Serum and pancreatic juice carcinoembryonic antigen in pancreatic and biliary disease

D L CARR-LOCKE*

From the Department of Medicine, University of Leicester, Leicester General Hospital, Leicester

SUMMARY Serum and pancreatic juice carcinoembryonic antigen (CEA) concentrations were studied in a group of 144 patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) with a variety of benign and malignant pancreatic and biliary diseases. Serum CEA was found to be a poor diagnostic and discriminating marker for pancreatic disorders and was raised in obstructive jaundice from various causes correlating with serum alkaline phosphatase. A pancreatic juice CEA concentration of greater than 106 mcg/l was associated with pancreatic disease but did not distinguish benign from malignant lesions. Criteria derived from pancreatic juice volumes and bicarbonate responses provided additional diagnostic differentiation of normal from pancreatic disease but not cancer from pancreatitis. Pancreatic juice CEA may have a limited application where imaging techniques have failed or are not available and additional study of pancreatic juice biochemistry is required before adequate diagnostic criteria can be established.

After carcinoembryonic antigen (CEA) was demonstrated in pancreatic juice by direct endoscopic cannulation of the pancreatic duct,^{1,2} it was suggested that values of CEA so obtained could be used to diagnose pancreatic disease and perhaps differentiate chronic pancreatitis from pancreatic cancer.^{3,4} Duodenal juice CEA has also been measured during evocative tests of pancreatic function⁵ with little additional diagnostic benefit.^{6,7} Although raised circulating CEA is present in a high percentage of patients with pancreatic cancer,⁸⁻¹¹ serum CEA alone has been shown to be of limited diagnostic value in the investigation of suspected pancreatic disease.^{4,12,13} It is also known to rise in benign pancreatic disease,^{12,14} biliary obstruction,¹⁵ a variety of liver conditions,¹⁶ as well as colonic disease and various benign and malignant gastrointestinal and non-gastrointestinal disorders.¹⁷

In an attempt to clarify the position of CEA a prospective study was undertaken to assess the diagnostic benefit of measuring serum and pancreatic juice CEA in conjunction with pancreatic juice biochemistry in patients suspected of having pancreatic or biliary disease.

Methods

PATIENTS

One-hundred-and-forty-four patients referred to the Leicester Area Endoscopy Unit for endoscopic retrograde cholangiopancreatography (ERCP) were studied and all gave informed consent to undergo a preliminary endoscopy at which pancreatic juice was collected. Subsequent ERCP was performed as a separate procedure and followed juice collection within seven days. This study was approved by the Leicester Area Health Authority Ethics Committee. The patients were divided into five diagnostic groups on the basis of standard investigations, ERCP, operation, follow-up, or post-mortem findings.

Group N (normal pancreas) consisted of 37 patients with no demonstrable pancreatic disease but included a gastric ulcer in one, duodenal ulcer in eight, atrophic gastritis in one, gallstones confined to the gallbladder in five without evidence of active cholecystitis, drug-induced pyrexia in one, previous cholecystectomy in three, vagotomy and pyloroplasty in one, and no gastrointestinal disease in the remaining 17. Serum levels of bilirubin, alanine transaminase, gamma-glutamyl transferase, and alkaline phosphatase for this and other groups are summarised in Table 1.

Group N+BC (normal pancreas + benign chole-

*Address for correspondence: Dr D L Carr-Locke, Department of Medicine, Clinical Sciences Building, Leicester Royal Infirmary, PO Box 65, Leicester LE2 7LX.

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stasis) consisted of 32 patients with cholestasis from benign causes but no detectable pancreatic abnormality. Cholestasis was extrahepatic in 25, due to common duct stones in all, and intrahepatic in seven, due to nitrofurantoin (Furadantin) in one, imipramine (Tofranil) in two, amitriptyline (Tryptizol) in one, Caroli's disease in one, and cryptogenic cirrhosis in two.

Group N+MC (normal pancreas+malignant cholestasis) consisted of 10 patients with no detectable pancreatic abnormality but cholestasis due to malignant non-pancreatic bile duct obstruction. This was due to bile duct cancer in eight and ampullary cancer in two.

