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# The Effect of Moderate Sedation on Exocrine Pancreas Function in Normal Healthy Subjects: A Prospective, Randomized, Cross-Over Trial Using the Synthetic Porcine Secretin Stimulated Endoscopic Pancreatic Function Test (ePFT)

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**BACKGROUND:** We have developed a purely endoscopic collection method for the assessment of pancreatic secretory function (ePFT). The pancreatic secretory effects of sedation medications utilized during endoscopic procedures are not completely known.

**AIMS:** To study the effect of moderate sedation on the exocrine pancreas gland in a prospective, randomized trial.

**METHODS:** Healthy volunteers were randomized by computers to one of two treatments (A—no sedation, B—sedation) in period 1 and crossed-over to the other treatment in period 2 with a minimal washout interval of 7 days. Sedation dosage was standardized for each patient based on age, gender and weight from a previously published dosing nomogram. Synthetic porcine secretin (ChiRhoClin, Inc., Burtonsville, Maryland) was used as the pancreatic stimulant. Duodenal fluid samples were aspirated via the endoscope every 5 min for 1 h and sent on ice to our hospital laboratory for the measurement of pancreatic secretory electrolyte concentrations by autoanalyzer.

**RESULTS:** A total of 17 healthy volunteers were enrolled. Sixteen subjects (8 males and 8 females) completed the randomized prospective trial. Median intravenous meperidine and midazolam sedation dose was 62.5 mg and 2.5 mg, respectively. Maximum pancreatic juice flow occurred during the early phase of secretion and maximum bicarbonate concentration occurred during the late phase of secretion. Analysis of the electrolyte composition of the endoscopically collected duodenal drainage fluid revealed a constant cation concentration for both sodium and potassium over the 1 h collection period. The anions, chloride and bicarbonate, exhibited a reciprocal relationship identical to that seen in traditional gastroduodenal tube collection studies. There was no statistical difference observed between the sedation and no sedation groups. The estimated total bicarbonate output (area under curve, AUC) for the sedated and non-sedated groups were 5,017 meq + 724 (range 3,663–6,173) and 5,364 meq ± 583 (range 4,323–6563) respectively ($p = 0.0656$). The mean peak bicarbonate concentrations for sedated (n = 8) *versus* non-sedated (n = 8) groups were 103 ± 11 meq/L (range 78–125) and 106 ± 11 meq/L (range 87–138), respectively ($p = 0.1346$). There was excellent correlation of peak bicarbonate concentrations when sedation and no sedation groups were compared ($r = 0.744$, $p < 0.05$; Spearman rank correlation). There were no episodes of pancreatitis.

**CONCLUSIONS:** (a) Moderate sedation used for upper endoscopy does not effect the clinical diagnostic parameters (peak bicarbonate concentration or total bicarbonate output) utilized to diagnose pancreatic insufficiency. (b) Analysis of duodenal drainage fluid collected endoscopically after synthetic secretin stimulation produces an identical pancreatic secretory curve described with traditional gastroduodenal tube collection methods.

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## INTRODUCTION

Direct tests of pancreatic function using secretin or cholecystokinin are the most accurate for establishing the earliest physiologic changes of pancreatic insufficiency (1–3). Traditional pancreatic function tests are cumbersome, time consuming, and usually require a specialized laboratory which is not available to most practicing gastroenterologists. In addition, the Dreiling gastroduodenal aspiration tubes used for pancreatic fluid collection are no longer manufactured. We have developed a less cumbersome, purely endoscopic pancreatic function test using synthetic porcine secretin or cholecystokinin (4, 5). While our endoscopic collection method is simple, it does require the use of sedation. The effects of moderate sedation on pancreatic exocrine function are yet to be determined (6).

The purpose of this investigation is to study the effects of moderate sedation on the pharmacological effects of synthetic porcine secretin on the exocrine pancreas gland in normal human subjects.

## METHODS

### *Study Population*

The Institutional Review Board at the Cleveland Clinic Foundation approved the research protocol. Healthy, adult subjects who were able to give verbal and written informed consent were recruited into the study. A focused medical history and physical examination was obtained from every subject. All female patients underwent a urine pregnancy test prior to each procedure.

