

# Use of the SeHCAT test in the investigation of diarrhoea

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**Summary:** The SeHCAT test was used to investigate possible bile acid malabsorption in 166 patients presenting to a district general hospital with chronic diarrhoea of uncertain cause. Eighty-four (51%) patients had impaired SeHCAT retention. These included 23 of 28 patients with a possible type I abnormality (terminal ileal resection or disease, previous pelvic radiotherapy), 20 of 74 with a possible type II abnormality (idiopathic diarrhoea), 32 of 45 with a possible type III abnormality (post-cholecystectomy, post-vagotomy), and 9 of 19 with diarrhoea associated with diabetes. Patients with severe bile acid malabsorption demonstrated a good response to cholestyramine whereas the response in patients with a mildly abnormal SeHCAT retention was variable. Bile acid malabsorption is an important cause of diarrhoea in patients presenting with unexplained chronic diarrhoea.

## Introduction

Bile acid malabsorption is recognized as a cause of chronic diarrhoea.<sup>1</sup> In healthy individuals bile acids are reabsorbed by the terminal ileum. Bile acids may induce diarrhoea if they enter the colon, through inhibition of water and electrolyte transport and possibly by increasing colonic motility.<sup>2–7</sup> Three types of bile acid malabsorption have been described: type I is associated with terminal ileal resection or with mucosal disease of the terminal ileum; type II is idiopathic and type III follows cholecystectomy or vagotomy.<sup>4</sup> The incidence of bile acid malabsorption in patients with chronic diarrhoea remains uncertain with suggestions that many patients with type II bile acid malabsorption are incorrectly labelled as irritable bowel disease.<sup>1</sup>

The specific diagnosis of bile acid malabsorption has previously involved complex bile acid measurements and been confined to specialist centres, often seeing highly selected groups of patients.<sup>8</sup> Since a synthetic radiolabelled bile acid 23-selena-25-homocholytaurine (SeHCAT) became available the diagnosis has become much easier.<sup>9</sup> SeHCAT retention at 7 days following oral administration has been demonstrated to be a reliable index of bile acid absorption.<sup>10</sup>

We report our experience of using the SeHCAT test to assess bile acid malabsorption in the investigation of diarrhoea in 166 patients during a 3 year period.

## Patients and methods

One hundred and sixty-six patients (89 female) aged 18–79 years were studied. Clinical details of all patients undergoing the SeHCAT test were obtained from retrospective review of patient records. Average stool frequency experienced by patients was recorded at the initial clinic visit. All patients had diarrhoea as their main complaint, defined by at least two loose stools daily (range 2–11; mean 3.5). These patients constituted approximately 10% of all patients referred for investigation of diarrhoea. History, physical examination and other investigations led to a diagnosis in the remaining 90%.

Twenty-eight patients were thought to have possible type I bile acid malabsorption. Seven had previous ileal resection. Twelve had pelvic radiotherapy up to 22 years previously. Radiotherapy was for malignancy in 10 patients (one ovarian, 4 uterine, 3 cervix and 2 bladder) and to induce menopause in one patient. Hydrogen breath tests were performed in 4 of the patients who had received radiotherapy and were normal. Four patients with known previous Crohn's disease were investigated because haematological and biochemical parameters suggested that the Crohn's disease was inactive. Five patients were suspected of having Crohn's disease despite normal small intestinal barium studies because of raised plasma viscosity or platelet values in association with diarrhoea and/or abdominal pain. The largest group consisted of 74 patients with unexplained diarrhoea, who had possible type II bile acid malabsorption. Intermittent abdominal pain was present

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in 23 (31%) patients but was not the main presenting complaint and was not severe. Forty-five patients had possible type III bile acid malabsorption, 30 following previous cholecystectomy, 11 following vagotomy and 4 following both cholecystectomy and vagotomy. Surgery had been carried out between one and 18 years ago. Diarrhoea had commenced within 6 months following surgery in all patients. Nineteen patients with diabetes and diarrhoea were investigated and were analysed separately.