Group PCa consisted of 29 patients with pancreatic cancer of whom 22 were jaundiced from direct bile duct involvement from cancer in the head of the gland. The other seven cancers were located in the body of the pancreas.

Group P consisted of 36 patients with pancreatitis with two or more of the following features: a clinical history of chronic continuous or relapsing pancreatic pain; more than two documented attacks of acute pancreatitis; a previous operative diagnosis of pancreatitis; pancreatic calcification on plain abdominal radiography; steatorrhoea responding to pancreatic enzyme replacement therapy; a diagnostic Lundh test meal, or a positive ERCP. Ten had steatorrhoea, nine had chronic continuous pain, four had diabetes mellitus, and 16 had recurrent attacks of acute pancreatitis. Pancreatitis was alcohol-related in 12, nine had gallstones, and in 15 no aetiological factors could be elucidated.

TECHNIQUE

Under diazepam (Valium, Roche) sedation and local pharyngeal anaesthesia (Xylocaine spray,

Astra) the papilla of Vater was cannulated using an Olympus JFB2 duodenoscope and a standard ERCP catheter. No glucagon or anticholinergic drugs were used and pancreatic juice flow was stimulated by a single intravenous bolus of 50 CHR units Boots secretin (Boots, Nottingham), which represented a submaximal stimulus of 0.8 to 0.9 CHR U/kg body weight. Samples were collected for five minutes by gentle aspiration with a 10 ml syringe attached to the catheter. Venous blood for serum CEA was taken before any drugs were administered and again at the completion of the pancreatic juice collection. Juice samples and serum were frozen immediately without the addition of aprotinin (Trasylol) and stored at -20°C until assayed for CEA activity by a double antibody radioimmunoassay modified from a previously described method.¹⁸ Samples were assayed neat, without perchloric acid extraction or addition of a proteolytic inhibitor in 100 mcl triplicates. Samples with a high CEA content were diluted with 0.1% albumen phosphate buffer and 100 mcl background pooled normal human serum was added to standards and diluted samples. After addition of goat anti-CEA antiserum (ACE 36) samples were incubated at 37°C for one hour. Labelled CEA was added and tubes incubated for another hour at 37°C . After addition of horse antiserum (BW 402) tubes were incubated for 18 hours at 4°C . The buffer used in this assay contained 0.1% albumen phosphate buffer, 0.04M phosphate, 0.04M saline, 0.01% merthiolate, and 0.3% EDTA. Tubes were finally filtered and counted.

Pancreatic juice volumes were recorded, juice bicarbonate was assayed by a pCO_2 electrode method¹⁹ using a Radiometer E5036 electrode, and juice protein was measured by UV spectro-

Table 1 Serum bilirubin and liver enzyme results in five diagnostic groups

Group	Bilirubin (mcml/l)	Gamma-glutamyl transferase (IU/l)	Alkaline phosphatase (IU/l)	Alanine transaminase (IU/l)
N (37)	12.2 (8-16)	26.1 (2-50)	196.0 (167-277)	22.4 (3-31)
N+BC (32)				
Extrahepatic cholestasis (25)	140.6 (31-590)	480.0 (57-1530)	786.7 (323-2170)	155.7 (46-673)
Intrahepatic cholestasis (7)	137.9 (37-435)	128.4 (42-326)	663.6 (304-1125)	233.0 (41-673)
N+MC (10)	235.0 (48-350)	919.0 (89-4060)	1697.9 (404-3900)	86.3 (43-233)
PCa (29)				
Jaundiced (22)	286.3 (32-702)	682.3 (68-1610)	1754.6 (575-3355)	147.2 (37-437)
Not jaundiced (7)	15.0 (10-17)	39.0 (11-50)	206.0 (150-280)	13.0 (10-23)
P (36)	13.8 (8-16)	62.0 (14-166)	178.4 (28-286)	23.3 (13-40)

Values given are mean and range. Group abbreviations as in text; numbers in each group shown in parentheses. Groups N+BC and PCa are subdivided as shown. Normal limits for our laboratory are as follows: bilirubin <17 mcml/l, gamma-glutamyl transferase <50 IU/l, alkaline phosphatase 60-260 IU/l, alanine transaminase <35 IU/l.

photometry²⁰ using a Unicam SP 1800 spectrophotometer.

