Influence of Pancreatic Duct Ligation on Gastric Acid Secretion

TAKESHI SEKINE, JIN-ICHI KAMEYAMA, IWAO SASAKI, JERMING LIN and TOSHI SATO

Department of Surgery, Tohoku University School of Medicine, Sendai 980

The influence of pancreatic duct ligation (PDL) on gastric secretion was investigated in dogs with a Heidenhain pouch. A test meal was given to the dogs before PDL, and following PDL the dogs were administered with the test meal mixed with pancreatic enzymes and with the test meal alone in succession. The responses to the test meal were examined in the control period and every one week for a period of 1 to 6 weeks following PDL to identify the changes in gastric acid secretion, serum gastrin levels, immunoreactive glucagon (IRG) levels and immunoreactive insulin (IRI) levels. Gastric acid secretion in response to food stimulations markedly increased after PDL. However, the acid secretion was significantly inhibited by the administration of pancreatic enzymes. Serum gastrin levels began to increase from the second week and continued to increase until the sixth week after PDL, revealing no effect of pancreatic enzymes. IRG levels also increased following PDL, particularly in cases administered with pancreatic enzymes. IRI levels were higher at the first week of PDL than before PDL, but tended to decrease thereafter. It is assumed that gastric hypersecretion after PDL would have complicated relations with IRG, gastric inhibitory polypeptide (GIP) as well as with antral gastrin. —— pancreatic duct ligation; pancreatic enzymes; gastric acid secretion; serum gastrin level; immunoreactive glucagon level

Complications of peptic ulcer in patients with chronic pancreatitis have so far been noted (Elliott et al. 1964; Elliott 1974), and it has been experimentally pointed out that gastric hypersecretion and ulcers are likely to develop following pancreatic duct ligation (Yesko 1928; Elliott et al. 1963; Hein et al. 1963; Kyle and Welbourn 1966; Peterson et al. 1974), external pancreatic fistulae (Greenlee et al. 1959), and total pancreatectomy (Barcena et al. 1956). However, its mechanism still remains obscure. With an aim to clarify the influence of pancreatic duct ligation on gastric acid secretion, the present study was undertaken. We ligated the pancreatic ducts in dogs with a Heidenhain pouch and studied their responses to food stimulation, i.e., changes in gastric acid secretion, serum gastrin levels, immunoreactive glucagon (IRG) levels and immunoreactive insulin (IRI) levels. A particular attention was paid on the effect of the administration of pancreatic enzymes.

Received for publication, July 15, 1980.
MATERIALS AND METHODS

A total of 9 mongrel dogs weighing 13–20 kg were used in this study. A Heidenhain pouch was constructed under intravenous thiopental anesthesia by inserting a Gregory cannula through the anterior wall into the fundus of stomach. Experiments were began at least 3–4 weeks after the operation. Gastric juice secreted from the Heidenhain pouch was collected and serum gastrin levels were determined as control. After the control period, the dogs underwent pancreatic duct ligation.

**Pancreatic duct ligation (PDL).** The main and accessory pancreatic ducts were ligated and divided. Complete separation of the pancreas from the duodenum was accomplished by interposition of omentum to interrupt any pancreatic duct communication between the pancreas and the gastrointestinal tract.

**Administration of the test meal with or without pancreatic enzymes.** During the control period, only a test meal (Dog food 300 g: Hokuetsu’s Dog Meal) was given. Following PDL, food stimulations were administered with only the test meal in four dogs, while in five others first with a mixture of the test meal and pancreatic enzymes (Berizym 3 g/kg: Shionogi Pharmaceutical Co.) for 4 days, followed by the test meal alone for 3 days. The responses to the food stimulations were observed for the control period and every one week for periods of 1 to 6 weeks following PDL.

**Gastric acid secretion.** Gastric juice from the Heidenhain pouch was collected in a rubber bag attached to the cannula at 30-min intervals for 6 hr. In each sample the volume and acid concentration were determined.

**Serum gastrin level, immunoreactive glucagon level and immunoreactive insulin level.** At the same time, blood was taken from the external jugular vein before, and at 15, 30, 60, 120, 240 min following food stimulations. In each sample, the levels of serum gastrin, immunoreactive glucagon and immunoreactive insulin were determined.

**Glucose tolerance test.** A solution of 20% glucose was intravenously infused in a dose of 1 g/kg for 2 min. Blood was taken from the external jugular vein at 1, 3, 5, 7, 10, 20, 30, and 60 min following the intravenous injection, and in each sample the levels of blood sugar and immunoreactive insulin were determined.

