

Comparison of Biologic Porcine Secretin, Synthetic Porcine Secretin, and Synthetic Human Secretin in Pancreatic Function Testing

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Background and Aims: Due to the unavailability of biologic porcine secretin (BPS), 2 synthetic forms of secretin were developed. Our aim is to determine the bioequivalency of the 3 forms of secretin in pancreatic function testing.

Methods: In a randomized, crossover design, synthetic porcine (SPS) and synthetic human secretin (SHS) were compared in a group of 12 subjects with chronic pancreatitis undergoing secretin stimulation test (SST). The 2 synthetic forms of secretin were then compared with BPS in 12 subjects utilizing a similar design. Finally, 18 healthy subjects underwent secretin stimulation testing with SHS.

Results: There was excellent correlation of peak bicarbonate measurements in the comparison of SPS to SHS ($R = 0.967$) as well as in the comparison of all 3 forms of secretin ($P = 0.08$, ANOVA for correlated samples). In the SST, each of the synthetic forms of secretin were 100% accurate in diagnosing chronic pancreatitis in disease subjects and in excluding chronic pancreatitis in normal controls. The synthetic forms of secretin were associated with fewer side effects when compared with BPS with the exception of transient tachycardia which occurred in up to 19% of subjects.

Conclusions: The synthetic porcine and human forms of secretin are equivalent to one another and to biologic porcine secretin and can be used interchangeably in pancreatic function testing.

Key Words: chronic pancreatitis, biologic porcine secretin, bicarbonate, synthetic porcine secretin, synthetic human secretin

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Secretin, first discovered almost 100 years ago,¹ is a gastrointestinal hormone that is produced by S-cells in the proximal small intestine and is responsible for a number of biologic

functions. Secretin is released into the circulation in response to food and/or acid within the proximal small intestine. Within the pancreas, secretin acts on pancreatic acinar cells and ductal epithelial cells stimulating the production of bicarbonate rich fluid. Tests exploiting this normal physiologic phenomenon were developed in an attempt to quantify pancreatic dysfunction and diagnose chronic pancreatitis. The secretin stimulation test (SST) was developed more than 60 years ago² and has primarily been used in academic medical centers throughout the world in the diagnosis of chronic pancreatitis. When directly compared with what many consider to be the gold standard, pancreatic histology, the secretin test has performed well.^{3,4} The SST has also been shown in a number of studies^{5–8} to be superior to all imaging modalities in diagnosing early or mild chronic pancreatitis.

Biologically derived porcine secretin (Ferring Pharmaceuticals, Inc., Tarrytown, NY) was the most widely used form of secretin in the United States and Europe up until production ceased in 1999. Over the past few years, the supply of biologic porcine secretin (BPS) has been rapidly depleted in the off-label use of the compound in the treatment of autism. Although initially reported anecdotally to improve behavior,⁹ secretin has not been found to be of significant benefit in subsequent placebo controlled trials.^{10–13}

The lack of an available form of secretin for gastrointestinal function testing led to the development of synthetic forms of both porcine and human secretin (ChiRhoClin, Inc., Silver Springs, MD). Synthetic porcine secretin (SPS) is identical to the 27 amino acid peptide, BPS. Synthetic human secretin (SHS) differs from the porcine secretins by only two amino acid residues, glutamine at position 15 and glycine at position 16. Both synthetic forms have the advantage of superior purity, >96% versus 60% compared with BPS. The purity of the synthetic forms and the identical peptide structure of SHS, specifically, has the potential advantages of providing more predictable pharmacologic effects, eliminating contamination with animal pathogens, and markedly reducing the potential for allergic reactions or development of neutralizing antibodies with repeated use.

