BILIARY TRACT

Outcome of endoscopic sphincterotomy in post cholecystectomy patients with sphincter of Oddi dysfunction as predicted by manometry and quantitative choledochoscintigraphy

M Cicala, F I Habib, P Vavassori, N Pallotta, O Schillaci, G Costamagna, M P L Guarino, F Scopinaro, F Fiocca, A Torsoli, E Corazziari

....

See end of article for authors' affiliations
....

Correspondence to:
Dr E Corazziari,
Dipartimento di Scienze Cliniche, Policlinico Umberto I, Università "La Sapienza", V le del Policlinico, 00161Roma, Italy; enrico.corazziari@ uniroma1.it

Background: Sphincter of Oddi dysfunction is diagnosed at manometry and, after cholecystectomy, non-invasively at quantitative choledochoscintigraphy. Patients may benefit from endoscopic sphincterotomy.

Aims: The aim of this study was to assess the usefulness of choledochoscintigraphy compared with manometry in predicting outcome of sphincterotomy in post cholecystectomy patients with sphincter of Oddi dysfunction.

Patients and methods: Thirty patients with biliary-type pain complying with the Rome diagnostic criteria of sphincter of Oddi dysfunction and belonging to biliary group I and II were subjected to clinical evaluation, choledochoscintigraphic assessment of the hepatic hilum-duodenum transit time, endoscopic retrograde cholangiopancreatography, and perendoscopic manometry. Twenty two biliary group I and II patients with prolonged hepatic hilum-duodenum transit times were invited to undergo sphincterotomy. Fourteen patients underwent sphincterotomy; eight refused. Clinical and scintigraphic assessments were performed at follow up.

Results: Hepatic hilum-duodenum transit time was delayed in all patients with manometric evidence of sphincter of Oddi dysfunction, in all biliary group I patients and in 64% of biliary group II patients. At follow up, all patients who underwent sphincterotomy were symptom free and hepatic hilum-duodenum transit time had either normalised or significantly improved. A favourable post sphincterotomy outcome was predicted in 93% of cases at choledochoscintigraphy and in 57% at manometry.

Conclusions: Quantitative choledochoscintigraphy is a useful and non-invasive test to diagnose sphincter of Oddi dysfunction as well as a reliable predictor of sphincterotomy outcome in post cholecystectomy biliary group I and II patients, irrespective of clinical classification and manometric findings.

S phincter of Oddi (SO) dysfunction, stenosis, and/or an abnormal motor activity of the SO, usually presents with biliary-like pain and acute pancreatitis in post cholecystectomy subjects.[1–3] Manometry is the only investigation that can directly assess SO motor activity but this is an invasive method not devoid of serious complications.[4–6] In addition, it is not a widely available technique as expertise is needed to correctly perform and interpret the manometric tracings due to the frequent occurrence of artefacts.[7] The difficulty in performing the technique and alleged low prevalence of the disorder has not favoured the widespread acceptance of SO manometry, which is performed mainly in third level referral centres with a specific interest in biliary tract disorders. Attempts have therefore been made to detect SO dysfunction by means of easily available laboratory and endoscopic findings as well as by other non-invasive techniques. A widely used clinical approach to post cholecystectomy patients presenting with diagnostic criteria of SO dysfunction[8 9] classifies patients into three biliary groups (I, II, and III) according to the presence/absence of laboratory and endoscopic data.

Of the non-invasive techniques, quantitative choledochoscintigraphy (QC)—that is, scintigraphic measurement of the hepatic hilum-duodenum transit time (HHDT)—appears to offer the best prerequisites for detecting the presence of SO dysfunction in post cholecystectomy patients. Measurement of HHDT has been shown: (a) to be reproducible and (b) to correlate with maximal SO resting pressure.[10–15] Furthermore,

HHDT has a high specificity and a satisfactory sensitivity in detecting SO dysfunction, and in preliminary observations performed in a small group of patients this scintigraphic method appeared to predict post sphincterotomy outcome.[11 13] Previous studies have assessed the response to sphincterotomy based on manometric results.[8 16 17] The aim of the present study was to assess the reliability of choledochoscintigraphy, relative to SO manometry, in the prediction of therapeutic outcome of endoscopic sphincterotomy (ES) in biliary group I and II patients.

