Mechanism and specificity of increased amylase/creatinine clearance ratio in pancreatitis

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Summary The amylase/creatinine clearance ratio (Cam/Ccr ratio) was determined in 239 subjects. In 87 hospitalised patients without pancreatic disease (controls) the Cam/Ccr ratio was 3.02 ± 0.69 (mean ± ISD). The ratio was above the normal range in all patients with acute pancreatitis but was normal in those with chronic pancreatitis and carcinoma of the pancreas. In 18 patients with choledocholithiasis a raised ratio distinguished those with pancreatitis as assessed independently by the surgeon at laparotomy from those with a macroscopically normal pancreas. Raised Cam/Ccr ratios were also found in diabetics with ketoacidosis and in three patients with fulminant alcoholic liver disease. Though a positive correlation was found between the Cam/Ccr ratio and serum creatinine concentration, abnormally high ratios did not occur in 30 patients with chronic renal failure. A significant increase in Cam/Ccr ratios was produced in six healthy volunteers by intravenous injection of glucagon. However, it is unlikely that hyperglucagonaemia alone accounts for the increased Cam/Ccr ratio seen in acute pancreatitis, as no correlation was found between the clearance ratio and the plasma glucagon concentration in a series of patients. In two other patients in whom excess circulating pancreatic polypeptide was detected the Cam/Ccr ratio was normal. It is concluded that, in view of the sensitivity and relative specificity of finding an increased Cam/Ccr ratio in acute pancreatitis, its determination should be valuable clinically, especially in those cases of hyperamylasaemia where the cause is in doubt. The mechanism whereby the ratio is increased is unknown, and it is unlikely that either glucagon or pancreatic polypeptide is a major factor in its production.

The diagnosis of acute pancreatitis remains a difficult clinical problem, especially in the less severe cases when the degree to which the serum amylase is raised is common to many other conditions (Salt and Schenker, 1976). The instantaneous renal amylase/creatinine clearance ratio (Cam/Ccr ratio) has been advocated as a more specific test for the diagnosis of acute pancreatitis (Levitt et al., 1969; Warshaw and Fuller, 1975).

The reporting of raised glucagon levels in acute pancreatitis (Paloyan et al., 1967), together with the finding of raised Cam/Ccr ratios in diabetic ketoacidosis and burns (Levine et al., 1975) in which hyperglucagonaemia also occurs (Müller et al., 1973; Wilmore et al., 1974) has prompted the suggestion that glucagon may be the mediator of enhanced renal amylase clearance in these conditions.

This report is of a study designed to test the specificity of the Cam/Ccr ratio and to observe the relationship of plasma glucagon to renal amylase clearance. Glucagon was administered intravenously to six normal subjects, and plasma glucagon levels have been correlated with the simultaneously determined Cam/Ccr ratio in a series of patients.

Methods

Subjects studied included 87 hospitalised patients without pancreatic disease (controls); 13 patients with acute pancreatitis; 18 with choledocholithiasis; 14 diabetics, 19 alcoholics with predominant liver disease; 30 patients with chronic pancreatitis; three with peptic ulcer; 12 with primary biliary cirrhosis without choledocholithiasis, though three had stones in the gallbladder; 13 with carcinoma of the pan-
creas; and 30 consecutive patients with chronic renal failure from the renal outpatient clinic. In each instance the clinical diagnosis was established without reference to the Cam/Ccr values.

Simultaneous blood and urine samples were taken in all subjects. Serum and urinary amylase concentrations were measured by the Phadebas amylase test using a tablet substrate which is hydrolysed by α-amylase (Irie et al., 1972). The absorbance of the resulting blue-coloured solution was measured in a 300-N Guilford spectrophotometer at 620 nm. The absorbance values were converted to U/l using the standard curve enclosed with the tablets. The upper limit of normal is 300 U/l.

The serum and urinary creatinine were determined by a modified technique of the Jaffe reaction as described by Yatzidis (1974), using an alkaline picrate reagent buffered at pH = 9-65 and measured in a 300-N Guilford spectrophotometer at 500 nm.

