

# A new synthetic porcine secretin for facilitation of cannulation of the dorsal pancreatic duct at ERCP in patients with pancreas divisum: a multicenter, randomized, double-blind comparative study

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**Background:** Secretin, a 27 amino acid polypeptide released in response to duodenal luminal acidification, stimulates secretion of water and bicarbonate from pancreatic ductal cells. To date the only secretin available for clinical use has been a biologically derived compound extracted from porcine duodenums. Although used to facilitate pancreatic duct cannulation, secretin has not been approved for this indication. In this study, a new synthetic porcine secretin with an identical amino acid composition was compared with saline solution for the facilitation of minor papilla cannulation in patients with pancreas divisum.

**Methods:** A multicenter, prospective, randomized, placebo-controlled, double-blind, comparative trial was conducted at 4 centers with expertise in pancreaticobiliary endoscopy. Patients with pancreas divisum in whom minor papilla cannulation initially was unsuccessful were enrolled. Either saline solution (placebo) or synthetic porcine secretin was administered. If the minor papilla orifice and/or pancreatic juice flow was noted, cannulation was attempted and success or failure was documented (phase 1), as well as the time taken for successful cannulation. If cannulation was unsuccessful, no juice flow was noted, or the orifice was not seen, the alternate agent was administered (phase 2).

**Results:** Twenty-nine patients (7 men, 22 women; mean age 51 years, range 21-76 years) were enrolled. In phase 1, cannulation was achieved in 1 of 13 patients (7.7%) after the placebo was given and in 13 of 16 patients (81.3%) after synthetic porcine secretin was given ( $p < 0.0001$ ). In phase 2, cannulation was achieved in 12 of 12 patients (100%) after synthetic porcine secretin was given and in 0 of 3 patients (0%) after the placebo was given ( $p = 0.0022$ ). Overall, cannulation was successful in 25 of 28 patients (89.3%) who received synthetic porcine secretin and in 1 of 16 (6.3%) who received the placebo ( $p < 0.0001$ ). Mean time to cannulation was significantly greater for the placebo than for the synthetic porcine secretin (4.75 min vs. 2.63 min;  $p = 0.0001$ ). No adverse events directly attributable to synthetic porcine secretin administration were documented.

**Conclusions:** This study confirmed the use and safety of synthetic porcine secretin in facilitating cannulation of the minor papilla in patients with pancreas divisum in whom cannulation was difficult. Use of this agent has the potential to further increase the cannulation success rate in this group of patients. (Gastrointest Endosc 2003;57:643-7.)

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Secretin is a 27 amino acid polypeptide that is secreted from mucosal cells in the proximal small intestine in response to luminal acidification. Circulating secretin acts via specific receptors to stimulate the secretion of water and bicarbonate from pancreatic duct cells. The only secretin available for widespread clinical application has been a biologically derived compound extracted from porcine duodenums (biological Porcine Secretin; bPS). This compound was first isolated in 1961 by Jorpes and Mutt.<sup>1</sup> It has been used clinically for more than 20 years for the diagnosis of pancreatic

insufficiency and gastrinoma, and to obtain exfoliated pancreatic cells for cytologic examination.<sup>2</sup> Although used to facilitate pancreatic duct cannulation at ERCP,<sup>3</sup> it has not been approved by the U.S. Food and Drug Administration for this indication.

Clinical use of secretin has been limited because the supply of bPS has been inadequate. In addition, the pancreatic secretory response to intravenous administration of secretin in normal subjects and in patients with pancreatic disease is known to vary because of the heterogeneity of extracted porcine secretin and batch variability.<sup>4</sup> A new synthetic porcine secretin (sPS) has been developed (ChiRhoClin, Inc., Silver Spring, Md.) with an amino acid composition and sequence that is identical to the biologically derived compound. It is more homogeneous and compositionally consistent than bPS, and its use is devoid of the theoretical risk of transmission of animal pathogens.

Pancreas divisum is a developmental anomaly of pancreatic ductal anatomy that is present in approximately 7% (range 1%-14%) of white Americans. The prevalence in African Americans is 2% and in Asians, 1% to 2%.<sup>5-7</sup> When contrast medium is injected via the major papilla at ERCP, pancreas divisum is identified by the finding of a small, terminal branching ductal system. The minor papilla may be relatively large in size, but this is an inconsistent finding. After locating the minor papilla, cannulation of the dorsal duct orifice can be challenging and may require the application of an array of special techniques and equipment.