METHODS

A total of 140 consecutive post cholecystectomy patients referred to our centre from June 1988 to November 1998 for upper abdominal pain of suspected biliopancreatic origin underwent clinical interview and a symptom scored questionnaire, physical examination, and laboratory assessment: liver

....

function tests (LFTs) (serum glutamic and alanine aminotransferases, protein, alkaline phosphatase, gamma glutamyl transpeptidase, conjugated and unconjugated bilirubin, prothrombin time), lipase, amylase, as well as ultrasound examination of the upper abdomen, upper gastrointestinal endoscopy, and endoscopic retrograde cholangiopancreatography (ERCP). Eighty two patients presented pathological alterations (choledocholithiasis, biliopancreatic tumours, chronic pancreatitis) and were excluded from the study. Of the remaining 58 patients, 30 reported biliary-type pain which complied with the Rome diagnostic criteria of SO dysfunction (18 females; mean age 50 years (range 23–66)) and belonged to biliary groups I and II in accordance with the following published definitions[18]: (A) biliary group I: presence of biliary-type pain, increased LFTs, dilated common bile duct (CBD), and delayed contrast drainage from the CBD at ERCP—eight patients (six females and two males; mean age 51 years (range 44–60)); (B) biliary group II: presence of biliary-type pain and one or two of the above mentioned alterations—22 patients (12 females and 10 males; mean age 49 years (range 23–66)). Three of the 22 biliary group II patients had a dilated CBD ($\geqslant 12$ mm) at ERCP. None of these patients had evidence of oesophago-gastro-duodenal disease, choledochal lithiasis, or pancreatic alterations at ERCP. None had undergone surgery on the upper gastrointestinal tract, pancreas, or biliary tract with the exception of cholecystectomy.

These 30 patients were enrolled in the study and underwent QC and, on the following day, perendoscopic manometry of the SO. ES of the SO was offered to those patients with HHDT exceeding nine minutes at QC, irrespective of SO manometric findings. A complete clinical assessment, including symptom scored questionnaire and laboratory assessment, was performed at medium term (5–7 months) and at long term (10–13 months) follow up after ES or initial evaluation; QC was performed in all patients 5–7 months after the initial evaluation or after ES.

Informed consent was obtained from all patients and the study protocol was approved by the local ethics committee.

Quantitative choledochoscintigraphy
All patients were injected with 175 MBq of Tc-99m hepatic iminodiacetic acid (HIDA), and a dynamic sequence of four 64×64 pixel frames/minute for 40 minutes were acquired in the standard supine view with a 40 cm diameter circular camera (Starcam 2000; General Electric, Milwaukee, Wisconsin, USA) equipped with a general purpose low energy collimator.

To calculate HHDT, the arrival time of radioactive bile into the hilum and its first entry into the duodenum were assessed. Liver parenchyma radioactivity was subtracted from the radioactivity present in the hilar region. To this end, four regions of interest (ROIs) were drawn: heart (He), peripheral liver parenchyma (L), visible bile ducts, including hilum (BD), and duodenum (D). The selection of ROIs has been described elsewhere.[10] The time/activity curves obtained from L and BD were fitted with a gamma variate function. These two curves are derived from ROIs with a different number of pixels, as well as different distances from and geometrical relationships with the gamma camera. To subtract one curve from the other the two time curves were normalised by multiplying one of the two curves by a factor (F) which takes into consideration the ratio between the two ROIs and their geometrical differences. In brief, the ratio between the gamma variate fit of the L time curve and the gamma variate of the BD curve has been calculated. In a Cartesian diagram, this ratio runs as a straight line parallel to the abscissa (time) axis for about three minutes after which it begins to progressively increase giving rise to a steady slope. The initial steady ratio expresses the F value as both curves are related to the same phenomenon—that is, uptake of Tc-99m HIDA by the liver parenchyma. The subsequent increasing ratio expresses the different distribution of radioactivity in the two zones.

To establish the duodenal entry time, the D curve is analysed. The D curve displays two slopes: the first, with slightly decreasing values, is roughly parallel to the curve obtained from the He ROI. This phase is related to the vascular activity in the abdomen and indicates that no radioactive bile is present in the D; this descending slope is interrupted and reversed with a sudden rise in the slope as soon as the radioactive bile enters the duodenum (second phase). The initial bile entry into the duodenum is detected by this deflection point whereas onset of hepatic hilum time corresponds to the onset of the deflection of the "net" hilar curve obtained by subtracting the L curve from the BD curve multiplied by F. The time elapsing between the first appearance of radioactivity in the BD and the first appearance in the D corresponds to the HHDT. A HHDT of nine minutes was considered the upper normal value, defined as the mean value plus 2 SDs of all the measurements performed using an identical technique in an asymptomatic control population.[10]

