Original Article

Effect of the Bile Acid–Binding Resin Colestimide in Refractory Bile Acid Malabsorption in Patients with Chronic Diarrhea

Hiroaki Zai Toshiyasu Watanabe Naoyuki Kawagoe
Ikutaka Takemoto Hideki Tanaka Sho Kijima
Tadashi Maeda Taito Miyazaki Yoshihisa Urita*
and Hitoshi Nakajima

Department of General Medicine and Emergency Care, School of Medicine,
Faculty of Medicine, Toho University

ABSTRACT

Background: Recent reports indicate that bile acid malabsorption is present in about 30% of patients with chronic diarrhea and a diagnosis of diarrhea-predominant irritable bowel syndrome (IBS-D) and that treatment with bile acid–binding resin is effective. We investigated the effects of colestimide on refractory chronic diarrhea in IBS-D.

Methods: Twenty-eight patients with refractory IBS-D or chronic diarrhea were enrolled and treated with colestimide. Fifteen had no past history of gastrointestinal surgery and 13 had undergone such surgery. Small intestinal bacterial overgrowth (SIBO) was also evaluated by lactulose breath testing in 21 patients. All patients were given 1500 mg of colestimide twice a day for 2 weeks, after which the effects of colestimide treatment were evaluated.

Results: Of the 21 patients examined for SIBO, 8 (38.1%) had a positive result. Prevalence of SIBO was not associated with past surgical history ($p = 0.472$). In 21 (75.0%) of the 28 patients, colestimide improved diarrhea and bowel habits ($p = 0.008$). The effectiveness of colestimide was not associated with past surgical history or presence of SIBO.

Conclusions: Colestimide treatment had a satisfactory effect for chronic diarrhea potentially attributable to bile acid malabsorption. The effectiveness of empirical administration of colestimide for patients with refractory chronic diarrhea and IBS-D should be assessed in a future study.

Toho J Med 2 (2): 61–66, 2016

KEYWORDS: diarrhea-predominant irritable bowel syndrome (IBS-D), chronic diarrhea, bile acid malabsorption, small intestinal bacterial overgrowth, colestimide

6–11–1 Omorinishi, Ota, Tokyo 143–8541, Japan
*Corresponding Author: tel: +81–(0)3–3762–4151
e-mail: foo@med.toho-u.ac.jp
DOI: 10.14994/tohojmed.2015.012

Received Sept. 24, 2015: Accepted Apr. 28, 2016
Toho Journal of Medicine 2 (2), June 1, 2016.
ISSN 2189–1990, CODEN: TJMOA2

Diarrhea-predominant irritable bowel syndrome (IBS-D) is diagnosed when no organic cause for chronic, recurrent, or functional diarrhea can be identified. However, bile acid malabsorption (BAM) is often the cause of diarrhea.[1, 2)]

Bile acids undergo portal enterohepatic circulation: they are secreted by the liver, pass into the intestine, are absorbed in the intestinal lumen, pass into portal circulation, and are efficiently extracted by the liver for re-secretion into bile. Enterohepatic circulation of bile acids is extremely efficient; less than 5% of intestinal bile acids escapes reabsorption and elimination in feces.[3)] Bile acids are actively transported across the ileal brush-border membrane by ileal apical sodium-dependent bile acid transporter (ASBT), which is expressed in tissues that facilitate enterohepatic circulation of bile acids. ASBT is found on the apical membrane of ileal enterocytes, proximal convoluted tubule cells, large cholangiocytes, and gallbladder epithelial cells. ASBT expression is tightly restricted to the terminal ileum in mice, hamsters, rats, and humans.[4–7)] When ileal dysfunction or resection causes BAM, the compensatory increase in hepatocyte bile acid biosynthesis may be sufficient to compensate for BAM. However, increased flux of bile acid into the colon may induce water and electrolyte secretion, which manifests clinically as diarrhea.[8)] When BAM occurs, bile acids may be present in greater concentrations in the colon, where they promote secretion from the colonic epithelium both by a direct effect and indirectly by activating mast cells. Bile acids also promote propulsive motility.

