World J. Surg. 24, 1236–1242, 2000
DOI: 10.1007/s002680010244

WORLD
Journal of
SURGERY

Manometric Evidence of Improved Early Gastric Stasis by Erythromycin after Pylorus-preserving Pancreatoduodenectomy

Hiroaki Matsunaga, M.D., Masao Tanaka, M.D., Ph.D., Shunichi Takahata, M.D., Yoshiaki Ogawa, M.D., Ph.D., Gen Naritomi, M.D., Ph.D., Kazunori Yokohata, M.D., Ph.D., Koji Yamaguchi, M.D., Ph.D., Kazuo Chijiiwa, M.D., Ph.D.

Department of Surgery and Oncology, Kyushu University Graduate School of Medical Sciences, Fukuoka 812-8582, Japan

Abstract. Gastric stasis is a frequent complication of pylorus-preserving pancreatoduodenectomy (PPPD). We demonstrated that it might be attributable to delayed recovery of phase III activity of the gastric migrating motor complex due to low concentrations of plasma motilin caused by resection of the duodenum. Leucine 13-motilin is effective for treating gastric stasis, but it is not yet available for clinical use. Whether erythromycin would improve early gastric stasis after PPPD was tested clinically and by manometry. A manometric tube assembly and a gastrostomy tube were inserted in the stomach of 10 patients at PPPD for pressure recording from the gastric antrum and jejunum and for gastric juice drainage, respectively. After baseline recording, erythromycin 5 mg/kg was given intravenously on day 14 and saline as a placebo on day 17 every 4 hours four times a day. The daily volume of gastric juice output and the gastric motility index were measured. The mean period until the return of gastric phase III was 31 ± 1 days. Erythromycin significantly increased the gastric motility index from 7.9 ± 1.3 mmHg to 15.7 ± 1.8 mmHg ($p = 0.0005$), whereas saline did not (7.2 ± 1.6 mmHg to 6.5 ± 1.2 mmHg; $p = 0.21$). Erythromycin significantly decreased the gastric juice output from 1080 ± 190 ml to 738 ± 199 ml ($p < 0.0001$), but the saline injections did not (1064 ± 174 ml to 1115 ± 189 ml; $p = 0.35$). Erythromycin, a universally available motilin agonist, is a safe, effective, potent drug for the treatment of early gastric stasis after PPPD.

It is well recognized that the morbidity and mortality associated with pylorus-preserving pancreatoduodenectomy (PPPD) are not different from those seen with standard pancreatoduodenectomy [1–3]. However, gastric stasis occurs in 20% to 50% of all patients during the early postoperative period after PPPD [3–6]. Gastric stasis, broadly defined as the need for gastric decompression for many days, results in prolonged loss of a large amount of gastric juice and delay of food ingestion. Also, gastric stasis lengthens the hospital stay and increases hospital costs. Previous treatments include prolonged nasogastric or gastrostomy tube decompression and administration of H_2-receptor antagonists, along with nutritional support.

Factors possibly responsible for gastric stasis after PPPD are ischemic and neural injury to the antropyloric muscle [2, 3], gastric dysrhythmia [7], and gastric atony after resection of a duodenal pacemaker or due to reduced circulating levels of motilin [8]. Enterochromaffin cells in the duodenum and proximal jejunum produce motilin [9, 10]. Peaks in the plasma motilin concentration are associated with the occurrence of phase III activity of the interdigestive migrating motor complex (MMC) in the stomach and duodenum [11]. Resection of the canine duodenum abolishes the cyclic increase in the plasma motilin concentration associated with the MMC and results in a loss of phase III activity of the gastric MMC [12]. Recently, we have shown slower recovery of gastric phase III and lower plasma concentrations of motilin in patients who underwent PPPD than in those who underwent duodenum-preserving pancreatic head resection [8]. Therefore we thought that gastric stasis after PPPD might be attributable at least in part to delayed recovery of gastric phase III due to low concentrations of plasma motilin caused by resection of the duodenum.

Exogenous motilin given intravenously during fasting initiates phase III-like contractions in the stomach and duodenum in dogs [13–15]. Motilin induces phase III-like gastric contractions even after duodenectomy that abolishes the gastric MMC in dogs [16]. We have recently demonstrated that exogenous motilin produces phase III-like gastric contractions and reduces gastric juice output in patients after PPPD [17]. However, motilin is not yet available for clinical use. Instead, the use of erythromycin is of current interest, as it has been reported to be effective for treating gastric stasis after PPPD without assessing gastric motility [18]. Several studies have demonstrated that erythromycin mimics the effect of motilin on the motility of the canine and human upper gastrointestinal (GI) tract [19–23]. The present prospective placebo-controlled study addresses a hypothesis that erythromycin might improve gastric stasis and reduce the gastric juice output after PPPD.

Materials and Methods

Patients

Between January 1995 and September 1997 ten patients chosen for this study underwent PPPD in our department at Kyushu University Hospital. Six patients were male and four female. The

Correspondence to: M. Tanaka, M.D., Ph.D., e-mail: masaotan@linne.med.kyushu-u.ac.jp

age ranged from 46 to 81 years (mean 68 years). Five patients had a mucin-hyperproducing tumor in the head of the pancreas, three had a cancer in the head of the pancreas, and one each had a cancer of the duodenal papilla and groove pancreatitis. Two patients were diabetic.