Previous work both in a cat bioassay model (ChiRhoClin, data on file) and more recently in healthy human con-

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trols.¹⁴ has shown that 0.2 µg of SPS provides the same clinical activity as 1 CU of BPS using pancreatic bicarbonate output as the parameter studied. Furthermore, work from our laboratory has shown that SPS in doses of 0.2 µg/kg is biologically equivalent to 1 CU of BPS when administered during the secretin stimulation test in subjects with documented chronic pancreatitis.¹⁵ To date, there are no published data comparing SHS to either BPS or SPS. Additionally, there are no published data establishing the pharmacologic activity of SHS in normal healthy subjects undergoing evaluation of exocrine pancreatic insufficiency using the secretin stimulation test. The aim of this study is to investigate the reliability of SHS in pancreatic function testing in both healthy subjects and disease controls.

MATERIALS AND METHODS

The research protocols were reviewed and approved by the University of Florida Institutional Review Board. After obtaining signed informed consent, patients were enrolled to participate in 1 of 3 parts of the study. All patients were over the age of 18, of non-child bearing potential or with a documented negative pregnancy test. Patients could not have acute pancreatitis, used anticholinergic medications within 1 week of the study, or have a known sensitivity or previous adverse reaction to secretin.

Comparison of synthetic porcine and synthetic human secretin

Twelve patients with a diagnosis of chronic pancreatitis were enrolled in part 1 of the study. The diagnosis of chronic pancreatitis was based on a prior abnormal secretin stimulation test using biologic porcine secretin supported by at least 1 other abnormal test, including serum trypsin, ultrasound, computed tomography, or endoscopic retrograde pancreatography. These patients were then randomized to receive either synthetic porcine or synthetic human secretin in a blinded fashion given during the secretin stimulation test. On the following day, each patient returned and the alternative form of synthetic secretin was administered during a repeat secretin stimulation test.

Comparison of all 3 forms of secretin

An additional 6 subjects with a diagnosis of chronic pancreatitis were enrolled for the second part of the study. Subjects were recruited from those found to have an abnormal secretin stimulation test, performed as a diagnostic study by their referring physician, using synthetic human secretin. In addition to the abnormal secretin stimulation test, the diagnosis of chronic pancreatitis was supported by 1 or more criteria as previously described. Using a double-blind, randomized, crossover design, the subjects were then assigned to receive either biologic porcine secretin at a dose of 1 CU/kg or synthetic por-

cine secretin at a dose of 0.2 µg/kg during secretin stimulation tests performed on sequential days.

Synthetic human secretin in healthy controls

Twenty-four healthy, volunteer subjects were then enrolled in the final part of the study. They were all between the ages of 18 and 75 years, of non-child bearing potential or using contraception with a documented negative urine pregnancy test on enrollment. Subjects were without a history of pancreatic disease, vagotomy, or alcohol abuse. No anticholinergic medications were allowed for 1 week and no alcohol consumption allowed for 72 hours prior to enrollment. Subjects were allowed to take their routine outpatient medications during the study period.

Secretin stimulation test

Following a 12-hour fast, subjects entered the study center where their weight, temperature, blood pressure, and pulse were recorded. Additional blood pressure and pulse measurements were obtained 1 minute before as well as 1, 15, and 60 minutes after administration of secretin. Local anesthesia of the oropharynx was achieved with a combination of 4% lidocaine solution and 20% benzocaine spray. The esophagus was orally intubated with a double lumen, weighted tube (Dreiling Tube) preloaded with a radio-opaque guidewire. The tube was then advanced under fluoroscopic guidance so that the proximal aspiration ports were positioned in the stomach and the distal ports positioned in the second and third portion of the duodenum. After removal of the guidewire, the proximal end of the tube was taped to the subjects face to prevent migration and each lumen connected to separate flasks to which constant suction (3–5 mm Hg) was applied. The test was completed with the subject in a sitting position and the suction was periodically released to prevent clogging of the aspiration ports with gastric or duodenal mucosa. Although minor fluid losses are expected with this method, no marker substrate was perfused because the primary parameter studied, peak bicarbonate concentration is independent of the total volume. In addition, previous evaluations in our laboratory utilizing [¹⁴C]PEG and [⁵⁷Co]cyanocobalamin as small intestinal and gastric markers, respectively, indicated a maximum volume loss of 15% during the performance of the secretin test (unpublished data). This was not felt to be clinically relevant. Following a 15-minute baseline collection, a 0.1 mL test dose of 0.2 µg/kg SPS/SHS or 1 CU/kg of BPS was administered intravenously over 1 minute. If no adverse reaction was noted with the test dose, the remainder of the dose was infused over another minute. The duodenal aspirates were then collected in 15-minute aliquots over 1 hour. The total volume of each sample was then determined, pH measured, and bicarbonate concentration determined using back titration. The total volume and pH of the gastric aspirate collected over the entire hour was then measured. In addition to the total volume and bicarbonate concen-

