Altered cyclosporine absorption in a patient with ulcerative colitis, sclerosing cholangitis and pancreatic insufficiency

MARK G SWAIN, MD, HELGA WITT-SULLIVAN, MD, RICHARD OGILVIE, MD, IAN WANLESS, MD, JENNY HEATHCOTE, MD

MG SWAIN, H WITT-SULLIVAN, R OGILVIE, I WANLESS, J HEATHCOTE. Altered cyclosporine absorption in a patient with ulcerative colitis, sclerosing cholangitis and pancreatic insufficiency. *Can J Gastroenterol* 1991;5(4): 133-136. Pancreatic insufficiency leading to altered cyclosporine absorption is reported in a 37-year-old man with ulcerative colitis and sclerosing cholangitis. Asymptomatic chronic pancreatitis occurs frequently in patients with ulcerative colitis, and even more commonly when there is coexistent sclerosing cholangitis. However, pancreatic insufficiency has been documented in only one patient previously with ulcerative colitis and sclerosing cholangitis. Pancreatic function testing can help to identify the complex etiology of malabsorption in these patients and is recommended in patients when liver transplantation is contemplated, as pancreatic insufficiency may alter the absorption of cyclosporine.

Key Words: *Cyclosporine, Absorption, Pancreatic insufficiency, Sclerosing cholangitis*

Troubles d'absorption de la ciclosporine chez un patient porteur de colite ulcéreuse, de cholangite sclérosante et d'insuffisance pancréatique

RESUME: On rapporte des troubles d'absorption de la ciclosporine attribuables à une insuffisance pancréatique chez un patient âgé de 37 ans et porteur d'une colite ulcéreuse et d'une cholangite sclérosante. Une pancréatite chronique asymptomatique accompagne souvent une colite ulcéreuse, surtout doublée d'une cholangite sclérosante. Pourtant, l'insuffisance pancréatique n'a été rapportée que chez un seul patient souffrant des deux affections citées. Les examens de la fonction pancréatique peuvent aider à reconnaître les causes complexes de malabsorption chez ces malades. On les recommande dans le cas des candidats à la transplantation du foie, étant donné qu'une insuffisance pancréatique peut perturber l'absorption de la ciclosporine.

Departments of Medicine, Pharmacology and Pathology, University of Toronto, Toronto, Ontario

Correspondence and reprints: Dr Jenny Heathcote, 7006 ECW, The Toronto Hospital (Western Division), 399 Bathurst Street, Toronto, Ontario M5T 2S8. Telephone (416) 363-9642

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THE ASSOCIATION BETWEEN ulcerative colitis and sclerosing cholangitis is well established (1-3). However, a relationship between these two conditions and pancreatic disease has also been noted (4-9). Pancreatic ductal abnormalities and interstitial changes consistent with chronic pancreatitis have been described in patients with ulcerative colitis (4-9), and pancreatitis occurs more commonly in patients with primary sclerosing cholangitis than would be expected by chance alone (8,9). Elevation of pancreatic isoamylase levels, indicative of pancreatic damage, have been noted in patients with primary sclerosing cholangitis, but none of these patients had pancreatic insufficiency (9). However, pancreatic insufficiency has been documented in one patient previously with sclerosing cholangitis and ulcerative colitis (10); the present case record describes a similar patient. Pancreatic disease in patients with ulcerative colitis coupled with sclerosing cholangitis could lead to altered absorption of fat-soluble compounds such as cyclosporine. This possibility has implications for patients who receive liver transplants for primary sclerosing cholangitis and who thus require adequate absorption of cyclosporine to prevent graft rejection.

