

# Use of $^{99m}\text{Tc}$ -DISIDA biliary scanning with morphine provocation for the detection of elevated sphincter of Oddi basal pressure

P D Thomas, J G Turner, B R Dobbs, M J Burt, B A Chapman

## Abstract

**Background**—Endoscopic biliary manometry is useful in the assessment of patients with types II and III sphincter of Oddi dysfunction, but it is time consuming and invasive.

**Aim**—To investigate the role of  $^{99m}\text{Tc}$ -DISIDA scanning, with and without morphine provocation, as a non-invasive investigation in these patients compared with endoscopic biliary manometry.

**Subjects and methods**—A total of 34 patients with a clinical diagnosis of type II (n=21) or III (n=13) sphincter of Oddi dysfunction were studied. Biliary scintigraphy with 100 MBq of  $^{99m}\text{Tc}$ -DISIDA was carried out with and without morphine provocation (0.04 mg/kg intravenously) and time/activity curves were compared with the results of subsequent endoscopic biliary manometry.

**Results**—Eighteen (nine type II, nine type III) of the 34 (53%) patients had sphincter of Oddi basal pressures above the upper limit of normal (40 mm Hg). In the standard DISIDA scan without morphine, no significant differences were observed in time to maximal activity (Tmax) or percentage excretion at 45 or 60 minutes between those with normal and those with abnormal biliary manometry. However, following morphine provocation, median percentage excretion at 60 minutes was 4.9% in those with abnormal manometry and 28.2% in the normal manometry group (p=0.002). Using a cut off value of 15% excretion at 60 minutes, the sensitivity for detecting elevated sphincter of Oddi basal pressure by the morphine augmented DISIDA scan was 83% and specificity was 81%. Also, 14 of the 18 patients with abnormal manometry complained of biliary-type pain after morphine infusion compared with only two of 16 patients in the normal manometry group (p=0.001).

**Conclusions**— $^{99m}\text{Tc}$ -DISIDA with morphine provocation is a useful non-invasive investigation for types II and III sphincter of Oddi dysfunction to detect those with elevated sphincter basal pressures who may respond to endoscopic sphincterotomy.

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Keywords: sphincter of Oddi dysfunction; biliary manometry;  $^{99m}\text{Tc}$ -DISIDA biliary scanning; radionuclide biliary imaging; biliary scintigraphy

Recurrent biliary-type pain following cholecystectomy in the absence of pancreatobiliary abnormalities is often attributed to sphincter of Oddi dysfunction (SOD). Endoscopic biliary manometry (EBM) remains the investigation of choice<sup>1-3</sup> and has been shown to predict response to endoscopic sphincterotomy.<sup>3</sup> However, EBM is time consuming, not widely available, and may be associated with complications such as pancreatitis. Clinical differentiation of SOD into types I, II, and III on the basis of transaminase and endoscopic retrograde cholangiopancreatography (ERCP) abnormalities has shown that type I patients generally have a good response to endoscopic sphincterotomy and do not necessarily require EBM confirmation.<sup>4-5</sup> However, a clinical diagnosis of type II or III SOD has a poor correlation with the results of EBM and a less predictable response to sphincterotomy.<sup>6-9</sup> These patients are best managed by EBM prior to sphincterotomy.

Because of the limitations of EBM, other less invasive approaches have been investigated for the diagnosis of SOD. Biliary scanning with  $^{99m}\text{Tc}$ -DISIDA has shown some promise<sup>10</sup> and has been used in selecting patients for endoscopic sphincterotomy<sup>11</sup> but it appears to be less sensitive in detecting elevated sphincter of Oddi pressures.<sup>12</sup> We have used a modification of the  $^{99m}\text{Tc}$ -DISIDA scan using morphine augmentation. Morphine has been shown to cause functional obstruction of the common bile duct and spasm of the sphincter of Oddi<sup>13-14</sup> and therefore we hypothesised that morphine administration may accentuate functional abnormalities in patients with SOD. We studied a cohort of patients referred to our unit with types II and III SOD using  $^{99m}\text{Tc}$ -DISIDA biliary scanning both with and without morphine provocation and correlated the results with those of EBM.

