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Idiopathic bile acid malabsorption – a review of clinical presentation, diagnosis, and response to treatment

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Abstract

Between 1982 and 1989, the seven day retention of ^{75}SeHCAT was measured in 181 patients with chronic diarrhoea that remained unexplained after full investigation. Altogether 121 of the 181 had a seven day ^{75}SeHCAT retention ≥15% and thus had no evidence of abnormal bile acid turnover. Twenty one had a seven day ^{75}SeHCAT retention ≥10% but <15%. Their clinical features were typical of the irritable bowel syndrome, and none of eight treated with cholestyramine showed symptomatic improvement. Sixteen patients had a seven day retention ≥5% and <10%, six of whom had improved symptoms after treatment with bile acid chelating agents. The remaining 23 patients had a ^{75}SeHCAT retention of <5% at seven days and responded to bile acid chelators. This group had a characteristic illness with intermittent watery diarrhoea, but no constitutional upset. It was not possible to distinguish the patients with bile acid malabsorption exclusively on the basis of the clinical symptoms and investigations, other than ^{75}SeHCAT retention. We conclude that the measurement of ^{75}SeHCAT retention is useful, appropriate, and necessary in patients with unexplained chronic diarrhoea.

Although bile acids are absorbed both actively and passively, symptomatic bile acid malabsorption results from failure of the active transport of bile acids in the terminal one metre of the ileum.[1] Three types of bile acid malabsorption are recognised as follows:[2–4]

Type 1, following ileal resection, disease, or bypass of the terminal ileum;

Type 2, primary idiopathic malabsorption;

Type 3, associated with cholecystectomy,[5 6] peptic ulcer surgery, chronic pancreatitis, coeliac disease,[7] and diabetes mellitus.

The aetiology of types 2 and 3 is unclear. Only the dihydroxy bile acids (chenodeoxycholic acid and deoxycholic acid) are cathartic to the human colonic mucosa. They inhibit colonic sodium reabsorption and thus reduce water transport when the concentration in the aqueous faecal phase is greater than 1·5 mmol/l.[8]

Diarrhoea caused by primary idiopathic bile acid malabsorption is considered very rare.[9] One centre with a special interest in the disease saw only 12 cases in 10 years.[10] However, detection by direct measurement of faecal bile acids is a difficult and unpleasant procedure in patients experiencing multiple bowel actions. The ^{75}SeHCAT test has previously been shown to correlate very closely with the direct measurement of faecal bile acid excretion, but is much simpler to perform.[11 12] We have reviewed a total of 500 patients with diarrhoea investigated with the ^{75}SeHCAT test since 1982 in order to determine its impact on the management of individual patients when used as a routine clinical investigation rather than a research one.

This study considers 181 of the 500 investigated because of idiopathic diarrhoea – the group in whom no cause had been found after extensive investigation.

SeHCAT is the taurine conjugate of a synthetic cholic acid analogue.[13] It is absorbed and excreted at the same rate as cholic acid[14] but is resistant to deconjugation and dehydroxylation.[6] Because there is effectively no passive diffusion of this compound, it is a pure tracer for active transport.

^{75}SeHCAT has been shown to be a simple and reliable method of assessing bile acid absorption.[11 12 15] The aim of the present study was to determine the clinical characteristics of patients with idiopathic bile acid malabsorption and to identify their response to treatment.

Patients and methods

All patients referred for measurement of ^{75}SeHCAT retention were entered prospectively into a departmental data base which recorded the a priori diagnosis and relevant diagnostic information. This was scanned in mid-1989, and 181 patients were identified who had been referred during this period because of unexplained diarrhoea. Patients with inflammatory bowel disease who had undergone previous radiotherapy to the abdomen, any form of bowel resection, or other abdominal surgery were excluded. Stool culture, rigid sigmoidoscopy, barium enema, barium follow through, jejunal biopsy, and vitamin B-12 absorption studies were performed in all patients, and were normal. Those patients who were investigated as inpatients underwent three day stool collection for weight and inspection. The notes of all patients with a retention of less than 15% were retrieved between January and May 1989 and the final diagnosis, management, and any follow up determined.

