REVISTA ESPAÑOLA DE
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The Spanish Journal of Gastroenterology

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DOI: 10.17235/reed.2018.5376/2017
Link: PubMed (Epub ahead of print)

Please cite this article as:
Mena Bares Luisa M.ª, Benítez Cantero José M., Iglesias Flores Eva, Gros Alcalde Beatriz, Moreno Ortega Estefanía, Maza Muret Francisco R., Carmona Asenjo Elvira, García Sánchez M.ª Valle, Vallejo Casas Juan A.. Bile acid malabsorption in patients with chronic diarrhea and Crohn's disease. Rev Esp Enferm Dig 2018. doi: 10.17235/reed.2018.5376/2017.

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OR 5376 inglés

Bile acid malabsorption in patients with chronic diarrhea and Crohn's disease

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Received: 21/11/2017

Accepted: 10/07/2018

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ABSTRACT

Introduction and aim: Crohn's disease (CD) is a form of inflammatory bowel disease and is mainly characterized by diarrhea and abdominal pain. The aim of our study was to analyze the usefulness of performing a ^{75}SeHCAT scan in CD patients with chronic diarrhea and suspected bile acid malabsorption (BAM). In addition, we aimed to determine whether there was a relationship with the clinical features of the disease and a previous bowel resection.

Patients and methods: this was an observational cross-sectional study of 39 patients with a diagnosis of CD and chronic diarrhea. All cases underwent a ^{75}SeHCAT scan for BAM diagnosis, after discarding disease activity.

Results: the study cohort included 19 females and 20 males. The median age was 44 years and the majority of patients were A2 L1 B1 according to the Montreal classification; 84.6% of patients had undergone a previous bowel resection. BAM was present in 97.4% of patients (100% and 83.3% of patients with and without previous surgery, respectively), which was severe in 92.1% of cases. Treatment with bile acid

sequestrants was initiated and a favorable response was obtained in 72.2% of patients. The relationship between BAM degree (moderate or severe), bowel surgery and the response to bile acid sequestrant treatment was also analyzed but not statistically significant.

Conclusion: BAM is a frequent cause of diarrhea in CD patients in endoscopic or radiological remission. This condition was present in all patients with a history of a bowel resection. A response to bile acid sequestrants treatment was observed in 73% of patients.

Key words: ^{75}SeHCAT. Chronic diarrhea. Crohn's disease. Bile acid malabsorption. Ileal resection. Bile acid sequestrants.

INTRODUCTION

Inflammatory bowel disease (IBD) encompasses a group of clinic entities characterized by their inflammatory nature, unknown etiology and tendency to affect (although not exclusively) the intestine. The etiology of IBD is complex, comprising a combination of genetic and environmental factors (1). Crohn's disease (CD) is one form of IBD. It can affect any part of the intestine, although it is mainly found at the ileocecal level. The prevalence of CD with an ileocecal location in Spain is 42% when considering all IBD patients (2). CD is transmural and mainly accompanied by diarrhea and/or abdominal pain. It is classified according to the location (ileal, colonic, ileocolonic, or upper gastrointestinal tract), clinical pattern (inflammatory, stenotic or fistulising) and severity (mild, moderate or severe). In line with this, the Montreal classification for CD has been internationally generalized and accepted (3,4).

As previously mentioned, diarrhea is one of the main symptoms in CD patients. Diarrhea is considered as chronic when it lasts for four weeks or longer (5). In order to diagnose chronic diarrhea in CD patients, it is essential to establish whether it is a consequence of the disease activity itself or whether it is due to other causes. Thus, a diagnosis will be based on laboratory and imaging tests such as colonoscopy/ileoscopy, bowel transit, magnetic resonance enterography (MRE), capsule endoscopy, abdominal ultrasound, anorectal manometry or ^{75}SeHCAT scan (6).

BAM is one of the causes of chronic diarrhea in CD patients, once disease activity has been ruled out. Three types of MAB have been described: type I is secondary to ileal dysfunction (patients with ileal resection and/or bypass, and patients with CD), type II is due to idiopathic primary conditions and type III is caused by intestinal conditions that impair the normal reabsorption of bile acids. There is an alteration in the enterohepatic circulation in BAM that leads to fat malabsorption. This, in turn, causes both steatorrhea and an increase in the proportion of secreted bile acids, which are not reabsorbed in the ileum. Instead, bile acids reach the colon, where they cause diarrhea (7,8).

