careful monitoring of blood levels and renal functions is very important in patients on parenteral cyclosporin.

One of the major drawbacks of cyclosporin therapy is the occurrence of significant side effects like nephrotoxicity, hypertension, infections, increased risk of neoplasia and hepatotoxicity (Transplant Proc 1983; 15: Suppl 1): 5748-55). However, a majority of side effects are dose-dependent and reversible. There are only occasional reports of serious, non-reversible complications which usually occur on prolonged high dose therapy as used for organ transplantation (N Engl J Med 1984; 311: 699-705). The risk is minimal: when low dose therapy is used for a period of less than 6 months, as in the treatment of various auto-immune diseases (Transplant Proc 1983; 31: Suppl 1): 97-112). The dose of cyclosporin used in the present study was adjusted to achieve blood levels in the range of 400-600 mg/ml; this is similar to an earlier report (Dig Dis Sci 1989; 34: 1387-92). However, some authors found a smaller dose with blood levels of 600-800 mg/ml to be quite effective (Lancet 1985: ii: 1775-8). If this observation is confirmed, this may reduce the side effects. Rebound phenomena leading to rejection has been another factor of cyclosporin therapy in inflammatory bowel disease (Dig Dis Sci 1989; 34: 1387-92). This has been taken care of in the present study by gradual tapering of drug dose during cyclosporin withdrawal.

Therefore, as shown by the present as well as an earlier study (Dig Dis Sci 1989; 34: 1387-92), dose-dependent adverse effects are unlikely to limit the use of this drug in UC, especially the control of fulminant colitis. Cost and difficulty in monitoring the blood levels of the drug, however, would be important limitations for its use in our circumstances.

A New Approach to Improving Results of Medical Gallstone Dissolution

Niu N, Smith BF (Section of Gastroenterology and Hepatology, Department of Medicine, Boston City Hospital, Boston University Medical School, Boston, Massachusetts, USA). Addition of N-acetylglucosamine to aqueous model bile systems accelerates dissolution of cholesterol gallstones in Gastroenterology 1990; 98: 484-6.

The organic matrix of cholesterol gallstones (GS) contains a macromolecular complex of mucin and bilirubin that may inhibit stone dissolution by limiting contact of desaturated bile with crystalline cholesterol. The present study was carried out to examine the aqueous solubility of cholesterol GS matrix, and the effect of N-acetylglucosamine (NAG), a mucolytic agent, on cholesterol GS dissolution in aqueous solutions of various pure bile salts and in bovine bile supplied with these bile acids. Human cholesterol stones obtained from 37 patients with multiple, morphologically similar GS were washed, dried, measured, weighted and subjected to chemical compositional analysis. The average cholesterol (75.7 ± 0.7%) and matrix (34.2 ± 0.2%) content of these stones was determined. For paired dissolution studies, two stones from the same gallbladder (GB) near in size and weight were used. For GS matrix solubility experiments, matrix was obtained by dissolving the stones in ethanol/ether mixture at 4°C, removal of supernatant and purification and lyophilization of the precipitated residue obtained. The effect of pH (range 2-10), ionic strength of the solvent and of addition of NAG on the solubility of the GS matrix was studied. Optical absorbance of the supernatant at 453 nm provided a measure of the solubility of the matrix. Simultaneously, the effect of all these factors on the solubility of pure bilirubin ditraceate was also studied.

Varying pH had a significant effect on matrix solubility, with maximum solubility at pH 5-6 and another smaller peak at pH 10. Ionic strength of solvent had no effect, but NAG caused significant concentration dependent increase in matrix solubility. On the other hand, the solubility of bilirubin ditraceate progressively decreased with increase in pH and was independent of the presence of NAG, indicating that the solubility of GS matrix is not due to the solubility of bilirubin.

