Biliary sequelae of endoscopic sphincterotomy

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Summary: Twenty five patients were reviewed a mean of 36 months after successful endoscopic sphincterotomy for the removal of bile duct stones. All the patients had improved symptomatically but 20% had episodes of mild abdominal pain and a similar number had elevated serum gamma glutamyltranspeptidase activities (up to 3 times normal). In 12 patients (50%) biliary gas was demonstrated indicating reflux of duodenal contents. Clinical cholangitis did not occur. Aspiration liver biopsy revealed mild portal tract fibrosis and inflammation in patients with biliary reflux. Biliary reflux was significantly associated with mild upper abdominal pain ($P < 0.05$). This study has shown that mild abnormalities of biliary function persist after endoscopic sphincterotomy. The long term consequence of these changes is unclear.

Introduction

Surgical exploration for stones in the common bile duct (CBD) is a major operation, especially following previous bile duct surgery, in the presence of cholangitis, and in the elderly (McSherry & Glenn, 1980; Vellacott & Powell, 1979; Kune & Sali, 1980). In contrast, endoscopic sphincterotomy has a high success rate with a low morbidity and mortality (Cotton, 1980; Summerfield *et al.*, 1980; Safrany, 1978). However, little is known about the long term sequelae of this procedure – recurrent cholangitis, bacterial deconjugation of bile salts causing diarrhoea, and restenosis are all potential complications. In this paper we have reviewed sphincterotomy patients to determine whether duodenal contents refluxed into the biliary system and whether this related to the patients' symptoms and abnormal biochemical tests.

Patients and methods

Between January 1976 and January 1981, endoscopic sphincterotomy was performed at the Royal Free

Hospital in 59 patients. By the time of follow-up 34 of the patients could not be reassessed because of unrelated death (13), unrelated illness (7), residence abroad (5), refusal (2), or failure to achieve stone clearance at the sphincterotomy (6). One patient could not be traced. The remaining 25 patients were studied. The sex ratio (12 males) and age (mean 63 y, range 34 to 85 y) of this group was representative of the original group of patients. The mean length of follow-up from sphincterotomy was 36 months. The minimum follow up was 20 months. All patients were questioned about fever, rigors, abdominal pain, jaundice and changes in bowel frequency. Laboratory investigations included a full blood count, MCV, MCHC, ESR, liver function tests and estimation of the serum gamma glutamyltranspeptidase (γ GT) activity and serum B_{12} concentration. After an overnight fast a plain supine X-ray was taken of the right hypochondrium and a second exposure was made after the patient had swallowed 300 ml of 'Coca-Cola'. Eight patients with gas in the biliary tree had ^{14}C -glycocholate breath tests. Aspiration liver biopsies were performed in 4 patients with abnormal liver function tests and 1 patient with an abnormal ^{14}C -glycocholate breath test and gas in the biliary tree. Endoscopic retrograde cholangiopancreatography (ERCP) was performed in 3 of the 6 patients with episodic abdominal pain. Twenty patients were chosen randomly from routine barium enema lists to act as a control group for the 'cocacologram'.

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Results

Six of the 25 patients had mild upper abdominal pain and 7 described an increase in stool frequency (up to 3 times a day) without diarrhoea or steatorrhoea. Fifteen were completely asymptomatic. None of the patients had a history of cholangitis or jaundice. All patients reported improvement. In 15 patients (60%) all the haematological and biochemical investigations were normal. Liver function tests were abnormal in 8 patients (32%). All of these patients had elevated serum γ GT activities (range 56–219 U/l; upper limit of normal 48 U/l). One patient also had a raised serum alkaline phosphatase activity (160 U/l; upper limit of normal 110 U/l) and another also had an elevated serum aspartate transaminase activity (97 U/l; upper limit of normal 40 U/l). Two patients had low serum B₁₂ concentrations (40,60 ng/l; normal range 160–925 ng/l). In both patients this was due to pernicious anaemia.

Gas in the biliary tree was shown in 8 patients before drinking Coca-Cola and a further 4 afterwards. Thus 50% (12/25) of sphincterotomy patients had gas in their biliary system whereas none was detected in the 20 'barium enema' patients who acted as the control group. There was no significant difference in the total frequency of symptoms between sphincterotomy patients with (6/12) and without (4/13) biliary gas. However, abdominal pain was significantly associated with the presence of gas in the biliary system (5/12 with biliary gas compared 1/13 with no biliary gas; $\chi^2 = 3.95$, $P < 0.05$) (Table I). Of the 13 patients without biliary gas, 3 had raised γ GT values but in 2 patients this could be attributed to either a drug (prednisolone) or excessive alcohol intake. Of the 12 patients with biliary gas, 5 had elevated γ GT values but in only one patient could a drug (phenobarbital) be implicated. Three of these 5 patients had attacks of mild epigastric pain. ERCP performed on these 3 patients revealed normal biliary tracts. The ¹⁴C-glycocholate breath test (Fromm & Hoffman, 1971; James *et al.*, 1973) was performed in 8 patients with biliary gas; it was normal in 5. The 3 patients with an abnormal test were asymptomatic and 2 had normal liver function tests and serum vitamin B₁₂ concentrations.

