BMJ Case Reports

Unexpected outcome (positive or negative) including adverse drug reactions

Ischaemic colitis associated with oral contraceptive and bisacodyl use

Shahnaz Ajani,[1] Ryan T Hurt,[2,3] David A Teeters,[1] Lawrence R Bellmore[1]

[1]Department of Medicine, Mayo Clinic, Rochester, Minnesota, USA
[2]Division of General Internal Medicine, Mayo Clinic, Rochester, Minnesota, USA
[3]Department of Medicine, University of Louisville, Louisville, Kentucky, USA

Correspondence to Dr Ryan T Hurt, hurt.ryan@mayo.edu

Summary

A woman with a history of hip replacement presented 3 days prior to revision of the hip with abdominal pain, diarrhoea and haematochezia. These symptoms began 6 h after she began taking bisacodyl in preparation for her upcoming surgery. She was on low-dose estradiol for hormone replacement therapy (HRT). Subsequent colonoscopy and biopsies were consistent with acute colonic ischaemia (CI). She was treated with intravenous fluids and antibiotics and discharged and told to stop HRT and bisacodyl. Follow-up colonoscopy 1 month after discharge was normal. This case adds to the three other previously reported cases of bisacodyl-associated CI.

BACKGROUND

Intestinal hypoperfusion, vasospasm or stenosis may lead to mesenteric ischaemia. Mesenteric ischaemia can lead to gangrene-associated bowel infarction, sepsis and death. Colonic ischaemia (CI) is generally associated with older adults (>60) and is the most common presentation of mesenteric ischaemia.[1] Ischaemia involving the left side of the colon is more common and has lower rates of surgical intervention and mortality compared to bilateral, right side or transverse colon involvement only.[2 3] Overall mortality is lower in patients who do not require surgical intervention (4%) compared to those operated on (23%).[3] The clinical presentation of CI is variable but typically includes abdominal pain, gross rectal bleeding, diarrhoea, vomiting and dizziness.[3] Co-morbid conditions most commonly associated with CI are hypertension, diabetes, chronic obstructive pulmonary disease, coronary artery disease and atrial fibrillation.[2 4] CI has been associated with pharmaceuticals such as estrogen, opioids, diuretics, alosetron and tegaserod. There are three case reports of CI associated with acute administration of the stimulant laxative bisacodyl with no other identifiable comorbidities.[5 6] We present a case of CI in a patient who was taking estrogen and was started on bisacodyl for constipation prior to orthopaedic surgery.

CASE PRESENTATION

A 54-year-old woman was being evaluated in the orthopaedic clinic regarding her previous right total hip arthroplasty. She was scheduled to undergo right acetabular revision 3 days following her office visit. She had a history of chronic constipation (two to three bowel movements per week) for years and it was recommended that she might benefit from laxative therapy prior to her operation. The evening prior to admission she took three bisacodyl tablets orally around 18:00. Approximately 6 h later, she had a normal bowel movement. This was followed by abdominal pain that was described as crampy with associated loose stool. Her bowel movements were eventually accompanied by haematochezia, which she initially described as bright red blood in the toilet bowl. Subsequently, she passed a large amount of clotted blood.

She presented to our emergency department (ED) where she was noted to have leucocytosis of 25.1×10^9 per litre (white cell count in the orthopaedic clinic was 6.7×10^9 per litre). The patient was also complaining of a dull left-sided abdominal pain, and for this reason, a CT scan of the abdomen and pelvis was obtained. The CT scan was remarkable for mild inflammatory changes around the descending and sigmoid colon. There was evidence of minimal wall thickening but no evidence of diverticular disease. Her mesenteric vasculature was widely patent, and there was no evidence of significant calcification of the vessels. In the ED, she was given 1 litre of fluid, Cipro and Flagyl IV for antibiotic coverage and 150 μg of Fentanyl over 4 h for pain control. She was admitted to the general internal medicine service for observation.

