ISSN: 2469-584X

Powers. J Clin Gastroenterol Treat 2022, 8:086
DOI: 10.23937/2469-584X/1510086
Volume 8 | Issue 1
Open Access

Journal of
Clinical Gastroenterology and Treatment

CASE REPORT

Improved Electrolyte and Fluid Balance Results in Control of Diarrhea with Crofelemer in Patient with Short Bowel Syndrome: A Case Report

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Abstract

Short bowel syndrome (SBS) is a rare malabsorptive disorder characterized by the inability to maintain a balance of fluids, electrolytes, and nutrients when taking a conventional diet. SBS can cause chronic, severe diarrhea and malnutrition, often requiring dependence on parenteral nutrition. We present the case of a 55-year-old female with a complete colectomy and partial small bowel resection who experienced chronic, severe diarrhea for over a decade, resulting in her being housebound and malnourished. Traditional antidiarrheals provided limited relief, even with maximum dosages of multiple medications. Off-label treatment with crofelemer, an FDA-approved antidiarrheal with a novel mechanism of action, resulted in near-immediate relief and improved stool consistency resulting in significant normalization of bowel movements. Low doses of other antidiarrheals were used with crofelemer for additional control. Long-term, the patient gained weight and improved her nutritional status by using crofelemer. This case suggests that crofelemer warrants investigation in improving SBS-induced fluid imbalance and subsequent chronic diarrhea and malnutrition.

Introduction

Short bowel syndrome (SBS) is a severe condition characterized by an extremely shortened small and/or large intestine, resulting in decreased intestinal surface area and consequently poor absorption of fluids and nutrients. SBS is largely caused by extensive surgical resection of the small and large intestines due to a variety of causes, including complications from previous operations, cancer and related irradiation treatment, mesenteric vascular disease, Crohn's disease, trauma, volvulus, or motility disorders. SBS in children may also result from congenital defects throughout the gastrointestinal tract and necrotizing enterocolitis in premature infants.

There is no patient database for SBS. Therefore, as a rare disease, its true incidence and prevalence are unknown. Due to the high percentage of SBS patients who are dependent on parenteral nutrition (PN), PN dependence has been used as a proxy for SBS epidemiology. In the U.S. there are about 40,000 cases of PN dependence and roughly 25% of those cases have been attributed to SBS [1]. SBS carries a heightened risk of mortality. In a study of 268 SBS patients, patients were found to have 1-, 5-, and 10-year survival probabilities of 94%, 70%, and 52%, respectively [2].

SBS has been traditionally defined anatomically as less than 30% of the normal small intestine length (i.e., less than 200 cm) [3]. However, the clinical view of SBS has evolved to encompass both the physical length and functional capacity of the small intestine, which can be hampered by intestinal obstructions or dysmotility [4]. Therefore, SBS severity varies depending on the length of the small and large intestine remaining and the ability of the remnant intestine to absorb sufficient nutrients. Loss of the ileum results in more severe disease compared to resection of the jejunum, and loss of part or all of the colon can further complicate the syndrome [5,6].

Diarrhea, dehydration, malnutrition, and weight loss

Citation: Powers W (2022) Improved Electrolyte and Fluid Balance Results in Control of Diarrhea with Crofelemer in Patient with Short Bowel Syndrome: A Case Report. J Clin Gastroenterol Treat 8:086. doi.org/10.23937/2469-584X/1510086

Accepted: May 07, 2022: **Published:** May 09, 2022

are the most common symptoms of SBS [4]. Diarrhea is caused by elevated secretion of fluid and electrolytes into the intestine [7] through active chloride ion (Cl^-) transport across intestinal epithelium coupled with significantly decreased absorptive capacity of the remaining small and large bowel. In SBS patients, the reduced surface area of the small intestine also leads to malabsorption of bile acids, stimulating fluid secretion (via Cl^- transporters) into the small intestine and colon [1].

Current treatment strategies for chronic diarrhea associated with SBS are inadequate, relying on slowing intestinal transit time or reducing gastrointestinal secretion [4]. Therapies that slow transit include diphenoxylate-atropine (Lomotil) and loperamide (Imodium), which are antimotility drugs that act on opiod receptors and relax intestinal muscles to slow peristalsis. Diphenoxylate-atropine crosses the blood-brain barrier thereby causing central nervous system (CNS)-related side effects such as dizziness, lethargy, euphoria and confusion, thus limiting its use and dosage [5]. Loperamide has less CNS involvement that permits exceeding the maximum approved dose, but this may result in dose-limiting nausea and constipation [5]. Other gastrointestinal transit-slowing therapies include cholestyramine, which is a resin that binds bile acids, but its use is limited to patients who have had less than 100 cm of the ileum resected [5]. In patients with more significant resections, it binds to dietary lipids and may cause steatorrhea and worsened malnutrition. Narcotics such as codeine, morphine, and tincture of opium also slow gastrointestinal transit but are only used in patients with refractory diarrhea due to their potential for abuse and addiction [5].

