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Diagnosis and treatment of post-cholecystectomy diarrhoea

Huang RL *et al.* Diagnosis and treatment of PCD

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Abstract

The incidence of cholecystitis is relatively high in developed countries and may usually be attributed to gallstones, the treatment for which involves complete surgical removal of the gallbladder (cholecystectomy). Bile acids produced following cholecystectomy continue to flow into the duodenum but are poorly absorbed by the colon. Excessive bile acids in the colon stimulate mucosal secretion of water and electrolytes leading, in severe cases, to diarrhoea. Bile acid diarrhoea (BAD) is difficult to diagnose, requiring a comprehensive medical history and physical examination in combination with laboratory evaluation. The current work reviews the diagnosis and treatment of BAD following cholecystectomy.

Key Words: Cholecystitis; Gallstones; Bile acids; Colon; Bile acid diarrhoea

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Core Tip: Cholecystitis is relatively high in developed countries and the treatment for which involves complete surgical removal of the gallbladder. Bile acids produced following cholecystectomy are poorly absorbed by the colon. Excessive bile acids in the colon stimulate mucosal secretion of water and electrolytes leading, in severe cases, to diarrhoea. The current work reviews the diagnosis and treatment of bile acid diarrhoea following cholecystectomy.

INTRODUCTION

The incidence of diarrhoea after cholecystectomy is extremely high, affecting 57.2%^[1-3] of patients in a multimedical center study in which only a small proportion of post-cholecystectomy patients were investigated and for which there was a time delay in

diagnosis. The true prevalence of bile acid diarrhoea (BAD) after cholecystectomy may be much higher and clinicians need to raise awareness of this treatable disease which seriously impacts patient quality of life^[4-6]. Post-cholecystectomy diarrhoea (PCD) may be multifactorial^[2]. No storage of bile acids is possible following cholecystectomy, resulting in the slow release of unconcentrated bile into the small intestine. Post-prandial gastrointestinal reflex causes large-scale movement of bile from the small intestine to the colon, resulting in biliary acid-mediated diarrhoea^[1,6-8]. Indeed, the frequency of bowel movement may change from a pre-operative once a day to a post-operative 4-5 times per day. The risk of post-operative diarrhoea depends on age, weight and sex^[2]. One review published in the US has estimated that, of the 750000 cases of cholecystectomy per annum, 5%-12% are followed by diarrhoea^[9]. A prospective study which assessed 93 patients in the two years before and after surgery found that 8 had diluted or recurrent watery diarrhoea during the two years following cholecystectomy^[10].

DIAGNOSIS OF BAD

BAD is more common among patients with chronic watery diarrhoea and prior cholecystectomy^[11,12] and diagnosis requires a comprehensive medical history and examination (including digital rectal examination) in combination with laboratory assessments, including total blood count, catabolic status, C-reactive protein level, faecal latent blood test, faecal lactoferritin test, white blood cell smear test and microbiological assessment^[13]. Laboratory confirmation of BAD remains a challenge. Five diagnostic tools are available: (1) ¹⁴C cholesterol choline and breath test; (2) ⁷⁵Selenium homocholic acid taurine (SeHCAT) test^[12,14-18]; (3) serum measurements of C4 and FGF19^[18]; (4) 48-h faecal bile acid test^[18-20]; and (5) the bile acid chelator trial^[18,21-23] (Figure 1).

The British Society of Gastroenterology Guidelines for Chronic Diarrhoea Investigation recommend endoscopy and the SeHCAT test as the first-line diagnostic modality^[24]. Currently, clinicians pay insufficient attention to the diagnosis of diarrhoea

after cholecystectomy and approximately 10%-30% of BAD patients are misdiagnosed with irritable bowel syndrome (IBS-D)^[5,25-27]. The SeHCAT test allows differentiation between PCD and IBS-D^[28]. The 48-h faecal bile acid test is the alternative to the SeHCAT test and may reduce healthcare utilization and costs in patients with chronic non-bloody, unexplained diarrhoea^[19].

TREATMENT AND MANAGEMENT OF BAD

Cholecystectomy has an effect on bile concentration and excretion and changes the circulation of bile acids between the liver and intestine. The orthodox explanation for altered intestinal function refers to the loss of gallbladder fluid storage and changes in bile acid metabolism. In particular, the concentration of deoxycholic acid in the faeces increases which enhances rectal sensitivity, causing an urge to defecate^[29]. The accompanying physiological changes expose therapeutic targets for the post-cholecystectomy syndrome. BAD is usually regarded as incurable^[17,28,30], and the chronic condition may be treated by drugs targeted to bile acid receptors and transporters or which aim to change bile acid pools. The diarrhoea is considered difficult to treat and is only reduced in half of cases, significantly affecting quality of life. Long-term follow-up is thus necessary, accompanied by adjustment of treatment methods and the development of new approaches^[12] (Table 1).