## Methods

### PATIENTS

A total of 42 consecutive post-cholecystectomy patients referred with a clinical diagnosis of type II or III SOD were studied. The criteria for type II SOD were (a) unexplained biliary-type pain persisting for more than six months

**Abbreviations used in this paper:** EBM, endoscopic biliary manometry; ERCP, endoscopic retrograde cholangiopancreatography; GE, General Electric; E45/60, per cent biliary emptying at 45/60 minutes; SOD, sphincter of Oddi dysfunction; SOBP, sphincter of Oddi basal pressure; Tmax, time in minutes to maximal counts.

Department of  
Gastroenterology,  
Christchurch Hospital,  
Private Bag 4710,  
Christchurch, New  
Zealand  
P D Thomas  
B R Dobbs  
M J Burt  
B A Chapman

Department of  
Nuclear Medicine,  
Christchurch Hospital,  
Private Bag 4710,  
Christchurch, New  
Zealand  
J G Turner

Correspondence to:  
Dr M J Burt. Email:  
michael.burt@chmeds.ac.nz

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after cholecystectomy and (b) either one or two of the following objective findings suggesting partial common duct obstruction: common duct dilatation to more than 12 mm as determined by ERCP; delayed emptying of contrast medium during ERCP (longer than 45 minutes); and abnormal liver function tests (elevation of serum alkaline phosphatase or alanine aminotransaminase levels to greater than twice the upper limit of normal during or following an episode of pain). Type III patients were defined as those with typical pain but without any of the objective signs listed. All patients had previously been investigated with gastroscopy, ultrasonography, and ERCP to exclude concurrent gastrointestinal or pancreatic disease.

Eight of the 42 patients were excluded. In two cases EBM was not performed because of previous post-ERCP pancreatitis and in a further six patients the results of EBM were unsatisfactory because of either technical difficulties (four patients) or intolerance of the procedure (two patients). Four of the excluded patients had type II and four had type III SOD and the clinical characteristics of these patients did not differ significantly from the other patients. All but two of the remaining 34 patients included in the study were female and 25 had gall stones at the time of cholecystectomy. There were 21 type II patients (62%), of whom five had evidence of common duct dilatation, eight had delayed drainage of contrast at ERCP, and 15 had abnormal liver function tests.

INVESTIGATIONS

Biliary scintigraphy, with and without morphine provocation, was performed in all patients prior to EBM and the results were analysed by one physician (JT). The method has been described previously<sup>9</sup> but briefly, after an overnight fast, 100 MBq of <sup>99m</sup>Tc-DISIDA

were given intravenously (time 0). Imaging was performed with either a General Electric (GE) 400 XC/T or 400 AT gamma camera linked to a GE STARCAM 3000i computer. Data were recorded in one minute frames for 90 minutes in a 128 matrix with the patient supine. Regions of interest were drawn around the hepatobiliary system and background corrected time/activity curves were created by computer analysis after correction for radioactive decay. Results are expressed as Tmax (time in minutes from zero to maximum counts), E45 (per cent biliary emptying at 45 minutes—that is, activity cleared at 45 minutes as a percentage of the maximum counts in the region of interest) and E60 (per cent biliary emptying at 60 minutes). Scans with morphine provocation were performed in a similar manner subsequent to the initial scans allowing an interval of not less than 48 hours. Morphine (0.04 mg/kg in 10 ml of normal saline)<sup>13</sup> was given over five minutes intravenously immediately after administration of <sup>99m</sup>Tc-DISIDA.

