PRELIMINARY COMMUNICATIONS

Possible use of Glucagon in the Treatment of Pancreatitis

MICHAEL J. KNIGHT, JOHN R. CONDON,
RODNEY SMITH

British Medical Journal, 1971, 2, 440-442

Summary

Four patients with pancreatic disease received glucagon intravenously. In two a definite decrease in the volume of pancreatic exocrine secretion was shown, and in one of these pancreatic juice protein and bicarbonate levels also fell. Two patients with acute pancreatitis had pronounced relief of epigastric pain associated with falls in plasma amylase after intravenous glucagon.

Several mechanisms could account for the possible beneficial effect of glucagon in pancreatitis, and further studies of its use in this disease are justified.

Introduction

Administration of glucagon to dogs with pancreatic fistulae depresses the rate of flow, volume, and enzyme concentration of pancreatic juice secreted by the pancreozymin/secretin-stimulated gland (Dyck *et al.*, 1969). These observations were confirmed by Nakajima and Magee (1970). More recently (Dyck *et al.*, 1970) published similar observations in normal human subjects and suggested a possible regulatory role for glucagon in the control of pancreatic exocrine secretion. Reduction of pancreatic exocrine secretion is generally accepted to be of possible benefit to patients with various forms of pancreatic disease, and it is thought that glucagon may therefore be of therapeutic use in such subjects.

Clinical and experimental observations in four patients with pancreatic disease who received glucagon are reported.

Case 1

A 72-year-old man with a postoperative pancreatic fistula was referred for further surgery. Five months previously several large pancreatic cysts were discovered and drained at laparotomy. After this procedure he developed a persistent pancreatic fistula which was shown by means of a fistulogram to communicate with the main pancreatic duct.

At laparotomy the pancreas showed the changes of chronic pancreatitis. The dilated main pancreatic duct was anastomosed to a jejunal Roux-en-Y with mucosal apposition. A plastic T-tube was positioned in the main pancreatic duct, the long arm of the tube passing through the anastomosis, jejunal lumen, jejunal wall, and parietes to a collecting apparatus. Thus for practical purposes a supply of pure pancreatic juice, uncontaminated by gastric and duodenal contents, was readily available.

With the patient's informed consent the effect of glucagon on the secretin/pancreozymin-stimulated gland was studied. An intravenous infusion of secretin (210 units/hour) and pancreozymin (70 units/hour) was started and continued for 110 minutes. Thirty minutes after beginning secretin/pancreozymin infusion a separate intravenous infusion of glucagon in dextrose 5% was started and delivered at a dose rate of 1 mg/hour for 30 minutes. At this point

the dose of glucagon was increased to 2 mg/hour for 20 minutes and then stopped.

Pancreatic juice was collected at 10-minute intervals throughout the study and the volume and the bicarbonate and total protein content of each sample measured. The total protein content of pancreatic juice was estimated by the method of Lowry *et al.* (1951) and serves as a measurement of enzyme secretion.

The results are shown in Fig. 1. Secretin/pancreozymin infusion induced an increase in the volume of pancreatic exocrine secretion, a rise in pancreatic juice bicarbonate, but no significant change in total protein content. Glucagon infusion resulted in a fall in the volume and the bicarbonate and protein content of the pancreatic juice. On stopping the glucagon infusion the pancreatic juice volume and the bicarbonate and protein concentrations rose.

FIG. 1—Case 1. Volume of pancreatic juice and bicarbonate and total protein levels in patient with chronic pancreatitis.

Case 2

A 57-year-old man developed a pancreatic fistula five months after a pancreatico-jejunostomy for severe chronic pancreatitis and he was admitted for revisional surgery.

At operation the pancreatic duct anastomosis was reconstructed but 10 days postoperatively the pancreatic fistula recurred. A suction catheter introduced into the fistula collected between 500 and 700 ml of pancreatic juice each day. Electrolyte imbalance was corrected with intravenous therapy, and five days later the effect of glucagon on pancreatic juice secretion was observed.

Pancreatic juice was collected at 15-minute intervals for one hour. Glucagon 1 mg intravenously was then given and further 15-minute collections of pancreatic juice were made for the next 60 minutes. The volume of each specimen was measured and a decrease in the flow of pancreatic juice was noted after glucagon administration (Fig. 2). A continuous glucagon infusion given at a dose of 1 mg every six hours was started and continued for four and a half days. The volume of pancreatic juice collected from the fistula was measured every 24 hours. It can be seen from Fig. 2 that the volume of pancreatic juice fell significantly during glucagon therapy. Five days

St. George's Hospital, London S.W.1

MICHAEL J. KNIGHT, M.B., F.R.C.S., Registrar in Surgery
JOHN R. CONDON, B.Sc., M.R.C.P., Senior Registrar in Medicine
RODNEY SMITH, M.S., F.R.C.S., Surgeon

after starting glucagon the flow from the fistula ceased. Glucagon was stopped, and 24 hours later the patient had abdominal discomfort, which was relieved when leakage of pancreatic juice from the fistula recurred. This time, however, the leakage was on a reduced scale and the fistula later closed spontaneously.