Bile acid sequestrants trial

The Canadian association of gastroenterology clinical practice guidelines recommend bile acid sequestrants (BAS) as the first-line treatment for BAD^[31,32]. For patients with suspected or confirmed BAD, a BAS trial (BAST), initially with cholestyramine, is suggested. However, the BAST must be carefully managed to avoid under- or over-treatment^[33]. BAS, such as cholestyramine, colestipol and colesevelam, bind bile acids secreted into the intestine to reduce damage to intestinal tissues. Cholestyramine was the first BAS used to treat BAD in 1972, and Hoffman and Poley found favourable results in patients following resection of the small intestine. A study of 8 patients with

PCD, defined as more than 4 Loose stools in a 24-h period for 1 to 20 years, included 6 subjects with elevated stool bile acids and stool weight greater than 200 g/24 h. Treatment with 4 to 16 g/d oral cholestyramine reduced the number of daily bowel movements within 72 h. Diarrhoea recurred in all patients after cessation of cholestyramine treatment^[28,32]. A meta-analysis of the medical records of 291 patients with chronic watery diarrhoea tested by SeHCAT including 74 patients with a previous cholecystectomy^[11] and a multi-centre study across three sites in the United Kingdom^[5] found that 60%-70% of patients discontinue cholestyramine and colestipol within 5 years due to adverse reactions, including constipation, excessive diarrhoea, stomach pain, bloating, flatulence, nausea and vomiting. Colesevelam is often better tolerated and results in firmer stools but may be less effective in improving stool frequency than cholestyramine. In addition, colesevelam may be prohibitively expensive in countries such as Spain. The need for superior BAD treatments is clear and the colon release preparation of bile glycol, A3384, has been shown to be well-tolerated and effective in clinical trials.

Bile acid receptor agonist therapy

Sequestrants bind and remove excessive bile acids to reduce colon secretion but the primary causes of bile acid production remain unresolved^[34]. The farnesoid X receptor (FXR) is highly expressed in the intestine and liver^[35-38] and receptor agonists reduce bile acid synthesis to relieve symptoms of diarrhoea. Both FXR and Takeda G-protein receptor 5 are bile acid receptors on the nucleus and cell surface and have been considered to participate in the mechanisms by which bile acids regulate physiological functions since 2000. FXR has since been assigned roles in the extrahepatic metabolism of cholesterol, lipid and glucose. FXR agonists are under development for treatment of liver and intestinal diseases and have excellent potential as anti-diarrheal drugs due to inhibition of calcium- and cyclic adenosine monophosphate-dependent chloride secretion by the colonic epithelium. The impact of FXR agonists on fluid and electrolyte transport by colonic epithelial cells gives these drugs a broader efficacy than pre-

existing treatments while generating fewer side effects^[39]. Walters *et al*^[37] have proposed that FXR agonists that influence the fibroblast growth factor 15/19 (FGF15/19) pathway may alleviate cholestatic liver injury and diarrhoea. A reduction of FGF19 synthesis by the ileum would lead to impaired feedback inhibition of hepatic CYP7A1 in the liver and increased bile acid synthesis, reflected by increased C4 Levels. It is the excessive production of bile acids by the liver which are secreted into the small intestine and exceed the reabsorption capacity of the ileum that allows bile acids to enter the colon and cause diarrhoea. Many agonists, including GW4064, PX-102, LJN452 and Ec001, have been developed and INT-747 obberic acid (OCA)⁷ was approved by the United States Food and Drug Administration (FDA) for clinical use in 2016. OCA has been shown to be 100 times more potent as an FXR agonist than goose deoxycholic acid^[40]. OCA is often combined with ursodeoxycholic acid (UDCA) to treat primary biliary cholangitis and other liver diseases, such as non-alcoholic steatohepatitis and primary sclerosing cholangitis.¹² A recent phase II clinical trial at Imperial College London¹ demonstrated that OCA improved serum FGF19 Levels and decreased C4 and faecal BAs, reducing diarrheal symptoms in BAD patients. OCA inhibited colonic fluid secretion and reduced bile acid biosynthesis, decreasing the flow of bile acids into the colon^[41]. FXR agonists also have the potential for the treatment of inflammatory diseases and reduced FXR expression was found in intestinal epithelial cells of patients with inflammatory bowel disease (IBD).¹¹ This finding suggests that changes in bile acid synthesis and FXR expression may be involved in the dysregulation of the immune response and development of inflammatory diseases, such as IBD, an observation that merits further study. A two-week clinical study of patients with primary and secondary bile acid malabsorption (BAM)-induced diarrhoea had improved stool frequency, stool morphology and total diarrhoea index with increased FGF19 and decreased C4 and faecal BA after treatment with OCA^[42]. However, potent FXR agonists may have adverse side effects, such as lowering HDL levels, and receptors must be carefully selected to achieve the desired treatment effects.