^{75}SeHCAT absorption was assessed as previously described, by administering one capsule containing 40 kBq (1 μCi) ^{75}SeHCAT after an overnight fast. The 100% value for whole body retention was obtained at 30 minutes and the measurement was repeated at seven days using a shadow shield whole body counter. During the initial evaluation of ^{75}SeHCAT a lower limit of 15% retention at seven days was established on

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TABLE I *Characteristics of 23 patients with severe bile acid malabsorption (<5% retention of ^{75}SeHCAT)*

Sex (M/F)	10/13
Age (yrs), mean (range)	45 (17–77)
Duration of symptoms (yrs), mean (range)	3·3 (0·08–5)
Stool frequency (motions/24 hrs), mean (range)	8 (4–12)*
Stool weight (g), mean (range)	450 (400–800)*
Nocturnal diarrhoea (%)	11/23 (48)
Dose of cholestyramine (g), mean (range)	12 (8–24)

*Data from 8 patients

the basis of comparison with normal controls.[14]

Sixty patients had a ^{75}SeHCAT retention of <15% at seven days and were therefore considered abnormal by our published criteria. These patients were subdivided into three groups – those with a retention <5%, those with a retention ≥ 5% but <10%, and those with a retention ≥10% but <15%. The clinical characteristics of each group were identified by reference to the clinical notes and the response to bile acid chelators when administered.

Results

Table I lists the characteristics of patients with a seven day retention of <5%. All these patients complained of intermittent watery diarrhoea, with a nocturnal component in 11 of the 23.

The diarrhoeal illness was of variable duration with no associated constitutional upset. In all cases it began abruptly and was not associated with any other discernible illness. In two it started while the patient was abroad. Twenty one patients were treated with cholestyramine, which resulted in a reduction in stool frequency and improvement in stool consistency. Cholestyramine was administered in divided doses in powder form (4 g sachets) during the day. A therapeutic response was defined as a reduction in stool frequency to ≤2 bowel actions/day with a concomitant increase in stool consistency occurring within 48 hours of beginning treatment. The mean dose of cholestyramine was 12 g. Four patients required doses greater than 12 g/day to control their symptoms. One patient was intolerant of cholestyramine but responded to aluminium hydroxide. The remaining patient responded to aluminium hydroxide as the initial treatment.

Sixteen patients had a seven day ^{75}SeHCAT retention of ≥5% but <10% and 13 received treatment with bile acid chelators (Table II). Three responded to a dose of 12 g/day of cholestyramine, three to aluminium hydroxide, while the remaining seven did not respond to these agents. None of these patients had

TABLE II *Characteristics of 13 patients with moderate bile acid malabsorption (≥5%, <10% retention ^{75}SeHCAT) treated with bile acid chelators*

	Responders	*Non-responders*
No of patients	6	7
Sex (M/F)	4/2	5/2
Age (yrs), mean (range)	49 (25–64)	40 (28–52)
Duration of symptoms (yrs), mean (range)	2·35 (0·3–5)	4·3 (0·12–14)
Stool frequency (motions/24 hrs), mean (range)	4 (3–5)	4 (2–6)
Stool weight (g), mean (range)	280 (80–480)*	290 (200–400)*

*Data from 3 patients

TABLE III *Characteristics of 21 patients with mild bile acid malabsorption (≥10%, <15% retention of ^{75}SeHCAT)*

Sex (M/F)	18/13
Age (yrs), mean (range)	30 (13–72)
Duration of symptoms (yrs), mean (range)	7 (1–25)
Stool frequency (motions/24 hrs), mean (range)	4 (2–10)
Stool weight (g), mean (range)	160 (8–200)*

*Data from 8 patients.

nocturnal diarrhoea. The patients who responded to bile acid chelators could not be distinguished from those who did not respond.

Twenty one patients had a ^{75}SeHCAT retention of ≥10% but <15% at seven days (Table III). All complained of intermittent watery diarrhoea but none had a nocturnal component, and in five the diarrhoea was confined to the morning. Eight patients complained of urgency, lower abdominal pain relieved by defaecation, and bloating. None of the eight patients who received cholestyramine were improved.