BAM induces chronic diarrhea, and cholestyramine therapy is very effective for chronic diarrhea caused by BAM.[9, 10)] Numerous studies of BAM used ^{75}Se-homocholic acid taurine (^{75}SeHCAT) scanning and a method that classified BAM into 3 types.[11–15)] Type 1 BAM results from disease, resection, and/or bypass of the ileum. In these conditions, failure or frank inability to re-absorb bile acids causes bile acids to spill over into the colon, resulting in secretory diarrhea. Type 2 (idiopathic or primary) BAM is thought to be rare and results from a genetic defect in the ASBT protein responsible for the major portion of conjugated bile acid reabsorption. Type 3 BAM refers to BAM from causes other than those responsible for type 1 and 2 BAM, for example, previous gastric surgery, vagotomy, pancreatitis, microscopic colitis, celiac disease, diabetes, small bowel bacterial overgrowth, and previous cholecystectomy.

If BAM is sufficiently severe, the compensatory increase in bile acid biosynthesis is insufficient to restore normal bile acid secretion. Under these circumstances, bile acid concentration in the proximal small intestine decreases. Bile acids contribute to the gut's antimicrobial defenses through the direct bacteriostatic actions of bile acid − fatty acid mixed micelles in the proximal intestine and by inducing expression of antimicrobial genes in the distal small intestine.[16)] These roles of bile acid appear to be closely related to the development of small intestinal bacterial overgrowth (SIBO), another cause of chronic diarrhea.[17–19)] In addition, SIBO induced by some other factors also causes BAM.[1, 20, 21)]

Chronic diarrhea associated with BAM is caused by an unusual bile acid concentration in the lumen of the lower gut and/or SIBO. BAM is an important but underdiagnosed cause of long-standing diarrhea. The key point of the therapeutic strategy is identification of BAM. However, outside of Western countries, ^{75}SeHCAT scanning is available only in a few hospitals. Furthermore, diagnostic methods such as stool bile acid assay, stool ^{14}C-taurocholate testing, and measurement of fibroblast growth factor 19 function have disadvantages as well as advantages.[22)] A technical review of the evaluation and management of chronic diarrhea by the American Gastroenterological Association[23)] reported that many clinicians used a therapeutic trial of cholestyramine as an indirect test for the possibility that malabsorbed bile acids were the cause of diarrhea. This success of this clinical practice suggests that it is reasonable to administer a bile acid − binding resin (colestimide) to patients with refractory chronic diarrhea when an examination for BAM would be difficult. We investigated the effects of colestimide as a treatment for chronic diarrhea potentially caused by BAM.

Methods

Participants and study design

Twenty-eight patients participated in this study (11 males, 17 females; mean (± SD) age, 52.1 ± 16.7 years; age range, 17–81 years). All had received a diagnosis of IBS-D or refractory chronic diarrhea and had been referred to the Department of General Medicine and Emergency Care at Toho University Omori Medical Center for detailed examination and treatment. Patients with both chronic pancreatitis and organic colon disease were excluded. Patients with either chronic pancreatitis (as determined by blood testing) or organic colon disease (as determined by findings from a total colonoscopic examination) were enrolled.

All patients were examined by abdominal computed tomography or ultrasonography, to rule out the presence of other diseases. Among the 28 patients included, 15 had no past history of gastrointestinal surgery, 4 had had an appendectomy, 4 had had a cholecystectomy, 2 had undergone partial ileal resection for ileus (details unknown), and 3 had had a subtotal gastrectomy. Table 1 shows the characteristics of the participants, and Table 2 shows their medication history. The study was approved by the Ethics Committee of Toho University (No. 26-84). Informed consent was obtained from all patients.

