Drug Saf (2014) 37:109–121
DOI 10.1007/s40264-013-0134-7

ORIGINAL RESEARCH ARTICLE

Sumatriptan-Associated Ischemic Colitis: Case report and Review of the Literature and FAERS

Thuc Quyen Nguyen · James H. Lewis

Published online: 18 January 2014

Abstract
Background and Aims Ischemic colitis (IC) is being increasingly recognized, although specific etiological causes are observed in a minority of patients. While several drugs have been associated with IC, most remain anecdotal reports. We recently treated a patient with IC thought to be related to sumatriptan for migraines, and performed a literature review along with a review of the FDA Adverse Event Reporting System (FAERS) database to identify additional cases.
Methods A MEDLINE/PubMed literature review was conducted using standard IC search terms to identify published cases of sumatriptan and other related "triptan" drug causes of IC. In addition, through a *Freedom of Information Act* request, we reviewed the adverse gastrointestinal events linked to sumatriptan contained in the FAERS database for the 5-year period 12 March 2008–11 March 2013, in order to determine whether unpublished cases might exist. Our case of IC was analyzed using a causality assessment tool initially developed for use in cases of alosetron (a 5-HT_3 receptor antagonist)-related IC.
Results Five published reports (containing a total of seven patients) describing sumatriptan-associated IC in the English language literature were found and reviewed. Another four published reports of related 5-HT_1 receptor agonists causing IC (razitriptan $n = 1$ and naratriptan $n = 3$) were also analyzed. Among spontaneous reports of possible IC contained in the FAERS database for sumatriptan, there were 19 adverse events coded as "ischemic colitis" and another six coded as "intestinal ischemia" over a 5-year period ending March 2013, but clinical details were lacking. Similarly, five reports of possible IC from FAERS were mentioned in an earlier published report from the late 1990s. All of the published case reports of sumatriptan and related drugs were deemed to have the classic clinical findings and all recovered. There was one instance of possible recurrent IC symptoms in one patient re-exposed to sumatriptan, but not in another. We found that the IC scoring system developed for alosetron was applicable in our sumatriptan case.
Conclusions Among drug-related causes of IC, sumatriptan joins a growing list of agents with literature reports supported by the finding of suspected cases of IC in the FAERS database. However, the true incidence of IC due to sumatriptan, as well as other causes, cannot be accurately determined because of the likelihood of under-reporting. The structured IC scoring system appears to be applicable for drug-related as well as other etiological causes of IC.

1 Introduction

Ischemic colitis (IC) (also referred to as colonic ischemia) is the most common form of intestinal ischemia, usually resulting from an acute interruption of colonic blood flow due to low flow states as well as thromboembolic events [1]. Classic symptoms of IC include the acute onset of crampy mid or lower abdominal pain and bloody diarrhea in the absence of a known history of inflammatory bowel disorders, with a segmental acute colitis seen in most instances on colonoscopic exam [1, 2].

The incidence of IC has been estimated to range from 4.5 to 44 cases per 100,000 person-years, depending on the underlying comorbidities and/or medications being taken [3]. Historically, the populations at highest risk for IC are

T. Q. Nguyen · J. H. Lewis (✉)
Division of Gastroenterology, Georgetown University Hospital, 3800 Reservoir Road, NW, Washington, DC 20007, USA
e-mail: lewisjh@gunet.georgetown.edu

patients with coronary artery disease (CAD) or end-stage kidney disease requiring dialysis [1]. However, IC has also been observed in healthy patients with no significant risk factors, and several other underlying conditions and medications have been associated with IC [4, 5]. A two- to fourfold increase in the risk of IC is postulated to occur for patients with irritable bowel syndrome (IBS) or chronic obstructive pulmonary disease [3, 6, 7]. In a study from the Kaiser Health system, the annual incidence of acute IC was estimated to be 15.6 per 100,000 patient-years, with the rate increasing with age. However, in only a minority of the cases was the etiology established with a reasonable degree of certainty [4]. The most commonly associated conditions in the Kaiser series were hypertension, diabetes, chronic obstructive pulmonary disease, atrial fibrillation, congestive heart failure, depression, asthma, and CAD [5]. Among 313 patients in a large hospital-based series, a specific cause of IC was observed in only 43 (13.7 %) of the individuals [1].

Most instances of medication-induced IC have been limited to case reports or small case series. While several drug classes have been associated with IC [5], most published reports of individual agents remain anecdotal [8–35] (Table 1). The FDA Adverse Event Reporting System (FAERS) database is increasingly being utilized to identify agents specifically associated with IC to potentially bolster these limited number of published cases. Tumor necrosis factor (TNF)-α inhibitors [31] and type-1 interferons [32] are two recent examples of where the FAERS database has contributed to a better understanding of IC associated with these particular agents. The drug alosetron had IC reported during its clinical trials as well as in the post-marketing experience, and a reporting rate of approximately one case per 1,000 patient-years of use can be estimated [6, 19]. However, an estimate of the incidence for other medications associated with IC has not been determined, given the lack of a numerator generated from spontaneous, voluntary reporting, which may underestimate the problem. The specific mechanism by which alosetron (or related medications) might cause IC remains largely unknown [6, 36, 37]. In contrast, it is postulated that certain other agents, such as ergotamine, and the anti-migraine agents, including sumatriptan, might act through their vasoconstrictive effects [8, 33, 38]. For agents such as digitalis, a "low flow" state in the colonic vasculature has been postulated to occur, as no thromboembolic events have been identified in association with the IC attributed to its use [1]. The mechanism by which TNF-α inhibitors and interferons might cause IC remains a topic for additional study [31, 32].

Table 1 Published reports of specific drugs associated with ischemic colitis

Drug class	Drug name	References
5-HT_1 receptor agonists	Sumatriptan	[8–14]
	Rizatriptan	[15]
	Naratriptan	[16–18]
5-HT_3 receptor antagonists	Alosetron	[6, 19, 20]
5-HT_4 receptor agonists	Tegaserod	[21]
Diuretics	Furosemide	[22, 23]
Illicit drugs	Cocaine	[24, 25]
Na/K ATPase inhibitors	Digitalis	[26]
NSAIDs	Diclofenac	[27]
Oral contraceptives	Estrogen	[28–30]
TNF-α inhibitors	Infliximab, adalimumab, etanercept, certolizumab	[31]
Type-1 IFNs	IFN-α2a (Pegasys), IFN-α2b (PegIntron), IFN-β (Betaseron)	[32]
Miscellaneous agents	Ergotamine	[33]
	Sodium polystyrene sulfonate	[34]
	Pseudoephedrine	[35]

IFN interferon, *TNF* tumor necrosis factor

Longstreth and Yao [5] identified several dozen drugs that were prescribed often more to patients with IC than were used in controls. These included multiple antihypertensives, opioids, statins, female hormones, potentially constipating drugs, histamine H_2 antagonists, immunomodulators, digoxin, clopidogrel/ticlopidine, taxanes, vinca alkaloids, and antibiotics, although no specific causality assessment of individual agents was provided. Three triptans (sumatriptan, naratriptan and razitriptan) were listed as being associated with IC [5], but no individual clinical details were provided in their overview [5]. While IC associated with alosetron and other serotonergic agents has been well described [6], in general, few detailed analyses are available for other drug classes.