**Measurements.** The concentration of acid was determined by titration with 0.1 N NaOH to pH 7.0 on an automatic titrator (Radiometer, Copenhagen). Serum gastrin concentration was determined by radioimmunoassay, utilizing Gastrin-radiioimmunoassay Kit (CIS). The immunoreactive insulin level (IRI) was determined by the solid phase antibody method (Phadebas Insulin Test Kit, Pharmacia Co.), and the immunoreactive glucagon level (IRG) by the double antibody method. For the determination of blood sugar level was used the O-toluidine method (Glucose Test Wako).

At the end of the experiment, the dogs were scarified, and the stomach, duodenum, jejunum and liver were examined macroscopically as well as microscopically.

**Statistical analysis.** The measured values were expressed as the mean±s.d. Statistical comparisons were made with Student’s t-test for unpaired values and statistical significance was indicated with p<0.05.

RESULTS

**Effects of food stimulations before and after PDL**

Gastric acid secretion in response to food stimulation was 2.44 mEq/6 hr on the average before PDL (Fig. 1). After PDL, the average levels of secretion were 4.52, 8.08, 8.56, 13.86, 12.33 and 10.04 mEq/6 hr at 1, 2, 3, 4, 5 and 6 weeks, respectively. At 4 weeks, the acid secretion level attained to a peak showing 200–600% over the control value. After 4 weeks, the acid secretion tended to decrease, yet the level remained significantly high even at 6 weeks (p<0.01).

The fasting level of serum gastrin was 29 pg/ml on the average before PDL
Pancreatic Duct Ligation and Gastric Acid Secretion

(Fig. 2). After PDL, the level tended to rise showing average values of 52, 46, 46, 57 and 52 pg/ml at 2, 3, 4, 5 and 6 weeks, respectively. The rate of increase over the level before PDL was 96% at 5 weeks. After food stimulations, the serum gastrin level was 72 pg/ml on the average before PDL, but the level was elevated showing average values of 97, 107, 104, 105 and 101 pg/ml at 2, 3, 4, 5 and 6 weeks, respectively. The rate of increase over the level before PDL was 45% at 5 weeks. Differently from the case of gastric acid secretion, the serum gastrin level continued to increase even after 4 weeks of PDL.

Fig. 1. Acid outputs in response to food stimulations before and after PDL.
Mean±s.d.

Fig. 2. Serum gastrin levels before and after PDL.
Mean±s.d. ●—●, fasting; ○—○, food stimulation.
Effects of the administration of pancreatic enzymes in dogs after PDL

Increases in gastric acid secretion in response to food stimulations varied between the cases administered with and without pancreatic enzymes as indicated in Fig. 3. One week after PDL, the dogs showed markedly increased gastric acid secretion, disclosing no influence of the administration of pancreatic enzymes. At 2 weeks and later, however, the acid secretion was significantly inhibited ($p<0.02$) in the cases administered with pancreatic enzymes as compared with those without pancreatic enzymes. Acid outputs at 4 weeks after PDL were 3.22 mEq/6 hr on the average with the administration of pancreatic enzymes against 4.94 mEq/6hr without the administration, showing a 65% lower output in the former than in

![Graph 3](#)

Fig. 3. Rate of increase in acid outputs in response to food stimulations with (o--o) and without (●--●) the administration of pancreatic enzymes after PDL. Mean±s.D.

![Graph 4](#)

Fig. 4. Serum gastrin levels in response to food stimulations with (o--o) and without (●--●) the administration of pancreatic enzymes before and after PDL. Mean±s.D.
the latter. After 4 weeks, acid secretion tended to decrease indiscriminately in both groups.

Fig. 4 shows the levels of serum gastrin at fasting and at food stimulations with or without the administration of pancreatic enzymes. The fasting level of serum gastrin, 30 pg/ml on the average before PDL, tended to increase 2 weeks after PDL until 6 weeks. After food stimulations, the serum gastrin level was 86 pg/ml on the average before PDL. The level tended to rise 2 weeks after PDL, persistently up to 6 weeks, revealing no significant difference (p>0.05) between the cases administered with pancreatic enzymes and those without pancreatic enzymes.