Agents that reduce gastrointestinal secretion, fecal weight, and high-volume diarrhea include proton pump inhibitors and histamine-2 receptor blockers. However, these drugs cannot control excessive stool fluid volume. [5]. Octreotide, a somatostatin analog, also reduces gastrointestinal secretion but causes severe side effects such as steatorrhea and gallstones, and the alpha-adrenergic agonist clonidine, which is used as an antihypertensive agent with anti-diarrheal properties, cannot be used for dehydrated, hypotensive SBS patients [5].

Crofelemer is a novel antidiarrheal agent that modulates two of the apical intestinal Cl^- ion channels: the cAMP-stimulated cystic fibrosis transmembrane conductance regulator (CFTR) and the calcium-activated Cl^- channel (CaCC) [8]. These channels are distributed throughout the intestine, mostly in the duodenum and jejunum with decreasing density of channels through the rest of the small intestine and colon. They are responsible for the normal regulation of chloride ions into the intestinal lumen, allowing almost complete reabsorption of electrolytes and fluids of an average daily intestinal fluid volume of 7-9L by the small and large intestines. Crofelemer regulates CFTR and CaCC gating activity when these channels are overstimulated, thereby decreasing intestinal secretion of chloride ions and improving stool consistency and diarrhea. Crofelemer is currently FDA approved to treat noninfectious diarrhea in adults with HIV/AIDS on antiretroviral therapy. It is hypothesized that in short bowel syndrome, crofelemer may reduce the relatively excessive fluid and electrolyte secretion, increasing transit time, indirectly facilitating electrolyte, fluid and nutrient absorption, and improving stool consistency and mitigating debilitating diarrhea.

Here, we present a case study demonstrating off-label use of crofelemer in improving the stool consistency and diarrhea in a patient with partial resection of the ileum and a subtotal colectomy with intestinal malabsorption and aberrant motility and who was not dependent on parenteral nutrition.

Case Description

The patient is a 55-year-old female with an extensive surgical history involving the small bowel and colon and a long history of severe chronic diarrhea and malnutrition. The patient initially had a small bowel resection with end-to-end ileal anastomosis at age 19 to resolve an acute ileal volvulus in which roughly 24 cm of the ileum and her appendix were removed. The patient was prescribed cholestyramine for diarrhea following surgery but still experienced persistent intermittent diarrhea and abdominal pain. Four months after surgery, the patient still had 5-6 watery bowel movements per day and recurrence of bile salt diarrhea.

About six months following the initial surgery, the patient presented with signs and symptoms of a small bowel obstruction, requiring surgery in which extensive adhesiolysis was performed. Many of the adhesions were focused near the terminal ileum where the end-to-end ileal anastomosis was performed previously. Due to the recurrent incidence of bile salt diarrhea and accumulation of cholestyramine in the colon, the patient was prescribed colestipol instead of cholestyramine for controlling her diarrhea following surgery.

For the following 18 years, the patient had intermittent episodes of conservatively managed bowel obstruction but was able to live a relatively healthy life. At age 38, she began experiencing severe chronic diarrhea and abdominal pain and underwent two surgical procedures. In the first, the patient underwent abdominal exploration and lysis of adhesions. This resulted in a painful wound and intermittent obstructive symptoms, requiring a second surgical procedure about four months later. In the second surgery, the patient was found to have redundant transverse and sigmoid colon, including 2.5 feet of sigmoid colon. Thirteen inches of sigmoid colon were removed, and an end-to-end anastomosis was performed. She was discharged

only after she could tolerate a surgical soft diet with a normal bowel habit.

Over the next nine years, the patient continued to have intestinal issues involving cycles of 16-25 watery bowel movements per day, typically lasting for 1-16 days, followed by 1-3 days of constipation and complete cessation of bowel movements. As a result, the patient suffered from malnutrition and unintended weight loss. At age 47, she underwent a partial colectomy in which most of her colon was removed, leaving roughly 12 inches of her right colon, ending in a colostomy although the rectum remained intact. During the same surgery, the patient also underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy after a diagnosis of abnormal uterine bleeding. Subsequently the patient underwent a reversal of the colostomy, resection of the remaining colon, the ileocecal valve and part of the terminal ileum, and an ileorectal anastomosis a year later.

After the total colectomy and partial resection of the small bowel, the patient experienced severe chronic diarrhea with approximately 24-30 watery bowel movements per day resulting in the patient being housebound and suffering weight loss and malnutrition. The patient was only able to achieve complete relief from diarrhea through fasting. As a result of the patient's physical ailments, she also experienced chronic depression, anxiety, and periods of suicidal ideation.

The patient's diarrhea was not alleviated by traditional antimotility agents, including loperamide, diphenoxylate/atropine, cholestyramine, colestipol, and opioids, nor by other antidiarrheal agents, including omeprazole and antibiotics (ciprofloxacin and minocycline) for small intestine bacterial overgrowth. The patient's diarrhea was also not resolved by medications for irritable bowel syndrome-associated diarrhea including rifaximin, hyoscyamine, dicycloverine, and eluxadoline. The inability to maintain a healthy diet and resultant malnutrition, possibly confounded by an undetermined infection, vitamin deficiency, or loperamide overdose, gave rise to an episode of apparent metabolic encephalopathy for which the patient was neither hospitalized nor treated when she was 51 years of age.

