

Pure naratriptan-induced ischemic colitis: A case report

Naratriptan'a bağılı iskemik kolit: Olgu sunumu

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A 60-year-old female with sudden onset of abdominal pain and hematochezia was diagnosed with histology-proven ischemic colitis. She used naratriptan on a regular basis for migraine. By exclusion of other causes for colonic ischemia and the absence of cardiovascular risk factors, naratriptan was considered the causal agent. Discontinuation resulted in a complete clinical recovery. With the increasing use of triptans, health care providers should be aware of the possible serious ischemic events associated with these drugs.

Key words: Naratriptan, ischemia, colitis

Migren tedavisi için düzenli olarak naratriptan kullanan 60 yaşında kadın hastaya ani başlayan karın ağrısı ve hematokeziya nedeni ile yapılan tetkikleri ve biyopsi sonucunda iskemik kolit tanısı konulmuştur. Kolonik iskemiyeye neden olabilecek diğer faktörlerin ekarte edilmesi ve kardiyovasküler risk faktörlerinin de olmaması dikkate alınarak hastadaki iskemik kolitin naratriptan'a bağılı olabileceği düşünülmüştür. İlacın kesilmesi ile hastanın tam olarak iyileştiği görülmüştür. Sağlık çalışanlarının, triptanların kullanımındaki artışı da dikkate alarak, bu ilaçların olası ciddi iskemik yan etkileri hakkında bilgi sahibi olmaları gerekmektedir.

Anahtar kelimeler: Naratriptan, iske mi, kolit

INTRODUCTION

Triptans are selective 5-hydroxytryptophan (5HT)_{1B/1D}-receptor agonists, a class of drugs widely used for the treatment of acute symptoms of migraine. Their therapeutic effect is based on predominant vasoconstriction of the cerebral circulation. When prescribed to patients with low risk of cardiovascular events, triptans have proven to be safe without evidence of increased occurrence of ischemic conditions (e.g. stroke or ischemic heart disease) (1). However, triptans are contraindicated in all patients with a past history of coronary heart or cerebrovascular disease (2). Although rare, the use of sumatriptan and naratriptan has been associated with several cases of ischemic colitis (3-7). We present a case of a female patient suffering from ischemic colitis due to the prolonged use of naratriptan in the absence of cardiovascular risk factors.

CASE REPORT

A 60-year-old Caucasian female with a past history of migraine-associated headache presented

with a sudden onset of abdominal pain and hematochezia one day before admission. She reported with severe lower abdominal cramping pain with frequent episodes of bloody diarrhea accompanied by nausea without vomiting. She denied any fever or chills, and no signs of exposure to infectious agents (e.g. shellfish, undercooked food, or travel) were noted. Vigorous physical exercise, the use of illicit drugs and smoking were denied. Her past medical history was unremarkable except for prior appendectomy and hemorrhoids. In particular, there was no history of hypertension, diabetes mellitus or coronary artery disease.

Naratriptan was prescribed, which was used frequently on demand. Additional analysis of data retrieved from her pharmacist revealed the use of 12 tablets of naratriptan 2.5 mg every six weeks, with a maximum of 5.0 mg a day during the last eight years. Recently, three days before and eight hours after the onset of her symptoms, 5.0 mg of naratriptan had been used.

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Physical examination revealed a patient in mild distress due to abdominal discomfort. Her temperature was 37.6°C and she remained hemodynamically stable. Abdominal examination showed normal peristaltic sounds without murmurs and left lower quadrant tenderness without signs of local peritonitis. The presence of rectal blood loss was found on digital rectal examination.

Laboratory findings including full blood count, prothrombin time, electrolytes, creatinine, and liver enzymes were normal. Stool and blood cultures remained negative. On day one of admission, a colonoscopy was performed, revealing severe sub-mucosal edema and mucosal ulceration of the descending colon extending to a sharp delineated segment of at least 15 cm in the sigmoid, consistent with the blood supply of the inferior mesenteric artery. Due to an increased risk of perforation, the procedure was prematurely terminated. Multiple random colonic biopsies demonstrated ulcerating mucosa with extravasation of erythrocytes, crypt atrophy and dilated vessels in the lamina propria (Figure 1), compatible with ischemic colitis.

Combined abdominal computed tomography (CT-scan) and angiography demonstrated circumferential thickening of the descending colon without creeping fat or lymphadenopathy (Figure 2). The arterial and venous blood supply was normal.

After discontinuation of naratriptan and intravenous rehydration, she recovered quickly and could be discharged four days after admission. Due to persistent abdominal complaints, an upper and

(repeat) lower endoscopy was performed without signs of ischemia. A new CT-scan was unremarkable and two months later her complaints had fully resolved.

DISCUSSION

This case report demonstrates the occurrence of histology-proven ischemic colitis in the absence of major vascular obstruction, atrial fibrillation, blood dyscrasia, or intermittent low flow state of the systemic circulation. Often, a specific etiology can not be identified. However, drug-induced alterations of the mesenteric circulation resulting in ischemic mucosal damage is an under-recognized cause (8).