Assessment of bacterial overgrowth

Twenty-one of 28 patients underwent lactulose breath testing (LBT) to determine whether SIBO was present. After an overnight fast, end-expiratory breath samples were obtained at 9: 00 AM, before intake of 10 g of lactulose in 15-mL lactulose syrup, and at 10-minute intervals thereafter for the next 3 hours. Breath samples were collected from the mouth in breath collection bags (Model 20; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan). To prevent oral fermentation of glucose, which might cause an initial increase in the concentration of breath hydrogen or methane, the participants used a disinfectant mouthwash before intake of the test solution. Smoking and physical exercise were avoided during the test. Breath H_2 was measured using a breath gas analyzer (TGA-2000, Teramecs, Kyoto, Japan). The test result was considered suggestive of SIBO if it satisfied previously published criteria.[19, 24, 25] In this study, a variety of endpoints were used to define a positive test, including a fasting hydrogen level greater than 20 ppm, presence of a double peak with hydrogen levels, an early increase (within 90 minutes) of greater than 20 ppm, or a sustained increase of greater than 10 ppm as compared with baseline hydrogen levels. The study was approved by the Ethics Committee of Toho University Omori Medical Center (No. 17-64).

Colestimide treatment

Colestimide is a bile acid − binding resin composed of nonabsorbable polymers that bind to negatively charged bile salts in the intestine. This diverts bile acids from the enterohepatic cycle and increases their fecal excretion.[26] The end result is increased bile acid synthesis with upregulation of low-density lipoprotein receptors. Colestimide is indicated for treatment of low-density lipoprotein hypercholesterolemia in Japan. Patients took 1500 mg of colestimide perorally twice a day for 2 weeks. All examinations were performed at an outpatient clinic in Toho University Oomori Medical Center. The effect of colestimide treatment was evaluated 2 weeks after the start of colestimide administration. Positive response to treatment was defined as relief of abdominal discomfort and improved bowel habits.

Statistical analysis

The 95% confidence intervals were calculated for proportions (percentages), and associations between data for categorical variables were evaluated using the chi-square test. A pvalue of <0.05 was considered to indicate statistical significance.

Table 1 Characteristics of patients

All subjects (n = 28)	
Mean age (SD)	52.1 (16.7)
Males: females	11:17
No past surgical history (%)	15 (53.6)
Past surgical history (%)	13 (46.4)
Appendectomy	4
Cholecystectomy	4
Partial ileal resection	2
Subtotal gastrectomy	3

SD: standard deviation

Results

Diagnosis of SIBO

Twenty-one patients (11 males, 10 females; mean (± SD) age, 53.2 ± 16.1 years; range, 17 − 81 years) were referred for a breath test with a presumptive diagnosis of SIBO. Eight of the 21 patients (38.1%) had SIBO (Table 3). Four patients had unremarkable past medical histories, and 4

Table 2 Medication history of participants (multiple answers, n = 28)

Antibiotics	Ramosetron hydrochloride *	Polycarbophil calcium	Loperamide hydrochloride	Digestive enzymes	Anticholinergic drugs	Probiotics
42.9%	91.0% **	82.1%	69.6%	39.3%	46.4%	92.9%

*$5HT_3$ receptor antagonist; indicated for males only

**Percentage of males

$5HT_3$: 5-hydroxytriptamine3

Table 3 Results of lactulose breath testing

	Subjects tested for SIBO (n = 21)	P value *
Mean age, years (SD)	53.2 (16.1)	
Males: females	11:10	
SIBO-negative (%)	13 (61.9)	
Without past surgical history (%)	5 (38.5)	
With past surgical history (%)	8 (61.5)	
SIBO-positive (%)	8 (38.1)	
Without past surgical history (%)	4 (50.0)	
With past surgical history (%)	4 (50.0)	0.472

*Pearson chi-square test used for comparison of categorical data
SIBO: small intestinal bacterial overgrowth

Table 4 Effects of colestimide administration

	Subjects treated with colestimide (n = 28)	P value *
Negative report (%)	7 (25.0)	
Positive report (%)	21 (75.0)	0.008
With past surgical history	13	
Positive report (%)	10 (76.9)	
Without past surgical history	15	
Positive report (%)	11 (73.3)	0.558
	Subjects tested for SIBO (n = 21)	P value *
SIBO-negative	13	
Positive report (%)	9 (69.2)	
SIBO-positive	8	
Positive report (%)	8 (100.0)	0.119

*Pearson chi-square test used for comparison of categorical data
SIBO: small intestinal bacterial overgrowth

had previously undergone surgery, namely, appendectomy (n=2), subtotal gastrectomy (n=1), and partial ileal resection (n=1). The prevalence of SIBO did not differ between those with and without a past history of surgery (p =0.472).