Identification of the minor papilla orifice may be facilitated by increasing the production of pancreatic juice, which results in a visible flow of juice into the duodenum. Moreover, by increasing pancreatic juice flow, the orifice enlarges, simplifying guidewire or catheter insertion. Cholecystokinin can be used to increase pancreatic juice volume by stimulation of pancreatic enzyme production. Secretin, more specifically, increases pancreatic juice volume and has been used to facilitate pancreatic duct cannulation in a number of specialized centers.<sup>3</sup> In this study, sPS was compared with saline solution for the facilitation of minor papilla cannulation in patients with pancreas divisum.

#### PATIENTS AND METHODS

This multicenter, prospective, randomized, placebo-controlled, double-blind, comparative trial was conducted at 4 referral centers with expertise in ERCP. The study protocol was approved by the Institutional Review Board at each center. Patients were eligible for enrollment (pre-procedure) if there was a suspicion of pancreas divisum based on clinical history (e.g., unexplained recurrent pan-

creatitis), abdominal imaging studies (e.g., MRCP), or prior ERCP.

Patients underwent ERCP by an experienced pancreaticobiliary endoscopist for a variety of indications. If major pancreatic duct cannulation failed to opacify a ventral duct, raising the possibility of pancreas divisum, or revealed a ventral ductal system consistent with pancreas divisum, minor papilla cannulation and dorsal ductography were pursued, if clinically indicated. Ventral ductography was not attempted in patients with known pancreas divisum. Patients with pancreas divisum in whom minor papilla cannulation was difficult were enrolled.

A difficult cannulation was defined as an inability of the expert endoscopist to identify the minor papilla orifice after 1 minute of observation or failure of cannulation after an attempt 5 minutes in duration. Exclusion criteria were acute pancreatitis, use of anticholinergic medication within 1 week of ERCP, known hypersensitivity or adverse reaction to secretin, pregnancy, and breast feeding.

Because of a failure to identify or cannulate the minor papilla orifice, a placebo (saline solution) or sPS (0.2 µg/kg; maximum dose of 16 µg) was administered to patients in a randomized, double-blinded fashion. The papilla was observed for 3 minutes. Cannulation was attempted if pancreatic juice flow from the minor papilla was visualized and/or the minor papilla orifice was observed. Success or failure of cannulation was documented, as well as the time required for successful cannulation. Cannulation time was defined as the time elapsed from commencement of the cannulation attempt to successful cannulation of the dorsal duct. A time limit of 5 minutes was set for attempting cannulation. When cannulation was not attempted, cannulation time was recorded as 5 minutes. If no juice flow was documented or the orifice was not visualized, the alternate agent was administered and the observation/cannulation process was repeated. A time limit of 5 additional minutes was set for attempting cannulation.

The sPS and saline solution were prepared in identical syringes by the institutional pharmacist or endoscopy nurse; the fluids were identical in appearance. The sPS was reconstituted in 8 mL of sterile normal saline solution. The sequence for administration of sPS or placebo was determined by means of a randomization code provided to the research pharmacist in each participating center. Patients were randomized in blocks of 2 by using concealed envelopes. The study used a dosage of sPS (0.2 µg/kg), which is equivalent to the dosage of bPS (1 CU/kg) recommended for exocrine pancreas stimulation.

Demographic and medical history data were recorded in addition to the efficacy of the agent in facilitating cannulation. Safety data were recorded by documenting all adverse events. All patients gave informed consent for the administration of secretin.

#### Statistical methods

The outcomes for the secretin were compared with the outcomes for the placebo. The data were evaluated in 3 phases. Phase 1 refers to the outcome of cannulation (su-

**Table 1. Cannulation outcome with secretin and placebo: phase 1—first treatment period after randomization**

Cannulation outcome	Secretin	Placebo	<i>p</i> Value
Successful	13 (81.3%)	1 (7.7%)	<0.0001
Unsuccessful	3 (18.7%)	12 (92.3%)	

**Table 2. Cannulation outcome with secretin and placebo: phase 2—second treatment period after randomization for patients with unsuccessful cannulation during phase 1**

Cannulation outcome	Secretin	Placebo	<i>p</i> Value
Successful	12 (100%)	0 (0%)	0.0022
Unsuccessful	0 (0%)	3 (100%)	

**Table 3. Combined phase 1 and phase 2 results**

Cannulation outcome	Secretin	Placebo	<i>p</i> Value
Successful	25 (89.3%)	1 (6.3%)	<0.0001
Unsuccessful	3 (10.7%)	15 (93.7%)	