<sup>75</sup>Selenium-labelled taurohomocholic acid, an analogue of the naturally occurring taurocholic acid, was administered orally with a single dose of 370 kBq. The absorbed radiation from this dose of SeHCAT has been estimated to be low, being less than skin doses received during gastrointestinal fluoroscopy.<sup>11</sup> Retained activity was measured at day 0 and day 7 using an uncollimated gamma counter, a technique shown to correlate well with whole body counting.<sup>12</sup> Using the results of previous groups, retention of less than 15% of the isotope at day 7 was considered abnormal.

All patients with a positive SeHCAT test were initially treated with cholestyramine except for the patients with Crohn's disease. The initial dose prescribed was 2 g daily and patients were recommended to increase or decrease the dose according to response. A clinical assessment of the response to cholestyramine was made one month after commencing treatment. Patients were asked whether their stool frequency had returned to normal (formed stool once or twice daily) which was recorded as a complete response. Patients who did not demonstrate a complete response but reported a reduction in average stool frequency were recorded as showing a partial response.

## Results

Eighty-four (51%) of the 166 patients had a positive SeHCAT test (Table I), with a 7 day retention of 0–15%. Retention in the 82 remaining patients with a normal test ranged from 19 to 86%.

### *Possible type I bile acid malabsorption*

The SeHCAT test was abnormal in 23 (82%) of the 28 patients. All patients who had undergone ileal resection, 10 of the 12 who had received pelvic radiotherapy, and 3 of the 4 patients with known Crohn's disease had a positive test. SeHCAT retention ranged between 0 and 13%. Three of the 5 patients with suspected Crohn's disease had a positive test. The diagnosis was subsequently confirmed in these 3 patients by further small bowel barium studies in two and colonoscopy in the other. For this group as a whole, SeHCAT retention was strikingly low, being less than 5% in 19 of the 23 patients with a positive test.

### *Possible type II bile acid malabsorption*

The SeHCAT test was abnormal in 20 (27%) of the 74 patients, but in contrast to the type I group, a continuum of abnormal values was found (Table I).

### *Possible type III bile acid malabsorption*

The SeHCAT test was abnormal in 32 (71%) of the 45 patients. Twenty-four of 30 patients with post-cholecystectomy diarrhoea and 4 of 11 with post-vagotomy diarrhoea and all 4 who had undergone both procedures had a positive SeHCAT test.

**Table I** SeHCAT results (as % retention at 7 days) in 166 patients investigated for bile acid malabsorption (BAM)

	Positive		Negative	
	<5%	5–10%	11–15%	>15%
<b>Possible type I BAM</b>				
Ileal resection (7)	6	1	–	–
Previous radiotherapy (12)	8	2	–	2
Known Crohn's disease (4)	2	1	–	1
Suspected Crohn's disease (5)	3	–	–	2
<b>Possible type II BAM (74)</b>				
	3	12	5	54
<b>Possible type III BAM</b>				
Post-cholecystectomy (30)	11	4	9	6
Post-vagotomy (11)	–	4	–	7
Post-cholecystectomy (4) and vagotomy	1	3	–	–
Diabetics (19)	6	2	1	10
Total (166)	40	29	15	82

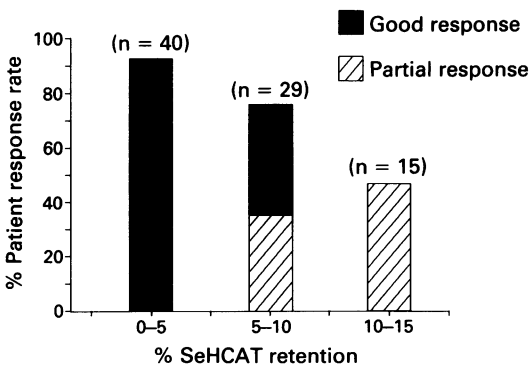
Again the results showed a continuum of abnormality.