First-line BAM treatment is based on the administration of bile acid sequestrants. Currently, three molecules are commercially available: cholestyramine and colestipol and more recently, colesevelam. With regard to BAM diagnosis, a ^{75}SeHCAT scan is considered to be the gold standard (sensitivity: 80-94%, specificity: 70-100%) due to its good correlation with the fecal loss of bile acids (9-11). Furthermore, it is an effective, safe and inexpensive technique, with a practically insignificant radiation dose (12). ^{75}SHCAT scan is based on the measurement of bile acid turnover using homotaurocolic acid, a synthetic bile acid labelled with ^{75}Se and resistant to bacterial degradation (13). ^{75}SeHCAT is administered as an oral capsule which is absorbed at the intestinal level. Following enterohepatic circulation, ^{75}SeHCAT is excreted by the liver and the gallbladder along with other bile acids and enzymes. A small proportion of the molecule is eliminated in the feces (14). The radiopharmaceutical retention of ^{75}SeHCAT seems to correlate with the ileal absorption. Therefore, a BAM diagnosis is established following the measurement of the retention according to sequential images of the patient (9).

The goal of our study was to analyze the usefulness of ^{75}SeHTCAT in patients with CD, chronic diarrhea and suspected BAM. In addition, we aimed to establish a relationship between the presence of BAM, the clinical features of CD and the history and location of surgery (ileal resection, colectomy, etc.) in these patients.

PATIENTS AND METHOD

Study design

Observational cross-sectional study.

Patients

Thirty-nine patients referred to the Nuclear Medicine Clinical Management Unit from August 2015 until September 2017 were included in the study. Patients had CD, chronic diarrhea that lasted for more than four weeks and also a suspicion of BAM. The clinical features of CD presented by the patients were analyzed according to the Montreal criteria. Disease activity was endoscopically (Rutgeerts score) and radiologically (MRE) discarded by a gastroenterologist. Patients had not previously received bile acid sequestrant therapy. In addition, any other cause of BAM was discarded, such as a history of cholecystostomy. For those patients who underwent surgery, information regarding the location (ileal, colonic, or ileocolonic) as well as the length of ileum resected was also collected. Treatment following BAM diagnosis was based on bile acid sequestrant. Therapy was considered as successful if the number of stools/day was lower than half of the daily number of stools prior to diagnosis. The response to treatment was assessed during the follow-up visit (a mean of six months after initiating treatment; standard deviation [SD] = 2.95 months).

^{75}SeHCAT test protocol

Written informed consent was obtained from all the patients included in the study and pregnancy was discarded in fertile women. ^{75}SeHCAT was administered as an oral capsule, with an activity of 0.37 MBq (15). Patients fasted four hours before taking the capsule until 3-4 hours after. The early phase of the study was acquired at this point and the second acquisition was performed one week after the administration of ^{75} SeHCAT.

The acquisition of the study (on both the day of ^{75}SeHCAT administration and one week later) was composed of background images that allowed the measurement of the room background and patient images in anterior and posterior projections. The acquisition time was five minutes per projection. Afterwards, the abdominal retention (AR) of ^{75}SeHCAT was calculated on the basis of the rate of counts provided by each projection. Firstly, the abdominal activity (AA) was calculated as the mean of patient

and background activities:

$$AA = ([ANT-BKG1] + [POST-BKG2])/2,$$

where ANT is the patient activity in the anterior projection, POST is the patient activity in the posterior projection, BKG1 is the mean background in the anterior projection (before and after patient acquisition) and BKG2 is the mean background in the posterior projection (before and after patient acquisition). Secondly, AR was calculated as the quotient between the AA obtained on day 7 (AA_7) and the AA on day 0 (AA_0) multiplied by 100 (16-18):

$$AR = (AA_7/AA_0)*100$$

A 10% retention was considered as an optimal cut-off for BAM diagnosis (BAM if AR was < 10%) (16).

Statistical analysis

Median and interquartile ranges were used to express quantitative variables, whereas absolute and relative frequencies were used for qualitative variables. BAM was classified as mild, moderate or severe according to AR values (7-10, 4-7 and < 4%, respectively). BAM was compared between the patients who underwent intestinal resection and those who did not. The relationship between BAM degree, CD features, previous surgery and the response to treatment was also evaluated. A p-value < 0.05 was considered as statistically significant. Statistical analysis was performed using the SPSS 19 software (SPSS Inc., Chicago, IL, USA) for Windows.

RESULTS

Thirty-nine CD patients were included in the study, with a median age of 44 years (range: 21-62 years). The median duration of the illness was 13 years (range: 2-31 years). With regard to the Montreal classification, the majority of patients were classified as A2 (17-40 years of age at diagnosis), L1 (location in terminal ileum) and B1 (inflammatory clinical pattern). No perianal affectation was detected in more than 50% of patients and very few had extra-intestinal manifestations of the disease. The majority of patients were on immunosuppressant therapy (16 out of 39 cases [41%]) (Table 1).