tration, the volume per kilogram body weight and total bicarbonate output were calculated for each 15-minute duodenal collection. Based on extensive prior experience in our institution, the normal values for the secretin stimulation test are peak bicarbonate concentration ≥ 80 mEq/L, volume per weight ≥ 1.5 ml/kg and total bicarbonate output ≥ 10.1 mEq/h.

Statistical method

Paired *t* test, ANOVA for 3 samples (repeated measures), means, standard deviation, and correlation coefficient were used to compare the groups using the StatView software (Version 4.57; Abacus Concepts Inc., Berkeley, CA).

RESULTS

SPS versus SHS

Twelve subjects with a previously abnormal secretin stimulation test and chronic pancreatitis as supported by at least 1 other test were enrolled. They then underwent secretin stimulation tests on consecutive days using synthetic porcine and synthetic human secretin in a randomized, crossover design. The group consisted of 8 women and 4 men with 6 having idiopathic pancreatitis, 5 having alcoholic pancreatitis, and 1 having pancreatitis resulting from trauma as well as alcohol. (Table 1) The peak bicarbonate concentration (mean \pm SD) obtained by using synthetic human and synthetic porcine secretin were 67 ± 19 mEq/L and 65 ± 18 mEq/L, respectively ($P = 0.31$), paired *t* test) (Table 2). There was no difference between the other results (total volume, volume/weight, total bicarbonate output) measured as shown in Table 3. The correlation between the results obtained with synthetic human and porcine secretin was excellent ($R = 0.967$). Based on a cutoff value for peak bicarbonate concentration of 80 mEq/L, the accuracy of human synthetic secretin in comparison to synthetic porcine secretin in diagnosing pancreatic insufficiency was 100%.

Comparison of all 3 forms

A total of 12 subjects had an abnormal secretin stimulation test with either biologic porcine or synthetic human secretin and then received the other 2 forms of secretin in a random-

TABLE 2. Comparison of results of secretin stimulation testing obtained with synthetic human and synthetic porcine secretin

	SPS	SHS	P
Peak bicarbonate (mEq/L)	65 \pm 18	67 \pm 19	0.31
Total volume (ml)	170 \pm 87	166 \pm 102	0.79
Volume/weight (ml/kg)	2.39 \pm 1.22	2.25 \pm 1.27	0.55
Total bicarbonate output (mEq/L)	9.93 \pm 8.02	9.72 \pm 8.18	0.87

Results expressed as mean \pm SD.

P-values obtained by using the paired *t*-test.

SPS, Synthetic porcine secretin; SHS, Synthetic human secretin.