The percentage of the amylase/creatinine clearance ratio was determined by the method of Levitt et al. (1969).

Expressed as a percentage the Cam/Ccr ratio is:

\[
\frac{\text{Cam}}{\text{Ccr}} \times 100
\]

With this formula the Cam/Ccr ratio is determined independently of volume and time (Dreiling et al., 1974; Warshaw et al., 1975).

Statistical analysis of the results was performed with Student’s t test.

Results

The Cam/Ccr ratio was determined in 11 different groups of patients (Fig. 1). In patients with acute pancreatitis the Cam/Ccr ratio (8.85 ± 1.11; mean ± 1 SD) was significantly higher than in the control group (3.02 ± 0.69; p < 0.001) and there was no overlap between these groups. Cam/Ccr ratio values were within the normal range for all patients in other groups except for the groups with alcoholic liver disease, choledocholithiasis, and diabetes mellitus.

Of the 19 patients with alcoholic liver disease, three died and they were the only patients in that group found to have an increased Cam/Ccr ratio. None of these three patients was diabetic and in none of them was a diagnosis of acute pancreatitis considered before death. One of them was a 35-year-old male in whom there was histological evidence of chronic pancreatitis at necropsy (Cam/Ccr ratio = 5.61). On admission to hospital investigations had shown serum bilirubin = 126 μmol/l (N 5-17), AsT = 50 U/l (N = 4-15), AP = 12 KAU/100 ml (N = 3-13), albumin = 26 g/l (N = 36-50), serum amylase = 210 U/l (N = < 300), fibrinogen = 1.25 g/l (N = 2.4). Death was caused three days after admission by bleeding oesophageal varices associated with micronodular cirrhosis of the liver. A 51-year-old female who died of acute alcoholic injury had raised Cam/Ccr ratio (5.80) but at necropsy had a normal pancreas. On admission investigations showed serum bilirubin = 214 μmol/l, AsT = 57 U/l, AP = 27 KAU/100 ml, albumin = 37 g/l, serum amylase = 380 U/l, fibrinogen = 2.5 g/l. The patient died 13 days later. Death was attributed to liver failure caused by fatty degeneration of the liver with developing cirrhosis. The third patient who died of alcoholic hepatitis was a 46-year-old female who also had raised Cam/Ccr ratio (5.43) but was not submitted to a post-mortem examination. Investigation on admission showed serum bilirubin = 462 μmol/l, AsT = 56 U/l, AP = 21 KAU/100 ml, albumin = 26 g/l, serum amylase = 332 U/l, and fibrinogen = 1.5 g/l. She died four days after admission. All three patients had prolonged pro-

Fig. 1 Shows the Cam/Ccr ratio in 239 patients grouped according to their final diagnosis. The horizontal line is the upper limit of normal for the ratio.
thrombin times and abnormal partial thromboplastin tests.

The Cam/Ccr ratio was high in 10 of the 18 patients with choledocholithiasis. Nine of the 10 were reported to have an abnormal pancreas at laparotomy, and the other patient with a high Cam/Ccr ratio was thought to have passed a stone recently through the ampulla of Vater from the appearances of the stoma at ERCP. As no other stones were found, laparotomy was not performed and so the pancreas was not visualised. In the eight patients with a normal Cam/Ccr ratio the pancreas was assessed as macroscopically normal by the surgeon.

Of the 14 patients with diabetes mellitus the four with abnormally high Cam/Ccr ratios were the only diabetics who presented with ketoacidosis.

Hyperamylasaemia was present in 12 of 30 subjects in chronic renal failure. None of them had evidence of acute pancreatitis nor a high Cam/Ccr ratio. However, there was a tendency for the Cam/Ccr ratio to increase as serum creatinine concentrations rose ($r = 0.419$, $p < 0.05$, $n = 30$).