We recently encountered a patient in whom sumatriptan appeared to be the cause of her IC. This widely prescribed anti-migraine agent is a 5-hydroxytryptamine (HT) 1 receptor agonist that causes predominantly cerebral vasoconstriction, but can also affect other vessels, such as coronary arteries [9, 10, 12]. Reports of IC with this agent, however, appear to be uncommon, and prompted us to perform a literature search for other published cases of sumatriptan-related as well as other triptan-associated reports of IC. In addition, we also undertook a review of the FAERS database for additional post-marketing cases of IC, possibly due to sumatriptan based on the primary adverse event code.

2 Case Report

A 50-year-old Caucasian woman with a long-standing history of migraines, hypertension, and chronic back pain was admitted to the hospital via the emergency department (ED) for evaluation of acute abdominal pain, nausea, vomiting and bloody diarrhea. She reported that 12 h earlier she awoke at 3 am experiencing severe left lower quadrant pain associated with diaphoresis and tenesmus, and subsequently had six bowel movements, each progressively becoming mixed with larger amounts of blood. The abdominal pain was described as being continuous, crampy, and non-radiating, with a pain score of 8/10, and required narcotics in the ED for relief. She had never experienced similar gastrointestinal (GI) symptoms previously, and in fact, had undergone a normal screening colonoscopy just 2 months previously. She had traveled to Mexico 3 weeks prior to this episode, but did not describe any traveler's diarrhea or other illnesses. She denied tobacco or any illicit drug use, had not participated in any marathon running or cycling, and drank two glasses of wine socially with dinner for the past 5 years.

Her history of migraine headaches began at puberty and typically occurred around her menses. She began using sumatriptan tablets (25 mg q 2–4 h as needed) about 15 years ago, usually once every other month. Periodically, she would use an injectable subcutaneous formulation of sumatriptan for more severe migraines. Indeed, she had administered a single injection of sumatriptan 6 mg subcutaneously 1 week prior to the onset of her symptoms. She was also chronically taking olmesartan for hypertension, cyclobenzaprine for back spasms, and naproxen for arthritis without any recent changes in these medications. She had no known drug allergies.

On admission, her temperature was 36.3 °C, pulse rate 84 beats per minute, blood pressure 125/83 mmHg sitting, and oxygen saturation 100 % on room air. Her abdominal exam revealed marked tenderness to palpation in the left lower quadrant, without guarding or rebound. However, her bowel sounds were hyperactive. The rest of her physical exam was unrevealing. Laboratory data revealed a white count of 16.7 k/mm^3 with 92 % neutrophils, 2 % lymphocytes, 2 % monocytes and 1 % basophils. Her hematocrit was 42.8 %. Her chemistry panel was all within normal limits.

A CT scan of the abdomen in the ED showed changes of inflammation and thickening in the area of the splenic flexure and descending colon. Colonoscopy was performed the next morning after a bowel prep and revealed a normal rectum and sigmoid. However, beginning abruptly in the upper descending colon, a broad area of exudate (colon "stripe sign") was noted, and there were severe changes of colitis consistent with ischemia at the splenic flexure (Fig. 1). Given the apparent severity of the colitis, the scope was not advanced beyond the splenic flexure, because of the risk of perforation. Biopsies were obtained and were consistent with a diagnosis of acute IC (Fig. 2).

The patient was treated conservatively with the empiric use of anti-inflammatory agents (pentoxyfylline 400 mg twice daily orally and mesalamine 400 mg every 4 h orally), placed on esomeprozole 40 mg orally daily, started on intravenous antibiotics (ciprofloxacin 400 mg every 12 h and metronidazole 500 mg every 12 h) and given hydromorphone as needed for pain. Stool studies all returned as negative for any infectious etiology. A magnetic resonance imaging (MRI) exam with a magnetic resonance angiogram (MRA) performed on hospital day 6 was still consistent with ongoing IC, demonstrating persistent edema and colonic wall thickening in the mid-transverse colon down to the distal sigmoid colon. No other anatomical and no vascular abnormalities were noted. A 2-D echo performed on day 7 demonstrated a normally sized and functioning heart with an ejection fraction of 60 % and no thrombus.

The hospital course proceeded uneventfully, and as the patient's pain and nausea diminished, she was able to tolerate a regular diet. Her leukocytosis resolved over the ensuing days, and she was discharged on day 10. At a follow-up out-patient visit in the GI clinic 2 weeks later, she reported continued improvement and had returned to work. Her repeat CBC showed a normal white blood cell count of 6.8 k/mm^3 and normal hemoglobin and hematocrit. A repeat colonoscopy was performed 6 weeks later, which showed complete healing of the involved mucosa, although some residual scarring was noted at the splenic flexure. No strictures or areas of persistent inflammation were seen. The right colon and cecum were normal (Fig. 3). To date she has not had any recurrent lower GI symptoms and has not resumed taking sumatriptan; her migraines are being treated with non-triptan agents.

2.1 IC Causality Assessment

The clinical presentation, along with the radiographic and colonoscopic findings strongly suggested IC as the clinical diagnosis on admission. A number of tools are available to assist the clinician in making a diagnosis of IC. These include descriptive criteria used by Longstreth and Yao [4, 5], and those of the FDA, as utilized by Chang et al. [6, 19]. Another assessment tool that was specifically developed to assist in the diagnosis of cases associated with alosetron utilizes a numerical scoring system for IC [6, 39], and is described in Table 2. It is based on six main clinical categories, each awarding (or subtracting) points correlating to the likelihood that the finding points toward (or away from) an IC diagnosis. The individual categories include the clinical presentation, colonoscopic (or flexible sigmoidoscopy) findings, radiological (CT or abdominal series) findings, other abdominal imaging findings (e.g., arteriography), histopathology, and the patient's clinical