The second part of the study involved GS dissolution experiments in vitro. GS dissolution in aqueous bile salt solutions was studied on paired gallstones in 140 mM taurocholate (TC), 100 mM CDC or UDC with or without NAG. The total mass of cholesterol in each stone was calculated from the weight of the stone and percentage of cholesterol in a paired stone from the same gallbladder and the amount of solvent used was proportional to the cholesterol content of the stone. Additional experiments compared the effect of NAG (500 mM) and N-acetylglucosamine (500 mM) on GS dissolution. Also, the effect of addition of NAC on the solubilization of pure crystalline cholesterol by bile salts (TC, UDC) was studied.

In the third part of the study, pooled fresh bovine gallbladder bile was supplemented with TC, CDC or UDC to bring the total bile salt concentration to 140 mM, 100 mM and 100 mM in each case respectively. Paired GS dissolution studies were performed in the presence and absence of NAG (100 mM) using these bile salt supplemented bovine gallbladder bile. Dissolution was quantitated as percent of initial stone weight remaining each week. Also, the percent of stones undergoing complete dissolution was calculated.

NAC (500 mM) significantly accelerated the GS dissolution rate in 140 mM TC and 100 mM UDC aqueous solution, when added at the start or after 4 weeks of start of incubation (P<0.001) in each case. But addition of NAC to aqueous solution of CDC resulted in a turbid emulsion (probably due to disruption of micelles) and a significant inhibition of GS dissolution (P<0.005). NAG had no effect on GS dissolution in the absence of bile salts and had an inhibitory effect on dissolution of pure crystalline cholesterol by TC and UDC. GS dissolution was significantly greater in bovine bile supplemented with bile acids (TC, CDC or UDC) than in aqueous pure corresponding bile salt solutions (P<0.001). NAG caused acceleration of GS dissolution in TC or UDC supplemented bovine bile but not in CDC supplemented bile though no turbidity was seen. N-acetylglucosamine differed from NAG and inhibited cholesterol GS dissolution (P<0.05). Also, NAG produced an increase in the percentage of GS undergoing complete dissolution in TC supplemented (P<0.001) and UDC supplemented (P<0.01) bile.

Comments: Though GS dissolution with oral agents had held out great hope, experience with CDC, UDC and its combination of the two has been disappointing (Ann Intern Med 1981; 95: 377-8). One of the main problems has been a high failure rate. In the recent past, certain new advances have added to our knowledge of the pathogenesis of cholesterol gallstones. It is now well recognized that cholesterol supersaturations is not by itself enough for stone formation. Bile composition events are possibly more important in the formation of these stones (Gastroenterology 1990; 11: 699-702). Gallbladder mucin, an important

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promoter of nucleation, also appears to play a role in GS growth as a component of GS matrix. The GS matrix is present in the center of a pigmented focus and at radial and circumferential bands in the periphery of the stone (Surg Gynecol Obstet 1983; 156: 446-8). Structurally, this matrix consists mainly of a macro-molecular complex of mucin and bile pigments (J Clin Invest 1985; 76: 439-45). The distribution of bilirubin conjugates in the bile stone (82% unconjugated bilirubin, 15% monoglycosylated bilirubin) is identical to that in the organic GS matrix (J Surg 1981; 114: 51-56, Gastroenterology 1986; 90: 567-70). This indicates that the matrix gel in the bile stone gets incorporated into the GS structure as organic matrix, forming a gel-like substance that bears the cholesterol crystal into a mature stone (Gastroenterology 1990; 11: 699-702). Electron micrographs of GS matrix have demonstrated bilirubin, probably mainly glucuronated bilirubin, into stone matrix (Gastroenterology 1979; 76: 549-55, Gut 1975; 16: 630-7). Further confirming the role of GS matrix in forming a scaffolding on which cholesterol crystals are laid.

It appears that this GS matrix is a major cause of failure of GS dissolution with bile acid therapy. GS dissolution only partially with or without bile acids, achieved by surgery reveals a pigmented, often calcified shell of organic matrix on its surface (Gastroenterology 1988; 91: 713-16).