Treatment of BAM

Twenty-eight patients were treated with colestimide. Table 4 shows the results of colestimide treatment and SIBO testing. Twenty-one patients (75.0%) reported less abdominal discomfort and improved bowel habits, which was a significant effect (p=0.008). Of the 28 patients who received colestimide treatment, 15 had no past history of gastrointestinal surgery. Eleven of the 15 patients (73.3%) without a past surgical history reported a positive effect, and 10 of the 13 patients (76.9%) with a past surgical history reported a positive effect. There was no significant difference in effectiveness between these groups (p=0.558). All 8 SIBO-positive patients (100%) reported a beneficial effect, while 9 of 13 patients without SIBO (69.2%) reported a beneficial effect. There was no significant difference between these groups (p=0.119).

Discussion

Various factors affect the pathophysiology of IBS, which explains why monotherapies have yielded limited benefits. An IBS diagnosis is based on patient symptoms and exclusion of certain organic diseases. Exclusion of organic disease is the most important aspect of diagnosing IBS; however, BAM diagnoses are often missed.

Recent studies reported that BAM was the cause of re-

fractory IBS-D and chronic diarrhea in approximately 30% of patients.[2, 22, 27, 28] In those studies, BAM in patients with IBS-D was confirmed by ^{75}SeHCAT scanning. However, as mentioned above, few medical centers are able to perform ^{75}SeHCAT scanning. Although other examinations are available, including stool bile acid assays and the stool ^{14}C taurocholate excretion and fibroblast growth factor 19 tests, these tests are difficult to administer as part of a routine examination.

The present patients had been previously treated with multiple medications for IBS, including anticholinergic drugs, 5-hydroxytriptamine 3 ($5HT_3$) receptor antagonists, probiotics, polycarbophil calcium, and antibiotics (Table 2). In such cases, psychological stress and problems related to the brain − gut axis may worsen symptoms. However, the present results show that colestimide treatment improved symptoms in 70% of patients with refractory IBS-D and chronic diarrhea, which indicates that administration of colestimide for refractory IBS-D and chronic diarrhea is more effective than some other therapies. These results are similar to those of a previous study of the effectiveness of cholestyramine (a bile acid binder) for IBS-D.[2]

The effect of colestimide did not differ between the present patients with and without a past history of gastrointestinal surgery. A small number of studies have investigated the association between type of surgery and BAM severity. Bile acids are actively absorbed in the terminal ileum.[29] Kurien et al reported that the median ileum resection length was 15 cm (range, 10–60 cm) in patients with BAM.[28] Existing evidence suggests that procedures such as appendectomy and partial ileum resection do not cause sufficient operative stress to induce BAM.

SIBO is causally related to BAM. All of the present patients with SIBO reported positive effects from colestimide. Colestimide appeared to be more effective for patients with SIBO than for those without SIBO, but the difference between these groups was not significant. It is difficult to determine whether the principal cause of chronic diarrhea is related to SIBO or BAM. In addition, the cause may differ among patients because BAM can induce SIBO and vice versa. The present results suggest that colestimide improves chronic diarrhea induced solely by excessive bile acid in the colon and relieves the adverse effects of SIBO. However, the reliability of breath testing in the diagnosis of SIBO is unproven. Some question remains as to whether a positive LBT result confirms SIBO. An early increase in breath hydrogen excretion might be the result of rapid orocecal transit, which is more likely in patients with diarrhea.[30, 31] Hence, the results of LBT should be interpreted with caution.

In conclusion, a colestimide trial would benefit patients with refractory and non-definitive diagnoses of chronic diarrhea and IBS-D. If successful, symptoms could be ameliorated, and such success would confirm the presence of BAM. Colestimide improved symptoms in over 70% of patients for whom multiple medications had been ineffective. With respect to the benefits to patients and healthcare economics, this result should be useful in developing a therapeutic strategy for refractory diarrhea and IBS-D. Further investigations of convenient, easily accessible diagnostic methods for BAM are expected. The present findings suggest that a trial of colestimide for refractory chronic diarrhea and IBS-D is warranted.

