

An endoscopic pancreatic function test with synthetic porcine secretin for the evaluation of chronic abdominal pain and suspected chronic pancreatitis

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Background: Pancreatic function tests are the most reliable methods for the diagnosis or exclusion of chronic pancreatitis in patients without obvious radiologic changes, but they are cumbersome, time consuming, and unavailable in clinical practice. Synthetic porcine secretin, a 27 amino acid peptide identical to the biologic form, is available for exocrine function testing. This study examined the utility of a simple, newly developed, purely endoscopic pancreatic function test with synthetic porcine secretin.

Methods: Three groups of patients were studied: patients with chronic abdominal pain with and without risk factors for chronic pancreatitis, and patients with advanced chronic pancreatitis. All patients with abdominal pain had "pancreatic type" pain for greater than 6 months and negative radiographic imaging studies. All patients with chronic pancreatitis had advanced disease based on retrograde pancreatography and/or CT findings. Participants underwent the following protocol: (1) standard endoscopy to the descending duodenum with the patient under conscious sedation; (2) intravenous administration of secretin (0.2 μ g/kg); (3) endoscopic duodenal fluid collection at 0, 15, 30, 45, and 60 minutes after secretin injection; and (4) fluid analysis for bicarbonate concentration.

Results: Eighteen patients were studied (5 abdominal pain without risk factors, 7 abdominal pain with risk factors, and 6 advanced chronic pancreatitis). Median peak (interquartile range) bicarbonate concentrations in meq/L for each group were, respectively, 87 (6, range 84-108), 72 (10, range 68-90), and 35 (27, range 18-88). Median peak bicarbonate concentration values for the 3 groups are significantly different ($p = 0.010$; Kruskal-Wallis test). Bicarbonate secretion in patients with chronic pancreatitis was markedly reduced compared with that in patients with abdominal pain without risk factors ($p = 0.038$; the Fisher exact test). The secretory function curve for patients with abdominal pain with risk factors was markedly abnormal, resembling the attenuated secretory curve seen in patients with chronic pancreatitis. The test was safe and well tolerated.

Conclusions: A simple endoscopic pancreatic function test with synthetic porcine secretin appears to distinguish patients with known chronic pancreatitis from those with chronic abdominal pain without chronic pancreatitis. This simple, practical endoscopic test can be performed during upper endoscopy and may decrease the need for invasive procedures in patients with abdominal pain and normal radiographic imaging studies. (Gastrointest Endosc 2003;57:37-40.)

Chronic abdominal pain suspected to be caused by chronic pancreatitis (CP) is a common reason for consultation with a gastroenterologist.¹ The diagnosis of CP is easily confirmed radiographically when the disease is advanced. Conversely, the diagnosis of early CP

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in patients who have not developed scarring or calcifications in the pancreatic parenchyma is a challenge. In these patients, pancreatic function testing is the most reliable method of diagnosis or exclusion of CP.² Synthetic porcine secretin, a 27 amino acid peptide identical to the biologic form, is now available for exocrine function testing. Dose response studies of this pure synthetic preparation have demonstrated pharmacologic efficacy. Peak bicarbonate concentrations (meq/L) are analogous to those achieved with the biologic form in normal subjects and patients with CP.³

Until now, pancreatic function tests have been relegated to highly specialized tertiary centers.^{4,5} In addition, there has been no improvement or advance in the methodology of function testing in the past 50 years.⁶ These tests in their current form involve fluoroscopic or endoscopic-guided placement of duodenal drainage tubes for prolonged periods.⁷ A purely endoscopic collection method was developed that

