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Lower gastrointestinal bleeding in a patient receiving sevelamer: Case report

Tessa S Schoot[1,2], Tessa EH Römkens[3] and Ellen K Hoogeveen[1]

Abstract

Phosphate binders such as sevelamer are widely used in patients with chronic kidney disease to lower serum phosphate levels. We present a case of a 67-year-old woman with lower gastrointestinal bleeding after 9 days of using sevelamer carbonate (Renvela®). Sigmoidoscopy revealed multiple deep ulcers (diameter 10–15 mm) and mucosal oedema. Histologic examination showed deposition of sevelamer crystals in these rectal ulcers. We hypothesized that the lower gastrointestinal bleeding was caused by deposition of sevelamer crystals. After cessation of sevelamer, gastrointestinal bleeding stopped. Deposition of sevelamer crystals in the gastrointestinal tract is a rare complication of sevelamer therapy. There are only 17 other recorded cases of gastrointestinal deposition of sevelamer crystals. This adverse effect should be considered in all patients taking sevelamer who present with gastrointestinal symptoms, such as gastrointestinal bleeding and abdominal pain. When sevelamer is discontinued, symptoms and mucosal damage appear to revert.

Keywords

Sevelamer, phosphate binder, gastrointestinal symptoms, gastrointestinal bleeding

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Introduction

Hyperphosphatemia is highly prevalent in patients with severe chronic kidney disease. It is caused by decreased filtration of phosphate and increased release of phosphate from the bone due to secondary hyperparathyroidism. Treatment and prevention of hyperphosphatemia are important as it is associated with an increased risk of all-cause mortality.[1] The main methods to manage hyperphosphatemia are dietary modification (i.e. low phosphate diet) and oral phosphate binders, such as sevelamer.[1] Sevelamer is a non-absorbable, calcium-free polymeric anion-exchange resin with multiple ammonia (NH_3) groups.[2] Phosphate will be bound to sevelamer after protonation of NH_3 to NH_4^+ in the acidic milieu of the stomach. The resorption of phosphate is decreased, as sevelamer with bound phosphate is excreted with the faeces. There are currently two subtypes of sevelamer available: sevelamer hydrochloride (Renagel®) and sevelamer carbonate (Renvela®). Dosing of sevelamer is individualized and based on serum phosphate concentration. The recommended starting dose is 2.4 g per day (if serum phosphate 1.8–2.4 mmol/l) or 4.8 g per day (if serum phosphate ⩾2.4 mmol/l) divided into three doses at mealtimes. Dose adjustments, when necessary, should be done every 1–3 weeks in increments of 800 mg per meal.[2]

Case

We present a 67-year-old female with chronic kidney failure stage G3b (estimated glomerular filtration rate (eGFR) 32 mL/min/1.73 m^2) due to vascular disease and diabetes mellitus type 2. The full medical history and medication use are listed in Table 1 (last row). The patient did not use non-steroidal anti-inflammatory drugs (NSAIDs). The patient was admitted to the hospital with acute-on-chronic renal insufficiency (eGFR

[1]Department of Nephrology, Jeroen Bosch Ziekenhuis, 's-Hertogenbosch, The Netherlands
[2]Department of Nephrology, Radboud University Medical Center, Nijmegen, The Netherlands
[3]Department of Gastroenterology and Hepatology, Jeroen Bosch Ziekenhuis, 's-Hertogenbosch, The Netherlands

Corresponding Author:
Tessa S Schoot, Department of Nephrology, Jeroen Bosch Ziekenhuis, 5223 GZ 's-Hertogenbosch, The Netherlands.
Email: Tessa.schoot@radboudumc.nl

Table 1. Overview of previously published cases with deposition of sevelamer crystals in the gastrointestinal tract.

