Lower gastrointestinal bleeding in a patient receiving sevelamer: Case report

Tessa S Schoot¹², Tessa EH Römkens³ and Ellen K Hoogeveen¹

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

Date received: 7 January 2021; accepted: 25 January 2021

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 (NH₃) groups.² Phosphate will be bound to sevelamer after protonation of NH₃ to NH₄⁺ 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 m²) 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

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

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).
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.  | 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 | – |
| 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 mucosal oesophagus | Extensive ulceration | – |
| Okwara et al.  | Male (70) A | 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. | Female (61) B | ESRD, HD, obesity | Heparin IV since 2 days; rest unknown | – | 2400 mg | – | Rectal bleeding | Uleration (50 mm) in sigmoid colon (25 cm above the anus) | Ulcer bed with attached fibrin and haemorrhage | – |
| Okwara et al.  | Male (79) A | ESRD, dialysis, DM, ischaemic heart disease | – | – | – | – | – | Diarrhoea, abdominal pain | Polyoid mass in caecum | Necrosis and ischaemic changes | – |
| Amer et al.  | Male (64) | ESRD, HD | – | – | – | – | – | Haematemesis, abdominal pain | Multiple ulcers in gastric body | – | – |
| Tieu et al. | 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 for 10 days. |

(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. | Male (53) | ESRD (crescentic glomerulonephritis), RTx 2 years previously, HD for last 6 years, sigmoidectomy, calciphylaxis | – | Renagel® | 8000 mg | – | Rectal bleeding | Inflammatory polyps in stomach and colon | Lesion ileocecal valve: pseudo-inflammatory 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® | 8000 mg | – | Rectal bleeding | Chronic gastritis, diverticulosis and several gastric and colonic polyps | Colorectal mucosa: chronic inflammation, superficial gastrectomy and colonic polyps 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. | 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. | Male (69) | CKD (diabetic nephropathy), DM, gastroesophageal reflux disease | – | – | – | – | Abdominal pain, diarrhoea | Mass (35 mm) in caecum, bezoar | Inflammation | – |
| Modi et al. | 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 | Female (67) C | CKD (diabetic nephropathy and vascular damage), DM type 2, HT, RA, PVD, lower leg amputation, appendectomy, Campylobacter infection, cholecystolithiasis | ASA, cholecalciferol, forrofumarate, 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.
11 mL/min/1.73 m²) 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 symptoms13 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...
(potassium-binding agent) and bile acid sequestrants (colesevelam, colestipol and cholestyramine), two other resins. 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. 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. 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 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. Moreover, the complete resolution of symptoms described in several cases after cessation of treatment with sevelamer, including ours, strongly suggests a causal relation.

**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**

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

**Ethical approval**

Our institution does not require ethical approval for reporting individual cases or case series.

**Funding**

The author(s) received no financial support for the research, authorship and/or publication of this article.

**Informed consent**

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

**ORCID iD**

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

**References**

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 clinical practice guideline update for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD-MBD). Kidney Int Suppl 2017; 7: 1–59.
2. Monograph of Renvela, http://products.sanofi.ca/en/Renvela.pdf
3. Swanson BJ, Limketkai BN, Liu T, et al. Sevelamer crystals in the gastrointestinal tract (GIT): a new entity associated with mucosal injury. Am J Surg Pathol 2013; 37(11): 1686–1693.
4. Okwara CJ, Gulati R, Rustagi T, et al. Upper gastrointestinal bleeding of unusual causation. Dig Dis Sci 2018; 63(10): 2541–2546.
5. Chintamaneni P, Das R, Kuan S, et al. Hematochezia associated with sevalamer-induced mucosal injury. ACG Case Rep J 2014; 1(3): 145–147.
6. Okwara C, Choi C and Park JY. Sevelamer-induced colitis presenting as a pseudotumor. Clin Gastroenterol Hepatol 2015; 13(7): A39–A40.

---

**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. and Gonzalez et al. H&E: hematoxylin and eosin; AFB: acid-fast bacillus; PAS/D: periodic acid–Schiff–alcian special staining with diastase.
7. Amer S, Nguyen C and DePetris G. Images of the month: gastric pneumatosis due to Sevelamer-mediated necrosis. *Am J Gastroenterol* 2015; 110(6): 799.

8. Tieu C, Moreira RK, Song LM, et al. A case report of sevelamer-associated recto-sigmoid ulcers. *BMC Gastroenterol* 2016; 24: 16.

9. Yuste C, Mérida E, Hernández E, et al. Gastrointestinal complications induced by sevelamer crystals. *Clin Kidney J* 2017; 10(4): 539–544.

10. Bansal V, Aggarwal P, Mittal A, et al. Colonic mass secondary to sevelamer-associated mucosal injury. *ACG Case Rep J* 2017; 4: e92.

11. Sy S, Siddiki H, Horsley-Silva J, et al. Sevelamer resin bezoar presenting as a cecal mass. *Gastrointest Endosc* 2017; 86(6): 1186–1187.

12. Modi RM, Swanson B and Duggirala V. Long-standing diarrhea associated with sevelamer crystalopathy in colonic mucosa. *Clin Gastroenterol Hepatol* 2017; 15(2): A26–A27.

13. Yamaguchi T, Ohyama S, Furukawa H, et al. Sigmoid colon diverticula perforation associated with sevelamer hydrochloride administration: a case report. *Ann Med Surg* 2016; 10: 57–60.

14. Desai M, Reiprich A, Khov N, et al. Crystal-associated colitis with ulceration leading to hematochezia and abdominal pain. *Case Rep Gastroenterol* 2016; 10(2): 332–337.

15. Gonzalez RS, Lagana SM, Szeto O, et al. Challenges in diagnosing medication resins in surgical pathology specimens: a crystal-clear review guide. *Arch Pathol Lab Med* 2017; 141(9): 1276–1282.