ORIGINAL ARTICLE

Pasireotide for Postoperative Pancreatic Fistula

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ABSTRACT

BACKGROUND

Postoperative pancreatic fistula is a major contributor to complications and death associated with pancreatic resection. Pasireotide, a somatostatin analogue that has a longer half-life than octreotide and a broader binding profile, decreases pancreatic exocrine secretions and may prevent postoperative pancreatic fistula.

METHODS

We conducted a single-center, randomized, double-blind trial of perioperative subcutaneous pasireotide in patients undergoing either pancreaticoduodenectomy or distal pancreatectomy. We randomly assigned 300 patients to receive 900 μg of subcutaneous pasireotide (152 patients) or placebo (148 patients) twice daily beginning preoperatively on the morning of the operation and continuing for 7 days (14 doses). Randomization was stratified according to the type of resection and whether the pancreatic duct was dilated at the site of transection. The primary end point was the development of pancreatic fistula, leak, or abscess of grade 3 or higher (i.e., requiring drainage).

RESULTS

The primary end point occurred in 45 of the 300 patients (15%). The rate of grade 3 or higher postoperative pancreatic fistula, leak, or abscess was significantly lower among patients who received pasireotide than among patients who received placebo (9% vs. 21%; relative risk, 0.44; 95% confidence interval [CI], 0.24 to 0.78; P=0.006). This finding was consistent among 220 patients who underwent pancreaticoduodenectomy (10% vs. 21%; relative risk, 0.49; 95% CI, 0.25 to 0.95) and 80 patients who underwent distal pancreatectomy (7% vs. 23%; relative risk, 0.32; 95% CI, 0.10 to 0.99), as well as among 136 patients with a dilated pancreatic duct (2% vs. 15%; relative risk, 0.11; 95% CI, 0.02 to 0.60) and 164 patients with a nondilated pancreatic duct (15% vs. 27%; relative risk, 0.55; 95% CI, 0.29 to 1.01).

CONCLUSIONS

Perioperative treatment with pasireotide decreased the rate of clinically significant postoperative pancreatic fistula, leak, or abscess. (Funded by Novartis Pharmaceuticals; ClinicalTrials.gov number, NCT00994110.)

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Although mortality after pancreatectomy has decreased to approximately 2% at high-volume centers, the operative morbidity after these procedures has remained between 30% and 50%.[1,2] Postoperative pancreatic fistula, leak, and abscess are complications that result from leakage of pancreatic exocrine secretions at the anastomosis or closure of the pancreatic remnant. Postoperative pancreatic fistula is the most common major complication after pancreatectomy, with reported rates between 10% and 28%. Studies suggest that patients in whom postoperative pancreatic fistula develops have a risk of death that is approximately doubled.[3,4]

Because of the magnitude of this problem, numerous studies have investigated methods for reducing the risk of postoperative pancreatic fistula. Prospective trials evaluating operative technique have identified multiple approaches that are associated with acceptable rates of postoperative pancreatic fistula. However, no single approach has been shown to be superior across institutions.[5-9] Since pancreatic exocrine secretion is the proposed mechanism by which postoperative pancreatic fistula occurs, inhibition of this secretion by means of the somatostatin analogue octreotide has been evaluated in multiple trials.[10] The results of these studies have been mixed. European studies have shown a decreased incidence of postoperative pancreatic fistula among patients who received perioperative octreotide, but in the United States, such a decrease has not been shown and the routine use of octreotide has been largely abandoned.[11-13]

Pasireotide is a somatostatin analogue that has a longer half-life than octreotide and a broader binding profile.[14] Data from in vitro studies have shown that pasireotide can decrease the release of trypsin, and data from in vivo animal models have shown decreased exocrine secretion and intestinal proteolytic activity in association with its use.[15,16] Because of these properties and the presumed mechanisms behind the development of postoperative pancreatic fistulas, we conducted a randomized trial of pasireotide for the prevention of postoperative pancreatic fistula.

METHODS

PATIENTS

Eligible patients whom we enrolled in this study were adults (≥18 years of age) who were scheduled to undergo either pancreaticoduodenectomy or distal pancreatectomy with or without splenectomy. Key exclusion criteria were a preoperative serum glucose level greater than 250 mg per deciliter (14 mmol per liter), an international normalized ratio greater than 1.5, and a history of clinically significant cardiac disease, including a corrected QT (QTc) interval longer than 450 msec. An additional electrocardiogram (ECG) was obtained on postoperative day 1 (at the request of the sponsor, Novartis), and patients with a QTc interval longer than 480 msec were considered ineligible and were withdrawn from the study at that time. Patients were also withdrawn if they did not undergo resection.