The Ethical Committee on Clinical Investigations of Kyushu University Faculty of Medicine approved the study protocol. Each patient was fully informed of the aim, methods, and possible complications of the study and gave written consent.

Manometric Apparatus

Four polyethylene tubes were bundled for GI pressure recording. The outer diameter of each tube was 2.0 mm and the inner diameter 1.4 mm. A 0.5-mm side hole was drilled just before the sealed end. The recording holes of the tube assembly were placed 0.5, 20, 35, and 38 cm from the tip, as previously reported [8, 17].

Operative Procedures

Operative procedures were carried out as described here for the treatment of malignant disease; lymph node dissection was not performed for benign disease. The extent of resection during PPPD included the head of the pancreas, gallbladder, common bile duct, duodenum, and 10 to 15 cm of the proximal jejunum. The proximal duodenum was meticulously preserved 3 to 4 cm distal to the pylorus. The stomach remained intact. The right gastroepiploic artery, right gastric artery, and gastroduodenal artery were tied. The pancreas was transected in front of the superior mesenteric vein and the common bile duct above the insertion of the cystic duct after cholecystectomy. Suprapyloric, infrapyloric, common hepatic arterial, hepatoduodenal, peripancreatic, and superior mesenteric lymph nodes were dissected. End-to-end duodenojejunostomy was followed by end-to-side pancreatojejunostomy 5 cm distally and hepaticojejunostomy at 5 cm more.

A polyethylene catheter was inserted into the main pancreatic duct via the pancreatojejunostomy and another through the hepaticojejunostomy. Both catheters were brought proximally via the duodenojejunostomy and farther out of the anterior gastric wall. The manometric tube assembly was inserted into the stomach and down into the jejunum through a stab incision on the anterior wall, and the recording holes were placed in the gastric antrum (two holes 3 cm apart) and jejunum (two holes 35 cm and 15 cm from the distal gastric hole). The jejunal catheter of the assembly was also used for enteral feeding when needed. In all patients a gastrostomy tube was positioned in the gastric fundus through the anterior wall of the gastric body for gastric juice drainage (Fig. 1).

Manometric Recording

Recording of GI motility was started 14 days after surgery. An H_2-receptor antagonist and gastrokinetic drugs were avoided beginning 2 days prior to recording. With the patient lying in bed in the supine position, the manometric tubes were infused with sterile distilled water at a rate of 0.25 ml/min using a low-compliance pneumohydraulic capillary infusion system. Each tube was connected to an external pressure transducer (DX-360, Spectramed Medical Products, Singapore). The GI pressure changes were recorded with the use of a thermal array multichannel recorder (RTA-1200M, Nihon Kohden, Tokyo, Japan) at a paper speed of 1 cm/min and the application software of Macintosh (Mac Lab Chart 3.5, Apple Co., New South Wales, Australia) at a count speed of 40 samplings per minute. Zero reference was set by placing the recording holes of an identical tube assembly connected to the recording system at the level of the midaxillary line of the patient at atmospheric pressure [8, 17].

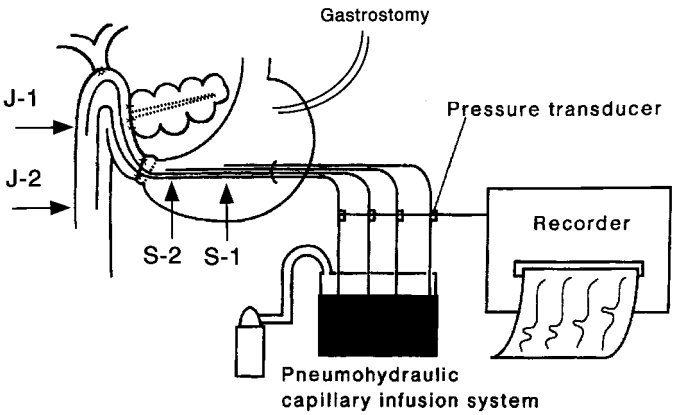

Fig. 1. Position of four manometric tubes for gastrointestinal pressure recording and a gastrostomy tube in a patient who underwent pylorus-preserving pancreatoduodenectomy (PPPD). The side holes for pressure recording were placed in the antrum (two holes) and jejunum (two holes). Two polyethylene catheters for biliary and pancreatic drainage inserted through the anterior gastric wall, such as the manometric and gastrostomy tubes, are not depicted to simplify the illustration.

On day 14 after surgery, the presence or absence of phase III of the gastric MMC was investigated by a 3-hour recording. After confirming that a cyclic pattern of the gastric MMC was absent, erythromycin 5 mg/kg (erythromycin lactobionate; Abbott Laboratories, North Chicago, IL, USA) dissolved in 100 ml physiologic saline was administered intravenously for 15 minute periods. The administration of erythromycin was repeated every 4 hours four times a day. On day 17 after surgery, the absence of phase III of the gastric MMC was reconfirmed by a 3-hour recording. Then an identical volume of normal saline was given intravenously every 4 hours four times a day (placebo study). Recording was continued for at least 2 hours after the first injection of erythromycin or saline. The motility recording was repeated at a weekly interval until the first appearance of gastric phase III; the daily volume of gastric juice output was measured every day. All the patients started to eat from day 18 after surgery.