Results

Serum and pancreatic juice CEA results showed a skewed distribution in all groups and statistical comparisons were therefore made using the *t* test after logarithmic transformation. For clarity, however, the accompanying figures show untransformed data only. Other serum and pancreatic juice data were compared using the *t* test without transformation.

Serum CEA was measured in 142 patients, there being one patient from group N+BC and one from group P where no value was available. Patients in group N had serum CEA values of 10.3 mcg/l or less (Fig. 1) in keeping with the normal range for the assaying laboratory (Professor K D Bagshawe, personal communication). This upper limit of 10 mcg/l was derived from 150 samples from a

mixed group of patients with non-malignant disorders.

Significantly raised levels were found in group N+BC (range 0.5 to 18 mcg/l, $P < 0.005$), N+MC (range 0.5 to 125 mcg/l, $P < 0.001$) and PCa (range 0.5 to 64 mcg/l, $P < 0.005$) compared with group N. There was no difference between CEA concentrations in patients with intrahepatic cholestasis (range 7 to 14 mcg/l) and extrahepatic cholestasis (range 0.5 to 18 mcg/l) in group N+BC. There was, however, a great overlap between groups and only six of 31 (19%) patients in group N+BC, five of 10 (50%) patients in group N+MC, and nine of 29 (31%) patients in group PCa had values above 10 mcg/l. There was no significant difference between patients with benign cholestasis or malignant bile duct obstruction when the bile duct and pancreatic cancer patients were compared separately with group N+BC. When taken together, however, 13 of 39 (33%) patients with malignant obstruction had levels greater than 10 mcg/l compared with six of 31 (19%) with benign cholestasis, but this was not a significant difference. Overall serum CEA was significantly higher in jaundiced patients ($P < 0.005$) compared with non-jaundiced patients but there was no correlation with bilirubin or gamma-glutamyl transferase. A weak positive correlation was found between serum CEA and alkaline phosphatase ($r = 0.5$, $P < 0.05$). Values in group P (range 0.5 to 29 mcg/l) were not significantly different from group N and only three of 35 (9%) patients with pancreatitis had levels above 10 mcg/l. There was also no difference in serum CEA between patients with pancreatitis and non-jaundiced patients with pancreatic cancer.

Serum CEA levels taken after completion of pancreatic juice collection, between five and 15 minutes after secretin injection, showed no change from the initial values.

Pancreatic juice CEA results were available in 112 patients, 29 in group N, 24 in group N+BC, six in group N+MC, 24 in group PCa, and 29 in group P. Results from groups N (range 0.5 to 88 mcg/l), N+BC (range 0.5 to 106 mcg/l), and N+MC (range 1.0 to 102 mcg/l) showed no statistical differences (Fig. 2) and, as all had no demonstrable pancreatic abnormality, they were grouped together for comparison with the two pancreatic disease groups. The 59 patients in this amalgamated group had values in the range 0.5 to 106 mcg/l but there was a marked skewed distribution. Group PCa reached statistical significance ($P < 0.05$) when compared with the amalgamated group but group P did not. Six of the 24 (25%) patients in group PCa and 11 of the 29 (38%) patients in group P had juice levels above 106 mcg/l. These percentages

Fig. 1 Serum CEA levels (mcg/l) in the five diagnostic groups: N: normal pancreas; N+BC: normal pancreas and benign cholestasis; N+MC: normal pancreas and malignant cholestasis; PCa: pancreatic cancer; P: pancreatitis; ○: patients with cholestasis; ●: patients without cholestasis. Significance of statistical difference from group N shown below groups. NS: not significant.