ized, crossover design on sequential days. Six of the patients had a previously abnormal secretin test with BPS as part of our prior study¹⁵ and then received the 2 synthetic forms of secretin in our comparison of SPS to SHS in part 1. Because these patients had also undergone secretin testing with all 3 forms in a similar randomized, crossover design, they were also included in the analysis. The mean time period between the abnormal entrance secretin test and the 2 subsequent tests was 11.7 weeks (range 1–22). This group consisted of 8 women and 4 men with a mean age of 56 years. Ten of the subjects were white and 2 African American. The etiology of chronic pancreatitis was idiopathic in 7 and alcohol in 5 individuals (Table 1). The peak bicarbonate concentration (mean \pm SD) using BPS, SPS, and SHS were 61 ± 13 , 56 ± 13 , and 61 ± 12 , respectively ($P = 0.08$, ANOVA for correlated samples; Table 3). Similarly, paired comparisons of the 3 forms of secretin showed excellent correlation ($R > 0.85$ with each comparison). There was no significant difference between the other parameters measured during the secretin tests, regardless of the form of secretin used. (Table 3) No subject was misdiagnosed as normal or abnormal with any of the 3 forms of secretin studied. (Fig. 1) The accuracy of the secretin stimulation test using either of the synthetic forms was 100% when compared with the biologic porcine secretin.

TABLE 1. Summary of demographic characteristics

	Normal controls (n = 18)	SPS versus SHS (n = 12)	BPS versus SPS versus SHS (n = 12)
Age	38.9 (20–75)	59.0 (27–76)	52.0 (35–70)
M:F	1:25:1	1:2	1:2
Race (W, B, O)	12W, 4B, 2O	10W, 2B	10W, 2B
Etiology of chronic pancreatitis	N/A	6 alcohol, 6 idiopathic	5 alcohol, 7 idiopathic

BPS, Biologic porcine secretin; SPS, Synthetic porcine secretin; SHS, Synthetic human secretin.

TABLE 3. Summary of the secretin stimulation test results using biologic and synthetic porcine secretin and synthetic human secretin

	BPS	SPS	SHS	P
Peak bicarbonate (mEq/L)	61 ± 13	56 ± 13	61 ± 12	0.08
Total volume (ml)	163 ± 98	171 ± 98	172 ± 118	0.77
Volume/weight (ml/kg)	2.1 ± 1.5	2.2 ± 1.5	2.2 ± 1.6	0.86
Total bicarbonate output (mEq/hr)	8.1 ± 5.4	8.0 ± 6.5	9.7 ± 6.8	0.22

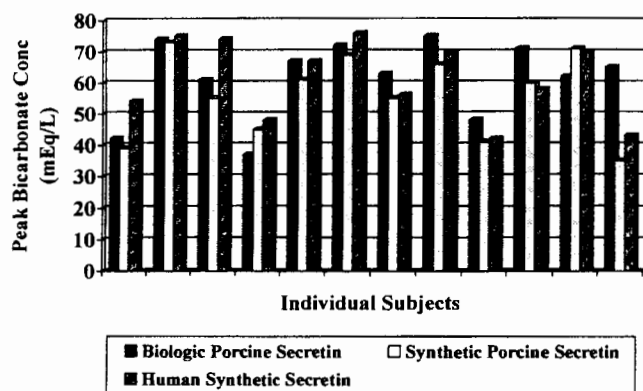
Results expressed as mean ± SD.

P value obtained by using ANOVA for correlated samples.

BPS, Biologic porcine secretin; SPS, Synthetic porcine secretin; SHS, Synthetic human secretin.

SHS in healthy controls

A total of 24 healthy control subjects (12 men, 12 women) were enrolled in the study. Two subjects failed to meet inclusion/exclusion criteria, one because of recent use of anticholinergic medications and another because of a history of heavy alcohol use. Four more subjects failed to complete the study because they were unable to tolerate placement of the Dreiling tube. These subjects were not included in any of the analysis. A total of 18 subjects completed the study. This group consisted of 10 men and 8 women with a mean age of 38.9 years. Racial representation included 12 whites, 4 African Americans, 1 Hispanic, and 1 Asian (Table 1). No clinically significant comorbid conditions or any gastrointestinal conditions were identified on history. The mean peak bicarbonate concentration, 96.3 mEq/L, was well within our previously established normal range (≥ 80 mEq/L) as were the other parameters summarized in Table 4. This mean ± 2 SD also falls within our previously established normal range using biologic porcine secretin. (Table 4) The accuracy of the test was 100% in excluding the diagnosis of chronic pancreatitis based on the