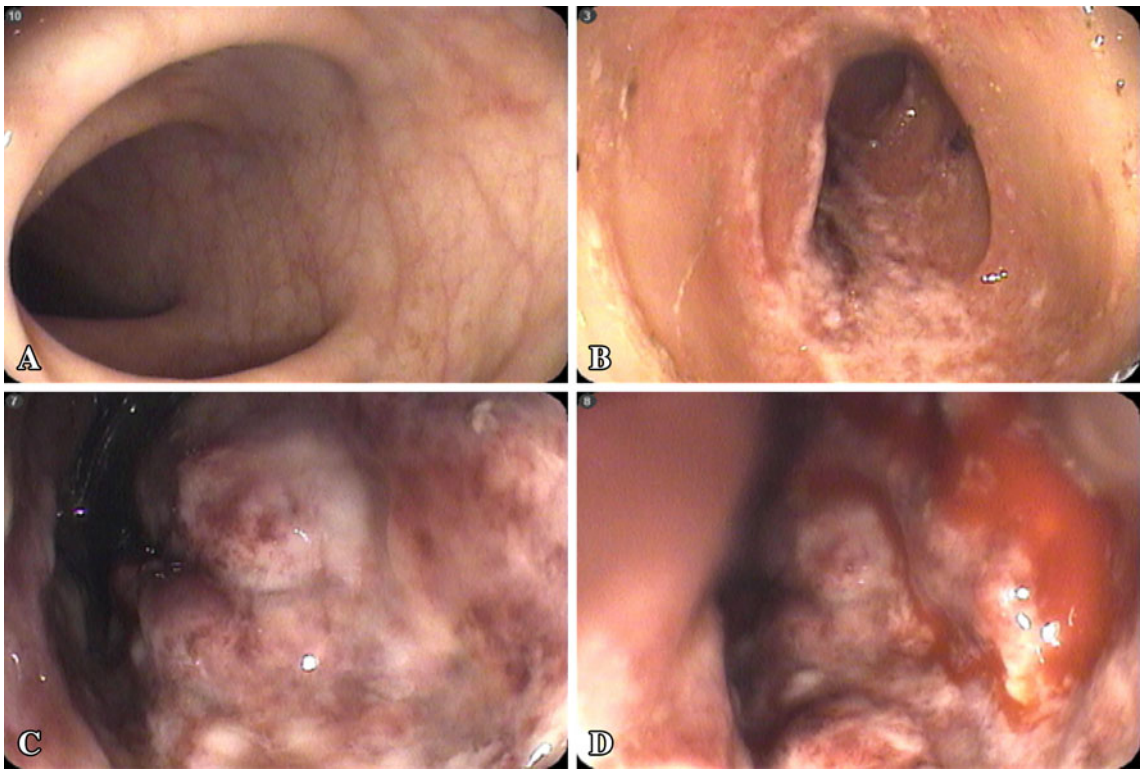

Fig. 1 Colonoscopic findings on presentation. **a** Normal sigmoid mucosa. **b** Broad area of whitish exudation ("stripe sign") in the proximal descending colon. **c** Severe changes of ischemic colitis at the splenic flexure characterized by purplish mucosal blebs. **d** Friability at a biopsy site in the splenic flexure. The colonoscope was not advanced beyond this area given the severity of the findings

course and outcome. The cumulative scores are added, and points totaling 4–6 denote a possible diagnosis of IC, with a score of 7–10 and 11 or greater defining probable and very likely IC diagnoses, respectively. A total of 3 points or less is considered unlikely to be IC.

A companion scoring system was also developed for the cases associated with alosetron, to determine if alosetron or another medication or medical/surgical condition was the most likely cause of the IC [6, 39]. Given the fact that both sumatriptan and alosetron are related serotonergic agents, we applied this scoring system to our patient (Table 3).

The scoring system was used to determine if IC was present in our patient, and the total score of 15 indicated a very high probability of IC. Similarly, using the scoring system to identify if the suspected drug (in this case, sumatriptan) was the cause, we calculated a score of 9 points, suggesting it was probably related.

3 Literature Review of Sumatriptan and Other Triptan-Associated IC Cases

3.1 Methods

A MEDLINE/PubMed search was conducted using the terms ischemic colitis, colonic ischemia, colitis, hematochezia, and abdominal pain, cross-referenced with sumatriptan and the six other approved 5-HT_1 receptor agonist triptan agents used in the treatment of migraines [40–46]. Only reports mentioning or discussing IC were further reviewed. The search dates were from 1990 to March 2013, which covers the time since the first triptan (sumatriptan) was approved.

3.2 Results

The literature search revealed a total of five published reports of sumatriptan-associated IC [8, 11–14], and four reports attributing IC to two of the other triptans [15–18] since 1990. The series by Knudsen et al. from 1998 [8] described the details of two patients with possible sumatriptan-induced IC, and another five cases that were mentioned as being contained in the FDA's Spontaneous Reporting System at the time, although few clinical details were provided. Although cases attributed to sumatriptan, naratriptan, and razitriptan were described in the series by Longstreth and Yao [5], no individual details were included. Table 4 provides the salient clinical details of the seven published sumatriptan cases, in addition to our patient, and Table 5 lists the clinical information from the four publications describing IC with razitriptan and naratriptan. At least two of the cases in the sumatriptan series

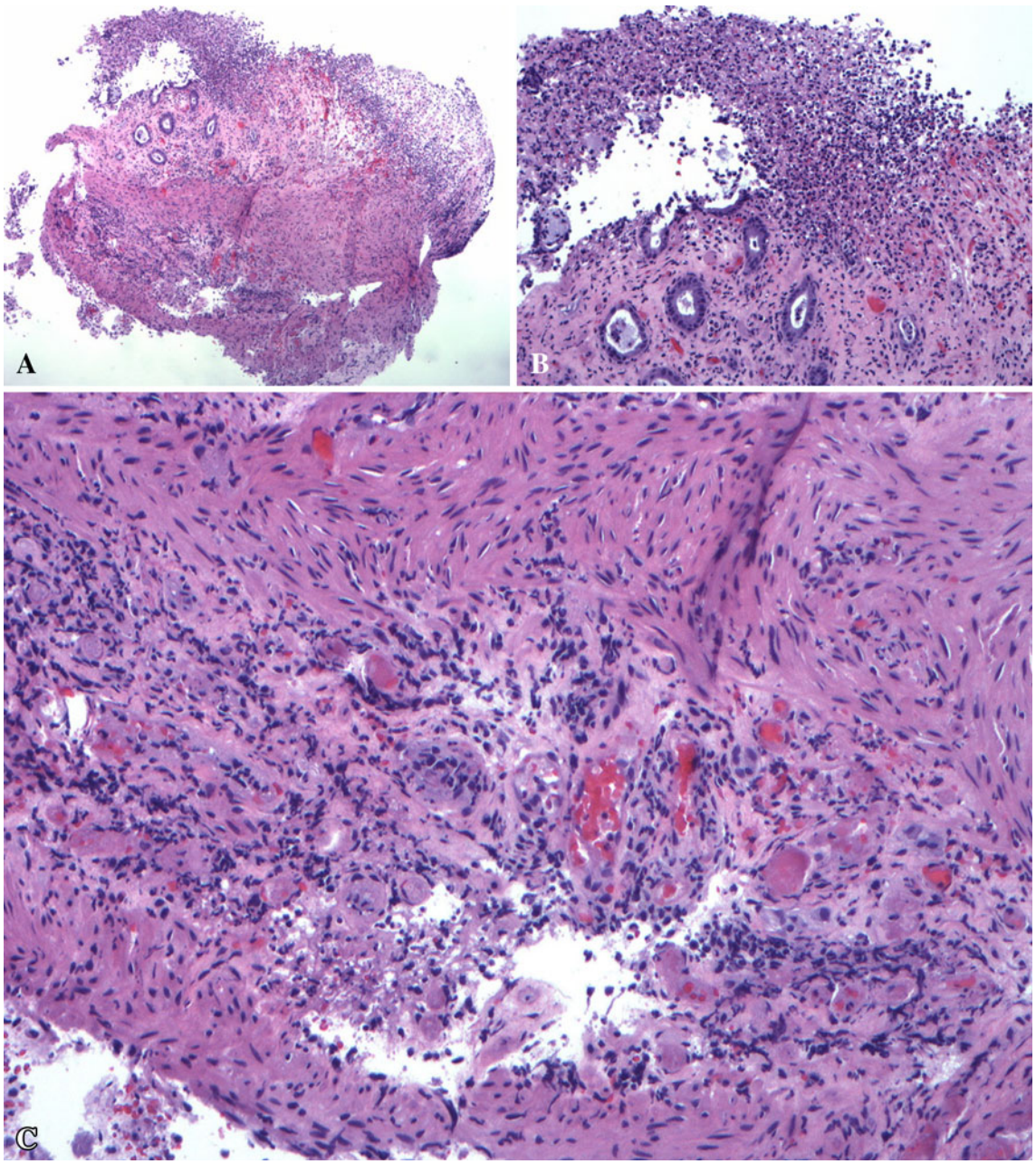

Fig. 2 Histopathology. **a** Low power view of a fragment of descending colonic mucosa that shows an area of ulceration covered by a layer of mucopurulent exudate. **b** Higher power view of the same specimen. Note the paucity of the intestinal crypts; the residual crypts appear atrophic and contain small crypt abscesses. **c** Higher power view beneath the muscularis mucosa, showing small capillaries plugged with fibrinoid thrombi consistent with ischemia