Paper	Patient characteristics				Sevelamer			Case details			
	Sex (age)	*Race*	*Medical history*	*Comedication*	*Type*	*Total daily dosage*	*Duration of use*	*Symptoms*	*Endoscopy*	*Pathology**	*Outcome*
Swanson et al.[3]	Male (68)	A	CKD, HT, DM	–	Renvela®	1600 mg	–	Asymptomatic	–	Inflammatory polyp in colon	–
	Male (38)	C	CKD, HUS, primary sclerosing cholangitis, liver Tx, ulcerative colitis	–	Renvela®	1600 mg	–	Asymptomatic	Colon polyps	Inflammation, inflammatory polyp, crypt distortion, cryptitis, Paneth cell metaplasia	–
	Female (49)	B	CKD, lupus, RTx, HT	–	Renvela®	2400 mg	–	Dyspepsia, nausea, vomiting	Diffuse peptic changes in oesophagus	Extensive ulceration	–
	Male (53)	B	CKD, DM, HT, hyperparathyroidism	–	Renvela®	800 mg	–	Asymptomatic	Colon polyp	Mucosal prolapse	–
	Male (66)	–	CKD, peptic ulcer disease, reflux oesophagitis, Barrett's oesophagus, HT, gout, PAF, non-invasive papillary urothelial carcinoma	–	Renvela®	–	–	Rectal bleeding	Colon polyps	Fragments of tubular adenoma	–
	Male (81)	H	CKD, PVD, HT, DM	–	Renagel®	1600 mg	–	Dysphagia, odynophagia, nausea, vomiting	Ulcerations and eroded mucosa oesophagus	Extensive ulceration	–
Okwara et al.[4]	Male (70)	–	ESRD, HD, DM, HT, pre-pyloric ulcer (*Helicobacter pylori* negative)	–	Renvela®	800 mg	9 months	Haematemesis, rectal bleeding, abdominal pain	Ulcerated mass at the pylorus	Chronic, focally active gastritis (*Helicobacter pylori* negative)	Stop sevelamer. Gastroscopy 7 months later: normal mucosa.
Chintamaneni et al.[5]	Female (61)	B	ESRD, HD, obesity	Heparin IV since 2 days; rest unknown	–	2400 mg	–	Rectal bleeding	Ulceration (50 mm) in sigmoid colon (25 cm ab anum)	Ulcer bed with attached fibrin and haemorrhage	Stop sevelamer: stop rectal bleeding
Okwara et al.[6]	Male (79)	A	ESRD, dialysis, DM, ischaemic heart disease	–	–	–	–	Diarrhoea, abdominal pain	Polypoid mass in caecum	Necrosis and ischaemic changes	–
Amer et al.[7]	Male (64)	–	ESRD, HD	–	–	–	–	Haematemesis, abdominal pain	Multiple ulcers in gastric body	–	–
Tieu et al.[8]	Female (64)		ESRD (diabetic nephropathy), HD, DM, C. difficile infection	–	Renvela®	1600 mg	2 months	Constipation, abdominal pain, rectal pain, rectal bleeding	Circumferential ulcerations, exudates and purplish hue to rectal mucosa	Fibrinopurulent/necrotic debris	Stop sevelamer: resolution of constipation. Vancomycin oral 10 days.

(Continued)

Table 1. (Continued)

