Evaluation of a tubeless pancreatic function test in patients with steatorrhoea in a district general hospital

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Summary

The Pancreolauryl Test (PLT), a tubeless pancreatic function test, has been evaluated in an unselected series of outpatients with steatorrhoea presenting to a district general hospital (DGH). This is the first study of the PLT in a DGH, involving an unselected series of patients and not those from secondary or tertiary referral hospitals. Healthy controls ($n=15$) and patients with self-limiting diarrhoea ($n=8$) had normal urinary excretion indices ($\geqslant 30$). Coeliac disease ($n=13$) and small bowel bacterial overgrowth ($n=12$) were the commonest causes of steatorrhoea and there were no false-positive results in these patients. The mean urinary excretion index in patients with untreated coeliac disease (mean index=38%) was lower than in healthy controls ($n=15$, mean index=53%; $P<0.05>0.02$). No patient with proven pancreatic steatorrhoea had a normal PLT result, confirming the high negative predictive value found by others[1]. Low results in patients with steatorrhoea following gastric surgery indicate poor mixing of food with pancreatic juices. The PLT proved to be a simple, inexpensive and noninvasive outpatient screening test suitable for use in a DGH to exclude a pancreatic origin of steatorrhoea.

Introduction

The ready exclusion of a pancreatic origin of steatorrhoea by use of a simple test would be welcomed by the physician in a district general hospital (DGH) with limited investigatory facilities at his disposal. The Pancreolauryl Test (PLT), only available commercially in the UK since 1985, is a tubeless test of pancreatic exocrine function which is easily performed by the patient, requires standard laboratory equipment for analysis, is inexpensive and which appears to have a high negative predictive value[1]. Studies to date have been largely undertaken in specialist referral centres[2,3]. For these reasons a prospective evaluation of the PLT was undertaken in a DGH serving a population of 167 000.

The PLT is based on the hydrolysis of fluorescein from a conjugate of dilauric acid and fluorescein by pancreatic esterases[4]. The amount of fluorescein excreted in the urine in a fixed period (10 hours) following ingestion of the conjugate with a standard breakfast reflects pancreatic esterase activity. The test incorporates an internal control whereby the amount of fluorescein liberated after ingestion of the conjugate is compared with that excreted after fluorescein alone is ingested, thus necessitating urine collection on two consecutive days. The result is expressed as the percentage ratio of urinary fluorescein excretion on the test and control days (T/K ratio). A value greater than 30% is taken to indicate normal pancreatic exocrine function and below 20% as indicative of exocrine insufficiency. Results of 20-30% are considered non-diagnostic[5].

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Methods

The PLT was carried out according to the manufacturer's instructions (International Laboratories, Alton). Particular attention was paid to giving each patient verbal instructions, which were reinforced by a typewritten instruction sheet. The importance of closely following the directions concerning fluid intake was stressed. The results of PLTs with 10-hour urine volumes of less than 600 ml are excluded from this study. Patients taking pancreatic supplements were asked to stop these during, and for 48 hours before, the test. Sulphasalazine was similarly withheld.

Over a 3-year period patients attending a general medical and gastroenterology outpatients' clinic at a DGH were studied. In the absence of an available quantitative laboratory estimation of faecal fat excretion, the confirmation of clinically suspected steatorrhoea was based upon the semi-quantitative Nile Blue test[6]. Nile Blue reacts with faecal oleates in an alkaline solution to give a colour the intensity of which is proportional to the concentration of fat. The result is recorded as +, ++ or +++. A result of ++ or +++ indicates more than 5 or 10 g fat/100 g faeces respectively. Additional information concerning fat absorption was obtained in some patients by measurement of the rise in serum lipids after a fatty test meal[7].

Statistical comparisons were made using a two-tailed Mann-Whitney U test or the Wilcoxon matched-pairs signed-ranks test[8].

Patients

Fifteen healthy controls and 55 patients were studied. The controls were asymptomatic hospital staff (8 female; age range 22-53; average age 38). Eight additional patients presenting with diarrhoea but without steatorrhoea were also studied. These patients were diagnosed as having the irritable bowel syndrome or self-limiting diarrhoea of undetermined cause (6 female; age range 49-82; average age 65).

Fourteen patients with coeliac disease were studied (11 female; age range 20-82; average age 50). In 10 a PLT was performed both before and an average of 3.5 months (range 3-6 months) after starting a gluten-free diet (GFD).

Small bowel bacterial overgrowth was diagnosed in 12 patients (10 female; age range 26-80; average age 55). Steatorrhoea, defined as a positive Nile Blue test, was present in all of these patients and all showed

a clear clinical response to either metronidazole or oxytetracycline.