Analysis of Data

Manometric tracings from the stomach and jejunum were analyzed by visual inspection and with the use of the application software of the Macintosh computer. The record at the distal gastric hole (S-2) allowed better recognition of gastric motility than at the proximal gastric hole (S-1). Phase III of the gastric MMC was identified as three regular and high-amplitude contractions per minute that lasted for at least 2 minutes followed by phase I. Phase III-like activity was defined as regular and high-amplitude contractions that lasted for at least 2 minutes.

Erythromycin was considered to be effective for inducing gastric or jejunal phase III-like contractions when such contractions oc-

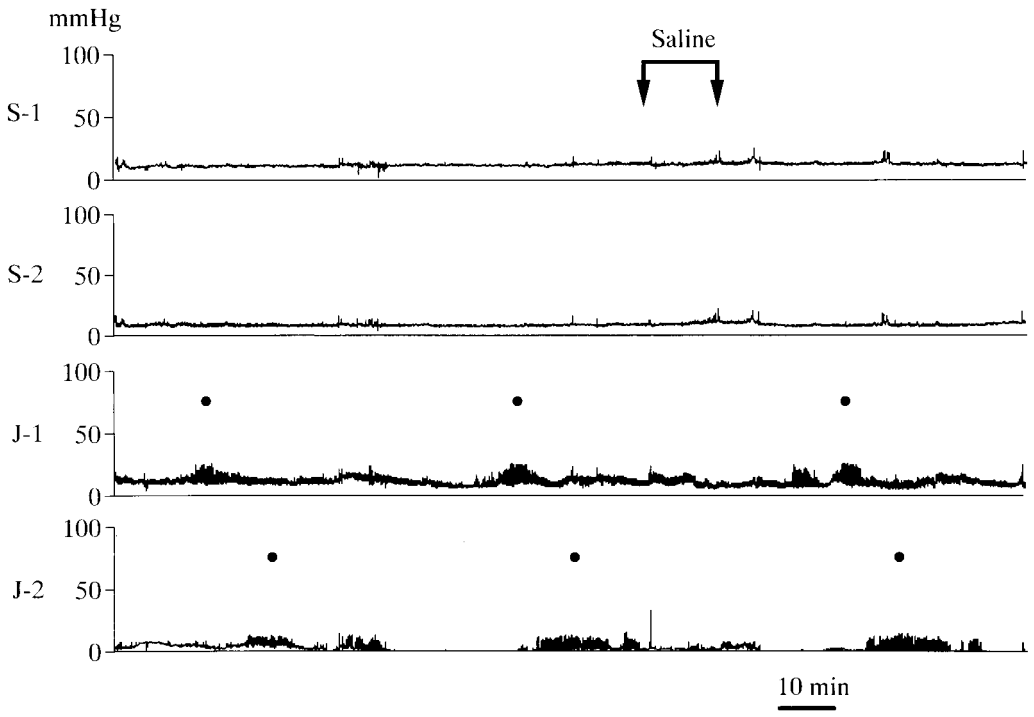

Fig. 2. Manometric recordings from the gastric antrum (S-1, S-2) and jejunum (J-1, J-2) showing the effect of saline in a patient who underwent PPPD. Two spontaneous phase III activities are seen in the jejunum before the injection of saline without gastric phase III (filled circles). Administration of saline caused no change in gastric or jejunal motility.

curred within 15 minutes after the injection. Latency was defined as the time elapsed from the start of the erythromycin injection to the onset of the erythromycin-induced gastric phase III-like contractions. The motility index was determined as a value of integrated amplitude of gastric contractions divided by the time. The response to erythromycin and saline was analyzed by comparing the motility index calculated for 30-minute periods before and after the injection. The volume of the daily output of gastric juice through the gastrostomy was also measured.

Statistical Analysis

All data were expressed as a mean ± standard error of the mean (SEM). Mean values were compared using the paired *t*-test. The difference was considered significant when p was < 0.05.

Results

Spontaneous Motility

Our patients had no serious complications. The GI pressure recordings showed no gastric MMC from days 14 through 17 after surgery in all patients. A few irregular contractions of moderate to large amplitude occurred but did not have any cyclic pattern. These contractions were similar to those seen during phase II of the gastric MMC. In contrast, jejunal motility showed a characteristic MMC pattern in all patients.

The return of phase III activity of the gastric MMC was not seen for the 3 weeks after PPPD. The earliest recovery was observed on day 22 after surgery and the latest on day 35. The mean period until the first appearance of gastric phase III was 31.0 ± 1.2 days.

Effect of Erythromycin

Administration of saline caused no change in gastric or jejunal motility (Fig. 2). In contrast, erythromycin induced phase III-like gastric contractions in all patients (Fig. 3). These gastric contractions did not migrate caudally. The latency of erythromycin-induced gastric contractions was 2.5 ± 0.5 minutes. The antral phase III-like contractions consisted of an initial burst of several contractions, occurring at a frequency of three contractions per minute, and were followed by a prolonged period (>1 hour) of strong contractions occurring at a frequency of about one contraction per minute. Erythromycin produced no phase III-like contractions in the jejunum of any of the patients.