**FIGURE 1.** Summary of Individual Subjects.**TABLE 4.** Summary of secretin stimulation test using synthetic human secretin in healthy controls

	Mean ± SD	±2 SD	Normal†
Peak bicarbonate (mEq/L)	96 ± 8	81–112	80–130
Volume/weight (ml/kg)	3.6 ± 1.0	1.6–5.6	1.5–5.7
Total bicarbonate output (mEq/hr)	23.0 ± 7.5	8.0–38.0	10.1–37.0

†Normal ranges established in our gastrointestinal function lab (unpublished data).

normal range of peak bicarbonate concentration previously established using biologic porcine secretin.

Safety

There were no severe adverse reactions reported with any of the 3 forms of secretin used in this study. Two patients reported symptoms following infusion of the biologic porcine secretin that resolved within 5 minutes. One subject had mild flushing and the other mild nausea. Of note, 80% of subjects did have an asymptomatic, transient elevation in their heart rate, up to 20% over baseline, associated with the synthetic secretin infusions which again returned to baseline on repeat measurement 15 minutes later. The tachycardia tended to be more pronounced with the synthetic forms of secretin, 19% and 15% increase over baseline with SHS and SPS respectively, than with biologic porcine secretin which was associated with a 9% increase in heart rate over baseline.

DISCUSSION

In previous work comparing synthetic to biologically derived porcine secretin in pancreatic function testing, Lankisch and Creutzfeldt¹⁶ reported significantly higher volumes and total bicarbonate output with the synthetic form. Other work^{15,17,18} has not supported this observation. Previous work from our institution¹⁵ has shown that synthetic porcine secretin is reliable in pancreatic function testing in individuals with previously documented chronic pancreatitis. This is the first study to investigate the utility of synthetic human secretin in pancreatic function testing. Our results establish the equivalency of synthetic porcine and human secretin to biologic porcine secretin in pancreatic function testing. Additionally, we have demonstrated the accuracy of pancreatic function testing using synthetic human secretin both in excluding pancreatic exocrine dysfunction in a group of normal controls and in confirming pancreatic exocrine insufficiency in a group of subjects with established chronic pancreatitis.

Nine of the 12 subjects with chronic pancreatitis that participated in the current study comparing synthetic porcine to synthetic human secretin had also participated in our previous study comparing biologic to synthetic porcine secretin.¹⁵

The median time between the 2 tests using synthetic porcine secretin was 4 months with a range of 2 to 6 months. Although not a primary objective of this study, we did find that repeated stimulation of the pancreas with synthetic porcine secretin produced highly reproducible peak bicarbonate concentrations ($R = 0.91$).

The advantages of the synthetic forms of secretin are many; not the least of which is the potential for unlimited supply, which has been particularly problematic with the biologically derived porcine product. Additionally, the synthetic forms have the advantage of purity over the biologically derived compound. Theoretically, this difference may result in a more predictable physiologic response as well as a decreased potential for immunogenicity. Both synthetic forms appear to have equivalent physiologic effects on the pancreas at the dose of 0.2 $\mu\text{g}/\text{kg}$. In this study, no adverse effects were seen with either of the synthetic forms as compared with 33% seen with the biologic form. In our gastrointestinal function laboratory, 128 patients have received synthetic human secretin as part of an open label study with only 1 patient experiencing a possible exacerbation of their chronic, non-pancreatic abdominal pain. The tachycardia observed in many of the study subjects has been previously reported with biologic porcine secretin.¹⁹ In this study, heart rate also increased by 20% over baseline and was not altered by pretreatment with IV propranolol, making mediation by beta-adrenergic receptors an unlikely mechanism.¹⁹

We conclude that the 2 synthetic preparations are equivalent and can be used interchangeably in pancreatic function testing. Synthetic human secretin should be used when repeated exposure is anticipated. Our data also demonstrates the reproducibility of the secretin test thus underscoring its role in the diagnosis of chronic pancreatitis.

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