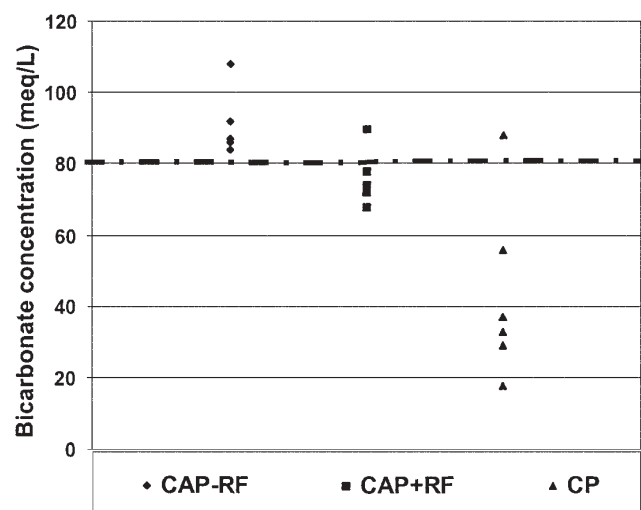


Figure 1. Peak bicarbonate concentrations by study group (n = 18).

does not require a specialized GI laboratory and can be performed during routine upper endoscopy. In addition, there is no radiation exposure to patients or endoscopy unit personnel. The utility of this endoscopic pancreatic function test (EPFT) with synthetic porcine secretin was evaluated in patients with advanced CP and patients with chronic abdominal pain and a clinical suspicion of early CP.

PATIENTS AND METHODS

Contraindications to the use of synthetic secretin included pregnancy, breast feeding of infants, recent administration of anticholinergic medication (within 4 weeks), acute pancreatitis, and history of allergy to secretin. All patients 18 years of age or older referred with known or suspected CP were offered enrollment in the study. The protocol was approved by our Institutional Review Board. Verbal and written informed consent was obtained from study participants.

Patients were divided into 3 groups: Group 1, chronic abdominal pain without risk factors for pancreatitis (CAP-RF); Group 2, chronic abdominal pain with risk factors for CP (CAP+RF); and Group 3, advanced CP (CP). All patients in Groups 1 and 2 had negative and/or equivocal imaging studies (CT, retrograde pancreatography, EUS) for the diagnosis of CP. The diagnosis of advanced CP was confirmed for all patients in Group 3 by definitive evidence on prior endoscopic retrograde pancreatography or imaging studies (MRI, CT) (calcifications, moderate-advanced Cambridge classification). Risk factors for CP were defined as the following: a history of excessive ingestion of alcohol, idiopathic acute recurrent pancreatitis (>3 episodes), prolonged, pancreatic duct stent insertion (>4 weeks), and sphincter of Oddi dysfunction with acute recurrent pancreatitis.

Endoscopic collection method

Patients were given a test dose (0.2 µg) of synthetic porcine secretin (ChiRhoClin, Inc., Silver Spring, Md.)

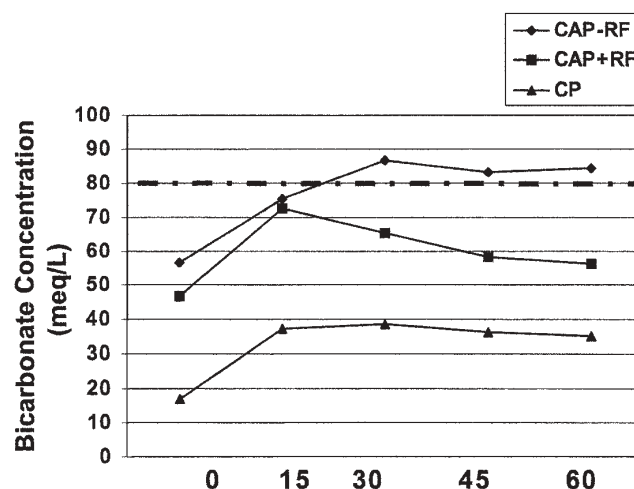


Figure 2. Pancreatic secretory curve: median bicarbonate concentration at each time point (n = 18).