Change in Gastric Motility Index

Injection of saline caused no significant change in the gastric motility index (7.2 ± 1.6 mmHg before the injection versus 6.5 ± 1.2 mmHg afterward) ($p = 0.21$) (Fig. 4). In contrast, injection of erythromycin resulted in a significant increase in the gastric motility index, from 7.9 ± 1.3 mmHg to 15.7 ± 1.8 mmHg ($p = 0.0005$).

Change in Daily Volume of Gastric Juice Output

The mean gastric juice output was 371 ± 30 ml between days 1 and 11 after surgery owing to the use of an H_2-receptor antagonist. On postoperative day 12, when the H_2-receptor blocker was withdrawn for the study, the gastric juice output increased to a mean of 740 ± 165 ml and on day 13 to 1080 ± 190 ml. Injection of saline resulted in no significant change in the volume of gastric juice output (1064 ± 174 ml before versus 1115 ± 189 ml after the

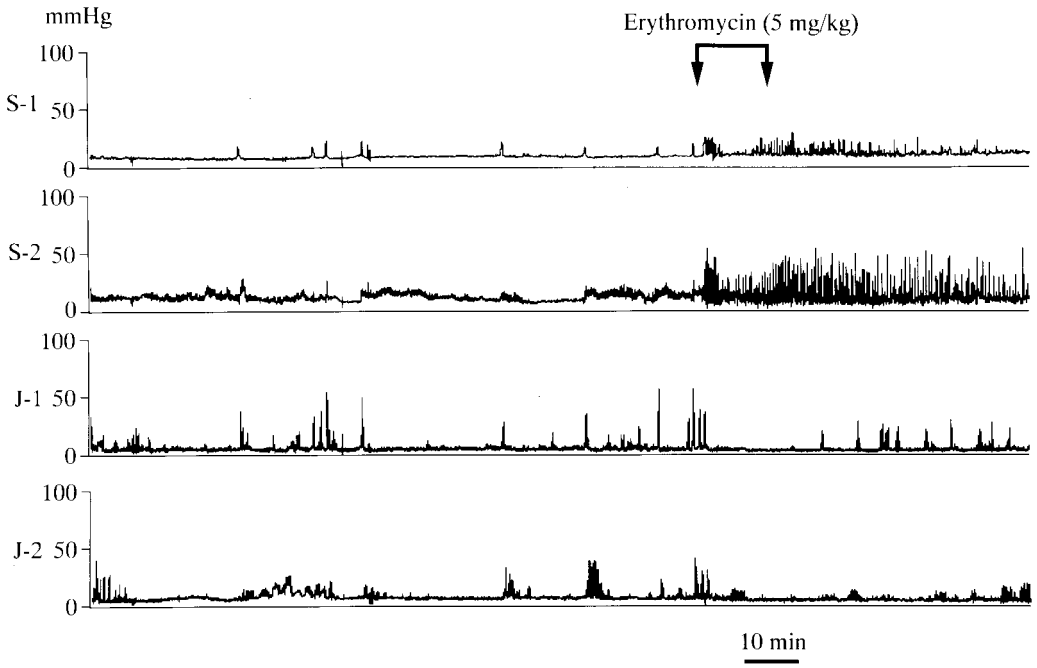

Fig. 3. Effect of intravenous administration of erythromycin in a patient who underwent PPPD. An injection of erythromycin induced phase III-like contractions, followed by a prolonged period (> 1 hour) of vigorous contractions in the stomach but not in the jejunum.

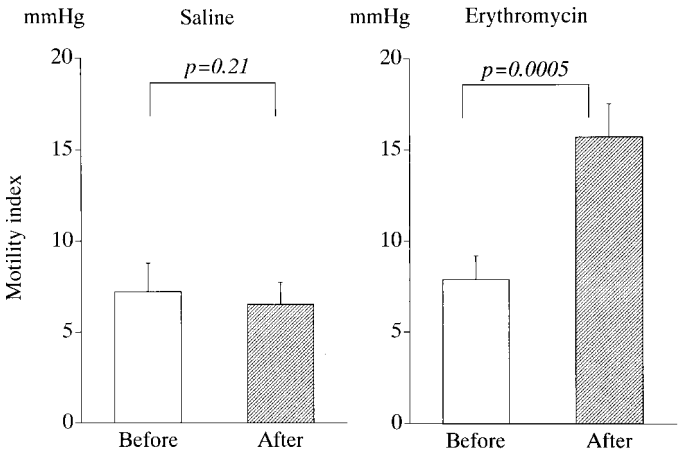

Fig. 4. Effect of the injection of saline and erythromycin on the gastric motility index after PPPD. Saline injections caused no change, but erythromycin resulted in a significant increase in the gastric motility index.

