Bile acid malabsorption in persistent diarrhoea

M J Smith, P Cherian, G S Raju, B F Dawson, S Mahon and K D Bardhan

ABSTRACT – We have investigated bile acid malabsorption (BAM), and its response to treatment, in patients seen in this district general hospital with chronic continuous or recurrent diarrhoea.

Methods: Seven-day retention of 75-SeHCAT was measured (normal: >10%).

Treatment: Patients were initially given conventional therapy (prednisolone ± ASA drugs in Crohn’s disease, and antidiarrhoeals in the others). If this therapy failed, bile acid sequestrants (BAS) were prescribed. The definition of successful response was based on the patient’s perception of sustained improvement.

Patients: The 304 patients were categorised as follows: Group 1: Crohn’s disease patients with ileal resection, in clinical remission (n=37). Group 2: Crohn’s disease, unoperated and in clinical remission (n=44). Group 3: vagotomy and pyloroplasty, with/without cholecystectomy (n=26). Group 4: diarrhoea predominant ‘irritable bowel syndrome’ (IBS) (n=197).

Results: BAM was found in 97% (36/37), 54% (24/44) and 58% (15/26) of patients in groups 1, 2 and 3 respectively. One third (65/197) of patients with IBS had BAM. The outcome of treatment was available in 96 patients with BAM: of the patients with ileal resection 32% responded to antidiarrhoeals, 60% to BAS. Of the unoperated Crohn’s patients 55% responded to disease-specific therapy, 40% to BAS. Of the gastric surgery patients 18% responded to conventional treatment, 64% to BAS. Of the IBS patients 15% of responded to conventional therapy, 70% to BAS.

Conclusions: This observational study indicates that BAM is common in patients with chronic diarrhoea, and is frequently found in IBS. The results of open treatment suggest that, where antidiarrhoeal drugs fail in such patients, BAS are often effective.

Persistent chronic diarrhoea is a common problem in clinical practice that is often difficult to diagnose and treat. Bile acid malabsorption (BAM) has been identified as a possible explanation for such unexplained diarrhoea, but has commonly been regarded as rare and of limited importance in day-to-day practice in the district general hospital (DGH). The diagnosis has traditionally rested on detecting excess faecal bile acid loss in stool samples, a complex procedure. Since 1983 it has been possible to diagnose BAM accurately and non-invasively by measuring the retention of a radiolabelled synthetic bile acid2–5. Selenium-75 labelled homocholic acid conjugated with taurine (SeHCAT) is a synthetic analogue of naturally occurring taurocholic acid; it is handled like the native substance but is inactive and resists deconjugation. It is absorbed in the terminal ileum by an active process, like other bile acids, and so tracks the enterohepatic circulation. Its retention in the body mirrors its faecal excretion. The technique relies on external scanning, rather than stool samples; the only equipment required is a commonly available standard gamma camera.

Most cases of persistent diarrhoea are attributed to one of the following causes: irritable bowel syndrome (IBS), infection, inflammatory bowel disease (IBD), and gut resection. However, there is increasing evidence from studies at university centres that BAM plays a causal role in many patients suffering from chronic diarrhoea but with no ileal pathology6–9. This evidence would suggest the problem might indeed be a significant factor in diarrhoeal disease presenting in the district general hospital setting.

We have reviewed the results of SeHCAT retention in our patients whose diarrhoea was otherwise unexplained. We observed that BAM was common, and many patients responded well to treatment with BAS.

Patients

The 304 patients were categorised as follows:

Group 1: ileal resection for Crohn’s disease (n=36) or ischaemia (n=1). This group of patients with clinically inactive Crohn’s disease would be expected to have BAM.

Group 2: Crohn’s disease (n=44). These patients had clinically inactive Crohn’s disease, but continued to be troubled by chronic diarrhoea. Disease inactivity was based on otherwise good health, normal haematology, plasma viscosity and normal C-reactive protein.

