Plasma Pancreatic Polypeptide Concentrations in Acute Pancreatitis

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SUMMARY

Plasma human pancreatic polypeptide (hPP) concentrations were measured in 17 patients with acute pancreatitis. On admission the mean plasma hPP concentration was 33 ± 6.9 pmol/l (range 11 - 92 pmol/l), which was similar to the mean hPP concentration of 43 ± 4 pmol/l (range 11 - 92 pmol/l) in age-matched healthy subjects. The plasma immunoreactive glucagon (IRG) concentration was elevated 5-fold. Nine patients were managed conventionally and received prolonged glucagon infusion, and 8 were managed conventionally and received saline infusion. Treatment was carried out in a double-blind manner. Glucagon infusion caused a further 5-fold rise in circulating IRG concentrations and an increase in the blood glucose concentration from 7.5 to 9.7 mmol/l. This was associated with a fall in hPP concentrations and a significant reduction in variability. It is suggested that plasma hPP levels are not elevated in patients with acute pancreatitis and, therefore, do not reflect acute pancreatic damage.


Immunohistochemical techniques have shown that pancreatic polypeptide is located in specific endocrine cells which are distinct from the A, B, and D cells of the pancreas. These cells are found in the acinar pancreas as well as in the islets of Langerhans. Plasma human pancreatic polypeptide (hPP) concentrations are often raised in patients with endocrine pancreatic neoplasms, in those with multiple endocrine adenomatosis type 1 and in their non-affected family members, and in patients with diabetes mellitus. We have previously reported that immunoreactive glucagon (IRG) levels are raised in patients with acute pancreatitis. Furthermore, glucagon infusion hastened recovery and increased the rate of fall of circulating pancreatic enzymes. We report that hPP levels are not elevated in acute pancreatitis, but glucagon infusion may lower and eliminate spontaneous fluctuations in hPP concentrations.

PATIENTS AND METHODS

Basal blood samples were taken on admission from 17 patients aged 30 - 50 years with a typical history of acute pancreatitis and an initial serum amylase concentration of greater than 600 Pimstone units per 10 ml (normal range 40 - 140 Pimstone units per 10 ml). The patients stated that they had not eaten or taken any medication for 4 - 6 hours before admission. Alchohol was an aetiological factor in the majority of cases.

The patients were then treated according to two randomized regimens. They were all fasted for at least 24 hours, received an intravenous infusion of 0.25% saline with 5% dextrose, had nasogastric decompression and received analgesics. Anticholinergic drugs were withheld. Eight patients received an intravenous bolus dose of 1 mg glucagon (Eli Lilly) on admission and a constant infusion of glucagon 15 μg/kg/h in 0,15M saline for 6 hours, followed by 10 μg/kg/h for a further 18 hours. The glucagon was free from PP contamination. The other 9 patients each received an equivalent volume of 0,15M NaCl only. Blood samples were taken 30 minutes after the start of treatment, every 3 hours for 12 hours, every 6 hours for the next 36 hours, and then daily until the patients were discharged. 'Untreated' refers to patients who did not receive glucagon. Blood glucose and plasma IRG levels were measured in 6 of the treated patients and in all the untreated patients, and the plasma hPP concentration was measured in all the patients. The blood samples for IRG and hPP radio-immunoassay were collected in heparinized tubes to which 1 000 U of aprotinin (Trasylol) per millilitre of whole blood were added. A separate blood sample was taken for glucose estimation. The plasma was separated by centrifugation and stored at −20°C; 0,5 ml of plasma was later lyophilized and sent to the Institute of Medical Biochemistry, University of Aarhus, Denmark, for hPP radio-immunoassay. Blood glucose concentrations were measured with an AutoAnalyzer using the neocuprine method. The glucagon (IRG) method using Unger's 30 K antiserum has previously been published, and hPP was assayed by one of us (T.W.S.) using the method previously published. Results are reported as mean ± SE. The IRG and glucose data were analysed for statistical significance using Student's t test. The inter- and intra-patient variability of the serum hPP concentration was assessed by the analysis of variance. Four one-way analyses were done: on the treated patients during glucagon infusion, on the treated patients after discontinuation of the glucagon infusion, on the untreated patients during the saline infusion, and on the untreated patients after discontinuation of the saline infusion. Significance was accepted at the 5% level.
RESULTS

On admission the mean plasma hPP concentration was 33 ± 6.9 pmol/l (range 11 - 92 pmol/l). These levels are similar to the hPP concentrations in healthy subjects of the same age (mean 43 ± 4 pmol/l; range 20 - 88 pmol/l). No correlation was found between the initial plasma hPP concentration and the serum amylase concentration.

Glucagon infusion hastened recovery and caused a more rapid fall in circulating pancreatic enzymes. In patients who received glucagon, plasma hPP concentration fell from 37 ± 10.9 pmol/l to a nadir of 22 ± 3.2 pmol/l at 24 hours, while in the untreated group virtually no change was observed (Fig. 1).

Fig. 1. Plasma hPP concentrations (pmol/l) in 17 patients with acute pancreatitis. The solid line indicates the concentrations in 9 patients who received a bolus dose of 1 mg glucagon, followed by an infusion of 15 μg/kg/h for 6 hours, and then 10 μg/kg/h for a further 18 hours. The broken line indicates the concentrations in 8 patients who received saline.