### *Inclusion and Exclusion Criteria*

Equal number of male and female patients of non-childbearing potential were recruited into the study. The inclusion criteria included: age 18–65 yr, weight 40–100 kg, good health based on medical history, abstinence from alcohol 72 h prior to study enrollment, and the willingness and ability to sign the written informed consent. The exclusion criteria included pregnancy, allergy or known sensitivity to secretin, history of alcohol or drug abuse, history of acute or chronic pancreatitis, history of vagotomy or gastrectomy, history of inflammatory bowel disease or liver disease, or recent use of narcotic analgesics or anticholinergic medications.

### *Study Design*

Study participants meeting the inclusion/exclusion criteria underwent a medical history and physical examination including vital signs, review of medical records, and assessment for sedation. The subjects meeting all entry criteria underwent our endoscopic pancreatic function testing method and were randomized into one of the two treatment arms (synthetic porcine secretin at a dose of 0.2 mcg/kg without meperidine and midazolam or synthetic porcine secretin at a dose of 0.2 mcg/kg with meperidine and midazolam) during period 1 and crossed-over to the other treatment in period 2 (Fig. 1).

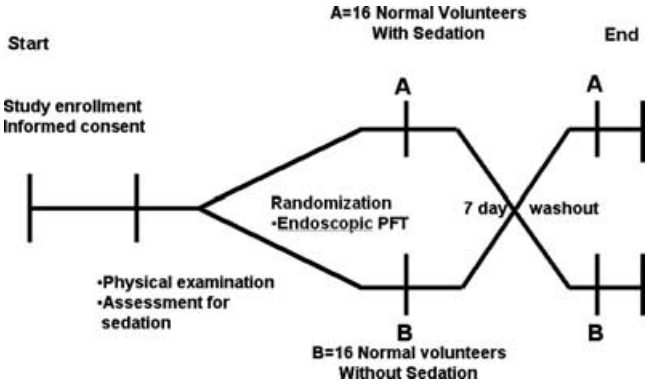


**Figure 1.** Study design.

The sedation dosage was determined from our previously published dosing nomogram based on age, gender, and weight (7). The endoscopically collected fluid was sent to the lab for biochemical analysis. Study participants were recovered in our endoscopy suite and discharged based on standard hospital procedural guidelines for outpatient sedation and analgesia.

### *Endoscopic Collection Method*

After informed consent, a test dose (0.2 mcg) of synthetic porcine secretin (ChiRhoClin, Inc. Burtonsville, MD) was given intravenously and study subjects were observed for 1 min. Topical lidocaine spray was administered to the posterior pharynx for local anesthesia and a bite block was placed into the mouth. A standard upper endoscopy in the left lateral position with or without sedation was performed using an Olympus "ultra-thin" GIF 160-XP endoscope (Olympus, Corp., Melville, NY) to improve patient tolerance. After gastric insufflation, all gastric fluid was aspirated through the endoscope and discarded. The endoscope was then passed through the pylorus into the duodenum and baseline duodenal fluid was aspirated from the second through fourth portions of the duodenum. The endoscope was then positioned in the third portion of the duodenum. Synthetic porcine secretin (0.2 mcg/kg) and a combination of meperidine and midazolam, at a ratio of 25:1 was administered at time 0 min (end of secretin administration). Duodenal aspirates were then obtained at 5 min intervals into separate collection vials for 1 h. All duodenal fluid samples were immediately placed on ice and transferred to the laboratory for analysis.