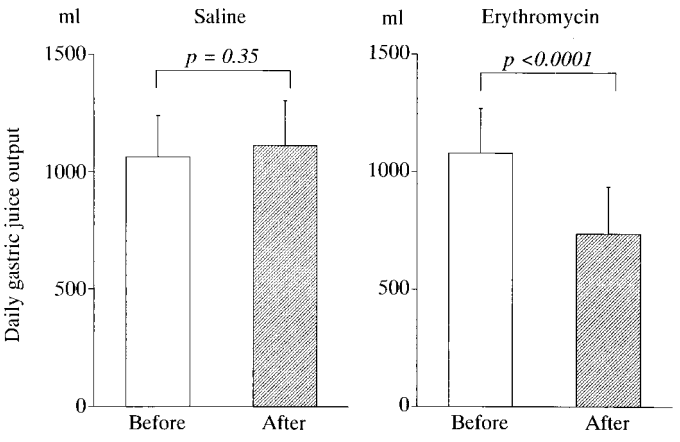

Fig. 5. Effect of saline and erythromycin on the daily volume of the gastric juice output after PPPD. Saline injections produced no significant change, but erythromycin caused a significant decrease in the volume of gastric juice.

injection on day 17) ($p = 0.35$) (Fig. 5). In contrast, erythromycin caused a significant decrease in gastric juice output from 1080 ± 190 ml (day 13) to 738 ± 199 ml (day 14) ($p < 0.0001$) (Fig. 5).

Complications

There were no major adverse reactions to the study drugs (erythromycin and saline) in the patients.

Discussion

The study demonstrated that phase III activity of the gastric MMC did not return until postoperative day 31.0 ± 1.2 in patients after PPPD, and that erythromycin effectively induced bursts of gastric phase III-like contractions and a prolonged period of increased antral contractions in these patients. Erythromycin injections resulted in a striking increase in the gastric motility index and a significant decrease in the daily output of gastric juice through the gastrostomy. Although erythromycin was always tested earlier than saline to negate the effect of postoperative time on the recovery of gastric phase III, erythromycin was always effective in inducing strong continuous gastric contractions.

The cyclic pattern of the gastric MMC was absent in our patients during the early phase after PPPD. The jejunal MMC recovered relatively early after PPPD, although it showed a shorter period for the cyclic pattern. The wall of the gastric corpus was fixed owing to insertion of manometric catheters, drainage tubes, and a gastrostomy tube. The gastric wall fixation, however,

does not seem to affect gastric motility, as we previously demonstrated early recovery of phase III activity of the gastric MMC in patients who had undergone duodenum-preserving pancreatic head resection with similar gastric wall fixation [8]. Tanaka and Sarr [12] demonstrated a loss of the characteristic phase III of the gastric MMC after total duodenectomy in dogs and attributed it to a lack of the cyclic change in the plasma concentration of motilin. The plasma motilin concentration was not measured in this study, but we previously reported low concentrations of motilin at phase III of the MMC in patients who underwent PPPD [8]. These findings suggest that the cyclic increase of motilin released by the duodenum might initiate and consolidate gastric phase III in humans and dogs.

Erythromycin mimics motilin in its effect on GI motility of dogs and humans in doses that are lower than those used for antibiotic effects (1–3 mg/kg/hr) [21, 22]. Tack et al. [23] demonstrated that a low dose (40 mg) of erythromycin induced a premature phase III that started in the stomach and migrated through the small intestine with the same characteristics as the spontaneously occurring phase III in healthy volunteers. High doses of erythromycin (200 and 350 mg) induced bursts of strong rhythmic antral contractions that did not propagate to the small intestine and were not followed by phase I but, instead, by a prolonged period of increased antral contractions. In the present study we confirmed that the same reactions in the stomach were preserved after PPPD using a high dose (5 mg/kg) of erythromycin. This dose is almost the same as that used by Janssens et al. [22] to improve gastric emptying during diabetic gastroparesis. It is unclear whether the effect of the high dose of erythromycin is related to the motilin agonist effect or if other actions of erythromycin intervene.

We did not investigate the effect of a low dose of erythromycin. Even if a low dose were administered, however, erythromycin would have induced phase III-like gastric contractions but no jejunal phase III in our patients. Disruption of intrinsic neural continuity across the duodenojejunostomy is a possible explanation for this phenomenon. Sarna et al. [24] showed in dogs that intrinsic nerves regenerate after transection and reanastomosis of the small intestine. Propagation of the MMC across the site of transection started to recover 45 to 60 days after surgery and recovered fully by 98 to 108 days. It is conceivable, therefore, that the erythromycin-induced gastric contractions would not propagate down to the jejunum across the anastomosis during the study period in our patients.

Different distribution of motilin-binding receptors in the human GI tract is another possible explanation for the absence of erythromycin-induced phase III in the jejunum. Peeters et al. [25] reported that the motilin receptors were densely present in the gastric corpus and antrum and the duodenum but absent in the jejunum and ileum. Their data indicate that the gastroduodenal region, but not the jejunum, is reactive to motilin agonists. Therefore it would be judicious to think that erythromycin initiates phase III-like contractions in the stomach preserved after PPPD but not in the jejunum because of difference in the distribution of motilin receptors.

Yeo et al. [18] demonstrated that administration of erythromycin was associated with a significant improvement in gastric emptying of a radionuclide-labeled test meal and reduced the need to reinsert a nasogastric tube for delayed gastric emptying after PPPD. Important differences between our study and theirs are twofold. First, we investigated interdigestive GI motility, focusing on the gastric MMC, whereas they measured gastric emptying during the digestive state. For assessing early postoperative gastric stasis, which delays resumption of oral intake, measuring the interdigestive gastric contractions might be more appropriate in our opinion. Second, we inserted a gastrostomy tube for drainage and measurement of the daily output of gastric juice; they did not quantify the gastric juice directly. Therefore, whether erythromycin reduced the output of gastric juice after PPPD was not determined by Yeo et al. [18].