The relationship between the Cam/Ccr ratio and serum amylase in patients with choledocholithiasis, diabetes mellitus, chronic renal failure, acute pancreatitis, and controls is shown in Fig. 2.

The Table gives some clinical and laboratory findings related to acute pancreatitis in all patients with either a high Cam/Ccr ratio or hyperamylasaemia. All of the 13 patients with acute pancreatitis had persistent abdominal pain, fever, leucocytosis, hyperamylasaemia, and hyperamylasuria. Hypocalcaemia was present in eight, but only two had a laparotomy, an abnormal pancreas being seen in both. None of the patients with choledocholithiasis had hypocalcaemia. Of the four diabetics with ketoacidosis and a high Cam/Ccr ratio only one had persistent abdominal pain, fever, and leucocytosis associated with decompensated diabetes and hyperglycaemia (glucose = 24 mmol/l). Of 12 patients with chronic renal failure and hyperamylasaemia, one had persistent abdominal pain, fever, and leucocytosis and another one had fever and leucocytosis. Both had rejection problems with their renal transplants.

Six fasting normal volunteer subjects were each given an intravenous bolus injection of glucagon (1 mg) (Glucagon for injection, U.S.P., Eli Lilly and Company) and the Cam/Ccr ratio was measured 30, 60, 120, and 240 minutes later.

Though in five of the six the Cam/Ccr ratio was decreased after 30 minutes this did not reach a level of statistical significance. The mean basal Cam/Ccr ratio of 2.66 ± 1.18 increased significantly to 4.79 ± 1.31 ($p < 0.025$) 60 minutes after the glucagon injection, and in four of the six was above the normal range (Fig. 3). Corresponding serum amylase levels fell from 235.5 ± 53.3 to 214.2 ± 49.9 (Fig. 3), but this was not statistically significant ($p > 0.4$).

At 240 minutes the Cam/Ccr ratio had returned to near normal values in all six subjects (2.65 ± 1.08).

Pancreatic glucagon was measured by Dr S. R. Bloom in 25 fasting samples from 22 patients. The mean plasma glucagon level in nine samples from seven patients with acute pancreatitis and an increased Cam/Ccr ratio (22.4 ± 19.2) was not significantly different from levels in those patients with a normal Cam/Ccr ratio (12.7 ± 17.2) ($p > 0.2$). Regression analysis showed no significant correla-

### Table: Clinical and laboratory findings in patients with either hyperamylasaemia or a high Cam/Ccr ratio

<table>
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<th>Acute pancreatitis</th>
<th>Choledocholithiasis</th>
<th>DM</th>
<th>CRF</th>
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<tr>
<td>High Cam/Ccr ratio</td>
<td>13</td>
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<td>Persistent abdominal</td>
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<td>Fever</td>
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<td>Leucocytosis</td>
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<td>Hyperamylasaemia</td>
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<td>Hyperamylasuria</td>
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Fig. 2 Shows the relationship of the Cam/Ccr ratio to the simultaneous serum amylase levels in four groups of patients in whom raised levels of either variable were seen. All of the 87 controls fell within the shaded area.
Fig. 3 Shows the simultaneously determined levels of Cam/Ccr ratio and serum amylase in six healthy volunteers before and one hour after intravenous injection of 1 mg glucagon.

Warshaw et al. (1975) concluded that the finding of a high Cam/Ccr ratio is specific for acute pancreatitis. Doubt has been cast on this by Levine and co-workers (1975) who found raised ratios in patients with diabetic ketoacidosis or burns, though concurrent pancreatitis was not excluded. We have confirmed that raised Cam/Ccr ratios occur in diabetic ketoacidosis and have, in addition, observed abnormally high ratios in three patients with fatal alcoholic liver disease. Thirty patients with chronic renal failure without evidence of acute pancreatitis were found to have normal Cam/Ccr ratios, though raised ratios were reported in one (Morton et al., 1976) of three (Levitt et al., 1969; Blainey and Northam, 1973) other studies. A tendency for the ratio to increase as renal function deteriorated has been confirmed and was significant on regression analysis, but even at extremely high levels of serum creatinine the ratio remained within the normal range. This correlation reflects the tendency for creatinine clearance to fall more rapidly than amylase clearance as renal impairment progresses, and theoretically could lead to an abnormally raised Cam/Ccr ratio at extremely low levels of creatinine clearance. Though on the basis of these findings it appears that the Cam/Ccr ratio is not an entirely specific test for acute pancreatitis, its value
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is not greatly undermined as the other conditions in which a raised ratio may be found are unlikely to be overlooked clinically and can be readily excluded.

