Prospective Evaluation of the Accuracy of the Intraductal Secretin Stimulation Test in the Diagnosis of Chronic Pancreatitis

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Background & Aims: **The standard secretin stimulation test (SST) is the accepted gold standard for pancreatic function testing. The intraductal secretin stimulation test (IDST) performed at the time of endoscopic retrograde cholangiopancreatography (ERCP) has been proposed as a more feasible way to evaluate pancreatic function. The accuracy of the IDST for the diagnosis of chronic pancreatitis (CP) has not been well defined.** ***Methods:*** **We prospectively evaluated patients with suspected CP. The IDST, SST, and ERCP were performed in each of the 19 study patients. The SST and ERCP were used as independent diagnostic standards against which the results of the IDST were compared directly to determine the sensitivity, specificity, and accuracy of the IDST.** ***Results:*** **When the SST was used as a diagnostic standard for CP, the sensitivity of the IDST was 80% (95% confidence interval [CI], 44%–97%), the specificity was 22% (95% CI, 2%–60%), and the overall accuracy was 52% (95% CI, 28%–75%). The positive predictive value was 53% and the negative predictive value was 50%. When the pancreatogram was used as the diagnostic standard, the sensitivity of the IDST was 100% (95% CI, 69%–100%), the specificity was 55% (95% CI, 21%–86%), and the overall accuracy was 79% (95% CI, 54%–93%). Receiver operator curves showed that there was no optimal cut-off value for peak bicarbonate concentration that led to acceptable sensitivity and specificity.** ***Conclusions:*** **The IDST is not accurate for the diagnosis of CP.**

The diagnosis of chronic pancreatitis (CP) is based on the detection of abnormal structure or function of the diseased pancreas. The most accurate way to evaluate pancreatic function is the administration of a hormone stimulation test such as the secretin stimulation test. The reliability of the secretin stimulation test in detecting CP has been evaluated against histology in over 100 patients by Hayakawa et al.[1] In this study, the peak bicarbonate concentration of pancreatic secretion was the most accurate parameter for the diagnosis of CP.

Although the secretin stimulation test has been accepted to be the most sensitive and specific test to diagnose pancreatic exocrine insufficiency, it currently is not used widely.[2,3] The procedure is labor and time intensive and demands trained personnel and a designated laboratory. The passage of a large-size (26F) oroduodenal tube is required. The tube has to remain in place for more than 1 hour because the standard secretin stimulation test (SST) requires collection of pancreatic secretions for 60 minutes after injection with secretin.[4] During the insertion of the tube and during sample collection, sedation is not used because it may interfere with the test results.[3,5] The lack of sedation makes the performance of the SST uncomfortable for patients. The degree of discomfort is usually not great but occasionally a patient may not tolerate the test.

One proposed way to improve the feasibility of the SST is a shorter collection time. Some investigators have suggested a 10- to 15-minute collection of pancreatic secretions instead of the standard 60 minutes.[6,7] A shorter collection time certainly would make the secretin test easier to perform for both patients and personnel. Equally important, shorter collection times may allow an alternative method of collecting pancreatic secretions to the cumbersome standard oroduodenal tube. Indeed, intraductal placement of a catheter at the time of endoscopic retrograde cholangiopancreatography (ERCP), standard endoscopy, or transnasal passage of a small-caliber endoscope all have been used to collect pancreatic secretions after secretin stimulation.[6–9] From those methods the intraductal secretin test (IDST) performed at the time of ERCP had gained the most popularity in everyday practice and as a research tool.

Abbreviations used in this paper: CI, confidence interval; CP, chronic pancreatitis; ERCP, endoscopic retrograde cholangiopancreatography; IDST, intraductal secretin stimulation test; ROC, receiver operator curves; SST, standard secretin stimulation test.

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In some studies the IDST alone is used as a gold standard to diagnose CP.[6,10]

We recently found in a large patient population (633 patients) that the diagnostic accuracy of the first 15-minute duodenal collection obtained during a standard 60-minute secretin stimulation test for the diagnosis of CP to be only 57%.[11] These results, along with data from other investigators, suggest that the short 15-minute collection time used in the IDST may be inadequate to evaluate pancreatic function and diagnose CP.[8,11] We prospectively evaluated the accuracy of the IDST and SST for the diagnosis of CP.

Patients and Methods

Patients

The research protocol was approved by the institutional review board at the University of Florida. Patients in whom ERCP and SST had been ordered by the treating physician for the evaluation of suspected CP based on clinical presentation, as well as laboratory and radiologic tests, were considered for the study. If the patient did not meet any exclusion criteria (Table 1) he or she was asked to participate in the research protocol. Patients who signed the informed consent form were enrolled and the results are reported in this series. Twenty-three patients were enrolled between March of 1996 and July of 2002. For 2 years (July 1998–June 2000) no patients were enrolled because porcine secretin was not available and synthetic human secretin was not yet approved by the Food and Drug Administration. Patient demographics and the results of the SST, IDST, and ERCP were entered into a computer database prospectively.