STUDY OVERSIGHT

The trial was approved by the institutional review board at Memorial Sloan-Kettering Cancer Center (MSKCC). An independent data and safety monitoring board provided regulatory oversight by reviewing concealed patient data annually. The data and safety monitoring board also conducted a prespecified interim analysis after the enrollment of 150 patients who had been confirmed to be eligible for the study.

The study was designed and initiated by the academic investigators and was funded by Novartis Pharmaceuticals. Employees of Novartis did not have access to the data during the trial, did not participate in the data analysis, and did not participate in the preparation of the manuscript other than to review it. The first author wrote the first draft of the manuscript. All the authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol, which is available with the full text of this article at NEJM.org.

STUDY DESIGN

The study was a phase 3, single-center, randomized, double-blind, placebo-controlled trial. After providing written informed consent, patients were randomly assigned in a 1:1 ratio to receive 900 μg of subcutaneous pasireotide or placebo twice daily beginning preoperatively on the morning of the operation and continuing for 7 days (14 doses). We used permuted blocks of random size to stratify group assignments according to the type of procedure (pancreaticoduodenectomy or distal pancreatectomy) and the presence or absence of pancreatic-duct dilatation. Dilatation of the pancreatic duct was defined as a

main-duct diameter of greater than 4 mm at the site of pancreatic transection on preoperative imaging.

All members of the clinical team were unaware of the group assignments. The assignments were stored in a secured database and released to the data and safety monitoring board and the study statistician as coded assignments for all analyses. The clinical team had access to the data after the trial database had been locked and the study had been closed for accrual.

The primary outcome was grade 3 or higher postoperative pancreatic fistula, leak, or abscess at 60 days, as defined by the MSKCC Surgical Secondary Events system. This system has been validated and is similar to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) and other published surgical reporting systems (Table 1).[17,18] Secondary outcomes included the overall rate of pancreatic complications (all grades) and the rate of grade B or grade C pancreatic fistula as defined by the International Study Group on Pancreatic Fistula (ISGPF).[19]

OPERATIVE INTERVENTION

Operative procedures were performed by one of seven surgeons who specialize in pancreatic resection. The technique followed specific principles and guidelines, but the particular technique was chosen according to the patient's needs and the surgeon's preference. Pancreatic reconstruction after pancreaticoduodenectomy was typically performed by means of a pancreaticojejunostomy with a duct-to-mucosa anastomosis. Pancreatic transection during distal pancreatectomy was typically performed either with the use of a mechanical stapler, with or without absorbable mesh staple-line reinforcement (Seamguard [Gore]), or with the use of a scalpel and oversewing of the pancreatic remnant. Oversewing typically involved suture ligation of the pancreatic duct and interrupted mattress sutures to the remaining line of transection. Surgeons were asked to categorize pancreatic texture as either soft or firm. Surgically placed drains were used selectively. The surgeon determined when drain removal would occur; drains were typically removed when the effluent contained less than

Table 1. MSKCC and ISGPF Grading Systems for Postoperative Pancreatic Fistula, Leak, and Abscess.*

Grading System	Definition	Grade
MSKCC Surgical Secondary Events system		
Pancreatic fistula	Clinical signs and symptoms of pancreatic fistula, with amylase-rich drainage of >50 ml per day after postoperative day 10	1. Oral medication or bedside medical care required 2. Intravenous medical therapy with resolution or antibiotics or total parenteral nutrition required 3. Radiologic, endoscopic, or operative intervention required 4. Chronic deficit or disability associated with the event 5. Death associated with sequelae of this event
Pancreatic anastomotic leak	Clinical signs and symptoms or radiologic confirmation of pancreatic anastomotic leak, with amylase-rich drainage of >50 ml per day after postoperative day 5, without the development of a fistula	
Intraabdominal abscess	Clinical signs and symptoms or radiologic diagnosis of intraabdominal abscess or peritonitis	
ISGPF system		
Postoperative pancreatic fistula	Any volume of drainage with amylase that is more than three times as high as the normal volume on or after postoperative day 3	A. No clinical effect B. A requirement for postoperative placement of a percutaneous drain, delayed gastric emptying, the presence of an intraabdominal abscess, or a requirement for readmission C. A requirement for reoperation, or death due to sepsis

* ISGPF denotes International Study Group on Pancreatic Fistula, and MSKCC Memorial Sloan-Kettering Cancer Center.