Upon arrival to the medicine floor, she was in 6/10 pain after receiving a subsequent dose of Fentanyl 50 μg intravenously. She said her pain was localised to the left lower quadrant (LLQ) and was crampy and intermittent. When it would occur it would pass like a wave across her abdomen towards the right. She denied any recent illness or other sick contact. She works at a school with many small children but was not aware of any who had recently been ill. She had no recent travel history. There had been no recent medicine changes besides the bisacodyl, and she had not been on antibiotics for over a year. She had been on hormone replacement (estradiol 0.5 mg per day) for over 5 years. She was orthostatic upon arrival to the floor despite fluid resuscitation in the ED. Shortly after arrival to the medicine floor she had another bowel movement of gross, red blood, roughly 40–50 cm^3. Additional fluid was ordered and stool studies were obtained. The patient underwent a flexible sigmoidoscopy to determine the cause of her acute gastrointestinal bleeding.

INVESTIGATIONS

Basic blood counts demonstrated stable haemoglobins of between 13.0 and 15.0 g/dl and a leucocytosis of 25.1×10^9 per litre. Blood, urine and sputum cultures did not have any growth. Liver enzymes, pancreatic enzymes and lactate were normal. Stool studies did not reveal any fecal leucocytes and parasite testing was negative. *Clostridium difficile*, bacterial pathogens rapid PCR, and *Entamoeba histolytica* testing was negative. Our bacterial enteric pathogens PCR testing includes *Campylobacter jejuni*, *Campylobacter coli*, *Salmonella*, *Shigella*, *Yersinia*, shiga toxin-producing *Escherichia coli* and enteroinvasive *E coli* DNA. Viral testing for cytomegalovirus was not performed. Electrocardiogram was normal and no events were noted on 24 h cardiac monitoring. There was no coagulogram performed on the admission.

Flexible sigmoidoscopy demonstrated that beginning at 35 cm from the dentate line and extending upward, there was a severe colitis that had the endoscopic appearance of ischaemia. Multiple biopsy specimens were obtained. The distal 35 cm of colonic mucosa appeared grossly normal. Retroflexed view of the perianal area was normal. The biopsies were consistent with acute ischaemic colitis. There was oedema and haemorrhage in the lamina propria and superficial epithelial necrosis. Our pathology colleagues hypothesised that these changes could be due to vascular disease, low perfusion states, verotoxin-producing *E coli* O157:H7, other toxin-producing bacteria or drugs. Vascular disease and infectious aetiology were less likely given the CT scan findings.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for CI is very broad as the symptoms most often reported are abdominal pain (87%), rectal bleeding (84%) and diarrhoea (56%).[3] Consideration for infectious aetiologies, inflammatory bowel, diverticulitis, and colorectal cancer should be made. Serum and stool lab testing, CT imagining, and biopsies can help narrow the diagnosis. Colonoscopy is the diagnostic test of choice over barium enema and should be performed without preparation.[7] There are a number of diseases (table 1) and medications (table 2) which are associated with CI.[2 8] A large number of cases are idiopathic.[7]

TREATMENT

The treatment for CI is largely supportive and very few require surgical intervention.[7] The patient in our case was treated supportively with fluid resuscitation and, because of initial concern for infectious colitis, ciprofloxacin and metronidazole. Her bisacodyl and hormone replacement therapy were discontinued. There are few case reports regarding CI with estrogen or bisacodyl use. In the previously published cases, the patients were treated similarly with fluids, antibiotics and discontinuation of the offending drug.[5 6]

The risk of recurrence of CI is very low, with around 94% of patients remaining free of recurrence at 4 years.[3] CI is associated with an approximate 4% death rate.[3] Medications that could contribute to CI should be stopped. Colonic distension can be alleviated with a rectal tube. Repeat imaging tests, endoscopic procedures and basic lab monitoring can be performed until the patient stabilises.[8] The patient should be closely monitored for signs of colonic infarction, and surgery should be consulted as appropriate. However, surgical intervention is usually not necessary and in one retrospective study, 88% of patients who developed CI prior to hospitalisation did not require any surgery.[3]