The authors are very grateful to Teruo Nakamura, Professor Emeritus of Hirosaki University, for his general supervision of the study.

Funding: None declared.

Conflicts of interest: None declared.

References

1) Fernández-Bañares F, Esteve M, Salas A, Alsina M, Farré C, González C, et al. Systematic evaluation of the causes of chronic watery diarrhea with functional characteristics. Am J Gastroenterol. 2007; 102: 2520-8.
2) Wedlake L, A'Hern R, Russell D, Thomas K, Walters JR, Andreyev HJ. Systematic review: the prevalence of idiopathic bile acid malabsorption as diagnosed by SeHCAT scanning in patients with diarrhoea-predominant irritable bowel syndrome. Aliment Pharmacol Ther. 2009; 30: 707-17.
3) Pattni S, Walters JR. Recent advances in the understanding of bile acid malabsorption. Br Med Bull. 2009; 92: 79-93.
4) Saeki T, Matoba K, Furukawa H, Kirifuji K, Kanamoto R, Iwami K. Characterization, cDNA cloning, and functional expression of mouse ileal sodium-dependent bile acid transporter. J Biochem. 1999; 125: 846-51.
5) Håkansson P, Andersson I, Nyström S, Löfgren L, Amrot LF, Li H. Ontogenetic development and spatial distribution of the ileal apical sodium-dependent bile acid transporter and the ileal lipid-binding protein in apoE knockout and C57BL/6 mice. Scand J Gastroenterol. 2002; 37: 1089-96.
6) Stelzner M, Hoagland V, Somasundaram S. Distribution of bile acid absorption and bile acid transporter gene message in the hamster ileum. Pflugers Arch. 2000; 440: 157-62.
7) Craddock AL, Love MW, Daniel RW, Kirby LC, Walters HC, Wong MH, et al. Expression and transport properties of the human ileal and renal sodium-dependent bile acid transporter. Am