Biliary manometry was performed by one operator (BC) using an Olympus (JF 140) duodenoscope and an Arndorfer pneumohydraulic perfusion system with a reservoir pressure of 750 mm Hg and a flow rate of 0.3 ml/min per channel. Standard polyethylene triple lumen catheters were used (Arndorfer ER3 or Wilson-Cook SOM-21-5-LEHMAN) with three side holes 2 mm apart. The sphincter of Oddi basal pressure was defined as the baseline pressure between phasic contractions minus the end expiratory duodenal pressure recorded between or in the absence of duodenal contractions. An average of the maximal basal pressures recorded by all three catheters as they were withdrawn across the sphincter was taken. Values were averaged over at least two pull throughs. All patients gave consent and were sedation with intravenous diazepam or midazolam.

STATISTICAL ANALYSIS

Statistical analysis of the results was performed using the Mann-Whitney U and  $\chi^2$  tests.

Results

Patients were divided into two groups: those with and without elevated sphincter of Oddi basal pressure (SOBP). An SOBP of greater than 40 mm Hg was considered abnormal.<sup>3 15 16</sup> Sixteen patients had a normal SOBP (group I) and 18 (nine type II, nine type III) had an elevated SOBP greater than 40 mm Hg (group II). The characteristics of the patients in these groups are shown in table 1.

The parameters for time/activity curves without morphine provocation are shown in table 2. There were no significant differences in Tmax, E45, or E60 between those with normal and those with elevated SOBP. There was, however, a trend towards a difference in Tmax between the two groups (p=0.07).

In contrast, using morphine provocation prior to <sup>99m</sup>Tc-DISIDA scanning, there was a significant difference between the two groups in Tmax (p=0.03), E45 (p=0.04), and E60 (p=0.002). E60 had the greatest ability to dis-

Table 1 Clinical characteristics of patients with normal (group I) and elevated (>40 mm Hg) (group II) sphincter of Oddi basal pressure

	Group I	Group II
n	16	18
Patients with type II SOD (No (%))	12 (75)	9 (50)
Age (y)	41 (27-64)	45 (30-74)
Time from cholecystectomy (y)	7.5 (0-22)	4.0 (0-30)
Symptom duration (y)	2.5 (0-22)	3.0 (0-20)
Sphincter of Oddi basal pressure (mm Hg)*	20.0 (5-37)	60.5 (45-250)

Values are median (range).

\*Significant difference.

Table 2 Time/activity curve parameters for <sup>99m</sup>Tc-DISIDA biliary scanning with and without morphine provocation in patients with normal (group I) and elevated (>40 mm Hg) (group II) sphincter of Oddi basal pressure

	Group I	Group II	p Value
n	16	18	
Without morphine provocation			
Tmax (minutes)	16 (12-29)	22 (10-63)	0.07
E45 (%)	37.2 (10.2-58.4)	26.7 (0-62.3)	0.2
E60 (%)	55.5 (30.1-70.5)	38.8 (0-74.5)	0.1
With morphine provocation			
Tmax (minutes)	30.5 (18-49)	39.5 (23-70)	0.03
E45 (%)	9.5 (0-24.9)	1.8 (0-33.7)	0.04
E60 (%)	28.2 (3.5-43.6)	4.9 (0-51.6)	0.002

Values are median (range).

Tmax refers to time to maximal activity and E45 and E60 refer to the percentage of maximal activity cleared (emptied) from the biliary system at 45 and 60 minutes, respectively.