Seven patients with pancreatic disease were studied (3 female; age range 41-73; average age 60). A diagnosis of chronic pancreatitis was made in 6 (at laparotomy in 2 and on the basis of radiological pancreatic calcification in 4). Five of these patients had steatorrhoea. Carcinoma of the pancreas in a patient presenting with steatorrhoea was confirmed at postmortem. Steatorrhoea was defined as the presence of an abnormal Nile Blue test (5 out of 7 patients), abnormal fat absorption test (3 out of 4 patients tested) or both (2 patients).

Five patients with small bowel Crohn's disease and another with a short bowel syndrome following surgery for Crohn's disease were studied (2 female; age range 23-57; average age 39). Steatorrhoea (positive Nile Blue test) was present in all patients. Four patients with steatorrhoea (positive Nile Blue test) due to previous gastric surgery and responding to Pancrex were studied (2 female; age range 64-75; average age 70). Two patients had undergone vagotomy and pyloroplasty and two partial gastrectomy (one Polya and one Billroth I).

PLTs were carried out in 4 patients who had previously undergone cholecystectomy (all female; age range 26-53; average age 43). The additional diagnoses in these patients were bacterial overgrowth (2), recent acute pancreatitis (1) and functional abdominal pain (1).

Results

The results of the urinary excretion index (T/K ratio) in all patients studied are shown in Figure 1. Thirteen out of 15 healthy controls and all 8 patients with the irritable bowel syndrome or self-limiting diarrhoea had a fluorescein excretion index greater than 30%. Two control subjects had an excretion index of 18% and 28% respectively. On repeating the test these subjects produced excretion indices of 30% and 40% respectively.

Five out of 6 patients with pancreatic steatorrhoea had an excretion index of less than 20% (4-16%) and one patient, with alcoholic chronic pancreatitis, an index of 33%. This patient had undergone laparotomy for suspected carcinoma of the pancreas and a cholecystoduodenostomy performed. Repeat testing confirmed the presence of steatorrhoea with a urinary excretion index of 10%. One patient with chronic pancreatitis diagnosed at laparotomy did not have steatorrhoea and had an excretion index of 49%.

Patients with untreated coeliac disease (n=13) tended to have a lower excretion index than healthy controls (mean index 38% and 53% respectively;