intravenously and were monitored for 1 minute for evidence of adverse drug reaction (flushing, allergic reaction, alterations in hemodynamic parameters [heart rate, blood pressure, respiratory rate]). If there was no evidence of an adverse reaction, synthetic porcine secretin (0.2 µg/kg) was slowly injected intravenously over 1 minute. Upper endoscopy was performed with a standard endoscope with the patient under conscious sedation (meperidine, midazolam, droperidol) after induction of pharyngeal anesthesia with a topical agent (Hurricane, Beutlich Pharmaceuticals, Waukegan, Ill.). All gastric fluid was aspirated through the endoscope and discarded. After intubation to the second/third part of the duodenum, fluid was aspirated for 1 to 3 minutes and collected in 5 separate specimen traps (Sherwood, Davis and Geck, St. Louis, Mo.) at baseline (0), 15, 30, 45, and 60 minutes after secretin injection. Thus, the endoscope was maintained in the duodenum for 1 hour during the collection period.

Fluid was sent to the laboratory on ice for immediate measurement of bicarbonate concentration, or stored at -80°C and analyzed at a later time. Bicarbonate measurements will be falsely positive (low values) if specimens are not handled in this fashion. All patients recovered from the procedure and were discharged as specified by our protocol for conscious sedation and analgesia.

Fluid analysis

Bicarbonate concentrations in the aspirated fluid collections were determined as total carbon dioxide by a rate pH measurement using reagents and an analyzer (CX3 Delta, Beckman-Coulter, Brea, Calif.). In brief, with acidification of the specimen, bicarbonate forms carbon dioxide gas, which passes through a silicone membrane and results in a rate of pH change in a bicarbonate solution between the membrane and a pH electrode. The rate of pH change is related to the initial bicarbonate concentration. When necessary, fluid specimens were diluted with normal saline solution to bring the bicarbonate concentration within the measuring range of the method.

Table 1. Median bicarbonate concentration (IQR) at each time point

| Time point (min) | CAP-RF (Group 1) | CAP+RF (Group 2) | CP (Group 3) | <i>p</i> Value* | Pairwise |
|------------------|---------------------|---------------------|-----------------|-----------------|-------------|
| 0 | 66.0 (27) | 48.0 (30) | 18.0 (4) | 0.025 | 1=2=3 |
| 15 | 80.0 (3) | 72.0 (10) | 32.5 (8) | 0.010 | 2=1>3 |
| 30 | 87.0 (8) | 68.0 (16) | 34.0 (18) | 0.005 | 2>1,1=3,2>3 |
| 45 | 86.0 (12) | 58.0 (21) | 33.0 (19) | 0.017 | 1=2=3 |
| 60 | 84.0 (12) | 58.0 (33) | 30.0 (35) | 0.004 | 2>1,2>3,1=3 |
| Median peak | 87.0 (6) | 72.0 (10) | 35.0 (27) | 0.10 | 1=2=3 |

**p* Value from Kruskal-Wallis test. Table gives median values at each time point for each group. The last column gives the results of the pairwise comparison of the 3 groups based on the 2-sample Wilcoxon test, adjusted for the multiple comparisons.

Statistical methods

A one-way analysis of variance (1-way ANOVA) was used to compare the ages of the patients in the 3 groups. Age is reported as mean (standard deviation). A Kruskal-Wallis test was used for comparing the peak bicarbonate values for the 3 groups. If a difference was found among the 3 groups, comparisons were then made between each group by using the two-sample Wilcoxon test, with adjustment for multiple comparisons.⁸ Bicarbonate values are reported as median (interquartile range [IQR]). The peak bicarbonate values were also categorized into positive for CP (peak <80 meq/L) and negative for CP (peak >80 meq/L). The Fisher exact test was used to compare the 3 groups. If a difference was found among the 3 groups, comparisons were made between each group by using the Fisher exact test, with adjustments for multiple comparisons.⁹ A significance level of 0.05 (two-tailed) was used.

RESULTS

A total of 18 patients underwent the EPFT with synthetic porcine secretin (5 Group 1 [CAP-RF], 7 Group 2 [CAP+RF], 6 Group 3 [CP; 3 alcohol induced, 3 idiopathic]). Mean age (SD) for the 3 groups was, respectively, 37.2 years (11.3), 46.7 years (17.3), and 48 years (13.5). There was no statistically significant difference among the 3 groups with respect to age ($p = 0.438$; 1-way ANOVA) or gender ($p = 0.424$; Fisher exact test).