Fig. 5 shows the levels of serum glucagon at fasting and at food stimulations with or without the administration of pancreatic enzymes. The fasting level of serum glucagon before PDL was 295 pg/ml on the average. The level tended to rise after PDL. The serum glucagon level after food stimulations was 776 pg/ml on the average before PDL. The level at food stimulations decreased at 1 week after PDL in the cases either with or without the administration of pancreatic enzymes. At 2 weeks after PDL and later, the level tended to increase, being significantly higher with the administration of pancreatic enzymes than without the administration (p<0.02). The values at 4 weeks after PDL were 854 pg/ml on the average with the administration of pancreatic enzymes and 542 pg/ml without the administration, showing a 63% higher level in the former than in the latter.

The levels of serum insulin at fasting and at food stimulations with or without the administration of pancreatic enzymes are shown in Fig. 6. The fasting level of serum insulin was 36 µU/ml on the average before PDL. The level tended to decrease at 1 week after PDL, and persistently up to 6 weeks. After food stimulations, the level of serum insulin was 49 µU/ml on the average before PDL and

![Fig. 5. Serum glucagon levels in response to food stimulations with (○—○) and without (●—●) the administration of pancreatic enzymes before and after PDL. Mean±S.D.](image)
increased at 1 week after PDL, showing a level higher than before PDL either with or without the administration of pancreatic enzymes. At 2 weeks and later, however, the level tended to decrease, indicating average values of 33 µU/ml with the administration of pancreatic enzymes and 30 µU/ml without the administration at 4 weeks, either showing nearly 70% of the level before PDL.

**Glucose tolerance**

The sugar assimilation coefficient ($k$) at the intravenous glucose tolerance test (IVGTT) was 2.83 on the average before PDL. A notable drop in glucose tolerance was indicated with average values of 1.23 and 1.11 at 4 and 8 weeks after PDL,
respectively. Fig. 7 shows blood sugar levels and serum insulin levels observed in IVGTT. The level of blood sugar attained to a peak 1 min after the glucose injection and returned to its fasting level 60 min after the injection in dogs before PDL. The dogs, however, failed to show a return of blood sugar to the fasting level 60 min after the glucose injection at 4 and 8 weeks after PDL. The level of serum insulin determined at the same time showed a peak at 1 min after the glucose injection before PDL. At 4 and 8 weeks after PDL, however, the levels were lower than before PDL.

Pathologic findings on the stomach, duodenum, Heidenhain pouch, and pancreas

Multiple erosions of the gastric mucosa were found in two of the nine dogs, but there was no evidence of ulceration. Neither ulceration nor erosion was identified in the mucosa of the duodenum and Heidenhain pouch. The pancreas grossly indicated diffuse fibrosis and notable atrophy 8 weeks after PDL, and there was a conspicuous dilatation of the main pancreatic duct. Centering on the surroundings of the main pancreatic duct, depletion of acinar cells, fibrous hyperplasia, and infiltration of round cells were quite evident. The rate of pancreatic parenchymal integrity was identified as 42.62±11.37 vol % in histometrical method, showing a decrease in acinar cells. Fibrous hyperplasia and cell infiltration were evident in the pancreatic islets. There was no histological evidence of fatty liver.

DISCUSSION

It has been pointed out that gastric hypersecretion is likely to develop following pancreatic insufficiency, particularly pancreatic exocrine abnormalities. Yesko (1928), Elliott et al. (1963, 1964), Elliott (1974) and other researchers have strenuously pursued the mechanism of gastric hypersecretion, emphatically in dogs with pancreatic duct ligation. Gastric hypersecretion in response to food stimulations set in dissimilarly after PDL according to different authors; around 20–30 days (Kyle and Welbourn 1966), around 10 days (Chey and Lorber 1967) and around 5 days (Hein et al. 1963). In the present study, gastric acid secretion in dogs with PDL accelerated in response to food stimulations commencing 1 week after PDL, and at 4 weeks the acid output was as high as 200–600% of the level before PDL.

