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Facilitation of Pancreatic Duct Cannulation Using a New Synthetic Porcine Secretin

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OBJECTIVES: Cannulation of the pancreatic duct at ERCP can represent a technical challenge, even to experienced pancreaticobiliary endoscopists. Secretin is a polypeptide hormone that increases the volume and bicarbonate content of pancreatic secretions. We report our single center experience in the use of a new synthetic porcine secretin (sPS) for the facilitation of cannulation of either the major or minor pancreatic orifice during ERCP.

METHODS: Patients presenting for a variety of indications were enrolled. If identification or cannulation of the desired pancreatic duct was difficult, 0.2 μg/kg of sPS was administered *i.v.* Cannulation success or failure was recorded.

RESULTS: Between March, 1999, and May, 2000, a total of 25 patients (seven men and 18 women) were enrolled. The most frequent indication (15 of 25 cases) was facilitation of dorsal pancreatic duct cannulation in patients with pancreas divisum. The overall rate of successful cannulation secretin administration was 24 of 25 cases (96%). No adverse events directly attributable to secretin were observed.

CONCLUSIONS: The results of this study show that sPS is safe and efficacious in faciliting cannulation of either the major or minor pancreatic orifice at ERCP in the subset of patients who represent cannulation difficulties. Once commercially available, sPS can be added to the armamentarium of techniques to facilitate ERP. (Am J Gastroenterol 2002; 97:2279–2281. © 2002 by Am. Coll. of Gastroenterology)

INTRODUCTION

Over the past 15 yr, interventional ERP has continued to evolve. Cannulation and contrast imaging of the pancreatic duct is the primary objective for evaluating patients with pancreatic disorders such as unexplained acute pancreatitis, chronic pancreatitis and its complications, and pancreatic neoplasms. Cannulation of the pancreatic duct at ERCP can represent a technical challenge, even to experienced pancreaticobiliary endoscopists. More recently published series report successful cannulation of the main pancreatic duct in 90–98% of cases (1). Minor papilla cannulation is generally more difficult with failure rates in the range of 5–10% (1, 2). Cannulation failure may be secondary to duodenal or pancreatic pathology, variant anatomy, or operator inexperience. The major papilla orifice can be difficult to identify and to cannulate after biliary endoscopic sphincterotomy, particularly if the orifice is located at an aberrant site (*i.e.*, other than the "5 o'clock" position). Identification and cannulation of the minor papilla is frequently difficult, as the target orifice is usually of pinpoint size.

Secretin is a 27–amino acid polypeptide hormone released from duodenal mucosal cells in response to luminal acidification. Circulating secretin acts via specific receptors to increase the volume and bicarbonate content of pancreatic juice. This is in contrast to cholecystokinin, which increases pancreatic juice volume and enzyme content. Secretin also relaxes the sphincter of Oddi, possibly after an initial increase in sphincter of Oddi phasic wave amplitude and frequency (3). The *i.v.* administration of secretin may facilitate pancreatic duct cannulation as a result of widening of the orifice during the increase in juice flow and relaxation of the sphincter of Oddi.

To date, the only secretin available for widespread clinical use has been a biological secretin derived from porcine duodenum (biological porcine secretin; bPS) (Secretin-Ferring; Ferring Pharmaceuticals, Tarrytown, NY). It has been used clinically since 1981 for the diagnosis of pancreatic insufficiency, gastrinoma and to obtain exfoliated cells for cytological examination. Although it has been used to facilitate pancreatic duct cannulation at ERCP, secretin has not been approved by the United States Food and Drug Administration (FDA) for this indication. The pancreatic secretory response to *i.v.* secretin in normal subjects and in patients with pancreatic disease is known to vary because of heterogeneity of the extracted porcine secretin and batch variability (4). In addition, nearly exhausted supplies of this agent, resulting from discontinuation of bPS production by the manufacturer, have recently limited its clinical application.

A new synthetic porcine secretin (sPS) has been developed (ChiRhoClin, Silver Spring, MD). This agent has the identical amino acid sequence to the biologically derived compound but is more homogeneous and compositionally consistent than bPS.

We report on our single center experience in the use of

Table 1. Indications for Secretin

Indication	n
Minor papilla cannulation	
Pancreas divisum	15
Nondivisum	2
Major papilla cannulation	
Post–biliary sphincterotomy	5
Other	3
Total	25

this new synthetic porcine secretin for the facilitation of cannulation of either the major or minor pancreatic orifice during ERCP.

MATERIALS AND METHODS

Patients presenting for ERCP at Indiana University Medical Center for a variety of indications were enrolled. If attempts to identify or cannulate the desired pancreatic orifice (major or minor) were unsuccessful, secretin was administered *i.v.* A difficult cannulation was defined as inability to cannulate the desired pancreatic duct using a variety of cannulating devices of the endoscopist's choice including catheters, sphincterotomies, or guidewires. Consecutive patients undergoing pancreatic duct cannulation were not enrolled. Secretin was administered if, at the endoscopist's discretion, cannulation of the pancreatic duct was deemed necessary and all of the above maneuvers failed. The duration of the attempted pancreatic duct cannulation varied. In each case, an endoscopist who was expert at performing ERCP made a protracted effort to cannulate the desired pancreatic duct before administering secretin. Patients received 0.2 μg/kg of sPS (reconstituted in 8 ml of sterile saline; maximal dose, 16 μg), which is equivalent to the dose of biological porcine secretin bPS (1 clinical unit [CU] per kilogram) recommended for exocrine pancreas stimulation. After administration of sPS, the papilla was observed for a visible flow of pancreatic juice. After identification of the pancreatic duct orifice, cannulation was reattempted. Cannulation success or failure was recorded. In addition, the patients' demographic data and past medical history were documented. Safety data were recorded documenting all adverse events. Exclusion criteria were as follows: acute pancreatitis, use of anticholinergic medications within 1 wk of ERCP, known hypersensitivity or adverse reaction to secretin, and pregnancy or lactation.