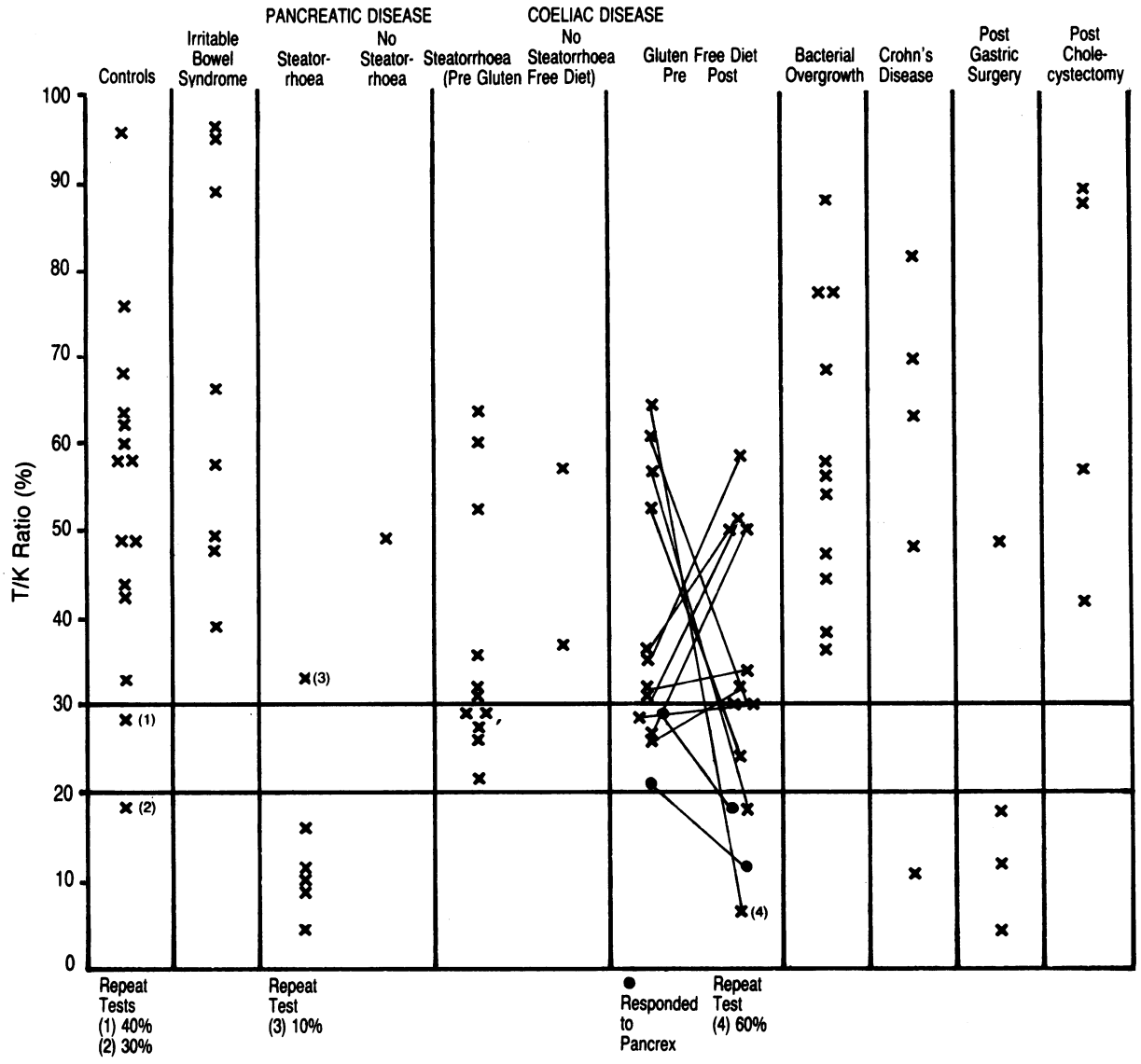

Figure 1. Pancreolauryl Test result in healthy controls, patients with diarrhoea and patients with steatorrhoea

$P<0.05>0.02$) but in no patient was this less than 20%. In 11 patients there was no consistent change in the excretion index after treatment with a GFD (mean excretion index before and after GFD 38% and 32%; $P>0.05$). One patient with mild asymptomatic steatorrhoea and subtotal villous atrophy on jejunal biopsy had a urinary excretion index of 64% before a GFD. On repeat testing 3.5 months after commencing a GFD the index was 7%; a further PLT carried out one month later gave an excretion index of 60%.

Three of these coeliac patients were considered to have coexistent pancreatic insufficency. In one, despite compliance with a GFD for 11 years and normal duodenal biopsies, mild impairment of the oral fat absorption test persisted and her PLT urinary excretion index was 4%. Following the addition of pancreatic supplements her stools became formed, she gained weight and there was overall clinical improvement. An 82-year-old woman presenting with marked steatorrhoea and anaemia due to combined iron and folate deficiency with severe partial villous atrophy responded to a GFD. Repeated PLTs gave urinary excretion indices of 29% (before GFD), 12% and 23%. She improved with weight gain, decreased stool frequency and a rising haemoglobin. Only following the introduction of Pancrex, however, did her bowels return fully to normal. A third patient, with biopsy-proven coeliac disease and total ulcerative colitis in remission, made a good response to a strict GFD but continued to have mild steatorrhoea and stool frequency. Urinary excretion index before a GFD was 21% and after a GFD 9% and 15%. It was only following treatment with Pancrex, 8 months after commencing a GFD, that stool frequency and steatorrhoea ceased and he gained a further 12 kg.

All patients with bacterial overgrowth and 4 out of 5 with Crohn's disease had a urinary excretion index above 20%. Two patients with bacterial overgrowth had results of 24% and 27% when initially tested, with results of 37% and 48% on re-testing. One patient with extensive jejunoileal Crohn's disease and mild steatorrhoea had a urinary excretion index of 11%.

Three out of 4 patients with steatorrhoea following gastric surgery had an excretion index of less than 20%. In the fourth patient repeat PLTs gave results of 24%, 28%, 48% and 50%. The excretion index was normal in 2 other patients, without steatorrhoea, following vagotomy and pyloroplasty (1) and vagotomy and gastrojejunostomy (1).

A normal urinary excretion index was found in all 4 patients who had undergone previous cholecystectomy (2 of these patients appear in the bacterial overgrowth category also).

Discussion

The PLT proved easy for patients to carry out provided it was reinforced by adequate written and verbal instructions[9]. The test appears particularly suitable for use with outpatients and can be repeated readily. In common with the experience of Barry[10], we found this test to be more accurately performed on outpatients than on the ward. Performing the two parts of the test on consecutive days, rather than with a longer interval[1], did not impair the accuracy of determination of the urinary fluorescein excretion index. Those patients who worked could conveniently perform the test over a weekend.