Table 1 Medical causes-induced colonic ischaemia

Cardiac/vascular
Hypercoagulable states
Vasculitis
Arterial emboli
Cholesterol emboli
Sickle cell disease
Atrial myxoma
Arrhythmias
Heat failure
Inferior mesenteric artery thrombosis
Shock
Amyloidosis
Atherosclerosis
Diabetes
Infectious
Escherichia coli O157:H7
Angiostrongylus
Hepatitis B
CMV
Surgical/iatrogenic
Colectomy with inferior mesenteric artery ligation
Colon bypass
Barium enema
Colon cancer
Pseudoobstruction
Ruptured ectopic pregnancy
Strangulated hernia
Pancreatitis
Other
Long-distance running
Idiopathic
Haemodialysis

CMV, cytomegalovirus.

OUTCOME AND FOLLOW-UP

Our patient did very well after discharge without any further bleeding. She had mild abdominal pain for about 10 days after discharge which subsequently completely resolved. She had a follow-up colonoscopy approximately

Table 2 Causes of drug and medication-induced colonic ischaemia

- Nonsteroidal anti-inflammatory drugs (NSAIDS)
- Progestins
- Estrogens
- Penicillin
- Cocaine
- Pseudoephedrine
- Alosetron
- Tegaserod
- Sumatriptan
- Glycerin enema
- Digitalis
- Saline laxatives
- Polyethylene glycol

BMJ Case Reports 2012; doi:10.1136/bcr-12-2011-5451

1 month after discharge which was normal with no signs of ischaemia. She has not had any clinical symptoms attributed to stopping the estrogen.

DISCUSSION

We present a fourth case of CI associated with acute bisacodyl use. The other risk factors for CI that we identified in our case were the use of low-dose estrogen and chronic constipation. Infectious and vascular causes were less likely and biopsies suggested ischaemia. Our patient's symptoms improved, and she was taken off the estrogen and bisacodyl. A follow-up colonoscopy was normal. It may have been that the estrogen use and chronic constipation predisposed her to the effects of the acute use of bisacodyl. This seems to be the most likely explanation as she had been on estradiol for over 5 years and had chronic constipation for years with no similar problems.

Cases of women developing CI while in high estrogen states either via pregnancy, HRT or oral contraception have been reported since 1979.[9 10] These were followed by a more recent retrospective study of acute ischaemic colitis in 12 postmenopausal women months after starting HRT.[11] This study found that the mean duration of HRT use was 5.7 months, and most patients woke up in the middle of the night with sudden onset of lower abdominal pain followed by diarrhoea and haematochezia. Notably, most women took the medication late in the evening (19:00–21:00). Colonoscopy found "diffuse bleeding with ischaemic lesions of the mucosa and bloody content from descending colon to sigmoid colon" in all cases with biopsy consistent with acute haemorrhagic colitis. The majority of patients had involvement of the descending or sigmoid colon or a combination of the two, while a single case had involvement of the transverse colon. The patients were followed up for a mean of 2.3 years and all 12 had a normal colonoscopy 3–4 months after the initial episode.[11]

There are three previous cases of possible bisacodyl-induced CI with our current case being the fourth (table 3). The first was a 33-year-old woman with a 1 week history of constipation. The patient was healthy had no other identifiable risk factors for CI including a denial of cocaine, tobacco or OCP use.[5] She took two tablets of bisacodyl to help with the constipation. Six hours later, she developed right lower quadrant (RLQ) pain. The next morning she developed diarrhoea with frank haematochezia. She had a slightly elevated WBC at 11.9×10^9 per litre, RLQ pain on exam, negative hypercoagulable workup, and patchy ulceration of the descending and sigmoid colon with biopsies consistent with ischaemic colitis.[5] She improved with intravenous fluids and antibiotics and after a short hospital stay discharged home.[5]