The clinical features of the patients were analyzed and the majority were asymptomatic (53%), while 20.5% presented with abdominal pain (Table 1). Thirty-three of 39 patients had a history of bowel resection. The median time from diagnosis to surgery was nine years (range: 1-23 years). Ileal resection was performed in 29 patients, with a median of 29 cm resected (range: 2-80 cm) (Table 2). Of these 33 patients, 31 had an endoscopic study prior to the SeHCAT test and the median time until the test was two months (range: 0-10 months). In addition, two of the 33 patients underwent MRE, with a median of three months (range: 2.8-3.2 months) in order to discard post-surgical recurrence of the disease. However, none of these 33 patients showed endoscopic (Rutgeerts score: i0 in 21 [67.75%] and i1 10 [32.25%] patients, respectively) (Fig. 1) and/or radiological (no evidence of inflammatory activity in MRE) signs of recurrence. The global percentage of BAM, i.e., with an AR value < 10%, was 97.4% (38 out of 39 patients). This was severe in 35 (92.1%) patients and moderate in three (7.9%) cases.

Patients were divided into two groups according to previous surgery (33/39 [84.6%]) or no previous surgery (6/39 [15.4%]). All patients who underwent surgery (n = 33) had BAM. Within this group, BAM was severe in 30 (90.9%) patients and moderate in three (9.1%) patients. In addition, BAM was present in five (83.3%) of the six patients with no history of surgery and was severe in all cases. Treatment with bile acid sequestrant was initiated following a BAM diagnosis in 33 of 38 patients. Treatment was not administered in five cases due to a bout of disease activity immediately after BAM diagnosis.

Cholestyramine was the treatment of choice in all patients, with doses ranging between 3 g/12-24 h and 4 g/24 h. Treatment was considered to be successful when the reduction in the number of stools/day was ≥ 50% of the daily number of stools prior to diagnosis. A favorable response to treatment was observed in 21 (63.6%) of 33 patients. The median of the daily number of stools prior to treatment administration was six, whereas three daily stools were reported after treatment (range: 1-10 stools). Treatment with colestipol or colesevelam was initiated in four of the 12 patients who did not respond to cholestyramine administration; a favorable response was obtained in three cases. Thus, the final percentage of favorable response was 72.7% (24/33

patients). No other sequestrant was administered in eight cases due to patient refusal. The side effects derived from cholestyramine therapy were present in ten (30.3%) of 33 patients, mainly related to digestive intolerance.

The clinical features of the patients on sequestrant therapy were assessed and abdominal pain was only present in 6.7% of cases (Table 1). In addition, whether any of the disease features or the bowel resection were associated with the degree of disease (moderate or severe) was analyzed but the results were non-significant ($p = 0.992$). Finally, the relationship between the response to sequestrant therapy and the degree of BAM was assessed. The rate of response in moderate and severe BAM was 50% and 74.2%, respectively. Nevertheless, there was no evidence of an association between both variables ($p = 0.824$).

DISCUSSION

Patients with CD normally have abdominal pain and diarrhea. However, symptoms may be variable and atypical. Diarrhea can be caused by the disease activity itself and may also be due to other causes such as bacterial overgrowth, intestinal motor disorders, and/or BAM (19,20). Once a bout of disease has been discarded, BAM is one possible cause of diarrhea in CD patients. As we have shown, this is the case in a large proportion of patients (97.4%) and is severe in the majority of cases (92.1%). Several authors have previously reported that the volume of circulating bile acids is lower in CD patients than in healthy individuals. Conversely, the level of conjugated bile acids is higher in CD (21). It has been hypothesized that the existence of BAM in these patients might be due to a lower expression of the apical sodium-dependent bile acid transporter (ASBT). This is reduced by approximately 50% and leads to a deficiency in bile acid reabsorption, even in patients with no previous surgery (22). Ileum resection is associated with ASBT loss due to the fact that a higher density of transporters are located in the last 100 cm from the ileocecal valve, therefore increasing the loss of bile acids (23).

When our patient cohort was classified according to previous bowel resection, we found that BAM was present in all cases with a previous surgery. Within this group of patients, BAM was severe or moderate in 90.9% and 9.1% of cases, respectively. BAM

was present in 83.3% of patients with no history of surgery and all cases were severe. Thus, no relationship could be established between BAM severity and history of surgery. This is in line with previous reports that the presence of BAM in patients with a previous surgery was higher than 90% and variable in patients with no surgery (24) when ^{75}SeHCAT was used as a diagnosis method. Here we also report a high percentage (> 80%), which is in agreement with the study by Kurien et al. (25).

It has been proposed that empirical treatment with bile acid sequestrants should be started in CD patients with chronic diarrhea and a previous bowel resection, instead of performing ^{75}SeHCAT for BAM diagnosis. However, the use of ^{75}SeHCAT to establish a diagnosis would avoid unnecessary treatments and consequently, the undesirable derived side effects. It is difficult to predict empirically an effective dose, since there may be up to 25% of false negatives. Other arguments against empirical treatment are that sequestrant therapy may inactivate the *Clostridium difficile* toxin (12) as well as impair the absorption of warfarin, digoxin, diuretic and beta-blocker molecules and fat-soluble vitamins. Thus, an early previous diagnosis is necessary before initiating treatment (11).