Glucagon-like peptide 1 receptor agonist: Liraglutide

Liraglutide is a commonly used drug for type 2 diabetes and obesity. It also has utility as second-line antisecretory therapy for BAD after cholecystectomy. Liraglutide delays gastric emptying and inhibits duodenal and small intestine motility^[43-45]. The peptide, Glucagon-like peptide 1 (GLP-1), is known to slow upper gastrointestinal motility and increase small intestine transit time which may enhance the passive resorption of bile acids from the gut to the bloodstream and reduce bile acid flow to the colon^[46]. GLP-1 receptor agonist therapy has been reported to reduce cholecystokinin (CCK)-induced gallbladder emptying^[47,48] and a study of liraglutide confirmed its safety for pancreatitis but indicated the increased risk of cholelithiasis^[49]. However, this adverse effect does not apply to post-cholecystectomy patients. A clinical trial at the Center for Clinical Metabolic Research at Copenhagen University Hospital compared the efficacy of liraglutide and colesevelam in reducing defecation frequency in BAD patients and indicated the superiority of liraglutide^[50]. Furthermore, case reports exist of two patients who experienced total remission of BAD symptoms after liraglutide treatment^[46]. GLP-1 receptor agonists have also been shown to have beneficial effects on outcomes and mortality for patients with cardiovascular and chronic kidney disease^[51-57]. Post-cholecystectomy patients experience mild disturbances in glucose homeostasis and slight deterioration in postprandial blood glucose, GLP-1, insulin and glucagon concentrations^[58]. Cholecystectomy has been reported to be associated with an increased diabetes risk^[59]. Therefore, we consider liraglutide to be very suitable for BAD patients with additional benefits for those who also suffer from diabetes, cardiovascular disease, chronic kidney disease or more than one of these conditions. Furthermore, treatment of PCD with liraglutide may prevent the development of type 2 DM. However, contrary views have been recorded previously. Smits *et al*^[60] report the results of a clinical trial in which liraglutide was found to be a cause of BAD. Further clinical trials and follow-up regarding the application of liraglutide for BAD are required.

Treatment of the intestinal microbiota

The changes in bowel habits and loss of bile acids during BAD following cholecystectomy may cause changes in the gut microbiota in some patients^[61,62]. However, a controlled study in South Korea in which stool samples were collected from 39 gallstone patients and 26 healthy controls found that cholecystectomy did not affect the gut microbiome three months after surgery, although an elevated relationship between microbes in the gallstone patients after surgery was found by network analysis. We suggest that PCD is a delayed postoperative complication that requires long-term follow-up data to determine changes in the gut microbiome^[61]. Previous studies have used microbial metabolomics to demonstrate differences between post-cholecystectomy patients and healthy controls, raising the question of whether the gut microbiome could be targeted as a treatment for BAD^[3,63-65]. The increasing scrutiny of probiotics in basic and clinical research has illustrated the potential health benefits that may follow sufficient dosages of these sterilized living microorganisms. Unlike drugs, probiotics may be taken by healthy subjects to reduce the risk of developing disease or to optimize physiological functions. Probiotics survive transit through stomach acid and bile, successfully reaching the small intestine and colon. A recent study has demonstrated increased BA binding, excretion in faeces and hepatic synthesis by an FGF-dependent mechanism after probiotic administration. Thus, a beneficial effect of BA on the gut microbiome and systemic metabolism is indicated. Treatment of post-cholecystectomy patients with probiotics to enhance intestinal microecology improves gut microbiome balance through an impact on Bacteroidetes and Firmicutes levels. A healthy gut microbiome balance has the effect of suppressing the growth of opportunistic pathogens and promoting intestinal microecology. *Lactobacillus plantarum* (pCBH1) is a genetically engineered strain which overexpresses bile salt hydrolase and degrades glycodeoxycholic acid and taurodeoxycholic acid *in vitro*. It has the potential to reduce bile acids in BAD patients. Genetic engineering of microbial strains allows the targeting of pathogenic molecules or metabolic pathways of interest, rather than affecting the entire intestinal microbial community and may represent a

superior form of BAD treatment. Intestinal dysbiosis may play a key role in PCD, exposing therapeutic targets for this disorder^[66].