Standard Secretin Stimulation Test Sample Collection Protocol

The SST was performed by placement of a Dreiling tube orally to the second portion of the duodenum. Fluoroscopy was used to guide the tube into position. The Dreiling tube has ports for simultaneous aspiration of gastric and duodenal contents. To decrease dilution of pancreatic secretions, 15 minutes of continuous aspiration of the stomach and duodenal contents was performed before intravenous secretin administration. Immediately after intravenous secretin bolus, duodenal juice was collected by continuous aspiration in 15-minute aliquots for a total of 60 minutes. Four samples (15, 30, 45, and 60 minutes) were collected and analyzed further.

Endoscopic Retrograde Cholangiopancreatography and Intraductal Secreting Stimulation Test Sample Collection Protocol

With the patient under conscious sedation using meperidine and midazolam, endoscopy was performed with side-viewing video duodenoscope (JF 130, TJF-130, or TJF-160; Olympus America, Inc., Melville, NY). The pancreatic duct was cannulated in a standard fashion by using a triple lumen catheter (Tandem; Microvasive Endoscopy, Boston Scientific Corp., Natick, MA). Glucagon was not used in any patient to avoid any interference with pancreatic exocrine function. The IDST was performed at the time of ERCP. Once deep cannulation of the main pancreatic duct was achieved an intravenous bolus of secretin was given. Pancreatic juice was collected via the wire port of the cannulating catheter in 5-minute aliquots for 15 minutes using a suction syringe. Three samples were collected (5, 10, and 15 minutes) and analyzed further. A pancreatogram then was obtained by using full-strength contrast.

Sample Processing Protocol and Endoscopic Retrograde Cholangiopancreatography Film Interpretation

During the collection process of pancreatic secretions by ether SST or IDST the samples were kept on ice. At the completion of the collection process the samples were analyzed immediately for bicarbonate concentration by back titration in our laboratory, which is located in our endoscopy suite. The pancreatic juice samples were kept on ice and promptly analyzed to avoid deterioration of the sample leading to falsely low bicarbonate concentrations. The highest concentration of bicarbonate among the 4 aliquots for the SST or among the 3 aliquots for the IDST was reported as the peak bicarbonate concentration, respectively. For the SST, a peak bicarbonate concentration of less than 80 mEq/L is diagnostic of chronic pancreatitis in our laboratory.[4]

All pancreatograms were read by 2 experienced pancreaticobiliary endoscopists (P.D. and C.F.) and graded from 0 to 4 according to the Cambridge classification of CP.[12] Any discrepancies were resolved after the films were reviewed by a third experienced endoscopist (A.F.). Pancreatogram changes graded as Cambridge class 0 and 1 were considered normal and classes 2, 3, and 4 were considered diagnostic of CP.

Results

Twenty-three patients were enrolled. Of those 23 patients, 19 patients (9 men, 10 women; mean age, 57 y; range, 21–82 y) successfully completed both the SST and IDST and the results are reported. For the remaining 4 patients, complete data were not available. One patient could not tolerate the passage of the Dreiling tube at the

Table 1. Exclusion Criteria

Age <18 y
History of pancreatic surgery
History of pancreatic cancer
Inability to cannulate pancreatic duct
Concurrent use of anticholinergic medications
Concurrent use of octreotide

time of the SST attempt, in 2 patients cannulation of the main pancreatic duct failed and therefore the IDST could not be performed, and, finally, 1 patient was found to have pancreas divisum and minor papilla cannulation was not obtained.

To avoid disease progression as a confounding factor, the SST and IDST were performed within a short time interval (maximum, 45 days), except in 1 patient (160 days apart). The mean interval between the 2 tests was 16 days, with most of the tests performed within 5 days (13 of 19). In all patients in whom the 2 tests were performed less than 5 days apart, the SST preceded the IDST to avoid any interference with the test results caused by post-ERCP pancreatitis. Nine patients received biologic porcine secretin (1 U/kg) for both SST and IDST, and 10 patients received an equivalent dose of synthetic human secretin (.2 μg/kg). Each of the study patients received the same type of secretin for the SST and IDST.