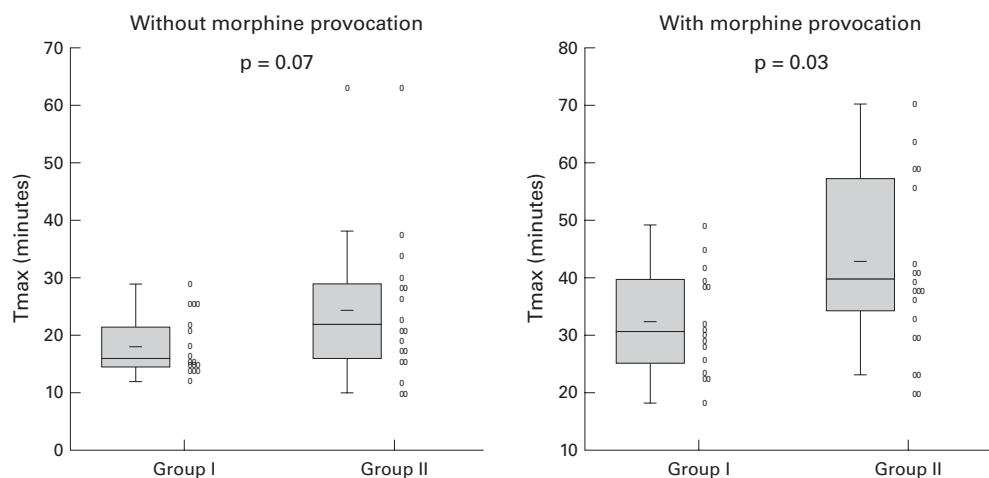


Figure 1 Time to maximal activity ( $T_{max}$ ) in patients with normal (group I) and elevated ( $>40$  mm Hg) (group II) sphincter of Oddi basal pressure after  $^{99m}\text{Tc}$ -DISIDA scanning, with and without morphine provocation. The shaded box indicates the interquartile range and the vertical line the upper and lower adjacent values (the upper or lower quartile  $\pm 1.5$  times the interquartile range).

criminate between those with normal and those with abnormal SOBP (table 2). These results are shown graphically for  $T_{max}$  (fig 1) and E60 (fig 2). Using an arbitrary cut off point for E60 of 15% as the lower limit of normal, only 3/16 patients with normal manometry had abnormal values for E60 compared with 15/18 patients with abnormal biliary manometry (sensitivity 83% and specificity 81%).

Thirteen of 18 patients with elevated SOBP complained of pain following morphine infusion. In contrast, only 2/16 patients with normal SOBP complained of pain ( $p=0.001$ ).

### Discussion

Subdivision of patients with suspected SOD into clinical types I, II, and III has proved useful.<sup>4</sup> Up to 90% of patients with type I SOD will have elevated SOBP<sup>17 18</sup> and, as the presence of an increased SOBP is predictive of a good response to sphincterotomy, this group may be selected for sphincterotomy without the need for biliary manometry. This clinical diagnosis becomes less reliable, however, when clinical types II and III are considered.

Between 16 and 86% of patients with type II will have elevated SOBP confirmed by EBM while in type III only 0–55% patients will have manometric abnormalities.<sup>17–21</sup> Our findings that 43% of type II and 69% of type III patients had abnormal SOBP are consistent with these previous reports. However, EBM is difficult to perform, is not widely available, and is associated with complications such as pancreatitis. A non-invasive method of predicting elevated SOBP would be of clinical benefit in selecting patients for endoscopic sphincterotomy without prior EBM.

$^{99m}\text{Tc}$ -DISIDA scanning has been used previously in the diagnosis of SOD.<sup>10 11 22 23</sup> Significant differences between patients with SOD and asymptomatic volunteers in  $T_{max}$ , E45, and E60 have been found.<sup>10 11</sup> However, these studies have largely been applied to type I patients. There is little information on the efficacy of this investigation in types II and III. In this study, which investigated only these clinical subgroups, no significant differences in the time/activity curves were observed between those with elevated and those with normal