Discussion

The cut off value of 15% was based on a comparison between normal controls and patients with known disease.[12] It is well known that such studies, although necessary in the initial stages of evaluating a new test, are likely to require modification on the basis of further clinical experience. It is clear from the present study that the lower limit of normal should be revised downwards – in any patient with a seven day ^{75}SeHCAT retention of 10% or more, bile acid malabsorption is not the cause of the diarrhoea.

The sustained response to specific treatment in all patients with a retention of <5% confirms that these patients did indeed have bile acid induced diarrhoea. The aetiology of this condition remains obscure. None of the patients had any systemic upset; all responded to treatment within 48 hours, and the response was sustained. This pattern is similar to that previously described.[10 15] Although initially characterised as causing continuous watery diarrhoea, two previously reported cases had intermittent diarrhoea with large volume stools which nevertheless responded overnight to cholestyramine.[10] The nocturnal component seen in half of our patients has not previously been described and is a useful diagnostic indicator when present. However, it was present in only 11 of the 23 patients with a retention of <5% and none of the patients with a retention of ≥5% and <10%. Thus, the absence of this feature does not exclude bile acid malabsorption.

The most puzzling group is the 16 who retained ≥5% and <10% ^{75}SeHCAT at seven days, six of whom responded to treatment with bile acid chelators. There were no features that enabled the patients who did respond to be distinguished from those who did not. The 21 patients with a retention of ≥10% and <15% had features typical of the irritable bowel syndrome and none improved with bile acid chelators. These findings are compatible with the role that has been proposed for bile acid in the pathogenesis of at least some patients with irritable bowel syndrome.[16]

The pathogenesis of idiopathic bile acid malabsorption remains unknown. Two mechanisms have been proposed[17] – an increased production of bile acids overwhelming the normal ileal transport system or a selective abnormality in the active transport of bile acids in the ileum. A priori, the latter is the more probable mechanism as overproduction of bile acids should be relatively easily measurable, but this has not been shown. The fact that all of the patients reported were adults and the condition has not been described in children is more suggestive of an acquired than an inherited condition. The severity of symptoms in any individual may well be related to the composition of the bile. Thus, if there is a continuous spectrum of bile acid absorption efficiency rather than an 'all or nothing' process, differences in the ratio of dihydroxy to trihydroxy bile acids and variations in faecal pH are likely to alter the severity of symptoms, especially in patients with intermediate levels of malabsorption.

It has been suggested that the ^{75}SeHCAT test is of no value in the routine investigation of patients with diarrhoea.[18] There are large amounts of documented data contradicting this viewpoint.[7 11 15 19] The ^{75}SeHCAT test must, however, be interpreted in the context of the patient's clinical condition, with particular reference to stool volumes and the results of other gastrointestinal investigations.

Cholestyramine does cause constipation in normal individuals, as reported in the hypolipidaemic drug trials.[20 21] In the American lipid research clinics program,[20] 39% of 2000 patients treated with a mean daily dose of 16 g of cholestyramine were constipated at one year compared with 10% of controls, although at seven years only 8% remained constipated. However, the facts that all patients with severe bile acid malabsorption responded to cholestyramine and no patient with mild bile acid malabsorption improved, and that the improvement was sustained, suggest a primary role of bile acids in the pathogenesis of their diarrhoea.

A therapeutic trial of cholestyramine has been suggested as an alternative to measuring ^{75}SeHCAT retention as an assessment of bile acid malabsorption causing diarrhoea.[18] In the present study, however, four of the 23 patients with diarrhoea and a ^{75}SeHCAT retention of $<5\%$ required more than 12 g/day of cholestyramine to control their symptoms and would therefore have been considered as negative with the cholestyramine test. The false negative rate of a therapeutic trial of cholestyramine has not previously been determined, but from the present data would be 25%. The false positive rate remains unknown and it is therefore impossible to determine the accuracy or specificity of the therapeutic trial. In view of the simplicity, accuracy, and reliability of the ^{75}SeHCAT test we believe that this should be regarded as a routine investigation in patients with idiopathic diarrhoea for which no explanation has been found after full investigation. The condition is substantially more common than is generally appreciated, but is readily treatable.

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