**Table 4. Time for cannulation**

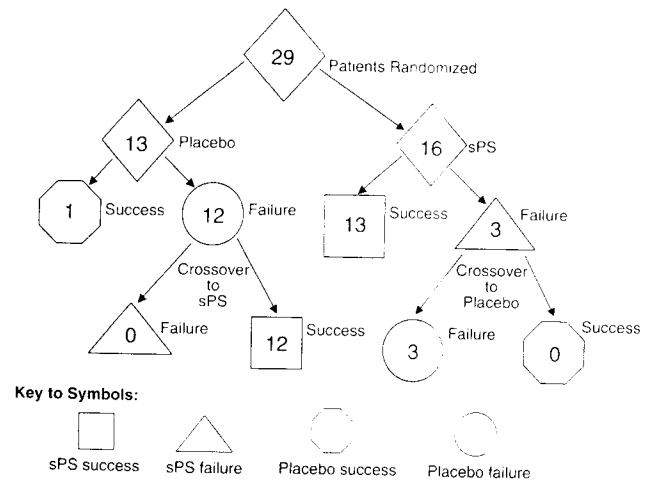
Drug (n)	Time (mean)	Time (SD)	<i>p</i> Value sPS
Secretin (28)	2.63	1.52	—
Placebo (16)	4.75	1.00	0.0001

successful or unsuccessful) after the initial randomization. Phase 2 refers to the outcome of cannulation after administration of the alternate agent when cannulation in phase 1 was unsuccessful. Phase 3 combines the results of phase 1 and phase 2. The comparison used the Fisher exact test. The method of Bonferroni was used to ensure that the stated *p* values were significant after correction for the multiple testing of data arising from a single patient. Statistical significance was declared if the two-sided *p* value was <0.0167 based on the adjustment for multiple testing using the method of Bonferroni. All computations were performed with statistical software (Statistical Analysis System [SAS], SAS Institute, Inc., Cary, N.C.).

## RESULTS

Twenty-nine patients (7 men, 22 women; mean age 51 years, range 21-76 years) were enrolled between October 1999 and June 2000 (Fig. 1). The number of patients enrolled in each of the study centers was the following: Indiana University 14, Duke University 5, Medical University of South Carolina 9, and University of Florida 1.

In phase 1, after randomization (Table 1), cannulation was achieved in 1 of 13 patients (7.7%) after the placebo was given and in 13 of 16 patients (81.3%) after the sPS was given ( $p < 0.0001$ ). When cannulation was unsuccessful in phase 1, the alter-

**Figure 1. Patient flow chart.**

nate agent was administered in phase 2 (Table 2). Cannulation was achieved in 12 of 12 patients (100%) after sPS was administered and in 0 of 3 patients (0%) after the placebo was administered ( $p = 0.0022$ ). The combined results of phase 1 and phase 2 are shown in Table 3. Of the 28 patients who received sPS, cannulation of the minor papilla was successful in 25 (89.3%). Of the successful cannulations, 13 occurred after sPS was administered first (phase 1) and 12 occurred after sPS was given second (phase 2) (after the placebo failed to facilitate cannulation because of the absence of a visible orifice and/or visible flow of pancreatic juice). In contrast, cannulation was successful in only 1 of 16 patients (6.3%) who received the placebo ( $p < 0.0001$ ).

The time used by the endoscopist to cannulate or attempt to cannulate the minor papilla was measured; mean times for sPS and placebo are shown in Table 4. This table documents that the effort, as measured by the mean time taken to attempt cannulation, was statistically significantly greater for the placebo compared with the sPS.

No adverse events directly attributable to sPS administration were documented. There were no episodes of pancreatitis after ERCP.

## DISCUSSION

Secretin is a GI peptide hormone that was first extracted from porcine duodenum by Jorpes and Mutt in 1961.<sup>1</sup> The heptacosapeptide was subsequently sequenced and synthesized by Mutt, Bodansky, and their coworkers at the Karolinska Institute.

The sPS is presented as a sterile lyophilized powder consisting of 16 µg of purified synthetic secretin. It is reconstituted with 8 mL of sodium chloride injection (USP), and each milliliter therefore contains 2 µg of secretin for intravenous use. The stan-

standard unit of activity of bPS is the clinical unit (CU) defined by Jorpes and Mutt in 1966.<sup>4,8</sup> One CU of bPS is equivalent to 0.2  $\mu\text{g}$  of sPS. In a study of 6 healthy subjects, the half-life for bPS was approximately 4 minutes, with a clearance rate of 540 mL/min.<sup>9</sup> Normal ranges for pancreatic secretory response to intravenously administered secretin in patients with defined pancreatic diseases are known to vary. The variation is related to the secretin product used, as well as interinvestigator differences in operative technique. It has been determined, however, that properly performed tests with secretin will identify pancreatic disease.<sup>10,11</sup>