Fig. 2 Pancreatic juice CEA results (mcg/l) in the five diagnostic groups. Abbreviations as in text and Fig. 1. ○: presence of cholestasis; ●: patients without cholestasis.

were not significantly different from each other. Thus 17 of 53 (32%) patients with pancreatic disease had pancreatic juice CEA concentrations above the amalgamated group range. There was no relationship between juice CEA and the length of pancreatic duct obstructed by cancer as shown at ERCP. Three of the patients in group P showed very high levels of 1978, 5369, and 11 736 mcg/l but, as a group, there was no significant difference from group PCa. These three patients all had acute relapsing pancreatitis but there were no clinical or investigative differences between them and the remainder of the group with similar patterns of pancreatitis. The timing of juice collection for these patients was also no different from the others.

The results of five minute pancreatic juice volumes, maximum bicarbonate concentrations, bicarbonate outputs, maximum protein concentrations, and protein outputs for all patient groups are shown in Table 2. There were no statistical differences between groups N, N+BC, and N+MC for any of the measured or calculated values. Five minute juice volume, maximum bicarbonate concentration, and five minute bicarbonate output were significantly lower in group PCa compared with group N. Similarly, five minute juice volume and bicarbonate output were significantly lower in group P and maximum protein concentration was significantly higher than in group N. There were no differences between groups for five minute protein output. As with the CEA results, there was great overlap between 'normal' groups and the two groups with pancreatic disease for all pancreatic juice measurements. All patients in groups N, N+BC and N+MC had five minute pancreatic juice volumes greater than 5 ml, whereas 19 of 24 (79%) patients in group PCa and 17 of 33 (52%) patients in group P produced volumes less than this. No patient in group PCa had a volume of 10 ml or more but this was achieved in 42 of 72 (58%) patients in amalgamated groups N, N+BC, and N+MC and also in nine of 31 (29%) patients in group P. Maximum bicarbonate concentrations were attained in all patients within the five minute study period and all patients in group PCa and group P had values within two standard deviations of the mean for group N (75 to 150 mmol/l). Values in the amalgamated group, however, fell below 100 mmol/l in only four of 70 (6%) patients compared with 15 of 24 (63%) patients in group PCa and 17 of 31 (55%) patients in group P. All five minute pancreatic juice bicarbonate outputs for the amalgamated group exceeded 0.5 mmol, while 12 of 24 (50%) patients in group PCa and 13 of 31 (42%) patients in group P fell below this. Maximum protein concentration and protein output results did not provide any differentiating features.

ERCP was performed in 128 patients and provided the correct pancreatic or biliary diagnosis in 120 (94%). Of the eight patients where ERCP

Table 2 Results of pancreatic juice biochemistry in five diagnostic groups

Group	5 minute volume (ml)	Maximum bicarbonate (mmol/l)	5 minute bicarb. output (mmol)	Maximum protein (g/l)	5 minute prot. output (mg)
N (33)	14.6 ± 2.3	117.3 ± 5.4	1.45 ± 0.3	5.8 ± 0.8	45.0 ± 9.8
N+BC (29)	12.0 ± 2.0	130.0 ± 5.6	1.42 ± 0.3	6.6 ± 0.9	32.1 ± 7.0
N+MC (10)	10.4 ± 2.2	123.8 ± 11.3	0.89 ± 0.1	6.8 ± 1.3	25.3 ± 5.9
PCa (24)	3.7 ± 0.6†	93.2 ± 8.8*	0.44 ± 0.1*	7.1 ± 1.2	26.4 ± 5.9
P (31)	5.7 ± 1.1‡	105.3 ± 7.3	0.58 ± 0.1†	9.1 ± 1.3*	31.7 ± 6.2

Values are mean and SE. Group abbreviations as in text, numbers in each group shown in parentheses. Statistical comparisons with group N shown as: * = $P < 0.05$, † = $P < 0.005$, ‡ = $P < 0.001$.

did not provide a diagnosis and the 16 patients not examined by ERCP, 14 were from group N, four from N+BC (three gallstones and one cirrhosis), two from group PCa, and four from group P. One of the patients in the latter group developed a mild attack of pancreatitis after juice collection and this was the only complication encountered in this study.