Paper	Patient characteristics				Sevelamer			Case details			
	Sex (age)	*Race*	*Medical history*	*Comedication*	*Type*	*Total daily dosage*	*Duration of use*	*Symptoms*	*Endoscopy*	*Pathology**	*Outcome*
Yuste et al.[9]	Male (53)	–	ESRD (crescentic glomerulonephritis), RTx 21 years previously, HD for last 6 years, sigmoidectomy, calciphylaxis	–	Renagel®	8000 mg	–	Rectal bleeding	Inflammatory polyps in stomach and colon	Lesion ileocecal valve: pseudoinflammatory polyp with fibrotic mucosal changes and foreign body reaction	Reduction of Renagel® dose: cessation of rectal bleeding and rise of haemoglobin level
	Female (76)	–	ESRD (diabetic nephropathy), HD, DM, obesity, HT, COPD	–	Renagel®	800 mg	–	Rectal bleeding	Chronic gastritis, diverticulosis and several gastric and colonic polyps	Colorectal mucosa: chronic inflammation, superficial erosions	Stop sevelamer (after RTx): stop rectal bleeding
	Female (51)	–	ESRD (polycystic kidney disease), RTx 9 years previously, PD for the last 5 years, parathyroidectomy	–	Renvela® and Renagel®	4800 and 4000 mg	–	Rectal bleeding since several months	Ulcer in ileocecal valve	Focal erosion, bacterial material	Stop sevelamer: rise of haemoglobin level and no blood on next stool examination.
Bansal et al.[10]	Female (42)	–	ESRD	–	–	2400 mg	–	Abdominal pain, diarrhoea	Mass (60 mm) in proximal sigmoid colon	Necrotic tissue with bacterial overgrowth	Stop sevelamer. Colonoscopy 3 months later: normal mucosa.
Sy et al.[11]	Male (69)	–	CKD (diabetic nephropathy), DM, gastroesophageal reflux disease	–	–	–	–	Subacute abdominal pain	Mass (35 mm) in caecum, bezoar	Inflammation	–
Modi et al.[12]	Female (60)	–	ESRD, HD, pulmonary fibrosis, right lung Tx, obesity	Sirolimus, tacrolimus, trimethoprim/ sulfamethoxazole; rest unknown	–	–	–	Abdominal pain, diarrhoea	Ulcer (14 mm) with surrounding erythema in distal rectum	Reactive mucosal changes, acute inflammation (lamina propria and submucosa)	
Schoot 2020 (our case)	Female (67)	C	CKD (diabetic nephropathy and vascular damage), DM type 2, HT, RA, PVD, lower leg amputation, appendectomy, Campylobacter infection, choledocholithiasis	ASA, cholecalciferol, ferrofumarate, Mircera, pantoprazole, prednisolone, simvastatin, calcium polystyrene sulphonate	Renvela®	4000 mg and later 6400 mg	7 days	Rectal bleeding	Multiple deep ulcers (diameter 10–15 mm) and diffuse oedematous mucosa in sigmoid and rectum	Ulcerated mucosa	Stop sevelamer: decrease of rectal bleeding 11 days later

A: Asian; ASA: acetylsalicylic acid; B: black; C: Caucasian; H: Hispanic; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; DM: diabetes mellitus; ESRD: end-stage renal disease; HD: haemodialysis; HIV: human immunodeficiency virus; HT: hypertension; HUS: haemolytic-uremic syndrome; PAF: paroxysmal atrium fibrillation; PD: peritoneal dialysis; PVD: peripheral vascular disease; RA: rheumatoid arthritis; RTx: renal transplant; Tx: transplant.

*In all biopsies and resection specimens, sevelamer crystals were identified.

