

## BRIEF REPORT

## Ischemic Colitis Related to Sumatriptan Overuse

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**Background:** Serotonin-1 5-hydroxytryptamine (5-HT<sub>1</sub>) receptor agonists are first line agents for migraine headaches. Patients with refractory headaches may use supratherapeutic doses of these medications. Described is a case of ischemic colitis related to overuse of sumatriptan.

**Case:** A 35-year-old woman presented with severe abdominal pain without diarrhea or hematochezia. For several days prior she had been self-treating a refractory migraine headache with frequent doses of sumatriptan. She is a nonsmoker and took no oral contraceptives or other serotonin agonists. A computed tomography scan of the abdomen revealed left-sided colitis. A colonoscopy with biopsy confirmed ischemic colitis and excluded inflammatory bowel disease (IBD).

**Discussion:** Previously published case reports have suggested an association between 5-HT<sub>1</sub> receptor agonists and ischemic colitis. These reports have been dismissed because the patients were taking oral contraceptives, serotonin agonists, or had other comorbidities. This healthy patient lacked risk factors for ischemia, is the youngest to be reported, and is the first without hematochezia.

**Conclusion:** 5-HT<sub>1</sub> receptor agonists are generally considered safe. Ischemic colitis is a potentially serious complication of these agents. A retrospective review of 5-HT<sub>1</sub> receptor agonist users who have presented with acute onset abdominal pain or hematochezia is necessary to elucidate the incidence of this adverse event. (J Am Board Fam Med 2010;23:124–127.)

Migraine headaches are commonly treated by family physicians. This primary headache disorder affects 18% of women and 6% of men in the United States.<sup>1</sup> One of the most frequently prescribed classes of medications for the acute treatment of migraine headaches is serotonin-1 5-hydroxytryptamine (5-HT<sub>1</sub>) receptor agonists. Sales in the United States for this class of medication are more than \$1.5 billion, with sumatriptan accounting for \$900 million of these sales.<sup>2</sup> For most patients these medications are considered safe. One exception is patients with known cardiovascular disease or significant cardiovascular risk factors because of the medication's vasoconstricting properties and the

risk for ischemia.<sup>3</sup> Healthy patients who take these medications as prescribed are at low risk for developing adverse events. However, patients who experience refractory headaches may inadvertently overuse these agents in an attempt to reduce their pain and disability. The most common complication of overuse of abortive medications is rebound headaches.<sup>4</sup> A potentially more severe consequence of medication overuse is ischemia. Described in this report is a case of ischemic colitis related to the use of supratherapeutic doses of sumatriptan in a previously healthy patient.

## Case

A 35-year-old white woman presented to the emergency department (ED) after enduring 6 hours of severe abdominal pain, rated as 10 out of 10. Her pain was nonfocal and nonradiating. She was nauseous but experienced no emesis, diarrhea, or bloody stools. During the 3 days before the onset of her abdominal pain she developed an intense refractory migraine headache requiring several doses of her usual abortive medications. She estimated that during the 36 hours before the abdominal pain developed she took 300 mg of sumatriptan orally and 12 mg subcutaneously. She has a long history of migraine headaches that have been difficult to

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**Table 1. Laboratory Data**

Laboratory Test (units)	Values		
	Normal	Before Admission	At Discharge
WBC count ( $\times 10^3/\text{mCL}$ )	3.5–10.8	19.2	5.9
Neutrophils (%)	52–75	75	48
Bands (%)	0–9	21	Not calculated
$\beta$ -HCG	—	Negative	—
Lipase (IU/L)	10–204	132	—
Aspartate aminotransferase (U/L)	0–32	12	9
Alanine aminotransferase (U/L)	0–32	16	13
Alkaline phosphatase (mg/dL)	35–105	52	52
Bilirubin (mg/dL)	0–1.0	0.4	0.4
Creatinine (mg/dL)	0.5–1.1	0.8	0.7
Sodium (mmol/L)	136–145	140	142
Chloride (mmol/L)	98–107	105	105
Carbon dioxide (mmol/L)	22–31	24	29
ESR (mm/h)	0–25	—	6
CRP (mg/dL)	0.071–0.500	—	<0.100
p-ANCA	—	—	Negative
ASCA IgA	0–20	—	5.1
ASCA IgG	0–20	—	6.1