The sensitivity of the test is borne out by its ability to detect otherwise unsuspected episodes of pancreatitis in patients with cholelithiasis (Lesser and Warshaw, 1975). In none of 18 patients was the serum amylase raised to an extent where it would be regarded as strongly suggestive of pancreatitis, but the independent anatomical assessment of their pancreas by the surgeon at laparotomy correlated extremely closely with the findings of the Cam/Ccr ratio determined preoperatively. In addition to establishing the diagnosis of acute pancreatitis when serum amylase levels are normal or near normal, the Cam/Ccr ratio is of value as it is usually normal in non-pancreatic causes of hyperamylasaemia (Berk et al., 1973; Warshaw and Fuller, 1975).

The mechanism whereby an increased Cam/Ccr ratio occurs in pancreatitis is not known. Recent work has suggested that it is not related to alterations in the isoenzyme pattern of amylase in serum and urine (Long and Grider, 1976). An increased ratio has been found in patients without acute pancreatitis, including the only three patients who died out of 20 admitted to hospital with severe alcoholic liver disease in this series. It is therefore necessary to postulate a factor that is common to acute pancreatitis, diabetic ketoacidosis, burns, and severe alcoholic liver disease which may influence renal handling of amylase. High levels of plasma glucagon have been reported in acute pancreatitis (Paloyan et al., 1967), diabetic ketoacidosis (Müller et al., 1973), and burns (Wilmore et al., 1974). We were able to increase significantly the Cam/Ccr ratio in six healthy volunteers by intravenous bolus injection of glucagon. The fall in serum amylase thus produced may account for the effect of glucagon administration in lowering serum amylase levels in patients with acute pancreatitis which has previously been reported (Condon et al., 1973). Care should therefore be taken in deducing such falls in serum amylase that glucagon has a beneficial effect on the pancreatitis per se. Though glucagon does exert an effect on the Cam/Ccr ratio it is unlikely to be the sole explanation of the high ratios found in acute pancreatitis. The massive dose of glucagon administered (1 mg) did not produce the extremely high ratios seen in acute pancreatitis. In addition, no statistical correlation was found between the Cam/Ccr ratio and plasma glucagon levels (kindly measured with a radioimmunoassay by Dr T. E. Adrian and Dr S. R. Bloom) in a number of patients, including several with acute pancreatitis. Pancreatic polypeptide is a newly described hormone which by virtue of its wide distribution in the acini (Heitz et al., 1976), might be released into the circulation in large amounts during pancreatic damage. We have found normal Cam/Ccr ratios in two patients with the extremely high plasma levels of pancreatic polypeptide (Dr T. E. Adrian and Dr S. R. Bloom) associated with endocrine tumours (Polak et al., 1976) (> 500 pg/ml) so that this hormone is also unlikely to mediate the alterations of renal amylase clearance seen in conditions which raise the Cam/Ccr ratio.

Determination of the Cam/Ccr ratio is a simple and extremely sensitive test for the diagnosis of acute pancreatitis. Its non-specificity barely detracts from its clinical usefulness, as the presence of diabetic ketoacidosis, fulminant alcoholic liver disease, or very advanced renal failure are unlikely to cause confusion by going unnoticed in the clinical situation. The ratio should be particularly useful when mild or moderate rises in serum amylase are found and pancreatitis is uncertain. The mechanism whereby the renal clearance of amylase is increased in pancreatitis remains to be elucidated.

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References


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