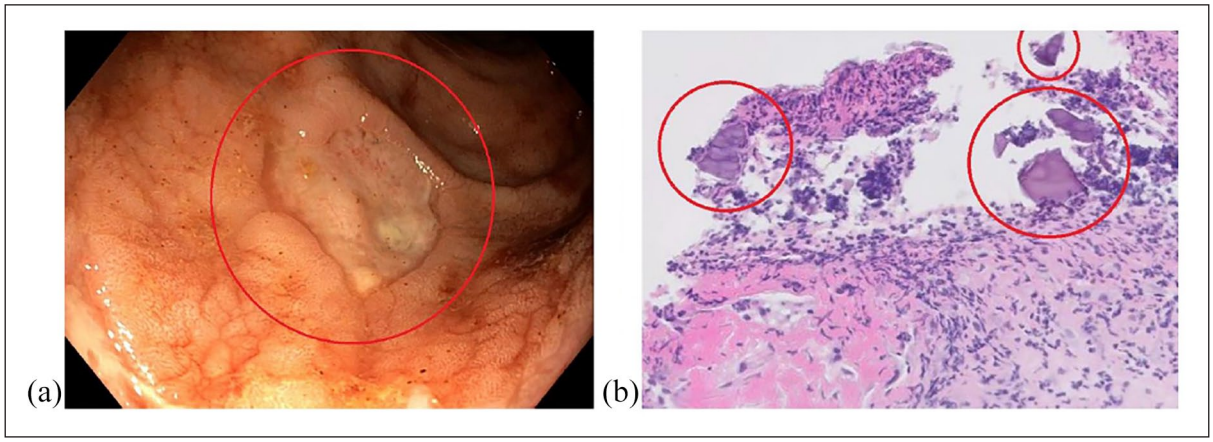

Figure 1. (a) Mucosal oedema and an ulcer with a diameter of 10–15 mm in the rectum. (b) Histologic examination: deposition of sevelamer crystals with the typical fish-scale appearance in the ulcerated mucosa.

11 mL/min/1.73 m^2) due to decompensated severe aortic valve stenosis. Treatment with sevelamer carbonate (Renvela® tablets of 800 mg, five tablets per day with meals) was started because serum phosphate was elevated (2.0 mmol/l; reference range: 0.8–1.5 mmol/l). The dosage of sevelamer carbonate was increased 6 days later to 6.4 g per day (1600 mg/2400 mg/2400 mg) because lower dosing was ineffective. Seven days after starting treatment with sevelamer carbonate, lower gastrointestinal (GI) bleeding began. Serum haemoglobin gradually decreased from 9.5 to 8.1 g/dL (reference range = 12.1–16.1 g/dL) despite six erythrocyte transfusions. Sigmoidoscopy revealed multiple deep ulcers with a diameter of 10–15 mm and diffuse mucosal oedema in the sigmoid colon and rectum (Figure 1(a)). This finding was atypical for inflammatory bowel disease or malignancy. Histologic examination showed deposition of crystals in ulcerated mucosa, without signs of dysplasia, malignancy or chronic inflammation (Figure 1(b)). The crystals were identified as sevelamer crystals by an experienced pathologist, based on the colour (purple, pink and yellow on haematoxylin and eosin (H&E) stain) and the typical fish-scale appearance. Unfortunately, no other stains were performed. Nevertheless, We suspect that the lower GI bleeding in this patient was caused by mucosal ulceration of sigmoid colon and rectum by the observed deposited sevelamer crystals. Fortunately, sevelamer carbonate had already been discontinued due to an inadequate response of serum phosphate. In total, the patient had taken 43 g sevelamer carbonate. Lower GI bleeding gradually diminished 11 days after cessation of sevelamer. We were not able to perform a control sigmoidoscopy, as the patient died several weeks later from acute heart failure secondary to severe aortic valve stenosis. An autopsy was not performed. This case was submitted to the Dutch National Pharmacovigilance.

Discussion

We described a case of a 67-year-old woman with lower GI bleeding, which we suspect was caused by sevelamer. Symptoms started seven days after start of sevelamer carbonate (Renvela®). Sigmoidoscopy revealed multiple deep ulcers and mucosal oedema and histologic examination showed deposition of sevelamer crystals in the rectal ulcers. After discontinuing treatment with sevelamer carbonate, lower GI bleeding stopped.

Mild GI symptoms – such as nausea, abdominal pain, diarrhoea, and constipation – are common side effects of sevelamer. However, deposition of sevelamer crystals in the GI tract is rare. To our knowledge, there are only 17 other case descriptions of this issue, and only seven with lower GI bleeding. Table 1 provides an overview of these cases, including ours.[3–12] Of note, two other case reports were excluded from this literature review because of the presence of other crystals that could have caused the described symptoms[13] coupled with an inability to identify the type of crystal.[14]

The clinical presentation of patients with deposition of sevelamer crystals in the GI tract varies widely (see Table 1). The most prevalent symptoms are lower GI bleeding (eight cases), abdominal pain (seven cases) and (haemat)emesis (four cases). Remarkably, in three cases, patients were asymptomatic. Main endoscopic findings were ulceration and inflammatory polyps. Sevelamer depositions were found in biopsies of the colon (14 cases), stomach (3 cases) and oesophagus (2 cases). Most biopsies showed inflammation, ulceration and/or necrosis. Obviously, a causal relation between these symptoms and the deposition of sevelamer crystals could not be proven in these small, observational studies.