The majority of patients in this study had steatorrhoea. In the absence of quantitative faecal fat estimations, use was made of the semi-quantitative Nile Blue test as a measure of faecal fat excretion. It is in patients with steatorrhoea that exclusion of pancreatic disease is necessary and often difficult without invasive inpatient tests. In this study the single commonest cause of steatorrhoea proved to be coeliac disease. The urinary excretion index was greater than 20% in all patients with coeliac disease with the exception of 3 with coexistent pancreatic insufficiency, the presence of which we consider to be supported by the clinical features already detailed and which is a recognized association[11-16]. The apparently high incidence of coexistent coeliac disease and pancreatic insufficiency (3 out of 14 cases) may have occurred by chance. Alternatively it may be an accurate reflection of a truly greater coexistence of these two diseases than has previously been recognized. A willingness to seek residual degrees of steatorrhoea because of the greater simplicity of the Nile Blue test compared to a three-day faecal fat collection may have contributed to the detection of pancreatic insufficiency in this situation.

The lower urinary excretion index in patients with untreated coeliac disease reflects the deficient, but reversible, release of cholecystokinin-pancreozymin (CCK-PZ) and secretin from the upper small intestinal mucosa[17,18] which occurs in this group of patients. This results in decreased pancreatic stimulation and gallbladder emptying[18], the latter contributing to a reduced urinary excretion index in the PLT[19]. This would not explain the failure of the urinary excretion index to return to control levels in treated coeliac disease, given that secretin[17] and CCK[18] profiles return to normal after a GFD. Similarly end-organ unresponsiveness to hormonal stimulation would not appear to be a factor[20].

Five out of 6 patients with proven pancreatic disease and steatorrhoea had urinary excretion indices of below 20%. When the PLT was repeated in the sixth patient a result of 10% was obtained compared to 33% on initial testing. These findings support the predictive value of a low PLT result in pointing towards a pancreatic cause of steatorrhoea.

In patients with steatorrhoea due to Crohn's disease ($n=5$) and bacterial overgrowth ($n=12$), only one PLT test result was below 20%. This gives an incidence of false-positive results of 6% in this group. This false-positive result was in a patient with very extensive small bowel Crohn's disease in whom steatorrhoea was mild; the presence of small bowel disease was obvious clinically and radiologically and there was little to suggest the presence of pancreatic disease. Failure of pancreatic stimulation as a result of impaired release of secretin and CCK coupled with rapid intestinal transit could explain this result. Alternatively this low result could indicate true pancreatic unresponsiveness in keeping with the reduced enzyme response to intravenous secretin in 8 out of 26 patients with jejunoileal Crohn's disease found by Dreiling[21].

The low urinary excretion index in 3 out of 4 patients with steatorrhoea after gastric surgery is not surprising. These results are similar to those of Braganza's group[19] who found an excretion index of less than 20% in 4 out of 7 patients after gastric surgery. The PLT is an integrated test of digestion rather than of pure pancreatic function, and the low results in these patients reflect poor mixing of food with pancreatic juices which occurs as a consequence

of the surgery. If this effect of gastric surgery on the PLT is remembered, then a low urinary excretion index will not be misinterpreted as a false-positive result. The results of the present study do not suggest that cholecystectomy alone significantly affects the PLT[19].

In 2 patients with small bowel disease it proved impossible to obtain adequate urine collection volumes even with repeated attempts. This occurred in 2 patients with steatorrhoea, one with coeliac disease and one with a blind loop syndrome due to a caecal carcinoma. Recent studies[22,23] suggest that this problem may be overcome by studying serum, as opposed to urinary, fluorescein levels. Three patients in our study (2 controls and one coeliac on a GFD) had abnormal or borderline urinary excretion indices which were normal on repeat testing. The coefficient of variation of the PLT in healthy controls appears high[24] and the reproducibility of the test in patients with steatorrhoea of pancreatic and other origins needs to be assessed. It must be stressed, as with all laboratory tests, that the PLT must be interpreted in a clinical context coupled with a willingness to repeat the test if appropriate.

It is concluded that, providing adequate attention is paid to patient instruction, helpful results can easily and inexpensively be obtained with the PLT in patients with steatorrhoea. Difficulty was occasionally experienced in obtaining adequate urine collection volumes in patients with small bowel disease, which could often be overcome by repeating the test. In one patient with jejunal Crohn's disease an unexpectedly low PLT test result was obtained but because of the clinical circumstances this was not misleading. A low test result in patients with steatorrhoea after gastric surgery may point to a functional pancreatic insufficiency which may respond to pancreatic supplements.

False-positive results were not obtained in patients with untreated coeliac disease or small bowel bacterial overgrowth, which proved to be the commonest causes of steatorrhoea in this study. This high negative predictive value of the test has been found by others[1]. The specificity of the PLT was 91%. There were too few patients with pancreatic steatorrhoea in this study for the calculated values for sensitivity (83%), negative predictive power (95%) and positive predictive power (71%) to be considered accurate.

The PLT has proved to be a valuable investigation in the initial assessment of the patient with steatorrhoea presenting to a district general hospital.

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