Peak bicarbonate concentration

Peak bicarbonate concentration (meq/L) for all study participants is shown in Figure 1. Median peak bicarbonate (IQR, range) for the CAP-RF, CAP+RF, and CP groups in meq/L were, respectively, 87 (6, range 84-108), 72 (10, range 68-90), and 35 (27, range 18-88). The median peak bicarbonate concentration values for the 3 groups are significantly different ($p = 0.010$; Kruskal-Wallis test). All patients in Group 1 (CAP-RF) had normal pancreatic function. Six patients (6/7, 86%) in the Group 2 (CAP+RF) and 5 (5/6, 83%) in Group 3 (CP) tested positive for pancreatic insufficiency.

Pancreatic secretory function

The secretory function curves for all 3 groups for the entire 1-hour collection period are represented in Figure 2. The peak bicarbonate values for the 3 groups are significantly different ($p = 0.010$; Kruskal-Wallis test). In patients with CP (Group 3) bicarbonate secretion was markedly reduced when compared with the normal secretory output in the CAP-RF group (adjusted p value, 0.038; Fisher exact test). The secretory function curve for patients with CAP+RF (Group 2) was also abnormal, resembling the attenuated secretory curve seen in patients with CP. In fact, there was no statistical difference in peak bicarbonate secretion when the CAP+RF and CP groups were compared ($p = 1.0$; Fisher exact test).

Comparison of collection periods

The 5 collection time points were analyzed for each of the 3 groups (Table 1). The pairwise comparison showed that a single aspiration at 30 minutes (adjusted p value 0.028) or 60 minutes (adjusted p value 0.036) is distinctive (Group 2 > Group 1) and can be diagnostic of early chronic pancreatic insufficiency (bicarbonate < 80 meq/L) in the setting of chronic abdominal pain. This separation of groups is also graphically displayed at those time intervals in Figure 2.

Tolerance and safety

The EPFT was well tolerated; there was no procedure-related complication including pancreatitis. One patient experienced a delayed reaction that consisted of flushing without other symptoms after injection of the full dose secretin despite there being no reaction to the test dose. There was no change in cardiopulmonary parameters for this patient (heart rate, blood pressure, pulse oximetry) and so the collection was completed.

DISCUSSION

This is the first report of endoscopic pancreatic function testing in adults. This study demonstrates

that our EPFT is feasible, well-tolerated and accurately assesses pancreatic secretory function. The use of synthetic porcine secretin as a secretagogue with measurement of peak bicarbonate concentration clearly differentiates patients with chronic abdominal pain into those with and without early stage CP. The EPFT is straightforward and suitable for clinical practice with proper laboratory support. Furthermore, a single aspiration between 30 and 60 minutes after secretin injection appears to be an effective screening test for patients with chronic abdominal pain when the diagnosis of early CP is suspected.

The current study has 2 limitations: First, larger numbers of patients are needed to confirm the observations. Second, normal control values for the test could not be established in healthy volunteers because of restrictions on the use of synthetic porcine secretin as specified by the Food and Drug Administration (FDA) and our institutional review board. The manufacturer of the synthetic porcine secretin (SecreFlo, Chi Rho Clin Inc., Silver Spring, Md.) has indicated that FDA approval is eminent for use in pancreatic function testing and the diagnosis of Zollinger-Ellison syndrome. With the anticipated regulatory approval, a larger trial with enrollment of healthy volunteers and larger numbers of patients will be needed to confirm the findings of the present study.

