Health and Labour Sciences Research Grants, Japanese Ministry of Health, Labour and Welfare. We are indebted to Taeko Yamamoto for her technical assistance and to Dr Eishi Hara of Iida Hospital, Japan, for his clinical assistance.

T Umemura

Department of Internal Medicine, Division of Hepatology and Gastroenterology, Shinshu University School of Medicine, Matsumoto, Japan

Y Zen

Division of Pathology, Kanazawa University Hospital, Kanazawa, Japan

H Hamano, T Ichijo

Department of Internal Medicine, Division of Hepatology and Gastroenterology, Shinshu University School of Medicine, Matsumoto, Japan

S Kawa

Centre for Health, Safety and Environmental Management, Shinshu University, Matsumoto, Japan

Y Nakanuma

Department of Human Pathology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan

K Kiyosawa

Department of Internal Medicine, Division of Hepatology and Gastroenterology, Shinshu University School of Medicine, Matsumoto, Japan

Correspondence to: Dr Takeji Umemura, Department of Internal Medicine, Division of Hepatology and Gastroenterology, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan; t-ume@hsp.md.shinshu-u.ac.jp

doi: 10.1136/gut.2007.122283

Conflict of interest: None declared.

References

- 1 Hamano H, Kawa S, Horiuchi A, *et al*. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001;**344**:732-8.
- 2 Zen Y, Harada K, Sasaki M, *et al*. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? *Am J Surg Pathol* 2004;**28**:1193-203.
- 3 Alvarez F, Berg PA, Bianchi FB, *et al*. International Autoimmune Hepatitis Group report: review of criteria for diagnosis of autoimmune hepatitis. *J Hepatol* 1999;**31**:929-38.
- 4 Umemura T, Zen Y, Hamano H, *et al*. IgG4-hepatopathy: association of IgG4-bearing plasma cells in liver with autoimmune pancreatitis. *Hepatology*, (in press).

The morphine-prostigmine provocation (Nardi) test for sphincter of Oddi dysfunction: results in healthy volunteers and in patients before and after transduodenal sphincteroplasty and transampullary septectomy

Sphincter of Oddi dysfunction is a complex and poorly understood syndrome that usually manifests as pain of apparently biliary or pancreatic origin in the absence of an organic cause after conventional investigations. Transduodenal sphincteroplasty with transampullary septectomy (TDS/TAS) is a therapeutic option.¹ Although biliary manometry is the gold standard diagnostic test, the morphine-prostigmine provocation (Nardi) test is

sometimes used to screen patients. A fourfold increase in either serum amylase or lipase and reproduction of pain after intramuscular injection of 10 mg morphine (to induce sphincteric spasm) and 1 mg prostigmine (to stimulate pancreatic exocrine secretions) is considered a positive test.^{2,3} However, the enzymatic changes may also occur in healthy subjects and in patients with irritable bowel syndrome,^{3,4} bringing the clinical value of the test into question. Conversely, when the Nardi test was carried out on 70 patients with chronic abdominal pain, enzyme elevation was detected in only 23 patients (33%), 16 (70%) of whom had ampullary stenosis.⁵

We undertook these studies to characterise the response to the Nardi test in 20 healthy young adult subjects and 24 patients with sphincter of Oddi dysfunction before and after TDS/TAS. Our diagnosis of sphincter of Oddi dysfunction was based on clinical history,

HIDA scanning, cross sectional imaging, endoscopic retrograde cholangiopancreatography, and exclusion of luminal pathology. All patients had significant debilitating upper abdominal pain requiring regular strong analgesia and had a poor quality of life. Patients were Milwaukee class I or II and had microscopic stenosis/fibrosis, but biliary manometry was not done routinely. We excluded from the healthy subject study those with recurrent abdominal pain, gallstones, or previous abdominal surgery, and those on regular medicines or with allergies.

Subjects abstained from alcohol for at least 24 hours. After sampling blood for baseline concentrations of amylase and lipase, subjects were given 1 ml of 0.9% saline intramuscularly as a sham test. Blood was resampled one hour after this injection. Subjects were then given 10 mg morphine and 1 mg prostigmine intramuscularly simultaneously and blood samples were

Figure 1 Scatter plot showing maximum increase in serum amylase (top) and lipase (bottom) over baseline values one hour after the sham test and after provocation with morphine and prostigmine in healthy subjects. The baseline value has arbitrarily been defined as 1 and increases are shown as multiples of the baseline value. The dashed line represents 4× baseline. A smaller than fourfold increase over baseline in both amylase and lipase was seen in only four of the 20 subjects.