300 U of amylase per liter or when the volume of effluent was less than 100 ml per 24 hours.

Postoperative care was provided in a dedicated surgical unit. Laboratory values, including serum amylase levels, were assessed daily. The level of amylase in the drainage fluid was measured daily when drainage catheters were present. Cross-sectional abdominal imaging was performed when there was concern about a possible intraabdominal complication.

EVALUATION OF OUTCOMES

All complications were reported by surgical attending physicians or house staff who were unaware of the treatment assignments but were directly involved in patient care. Postoperative events were further adjudicated at twice-monthly morbidity-and-mortality conferences at which the final classification and grade were assigned.

The primary end point was grade 3 or higher pancreatic fistula, leak, or abscess at 60 days postoperatively, as defined by the MSKCC Surgical Secondary Events system (Table 1). A classification of grade 3 required that a drain had to be placed during a surgical or endoscopic procedure or other intervention, and a classification of a leak or fistula required the presence of fluid rich in amylase. A culture of the drainage fluid that was positive for bacteria was required for the definition of abscess. Patients who met the definition for fistula, leak, or abscess and were treated with the placement of a drain during the initial operation were considered to have reached the primary end point.

Secondary end points included the overall rate of any grade of pancreatic complications as defined by the MSKCC system and the overall rate of grade B or grade C pancreatic fistula as defined by the ISGPF (Table 1). Grade B pancreatic fistula is associated with prolonged drainage, abscess formation, or the need for hospitalization or hospital readmission. Grade C pancreatic fistula results in sepsis, reoperation, or death. All adverse events were graded according to the NCI CTCAE and the criteria outlined in the MSKCC system.

STATISTICAL ANALYSIS

Previous studies performed at this institution have shown that the rate of grade 3 or higher pancreatic fistula, leak, or abscess is 18%.[4] We hypothesized that pasireotide could decrease this rate to 7%. We calculated that if 300 patients underwent randomization and could be included in the analyses, the study would have 80% power to detect this difference at a two-sided type I error rate of 5%, with the use of the chi-square test.

An interim analysis was planned after the enrollment of 150 patients, with the use of O'Brien–Fleming boundaries. If the two-sided P value at the interim analysis was less than 0.006, the trial would be stopped for efficacy. If the two-sided P value was greater than 0.49, the trial would be stopped for futility.

Specific circumstances of the treatments required the exclusion of some patients from the final analysis. Some patients who are taken to the operating room do not undergo pancreatectomy because their condition is inoperable. Such patients are not at risk for postoperative pancreatic fistula and were not included in the analysis. Preoperative initiation of treatment with pasireotide, however, requires that these patients undergo randomization. In addition, eligibility criteria could be satisfied only after the postoperative ECG was obtained. Adherence to these criteria results in a number of patients who undergo randomization but are never at risk for the study end point. Therefore, we defined our study population as consisting of eligible patients who underwent randomization and resection. All analyses comparing the two groups were stratified according to the same variables that were used for stratification during randomization.

RESULTS

CHARACTERISTICS OF THE PATIENTS

From November 2009 through June 2013, we assessed 539 patients for eligibility (Fig. 1), and 443 underwent randomization; 208 patients received pasireotide, and 202 patients received placebo. In the pasireotide group, 52 patients (25.0%) did not undergo resection (after having received one dose), and 4 patients (1.9%) had a prolonged QTc interval on their postoperative ECG (after three doses); these 56 patients were excluded from the analyses. In the placebo group, 51 patients (25.2%) did not undergo resection (after having received one dose), and 3 patients (1.5%) were ineligible because of ECG criteria (after three doses); these 54 patients were excluded. There-