Group 3: gastric surgery (n=26) – patients who had undergone either vagotomy and drainage, or partial gastrectomy. Seven of this group had also undergone cholecystectomy.

Group 4: diarrhoea predominant IBS (n=197). These patients had diarrhoea (loose watery stools), cramping, abdominal discomfort or pain partially relieved by opening of the bowels; they often complained of distension, but were otherwise in good health and of steady weight. They
had normal gastroscopy, distal duodenal histology, sigmoidoscopy, small and large intestinal radiology.

**Method**

The SeHCAT retention test was carried out in a standard manner according to the manufacturers' instructions. Patients swallowed a single capsule containing 370kBq SeHCAT (Nycomed-Amersham, UK). After three hours for physiological equilibration, baseline counts were measured over the abdomen using an uncollimated gamma camera. Background-corrected counts were obtained in both antero-posterior and postero-anterior views, and the geometric mean of these counts recorded. The percentage of the baseline value retained on the seventh day was calculated.

**Normal range**

We considered a seven-day retention value of less than 10% to be abnormal. The choice of cutoff value necessarily involves a compromise between sensitivity and specificity; the value chosen was based on the practical consideration that patients with retention less than 10% are most likely to respond to sequestrant therapy.

**Treatment**

At the outset of the study we were uncertain of the significance of BAM in causing diarrhoea, particularly in patients with structural gastrointestinal disease. Therefore, initial treatment was always conventional, i.e. prednisolone (with or without ASAs) in IBD, and codeine or loperamide (with or without bulking agents) in IBS and in post-gastric surgery patients. The BAS cholestyramine was used to treat patients in whom the above methods failed to control diarrhoea. Later, colestipol (orange-flavoured) was used instead of cholestyramine as it has a more acceptable flavour. Treatment with either drug was started at a low dose, one sachet (5g) daily, and gradually built up to a maximum of one sachet, three times daily, titrating the dose against clinical response.

The definition of a successful outcome was qualitative, based on the patient's frequency of bowel movements being reduced (typically to twice or three times daily), a reduction in urgency, or the stools becoming more formed and solid. The pattern of response varied considerably: for example, some patients had no reduction in bowel frequency but lost the sensation of urgency, or had stools of much improved consistency. The key consideration in identifying a 'successful' response was whether the patients felt there had been a marked improvement in the quality of their life.

**Results**

The results from all 304 individual studies are shown as a scatter plot (Fig 1).

BAM occurred in 97% (36/37) of patients with ileal resection, thus confirming our expectation. It was also found in 54% (24/44) of patients with quiescent Crohn's disease, apparently inactive ileal Crohn's disease, and in diarrhoea predominant irritable bowel syndrome (IBS).

**Key Points**

- Bile acid malabsorption (BAM) is a common cause of chronic diarrhoea.
- Consider this possibility in patients with ileal resection, apparently inactive ileal Crohn's disease, and in diarrhoea predominant irritable bowel syndrome (IBS).
- The SeHCAT retention test is an accurate tool (normal retention >10% at 7 days). It is simple, non-invasive, does not require faecal collection, and is available in most district general hospitals.
- Treatment with bile acid sequestrants (BAS), eg colestipol, is often effective.
disease, 58% (15/26) of patients with gastric surgery, and in 33% (65/197) of patients presumed to have diarrhoea predominant IBS.

Treatment and follow-up information were available in 96/140 patients with BAM. The other patients were lost to follow-up, declined therapy, or were not evaluable for other reasons, eg other illnesses. The results are shown in Table 1.

The diarrhoea in one third of the patients with ileal resection, and one half of patients with Crohn's disease, responded to prednisolone and/or 5-ASA drugs. In roughly half the remainder, cholestyramine or colestipol proved effective. Antidiarrhoeals with or without bulking agents benefited only 15% of patients with IBS. In contrast, 70% were helped with BAS. Only in 15% of patients did all therapies fail. A similar pattern was observed in patients who had undergone gastric surgery.