Perendoscopic manometry
Immediately before ERCP, patients were sedated with diazepam (10–20 mg intravenously). After completion of ERCP,[19] perendoscopic manometry was performed using a 200 cm polyethylene triple lumen catheter with three distal side holes located 2 mm apart (Arndorfer Medical Specialties, Inc Greendale, Wisconsin, USA), continuously infused with sterile bubble free water at a rate of 0.25 ml/min by a minimally compliant hydraulic capillary infusion system (Arndorfer Medical Specialties, Inc Greendale, Wisconsin, USA). The catheter, passed through the biopsy channel of a duodenoscope (Olympus Co., TJF 100/TJF 140, Tokjo, Japan), was introduced into the CBD and withdrawn across the SO in 2 mm step increments. The catheter was then positioned to record SO motor activity for at least two minutes with all three manometric sensors. Pressure recordings were divided into, and measured over, one minute intervals. Basal SO pressure was measured at the mid inspiratory phase and expressed as mm Hg with duodenal pressure as the zero reference. Mean basal SO pressure represented the mean of the basal pressures, recorded by the three sensors and measured on a steady baseline of at least 20 seconds. Maximal basal pressure was the highest value recorded by any one of the three sensors. The amplitude of the SO contractions was measured from the peak to the base of the waves and expressed as mm Hg with basal SO pressure as the zero reference. Duration of phasic SO contractions was measured from the onset of the ascending to the end of the descending slope of the wave. The frequency of the SO contractions was expressed as the number of waves per minute. Amplitude, duration, and frequency of phasic SO contractions were assessed at each recording level and expressed as the average of the three tracings.

A maximal basal SO pressure equal to or exceeding 40 mm Hg was considered as evidence of SO dysfunction.[11]

Acquisition and analysis of data
Definition of clinical biliary subgroupings, and of normal manometric and choledochoscintigraphic values, were established before recruitment of the patients and data were acquired in a prospective manner. Clinical, manometric, and scintigraphic data were each acquired by an independent observer unaware of the findings of the other techniques. A favourable therapeutic outcome at medium and long term follow up was defined if patients complied with the following: (a) absence of specific symptoms and (b) normalisation of LFTs, amylase, and lipase.

Intragroup changes were assessed using the Wilcoxon matched pairs signed rank test whereas the Mann-Whitney U test, two tailed probabilities, was used for analysis of intergroup differences. The Pearson coefficient of correlation and concordance test[20] were used to assess data relationship.
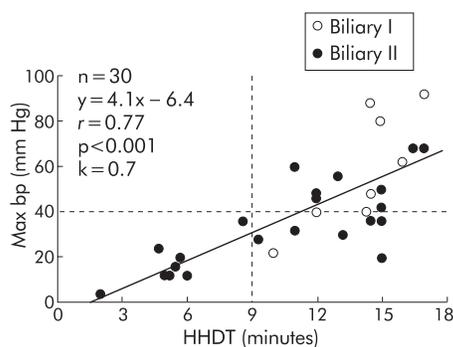
Table 1 Sphincter of Oddi (SO) manometric and choledochoscintigraphic variables in biliary group I and II patients

	Biliary I (n=8)	Biliary II (n=22)
SO manometry		
Basal SO pressure		
Mean basal SO pressure (mm Hg)	29.0 (17)	18.3 (9)
Maximal basal SO pressure (mm Hg)	59.0 (26)*	34.4 (19)*
Phasic activity		
Frequency (cycle/min)	2.2 (0.6)	1.8 (0.9)
Duration (s)	7.5 (1.8)	6.3 (1.7)
Amplitude (mm Hg)	111 (34)	85 (31)
Quantitative choledochoscintigraphy		
HHDT (min)	14.2 (2.2)	10.6 (4.5)

HHDT, hepatic hilum-duodenum transit time.
Values are mean (SD).
*Significant difference.

Figure 2 Individual data for hepatic hilum-duodenum transit time (HHDT) at referral and at follow up in patients with sphincter of Oddi (SO) dysfunction who underwent or did not undergo endoscopic sphincterotomy. Filled circles refer to individual patients with a maximal basal SO pressure value of <40 mm Hg. p<0.001, pre versus post sphincterotomy follow up; NS, not significant between time of referral and follow up.