Figure 1) Liver biopsy demonstrating the loss of bile ducts from portal tracts consistent with sclerosing cholangitis

TABLE 1

Cyclosporine blood concentrations after oral (5 mg/kg) or intravenous cyclosporine (2.5 mg/kg) with or without oral pancreatic supplementation (lipancreatin: three tablets with each meal)

Time (h)	Day 1 Oral cyclo	Day 2 IV cyclo	Day 3 IV cyclo + lipancreatin	Day 4 Oral cyclo + lipancreatin
01:00			177	156
07:00	<30	87	146	152
08:00	Cyclo	Cyclo	Cyclo	Cyclo
09:00	317	594	2768	749
10:00	361	332	1802	694
11:00	456	722	3067	578
12:00	279	1435	1210	541
14:00	740	727	494	353
16:00	470	517	424	254
20:00	188	284	264	157

The patient received a standard liquid breakfast at 08:00 with the cyclosporine and then standard meals were given at 12:30 and 17:00. Values were determined by radioimmunoassay, and are expressed as ng/mL. Cyclo Cyclosporine; IV Intravenous

CASE PRESENTATION

An asymptomatic 37-year-old man presented because of infertility and was found to have abnormal liver enzymes. Three years after presentation the patient noticed the gradual onset of fatigue, and subsequently complained of frequent, semi-liquid, foul-smelling, blood-tinged stools. He experienced an 11.4 kg (25 lb) weight loss over four months despite a good appetite. He did not complain of dry eyes. There was no past history of bowel, liver or pancreatic disease, ethanol abuse, or drug in-

gestion. Physical examination was within normal limits except for scleral icterus and a palpable spleen tip. Laboratory data revealed hemoglobin 123 g/L, leukocyte count 4.9×10^9 /L, platelets 264×10^9 /L, aspartate aminotransferase 157 U/L (normal less than 40), alanine aminotransferase 257 U/L (normal less than 40), gammaglutamyl transferase 969 U/L (normal nine to 43), 5' nucleotidase 178 U/L (normal five to 19), alkaline phosphatase 1080 U/L (normal 20 to 100), albumin 41 g/L (normal 39 to 51), amylase 606 U/L

(normal 0 to 1800), and total bilirubin 51 μ mol/L (normal two to 20). The prothrombin time and values for serum electrolytes, glucose, triglycerides and calcium were all normal, and an anti-mitochondrial antibody test was negative.

Liver biopsy showed fibrosis and the almost total absence of bile ducts in the portal tracts compatible with sclerosing cholangitis (Figure 1). Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated an apparently normal extrahepatic biliary system, but the intrahepatic branches were irregular, as was the pancreatic duct (Figure 2). Colonoscopy showed a pancolitis and biopsies were consistent with ulcerative colitis. Fecal fat excretion was elevated (37 and 61 mmol/day; normal less than 18). A secretin test showed decreased maximal bicarbonate secretion (77 mEq/L; normal greater than 90). A small bowel biopsy was normal. Computed tomography scan and ultrasound of the abdomen were normal.

As liver transplantation is the only known effective cure at present for sclerosing cholangitis, the patient was assessed as a potential candidate. Since cyclosporine would be used for immunosuppression after transplantation there was concern that with the patient's pancreatic insufficiency, cyclosporine, which is highly fat-soluble, would be bound in the gut and poorly absorbed. Therefore, oral cyclosporine absorption studies were performed and blood concentrations determined with no pancreatic supplementation and with pancreatic supplementation (lipancreatin: three tablets with each meal) (Table 1). Intravenous cyclosporine was given (2.5 mg/kg over 3 h) on days 2 and 3 (on and off lipancreatin, respectively) to reflect 100% bioavailability of the cyclosporine. Oral cyclosporine (5 mg/kg) was then administered with and without lipancreatin supplementation (days 4 and 1, respectively), and blood concentrations of cyclosporine were determined by radioimmunoassay specific for the parent compound. From the blood concentrations, pharmacokinetic analysis using a two compartment model with Gauss-Newton and New-

ton-Raphson procedures revealed no difference in the elimination kinetics of intravenous cyclosporine in the presence or absence of lipancreatin (area under the 'concentration over time' curve 14.2 mg·h/L versus 13.3; total clearance 12.3 L/h versus 13.2; beta half-life 8.6 h versus 8.8). The apparent initial volume of distribution for intravenous cyclosporine was smaller in the presence of lipancreatin (17 L versus 44), resulting in higher blood concentrations. The authors have no explanation for this. The oral administration of cyclosporine with lipancreatin supplementation resulted in a marked decrease in the time to peak blood cyclosporine concentrations (less than 1 h versus 5; normal 2 to 4). However, the overall bioavailability of cyclosporine was not improved by lipancreatin supplementation (16.4% with lipancreatin versus 24.0% without; normal 20 to 40%), and was in fact lower than that seen without lipancreatin supplementation.