### Discussion

BAM is generally regarded as an infrequent cause of chronic diarrhoea in patients presenting in a district general hospital; however, this study suggests otherwise, being identified in 140/304 (46%) of such patients.

All but one of the patients with ileal resections (group 1) had BAM, severe in most cases, with SeHCAT retention values clustered at the lower extreme (Fig 1). This finding was expected, since bile salts are absorbed exclusively in the terminal ileum. The Crohn's disease seemed to be in remission, judged both clinically and by laboratory studies, except for diarrhoea, the principal symptom. Nevertheless we were initially uncertain whether BAM would of itself account wholly for the diarrhoea, so we treated these patients conventionally with prednisolone, which proved effective in 8 (32%). BAS controlled diarrhoea in 15/17 of the remaining patients, and we presume therefore that such malabsorption rather than disease recurrence was responsible for the diarrhoea. This experience now allows us to proceed directly to BAS therapy in patients with ileal resection.

All the patients with unoperated Crohn's disease (group 2) were in remission both clinically and by laboratory indices. Nevertheless, prednisolone, with or without 5-ASA, was successful in 11/20 patients with abnormal SeHCAT results, raising the possibility that the malabsorption was a consequence of the occult inflammation. In eight of the remaining patients, however, BAM was found to be the cause of the diarrhoea, evidenced by their failure to respond to prednisolone, whilst responding to BAS.

BAM following gastric surgery, with or without cholecystectomy, has been previously recognised. The frequency of malabsorption found in our study (patient group 3) is similar to Fromm's, but less than that found by Al-Hadrami and Sciaretta, who found BAM in almost all their patients with post-vagotomy diarrhoea. The majority of our patients (7/11) responded to BAS.

The high frequency (33%, 65/197) of BAM in our patients with presumed diarrhoea-predominant IBS (group 4) was unexpected. Such malabsorption in patients with a structurally normal gut (judged by conventional radiology) has been attributed to a selective defect, and sometimes referred to as primary or idiopathic BAM; however, ileal villous atrophy on histology has been identified in such patients. Histological examination of the ileum was not carried out in our study so it is not possible to comment on how often this mechanism applies. Our findings correspond with those of Merrick, who found BAM in 20/51 patients (39%). Only 6/40 (15%) of our patients responded to conventional treatment with codeine or loperamide, whereas 28 (70%) responded to BAS. This finding has considerable practical importance for the management of this subgroup who have often been tried unsuccessfully on other treatments, sometimes for several years.

Our treatment of BAM was open, and not placebo controlled, so only limited conclusions can be drawn. Nevertheless, our observations strongly suggest that BAS are effective in the management of patients with BAM, a hypothesis that needs to be tested by a formal trial.

Little evidence exists at present with regard to the natural
history of BAM and the continued efficacy of long-term treatment in such patients. The exception is a small study with a five-year follow up. The malabsorption appeared to have cleared in some, who no longer required BAS, but persisted in the others in whom treatment remained effective. Of concern, a few patients (3/23) diagnosed earlier to have ‘idiopathic’ BAM were later found to have IBD. We have not observed this in our patients currently diagnosed as having IBS, but our follow-up has not been for as long.

Of what use is the SeHCAT test in a district general hospital? The identification of BAM has for many patients stopped the endless cycle of repeated investigations. This particularly applies to our patients presumed to have IBS, many of whom had been treated unsuccessfully with conventional anti-diarrhoeals. The SeHCAT test gives objective confirmation of BAM, and therefore allows physicians to embark on treatment with BAS more confidently, and to titrate the dose to achieve the optimum clinical response.

If facilities for the SeHCAT test are not available locally, a possible alternative has been described based on measurement of the serum concentration of an hepatic bile acid intermediary, 7-alpha-hydroxy-4-cholesten-3-one. This appears not to be quite as sensitive or specific as the ‘gold-standard’ SeHCAT test, but does identify likely responders to treatment almost as well. It has the merit that the blood sample can be analysed if necessary at a remote laboratory.