Pancreas divisum is the most common congenital pancreatic anatomic anomaly, with a frequency of approximately 7% in autopsy series (range 1%-14%). It is less prevalent in Asians and African Americans.<sup>5-7</sup> The pancreas is derived from dorsal and ventral buds that develop from the embryonic foregut. The ventral system also gives rise to the hepatobiliary system. The ventral pancreas rotates posterior to the duodenum during the eighth intrauterine week and comes to lie posterior and inferior to the head portion of the dorsal pancreas. Fusion of the ductal system occurs in just over 90% of individuals, although there are variations in the patency of the accessory duct.<sup>12</sup>

In pancreas divisum, only the ventral portion of the pancreas, or no duct at all, can be opacified by means of standard major papilla cannulation at ERCP. Incomplete ductography results in underevaluation of the dorsal pancreas unless minor papilla cannulation is performed. Typically, the ventral duct in pancreas divisum is 1 to 4 cm long and tapers terminally into multiple small side-branches.<sup>11,12</sup> Contrast injection results promptly in acinarization of the small ventral system, which is represented fluoroscopically as a focal, fluffy collection of contrast media, generally with sharp peripheral margins. This must be differentiated from submucosal injection (fuzzy peripheral margins), acinarization of a main duct side branch, filling of other cavities (pseudocyst, necrotic tumor, or diverticulum) and a stricture of the main pancreatic duct secondary to a benign process, or pancreatic cancer (pseudodivisum). Dorsal ductography is imperative to distinguish pancreas divisum from any of these pathologies.

Minor papilla cannulation generally should be attempted in cases where a short, terminally branching ventral duct is demonstrated by injection of a contrast medium via the major papilla or when attempts to achieve pancreatography via the major papilla are unsuccessful. Particularly in expert hands, the latest generation videoendoscopes and accessories clearly facilitate minor papilla identi-

cation and cannulation. Despite this, the minor papilla orifice still may not be evident initially in approximately a third of the cases,<sup>12</sup> and minor papilla cannulation may fail in 5% to 10% of patients with pancreas divisum.<sup>13,14</sup> In unsuccessful cases, the minor papilla is generally distorted because of inflammation or the presence of a diverticulum, a tumor, or an altered gastroduodenal anatomy (e.g., Billroth I or II).

Synthetic porcine secretin has been shown to be reliable for pancreatic function testing in healthy volunteers<sup>15-17</sup> and in individuals with chronic pancreatitis.<sup>18</sup> Somogyi et al.<sup>18</sup> used sPS for the secretin stimulation test in the latter group; in 12 patients with known chronic pancreatitis, there was an excellent correlation between bPS and sPS ( $R = 0.964$ ) for the diagnosis of chronic pancreatitis. In addition, at a dosage of 0.2  $\mu\text{g}/\text{kg}$ , sPS yielded results equal to those obtained with 1 CU/kg of bPS in pancreatic function testing. Somogyi et al.<sup>18</sup> concluded that the 2 agents could be used interchangeably.

The results of the present study demonstrate that sPS facilitates successful cannulation of the minor papilla in 89.3% of patients with pancreas divisum in whom cannulation was challenging. This was because of prompt identification of the minor papilla orifice secondary to increased flow of pancreatic juice. During vigorous flow, it may be difficult to force contrast media retrograde to the tail of the pancreas, and use of such force may induce post-ductography pancreatitis. Secretin use should, therefore, be reserved for cases in which cannulation is difficult and contrast injection upstream to the body of the pancreas is not recommended. At times, pancreatic juice flow after secretin stimulation may still be inconspicuous. In such cases, spraying a dilute (1:10) methylene blue solution over the face of the minor papilla often helps identify the orifice, as evidenced by clear juice washing away the background of blue dye.

This study confirms the use and safety of sPS in facilitating cannulation of the minor papilla orifice in patients with pancreas divisum when cannulation is difficult. Because the details of duct morphology were not recorded, the investigators cannot comment on the efficacy of sPS in specific subgroups (e.g., chronic pancreatitis). Use of this agent in units with expertise in pancreaticobiliary endoscopy has the potential to further increase the cannulation success rate in patients with pancreas divisum. Although not addressed in this study, as a consequence of greater cannulation success, therapeutic minor papilla and dorsal duct intervention may be possible in a higher proportion of these patients. Final U.S. Food and Drug Administration approval and market release of this agent is anticipated.

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### DISCLOSURE

ChiRhoClin, Inc. provided the synthetic porcine secretin for the study at no cost. Dr. Edward Purich is CEO of ChiRhoClin. Dr. Seymour Fein is medical director of ChiRhoClin. Both Drs. Purich and Fein are equity holders in ChiRhoClin, Inc. Dr. Richard Trout was a paid biostatistics consultant for this study.

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