Figure 2 Scatter plot showing maximum increase in serum amylase (top) and lipase (bottom) over baseline values after provocation with morphine and prostigmine before and after transduodenal sphincteroplasty and transampullary septectomy in 24 patients with sphincter of Oddi dysfunction. The baseline value has arbitrarily been defined as 1 and increases are shown as multiples of the baseline value. The dashed line represents 4× baseline. The differences between the maximum post-provocation enzyme concentrations in the preoperative period (median (interquartile range) amylase = 155 (92 to 339) U/l, lipase = 1283 (604 to 2994) U/l) and the postoperative period (amylase = 69 (50 to 136) U/l, lipase = 214 (74 to 971) U/l) were significant ($p = 0.002$ for amylase and 0.005 for lipase, Wilcoxon signed ranks test).

collected hourly for five hours. Abdominal pain was quantified using visual analogue pain scores. Reference ranges were 23 to 300 U/l for serum lipase and 30 to 110 U/l for serum amylase. The 24 patients subsequently underwent TDS/TAS and the Nardi test was repeated 12 months postoperatively. The gastrointestinal quality of life index (GIQLI)⁶ was measured preoperatively and 12 months postoperatively. The two studies were approved by the ethics committees of the University of Nottingham Medical School and Nottingham University Hospitals. Informed written consent was obtained.

The median (range) age of the 14 male and six female volunteers was 21 (18 to 23) years. Serum lipase and amylase concentrations

increased more than fourfold over baseline in 15 (75%) and 13 (65%) healthy subjects, respectively, after morphine–prostigmine provocation. The median (interquartile range) baseline and maximum post-provocation concentrations of serum lipase were 120 (74 to 138) and 2930 (344 to 7824) U/l, respectively; corresponding values for serum amylase were 61 (44 to 81) and 220 (91 to 545) U/l ($p < 0.001$, Wilcoxon signed ranks test). Figure 1 shows the maximum increase in enzymes over baseline for each subject, none of whom experienced pain during the study.

The median (range) age of the three male and 21 female patients was 42 (25 to 64) years. The post-provocation enzymatic increases were significantly greater preoperatively than post-

operatively (fig 2). Preoperatively, 21 of the 24 patients (87.5%) had a greater than fourfold increase in amylase or lipase or both after morphine–prostigmine provocation, compared with 12 (50%) postoperatively ($p = 0.01$, χ^2 test with Yates' correction). While pain was reproduced after pharmacological provocation in 20 patients (83%) preoperatively, this occurred in only four (17%) postoperatively. The mean (95% confidence interval) GIQLI score improved from 61 (55 to 66) preoperatively to 92 (82 to 102) postoperatively ($p < 0.0001$). Twelve months postoperatively, eight patients (33%) were symptom-free and 12 (50%) had reduced analgesia requirement. Four patients (17%) with no improvement also had a positive postoperative Nardi test.

In healthy volunteers increases in serum lipase and amylase after the Nardi test lack specificity. In patients with sphincter of Oddi dysfunction, pain is a universal accompaniment of enzyme elevation after the Nardi test. TDS/TAS significantly obtunds the enzymatic and nociceptive responses to the Nardi test in only 50% of patients with sphincter of Oddi dysfunction. The lack of specificity of the Nardi test makes it unsuitable as an objective diagnostic test for this condition.

D N Lobo, A S Takhar, A Thaper, M G Dube, B J Rowlands

Division of Gastrointestinal Surgery, Wolfson Digestive Diseases Centre, Nottingham University Hospitals, Queen's Medical Centre, Nottingham, UK

Correspondence to: Mr Dileep N Lobo, Division of Gastrointestinal Surgery, E Floor, West Block, Nottingham University Hospitals, Queen's Medical Centre, Nottingham NG7 2UH, UK; Dileep.Lobo@nottingham.ac.uk

doi: 10.1136/gut.2007.126375

Conflict of interest: None declared.

References

- 1 **Moody FG**, Becker JM, Potts JR. Transduodenal sphincteroplasty and transampullary septectomy for postcholecystectomy pain. *Ann Surg* 1983;**197**:627–36.
- 2 **Nardi GL**, Acosta JM. Papillitis as a cause of pancreatitis and abdominal pain: role of evocative test, operative pancreatography and histologic evaluation. *Ann Surg* 1966;**164**:611–21.
- 3 **LoGiudice JA**, Geenen JE, Hogan WJ, et al. Efficacy of the morphine–prostigmine test for evaluating patients with suspected papillary stenosis. *Dig Dis Sci* 1979;**24**:455–8.
- 4 **Steinberg WM**, Salvato RF, Toskes PP. The morphine–prostigmine provocative test – is it useful for making clinical decisions? *Gastroenterology* 1980;**78**:728–31.
- 5 **Gregg JA**, Taddeo AE, Milano AF, et al. Duodenoscopy and endoscopic pancreatography in patients with positive morphine prostigmine tests. *Am J Surg* 1977;**134**:318–21.
- 6 **Eypasch E**, Williams JL, Wood-Dauphinee S, et al. Gastrointestinal quality of life index: development, validation and application of a new instrument. *Br J Surg* 1995;**82**:216–22.

Urine based detection of intestinal mucosal cell damage in neonates with suspected necrotising enterocolitis

Necrotising enterocolitis (NEC) is a severe gastrointestinal disease with a mortality of 20–40%, affecting predominantly premature neonates.¹ In the early phase of the disease NEC continues to present a diagnostic challenge