Discussion

This study has confirmed that serum CEA alone is a poor marker for pancreatic disease,^{12,13} does not differentiate pancreatic cancer from pancreatitis, can become significantly raised in obstructive jaundice whatever the cause and, as reported by Lurie *et al.*,¹⁵ correlates with alkaline phosphatase but not bilirubin. It did not easily distinguish benign from malignant biliary obstruction, as has been suggested,^{21,22} although a greater proportion of raised levels was found in the malignant groups in this study. Only six of 39 (15%) patients with malignant biliary obstruction had CEA concentrations greater than 18 mcg/l, which was the highest value found in patients with benign jaundice, and this does not allow a degree of diagnostic separation as found by others.²² No potentiating effect of secretin in serum CEA was found but the time interval was much shorter than that reported by Lindstedt *et al.*²³

A pancreatic juice CEA concentration above the upper limit defined by the groups without demonstrable pancreatic disease, 106 mcg/l, was found in 32% of patients with pancreatic disease, although no discriminatory value between cancer and pancreatitis was present. Unlike the findings of Kawanishi *et al.*³ and Sharma *et al.*,⁴ who also found an overlap of results between pancreatitis and pancreatic cancer, the highest values in this study were found in juice from patients with acute relapsing pancreatitis and chronic pancreatitis and there was no correlation with the degree of pancreatic ductular abnormality as demonstrated at ERCP. Differing methodology for CEA estimation accounts for some of the non-comparability between reports in the literature and the various levels at which diagnostic limits have been set. No useful information was gained from calculation of CEA outputs probably because of juice losses around the collecting catheter, the wide range of CEA concentrations measured, and the lack of correlation between CEA and pancreatic juice volume.

There was no apparent relationship between serum and pancreatic juice CEA and no index could be formulated by combining the results to improve

diagnostic accuracy even in the way suggested by Sharma *et al.*⁴ where the presence of a juice CEA less than 30 mcg/l and plasma CEA less than 2.5 mcg/l excluded pancreatic cancer.

The pancreatic juice volume, bicarbonate and protein results reported above are in general agreement with other reported studies using a similar secretin stimulus,^{24–26} although the juice volumes in this study are somewhat lower. This is probably because of greater juice losses around the catheter rather than because of difference in patient selection or characteristics.²⁷ Despite the significantly lower juice volumes and bicarbonate outputs in patients with pancreatic disease and maximum bicarbonate concentrations in patients with pancreatic cancer, the great overlap between groups made clear diagnostic differentiation difficult as has been found by others.²⁷ Previous difficulties with the bicarbonate assay used in this study, in part because of the small timed samples often obtained, led to the erroneously low set of results reported earlier.^{28,29} Nevertheless, only approximate diagnostic criteria can be deduced from the results of this study—namely, a five minute pancreatic juice volume less than 5 ml, a maximum bicarbonate concentration less than 100 mmol/l, and a five minute bicarbonate output less than 0.5 mmol are unlikely with a normally functioning pancreas and thus imply the likelihood of pancreatic disease, while a five minute juice volume greater than 10 ml is unlikely in pancreatic cancer. It should be noted, however, that 75% of the patients in group PCa had cancers in the head of the pancreas with ductal obstruction.

It was of interest to combine the results of pancreatic juice CEA and biochemistry using the juice criteria outlined above for pancreatic disease. Of the 36 patients with pancreatic disease who were found to have juice CEA concentrations less than 106 mcg/l, 31 were placed in a category of likely pancreatic disease if one of the three juice criteria were taken as sufficient, 27 if two were sufficient, and 23 if all three biochemical criteria were satisfied. Thus five patients with pancreatic disease were not diagnosed by pancreatic juice CEA, volume, or bicarbonate data (one from group PCa and four from group P).

Despite the recent interest in CEA as an adjunct to the investigation of liver disease,^{16,22} it would seem from this study that serum CEA has little part to play in the distinction of benign from malignant lesions causing cholestasis. Pancreatic juice CEA was more successful in separating some patients with pancreatic disease from those without but the increasing accuracy of pancreatic imaging techniques, as shown by the 94% success rate

achieved by ERCP in this study, limits the wider application of such a measurement. There may be a place, therefore, for the limited use of pancreatic juice CEA for distinguishing normal from pancreatic disease but disappointingly it is unable to separate pancreatic cancer from pancreatitis.

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