In vitro dissolution of GS in bile salts solutions also shows that coagglutinability of GS matrix is exposed on its surface with partial dissolution of GS matrix in a solvent. Furthermore, this process is further disrupted by GS matrix in bile salts (Gut 1974; 15: 487-90). In addition, GS dissolution in bile salts is a highly significant negative predictor of in vitro stone dissolution in mucinosis, while percent of solubility as cholesterol has no influence (Gastroenterology 1987; 91: 92-105). All these studies indicate that GS dissolution of GS matrix on its surface dissolution. Mucin being a major component of the matrix, mucolytic agents like NAC and 3-MBOAT are used to increase the dissolution of GS matrix in bile salts (J Clin Invest 1985; 76: 439-45).

In the first part of the present study, NAC caused a concentration dependent decrease in GS matrix solubility. These experiments also showed that the solubility of the matrix does not depend upon its bile pigment component, which is solubilized at extremely alkaline pH; while the matrix showed a small increase in solubility at pH 5-6. A pH-induced decrease in solubility in mucin has been previously reported by the same group (Gastroenterology 1989; 97: 159-67). Thus mucin is the primary determinant of matrix solubility. NAC being a mucolytic agent increases its solubility.

In the second part of the study, addition of NAC produced (i) an acceleration of GS dissolution in aqueous solutions of the bile salts TC and UDC and in bovine bile supematant with one of these salts; and (ii) an increase in the frequency of complete GS dissolution in TC or UDC-supplemented bile. NAC alone or in the absence of bile salts did not increase the dissolution rate of GS, indicating that it acts only as an adjunct to bile salts. Also, NAC dissolved the GS matrix of pure crystalline cholesterol in bile salt mixtures. Therefore, the acceleration of GS dissolution produced by NAC is not due to an effect on cholesterol solubility. Solubilization of matrix probably facilitates contact of bile salts with cholesterol, increasing its dissolution.

Although this study provides an interesting avenue for improving the success rate of gallstone dissolution in gallstones, certain points need clarification. Firstly, the results of these in vitro experiments may not be applicable to in vivo events. Secondly, the results of this study are relevant for the use of medical therapy. The authors indicate an adequate number to test their hypothesis. However, a comparison of clinical studies with an NAC dose of 0.5 mg/kg has shown the treatment to be safe and effective in reducing the incidence of adverse effects. In the present study, both patients with and without NAC were studied and, hence, conclusions cannot be extrapolated to the entire group of IBS.

The first aim of the study was to determine the effect of fiber on symptoms. Fiber decreased the symptoms but patients felt better even on placebo treatment. The reasons for this are not

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Dietary Fiber and Irritable Bowel Syndrome

Cook JJ, Irvine EJ, Campbell D, et al (Division of Gastroenterology and Hepatology, McMaster University Medical Center, Hamilton, Ontario, Canada and Department of Medicine, Royal Adelaide Hospital, North Terrace, Adelaide, Australia). Effect of dietary fiber on symptoms and rectosigmoid pressure in patients with irritable bowel syndrome. A controlled, crossover study. Gastroenterology 1990; 98: 66-72.

A double blind, controlled, crossover study of 7 months' duration was carried out in 9 patients with irritable bowel syndrome (IBS) to determine (a) the effects of dietary fiber supplements on symptoms and rectosigmoid pressure, and (b) the relationship between rectosigmoid pressure and symptoms. Patients received 20 g of corn fiber or placebo and symptoms and compliance were evaluated monthly. Pain severity, stool frequency, stool consistency, other gastrointestinal symptoms and total symptom score improved with both placebo and fiber treatments. Rectosigmoid pressures were not significantly altered by fiber or placebo. The authors concluded that (a) corn fiber and placebo were both effective in alleviating symptoms.

Comments: This seemingly well-conducted study was designed to address questions relating to fiber therapy and rectosigmoid pressures in patients with IBS. The study has some drawbacks. Firstly, the study was carried out in a medical center. Secondly, the authors indicate an adequate number to test their hypothesis. However, a comparison of these subjects would have an NAC dose of 0.5 mg/kg has shown the treatment to be safe and effective in reducing the incidence of adverse effects. This study concludes relating to pain severity (power 0.76) can be drawn; no comment can be made regarding pain duration and stool frequency (power 0.61 and 0.65 respectively). Therefore, analysis is prone to a type II statistical error.

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