Extensive experience with HIV patients had given the patient's care team a familiarity with crofelemer. Based on crofelemer's unique physiological mechanism of action and the patient's chronic, intractable diarrhea for which she was approaching dose-limiting toxicity with her traditional antidiarrheal medications, crofelemer was prescribed off-label. The patient started taking 125 mg BID delayed-release crofelemer tablets, and within 48 hours, she experienced significant relief from diarrhea with well-formed stools 2-3 times per day. The patient continued taking crofelemer and supplementing with loperamide and diphenoxylate/atropine as needed but at significantly lower doses compared to those prior to crofelemer treatment.

The dosage of crofelemer was increased to 125 mg TID, which is higher than the indicated dosage for HIV-associated diarrhea, about five months after initiation, to further improve control of the patient's diarrhea. After another six months, the patient began crushing crofelemer delayed-release tablets before taking them after noticing the appearance of whole pills in her bowel movements due to her reduced bowel length. The patient experienced no adverse effects from taking the higher dose or crushing the pills despite crofelemer being formulated as a delayed-release tablet. The patient has continued at the 125 mg TID dose, taken crushed, for over 18 months and has seen steady weight gain and improvements in her nutritional status, mental health, and overall quality of life as a result of her relief from diarrhea with crofelemer.

Conclusions

SBS is a rare condition found primarily in patients with severly shortened intestines, most commonly due to extensive surgical resection or multiple resections over time, as described in this case report. Patients who have functionally poor intestinal absorption due to dysmotility or pseudo-obstructions are also considered to have SBS. Patients with SBS commonly experience severe, chronic diarrhea and malnutrition due to decreased transit time of the intestinal contents and malabsorption of fluids and nutrients. As a result, patients may require PN for some or all of their electrolyte, fluid and nutritional requirements. Alternatively, they may simply fail to thrive by gradually losing weight and becoming malnourished as they fail to successfully manage their diet and chronic diarrhea, having a significant impact on patients' mental and physical health and quality of life.

Here, we describe the use of off-label crofelemer for the successful management of diarrhea in a 55-year-old patient who underwent extensive resection of the small bowel and colon over the course of multiple abdominal surgical procedures and was not dependent on PN. The patient experienced severe, chronic diarrhea for several years that kept her housebound, malnourished, and unable to maintain a healthy weight. Her diarrhea was not controlled by traditional therapies used for diarrhea and SBS, even when used in combination and at higher dosages.

Use of crofelemer returned the patient to near-normal bowel function and enabled use of lower doses of other antidiarrheal medications to manage breakthrough diarrhea. Control of the patient's diarrhea improved the patient's nutrition and ability to gain and maintain a healthy weight. The provider also noted alleviation of the patient's depression and improvements in cosmesis and overall quality of life

as a result of the improvement in control of diarrhea. Notably, the patient presented here increased her daily dose to higher than the approved dose in HIV, and crushed the tablets, bypassing their delayed-release effect, without any adverse effects, thereby supporting the safety profile and negligible oral bioavailability of crofelemer, as reported previously [9-11].

Crofelemer is an antidiarrheal drug with a physiological mechanism of action that regulates Cl^- transport by normalizing the gating function of two chloride ion channels, CFTR and CaCC. It has been studied in patients with inflammatory and secretory noninfectious diarrhea in HIV patients receiving antiretroviral therapy due to HIV enteropathy. Crofelemer has also shown improvement in controlling infectious diarrhea in patients with cholera. The unique physiological mechanism of crofelemer results in inhibition of secretion of excess chloride ions and water into the intestine and normalization of electrolyte and fluid balance in the GI tract, thus improving stool consistency and relief from diarrhea. In this SBS patient, crofelemer also may have reduced the hypersecretion of chloride and fluids into the intestine that occurs due to bowel adaptation after extensive surgical resection. By reducing excess chloride and fluid secretion, crofelemer likely resulted in less fluid volume in the intestine, enabling better absorption of nutrients by the small intestine. Crofelemer has negligible oral bioavailability, no known food or drug interactions, and was well tolerated.

This case study demonstrates crofelemer's ability to improve the diarrheal control in an SBS patient with multiple abdominal surgeries and also improve the patient's nutritional status as evidenced by her weight gain and improved physical and psychosocial wellness. Crofelemer warrants further evaluation in clinical trials in patients with SBS, including those dependent on PN. However, because of the decreased intestinal transit time experienced in SBS patients, a reformulation of crofelemer and expanded dosing regimens should be studied.

Acknowledgements

We thank the patient for providing consent to report the history here.

Funding

This case study was supported by Napo Pharmaceuticals, Inc.

Competing Interests

None declared.

Sources of Support

Napo Pharmaceuticals.

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