### *Pancreatic Secretagogue*

Synthetic porcine secretin, provided by ChiRhoClin, Inc., Burtonsville, Maryland, was used as the hormonal stimulant. Synthetic porcine secretin has been shown to be equivalent to biologic secretin (8). The inventory, control, and dispensation of synthetic porcine secretin was provided by a designated research pharmacist at the Cleveland Clinic Foundation. The investigator, study nurses, and other personnel did not have access to secretin. The research pharmacist reconstituted the secretin dose for each patient in the study. Synthetic

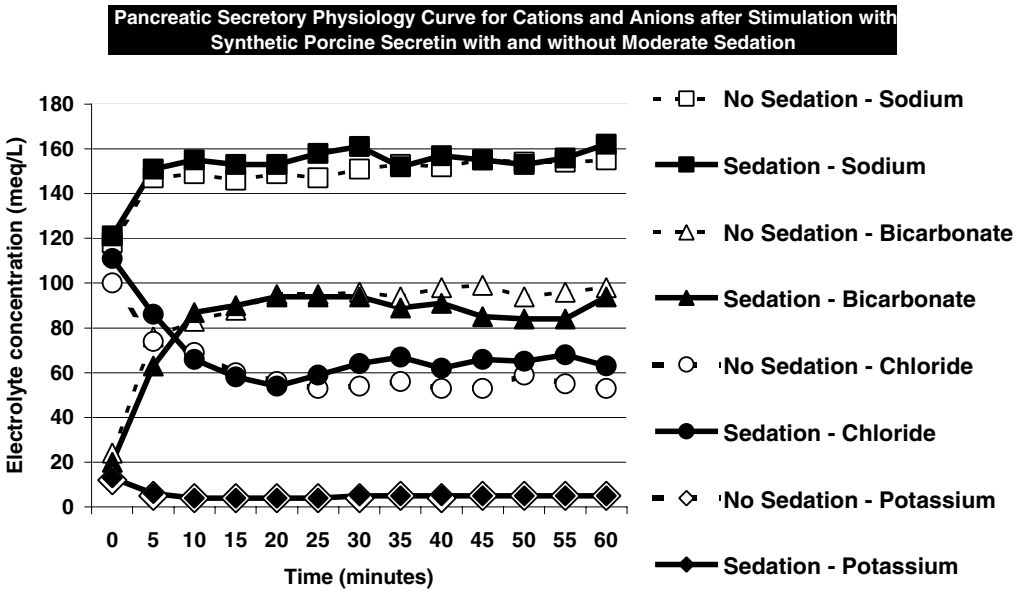


**Figure 2.** Pancreatic secretory curves.

porcine secretin of 16 mcg is supplied as a lyophilized sterile powder in 10 ml vials containing 15 mg L-cysteine hydrochloride and 20 mg of mannitol. The contents of each vial are dissolved in 8.0 ml of sodium chloride injection, USP for the 0.2 mcg/kg dose level.

### *Fluid Analysis*

Endoscopically collected duodenal fluid was analyzed for the electrolytes chloride, bicarbonate, potassium, and sodium with a lab autoanalyzer according to our previously published methods. Specifically, bicarbonate concentrations were determined as total carbon dioxide by a rate of pH measurement using reagents and an autoanalyzer (CX3 Delta, Beckman–Coulter, Brea, CA). After acidification of the specimen, the 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.

### *Statistical Methods*

This study is a cross-over randomized balanced design and was analyzed accordingly. As was intended prior to data collection, the goal of the statistical methods was to compare each timepoint individually and to objectively assess the shape of the observed concentration curves. Initial exploration of the data included means, standard deviations, and ranges of each of the four measured concentrations at every timepoint. Standard bioequivalence parameters for pharmacodynamics were used to compare treatment groups by evaluating the maximum concentration over time and area under the concentration profile curve. The timepoints where pooled by calcuting the average concentration at 15 min intervals, resulting in estimated concentrations at 0, 15, 30, 45, and 60 min. Upon confirming parametric assumptions of the data to be met, general linear models were constructed at each timepoint for the treatment effect within subject. A $p$-value less than 0.05 was considered to suggest a significant treatment effect. All analyses were carried out using SAS 8 (SAS Institute Inc. Cary, NC).

## RESULTS

### *Demographics*

A total of 17 patients were enrolled into the prospective, randomized trial: One patient withdrew from the study due to intolerance of the endoscope and 16 (8 male and 8 female) completed the study. The mean age was 35.2 yr. The median meperidine and midazolam dose was 62.5 mg and 2.5 mg, respectively. One patient noted nausea and vomiting 36 h after their first test and was classified as a possibly related adverse event. No problems occurred during their second procedure. There were no complications requiring medical observation or hospitalization during the study.