WBC, white blood cell; HCG, human chorionic gonadotropin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; p-ANCA, perinuclear antineutrophil cytoplasmic antibody; ASCA, antisaccharomyces cerevisiae antibody; IgA, immunoglobulin A; IgG, immunoglobulin G.

control and have required multiple doses of sumatriptan. She had never experienced similar abdominal pain during these other occasions of headache. She denied use of tobacco, alcohol, or illicit drugs. She takes no oral contraceptives or other serotonin agonists. Her other medications include ibuprofen, fluticasone propionate nasal spray, and cetirizine. She had taken one 800-mg dose of ibuprofen during the 72 hours before her ED visit.

At presentation our patient was afebrile and hemodynamically stable. Her abdomen was soft but diffusely tender to palpation. She exhibited voluntary guarding without rebound tenderness. Her white blood cell count was elevated,  $19.2 \times 10^3/\text{mCL}$ , with a left shift. All other laboratory studies were normal (Table 1). Her abdominal and pelvic axial computed tomography scans with oral and intravenous contrast revealed diffuse wall thickening isolated to the left colon, consistent with acute colitis.

During her stay in the ED the patient received 2 mg of hydromorphone and 4 mg of ondansetron, which reduced her abdominal pain to 8 of 10. She was diagnosed with colitis of undetermined etiology, discharged from the hospital, and prescribed 10 days of levofloxacin and metronidazole and hy-

drocodone-acetaminophen for pain. Her discharge instructions stated that she may continue to take her home medications as previously prescribed, including sumatriptan.

The patient continued to have abdominal pain and a severe headache. Within hours of returning home from the ED she sought care from her family physician. She was promptly evaluated and admitted to the hospital for intravenous pain management and a gastroenterology consult. She was prescribed bowel rest, intravenous hydration, morphine for pain control, and levofloxacin. A neurologist was also consulted because of her persistent headache. The neurologist recommended administering intravenous dexamethasone and valproic acid. The combination of these 2 agents produced complete headache resolution within 2 hours. Her headache did not return during the course of her hospitalization. During the next 72 hours the patient's abdominal pain and nausea slowly improved, and they were resolved by the time of discharge. Her white blood cell count also normalized. Her erythrocyte sedimentation rate and C-reactive protein were not elevated (6 mm/hr and <0.10 mg/dL, respectively). Her diet was slowly advanced to normal.

Per the instructions of her gastroenterologist, she was discharged from the hospital and returned a few days later for a colonoscopy. She tolerated the bowel preparation regimen without complication. Direct visualization of the sigmoid colon revealed a granular and erythematous appearance lacking ulceration or pseudomembrane. A biopsy was consistent with acute colitis without evidence of crypt architectural distortion or destruction. Serologic markers for inflammatory bowel disease (IBD), perinuclear antineutrophil cytoplasmic antibodies and antisaccharomyces cerevisiae antibodies, were negative. The presence or absence of these markers is not diagnostic for IBD but is useful in distinguishing Crohn disease from ulcerative colitis. Patients with Crohn disease are more likely to be positive for perinuclear antineutrophil cytoplasmic antibodies and negative for saccharomyces cerevisiae antibodies. The opposite is true for patients with ulcerative colitis.<sup>5</sup> Given the temporal relationship between the use of large doses of sumatriptan and the onset of our patient's symptoms, the lack of infectious signs and symptoms, and the negative IBD studies, the gastroenterologist and the admitting team felt confident that the most likely diagnosis was ischemic colitis directly related to the use of sumatriptan.

## Discussion

Ischemic colitis is a consequence of decreased arterial blood flow to the colon. It is associated with numerous disease processes and medications. Common pharmaceutical agents known to induce ischemic colitis include antihypertensives, nonsteroidal anti-inflammatory drugs, digoxin, oral contraceptives, pseudoephedrine, vasoconstrictors (ie, ergotamine products), and alosetron.<sup>6</sup>

There have been several published cases suggesting that 5-HT<sub>1</sub> receptor agonists may also induce ischemic colitis. A 1998 case series identified 8 cases of ischemic colitis potentially related to sumatriptan.<sup>7</sup> The median age in this series was 46 years. All of the patients presented with abdominal pain and hematochezia. Detailed information existed for only 2 of the 8 patients. Both were smokers and had long histories of chronic gastrointestinal issues before the use of sumatriptan. A more recent case described ischemic colitis in a 52-year-old woman.<sup>8</sup> This patient was concomitantly taking sumatriptan and citalopram. She too experienced hematochezia.