had IBS, which is now recognized as a potential risk factor for IC [6, 19]. No specific risk factors for the other published cases were identified. No published reports of the other four triptans were found citing an association with IC in this literature review, although all of the approved anti-migraine triptans approved in the USA carry a warning about the possible development of IC and all are contra-indicated in patients with a history of ischemic bowel disease as part of class labeling [40–46].

Consistent with the characteristic natural history and outcome of IC cases from other causes, the majority of the published triptan cases resolved after discontinuation of the drug. Two patients were described as having sumatriptan re-administered after their IC event had resolved. In one case, the reappearance of typical IC symptoms developed after this rechallenge [12]. However, in the other instance [13], the patient did not experience recurrent IC. In a third patient [14], two subsequent episodes of IC occurred after

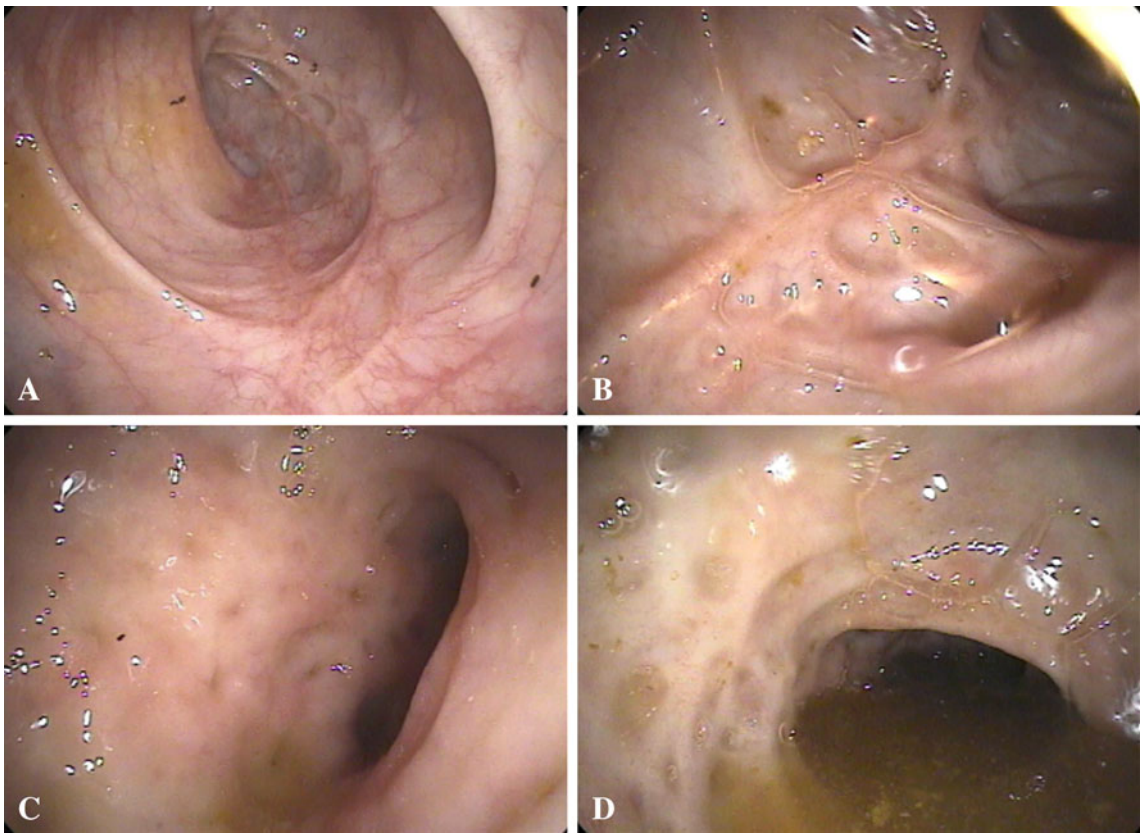

Fig. 3 Repeat colonoscopy performed approximately 7 weeks after the initial colonoscopy, showing healing of the descending colon mucosa (panel **a**). Scarring at the previous areas of severe inflammation in the region of the splenic flexure (panels **b**–**d**)

sumatriptan had been discontinued, raising the question of whether the drug was responsible for the initial occurrence. There was no mention of an attempted rechallenge with any of the other triptan cases in the literature reports. Nor has information on the clinical course of a rechallenge been published for other agents. For example, no rechallenge is mentioned in any of the FAERS cases described for TNF-α inhibitors [31] or type-1 interferons [32], and no patients in the published alosetron series were rechallenged [6, 19], although we have been made aware of at least one instance where recurrent symptoms developed after alosetron was restarted in the post-marketing setting [47].

4 Review of FAERS Database for Sumatriptan

To supplement our review of published IC cases related to sumatriptan, we requested information through the *Freedom of Information Act* from the FAERS. Although sumatriptan has been available for more than 2 decades, we chose to analyze adverse colonic event data from a recent 5-year period corresponding to the growing interest and reporting of IC cases with alosetron and other agents [4–6, 19]. We did not request data for the other triptans, which all carry class warnings about IC, since our main focus was sumatriptan.

We received adverse event data from the 5-year period 12 March 2008–11 March 2013, during which time a total of 3,659 spontaneous reports were filed, encompassing a total of 10,252 sumatriptan-associated events, representing all organ systems. The specific GI adverse event terms for sumatriptan from this dataset are listed in Table 6. While cases contained in FAERS do not imply causality, a total of 19 reports listed "IC" as the main adverse event, using the Medical Dictionary for Regulatory Activities (MedDRA)® term "ischemic colitis", and another six reports coded events as "intestinal ischemia." There were several other patients listed as having adverse events in FAERS that could be consistent with IC, including GI hemorrhage, hematochezia, and abdominal pain, although, from the data received, the clinical details of these patients were not available for any individual analysis.