### *Pancreas Secretory Physiology*

Figure 2 displays the pancreatic secretory curves for all of the major ions in pancreatic juice. The mean concentrations are shown for all electrolytes measured for each treatment arm. There was no statistical difference in electrolyte concentrations observed between sedation and no sedation at any of the collection time intervals. There was preservation of the relationship of pancreatic secretory rate and concentration of its major ions with endoscopic collection: (a) the cations, potassium, and sodium exhibited a relatively constant concentration as the pancreas was stimulated and (b)

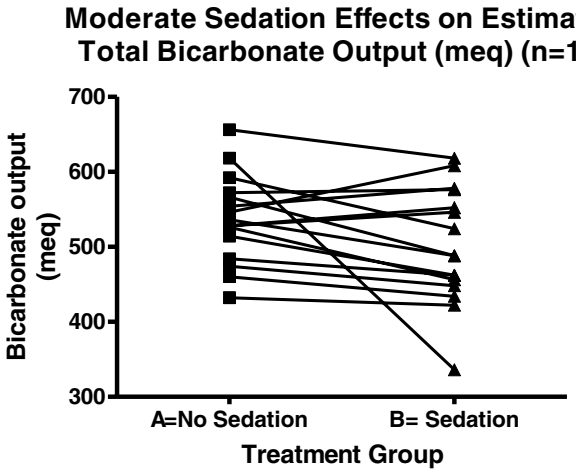


**Figure 3.** Comparison of changes in total bicarbonate output (meq) with moderate sedation.

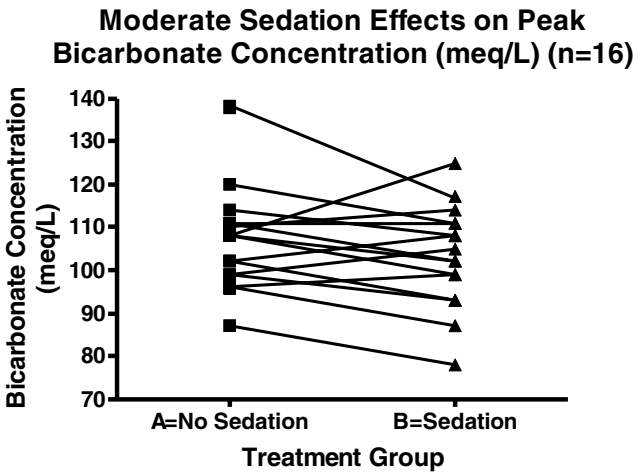


**Figure 4.** Comparison of changes in peak bicarbonate concentration (meq/L) with moderate sedation.

the anions, chloride, and bicarbonate exhibited a reciprocal secretory relationship during pancreatic stimulation, *i.e.*, as the bicarbonate concentration increased, the chloride concentration decreased. In addition, the maximum bicarbonate secretory flow rate (slope of curve, change in bicarbonate concentration over time) occurred during the first 15 min of collection and bicarbonate concentration reached a maximum and steady state concentration approximately 30 min after secretin stimulation.

### *Clinical Diagnostics for Pancreatic Insufficiency*

There was no statistical difference between the two treatment arms in terms of peak bicarbonate concentration or bicarbonate output. Figures 3 and 4 display the peak bicarbonate concentrations and total bicarbonate outputs before and after sedation. The estimated mean total bicarbonate output (area under curve, AUC) for the sedated and non-sedated groups were 5,017 meq ± 724 (range 3,663–6,173) and 5,364 meq ± 583 (range 4,323–6,563), respectively ($p = 0.0656$). The mean peak bicarbonate concentrations for sedated (n = 8) *versus* non-sedated (n = 8) groups were 103 ± 11 meq/L (range 78–125) and 106 ± 11 meq/L (range 87–138), respectively ($p = 0.1346$). The correlation ($r$-value) between peak bicarbonate concentration in the sedation and no sedation treatment groups was 0.744 (Spearman Rank, $p < 0.001$, Fig. 5). There were no episodes of pancreatitis.