Traditional tests of pancreatic function require prolonged fluoroscopically guided oroduodenal intubation, followed by stimulation of pancreatic secretion and collection of duodenal fluid.^{10,11} These tests are cumbersome, technically demanding, and uncomfortable for patients. For these reasons, their use in clinical practice has been limited despite their known accuracy for the diagnosis of early stage CP.¹² The EPFT has performance characteristics comparable with those of the traditional Dreiling tube methods for the diagnosis of advanced CP. By comparison, the EPFT is less cumbersome and does not expose the patient or endoscopy personnel to ionizing radiation. Reimbursement is unlikely to be problematic with the EPFT because upper endoscopy is indicated for the evaluation of patients with chronic abdominal pain, and technical charges have been established for endoscopic collection of biliary/pancreatic fluid (CPT code 89105). Unlike the intraductal secretin test, the EPFT does not require pancreatic duct cannulation and thus does not place patients at risk for procedure-related acute pancreatitis.¹³ The procedure did not cause pancreatitis in any patient in the current study.

Secretin has been more widely used for pancreatic function testing compared with cholecystokinin but has not been available for several years in the United States. Measurement of peak bicarbonate concentration after secretin stimulation is the most

reliable test for the assessment of pancreatic secretory function.¹² A new synthetic porcine form is now available for clinical use with institutional review board approval and documentation of informed consent. In the present study, peak bicarbonate concentrations in patients with chronic abdominal pain and no risk factors for pancreatitis were in the normal range as determined by Dreiling tube studies; all patients in this group had normal secretory function (peak bicarbonate >80 meq/L). Conversely, patients suspected to have early stage CP had abnormal secretory function (mean peak bicarbonate <80 meq/L) characteristic of pancreatic insufficiency.

The promising early results of the present study introduce pancreatic function testing to the modern era of GI endoscopy. The EPFT appears to distinguish patients with known CP from those with chronic abdominal pain without CP. It is our belief that in the future a simple timed aspiration after secretin injection will be the preferred screening test for assessment of pancreatic secretory function in patients with chronic abdominal pain. More importantly, the EPFT may broaden the availability of pancreatic function testing and place it in the hands of practicing clinical gastroenterologists.

REFERENCES

1. Forsmark C. The diagnosis of chronic pancreatitis. *Gastrointest Endosc* 2000;52:293-8.
2. Owyang C. Chronic pancreatitis. In: Yamada T, Alpers D, editors. *Textbook of gastroenterology*. Philadelphia: JB Lippincott; 1991. p. 2091-112.
3. Jowell PS, Robuck-Mangum G, Mergener K, Branch MS, Purich ED, Fein SH. A double-blind, randomized, dose response study testing the pharmacological efficacy of synthetic porcine secretin. *Aliment Pharmacol Ther* 2000;14:1679-84.
4. DiMagno EP, Layer P, Clain JE. In: Go VLW, editor. *The pancreas: biology, pathobiology and disease*. 2nd ed. New York: Raven Press; 1993. p. 665-706.
5. Go VLW, Hoffman AF, Summerskill WHJ. Simultaneous measurements of total pancreatic, biliary and gastric outputs in man using perfusion technique. *Gastroenterology* 1970;58:321-8.
6. Dreiling DA, Hollander F. Studies in pancreatic function, preliminary series of clinical studies with the secretin test. *Gastroenterology* 1948;11:714-29.
7. Jorpes E, Mutt V. On the biological assay of secretin. The reference standard. *Acta Physiol Scand* 1966;66:316-25.
8. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Statistics* 1979;6:65-70.
9. Mehta CR, Patel NR. A network algorithm for performing Fisher's exact test in rxc contingency tables. *J Am Statistical Assoc* 1983;78:427-34.
10. Lankisch PG, Andren-Sandberg A. Standards for the diagnosis of chronic pancreatitis and for the evaluation of treatment. *Int J Pancreatol* 1993;14:205-12.
11. Steer ML, Waxman I, Freedman SF. Chronic pancreatitis. *N Engl J Med* 1995;332:1482-90.
12. Clain JE, Pearson RK. Diagnosis of chronic pancreatitis. Is a gold standard necessary? *Surg Clin N Am* 1999;79:829-45.
13. Gregg JA. The intraductal secretin test (IDST). In: Sivak MV Jr, editor. *Gastroenterologic endoscopy*. Philadelphia: WB Saunders; 1987. p. 794-807.