Figure 1 Correlation between hepatic hilum-duodenum transit time (HHDT) and maximal basal sphincter of Oddi (SO) pressure (max bp) in biliary group I and II patients. The solid line represents the regression line and the broken lines show the cut offs between normal and abnormal values.

RESULTS

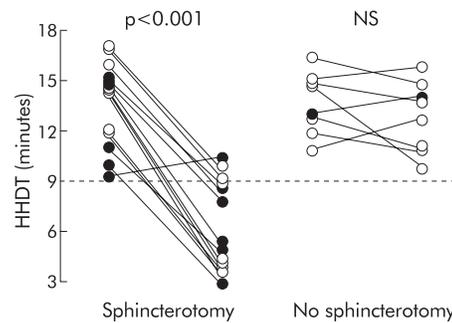The sex and age of the patients in the two biliary groups were not significantly different.

Choledochoscintigraphic data in the two groups are reported in table 1. The HHDT was prolonged in all biliary group I patients and in 14/22 (64%) biliary group II patients.

SO manometric variables in the two biliary groups are reported in table 1. Maximal basal SO pressure was ≥40 mm Hg in all but one biliary group I patient; it was ≥40 mm Hg in 8/22 (36%) biliary group II patients.

Maximal basal SO pressure was directly correlated with choledochoscintigraphic values of HHDT (r=0.77, p<0.001; k=0.7) (fig 1). Amplitude, duration, and frequency of phasic SO contractions did not differ significantly between the two biliary groups.

No significant relationship was found between HHDT and CBD diameter or amplitude, duration, or frequency of phasic SO contractions.

HHDT was abnormally prolonged in all patients with maximal basal SO pressure ≥40 mm Hg and in 7/15 (47%) patients with a normal maximal basal SO pressure (<40 mm Hg). Twenty two biliary group I and II patients had a prolonged (>9 minutes) HHDT and were invited to undergo ES. Eight (two from biliary group I and six from biliary group II) refused and thus 14 patients underwent ES. At medium term follow up, all 14 patients (six from biliary group I and eight from biliary group II) who underwent ES had a favourable outcome except for one biliary II group patient who was still symptomatic and showed an increased alkaline phosphatase and whose HHDT did not vary. All patients were asymptomatic and did not have LFTs, amylase, or lipase alterations at long term follow up. HHDT decreased from 13.7 (2.5) minutes (mean (SD)) pre-ES to 6.4 (2.8) minutes (p<0.001) post-ES at medium term follow up. At follow up, all eight patients who refused ES were still symptomatic and their HHDT did not vary (13.8 (1.8) minutes at referral, 13.0 (2.2) minutes at medium term follow up) (fig 2).

In the 14 biliary group I and II patients who underwent ES and in whom both SO manometry and QC were performed, the favourable post-ES outcome was predicted by QC in 13 patients (93%) and by manometry in eight (57%).

DISCUSSION

SO dysfunction is usually suspected in symptomatic patients who have previously undergone cholecystectomy. As symptoms have low diagnostic specificity and sensitivity, detection of SO dysfunction usually requires an extensive diagnostic workup which includes invasive examinations such as ERCP and perendoscopic manometry of the SO.[21]

Attempts have thus been made to limit these invasive techniques to those patients who would most benefit so as to reduce the unnecessary risks of complications and the costs. Clinical clues and more available tests have been used to detect or at least to reduce the diagnostic uncertainty of SO dysfunction. The subdivision of post cholecystectomy patients into three subgroups according to an arbitrary classification based on clinical, laboratory, and endoscopic findings proved over the years to offer a simple and practical approach. Patients with biliary group I characteristics have a high probability of presenting manometric evidence of SO dysfunction, a finding confirmed by the present study which showed that the presence of the biliary I clinical characteristics predicted a favourable response to ES in 100% of those post cholecystectomy patients complying with the Rome diagnostic criteria of SO dysfunction. This finding is in agreement with previous observations reporting a favourable response after ES in patients classified as belonging to biliary group I.[8 9 17 22 23] It is not surprising that biliary group I patients benefit to such a high degree from sphincter bisection as the combined occurrence of dilated CBD, increased serum LFTs, and delayed contrast drainage from the CBD converge to indicate the presence of an obstruction at the SO level. On the other hand, as confirmed in the present study, a large number of biliary group II patients do not have any SO alteration at manometry and further investigations are then required to ascertain the presence of SO dysfunction.