5 Discussion

Sumatriptan succinate is a 5-HT_1 receptor agonist belonging to the class of medications commonly referred to

Table 2 Ischemic colitis (IC) clinical diagnosis assessment instrument (ICCAI), after Lewis [6] and Ringel et al. [39]

Parameter evaluated	Points[a]
I. Clinical presentation	
A. Classic	+3
B. Symptoms consistent (not classic)	+2
C. Nonspecific symptoms	+1
D. Symptoms or history suggests another diagnosis	–1
II. Colonoscopic (flexible sigmoidoscopy) findings	
A. Typical appearance/distribution	
1. Splenic flexure, descending and/or sigmoid colon	+4
2. Transverse, hepatic flexure	+3
3. Rectum, cecum	+2
B. Nonspecific appearance	+1
C. Normal or findings suggest another diagnosis	–1
D. Not performed or done >2 weeks after symptom onset and found to be normal	0
III. CT scan or abdominal film findings	
A. Thumbprinting or wall thickening	+2
B. Nonspecific features	+1
C. Normal or not suggestive of IC	–1
D. Not performed or obtained >2 weeks after symptom onset and found to be normal	0
IV. Other abdominal imaging (if performed)	
A. Barium enema or angiography findings suggestive of IC	+2
B. Nonspecific findings	+1
C. Not compatible with IC	–1
D. Not performed or obtained >2 weeks after symptom onset and found to be normal	0
V. Histopathology	
A. Biopsy "diagnostic" of IC	+3
B. Consistent with IC	+2
C. Nonspecific	+1
D. Suggests another diagnosis	–1
E. Not performed or obtained >2 weeks after symptom onset and found to be normal	0
VI. Clinical course	
A. Self-limited, reversible with symptoms resolved within 2 weeks	+3
B. Symptoms resolve over 2–8 weeks	+2
C. Symptoms resolve after >8 weeks	+1
D. Symptoms resolve—time not stated	+1
E. Symptoms not resolved due to stricture, chronic ulceration, etc., attributed to IC	+2
F. Outcome not stated	0
G. Course inconsistent with IC	–1

Assessment (minimum points needed per criterion)[a]		I	II	III	IV	V	VI
Very likely IC	≥11	3	3	0	0	2	3
Probable IC	7–10	2	2	0	0	0	3
Possible IC	4–6	1	1	0	0	0	2
Unlikely IC	≤3	0	0	0	0	0	0

Copied from [6]

[a] Scoring

as "triptans," which are indicated for the treatment of migraine headaches. A total of seven triptan agents are currently approved by the FDA, including almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, and zolmitriptan in addition to sumatriptan [40–46, 48]. The individual 5-HT_1 receptor agonists differ in terms of their

Table 3 Proposed causality assessment method to determine if alosetron is the specific cause of ischemic colitis (IC), after Lewis [6] and Ringel et al. [39]

Criteria	Point value
I. Temporal compatibility	
A. IC develops on alosetron	+3
B. IC develops within 2 weeks off alosetron	+1
C. IC develops >2 weeks but <12 weeks after stopping alosetron	0
D. IC develops prior to alosetron or >12 weeks after alosetron stopped	−1
II. Pre-existing colonic pathology	
A. Normal findings on barium enema, colonoscopy or flexible sigmoidoscopy pretreatment	+2
B. No diagnostic testing performed or not stated	0
C. Pre-existing pathology	
Diverticular disease	−1
Inflammatory bowel disease or other colitis	−2
III. Risk factors for IC[a]	
A. None present (no. stated)	+1 to +3
B. Not stated	0
C. One or more present (no. stated)	−1 to −3
Prior history of IC	
Vasculitis (e.g., systemic lupus erythematosus, polyarteritis nodosa	
Hypercoagulable state	
Infectious colitis	
Long-distance running, cycling	
Medications (e.g., digoxin, oral contraceptives, triptans, cocaine)	
Abdominal aortic aneurysm repair, etc.	
IV. IC confounders	
A. None	+2
B. Secondary causes of IC (e.g., distal obstructing carcinoma, volvulus, radiation, AAA repair)	–2
C. Severe constipation/fecal impaction due to alosetron	+1
D. Diverticulitis	–1
E. None stated	0
V. Clinical course (if alosetron discontinued)	
A. Prompt resolution within 14 days	+2
B. Slow resolution (>2 weeks)	+1
C. Not stated	0
D. Fails to resolve and not suggestive of IC	–1
E. Fails to resolve due to stricture, chronic colitis attributed to IC	+1
F. Resolves despite continued alosetron	–3
VI. Response to rechallenge	
A. Positive (IC reoccurs on alosetron)	+3
B. Negative (IC fails to recur on alosetron)	–1
C. Indeterminant	+1
D. Not performed	0

Assessment (minimum points needed per criterion)[a]		I	II	III	IV	V	VI
Definitely related to alosetron	≥11 points	3	2	1	2	2	0–1
Probably related to alosetron	7–10 points	2	2	0	2	1	0
Possibly related to alosetron	4–6 points	1	0	0	2	1	0
Unlikely to be related	≤3 points						

[a] Score 1 point per risk factor, up to total of 3

Copied from [6]

Table 4 Clinical details of sumatriptan-associated ischemic colitis in the literature

Patient	Gender	Age (years)	Underlying systemic disease	Sumatriptan dose and formulation and other medications	Location	Outcome/treatment	Reference
1	F	50	Hypertension	Took 25 mg p.o. approximately once a month. Took SQ injection 6 mg 1 week prior to her presentation	Watershed area (proximal descending—splenic flexure)	Resolved	Current case
2	F	39	"Colitis". Sigmoid colon adhesions; history of low blood pressure	25 mg p.o., last dose taken in 24 h prior to presenting. Took four doses in 10 days	Sigmoid	Supportive care; resolved. Unknown if ever rechallenged	[8]
3	F	38	Irritable colon	Initially took two 50 mg p.o. + 6 mg SQ, then another two 50 mg p.o. 2 days later. Fluoxetine	Descending colon	Supportive care; resolved	[8]
4	F	52	Depression	Usually took one 50 mg p.o. in 1 week, but in 7 days prior to admission used five 50 mg tablets, one taken 6 h prior to presentation. Started on citalopram 10 days prior to incident (changed from amitriptyline to citalopram)	Splenic flexure and extending proximally	Unknown	[11]
5	F	46	Irritable bowel syndrome	Unknown formulation and dose. However, noted to be taking more frequently than usual dose. On oral contraceptives	Not stated	Supportive care; resolved. Patient was rechallenged with sumatriptan, with resulting abdominal pain	[12]
6	F	35	Unknown	Estimated total of 300 mg p.o. and 12 mg SQ in 3 h prior to abdominal pain. Other medications: ibuprofen, fluticasone propionate nasal spray, cetirizine	Not stated	Supportive care with antibiotics (levofloxacin). Restarted sumatriptan without complication	[13]
7	F	45	Unknown	Took up to ten 5-mg doses of the SQ formulation per week	Right colon	Discontinued and remained symptom-free for 14 months, but has since experienced two additional episodes	[14]
8	F	63	Unknown	50 mg p.o. once	Distal left colon	After discontinuation remained symptom free for 4 months	[14]

p.o. orally (per os), *SQ* subcutaneous

pharmacological half-lives, rates of absorption, and bioavailability [49].