Aspiration liver biopsy revealed portal fibrosis in 4/5 patients and portal tract inflammation in 3/5 patients. Portal tract fibrosis was mild in 3 and moderate in 1 patient. Portal tract inflammation was always mild and no evidence of cholangitis was found in the 5 patients. The patient without portal tract abnormalities had fatty infiltration and consumed excessive alcohol. The patients with portal tract abnormalities all had gas in the biliary tree. One other who took phenobarbital had swollen hepatocytes containing abundant pale cytoplasm compatible with induction of the endoplasmic reticulum. The mean period of follow-up from sphincterotomy was similar in patients with or without symptoms (32 and 41 months respectively).

Discussion

Clinical assessment of patients after endoscopic sphincterotomy usually indicated excellent symptomatic improvement (Summerfield *et al.*, 1980; Safrany, 1978; Mee *et al.*, 1981; Rosch *et al.*, 1981; Seifert *et al.*, 1982). The aim of this study was to investigate sphincterotomy patients in more detail with specific regard to symptoms, alterations in liver function tests particularly gamma glutamyltranspeptidase activity, alterations in hepatic histology and the presence of biliary gas. The low percentage (42%) of the initial group available for reassessment was largely a reflection of the elderly and high risk patients who undergo endoscopic sphincterotomy. A higher percentage of our patients (40%) had symptoms compared to the 13% reported by Rosch *et al.* (1981). Symptomatic patients are of course more likely to respond to an invitation for follow-up study, but this may also reflect more thorough enquiry. Increased bowel frequency was not reported previously (Summerfield *et al.*, 1980; Safrany, 1978; Mee *et al.*, 1981; Rosch *et al.*, 1981; Seifert *et al.*, 1982). Attacks of cholangitis were not seen although a number of patients did continue to have mild upper abdominal pain. The symptoms could not be related to the period elapsed since sphincterotomy, retained bile duct stones or strictures or hepatic histological changes. Mild elevations of gamma glutamyltranspeptidase activity

Table I Summary of findings in sphincterotomy patients

Biliary gas	Number of patients					Hepatic histology		
	Total	All symptoms	Increased stool frequency	Abdominal pain	Raised γ -GT	Positive ¹⁴ C-glycocholate breath test	Portal fibrosis	Portal inflammation
Absent	13	4	4	1	3	Not done	0/1	0/1
Present	12	6	3	5	5	3/8	4/4	3/4

were usually the only biochemical abnormalities found and in 20% of the patients no other cause (such as drugs or alcohol) could be found.

Fifty per cent of patients had gas in their biliary tree, reflecting free reflux of duodenal contents. However in 4 of these 12 patients this was shown only after the provocation of a carbonated drink. Other workers (Peel *et al.*, 1975) using different techniques have shown a similar incidence of reflux into the common bile duct following operative sphincterotomy although clinical cholangitis was rare. However in our study biliary reflux was significantly associated with upper abdominal pain despite cholangiography showing normal biliary ducts.

The combination of an elevated gamma glutamyl-transpeptidase activity and biliary reflux probably reflects subclinical inflammation of the biliary tree and this was probably the cause of the mild portal tract fibrosis and inflammation present in the liver biopsy specimens of 4 patients. Significant bacterial contamination of bile has been reported (Vallon *et al.*, 1981) although it was unclear how long after sphincterotomy the bile samples were obtained. Bacterial overgrowth in the biliary system may also result in bile

salt deconjugation (Scott and Kahn, 1968). We found 3 patients with a positive ^{14}C -glycocholate breath test, however this test is reported to be quite insensitive and yields about 30% false negative results (Lauterburg *et al.*, 1978).

In conclusion, mild gastrointestinal symptoms and biliary reflux are common for at least 3 years after endoscopic sphincterotomy. About 20% of patients have elevated gamma glutamyltranspeptidase levels. Hepatic histological changes are mild and confined to portal tract fibrosis and inflammation, probably related to biliary reflux. Attacks of mild upper abdominal pain were significantly associated with this biliary reflux. There is now a need to investigate a larger cohort of patients to confirm these preliminary findings.

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