SO manometry is the only method that can directly assess SO motor function. As expected, in the present study perendoscopic manometry, confirming previous

observations,[9] [23] showed that maximal basal SO pressure was frequently increased in biliary group I and less so in biliary group II. In the absence of a pathological reference marker of SO dysfunction, SO manometry has gained acceptance as the gold standard for the diagnosis of this condition as the finding of increased SO pressure has a high predictive value for a favourable response to ES.[8] [9] [16] [23] Data emerging from the present study confirm that the manometric finding of SO dysfunction predicts a favourable outcome after ES but the reverse does not hold true as one biliary group I and five biliary group II patients with normal SO manometry benefited from ES, indicated on the basis of QC abnormalities.

The results of the present study show that the non-invasive technique of QC identified all patients with a maximal basal SO pressure of 40 mm Hg or more and all patients belonging to biliary group I. The satisfactory diagnostic agreement between QC and SO manometry reflects the highly statistical direct correlation between the HHDT value and the manometric value of maximal basal SO pressure.[11] [15] Despite the highly statistical correlation between HHDT and maximal basal SO pressure values, not all patients belonging to biliary group I presenting a prolonged HHDT at QC had abnormal findings at SO manometry; one patient had a maximal basal SO pressure within the normal range and one patient a borderline value of 40 mm Hg. These two patients underwent perendoscopic sphincterotomy: at follow up they became asymptomatic and QC had normalised. Also, six patients belonging to biliary group II had normal basal SO pressure and a prolonged HHDT; five of these biliary group II patients underwent ES and at follow up they became asymptomatic and showed a normal QC value.

The lack of agreement between manometry and QC findings in the individual patient could be interpreted as a drawback of either one or both techniques which necessarily offer a spot measurement of a variable which may vary over time and the values of which are acquired by the two techniques at different times.

We cannot exclude the fact however that an SO pressure of less than 40 mm Hg may still offer resistance to bile flow. The threshold of 40 mm Hg that discriminates normal from abnormal SO motor function was determined in studies which lacked control values from healthy populations. The only study[24] performed in healthy volunteers reported that normal basal SO pressure does not exceed 30 mm Hg. Hence patients with basal SO pressure exceeding 30 mm Hg could also be considered to have SO dysfunction and would likely benefit from ES. In addition, although mean phasic SO contractions did not differ among the investigated subgroups, abnormal phasic SO motor activity may have hindered bile flow in the individual patient.

It is also possible that, in addition to maximal basal SO pressure, other factors not detectable at perendoscopic manometry may contribute to prolong intracholedochal bile transit.

All biliary group I and II patients with prolonged HHDT were invited to undergo ES irrespective of manometric findings, and the comparison between the outcome of those who agreed with those who refused this treatment offers an indication of the extent to which QC per se, and relative to SO manometry, can predict the therapeutic effect of ES in these subgroups of patients. The results of the present study indicate that a prolonged HHDT at QC could predict a favourable response to ES, irrespective of the clinical classification into biliary group I or II.

In conclusion, within the limits of the present study, in which no attempt was made to compare randomised therapeutic groups of patients, it would appear that at least in post cholecystectomy patients belonging to biliary group II, a prolonged HHDT at QC is a better predictor of ES outcome than manometric findings.

. . . .
Authors' affiliations
M Cicala, P Vavassori, G Costamagna, M P L Guarino, DPT Gastroenterologia, Università "Campus Bio-Medico" Roma, Italy
F I Habib, N Pallotta, A Torsoli, E Corazziari, DPT Scienze Cliniche, Università "La Sapienza" Roma, Italy
O Schillaci, F Scopinaro, DPT Medicina Sperimentale, Università "La Sapienza" Roma, Italy
F Fiocca, DPT Chirurgia, Stefanini Università "La Sapienza" Roma, Italy