Conclusion

The SeHCAT test has demonstrated that BAM is common in patients with chronic diarrhoea, particularly when structural disease cannot account for it. One third of our patients with diarrhoea predominant IBS had BAM. When conventional anti-inflammatory and anti-diarrhoeal drugs fail in such patients, BAS are often effective, and improve the quality of life.

The results in this paper were presented at the meeting of the American Gastroenterological Association, New Orleans, May 1998 and appeared as an abstract in Gastroenterology 1998; 114: A42-G1070.

References

1 Hoffman AF. The syndrome of ileal disease and the broken enterohepatic circulation: choleretic enteropathy. Gastroenterology 1967;52:752-7.
2 Merrick MV, Eastwood MA, Anderson JR, Ross HM. Enterohepatic circulation in man of a gamma-emitting bile-acid conjugate, 23-selena-25-homotaurocholic acid (SeHCAT). J Nucl Med 1982; 23:126-30.
3 Nyhlin H, Merrick MV, Eastwood MA, Brydon WG. Evaluation of ileal function using 23 selena-25 homotaurocholate, a gamma labelled conjugated bile acid. Gastroenterology 1983;84:63-8.
4 Hames TK, Condon BR, Fleming JS, Phillips G, et al A comparison between the use of a shadow shield whole body counter and an uncollimated gamma camera in the assessment of the seven-day retention of SeHCAT. Br J Radiol 1984;57:581-4.
5 Hoffman AF. Progress in idiopathic bile acid malabsorption. Gut 1998;43:738-9.
6 Merrick MV, Eastwood MA, Ford MJ. Is bile acid malabsorption underdiagnosed? An evaluation of accuracy of diagnosis by measurement of SeHCAT retention. Br Med J 1985;290:665-8.
7 Galatola G and the 75-SeHCAT multicentre study group. The prevalence of bile acid malabsorption in irritable bowel syndrome and the effect of cholestyramine: an uncontrolled multicentre study. Eur J Gastroenterol Hepatol 1992;4:533-7.
8 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.
9 Williams AJK, Merrick MV, Eastwood MA. Idiopathic bile acid malabsorption – a review of clinical presentation, diagnosis and response to treatment. Gut 1991;32:1004-6.
10 Al-Hadrani A, Lavell-Jones M, Kennedy N, Neill G, et al. Bile acid malabsorption in patients with post vagotomy diarrhoea. Ann Chir Gynaecol 1992;81:351-3.
11 Fromm H, Tunuguntla AK, Malavoti M, Sherman C, Ceryak S. Absence of a significant role of bile acids in diarrhoea of a heterogenous group of postcholecystectomy patients. Dig Dis Sci 1987;32:33-46.
12 Sciarretta G, Furno A, Mazzoni M, Malaguti P. Post-cholecystectomy diarrhoea: evidence of bile acid malabsorption assessed by SeHCAT test. Am J Gastroenterol 1992;87:1852-4.
13 Popovic OS, Kostic KM, Milovic VB, Milutinovic-Djuric S, et al. Primary bile acid malabsorption. Histologic and immunologic study in three patients. Gastroenterology 1987;92:1851-8.
14 Sciarretta G, Furno A, Morrone B, Malaguti P. Absence of histopathological changes of ileum and colon in functional chronic diarrhoea associated with bile acid malabsorption, assessed by SeHCAT test: a prospective study. Am J Gastroenterol 1994;89: 1058-61.
15 Luman W, Williams AJK, Merrick MV, Eastwood MA. Idiopathic bile acid malabsorption: long-term outcome. Eur J Gastroenterol Hepatol 1995;7:641-5.
16 Brydon WG, Nyhlin H, Eastwood MA, Merrick MV. Serum 7-alpha-hydroxy-4-cholesto-3-one and selenohomocholytaurine (SeHCAT) whole body retention in the assessment of bile acid induced diarrhoea. Eur J Gastroenterol Hepatol 1996;8:117-23.