Naratriptan is known to be a selective 5-HT_{1B/1D} agonist with minimal affinity to other 5-HT receptors. It has a relative short elimination half-life ($T_{1/2}$ = 6 hours) and excellent renal clearance (9). Serotonin-induced mesenteric vasoconstriction is mainly mediated through 5-HT_{2A} receptors (10). However, vasoconstriction is also mediated, albeit in a less and variable extent, by 5-HT_{1B/1D} receptors. This 5-HT_{1B/1D} mediated response varies greatly among patients (11). Sumatriptan, a triptan with similarity to naratriptan, exerts even more effect when mesenteric vasoconstriction is amplified by precontraction with various contractile substances (e.g. phenylephrine, histamine or potassium chloride) or by endogenous factors (12). The Naranjo Adverse Drug Reactions Probability Scale (NADRPS) is a tool used to determine the like-

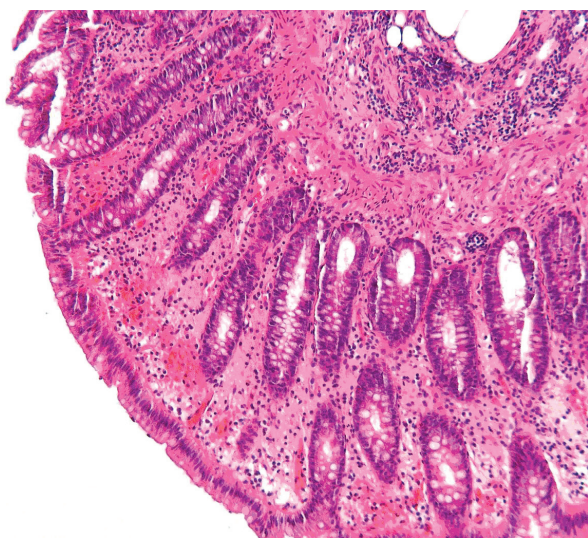


Figure 1. Ulcerative epithelium and vasodilatation with extravasation of erythrocytes and inflammation.

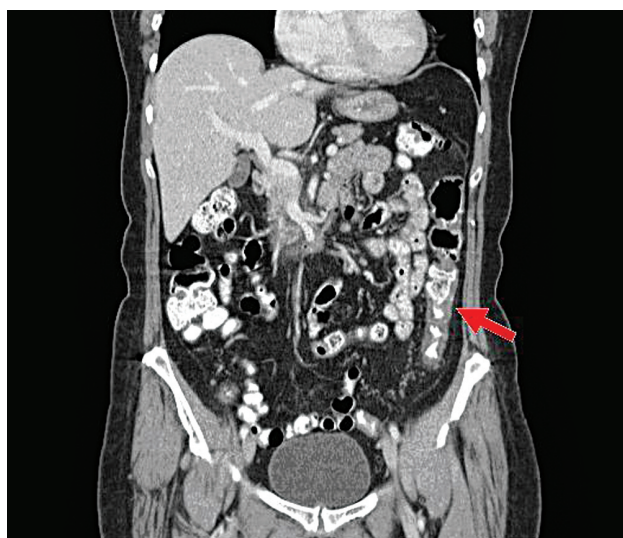


Figure 2. Left-sided colonic wall thickening (arrow) consistent with colitis.

likelihood that an adverse drug reaction is caused by the implicated medication (13). Ten questions are answered and assigned a weighted score of +2 to -2. Where there is insufficient data available, the particular question receives a 0. Based on this score (<1 - >9), an assessment of the likelihood of causing an adverse drug reaction can be made. When applied in this case, a score of 8 indicates a probable likelihood of naratriptan as the cause for ischemic colitis.

The frequency of ischemic colitis associated with naratriptan, according to the Netherlands Pharmacovigilance Centre, is rare (<1:1000). Although rare, there have been reports of sumatriptan-associated ischemic colitis (14-16) and naratriptan-associated ischemic colitis with oral contraceptive use (17) or other co-medication including quetiapine and topiramate (18). No reports of ischemic colitis associated with the other triptans (zolmitriptan, rizatriptan, almotriptan, frovatriptan and eletriptan) are available.

As far as we know, this is the first report of naratriptan-induced ischemic colitis without co-medica-

tion and normal renal function in the absence of any other risk factor. Despite the latency of eight years, we suggest a direct causal relation by exclusion of other causes, the disappearance of symptoms and resolution of mucosal lesions after discontinuation of naratriptan, and a NADRPS of 8. Rechallenge with this drug was not performed due to its severe adverse reaction.

A proposed pathophysiological mechanism is the agonistic effect of triptans on the mesenteric 5-HT_{1B/1D} receptors leading to vasoconstriction, amplified by unknown endogenous conditions.

In conclusion, although ischemic colitis may occur without an obvious precipitating event, the use of triptans can act as an etiological factor for ischemic complications including ischemic colitis. With the increasing use of triptans prescribed by different healthcare providers, awareness of this potential severe adverse event is needed.

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