In each patient we evaluated the diagnostic accuracy of the peak bicarbonate concentration obtained at the time of IDST for the diagnosis of CP against 2 diagnostic standards: standard #1 was the peak bicarbonate concentration obtained at the time of SST, and standard #2 was the pancreatic duct changes seen on the pancreatogram obtained at the time of ERCP. Ten of 19 patients had CP by SST and 9 of 19 patients had CP by ERCP criteria. There was poor correlation between the SST and pancreatogram findings. Of the 9 patients with normal SST, 4 patients had an abnormal cholangiogram; of the 10 patients with a normal pancreatogram, 4 patients had abnormal SST.

We initially evaluated the diagnostic accuracy of the IDST with the accepted cut-off level for peak bicarbonate concentrations of less than 105 mEq/L, which is considered to be diagnostic for CP.[2] The IDST was positive in the vast majority of our patients (15 of 19). Against the results of the SST used as a diagnostic gold standard the sensitivity of IDST was 80% (95% confidence interval [CI], 44%–97%), the specificity was 22% (95% CI, 2%–60%), and the overall accuracy was 52% (95% CI, 28%–75%). In our population the positive predictive value for CP was 53% and the negative predictive value was 50%. Against the results of the pancreatogram changes used as the diagnostic gold standard the sensitivity of IDST was 100% (95% CI, 69%–100%), the specificity was 55% (95% CI, 21%–86%), and the overall accuracy was 79% (95% CI, 54%–93%).

The large number of false-positive IDST test results leading to poor specificity led us to reevaluate IDST performance while varying the peak bicarbonate value considered diagnostic for CP. Receiver operator curves (ROC) were built in an attempt to define the optimal normal value for IDST peak bicarbonate concentrations, which will lead to improved sensitivity and specificity (Figures 1 and 2). As seen on the ROC, at no point did the sensitivity and specificity reach an acceptable value.

At the time of SST, no single patient achieved peak bicarbonate concentration in the first 15 minutes of the test. Peak bicarbonate concentration was recorded in 4 patients in the 15- to 30-minute time interval and in 5 patients in the 30- to 45-minute time interval. The remaining 10 patients achieved peak bicarbonate concentration in the 45- to 60-minute time interval.

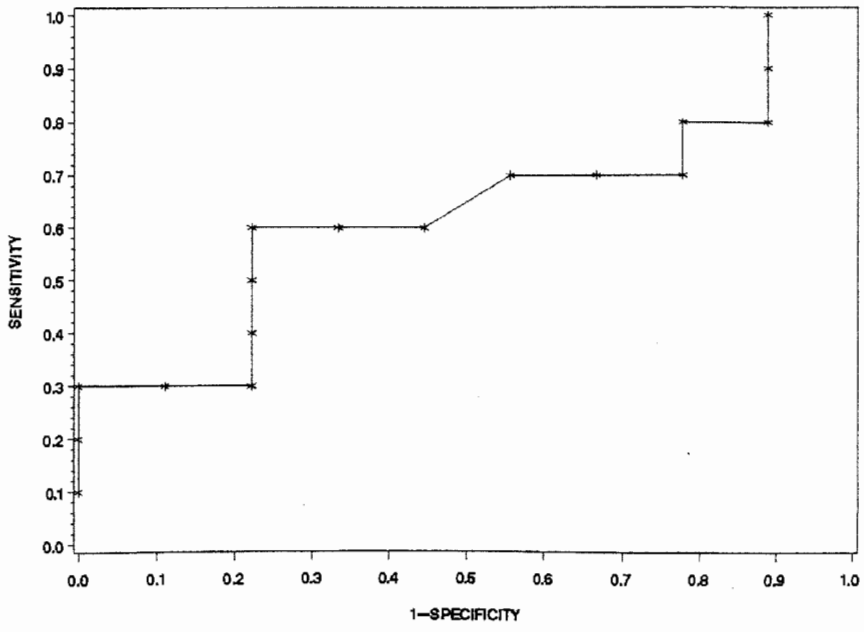

Figure 1. Plot of the ROC curve for the IDST vs standard # 1 (standard secretin test).