DISCUSSION

The present patient had concomitant ulcerative colitis, sclerosing cholangitis and pancreatic exocrine insufficiency. The association between ulcerative colitis and sclerosing cholangitis is well established (1-3). However, the relationship between these two conditions and clinically significant pancreatic abnormality is incompletely documented (4-10). An increased frequency of pancreatic changes in ulcerative colitis consistent with chronic pancreatitis has been described in post mortem and ERCP examinations. Ball et al (5) described interstitial pancreatitis in 46 of 86 consecutive post mortem examinations performed in patients with ulcerative colitis. ERCP changes compatible with chronic pancreatitis were described by Axon et al (4) in 59 patients, five of whom had inflammatory bowel disease; however, none had symptomatic pancreatic insufficiency. Seven patients with ulcerative colitis and sclerosing cholangitis were described by Borkje et al (6) and four of these also had abnormal pancreatograms at ERCP. None had clinically significant pancreatic

Figure 2) Endoscopic retrograde cholangiopancreatography demonstrating an irregular intrahepatic biliary system and an irregular, beaded pancreatic duct with total absence of filling of the side branches

insufficiency. In a series of 20 patients with primary sclerosing cholangitis, 13 had associated ulcerative colitis and two had ERCPs consistent with pancreatitis. Pancreatic secretin stimulation tests were performed on these patients and all were normal (9).

Pancreatic insufficiency associated with ulcerative colitis and intrahepatic sclerosing cholangitis has been described in a 19-year-old female (10). This patient developed steatorrhea and jaundice simultaneously one year prior to the diagnosis of ulcerative colitis. The present patient became jaundiced before developing symptoms of ulcerative colitis or pancreatic insufficiency. There was no evidence of alcohol abuse, gallstones, hypercalcemia or hyperlipidemia, and the patient had never received systemic steroids or sulphasalazine. 5-Aminosalicylic acid therapy was begun after the diagnosis of pancreatic insufficiency was made.

The pathogenesis of the pancreatic

abnormality in association with ulcerative colitis and sclerosing cholangitis is unknown. Borkje et al (6) postulated that the triad of ulcerative colitis, sclerosing cholangitis and pancreatitis might be manifestations of an autoimmune disease with genetic predisposition. This hypothesis has been supported by the finding of an association between chronic pancreatitis, sclerosing cholangitis and the sicca complex (11,12). Recently, the specific human lymphocyte antigen (HLA) haplotype, HLA-DRw52a, has been described in patients with sclerosing cholangitis, again suggesting a genetic predisposition (13). Epstein et al (9) have proposed the same hypothesis in their primary biliary cirrhosis patients with pancreatic abnormalities. Sicca syndrome was also noted to be an additional feature of primary biliary cirrhosis but not sclerosing cholangitis (9). It has also been suggested that sclerosing cholangitis might predispose to bile

reflux into the pancreatic duct and so give rise to chronic pancreatitis (6,14).

Pancreatic ductal abnormalities have been demonstrated in patients with ulcerative colitis without sclerosing cholangitis (4). However, pancreatic insufficiency has only been demonstrated in ulcerative colitis patients with sclerosing cholangitis (10). This suggests that there is a correlation between symptomatic disease of the bile duct and that of the pancreatic duct. Pancreatic insufficiency in the present patient resulted in a de-

creased rate of absorption of cyclosporine which was corrected by pancreatic enzyme supplementation. However, the overall bioavailability of oral cyclosporine was not improved by the addition of pancreatic supplements. Blood cyclosporine concentrations were higher after intravenous cyclosporine in the presence of lipancreatin supplementation due to a smaller apparent initial volume of distribution without alteration of elimination kinetics. There is no ready explanation for this, but an alteration in circulating lipid

profiles in spite of a fixed diet may be responsible. Since the radioimmunoassay was specific for the parent compound, enterohepatic recirculation of cyclosporine metabolites cannot account for the higher blood concentrations of cyclosporine.

In summary, pancreatic function testing in patients with ulcerative colitis and sclerosing cholangitis should be considered if liver transplantation is contemplated, since pancreatic insufficiency may alter the absorption kinetics of cyclosporine.

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