REFERENCES

1 **Bar-Meir S**, Halpern Z, Bardan E, et al. Frequency of papillary dysfunction among cholecystectomized patients. Hepatology 1984;**4**:328–30.
2 **Sherman S**, Troiano FP, Hawes RH, et al. Frequency of abnormal sphincter of Oddi manometry compared with the clinical suspicion of sphincter of Oddi dysfunction. Am J Gastroenterol 1991;**86**:586–90.
3 **Eversman D**, Sherman S, Bucksot L, et al. Frequency of abnormal biliary and pancreatic basal sphincter pressure at sphincter of Oddi manometry (SOM) in 593 patients. Gastrointest Endosc 1997;**45**:426A.
4 **Maldonado ME**, Brady PG, Mamel JJ, et al. Incidence of pancreatitis in patients undergoing sphincter of Oddi manometry (SOM). Am J Gastroenterol 1999;**94**:387–90.
5 **Freeman ML**, Nelson DB, Sherman S, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med 1996;**335**:909–18.
6 **Sherman S**, Troiano F, Hawes RH, et al. Sphincter of Oddi manometry: decreased risk of clinical pancreatitis with use of a modified aspirating catheter. Gastrointest Endosc 1990;**36**:462–6.
7 **Corazziari E**, Habib FI, Biliotti D, et al. Reading error and time variability of sphincter of Oddi (SO) recordings. Ital J Gastroenterol 1985;**17**:343–7.
8 **Geenen JE**, Hogan WJ, Dodds WJ, et al. The efficacy of endoscopic sphincterotomy after cholecystectomy in patients with sphincter of Oddi dysfunction. N Engl J Med 1989;**320**:82–7.
9 **Rolny P**, Geenen JE, Hogan WJ. Post-cholecystectomy patients with "objective signs" of partial bile outflow obstruction: clinical characteristics, sphincter of Oddi manometry findings, and results of therapy. Gastrointest Endosc 1993;**39**:778–81.
10 **Cicala M**, Scopinaro F, Corazziari E, et al. Quantitative cholescintigraphy in the assessment of choledochoduodenal bile flow. Gastroenterology 1991;**100**:1106–13.
11 **Corazziari E**, Cicala M, Habib FI, et al. Hepato-duodenal transit in cholecystectomized subjects: relationship with sphincter of Oddi function and diagnostic value. Dig Dis Sci 1994;**19**:1985–93.
12 **Sostre S**, Kalloo AN, Spiegler EJ, et al. A noninvasive test of sphincter of Oddi dysfunction in postcholecystectomy patients: the scintigraphic score. J Nucl Med 1992;**33**:1216–22.
13 **Cicala M**, Corazziari E, Habib FI, et al. The cholescintigraphic measurement of hepatic hilum-duodenum transit time is a sensitive diagnostic test of sphincter of Oddi (SO) dysfunction and predicts post-sphincterotomy outcome. Gastroenterology 1994;**106**:A337.
14 **Thomas PD**, Turner JG, Dobbs BR, et al. Use of 99m-Tc-DISIDA biliary scanning with morphine provocation for the detection of elevated sphincter of Oddi basal pressure. Gut 2000;**46**:838–41.
15 **Madacsy L**, Middelfart HV, Matzen P, et al. Quantitative hepatobiliary scintigraphy and endoscopic sphincter of Oddi manometry in patients with suspected sphincter of Oddi dysfunction: assessment of flow-pressure relationship in the biliary tract. Eur J Gastroenterol Hepatol 2000;**12**:777–86.
16 **Toouli J**, Roberts-Thomson IC, Kellow J, et al. Manometry based randomised trial of endoscopic sphincterotomy for sphincter of Oddi dysfunction. Gut 2000;**46**:98–102.
17 **Neoptolemos JP**, Bailey IS, Carr-Locke DL. Sphincter of Oddi dysfunction: results of treatment by endoscopic sphincterotomy. Br J Surg 1988;**75**:454–9.
18 The functional gastrointestinal disorders. McLean, VA, USA: Degnon Associates, 2000.
19 **Dodds WJ**. Biliary tract motility and its relationship to clinical disorders. AJR Am J Roentgenol 1990;**155**:247–58.
20 **Kramer MS**, Feinstein AR. Clinical biostatistics. The biostatistics of concordance. Clin Pharmacol Ther 1981;**29**:111–23.
21 **Corazziari E**, Shaffer EA, Hogan WJ, et al. Functional disorders of the biliary tract and pancreas. Gut 1999;**45**(suppl 2):II48–54.
22 **Kumar S**, Rathgaber S, Atherley N, et al. Endoscopic sphincterotomy in post-cholecystectomy patients with type III sphincter of Oddi dysfunction. Gastrointest Endosc 1992;**38**:255.
23 **Botoman VA**, Kozarek RA, Novel RA, et al. Longterm outcome after endoscopic sphincterotomy in patients with biliary colic and suspected sphincter of Oddi dysfunction. Gastrointest Endosc 1994;**40**:165–70.
24 **Guelrud M**, Mendoza S, Rossiter G, et al. Sphincter of Oddi manometry in healthy volunteers. Dig Dis Sci 1990;**35**:38–46.