No correlation was found between the changes in plasma hPP concentrations and the serum amylase concentrations. Two untreated patients and 2 patients who received glucagon had hPP levels at the upper limit of the normal range (62 and 61 pmol/l, and 63 and 93 pmol/l, respectively) on admission (Fig. 2). In the 2 patients treated with glucagon, hPP concentrations fell within 3 hours to 36 and 40 pmol/l, respectively, while in the 2 untreated patients high levels persisted (86 pmol/l at 18 hours and 76 pmol/l at 24 hours, respectively). Furthermore, glucagon treatment significantly reduced both intra- and interpatient variability of serum hPP concentrations. When the glucagon treatment was discontinued, the variation returned to the original levels.

One patient in the untreated group had low-normal hPP levels on admission, and, in spite of clinical deterioration from day 1 when he developed hypocalcaemia, renal failure and adult respiratory distress syndrome, no elevation in the hPP concentration was observed until day 11, 9 days before his death, when hPP concentrations started rising and reached 214 pmol/l on the day of his death. The plasma IRG concentration was elevated throughout his illness and was 929 pmol/l on day 14.

The mean blood glucose level (Fig. 3) was significantly higher 3 hours after starting the glucagon infusion, after which the concentration began to fall towards levels observed in the untreated patients. Within 6 hours of discontinuation of the infusion, the mean blood glucose values in the two groups were similar. The plasma IRG concentration (Fig. 3) was 5 - 10 times the normal value (11.4 ± 2.85 pmol/l), but was not significantly different in the two groups on admission (untreated group 105 ± 36.0 pmol/l, treated group 143 ± 37.7 pmol/l). Glucagon infusion brought about a further 5-fold elevation. The plasma IRG concentrations fell to similar levels within 6 hours of discontinuation of the infusion.

Fig. 2. Plasma hPP concentrations (pmol/l) in 4 patients with acute pancreatitis and high hPP levels. The solid lines show the concentrations in 2 patients treated with glucagon according to the protocol described in the legend to Fig. 1.

DISCUSSION

These patients had the typical clinical features of acute pancreatitis, associated with raised circulating amylase and glucagon concentrations. Presumably the damaged pancreas 'leaks' these substances into the circulation. We were, therefore, surprised not to find elevated plasma hPP concentrations, even though the greatest proportion of PP cells are situated in the pancreatic parenchyma. Previous attacks of pancreatitis which reduced the degree of elevation of the plasma IRG concentration may have influenced the initial hPP concentration, but the fasting hPP levels in patients who have had repeated episodes of
pancreatitis were reported as normal, despite an impaired response to stimulation."

The patient who died had a very high IRG concentration and elevated hPP values, which may reflect gross pancreatic destruction. However, the renal failure may have impaired the removal of circulating hPP and accounted for the abnormal concentrations found in this situation."

In conclusion, hPP concentrations do not reflect acute pancreatic damage. Pharmacological doses of glucagon hasten recovery, lower pancreatic enzyme levels, and cause a fall in hPP concentration.

In hPP concentrations gradually returned. This pattern was clear in the 4 patients who had the highest hPP concentrations on admission; in the 2 patients who received glucagon infusion there was a fall, whereas in the 2 untreated patients hPP concentrations fluctuated at high levels. This suggests that glucagon in pathophysiological and pharmacological doses may directly or indirectly lower hPP concentrations. However, glucagon infused to achieve plasma IRG concentrations which were in the physiological range had no effect on the fasting hPP levels in normal subjects. Floyd et al. and Sive et al. have shown that a rise in the blood glucose level induced by intravenous injections was associated with a fall in hPP concentrations. Glucagon infusions did raise blood glucose levels, but there was no correlation between glucose and hPP levels. Although the glucagon effect may not reflect a physiological interaction between pancreatic alpha and pancreatic polypeptide cells, the observation that glucagon treatment reduced the enzyme leak in acute pancreatitis suggests that glucagon may similarly affect hPP release in this disorder.

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**Fig. 3. Plasma glucose (mmol/l) and plasma IRG concentrations (pmol/l) in 8 untreated patients and 6 patients who received glucagon according to the protocol described in the legend to Fig. 1. The normal fasting IRG concentration is shown by the hatched area.**

The plasma IRG concentration was 5 - 10 times higher than normal, but not statistically different in the groups on admission. With glucagon infusion there was a further 5-fold elevation in the plasma IRG concentration, which was associated with a small fall in hPP levels, but a significant reduction in the spontaneous fluctuations as evidenced by the diminution in variance. After discontinuation of glucagon treatment, variability in hPP concentrations gradually returned. This pattern was clear in the 4 patients who had the highest hPP concentrations on admission; in the 2 patients who received glucagon infusion there was a fall, whereas in the 2 untreated patients hPP concentrations fluctuated at high levels. This suggests that glucagon in pathophysiological and pharmacological doses may directly or indirectly lower hPP concentrations. However, glucagon infused to achieve plasma IRG concentrations which were in the physiological range had no effect on the fasting hPP levels in normal subjects. Floyd et al. and Sive et al. have shown that a rise in the blood glucose level induced by intravenous injections was associated with a fall in hPP concentrations. Glucagon infusions did raise blood glucose levels, but there was no correlation between glucose and hPP levels. Although the glucagon effect may not reflect a physiological interaction between pancreatic alpha and pancreatic polypeptide cells, the observation that glucagon treatment reduced the enzyme leak in acute pancreatitis suggests that glucagon may similarly affect hPP release in this disorder.

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**REFERENCES**