### Diabetic patients

Nine (47%) of the 19 diabetic patients had a positive test. SeHCAT retention was less than 5% of 6 patients.

### Response to cholestyramine

The clinical assessment of the effectiveness of cholestyramine was dependent upon the severity of the abnormality of SeHCAT retention. Figure 1 shows the response to cholestyramine for 3 ranges of SeHCAT retention. The lower the retention the better the response to cholestyramine. Thirty-seven of 40 patients with retention less than 5% reported a complete resolution of diarrhoea with doses ranging from 1 to 8 g daily. Two of the 3 non-responders were subsequently found to have pancreatic malabsorption on the basis of a positive pancreolauryl test and the other patient was found to have disseminated malignancy of unknown primary origin. In the 29 patients with a SeHCAT retention of 5–10%, 12 reported complete resolution of symptoms, 10 had a partial response and 7 patients reported no improvement. Of the 15 patients with a SeHCAT retention of 11–15%, none reported complete resolution of diarrhoea and only 7 had a partial response. Thirteen (26%) of the 49 patients who responded well to cholestyramine found it unpalatable and did not wish to continue with treatment. They were prescribed aluminium hydroxide which was equally effective in 10.



**Figure 1** Clinical response in 84 patients with diarrhoea and abnormal SeHCAT retention, treated with cholestyramine. % response rates (full or partial) are shown for 3 ranges of SeHCAT retention with the total number of patients in each group indicated.

### Discussion

The present study confirms the feasibility of using the SeHCAT test in investigating the cause of diarrhoea in patients attending a District General Hospital. These results also confirm that bile acid malabsorption is a relatively common problem. The spectrum of patients seen was broadly similar to that reported from specialist centres, except that a larger proportion of patients had abnormalities secondary to pelvic radiotherapy or following cholecystectomy.<sup>1,6</sup>

Bile acid malabsorption following pelvic radiotherapy has previously been described with the use of breath tests of bile acid metabolism.<sup>13</sup> The mechanisms responsible for radiotherapy producing bile acid malabsorption are unclear. Presumably the terminal ileal bile acid transport mechanisms are damaged by radiotherapy. Bacterial overgrowth may also be a contributory factor although the normal hydrogen breath tests obtained in 4 patients argue against this.

We rarely found it necessary to utilize the SeHCAT test in investigating patients with possible or known Crohn's disease, although 3 patients had evidence of terminal ileal involvement with normal small bowel contrast studies, suggesting that the test may be more sensitive in detecting early terminal involvement in some patients.

The finding of several patients with idiopathic bile acid malabsorption is in keeping with observations of Merrick *et al.*, who have suggested this is an underdiagnosed condition, frequently labelled as irritable bowel syndrome.<sup>1</sup> The symptoms histories obtained from the patients with an abnormal SeHCAT test were compared with those of patients with unexplained diarrhoea with a normal SeHCAT test. The symptoms of patients with an abnormal SeHCAT test differed in that the diarrhoea was described as painless, watery, often nocturnal and not related to stress. Two possible mechanisms have been suggested for this syndrome of idiopathic bile acid malabsorption. Firstly, rapid ileal transit may be responsible, although studies of transit time with hydrogen breath tests failed to confirm this in one study.<sup>14</sup> Alternatively a defect in active bile acid transport may be responsible. Thaysen and Pedersen suggested this could be a genetic defect.<sup>2</sup> Popovic *et al.* propose an alternative mechanism of an immunological disorder of the terminal ileum. Their patients had reduced complement levels, a high incidence of organ-specific autoantibodies and an inflammatory infiltrate in terminal ileal biopsies.<sup>15</sup>

Diarrhoea following cholecystectomy or vagotomy is well recognized.<sup>16,17</sup> Bile acid malabsorption has been previously reported to be a contributory factor.<sup>18</sup> Our experience suggests this may be the largest group of patients with bile acid malabsorp-

tion in a district general hospital.

