Ischemic colitis after weight-loss medication

Dan Comay MD¹, Jennifer Ramsay MD², E Jan Irvine MD³

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BACKGROUND: Previous weight-loss medications have received cautious support due to their association with pulmonary hypertension and valvular heart disease. However, newer drugs are increasingly being recommended as potentially safer and more efficacious. We report a case of ischemic colitis possibly linked to the use of a weight-loss drug, and review the literature to highlight an important latent consequence of these medications.

CASE REPORT: A 59-year-old obese woman presented to the emergency room with rectal bleeding and suprapubic abdominal pain. Her medical history was unremarkable for risk factors for bowel ischemia. An appetite suppressant, phentermine 15 mg daily, had been prescribed, and had resulted in a 12 kg weight loss over 10 weeks. Colonoscopy and biopsies both demonstrated findings typical of mild ischemia at the splenic flexure.

DISCUSSION: Phentermine, an amphetamine-derived sympathomimetic, acts centrally to suppress appetite. While there are no published reports linking the use of phentermine as a single agent to ischemic colitis, phentermine alone has been associated with ischemic neurological events and, when used in combination with fenfluramine, has been implicated in a single case of acute ischemic colitis. Other sympathomimetics, such as cocaine, have been clearly linked with ischemic colitis.

CONCLUSIONS: This report describes a temporal association with the use of phentermine and the development of ischemic colitis. Heightened awareness and appropriate surveillance is warranted to determine whether the use of weight-loss drugs, such as phentermine, can lead to ischemic colitis.

Key Words: Ischemic colitis; Obesity; Weight-loss medications

Ischemic colitis is a common cause of lower gastrointestinal bleeding, accounting for 10% to 19% of hospital admissions for lower gastrointestinal bleeding (1,2). Ischemic colitis is a consequence of inadequate mesenteric blood flow that fails to meet intestinal metabolic demands, and is frequently observed in the arterial watershed areas, such as the splenic flexure (3). Several additional risk factors have been implicated to contribute to the development of ischemic colitis and are shown in Table 1.

Phentermine, a commonly prescribed weight-loss drug, is currently approved for short term weight loss (4). It is an amphetamine derivative that stimulates norepinephrine release in the hypothalamus to suppress appetite centrally (5). Its use, in combination with fenfluramine, increased sharply following the publication of the fenfluramine-phentermine ("fen-phen") study, demonstrating its superiority to placebo for

Une colite ischémique après la prise d'un médicament amaigrissant

HISTORIQUE : Des médicaments amaigrissants ont déjà reçu un accord prudent en raison de leur association avec une hypertension pulmonaire et une cardiopathie valvulaire. Cependant, de nouveaux médicaments sont de plus en plus recommandés en raison de leur potentiel d'innocuité et d'efficacité plus élevé. Nous déclarons un cas de colite ischémique pouvant être relié à la prise d'un médicament amaigrissant et procédons à une analyse bibliographique pour souligner une conséquence latente grave de ces types de médicament.

RAPPORT DE CAS : Une femme obèse de 59 ans s'est présentée à l'urgence en raison d'une hémorragie rectale et de douleurs abdominales suprapubiennes. Ses antécédents médicaux ne laissaient songer à aucun facteur de risque d'ischémie intestinale. Un coupe-faim, sous forme de 15 mg par jour de phentermine, lui avait été prescrit et lui avait fait perdre 12 kg en dix semaines. La coloscopie et les biopsies ont permis de découvrir des constatations types d'une ischémie bénigne à l'angle splénique.

EXPOSÉ : Le phentermine, un sympathomimétique dérivé de l'amphétamine, agit centralement pour couper l'appétit. Bien qu'il n'existe aucun compte rendu publié reliant l'utilisation du seul phentermine à la colite ischémique, le phentermine seul s'associe à des atteintes neurologiques ischémiques et, combiné à la fenfluramine, à un seul cas de colite ischémique aiguë. D'autres sympathomimétiques, tels que la cocaïne, sont clairement reliés à la colite ischémique.

CONCLUSIONS : Le présent compte rendu décrit une association temporelle entre l'utilisation de phentermine et l'apparition d'une colite ischémique. Une sensibilisation accrue et une surveillance convenable s'imposent pour déterminer si l'usage de coupe-faim comme le phentermine peut provoquer une colite ischémique.

weight reduction (6). However, subsequent reports linking fenfluramine and dexfenfluramine to the development of pulmonary hypertension and cardiac valvular abnormalities led to a dramatic decline in their use, as well as that of phentermine (7-10). Both fenfluramine and dexfenfluramine were subsequently withdrawn from the market (11).

We report a case of ischemic colitis following the use of a common weight-loss drug, phentermine, in a patient without other risk factors for large bowel ischemia, and review the literature to illustrate a potential important consequence of this medication.