The mean volume of the gastric juice output measured in this study was 1115 ± 189 ml/day at most. The relatively small amount of gastric juice output in this series may be due to preserving as long a segment of the duodenum as possible. In our clinical practice, we usually use an H_2-receptor blocker to reduce gastric juice output. This was also the case in our patients before postoperative day 11. It would be more logical to employ a prokinetic drug than to administer the H_2-blocker to reduce gastric juice output if the prokinetic drug has been proved effective.

Although we previously reported that leucine 13-motilin, which can be administered to humans, effectively reduced gastric juice output in patients with gastric stasis after PPPD, this agent is not yet available for clinical use. Erythromycin is a universally available motilin agonist and is a safe, effective, even more potent drug for treating early gastric stasis after PPPD.

Résumé

La stase gastrique est une complication fréquente de la duodénopancréatectomie avec conservation du pylore (DPCP). Nous avons démontré que celle-ci pourrait être en rapport avec une récupération tardive de l'activité phase III du complexe moteur migrant de l'estomac en raison de la concentration peu élevée de motiline plasmatique, secondaire à la résection du duodénum. La motiline à la leucine 13 est efficace dans le traitement de la stase gastrique. Cependant, on n'en dispose pas encore en pratique clinique. On a donc mené une étude manométrique pour savoir si l'érythromycine pouvait améliorer la stase gastrique précoce survenant après une DPCP en pratique clinique. Au moment de la DPCP, on a inséré une sonde de manométrie et pratiqué une gastrostomie pour enregistrer la pression dans l'antre gastrique et le jéjunum et pour drainer le suc gastrique, respectivement, chez 10 patients. Après l'enregistrement de base, on a administré de l'érythromycine, 5 mg/kg, par voie intraveineuse au jour 14 et du sérum physiologique au jour 17, toutes les quatre heures, quatre fois par jour. Le volume quotidien de suc gastrique et la motilité gastrique ont été mesurés. Le délai moyen pour le retour de la phase III gastrique a été de 31 ± 1 jours. L'érythromycine a significativement augmenté l'indexe de motilité gastrique, de 7,9 ± 1,3 à 15,7 ± 1,8 mmHg ($p = 0{,}0005$), alors que le sérum physiologique n'a pas eu d'effet (7,2 ± 1,6 vs 6,5 ± 1,2 mm Hg, $p = 0{,}21$). L'érythromycine a significativement diminué le volume gastrique, de 1080 ± 190 à 738 ± 199 ml ($p < 0{,}0001$), mais ceci n'a pas été le cas pour le sérum physiologique (1064 ± 174 vs 1115 ± 189 ml, $p = 0{,}35$). L'érythromycine, un agoniste universellement disponible, serait un médicament sûr, efficace et puissant dans le traitement de la stase gastrique précoce après DPCP.

Resumen

La estasis gástrica es una complicación frecuente de la pancreatoduodenectomía con preservación del píloro (PDPP). Hemos demostrado que ello puede atribuirse a retardo en la recuperación de la fase III de la actividad del complejo motriz migratorio gástrico, debido a bajas concentraciones de la motilina gástrica causadas por la resección del duodeno. La motilina -13 leucina es efectiva en el tratamiento de la estasis gástrica; sin embargo, todavía no está disponible para uso clínico. Por medios clínicos y manométricos se estudió la efectividad de la eritromicina en cuanto a mejorar la estasis gástrica luego de PDPP. En el curso de la PDPP realizada en 10 pacientes, se colocó en el estómago un dispositivo de manometría y un tubo de gastrostomía para la medición de presiones a nivel del antro gástrico y del yeyuno y para drenaje del jugo gástrico, respectivamente. Luego de una medición basal, se administró eritromicina en dosis de 5 mg/kg por vía intravenosa cada 4 horas y 4 veces diarias en el día 14 y solución salina como placebo en el día 17. Se hizo la medición del volumen diario de jugo gástrico y del índice de motilidad gástrica. El lapso promedio hasta el retorno de la fase gástrica III fue 31 $\pm$ 1 día. La eritromicina incrementó en forma significativa el índice de motilidad gástrica de 7.9 $\pm$ 1.3 a 15.7 $\pm$ 1.8 mm Hg ($p = 0.0005$), en tanto que ello no ocurrió con la solución salina (7.2 $\pm$ 1.6 a 6.5 $\pm$ 1.2 mmHg, $p = 0.21$). La eritromicina disminuyó significativamente la producción de jugo gástrico de 1080 $\pm$ 190 a 738 $\pm$ 199 ml ($p < 0.0001$), pero no así la solución salina (1064 $\pm$ 174 a 1115 $\pm$ 189 ml, $p = 0.35$). La eritromicina, un agonista de la motilina de disponibilidad universal, parece ser una droga segura, efectiva y potente en el tratamiento de estasis gástrica precoz luego de PDPP.