In search of the mechanism of gastric hypersecretion after PDL, many researchers advocated different factors: 1) release of gastric secretagogue from the atrophic pancreas, 2) hepatocellular damage, 3) hyperplasia of parietal cells, 4) release of gastrin from the pyloric antrum and duodenum, and 5) absence or deficiency of the normally present inhibitory influences from the proximal small bowel — gastric inhibitory polypeptide (GIP). Among these, the release of a gastrin-like substance from the atrophic pancreas reported by Zollinger et al. (1962) has been denied on the ground of failure in extraction of such a substance (Kyle and Welbourn 1966). Likewise, hepatocellular damage was already ignored by Hein et al. (1963) and neglected in the light of no fatty liver in the present study.
As to the release of gastrin from the pyloric antrum, Elliott et al. (1963), Basso et al. (1972), and Sakazaki et al. (1976), citing hypergastrinemia following PDL, emphasized such release of gastrin as an influential factor constituting the mechanism of gastric hypersecretion after PDL. According to Elliott et al. (1963), gastric hypersecretion after PDL almost disappeared after antrectomy. Basso et al. (1972) reported that antrectomy performed prior to PDL could accompany no development of either acid hypersecretion or hypergastrinemia. Sakazaki et al. (1976), studying the changes in serum gastrin levels after total and simple pancreatic duct ligations, concluded gastrin from the pyloric antrum to be primarily responsible for the development of hypergastrinemia. However, Greenlee et al. (1959) reported that even with antrectomy performed beforehand, acid hypersecretion after PDL was not thwarted contrarily to the results of Basso et al. (1972). Another intricate theory was offered by Peterson et al. (1974) based on their experimental results that the fasting level of gastrin after PDL did not rise but the total of the gastrin levels 2 hr after feeding apparently indicated their rising tendency. Our present results show that acid output began to increase 1 week after PDL, attained to a peak at 4 weeks and then gradually decreased, while a rising trend of the level of serum gastrin was persistent even after 4 weeks. With the administration of pancreatic enzymes, however, hypersecretion of gastric acid was markedly inhibited 2 weeks after PDL, while the unaffected level of serum gastrin continued its rising trend up to 6 weeks of PDL. This implies that gastric hypersecretion after PDL may be sustained by intervention of some gut hormone other than antral gastrin.

On the other hand, it has been reported by Elliott et al. (1964), and Hein et al. (1962) that the administration of pancreatic enzymes together with the test meal led gastric secretion to decrease. According to Elliott et al. (1964), the administration of pancreatic enzymes, unless it was early enough ahead of gastric hypersecretion after PDL, could not produce any inhibitory effect. Pairent et al. (1969) and Pairent and Howard (1975) reported that various pancreatic enzymes used in dogs with PDL had their absorptive effects divergent from one another. In the present study, gastric secretion in response to food stimulations was examined in the same dogs with and without the administration of pancreatic enzymes. Acid secretion in dogs administered with pancreatic enzymes was markedly inhibited at 2 weeks and later following PDL. This fact probably explains that the administration of pancreatic enzymes helps fat absorption to come back near normal, with a result that gastric inhibitory polypeptide from the proximal small bowel is released to inhibit gastric secretion. Chey and Lorber (1967) noted that the administration of 40–60 ml of pancreatic juice combined in the test meal could suppress gastric hypersecretion of dogs after PDL. Similarly, Kyle and Welbourn (1966) reported that the administration of fat after PDL accelerated acid secretion from the Heidenhain pouch, but this was suppressed when pancreatic juice was administered simultaneously. Hofmann et al. (1975) found that instillation of olive oil and oleic acid into the duodenum in the presence of pancreatic juice could
inhibit gastric acid secretion, but in the absence of pancreatic juice, the inhibitory effect was only recognized with the instillation of oleic acid. Sakazaki et al. (1976), however, contended that only lack of lipase in pancreatic juice or pancreatic atrophy is not enough for full explanation of gastric hypersecretion after PDL. In this regard, recently, Elliott (1974), studying the relation between loss of pancreatic juice and acid secretion, suggested that gastric hypersecretion after PDL can probably be traced to pancreatic atrophy and the accompanying indigestion of fat that has been brought about by the absence or lack of gastric inhibitory hormone from the duodenum and proximal small bowel.

Furthermore, we investigated the levels of serum glucagon and serum insulin as indices to pancreatic endocrine function. In dogs with pancreatic exocrine abnormalities, Hayakawa et al. (1977) noted that the level of serum glucagon after the administration of glucose did not rise. In this regard, Matsuyama and Foà (1974) noted a high level of pancreatic glucagon indicated by the value of serum glucagon determined by specific antibodies in dogs that had undergone total pancreatectomy. The finding obtained in the present study that the level of serum glucagon was higher in dogs with than without the administration of pancreatic enzymes may be attributed to the remaining function of the cells of the pancreatic islets. Concerning changes in the level of serum insulin, Ambromovage et al. (1973) observed that the fasting level was high in dogs 6 weeks after PDL, but low at 12 weeks, coinciding with the consummation of atrophy and fibrosis of the pancreatic islets. In the present study, the level of serum insulin turned to fall lower than before PDL, commencing 1 week and 2 weeks following PDL for the fasting level and the level after food stimulations, respectively, suggesting fibrosis and atrophy of the pancreatic islets occurring early after PDL.

References