Swanson et al.[3] were first to describe the histological features of sevelamer crystals. The typical appearance of sevelamer crystals is broad, curved and irregularly spaced ‘fish scales’. Most crystals have bright pink linear accentuations with a rusty yellow background on H&E stain and are violet on periodic acid–Schiff–alcian special stain with diastase (PAS/D). However, crystal colour may vary: descriptions include rusty brown or eosinophilic.[3] Sevelamer crystals may resemble crystals of sodium polystyrene sulphonate

Table 2. Typical characteristics of crystals of different resins.

	Sevelamer	Sodium polystyrene sulphonate	Bile acid sequestrants
Fish-scale pattern	Yes	Yes	No
Colour on H&E	Pink and yellow (two-toned)	Violet	Orange
Colour on AFB	Magenta	Black	Yellow
Colour on PAS/D	Violet	Magenta	Pink

Source: Swanson et al.[3] and Gonzalez et al.[15]
H&E: haematoxylin and eosin; AFB: acid-fast bacillus; PAS/D: periodic acid–Schiff–alcian special staining with diastase.

(potassium-binding agent) and bile acid sequestrants (colesevelam, colestipol and cholestyramine), two other resins.[3,15] It is important to identify crystals correctly, because clinical implications and treatment are different. However, in an online survey, only 76% of pathologists correctly identified the classic crystal appearance of sevelamer, sodium polystyrene sulphonate and bile acid sequestrants on H&E stain.[15] The typical characteristics of these crystals are summarized in Table 2. Recognition remains challenging as there are several atypical appearances of resin crystals, for example, light purple sevelamer crystals on H&E stain (like in our case) and bile acid sequestrants with fish scales.[15] To improve the chances of getting the correct diagnosis, we recommend that clinicians include a medication overview in their pathology requests. Moreover, dedicated learning paths for pathologists might improve recognition of sevelamer crystals. Finally, if in doubt, we advise performing an acid-fast bacillus (AFB) and/or PAS/D stain, in addition to the H&E stain.

This study has some limitations. First, the pathologist only performed an H&E stain. However, the pathologist had no doubt about the nature of the crystals because of the typical sevelamer crystal aspect with fish scales. Moreover, the patient did not use drugs with crystals that that resemble sevelamer crystals (i.e. sodium polystyrene sulphonate and bile acid sequestrants). Second, the observational design of the available studies, including ours, prevents us from making causal inferences. Thus, we cannot proof a causal relation between the presence of sevelamer crystals and the clinical presentation. In addition, we were not able to perform a control sigmoidoscopy because of the death of our patient. However, two other studies describe a remarkable resolution of macroscopic mucosal damage after cessation of sevelamer.[4,10] Moreover, the complete resolution of symptoms described in several cases after cessation of treatment with sevelamer, including ours, strongly suggests a causal relation.[4,5,8–10]

Conclusion

Deposition of sevelamer in the GI tract is a rare side effect of sevelamer. This case suggests that deposition of sevelamer crystals can induce mucosal ulceration in the GI tract. Although this adverse effect is mentioned in the Renvela monograph, it is often overlooked. It should be considered in all patients using sevelamer who present with GI symptoms, especially GI bleeding. There are indications that when sevelamer is discontinued, symptoms and mucosal damage may revert.

Declaration of conflicting interests

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Ethical approval

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ORCID iD

Tessa S Schoot https://orcid.org/0000-0001-5575-617X

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