Two other published cases have reported an association between naratriptan use and ischemic colitis.<sup>9,10</sup> One of these involved a 42-year-old woman who was also taking oral contraceptives. The other case involved a 52-year-old woman. Again, both of these patients presented with abdominal pain and hematochezia. In addition to potentially inducing ischemic colitis, there have been other published reports of sumatriptan causing mesenteric ischemia.<sup>11,12</sup>

This case is unique for several reasons. First, the patient is the youngest reported to date in the literature. Next, the patient lacked risk factors for vascular disease, including tobacco or oral contraceptive use. Although she did take one dose of ibuprofen, the likelihood of this medication inducing colitis is very low, as previously published reports of nonsteroidal anti-inflammatory drug-related ischemic colitis involved patients over the age of 49 who took the medication for at least 3 continuous days.<sup>13–15</sup> Finally, she presented with severe abdominal pain without hematochezia.

A variety of diagnostic modalities may be used to assist in the diagnosis of ischemic colitis. Colonoscopy is considered the primary tool. Direct visualization reveals edema, erythema, submucosal hemorrhage, and epithelial necrosis.<sup>16</sup> Histologic findings are not unique to ischemic colitis and include edema, distorted crypts, inflammatory infiltration, submucosal and mucosal hemorrhage, and necrosis.<sup>17</sup> In the United States, computed tomography is the imaging test of choice, but ultrasound, which is less expensive and less invasive, is also an option.<sup>18</sup> Ultimately, this disease remains a clinical diagnosis and requires a high degree of suspicion. A common differential diagnosis includes infectious colitis, inflammatory bowel disease, neoplasm, and diverticulitis.<sup>19</sup>

Two thirds of patients with ischemic colitis will have complete resolution of their symptoms within 24 to 48 hours of initial presentation provided the offending agent has been eliminated. Twenty percent of patients will require surgical intervention. Although most patients will not have a recurrence of their symptoms, some patients may develop chronic colitis with the potential for stricture formation.<sup>20</sup>

The patient presented in this case report was followed for 1 year after her initial diagnosis. She has had no further episodes of colitis. She continues to have intermittent migraine headaches that she safely treats with sumatriptan. She has received

strict guidance not to exceed the Food and Drug Administration-approved maximum daily dose for this medication. Her headache frequency has decreased with the combined use of topiramate and periodic acupuncture.

## Conclusion

5-HT<sub>1</sub> receptor agonists are routinely prescribed by family physicians as abortive agents for migraine headaches. This case illustrates a potential severe complication of these medications in a patient not considered to be at risk for vascular disease. Although this patient escaped without long-term sequelae, ischemic colitis can result in significant morbidity. This case is important for 2 reasons. First, the incidence of this unintended consequence of 5-HT<sub>1</sub> receptor agonist therapy needs to be elucidated. All other cases of ischemic colitis previously reported in the literature involved patients presenting with hematochezia. This case uniquely describes a patient with abdominal pain and no bleeding. It is possible that numerous cases of ischemic colitis go undiagnosed in younger patients because they present without hematochezia and have no vascular risk factors. A retrospective chart review of 5-HT<sub>1</sub> receptor agonist users who have presented to a primary care clinic or ED with acute abdominal pain with and without bloody stools should be initiated. A temporal relationship between medication use and symptoms needs to be explored.

Second, this case highlights the need for providers to thoroughly educate their patients about the correct use of medications. Not only are migraine headache sufferers at risk for rebound headaches from medication overuse but they are at risk for ischemic complications. These patients must receive detailed instructions about the maximum dose and frequency of medication administration. Patients should communicate understanding of the potential risks associated with medications before leaving the provider's office.

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