All patients gave informed consent to participate, and the study protocol was approved by the FDA and the Institutional Review Board.

RESULTS

Between March, 1999, and May, 2000, a total of 25 patients (seven men and 18 women; mean age 55 yr, range 22–81 yr), who represented difficult cannulation cases, were enrolled. The indications for secretin are listed in Table 1. The most frequent indication (15 of 25) was facilitation of dorsal pancreatic duct cannulation in patients with pancreas divisum. Two patients received secretin for minor papilla identification and cannulation in the absence of pancreas divisum: in one case, to further delineate the pancreatic ductal anatomy in a patient with a cystic lesion in the pancreatic head, and in the other case, to exclude incomplete pancreas divisum in a patient with almost complete obstruction of the main pancreatic duct in the region of the pancreatic head. The second most frequent indication (five of 25) was identification of the pancreatic orifice after biliary sphincterotomy. Assistance in major papilla cannulation was necessary in three other patients: two with sphincter of Oddi dysfunction and one with annular pancreas.

Cannulation was successful after secretin administration in 24 of 25 patients (96%). In the single unsuccessful case, cannulation of the minor papilla failed. It was located in a shallow diverticulum in the proximal portion of the descending duodenum.

No adverse events directly attributable to sPS were documented

DISCUSSION

This study demonstrates the efficacy of a new synthetic porcine secretin (sPS) for the facilitation of pancreatic duct cannulation at ERCP in a subset of patients who represented cannulation difficulties. Cannulation was successful in 24 of 25 cases (96%). Previously, bPS has been the only secretin available for clinical use. This GI peptide agent was first extracted from porcine duodenums in 1961 (5). It was subsequently sequenced by Mutt *et al.* at the Karolinska Institute and isolated by Jorpes and Mutt. The standard unit of activity of bPS is the clinical unit (CU) defined by Jorpes and Mutt in 1966 (4). A quantity of 1 CU of bPS is equivalent to 0.2 μg of sPS. In a study of six healthy subjects, the $t_{1/2}$ for bPS was approximately 4 min with a clearance rate of 540 ml/min (6). Normal ranges for pancreatic secretory response to *i.v.* secretin in patients with defined pancreatic diseases have been known to vary. The variation is related to the secretin product used as well as to inter-investigator differences in operative technique. It has been identified, however, that properly performed tests with secretin will identify pancreatic disease (7, 8).

The clinical utility of this biological porcine secretin for faciliting cannulation of the accessory pancreatic duct in patients with pancreas divisum has previously been reported (9). Gregg has previously reported that secretin stimulates a disproportionately large volume of fluid through the accessory papilla in pancreas divisum patients, with 90% of the pancreatic juice stimulated by secretin exiting via this orifice (10).

To date, bPS has been the only secretin formulation available for clinical use. Its availability has been greatly restricted in recent years because of its potential as an effective means of therapy for autism. More recently, the

manufacturer has ceased production of bPS. Cholecystokinin has also been used for the facilitation of both bile duct and pancreatic duct cannulation at ERCP. However, a small randomized, double blind trial, revealed no benefit of cholecystokinin compared to placebo for facilitation of the bile or pancreatic ducts at ERCP (11). A weakness of our study is that it is not a blinded controlled study. It is possible that persistent cannulation efforts rather than hormone stimulation effects resulted in the success of cannulations.

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 1 ml therefore contains 2 μg of secretin for *i.v.* use. SPS is almost completely pure (96%) as compared to bPS (60%). It has a number of advantages over bPS: 1) sPS is homogeneous and compositionally consistent and should produce a consistent pharmacological effect; 2) it is a defined chemical entity and is free of animal pathogens that may be present in the porcine intestine; and 3) it may be produced in large quantities to provide a reliable supply (12).

It has been shown that sPS is reliable for pancreatic function testing in healthy volunteers (12–14) and in individuals with chronic pancreatitis (15). Somogyi *et al.* (15) reported on the use of sPS for the secretin stimulation test in the latter group. In 12 patients with known chronic pancreatitis, there was an excellent correlation between biological porcine secretin and sPS ($R = 0.964$) for diagnosing chronic pancreatitis. In addition, at a dose of 0.2 μg/kg, sPS yielded equal results as 1 CU/kg of biological porcine secretin in pancreatic function testing. It was concluded that the two agents could be used interchangeably.

In this series, no complications directly attributable to secretin were encountered. Potential relative disadvantages to secretin administration include increased difficulty in filling the tail of the pancreas with contrast medium after secretin stimulation. We recommend limiting contrast filling to the head and body in such circumstances unless tail disease is strongly clinically suspected. In addition, the combination of distension of the ductal system by contrast and secretin stimulated pancreatic secretions may contribute to pain during contrast injection and possibly post-ERCP pancreatitis. The more frequent use of MRCP may help avoid contrast injection risks and permit direct therapeutic maneuvers, once deep cannulation is achieved. Two previous studies, however, reported no increase in post-ERCP pancreatitis when performing ductography after secretin stimulated cytology collection (16, 17).

In conclusion, we have demonstrated the probable efficacy and safety of a new synthetic porcine secretin for the facilitation of cannulation of either the major or minor pancreatic orifice at ERCP in the subset of patients who represent cannulation difficulties. Cannulation success was achieved after sPS administration in 24 of 25 patients (96%). No adverse events attributable to sPS were encountered. SPS can be added to the armamentarium of techniques for the facilitation of pancreatic duct cannulation at ERCP. FDA approval is pending.

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