The second case was a healthy 19- year-old man with a history of intermittent constipation. Approximately 1 hour after taking one tablet of bisacodyl, he presented with intense abdominal pain and hard stools, followed by diarrhoea and frank haematochezia.[5] He denied cocaine and tobacco use and took no other medications. He had a slight temperature of 100.3°F and LLQ abdominal pain on exam. His WBC count was 10.9×10^9 per litre and stool cultures were negative. CT scan demonstrated mildly thickened colon and colonoscopy revealed patchy haemorrhage and inflammation at the splenic flexure.[5] Biopsies were performed and consistent with CI. He improved with intravenous fluids and antibiotics and was discharged home.[5]

The third case was a 68-year-old man who was undergoing a low-volume bowel preparation for colon cancer screening. He had a history of polyps on his colonoscopy 5 years previously.[6] The previous colonoscopy preparation was a traditional preparation, and he had no side effects. Approximately 2 h after taking bisacodyl he reported LLQ abdominal pain followed by haematochezia. Colonoscopy examination found segmental colitis at the splenic flexure and biopsies were suggestive of CI.[6] He apparently did well and presented for follow-up colonoscopy 2 years later and again was prepped using a low volume bowel preparation including bisacodyl. Shortly after taking the bisacodyl he reported abdominal pain and haematochezia. Colonoscopy and biopsies were again consistent with CI. A follow-up colonoscopy 3 years later with a traditional preparation was well tolerated with no abdominal pain or signs of CI.[6]

The explanation for bisacodyl-induced CI is not clear. Sudden reduction of colonic blood flow can lead to CI.[6] Bisacodyl increases motility which can lead to increased pressure in the colon.[6] This increased pressure can potentially lead to decreased colonic perfusion. Bisacodyl is an over-the-counter treatment for constipation and is often used in low-volume colon preparations.[12] All four cases had a similar pattern of abdominal pain approximately 1–6 h following bisacodyl use, with our patient experiencing pain at 6 h. Our patient had two risk factors for CI

Table 3 Cases of bisacodyl-induced colonic ischaemia (CI)

Age	Sex	PMH	Symptoms	Colonoscopy findings	Pathology	Treatment	Outcome
33	F	Depression	Abdominal pain, diarrhoea, haematochezia	Oedema, patchy ulceration, descending and sigmoid colon	Compatible with CI	Intravenous fluids, antibiotics	Resolved[5]
19	M	Constipation, anal fissure	Abdominal pain, fever, diarrhoea, haematochezia	Patchy haemorrhage and inflammation at the splenic flexure	Compatible with CI	Intravenous fluids, antibiotics	Resolved[5]
68	M	Colon polyps	Abdominal pain, haematochezia	Oedema and segmental colitis at the splenic flexure	Compatible with CI	Intravenous fluids antibiotics	Had recurrence of CI 2 years later associated with bisacodyl. No CI during traditional prep on most recent scope[6]
54	F	Total hip replacement, on HRT	Abdominal pain, diarrhoea, haematochezia	Descending colitis	Compatible with CI	Intravenous fluids, pain medicines, antibiotics	Resolved with 1 month follow-up scope normal

(HRT and chronic constipation) that had been unchanged for years. It is likely that these risk factors predisposed her to the acute administration of bisacodyl. The only way to determine definitively if the bisacodyl contributed to the CI in the setting of these risk factors would be to re-challenge her with bisacodyl, which would be unnecessary and unethical. Bisacodyl has been shown to be safe and effective and further data are needed to determine if bisacodyl should be avoided in patients with risk factors for CI.

Learning points

- Colonic ischaemia (CI) is the most frequent cause of intestinal ischaemia.
- The most frequent signs are abdominal pain, haematochezia, and diarrhoea.
- Medications including hormone replacement are rare causes of CI.
- Bisacodyl has been associated with CI.
- Clinicians should use caution when recommending medications associated with CI in patients with risk factors such as hormone replacement use.

Competing interests None.

Patient consent Obtained.

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