FIG. 2—Case 2. Volume of pancreatic juice in patient with postoperative pancreatic fistula.

Case 3

A 56-year-old man was referred with a history of recurrent attacks of acute pancreatitis after a choledochoduodenostomy which had been performed in another hospital three months previously for a mass in the head of the pancreas.

On clinical examination there was no jaundice. He had a well-healed laparotomy scar, mild tenderness in the upper abdomen, and an epigastric mass.

Six days after admission he developed acute epigastric pain and vomiting associated with upper abdominal tenderness and guarding. The plasma amylase was 914 Somogyi units/100 ml and a diagnosis of an acute exacerbation of pancreatitis was made. Over the next two hours the plasma amylase rose to 1,066 Somogyi units/100 ml and the plasma calcium fell from 9.4 to 9.0 mg/100 ml. Glucagon 1 mg was given intravenously and repeated 60 minutes later. The patient's general condition improved and the epigastric pain was completely relieved three hours after the second injection. The plasma amylase, glucose, and calcium were estimated every two hours and the results are shown in Fig. 3. Plasma amylase fell from 1,066 to 915 Somogyi units/100 ml within eight hours, and to 533 Somogyi units/100 ml within 24 hours. Though relief of epigastric pain occurred three hours after the second glucagon injection pain recurred five hours later, but the plasma amylase continued to fall.

Two days later laparotomy confirmed acute pancreatitis associated with a pancreatic pseudocyst and a carcinoma of the head of the pancreas.

Case 4

A 23-year-old man who had had an attack of acute pancreatitis three months previously was admitted to hospital with a 14-hour history of acute severe epigastric pain and vomiting. On admission he was pyrexial, with pronounced epigastric tenderness, guarding, and rigidity. The plasma amylase was 1,000 Somogyi units/100 ml, and a diagnosis of acute pancreatitis was made. He was treated with intravenous dextrose and saline, nasogastric suction, pethidine, propantheline bromide, and antibiotics. The plasma amylase rose

FIG. 3—Case 3. Plasma amylase, glucose, and calcium levels in patient with acute pancreatitis.

to 2,280 Somogyi units/100 ml 12 hours after admission, and severe epigastric pain persisted for 24 hours. Moderate epigastric pain continued for a further four days and he required analgesic therapy. Plasma amylase fell to 800 and 421 Somogyi units/100 ml on the third and fourth days of the illness.

On the evening of the fourth day severe epigastric pain recurred and was associated with upper abdominal tenderness, guarding, and rigidity. The plasma amylase was 355 Somogyi units/100 ml. A loading dose of 1 mg of glucagon was given intravenously and a continuous glucagon infusion at a dose rate of 1 mg every six hours was started. Within 15 minutes epigastric pain decreased and by 30 minutes was completely relieved. There was a noticeable improvement in the patient's general condition. No other drugs had been given. The plasma amylase levels fell from 355 to 266 Somogyi units/100 ml within one hour. The glucagon infusion was continued for 24 hours without any recurrence of abdominal pain.

Three weeks later he was readmitted with a further attack of acute pancreatitis. His plasma amylase on admission was 435 Somogyi units/100 ml. It rose to 800 Somogyi units/100 ml over the next 10 hours and this was associated with increasing abdominal pain, epigastric tenderness, guarding, and the development of rebound tenderness. Glucagon 1 mg intravenously was given and this was followed by a continuous intravenous infusion of glucagon in 5% dextrose at a dose rate of 1 mg every six hours. The epigastric pain was greatly relieved at one hour and within two hours the pain had ceased. Over this period of time signs of peritoneal irritation subsided. The plasma amylase fell from 800 to 535 Somogyi units within 40 minutes of giving the glucagon and continued to fall as shown in Fig. 4.

Discussion

Glucagon therapy had a demonstrable effect in all four patients with pancreatic disease treated by us.

In Cases 1 and 2 a definite decrease in the volume of pancreatic exocrine secretion was shown to occur after glucagon

FIG. 4—Case 4. Plasma amylase, glucose, and calcium levels in patient with acute pancreatitis.

therapy. Furthermore, in Case 1 both pancreatic juice protein and bicarbonate levels fell during glucagon infusion. Cases 3 and 4 had marked relief of epigastric pain associated with falls in plasma amylase.