UDCA

¹ UDCA from bear bile has been used in traditional Chinese medicine for hundreds of years to treat a range of diseases, including liver and intestinal disorders. In Western medicine, UDCA has been used for many years to treat liver diseases, especially PBC, ⁵ and as a bile acid replacement therapy to reduce bile acid toxicity in patients with deficient bile acid synthesis, gallstone dissolution and digestive diseases^[67,68]. Its potential for the prevention of primary sclerosing cholangitis and IBD has also been investigated. UDCA has shown therapeutic efficacy in treating a variety of extrahepatic diseases, including IBD, in clinical and preclinical studies^[69] and UDCA or taurine conjugated derivatives have demonstrated pharmacological effects in reducing disease severity, mucosal cytokine levels, release of antimicrobial peptides and preventing apoptosis in animal models of IBD. UDCA also inhibited activation of and release of pro-inflammatory cytokines by mucosal immune cells. However, the UDCA metabolite, LCA, is considered the most toxic of the colonic bile acids and it may be necessary for LCA metabolism to take place to allow the full pharmacological effects of UDCA^[70]. ¹ Clearly, much work is still needed to elucidate the relationship among UDCA, its metabolites, the microbiome and mucosal inflammatory responses.

Anti-diarrhoeal agents

⁶ Loperamide is a synthetic phenylpiperidine derivative approved by the FDA in 1976 for the treatment of diarrhoea. Loperamide inhibits intestinal secretion and peristalsis, slowing intestinal transit and allowing increased fluid reabsorption to alleviate diarrheal symptoms. Diphenoxylate-atropine is a combination treatment for acute and chronic diarrhoea symptoms^[71] but exposure to high doses during use and abuse may cause cardiotoxicity^[72,73].

Dietary therapy

PCD may respond to a reduction of dietary cholesterol, fats, animal protein and eggs and an increase in dietary fruit and vegetables^[74-77]. Vegetable dietary fiber can prevent gastrointestinal diarrhea by reducing gastric emptying, improving intestinal barrier function, increasing epithelial cell regrowth, and increasing colonic fluid and electrolyte uptake^[78,79].

PROSPECTS

The last two decades have seen great progress in the understanding of the role of bile acids in modulating the intestinal epithelium in health and disease. There has been corresponding interest from the pharmaceutical industry in the utilization of bile acids for the treatment of enteric and parenteral diseases. The discovery of novel bile acid receptors has driven an appreciation of the sensing of luminal bile acid characteristics by intestinal epithelial cells with the resulting activation of molecular pathways. Understanding of the endogenous and exogenous factors that influence bile acid pool size and composition has increased but there remain many unknown areas.

An ideal therapeutic approach would involve a gut-specific FXR activator to alleviate bile enterostasis by inducing FGF19 and reducing hepatic bile acid synthesis. Side effects of hepatic FXR activation would thus be avoided. However, whereas the main site of FGF19 secretion into bile was found to be the gallbladder mucosa, FGF19 is also an endocrine hormone which exerts metabolic effects on distant tissues. FGF19 has a pro-mitogenic function and a concern is potential tumorigenic activity. Long-term treatment of diarrhoea with FXR agonists requires consideration of this possible side effect. A clearer understanding of the regulation of cellular signalling pathways involved in bile acid synthesis, transport and metabolism is required to avoid bile acid toxicity in the gut and liver. In addition to selective enterohepatic circulating FXR modulators, genetic and metabolic pathway-specific FXR modulators may be possible therapeutic strategies to treat cholestasis and metabolic diseases.

Liraglutide has utility as a second-line treatment for PCD associated with diabetes, metabolic syndrome and obesity. It is an effective anti-diarrhoea treatment but remains too expensive to be used as a first-line anti-diarrhoea treatment alone.

Examination of faecal samples indicates that post-cholecystectomy patients have significant gut microflora differences compared with controls but gut microbiome changes could not be accurately correlated with the time after cholecystectomy during the current review. Studies are underway to elucidate the association between cholecystectomy and changes to intestinal microbiota at 3 mo, 1 year and 5 years after surgery. A study of signalling by bile acids as intermediaries between host and gut microbes and the integration and transduction of signals into biological responses are planned and may expose novel therapeutic targets for diarrhoea.

The apical sodium-dependent bile acid transporter (ASBT) has a theoretical role in hepatic and intestinal bile acid circulation with the potential to influence liver disease. Several ASBT inhibitors are under development, although none has so far been FDA-approved. These small-molecule inhibitors lower plasma LDL levels and have shown therapeutic promise for chronic constipation in preclinical and clinical studies.

CONCLUSION

Finally, the influence of diet should be stressed. Patient follow-up after surgery indicates that diarrhoea is often linked to diet, particularly to the consumption of greasy foods. A diet low in fat and animal protein may alleviate PCD.

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