Bile acid malabsorption has been reported in the occasional diabetic patient with diarrhoea.<sup>19-21</sup> The largest study in 7 diabetics with diarrhoea demonstrated these patients to have a smaller bile-salt pool, an altered bile acid profile and increased faecal bile acid excretion compared to healthy controls.<sup>22</sup> Diabetics with autonomic neuropathy but without diarrhoea had a larger bile acid pool and increased faecal bile acid excretion. The increase in pool size was thought to be secondary to decreased intestinal motility and impaired gall bladder emptying, which would lead to reduced entero-hepatic cycling of bile acids. The SeHCAT test has not previously been used to evaluate diabetic diarrhoea. Our results are consistent with the findings of increased faecal bile acid excretion from this previous study. Other work indicates bacterial overgrowth and autonomic neuropathy are pathogenic factors in some diabetic patients. The results of this study and that of Molloy and Tomkin<sup>21</sup> suggest that bile acid malabsorption may be the cause in a significant number of these patients. The significance of bile acid malabsorption in diabetic patients with diarrhoea merits further study.

The finding of pancreatic insufficiency in two patients with unexplained diarrhoea and a SeHCAT retention less than 5% who failed to respond to cholestyramine is of interest. Fat and protein malabsorption may result in concomitant bile acid malabsorption, through binding of intraluminal bile acids and resultant reduction in ileal absorption of bile acids. This does not, however, appear to be a universal feature of pancreatic malabsorption, as other authors have reported a normal SeHCAT result in two patients with pancreatic insufficiency.<sup>16</sup> Our observations suggest that a non-response to cholestyramine in the context of a markedly positive (i.e. <5% retention) SeHCAT test should raise the possibility of pancreatic malabsorption as being the primary problem.

The excellent clinical response to cholestyramine seen in patients with a SeHCAT retention of less than 5% has previously been reported.<sup>22</sup> The poor response of patients with diarrhoea and a SeHCAT retention of 11-15% at 7 days raises the question of whether this group of patients can be regarded as having pathological bile acid malabsorption as a

primary problem. Williams *et al.* have also shown cholestyramine to be ineffective in such patients.<sup>22</sup> Increased intestinal transit, with a secondary clinically non-significant reduction in bile acid reabsorption, may be the primary problem in such patients.

It has been argued that the SeHCAT test is an expensive, unnecessary investigation and that a therapeutic trial of cholestyramine is adequate in clinical practice.<sup>16,23</sup> Although our data suggest that the majority of patients with established bile acid malabsorption will show a good therapeutic response, this does not establish that cholestyramine would be useful as a diagnostic test for bile acid malabsorption. Placebo responses and non-specific effects would reduce the specificity of such a therapeutic test. A prospective study comparing this empirical approach with performing the SeHCAT test has yet to be performed. However, we find this approach difficult to accept as cholestyramine may be effective in non-specific diarrhoea.<sup>4</sup> Diarrhoea due to bile acid malabsorption may be intermittent and patients with irritable bowel syndrome frequently show a placebo response to any treatment. Objective assessment of a therapeutic trial is not possible in many patients. Published literature and clinical experience indicate that bile acid malabsorption is a chronic disorder in which life-long therapy may be necessary. Cholestyramine may produce steatorrhoea and calcium malabsorption, and emphasize the importance of using the minimal effective dose.<sup>24</sup> The debate concerning the use of such an empirical therapeutic approach as opposed to undertaking investigations to confirm a diagnosis objectively is similar to the debate concerning the role of endoscopy and oesophageal investigation versus empirical drug therapy in the investigation of dyspepsia. Studies comparing such differing approaches and patient outcome in clinical practice would be of interest.

Our results suggest that approximately 5% of all patients presenting with chronic diarrhoea as the main symptom to a gastroenterology service have bile acid malabsorption. If diarrhoea follows pelvic radiotherapy, cholecystectomy or vagotomy or the patient is diabetic, use of the SeHCAT test early in the course of investigation might avoid the use of other investigations such as barium studies and colonoscopy.

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