Glucagon may prove to be of therapeutic value in pancreatic disease for a number of reasons. It suppresses gastric secretion in dogs (Quirarte *et al.*, 1966) and man (Dreiling and Janowitz, 1959) and also inhibits gastric and jejunal motility (Stunkard *et al.*, 1955). The role of pancreatico-zymin in gastrointestinal physiology has not yet been fully elucidated. It has, however, been shown that pancreatico-zymin increases plasma glucagon levels (Unger *et al.*, 1967), and it has been suggested that pancreatico-zymin secretion in response to a meal promotes release of glucagon. Glucagon has been shown to suppress pancreatic exocrine secretion in normal subjects (Dyck *et al.*, 1970), and the normal physiological role of glucagon might be to suppress pancreatic exocrine secretion when its digestive action was no longer required (Lawrence, 1969).

It is known that glucagon levels are raised in acute pancreatitis in dogs (D. Paloyan *et al.*, 1966) and man (Lawrence, 1966; E. Paloyan *et al.*, 1966), and hyperglucagonaemia in a patient with hyperparathyroidism and pancreatitis has been reported (Paloyan *et al.*, 1967). These findings suggest an interplay between glucagon, calcium metabolism, and pancreatitis.

Our studies suggest that hyperglucagonaemia is of benefit in pancreatitis, and this raises the possibility of a compensatory hypersecretion of glucagon in acute pancreatitis. This would result in suppression of pancreatic and gastric secretions with inhibition of gastrointestinal motility. If indeed the reported hyperglucagonaemia in acute pancreatitis is a compensatory mechanism it is possible that in the fully-developed clinical syndrome the plasma glucagon levels attained are not high enough to inhibit pancreatic exocrine secretion. Relatively large doses of glucagon were used to suppress secretion of pancreatic juice in Cases 1 and 2, and one would suspect that with this regimen a similar inhibition of pancreatic exocrine secretion occurred in Cases 3 and 4. In both these individuals there was rapid relief of abdominal pain, and it is tempting to attribute this to the effect of glucagon which possibly resulted in a decreased secretion of pancreatic juice. In Cases 3 and 4 a reduction in plasma amylase levels occurred when they would have been expected to rise. Too much importance should not be attached to this finding, however, since there is a poor correlation between the severity of acute pancreatitis and plasma amylase concentration (Trapnell, 1966).

The evaluation of drugs in acute pancreatitis is difficult in view of the unpredictable clinical course of the disorder and the lack of a specific test of sufficient sensitivity to monitor the progress of the disease. Certainly no drug has been shown to be of unequivocal value in altering the prognosis of acute pancreatitis, and in the final analysis the only true index of successful therapy would be a significant decrease in mortality rate.

In view of the relatively high mortality rate of 23% to 26% in acute pancreatitis (Pollock, 1959; Trapnell 1966) and the absence of any serious side effects attributable to prolonged glucagon therapy (Brogan *et al.*, 1969) further studies of the use of glucagon in acute and chronic pancreatitis are justified.

We are grateful to Mr. Paul Rosswick for his permission to report Case 4.

References

- Brogan, E., Kozonis, M. C., and Overy, D. C. (1969). *Lancet*, **1**, 482.
- Dreiling, D. A., and Janowitz, H. D. (1959). *Gastroenterology*, **36**, 580.
- Dyck, W. P., Rudick, J., Hoexter, B., and Janowitz, H. D. (1969). *Gastroenterology*, **56**, 531.
- Dyck, W. P., Texter, E. C., Lasater, J. M., and Hightower, N. C. (1970). *Gastroenterology*, **58**, 532.
- Lawrence, A. M. (1966). *Proceedings of the National Academy of Sciences*, **55**, 316.
- Lawrence, A. M. (1969). *Annual Review of Medicine*, **20**, 207.
- Lowry, O. H., Rosebrough, N. J., Farr, A. L., and Randall, R. J. (1951). *Journal of Biological Chemistry*, **193**, 265.
- Nakajima, S., and Magee, D. F. (1970). *Canadian Journal of Physiology and Pharmacology*, **48**, 299.
- Paloyan, D., *et al.*, (1966). *Surgical Forum*, **17**, 348.
- Paloyan, E., *et al.*, (1966). *Federation Proceedings*, **25**, 495.
- Paloyan, E., *et al.*, (1967). *Journal of the American Medical Association*, **200**, 757.
- Pollock, A. V. (1959). *British Medical Journal*, **1**, 6.
- Quirarte, C., Woodward, E. R., and Dragstedt, L. R. (1966). *Archives of Surgery*, **93**, 475.
- Stunkard, A. J., Van Itallie, T. B., and Reis, B. B. (1955). *Proceedings of the Society for Experimental Biology and Medicine*, **89**, 258.
- Trapnell, J. E. (1966). *Annals of the Royal College of Surgeons of England*, **38**, 265.
- Unger, R. H., Ketterer, H., Dupré, J., and Eistentraut, A. M. (1967). *Journal of Clinical Investigation*, **46**, 630.