nervous system is discussed.

REPORT OF A CASE

A 43-year-old male mathematics teacher was healthy until he suddenly felt a pulsatile, bioccipital headache while lifting an inner tube (day 0). The headache lasted several hours and was associated with nausea but not vomiting. He began having headaches every other day, lasting 2 to 24 hours. None of the recurrent headaches were as severe as the initial headache, and none were associated with nausea, aura, photophobia, or phonophobia. He sought medical attention when over-the-counter medications failed to relieve the headaches. Results of a computed tomographic scan of the head obtained on day 3 were normal. At that time he was treated with prednisone and intramuscular meperidine hydrochloride. The prednisone was tapered during the next 6 days. The patient was prescribed Midrin on day 7, and getting little relief from it, oral sumatriptan was added on day 11. The patient noted a fixed right homonymous visual defect on day 12. Before stopping his medication use on day 14, he took a total of 32 Midrin tablets and 23 sumatriptan succinate (25-mg) tablets. A lumbar puncture showed clear, colorless fluid with a protein level of 52 mg/dL, a glucose level of 3.4 mmol/L (61 mg/dL), no red or white
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 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 nonhuman9,10 and human10 basilar artery preparations. In a recent review, Parsons11 concluded that there are contractile serotonin receptors in large pre- and post–circle of Willis vessels and relaxation receptors in small resistance pial arterioles.

**Table 1.** 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>NR</td>
<td>NR</td>
</tr>
<tr>
<td>3/F/22</td>
<td>NR</td>
<td>Left frontoparietal infarct and superior sagittal sinus thrombosis</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>4/M/39</td>
<td>Left cerebellar infarct</td>
<td>NR</td>
<td>Left occipital infarct</td>
<td>NR</td>
</tr>
<tr>
<td>5/M/43‡</td>
<td>Left occipital infarct</td>
<td>Differential segmental arterial narrowing that reverted to normal on repeated study</td>
<td>Normal ECG and transesophageal ECG results</td>
<td></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.

Figure 1. Bilateral carotid (A and B), posterior circulation (C), and digital subtraction angiograms initially showing segmental arterial narrowing (arrows), and noncontrast computed tomographic head scan demonstrating ischemic stroke in the left posterior cerebral artery territory (D).
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