Sumatriptan, being the first of its class, has an extensive history of use since the early 1990s. It is thought to act against migraines by causing cerebral vasoconstriction and by inhibiting neurogenic inflammation. Although highly specific to its CNS receptors, studies have shown that sumatriptan's effect is not limited to the cerebral arteries. In human studies, it has been found to cause increased arterial blood pressure, likely related to peripheral vasoconstriction. However, in animal studies, high doses of the drug cause a decrease in blood pressure which is thought to be due to sympathetic outflow. Sumatriptan also causes differing vascular effects in the CNS, namely vasoconstriction of the middle cerebral artery, and decreased blood flow in the carotid artery [9, 10, 38]. Importantly, sumatriptan is also found to vasoconstrict coronary arteries [38]. 5-HT_1 receptors mediate only 20–30 % of the coronary vessels' vasoconstriction, with the majority of vasoconstriction mediated by 5-HT_2 receptors [49, 50]. In patients without CAD, this vasoconstriction is not thought to be clinically significant [51]. However, in patients with CAD, this effect can lead to myocardial ischemia, and the drug is contraindicated in this patient population [52].

Despite the fact that our patient had used oral sumatriptan for years, her presentation was classic for IC, with no

Table 5 Cases of IC attributed to other "triptans" in the literature

Case	Gender	Age (years)	Underlying systemic disease	Dose and formulation of the triptan and other medications	Location of IC	Outcome/treatment	Reference
1	F	50	No history of vasculopathy	*Razitriptan* 10 mg p.o. Used intermittently for a few months; did not exceed 30 mg per 24 h	Severe disease in sigmoid and descending colon, with patchy erythema in the rectum and ascending colon	Razitriptan discontinued. No rechallenge, with gradual improvement of symptoms	[15]
2	F	54	IBS, depression, hyperthyroidism, GERD	*Naratriptan* 2.5 mg p.o. as needed for a few months; three doses over past week prior to presentation. Other medications: gabapentin, quetiapine, topiramate lansoprazole, zolpidem	Extending from the distal transverse colon to mid-descending colon	Supportive care	[16]
3	F	42	Menorrhagia	*Naratriptan* 2.5 mg as needed, last dose 24 h prior to symptoms. Other medications: topiramate 25 mg p.o. bid, drospiren 3 mg, and ethinyl estradiol 0.03 mg p.o.	Sigmoid to splenic flexure	Levofloxacin started. All medications discontinued. Repeat colonoscopy 1 year later was normal	[17]
4	F	60	Hemorrhoids	*Naratriptan* as needed. Was prescribed 2.5 mg × 12 pills p.o. every 6 weeks, with maximum of 5.0 mg per day. 5.0 mg p.o. had been used 3 days before and 8 h after the onset of symptoms	Sigmoid and descending colon	IV Rehydration and discontinuation of naratriptan. Repeat Colonoscopy performed with no signs of ischemia	[18]

GERD gastro-esophageal reflux disease, *IBS* irritable bowel syndrome, *IC* ischemic colitis, *IV* intravenous, *p.o.* orally (per os)

other causes or predispositions being found. She had had a normal screening colonoscopy just 2 months prior to her presentation, had no cardiac disease, and the only change in her medication regimen was that she used the parenteral form of subcutaneously administered sumatriptan rather than her usual oral formulation. A review of the pharmacokinetics of sumatriptan reveals that it can be given orally, intranasally, per rectum, as well as subcutaneously. The time to maximum plasma concentration (t_{max}) of therapeutic doses is approximately 1.5 h, with a corresponding bioavailability of 14, 15.8, and 19.2 %, respectively, for the oral, intranasal, and rectal formulations [49]. A subcutaneous injection of 6 mg of sumatriptan has a bioavailability of approximately 96 %, with the t_{max} shortened to only 10 min [49]. Therefore, in our patient, it is likely that this heightened exposure triggered the IC event.

Once she recovered, our patient was advised not to take sumatriptan in the future. There is at least one published report of a possible positive rechallenge causing recurrent IC in the literature [12]. However, there is also a case where readministration of sumatriptan did not result in recurrence of IC [13], and another report where two additional IC episodes occurred after sumatriptan had been discontinued [14]. It is not known if cross-reactivity exists with the other related 5-HT_1 triptans for migraines with respect to inducing recurrent IC, but all carry class labeling that they are contraindicated in patients who have experienced IC [40–46], presumably from any cause. While the limited information in the literature does not permit a clear understanding as to what the risk of recurrent IC might be upon rechallenge, we elected not to re-expose our patient, based on the labeled warnings and especially given the severity of the initial episode.

Naratriptan was developed for its improved pharmacokinetic properties. While a therapeutic oral dose of sumatriptan has a bioavailability of only 14 %, and an elimination half-life of 2 h, naratriptan has a greater bioavailability of 74 %, and a longer elimination half-life of 5.5 h [41]. Naratriptan also has better CNS penetration [16]. However, there have been at least three published reports of naratriptan-induced IC, two of which were associated with naratriptan alone, and one in combination with oral contraceptive use [16–18]. Similarly, razitriptan, with a bioavailability of 40 % and an elimination half-life time of 2.0 h [42], also has been reported to have caused "acute on chronic" IC [15].

Table 6 Adverse gastrointestinal events relating to sumatriptan from 12 March 2008 to 11 March 2013 in the FAERS database[a]

MedDRA GI event	Event count
Nausea	271
Abdominal discomfort	52
Diarrhea	39
Upper abdominal pain	37
Death	26
Abdominal pain	24
Dyspepsia	20
Ischemic colitis	19
Dysphagia	19
GERD	15
Gastric disorder	11
Gastrointestinal disorder	11
Appendicitis	10
Abdominal distention	8
Constipation	8
Hemorrhage	7
Vasospasm	7
Intestinal ischemia	6
Decreased appetite	5
Gastric ulcer	5
Gastroenteritis	5
Hepatic enzyme increased	5
Pancreatitis	5
Ulcer hemorrhage	5
Ulcerative colitis	4
Gastritis	4
Hematemesis	4
Irritable bowel syndrome	4
Cholelithiasis	3
Epigastric discomfort	3
Gastric hemorrhage	3
Gastrointestinal hemorrhage	3
Hematochezia	3
Hemorrhoids	3
Liver disorder	3
Oropharyngeal discomfort	3
Acute pancreatitis	3
Rectal hemorrhage	3
Salivary hypersecretion	3
Ulcer	3
Abdominal pain, lower	2
Amylase, increase	2
Diarrhea hemorrhagic	2
Erosive esophagitis	2
Hemoglobin decreased	2
Hepatic enzyme abnormality	2
Hiatus hernia	2
Malabsorption	2
Mastication disorder	2
Mucosal hemorrhage	2
Neurogenic bowel	2
Pancreatic duct obstruction	2
Pancreatic injury	2
Rectal tenesmus	2

FAERS FDA Adverse Event Reporting System, *GERD* gastroesophageal reflux disease, *GI* gastrointestinal, *MedDRA* Medical Dictionary for Regulatory Activities

[a] Other GI events reported in only a single individual ($n = 37$) are not included

The product label for sumatriptan oral tablets and subcutaneous injections stresses the potential for inducing coronary vasospastic disease with its use, and warns that the drug should not be given to patients with documented ischemic or vasospastic CAD, as well as to avoid its use in patients with unrecognized CAD predicted by the presence of one of several risk factors (e.g., hypertension, hypercholesterolemia, smoking, obesity, diabetes, strong family history of CAD, females with surgical or physiological menopause, and males over 40 years of age) [40]. In addition, the package insert also mentions that sumatriptan may cause vasospastic reactions other than coronary artery vasospasm, and lists both peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea as having been reported. It specifically describes IC by name as having occurred in the post-marketing setting, although no incidence data or specific clinical details are provided. In addition, in the section describing "Information for Patients", colonic ischemic events with symptoms of sudden or severe stomach pain and bloody diarrhea are listed by the manufacturer, GlaxoSmithKline, with warnings not to use the drug if CAD is present or if other vasoconstricting agents, such as ergotamine or other triptans have been taken within 24 h of use [40]. Indeed, all seven triptans carry class labeling that ischemic bowel disease may occur and all are contraindicated in patients with a history of IC [40–46]. As a result, at the present time we are unable to recommend a safe alternative triptan to use in a patient who has developed IC in association with one member of the class.