J Physiol. 1998; 274 (1 Pt 1): G157-69.
8) Hofmann AF, Poley JR. Role of bile acid malabsorption in pathogenesis of diarrhea and steatorrhea in patients with ileal resection. I. Response to cholestyramine or replacement of dietary long chain triglyceride by medium chain triglyceride. Gastroenterology. 1972; 62: 918-34.
9) Williams AJ, Merrick MV, Eastwood MA. Idiopathic bile acid malabsorption--a review of clinical presentation, diagnosis, and response to treatment. Gut. 1991; 32: 1004-6.
10) Sinha L, Liston R, Testa HJ, Moriarty KJ. Idiopathic bile acid malabsorption: qualitative and quantitative clinical features and response to cholestyramine. Aliment Pharmacol Ther. 1998; 12: 839-44.
11) Ferraris R, Galatola G, Barlotta A, Pellerito R, Fracchia M, Cottino F, et al. Measurement of bile acid half-life using [75Se] HCAT in health and intestinal diseases. Comparison with [75Se] HCAT abdominal retention methods. Dig Dis Sci. 1992; 37: 225-32.
12) Sciarretta G, Fagioli G, Furno A, Vicini G, Cecchetti L, Grigolo B, et al. 75Se HCAT test in the detection of bile acid malabsorption in functional diarrhoea and its correlation with small bowel transit. Gut. 1987; 28: 970-5.
13) Smith T, Bjarnason I, Hesp R. Critical analysis of the accuracy of a combined test (75Se-HCAT and 58Co-B12) of ileal function using a whole-body counter. Clin Phys Physiol Meas. 1987; 8: 159-71.
14) Furno A, Sciarretta G, Fagioli G, Pozzato R, Malaguti P. Scintigraphic evaluation of enterogastric reflux using 75Se-HCAT: methodology and first clinical observations. Eur J Nucl Med. 1987; 13: 230-3.
15) Schroth HJ, Berberich R, Feifel G, Müller KP, Ecker KW. Tests for the absorption of 75Se-labelled homocholic acid conjugated with taurine (75Se-HCAT). Eur J Nucl Med. 1985; 10: 455-7.
16) Lorenzo-Zúñiga V, Bartoli R, Planas R, Hofmann AF, Viñado B, Hagey LR, et al. Oral bile acids reduce bacterial overgrowth, bacterial translocation, and endotoxemia in cirrhotic rats. Hepatology. 2003; 37: 551-7.
17) Ghoshal UC, Kumar S, Mehrotra M, Lakshmi C, Misra A. Frequency of small intestinal bacterial overgrowth in patients with irritable bowel syndrome and chronic non-specific diarrhea. J Neurogastroenterol Motil. 2010; 16: 40-6.
18) Zhao J, Fox M, Cong Y, Chu H, Shang Y, Fried M, et al. Lactose intolerance in patients with chronic functional diarrhoea: the role of small intestinal bacterial overgrowth. Aliment Pharmacol Ther. 2010; 31: 892-900.
19) Rana SV, Bhardwaj SB. Small intestinal bacterial overgrowth. Scand J Gastroenterol. 2008; 43: 1030-7.
20) Egger G, Kessler JI. Clinical experience with a simple test for the detection of bacterial deconjugation of bile salts and the site and extent of bacterial overgrowth in the small intestine. Gastroenterology. 1973; 64: 545-51.
21) Fan X, Sellin JH. Review article: Small intestinal bacterial overgrowth, bile acid malabsorption and gluten intolerance as possible causes of chronic watery diarrhoea. Aliment Pharmacol Ther. 2009; 29: 1069-77.
22) Johnston I, Nolan J, Pattni SS, Walters JR. New insights into bile acid malabsorption. Curr Gastroenterol Rep. 2011; 13: 418-25.
23) Fine KD, Schiller LR. AGA technical review on the evaluation and management of chronic diarrhea. Gastroenterology. 1999; 116: 1464-86.
24) Rhodes JM, Middleton P, Jewell DP. The lactulose hydrogen breath test as a diagnostic test for small-bowel bacterial overgrowth. Scand J Gastroenterol. 1979; 14: 333-6.
25) King CE, Toskes PP. Comparison of the 1-gram [14C]xylose, 10-gram lactulose-H2, and 80-gram glucose-H2 breath tests in patients with small intestine bacterial overgrowth. Gastroenterology. 1986; 91: 1447-51.
26) Staels B, Kuipers F. Bile acid sequestrants and the treatment of type 2 diabetes mellitus. Drugs. 2007; 67: 1383-92.
27) Gracie DJ, Kane JS, Mumtaz S, Scarsbrook AF, Chowdhury FU, Ford AC. Prevalence of, and predictors of, bile acid malabsorption in outpatients with chronic diarrhea. Neurogastroenterol Motil. 2012; 24: 983-e538.
28) Kurien M, Evans KE, Leeds JS, Hopper AD, Harris A, Sanders DS. Bile acid malabsorption: an under-investigated differential diagnosis in patients presenting with diarrhea predominant irritable bowel syndrome type symptoms. Scand J Gastroenterol. 2011; 46: 818-22.
29) Ung KA, Olofsson G, Fae A, Kilander A, Ohlsson C, Jonsson O. *In vitro* determination of active bile acid absorption in small biopsy specimens obtained endoscopically or surgically from the human intestine. Eur J Clin Invest. 2002; 32: 115-21.
30) Yu D, Cheeseman F, Vanner S. Combined oro-caecal scintigraphy and lactulose hydrogen breath testing demonstrate that breath testing detects oro-caecal transit, not small intestinal bacterial overgrowth in patients with IBS. Gut. 2011; 60: 334-40.
31) Riordan SM, McIver CJ, Walker BM, Duncombe VM, Bolin TD, Thomas MC. The lactulose breath hydrogen test and small intestinal bacterial overgrowth. Am J Gastroenterol. 1996; 91: 1795-803.