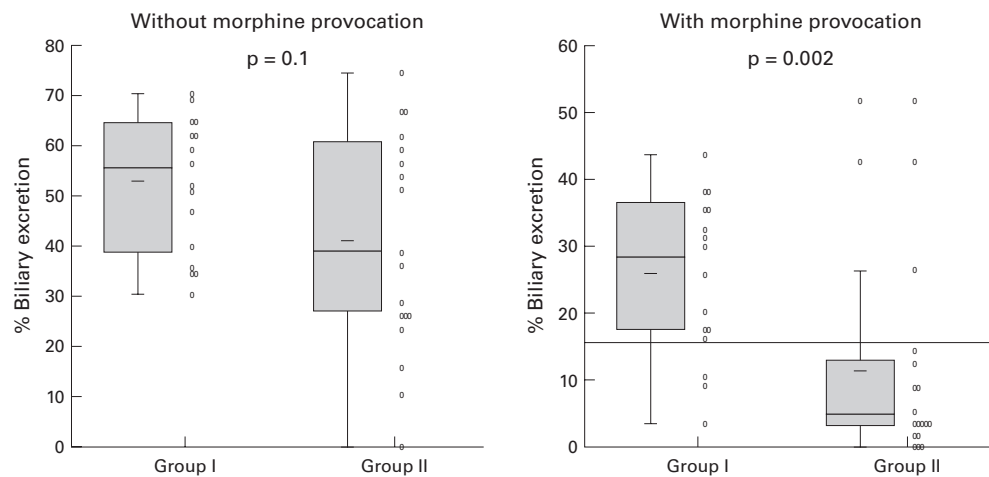


Figure 2 Percentage of maximal activity cleared from the biliary system at 60 minutes (E60) in patients with normal (group I) and elevated ( $>40$  mm Hg) (group II) sphincter of Oddi basal pressure after  $^{99m}\text{Tc}$ -DISIDA scanning, with and without morphine provocation. The shaded box indicates the interquartile range and the vertical line the upper and lower adjacent values (the upper or lower quartile  $\pm 1.5$  times the interquartile range).



SOBP using conventional <sup>99m</sup>Tc-DISIDA scanning. Our findings are supported by previous work in which no differences in Tmax, E45, or E60 were demonstrated in symptomatic manometric positive and negative type III patients, although significant differences between asymptomatic controls and patients with abnormal manometry were apparent in E45 and E60.<sup>22</sup> In contrast with our findings with conventional <sup>99m</sup>Tc-DISIDA scanning, morphine provocation differentiated between patients with normal and abnormal manometry in all three time/activity curve parameters. Morphine has complex effects on the sphincter of Oddi. In normal individuals it causes "spasm" of the sphincter, increasing common bile duct pressure, with increased phasic pressure waves, increased basal sphincter pressure, and phasic wave amplitude.<sup>13</sup> It has also been shown to reduce the flow of radiographic contrast into the duodenum.<sup>24 25</sup> This was confirmed by our findings that morphine provocation increased Tmax and reduced E45 and E60 in those individuals with normal SOBP. However, in patients with abnormal SOBP this effect was greatly enhanced. This was highly significant for E60, and using a lower limit of normal of 15%, sensitivity and specificity were 83% and 81%, respectively, for determining elevated SOBP in these patients. These results are comparable with those reported for DISIDA scanning in type I patients.<sup>10 23</sup>

Morphine injection was found to induce pain in patients with elevated SOBP. Morphine has previously been combined with neostigmine and used as a provocative test<sup>26-28</sup> although this was subsequently found to be of little clinical value. However, the close correlation between symptoms of pain, abnormal morphine augmented <sup>99m</sup>Tc-DISIDA scanning, and elevated SOBP suggests that morphine may be precipitating papillary spasm in this subgroup of SOD patients. This may represent a different mechanism of disease to that seen in type I SOD.

This study assumed that EBM is the "gold standard" in the diagnosis of SOD but this may not necessarily be true.<sup>4</sup> Cannulation of the sphincter of Oddi gives limited information on its physiology and may lead to pancreatitis. A non-invasive, dynamic provocation test such as <sup>99m</sup>Tc-DISIDA scanning may be advantageous in the investigation of patients with possible SOD, especially if spasm is suspected. Unfortunately, in this study we were unable to obtain information on the outcome of a number of patients who underwent sphincterotomy. Such an analysis of the response to sphincterotomy will help determine the value of morphine augmented <sup>99m</sup>Tc-DISIDA scanning in selecting patients who may benefit from intervention. However, the results of the study suggest that <sup>99m</sup>Tc-DISIDA scanning with morphine provocation is a useful non-invasive investigation for patients with types II and III sphincter of Oddi dysfunction to detect those with elevated SOBP who may respond to endoscopic sphincterotomy.

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