The FAERS is a database that supports the FDA's post-marketing safety surveillance program for drugs and biological products [53]. Adverse events and medication errors are coded according to terminology contained in the MedDRA. While FAERS is considered to be a useful tool for looking for new safety concerns that might be related to

a marketed product, the reports submitted to the database are not required to have an established causal relationship between a product and the event, and many reports do not contain sufficient clinical or laboratory details to fully adjudicate an event. Moreover, reporting is mostly done on a voluntary basis, and under-reporting is a recognized limitation in FAERS. As a result, FAERS data cannot be used to calculate the incidence of an adverse event. Nevertheless, information contained within FAERS can be supportive of data found in the published literature, and in some cases, may provide a useful post-marketing signal of a rare adverse event not seen in clinical trials. Such data-mining of FAERS has been recently utilized to describe an association between two drug classes not traditionally implicated as a cause of IC—namely TNF-α inhibitors [31] and type-1 interferons [32]. The database thus holds promise with regard to researching the possible relationship between other drug classes and IC as well. In the case of sumatriptan, the adverse event reports coded as IC or colonic ischemia are consistent with the package labeling and published literature. Although the individual clinical details of these reports in FAERS were not reviewed, the terms "IC" and "intestinal ischemia" are fairly specific, and fit well with the known experience and labeling of the drug.

6 Conclusions

IC has many etiological associations, including several comorbid conditions and more than a dozen drug classes [4–6]. However, only a few medications have been adequately described as a cause of IC based on an analysis of the literature. Clinical trial and post-marketing reports related to alosetron appear convincing [6], despite not having a confirmed pathophysiological mechanism [36]. Similarly, a review of the FAERS database for TNF-α inhibitors [31] and type-1 interferons [32] uncovered numerous IC reports for these agents, which when analyzed further, provide adequate evidence for an association. The several published case reports and case series attest to the fact that sumatriptan can cause IC, and the adverse event codes for IC contained in the FAERS database lend further support to those in the literature and reinforce the information contained in the drug label. While an incidence of IC cannot be reliably calculated based on voluntary spontaneous reports, the number of cases attributed to sumatriptan would appear to place this agent among the most common drug-induced causes. As a result, a high index of suspicion for IC should be maintained for any patient taking sumatriptan (or another triptan) who develops acute abdominal pain and rectal bleeding. The IC scoring instruments that were developed for alosetron [6, 39] appear to have utility for diagnosing or confirming other drug causes as well, but deserve further validation with other etiologies.

Acknowledgments The authors thank Adrien Mazer, MD (Department of Medicine) for his assistance with managing the patient, and Bhaskar Kallakury, MD (Department of Pathology) for his help in preparing the pathology photomicrographs.

Author Contributions Thuc Quyen Nguyen drafted the manuscript. James H. Lewis conceived, drafted, and critically revised the manuscript.

Disclosures No sources of funding were used to assist in the preparation of this study. Thus Quyen Nguyen and James H. Lewis have no conflicts of interest that are directly relevant to the content of this study.

References

1. Brandt LJ, Feuerstat P, Blaszka MS. Anatomic patterns, patient characteristics and clinical outcomes in ischemic colitis: a study of 313 cases supported by histology. Am J Gastroenterol. 2010;105(10):2245–52.
2. Gandhi SK, Hanson MM, Vernava AM, et al. Ischemic colitis. Dis Colon Rectum. 1996;39(1):88–100.
3. Higgins PD. Systematic review: the epidemiology of ischaemic colitis. Aliment Pharmacol Ther. 2004;19(7):729–38.
4. Longstreth GF, Yao JF. Epidemiology, clinical features, high-risk factors, and outcome of acute large bowel ischemia. Clin Gastroenterol Hepatol. 2009;7:1075–80.
5. Longstreth GF, Yao JF. Diseases and drugs that increase risk of acute large bowel ischemia. Clin Gastroenterol Hepatol. 2010;8:49–54.
6. Lewis JH. The risk of ischaemic colitis in irritable bowel syndrome patients treated with serotonergic therapies. Drug Saf. 2011;34:545–65.
7. Suh DC, Kahler KH, Choi IS, Shin H, Kralstein J, Shetzline M. Patients with irritable bowel syndrome or constipation have an increased risk for ischaemic colitis. Aliment Pharmacol Ther. 2007;25:681–92.
8. Knudsen JF, Friedman B, Chen M, Goldwasser JE. Ischemic colitis and sumatriptan use. Arch Intern Med. 1998;158:1946–8.
9. Caekebeke JF, Ferrari MD, Zwetsloot CP, Jansen J, Saxena PR. Antimigraine drug sumatriptan increases blood flow velocity in large cerebral arteries during migraine attacks. Neurology. 1992;42:1522–6.
10. Friberg L, Olesen J, Iversen HK, Sperling B. Migraine pain associated with middle cerebral artery dilatation: reversal by sumatriptan. Lancet. 1991;338:13–7.
11. Naik M, Potluri R, Almasri E, Arnold G. Sumatriptan-associated ischemic colitis. Dig Dis Sci. 2002;47:2015–6.
12. Moawad FJ, Goldkind L. An unusual case of colonic ischemia. South Med J. 2009;102:405–7.
13. Hodge JA, Hodge KD. Ischemic colitis related to sumatriptan overdose. JABFM. 2010;23:124–7.
14. Liu JJ, Ardolf JC. Sumatriptan-associated mesenteric ischemia. Ann Intern Med. 2000;132:597.
15. Alkhatib AA, Gangotena F, Peterson KA. Rizatriptan induced acute on top of chronic ischemic colitis. Am J Gasterolenterol. 2009;104:2643–4.
16. Schwartz DC, Smith DJ. Colonic ischemia associated with naratriptan use. J Clin Gastroenterol. 2004;38:790–2.