## DISCUSSION

We have shown that moderate sedation commonly used in upper endoscopy has no effect on exocrine pancreas function as assessed by total bicarbonate output and peak bicarbonate concentration. Furthermore, biochemical analysis of endoscopically collected pancreatic fluid reveals that our endoscopic collection method replicates the pancreatic secretory physiology curve seen with traditional gastroduodenal tube collection: (a) cation concentrations for sodium and potassium remain relatively constant; (b) anion concentrations for bicarbonate and chloride exhibit a reciprocal relationship; and after secretin stimulation (c) maximum bicarbonate flow occurs during the early phase of secretion while maximum bicarbonate concentration occurs during the later phase of pancreatic secretion.

Gastroenterologists commonly see patients with chronic abdominal pain and suspected chronic pancreatitis. The diagnosis of chronic pancreatitis is easily confirmed radiographically in advanced pancreatic disease. The major clinical challenge occurs in those patients with early chronic pancreatitis, who have not developed scarring or calcifications in the pancreatic parenchyma. This subset of patients accounts for a small minority of chronic pancreatitis patients. And diagnosis by pancreatography alone is difficult and places the patient at a substantial risk for procedure related complications. Since a decrease in stimulated secretory capacity is seen in

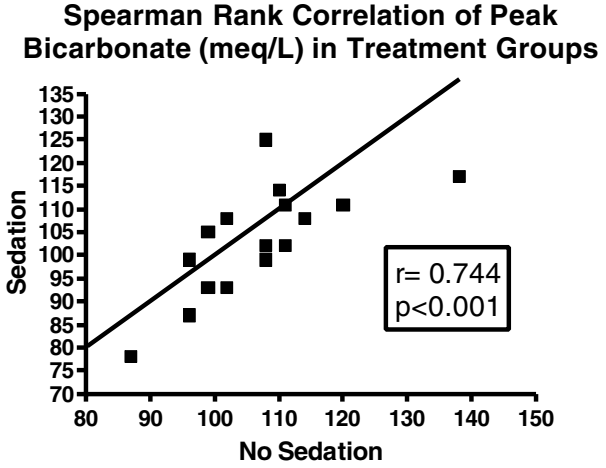


**Figure 5.** Correlation of peak bicarbonate concentration with and without moderate sedation.

patients with chronic pancreatitis, function testing has been traditionally believed to play a key role in early diagnosis (8, 9). Furthermore, pancreatic function tests are also considered the non-histologic "gold standard" and the most reliable methods to diagnose or exclude chronic pancreatitis in patients without obvious radiographic changes (10).

Until now, pancreatic function tests have been relegated to highly specialized tertiary centers with a gastrointestinal laboratory. These tests are cumbersome and labor intensive, limiting wide clinical applicability. There has been no improvement or advance in function testing methodology in the past 50 yr. These tests in their current form involve fluoroscopic or endoscopic guided placement of gastroduodenal drainage tubes for prolonged periods. In addition, biologic secretin, the most widely used secretagogue has not been available for several years in the United States. Synthetic secretin, an identical 27 amino acid peptide to the biologic form, is now commercially available and FDA approved for exocrine function testing (11), facilitating cannulation of the pancreatic duct (12) and diagnosing the Zollinger–Ellison Syndrome (13). Dose response studies of this pure synthetic preparation have shown pharmacological efficacy to the biologic preparation (14). Gastroenterologists now have an unlimited supply of secretin for gastrointestinal physiology testing.

We have developed a safe and purely endoscopic collection method. This test does not require a specialized gastrointestinal laboratory and can be performed by any gastroenterologist skilled in upper endoscopy. In addition, there is no radiation exposure for the patient or endoscopy unit personnel. We believe our endoscopic collection method is the next step in the evolution of pancreatic function testing.