CASE PRESENTATION

A 59-year-old woman presented to the emergency department at Hamilton Health Sciences (McMaster University, Hamilton, Ontario) with a history of passing bright red loose

Departments of ¹Medicine (Gastroenterology) and ²Pathology, McMaster University, Hamilton, Ontario; ³Department of Medicine (Gastroenterology), University of Toronto, Toronto, Ontario

Correspondence: Dr EJ Irvine, Division of Gastroenterology, St Michael's Hospital, Room 16-052 Cardinal Carter Wing, 30 Bond Street, Toronto, Ontario M5B 1W8. Telephone 416-864-5060, fax 416-861-8378, e-mail irvinej@smh.toronto.on.ca

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TABLE 1
Selected risk factors for ischemic colitis

Aortic or cardiac surgery (23,24)
Major cardiovascular episode (eg, cardiac failure, shock) (25)
Major vascular occlusion (eg, mesenteric venous thrombosis) (26)
Vasculitis (eg, systemic lupus erythematosus, polyarteritis nodosa) (27,28)
Hypercoagulable state (29)
Infection (eg, <i>Escherichia coli</i> O157:H7, cytomegalovirus) (30,31)
Prolonged physical exertion (eg, long-distance running) (32)
Drugs: estrogen (33), pseudoephedrine (15-17), methamphetamine (18-20), cocaine (21,22), nonsteroidal anti-inflammatory drugs (34), aloestron hydrochloride (35)

Figure 1) Acute ischemic colitis (biopsy magnification 100×). There is hemorrhage and a mixed inflammatory cell infiltrate in the lamina propria. The mucosa shows regenerative changes of increased basophilia and mucin depletion

stool that was preceded by several hours of severe, crampy, suprapubic abdominal pain. She had three bloody bowel movements that produced approximately 175 mL and a one-day history of nausea and bilious vomiting without blood or coffee-ground material. She denied having fevers or rigors and had noted an intentional weight loss of 12 kg (from 82 kg to 70 kg) over 10 weeks, after starting the phentermine. She had also experienced two self-limited episodes of suprapubic abdominal pain with nonbloody diarrhea four weeks and eight weeks after starting the drug, but did not seek medical attention.

She had no prior history or symptoms suggestive of inflammatory bowel disease and no recent history of antibiotic use, well-water consumption or eating commercially prepared meals. She had recently travelled to Virginia and eaten in a communal dining hall, but no known contacts had fallen ill and her travelling companion had remained well.

Her medical history was significant for inflammatory osteoarthritis, asthma, gastroesophageal reflux disease, mild hypertension and paroxysmal supraventricular tachycardia. She had no symptoms of ischemic heart disease, and an extensive cardiac work-up, performed one year previously for tachycardia, had been normal. Her mother had left-sided ulcerative colitis.

Her medications included prednisone 5 mg daily, verapamil 180 mg twice daily, albuterol puffer as needed, budesonide two puffs twice daily, esomeprazole 40 mg daily, acetaminophen

Figure 2) Remote ischemic injury (biopsy magnification 100×). There is marked fibrosis and loss of glandular mucosa (gland drop-out) in the lamina propria

with codeine as needed for arthralgia and phentermine resin (Ionamin, Celltech Pharmaceuticals, USA) one 15 mg capsule taken daily before breakfast. She had previously taken estrogen replacement for postmenopausal symptoms but discontinued this medication on her physician's advice three months before her presentation.

She was a lifelong nonsmoker, rarely consumed alcohol and drank four to six cups of tea daily. She had a sedentary lifestyle with no high-endurance pursuits. She had a remote cholecystectomy and had an allergy to nonsteroidal anti-inflammatory drugs, which caused her to wheeze.

On arrival at the emergency department, her blood pressure was 144/80 mmHg, heart rate was 90 beats/min and regular, and there was no postural change in either. She was afebrile. Her cardiovascular and respiratory examinations were within normal limits. On examination of the abdomen, bowel sounds were present and she had mild left lower quadrant tenderness without rebound tenderness or guarding. A digital rectal examination revealed an empty rectal vault with bright red blood on the examining glove.

Blood chemistry panel and coagulation profiles were normal. Apart from a mildly elevated white blood cell count of $11.9 \times 10^9/L$, the complete blood count was normal. A selected panel of bloodwork to exclude vasculitis – including C-reactive protein, antinuclear antibodies, extractable nuclear antibodies, rheumatoid factor, and C3 and C4 levels – was normal. Screening for antineutrophilic cytoplasmic antibodies was not performed.

Stool examinations were performed to exclude the presence of pathogens and *Clostridium difficile* toxin. Abdominal x-rays revealed multiple fluid-filled loops of bowel without distension, thumb-printing, air-fluid levels or free intraperitoneal air.

A colonoscopy, performed within 12 h of hospitalization, demonstrated 10 cm of edematous, ulcerated, hemorrhagic mucosa at the splenic flexure with normal flanking mucosa. Biopsies showed features of both acute ischemic colitis (Figure 1) and chronic ischemic morphological features, such as fibrosis (Figure 2).

The patient improved quickly with intravenous fluid administration and supportive care and was discharged home after five days of observation. She remains asymptomatic four months later and has not resumed her weight-loss medication.

DISCUSSION

There are no published reports to date of phentermine use alone in association with ischemic colitis. There was, however, a single case report of a healthy 36-year-old woman who developed ischemic colitis while taking fenfluramine-phentermine (12). She had lost 14 kg while on a combination of fenfluramine 20 mg and phentermine 30 mg three times per day for three months. She had no risk factors for bowel ischemia, apart from remote birth-control pill use, rare nonsteroidal anti-inflammatory drug use and smoking five cigarettes per week.

Phentermine has also been described in association with ischemic neurological events in two patients (13). One patient had a seven-day hemisensory disturbance consistent with a transient ischemic attack, while the other patient had a right occipital infarct with multiple vascular abnormalities on cerebral angiogram.

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CONCLUSION

This case report describes a temporal association between the use of phentermine and the development of ischemic colitis. Heightened awareness and appropriate surveillance is warranted to determine whether the use of weight-loss drugs, such as phentermine, can lead to ischemic colitis.