17. Charles JA, Pullicino PM, Stoopack PM, Shroff Y. Ischemic colitis associated with naratriptan and oral contraceptive use. Headache. 2005;45:386–9.
18. Westgeest HM, Akol H, Schreuder CMA. Pure naratriptan-induced ischemic colitis: a case report. Turk J Gastroenterol. 2010;21:42–4.
19. Chang L, Tong K, Ameen V. Ischemic colitis and complications of constipation associated with the use of alosetron under a risk management plan: clinical characteristics, outcomes, and incidences. Am J Gastroenterol. 2010;105:866–75.
20. Gallo-Torres H, Brinker A, Avigan M. Alosetron: ischemic colitis and serious complications of constipation. Am J Gastroenterol. 2006;101:1080–3.
21. DeBaise JK. Tegaserod-associated ischemic colitis. Pharmacotherapy. 2005;25:620–5.
22. Cappell MS. Colonic toxicity of administered drugs and chemicals. Am J Gastroenterol. 2004;99:1175–90.
23. Kleespies A, Jonas S, Neuhaus P. Simulation of colon carcinoma: diuretic induced ulcerative-stricturing ischemic colitis. Dtsch Med Wochenschr. 2004;129(13):681–4.
24. Linder JD, Monkemuler KE, Raijman I, et al. Cocaine-associated ischemic colitis. South Med J. 2000;93:909–13.
25. Montgomery EM, Riddell RH. Ischemic colitis in a young patient. Pathol Case Rev. 2004;9:93–6.
26. Keller HW, Lorenz R, Mueller JM, Pichmaier H. Ischemic colitis following digitalis poisoning. Chirurg. 1984;55(12):830–1.
27. Ablassmaier B, Hartmann JA. Case of severe ischaemic colitis following non- steroidal anti-inflammatory drug intake. Zentralbl Chir. 2004;129(6):510–2.
28. Deana DG, Dean PJ. Reversible ischemic colitis in young women in association with oral contraceptive use. Am J Surg Pathol 19 (1995): :454- 62.
29. Giurbuz AK, Gurbuz B, Salas L, Rosenshein NB, Donowitz M, Giardiello FM. Premarin induced ischemic colitis. J Clin Gastro. 1994;19:108–11.
30. Preventza OA, Lazarides K, Sawyer MD. Ischemic colitis in young adults: a single-institution experience. J Gastrointest Surg. 2001;5:388–92.
31. Salk A, Stobaugh DJ, Deepak P, Ehrenpreis ED. Ischaemic colitis in rheumatoid arthritis patients receiving tumor necrosis factor-α inhibitors: an analysis of reports to the US FDA Adverse Event Reporting System. Drug Saf. 2013;36:329–34.
32. Salk A, Stobaugh DJ, Deepak P, Ehrenpreis ED. Ischemic colitis with type 1 interferons used in the treatment of hepatitis C and multiple sclerosis: an evaluation from the Food and Drug Administration Adverse Event Reporting System and review of the literature. Ann Pharmacother. 2013;47:537–42.
33. Rodman RE, Willson TD, Connolly MM, Podbielski FJ. Ischemic colitis secondary to ergotamine use: a case study. Case Rep Gastroenterol. 2011;5:1–4.
34. Rashid A, Hamilton SR. Necrosis of the gastrointestinal tract in uremic patients as a result of sodium polystyrene sulfonate in sorbitol: an underrecognized condition. Am J Surg Pathol. 1997;21:60–9.
35. Traino A, Buckley M, Bassett M. Probable ischemic colitis caused by pseudoephedrine with tramadol as a possible contributing factor. Ann Pharmacother. 2004;38:2068–70.
36. Camerilli M. Is there an experimental basis for the development of ischaemic colitis as a result of 5-HT3 antagonist treatment? Neurogastroenterol Motil. 2007;19:77–84.
37. Millson D, Sohail S, Lettis S, et al. Duration of inihibition of the flare response to intradermal 5-hydroxytryptamine in man by GR68755, an novel specific 5-HT3 receptor antagonist. Br J Clin Pharmacol. 1992;33:546–7.
38. Limmroth V, May A, Auerbach P, Wosnitza G, Eppe T, Diener HC. Changes in cerebral blood flow velocity after treatment with sumatriptan or placebo and implications for the pathophysiology of migraine. J Neurol Sci. 1996;138(1–2):60–5.
39. Ringle Y, Wilson J, D'Agostino R, Lewis JH. Development and validation of an ischemic colitis clinical diagnosis assessment instrument. Gastroenterology 2005;128.4 (Suppl 2):A467.
40. Imitrex tablets prescribing information, 2012. GlaxoSmithKline Research Triangle Park, NC 27709. http://us.gsk.com/products/assets/us_imitrex_tablets.pdf Accessed 7 Dec 2013.
41. Amerge (naratriptan hydrochloride) tablets prescribing information, October 2013. GlaxoSmithKline Research Triangle Park, NC 27709. http://us.gsk.com/products/assets/us_amerge.pdf. Accessed 7 Dec 2013.
42. Maxalt (rizatriptan benzoate) prescribing information, January 2013. Merck & Co. Whitehouse Station, NJ 08889. http://www.merck.com/product/usa/pi_circulars/m/maxalt/maxalt_pi.pdf. Accessed 7 Dec 2013.
43. Relpax (eletriptan hydrobromide) tablets prescribing information, May 2008; Roerig Division of Pfizer, NY,NY 10017. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=986dc112-b97b-44a3-bfaf-074f906f8bb2. Accessed 7 Dec 2013.
44. Axert (almotriptan malate) tablets prescribing information, April 2011; Ortho-McNeil Neurologics, Titusville, NJ 08560. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=b13ba9bf-1661-456a-8eae-6d110ea08c94. Accessed 7 Dec 2013.
45. Frova (frovatriptan succinate) prescribing information, April 2007; Endo Pharmaceuticals, Inc. 100 Endo Blvd, Chadds Ford, PA 19317. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=294d60f3-005b-40d9-a404-cdd77f62b820. Accessed 7 Dec 2013.
46. Zomig (zolmitriptan) prescribing information, September 2012; AstraZeneca/Impax Pharmaceuticals, Hawward, CA 94544. http://dailymed.nlm.nih.gov/dailymed/lookup.cfm?setid=294d60f3-005b-40d9-a404-cdd77f62b820. Accessed 7 Dec 2013.
47. Personal communication, JP Nicandro. Data on file with Prometheus Laboratories, San Diego, CA.
48. Loder E. Triptan therapy in migraine. N Engl J Med. 2010;363:63–70.
49. Tfelt-Hansen P, De Vries P, Saxena PR. Triptans in migraine: a comparative review of pharmacology, pharmacokinetics and efficacy. Drugs. 2000;60:1259–87.
50. Bax WA, Renzenbrink GJ, Van Heuven-Nolsen D, Thijssen EJ, Bos E, Saxena PR. 5-HT receptors mediating contractions of the isolated human coronary artery. Eur J Pharmacol. 1993;239:203–10.
51. Connor HE, Feniuk W, Humphrey PP. 5-Hydroxytryptamine contracts human coronary arteries predominantly via 5-HT2 receptor activation. Eur J Pharmacol. 1989;161:91–4.
52. Jamieson DG. The safety of triptans in the treatment of patients with migraine. Am J Med. 2002;112:135–40.
53. Szarfman A, Machado SG, O'Neill RT. Use of screening algorithms and computer systems to efficiently signal higher-than-expected combinations of drugs and events in the US FDA's spontaneous reports database. Drug Saf. 2002;25(6):381–92.