There are other theories supporting the presence of BAM in CD patients. It has been suggested that the release of pro-inflammatory cytokines (IL-1, IL-6, and TNFα) inhibits ASBT transcription and, consequently, reduces its expression in the ileal mucosa (26,27). Furthermore, the inflammation-mediated inhibition of the transcription of the FXR receptor, which is involved in the regulatory mechanism of bile acid synthesis, results in a “chronification” of disease (28). In addition, alterations in fecal microbiota have been observed in CD patients along with an elevated concentration of primary and conjugated bile acids in feces. Such alterations modify the composition of bile acids. Given that certain types of bile acids possess anti-inflammatory properties, it is likely that this mechanism also participates in the chronic inflammation process (24).

BAM treatment is based on the administration of bile acid sequestrants. Three molecules are currently available: cholestyramine, colestipol, and colesevelam. Cholestyramine and colestipol are the most frequently used, although their major disadvantage is their low tolerability (29). Colesevelam is administered as a tablet with an adequate tolerability, more potent action and lower rate of side effects than

cholestyramine and colestipol and does not affect the bioavailability of other molecules. However, colesevelam is more expensive than the other molecules (12). In this study, cholestyramine was administered as a first-line sequestrant in all patients with a diagnosis of BAM. Different parameters have been suggested to assess the response to treatment including a lower frequency of bowel movements, improved stool consistency, a lower number of stools (higher than 30%, 1-2 solid stools/day) or improvement in the quality of life (11,30-32).

Our group has established a reduction of 50% or higher in the number of stools/day as a positive response to treatment. This condition was met in 63.6% of cholestyramine-treated patients, while intolerance to treatment was observed in 23.7% out the 36.4% of patients that did not respond. The response rate was 72.7% when the three patients who responded to other sequestrants were included in the analysis. These findings are in line with previous studies such as the systematic review by Wilcox et al., which reported a cholestyramine response rate of 70% (range: 63-100%) (11). Other studies have also evaluated the relationship between BAM severity and response to treatment, with conflicting of results. Again, our findings support those reported by Wilcox et al. (11), which did not confirm an association or report an association with disease features and a previous bowel resection.

Finally, several shortcomings should be acknowledged in our study. First, the low number of patients included in the study. In fact, BAM was not present in only one of the 39 patients included in the analyses. Therefore, it is not possible to infer the possible influence of the clinical features of CD and previous bowel resection in the presence or absence of BAM. Second, the study has been carried out in a selected population. The majority of patients had previous surgery, and inflammatory activity had been discarded. Nevertheless, this issue could be avoided by increasing the size of the population and importantly, performing the ^{75}SeHCAT earlier and prior to other tests in CD patients with diarrhea. By doing this, treatment could be initiated earlier, with the associated improvement in the quality of life.

CONCLUSIONS

BAM is a frequent cause of diarrhea in CD patients in endoscopic or radiological remission and is present in all the patients with a previous bowel resection. The characteristics of the disease and the previous bowel resection are not related to BAM severity. The ^{75}SeHCAT scan allowed a BAM diagnosis to be determined and consequently, the initiation of bile acid sequestrant treatment. Such treatment was effective in 73% of patients, regardless of the BAM degree.

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Table 1. Clinical characteristics of the study population

	n	%
Patients		
Female	19	48.7
Male	20	51.3
Montreal classification		
A		
A1	2	5.1
A2	31	79.5
A3	6	15.4
L		
L1	19	48.7
L2	3	7.7
L3	14	35.9
L4	3	7.7
B		
B1	19	48.7
B2	12	30.8
B3	8	20.5
p (perianal affectation)		
No	24	61.5
Yes	15	38.5
Intestinal manifestations		
No	37	94.9
Yes	2	5.1
Therapy		
Immunosuppressant	16	41.0
Biological	4	10.3
Combined	10	25.6
Other/None	9	23.1

Pre-treatment abdominal symptoms		
No	18	53.0
Discomfort	9	26.5
Pain	7	20.5
Diarrhea (no. stools/day > 3)	33	86.8
Post-treatment abdominal symptoms		
No	25	83.3
Discomfort	3	10.0
Pain	2	6.7
Diarrhea (no. stools/day > 3)	13	37.1

Table 2. Previous surgery and location of the surgery

	n	%
Surgery		
Yes	33	84.6
No	6	15.4
Location of the surgery		
IR + cecum	18	54.5
IR + colon	11	33.3
Colon	4	12.2

IR: ileal resection.

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Fig. 1. Endoscopic assessment of post-surgical recurrence (Rutgeerts score). Post-surgical recurrence ≥ i2.