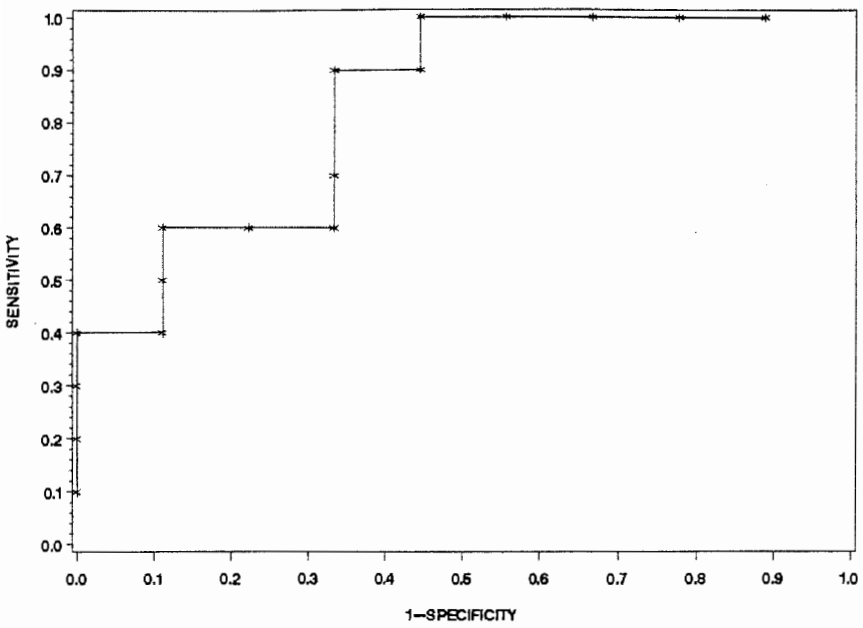

Figure 2. Plot of the ROC curve for the IDST vs standard # 2 (pancreatogram).

One complication of mild post-ERCP pancreatitis occurred after the performance of ERCP/IDST. The occurrence of post-ERCP pancreatitis in our study was within the historically expected rate of 5%.

Discussion

We prospectively evaluated the accuracy of the IDST for the diagnosis of CP by directly comparing the IDST with the SST and ERCP performed in the same patient. Our results show that the IDST does not measure overall pancreatic secretory capacity or diagnose CP accurately. Of concern is the fact that the IDST performance is particularly poor in patients with a normal SST, which could lead to overdiagnosis of CP. This can carry significant emotional and financial consequences and can affect insurability. In patients with a normal SST, the SST and IDST correlated in only 22% when the accepted cut-off value of less than 105 mEq for the IDST was considered abnormal. Furthermore, when we varied the cut-off value, at no point did the sensitivity and specificity of the IDST reach clinically acceptable values, as is well shown by the ROC curves (Figures 1 and 2). We believe that the most likely explanation for the poor correlation between the IDST and SST is the short collection time of pancreatic secretion (15 min) at the time of the IDST. Prior studies had shown that the maximal effect of secretin on bicarbonate concentration may not occur for 30 to 60 minutes after secretin injection.[11,13,14] If pancreatic secretions are collected only for the first 15 minutes after secretin injection as in the IDST, a patient with normal pancreatic function may have a peak bicarbonate concentration that is considered low and therefore be labeled inaccurately as having CP. The same patient can reach a normal peak bicarbonate concentration if collection is performed further for a total of 60 minutes as performed in the SST. Our data support that this is the most likely explanation of the high false-positive rate and poor specificity of the IDST. At the time of the SST not a single patient achieved a peak bicarbonate concentration in the first 15 minutes of the test. Therefore, not surprisingly, the IDST was abnormal in the majority of our patients (15 of 19). This appears to be the major problem with the use of the IDST. The IDST is positive in the majority of the patients regardless of whether they have or do not have CP. As in a number of previous studies, we also showed that there is only moderate correlation between functional testing (IDST or SST) and ERCP findings in CP.[15] This further emphasizes the current consensus that at present there is no single test that is sufficient to make the diagnosis of CP in all patients.[15]

The strengths of our study are as follows: (1) the information was acquired and recorded prospectively under a standardized protocol, (2) the secretin stimulation tests were performed in a laboratory with extensive experience in functional pancreatic testing, (3) a well-accepted gold standard for evaluating pancreatic function was used to define CP, (4) a comparable number of men and women and patients with and without CP were enrolled, (5) the time interval between the IDST and SST was very short, thus ruling out disease progression as a factor in test result discrepancies. A potential weakness

of our study is the use of 2 types of secretin, one of which is no longer available (porcine secretin). We believe that the types of secretin we used did not affect the results of our trial. We used the same type of secretin in a particular patient for both IDST and SST. Furthermore, it is well documented that the biologic porcine and synthetic human secretin are equivalent to one another and can be used interchangeably in pancreatic function testing.[4]

The diagnosis of CP remains one of the greatest challenges in gastroenterology. One has only to look at standard textbooks to note the variety of diagnostic tests available; the clear implication being that no one test is sufficient to make the diagnosis in all patients with CP. Clearly, the greatest need is for a simple and accurate test to diagnose CP when other tests are normal (so-called *small duct CP*). This diagnosis currently is possible only with the standard 60-minute hormonal stimulation function test, although there is ongoing work to evaluate endoscopic ultrasound in this patient population. Our findings show that the IDST does not measure pancreatic function accurately and is an inadequate method to diagnose CP.

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