There have been a number of attempts to measure pancreatic function by endoscopic collection of pure pancreatic juice (PPJ) at ERCP (11–15). This "intraductal secretin test" is much shorter than the conventional test using a 15 min collection period. Published results have reached different conclusions and none of the intraductal tests have gained widespread acceptance and are still considered investigational by most authorities in the field. Three major criticisms of the intraductal collection method have been (a) variable test results causing differences in bicarbonate cutpoints, (b) the potential risks of inducing acute pancreatitis, and (c) the unknown effects of sedation on pancreatic exocrine function (6). We believe our endoscopic collection method is superior to the previous attempts at intraductal collection and avoids these potential problems based on the following:

First of all, our data explains the variable results seen with the 15 min, "intraductal" collection. The intraductal test collects the juice during the early phase of pancreatic secretion. This is during maximum pancreatic juice flow and variability in bicarbonate concentration. The bicarbonate concentration reaches a maximum and steady state only after about 30 min of stimulation. The bicarbonate concentrations collected with the intraductal test are during the early phase (first 15 min) of pancreatic secretion. This is when bicarbonate concentration is most variable, thus leading to inaccurate assessments of "true" pancreatic function: total bicarbonate output and peak concentration. This has also been described by other authors when comparing the intraductal and traditional collection methods (16–20). Our 1 h endoscopic test captures the entire pancreatic secretory curve, which includes maximum flow rates and concentration thus allowing accurate determination of both bicarbonate output and concentration.

Secondly, the traditional "intraductal" test requires deep pancreatic duct cannulation via retrograde pancreatogram for pure pancreatic juice collection. This places the patient at risk for ERCP-induced acute pancreatitis. Our endoscopic test aspirates pancreatic fluid from the duodenal lumen with a forward viewing endoscope, avoiding the need for pancreatic duct cannulation or instrumentation. There have been no episodes of pancreatitis with our endoscopic collection method with CCK or secretin in over 400 patients at our institution.

And finally, endoscopic procedures usually require the use of sedation. Several medications utilized in endoscopic procedures have been shown to affect pancreatic secretion and must be avoided if accurate bicarbonate measurements are to be obtained. Glucagon, antispasmodics, and anticholinergics can decrease pancreatic secretion (21, 22). Benzodiazepines have not been shown to alter pancreatic secretion (23). Opioid medications have not been studied, and their effects on secretion are unknown. More importantly, until now, the effects of combination therapy with opiates and benzodiazepines have not been reported. Our study is the first to show that common doses of narcotics used to achieve moderate sedation do not significantly alter exocrine pancreas function.

A few comments need to be made in regard to our investigation. First of all, chronic pancreatitis is not an "all or none" disease. It is a continuum of chronic inflammation, fibrosis, and scarring in the gland with the gradual development of secretory dysfunction. Therefore, a true cutpoint to define the presence or absence of disease is theoretical. At what point is secretory dysfunction defined? For example, one of our patients went from 87 (normal) to 78 (abnormal). This in fact may be an indeterminate value that requires further testing or observation of the study subject. Or there may have been some gastric acid contamination with pancreatitis collection giving a false positive result. In fact, most authorities believe that function testing should not be interpreted by itself (or in a vacuum) but in combination with imaging and the overall clinical setting. Secondly, chronic pancreatitis patients generally will require a larger dose of sedation to perform a 1 h function test. Since benzodiazepines do not affect pancreatic secretion, we recommend the use of long acting agents such as diazepam to maintain sedation along with intermittent bolus dosing of short acting doses of midazolam. Finally, we used meperidine instead of fentanyl based on our prior published nomogram. We are aware that a lot of endoscopy units use fentanyl instead of meperidine. We do not think the use of fentanyl will change the study results but this has not been studied to date.

In conclusion, our data suggests that moderate sedation utilized in upper endoscopy has no pharmacologic effect on the physiologic secretory parameters (peak bicarbonate concentration or bicarbonate output) utilized to diagnose pancreatic insufficiency after secretin stimulation. Furthermore, analysis of endoscopically collected duodenal drainage fluid after synthetic porcine secretin stimulation produces an identical secretory curve to that seen in traditional gastroduodenal collection methods, thus preserving pancreatic secretory physiology.

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