References

1. Traverso, L.W., Longmire, W.P., Jr.: Preservation of the pylorus in pancreaticoduodenectomy: a follow-up evaluation. Ann. Surg. *192*: 306, 1980
2. Braasch, J.W., Rossi, R.L., Watkins, E., Jr., Deziel, D.J., Winter, P.F.: Pyloric and gastric preserving pancreatic resection: experience with 87 patients. Ann. Surg. *204*:411, 1986
3. Itani, K.M.F., Coleman, R.E., Akwari, O.E., Meyers, W.C.: Pylorus-preserving pancreatoduodenectomy: a clinical and physiologic appraisal. Ann. Surg. *204*:655, 1986
4. Patti, M.G., Pellegrini, C.A., Way, L.W.: Gastric emptying and small bowel transit of solid food after pylorus-preserving pancreaticoduodenectomy. Arch. Surg. *122*:528, 1987
5. Hunt, D.R., Mclean, R.: Pylorus-preserving pancreatectomy: functional results. Br. J. Surg. *76*:173, 1989
6. Williamson, R.C.N., Bliouras, N., Cooper, M.J., Davies, E.R.: Gastric emptying and enterogastric reflux after conservative and conventional pancreatoduodenectomy. Surgery *114*:82, 1993
7. Hocking, M.P., Harrison, W.D., Sninsky, C.A.: Gastric dysrhythmias following pylorus-preserving pancreaticoduodenectomy: possible mechanism for early delayed gastric emptying. Dig. Dis. Sci. *35*:1226, 1990
8. Naritomi, G., Tanaka, M., Matsunaga, H., Yokohata, K., Ogawa, Y., Chijiiwa, K., Yamaguchi, K.: Pancreatic head resection with and without preservation of the duodenum: different postoperative gastric motility. Surgery *120*:831, 1996
9. Brown, J.C., Cook, M.A., Dryburgh, J.R.: Motilin, a gastric motor activity-stimulating polypeptide: final purification, amino acid composition, and C-terminal residues. Gastroenterology *62*:401, 1972
10. Polak, J.M., Pearse, A.G.E., Heath, C.M.: Complete identification of endocrine cells in the gastrointestinal tract using semithin-thin sections to identify motilin cells in human and animal intestine. Gut *16*:225, 1975
11. Itoh, Z., Takeuchi, S., Aizawa, I., Mori, K., Tanimoto, T., Seino, Y., Imura, H., Yanaihara, N.: Changes in plasma motilin concentration and gastrointestinal contractile activity in conscious dogs. Am. J. Dig. Dis. *23*:929, 1978
12. Tanaka, M., Sarr, M.G.: Role of the duodenum in the control of canine gastrointestinal motility. Gastroenterology *94*:622, 1988
13. Itoh, Z., Honda, R., Hiwatashi, K., Takeuchi, S., Aizawa, I., Takayanagi, R., Couch, E.F.: Motilin-induced mechanical activity in the canine alimentary tract. Scand. J. Gastroenterol. *11*(Suppl. 39):93, 1976
14. Vantrappen, G., Janssens, J., Peeters, T.L., Bloom, S.R., Christofides, N.D., Hellemans, J.: Motilin and the interdigestive migrating motor complex in man. Dig. Dis. Sci. *24*:497, 1979
15. Sarna, S., Chey, W.Y., Condon, R.E., Dodds, W.J., Myers, T., Chang, T.M.: Cause-and-effect relationship between motilin and migrating myoelectric complexes. Am. J. Physiol. *245*:G277, 1983
16. Tanaka, M., Sarr, M.G.: Effects of exogenous motilin and morphine on interdigestive gastrointestinal motor activity after total duodenectomy in dogs. Surgery *104*:317, 1988
17. Matsunaga, H., Tanaka, M., Naritomi, G., Yokohata, K., Yamaguchi, K., Chijiiwa, K.: Effect of leucine 13-motilin (KW5139) on early gastric stasis after pylorus-preserving pancreatoduodenectomy. Ann. Surg. *227*:507, 1998
18. Yeo, C.J., Barry, M.K., Sauter, P.K., Sostre, S.R.N., Lillemoe, K.D., Pitt, H., Cameron, J.L.: Erythromycin accelerates gastric emptying after pancreatoduodenectomy: a prospective, randomized, placebo-controlled trial. Ann. Surg. *218*:229, 1993
19. Itoh, Z., Nakaya, M., Suzuki, T., Arai, H., Wakabayashi, K.: Erythromycin mimics exogenous motilin in gastrointestinal contractile activity in the dog. Am. J. Physiol. *247*:G688, 1984
20. Tomomasa, T., Kuroume, T., Arai, H., Wakabayashi, K., Itoh, Z.: Erythromycin induces migrating motor complex in human gastrointestinal tract. Dig. Dis. Sci. *31*:157, 1986
21. Peeters, T., Matthijs, G., Depoortere, I., Cachet, T., Hoogmartens, J., Vantrappen, G.: Erythromycin is a motilin receptor agonist. Am. J. Physiol. *257*:G470, 1989
22. Janssens, J., Peeters, T.L., Vantrappen, G., Tack, J., Urbain, J.L., DeRoo, M., Mulus, E., Bouillon, R.: Improvement of gastric emptying in diabetic gastroparesis by erythromycin: preliminary studies. N. Engl. J. Med. *322*:1028, 1989
23. Tack, J., Jansssens, J., Vantrappen, G., Peeters, T., Annese, V., Depoortere, I., Mulus, E., Bouillon, R.: Effect of erythromycin on gastric motility in controls and in diabetic gastroparesis. Gastroenterology *103*:72, 1992
24. Sarna, S., Condon, R.E., Cowles, V.: Enteric mechanisms of initiation of migrating myoelectric complexes in dogs. Gastroenterology *84*:814, 1983
25. Peeters, T.L., Bormans, V., Vantrappen, G.: Comparison of motilin binding to crude homogenates of human and canine gastrointestinal smooth muscle tissue. Regul. Pept. *23*:171, 1988

Invited Commentary

DOI: 10.1007/s002680010245

Charles J. Yeo, M.D.

Department of Surgery, The Johns Hopkins Hospital, Baltimore, Maryland, USA

This ambitious clinical study by Matsunaga et al. from Fukuoka, Japan looks at an important clinical problem following pancreaticoduodenectomy: that of early delayed gastric emptying. In various series, the incidence of early delayed gastric emptying ranges from a low frequency up to almost 50% of patients. The authors are correct to state that early delayed gastric emptying often lengthens the hospital stay and increases hospital cost. Additionally, in many instances early delayed gastric emptying is related to other complications, such as abscess formation or pancreatic fistula.

One of the prime hypotheses to explain the phenomenon of early delayed gastric emptying is that the duodenectomy leads to reduced circulating levels of motilin, resulting in a loss of phase III activity of the gastric migrating motor complex (MMC). The rationale for using erythromycin as an agent to improve gastric emptying is based on the fact that the 14-member macrolide ring of erythromycin serves as an agonist at gastric motilin receptors.

In this study, 10 patients who had undergone pylorus-preserving pancreaticoduodenectomy were evaluated. The anatomy of their reconstruction is a bit different than is normally performed in the United States, having an end-to-end duodenojejunostomy followed by end-to-side pancreaticojejunostomy and end-to-side hepaticojejunostomy (see their Fig. 1). These patients were all instrumented with catheters through the pancreaticojejunostomy and through the hepaticojejunostomy and by manometric tube assemblies placed via gastrotomy. One could quibble with some of the study methodology, although it would be minor quibbling. For example, the patients were studied in the supine position, although for most humans oral intake is in the upright or seated position, and we typically remain upright or seated immediately postprandially. Also, these patients were studied on days 14 through 17 postoperatively, a time that is quite far removed from their operative procedure. In fact, with the improvements in technical performance of pancreaticoduodenectomy and improved postoperative care, most postpancreaticoduodenectomy patients are discharged on postoperative days 8, 9, or 10 eating solid food and without any form of parenteral or enteral nutritional support.

These criticisms notwithstanding, the authors' data fit with my biases and with the results of our prospective, randomized blinded clinical study performed several years ago [1]. The authors show that the administration of erythromycin 5 mg/kg induced phase III-like gastric contractions in all patients, which corresponded with an increase in the gastric motility index and a decrease in the gastric juice recovered from the gastrostomy tube.

In essence, Matsunaga and his coauthors have lent additional support to the thesis that erythromycin can improve gastric motility following pancreaticoduodenectomy. We must not forget that the influence of erythromycin on the stomach has been known for years, as some of the most notorious side effects of erythromycin are upper abdominal cramping and nausea, the result of its effects on motilin receptors in the stomach.

Erythromycin is certainly a safe, nontoxic, inexpensive drug that can be given to postpancreaticoduodenectomy patients without complications. For the past several years, we have used erythromycin in all of our patients after pancreaticoduodenectomy. It has become a part of our Critical Pathway in these patients. It is administered as erythromycin lactobionate in a dose of 200 mg intravenously every 6 hours starting on postoperative day 2. We initiated this treatment based on the results of our prospective, randomized trial [1] in an effort to reduce the rate of early delayed gastric emptying and to speed hospital discharge. Certainly other factors are responsible for improvements in patient outcome as well [2], although the rate of early delayed gastric emptying has fallen at The Johns Hopkins Hospital in recent years from about 35% to less than 20%, and our median length of postoperative hospital stay has fallen from 15–16 days to 10 days. Five years ago it was typical to have several patients in the hospital receiving treatment for early delayed gastric emptying via nasogastric tube intubation, prokinetic agents, and total parenteral nutrition; today such patients are a rarity. Although many other factors are also at play here, some of the improved results may be attributable to the use of erythromycin.

References

1. Yeo, C.J., Barry, M.K., Sauter, P.K., Sostre, S., Lillemoe, K.D., Pitt, H.A., Cameron, J.L.: Erythromycin accelerates gastric emptying following pancreaticoduodenectomy: a prospective, randomized placebo controlled trial. Ann. Surg. *218*:229, 1993
2. Sosa, J.A., Bowman, H.M., Gordon, T.A., Bass, E.B., Yeo, C.J., Lillemoe, K.D., Pitt, H.A., Tielsch, J.M., Cameron, J.L.: Importance of hospital volume in the overall management of pancreatic cancer. Ann. Surg. *228*:429, 1998