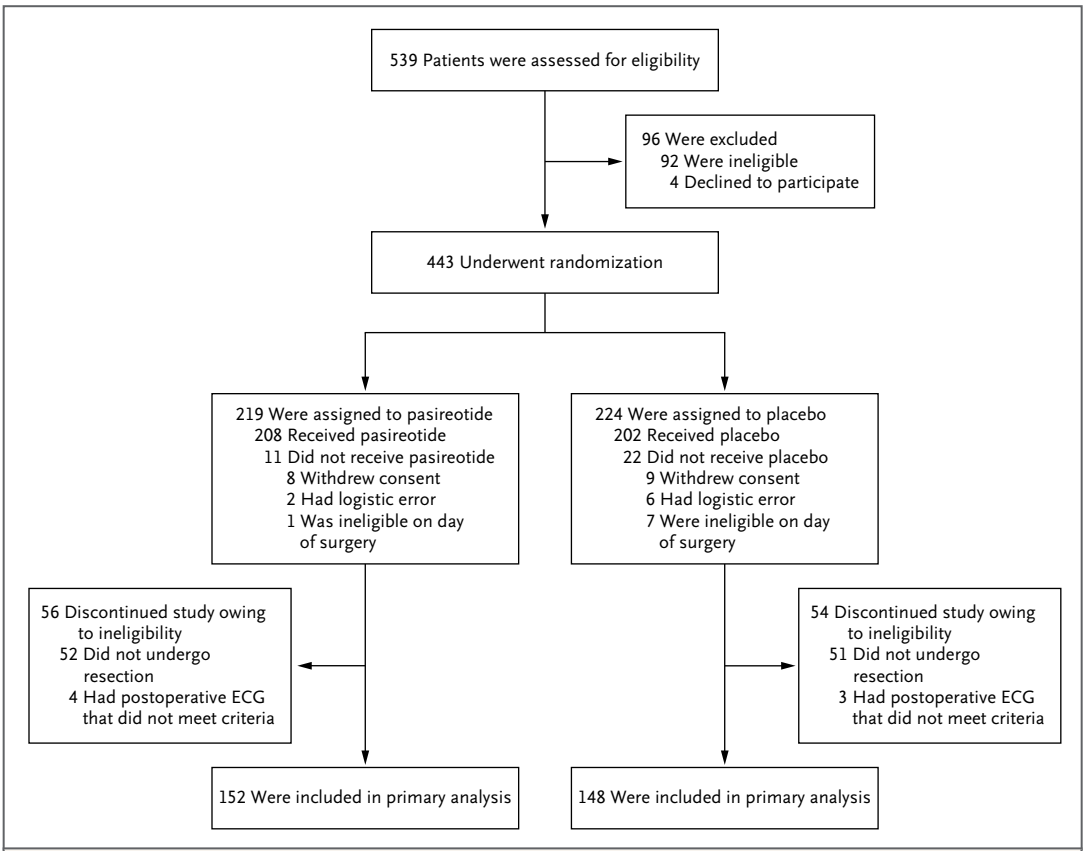

Figure 1. Enrollment and Randomization.
ECG denotes electrocardiogram.

fore, the population for analysis included 152 patients who received pasireotide and 148 who received placebo.

The preoperative and operative characteristics of the patients were similar in the two study groups (Table 2). Drains were surgically placed in 28% of the patients who received pasireotide and in 24% of the patients who received placebo (P=0.76). Final results of histopathological examination of resection specimens revealed pancreatic adenocarcinoma in 154 patients (51.3%), of whom 77 had received pasireotide and 77 had received placebo (for additional histopathological results, see Table S1 in the Supplementary Appendix, available at NEJM.org).

Patients in the pasireotide group had significantly higher postoperative serum glucose levels than did patients who received placebo (258 mg per deciliter [14.3 mmol per liter] vs. 215 mg per deciliter [11.9 mmol per liter], P<0.001) (Table 2). A smaller proportion of patients in the pasireotide group than in the placebo group were readmitted to the hospital (17.1% vs. 29.1%, P=0.02). Significantly fewer patients in the pasireotide group than in the placebo group received all 14 doses of the study drug (75.7% vs. 86.5%, P=0.02). In the pasireotide group, 26 of 37 patients (70.3%) who received fewer than 14 doses of the drug (i.e., 17.1% of all 152 patients receiving the drug) were withdrawn from the study because of nausea or vomiting that was temporally related to administration of the drug. In the placebo group, 3 patients withdrew from the study because of nausea.

STUDY OUTCOMES

The primary end point was met in 45 of the 300 patients who underwent randomization (15.0%) (Fig. 2, and Table S2 in the Supplementary Appendix). In the pasireotide group, 14 patients

Table 2. Baseline, Operative, and Postoperative Characteristics of the Patients.*

Characteristic	Pasireotide (N=152)	Placebo (N=148)	P Value
Baseline			
Male sex — no. (%)	82 (53.9)	83 (56.1)	0.28
Age — yr	64±11	64±13	0.78
Duct dilated — no. (%)	63 (41.4)	73 (49.3)	0.20
Operative			
Soft gland — no. (%)†	81 (53.3)	77 (52.0)	0.58
Pancreaticoduodenectomy — no. (%)‡	111 (73.0)	109 (73.6)	0.50
Distal pancreatectomy — no. (%)‡	41 (27.0)	39 (26.4)	0.50
Surgical placement of drain — no. (%)	43 (28.3)	36 (24.3)	0.76
Postoperative			
Pancreatic adenocarcinoma — no. (%)	77 (50.7)	77 (52.0)	0.81
Postoperative maximum serum amylase — U/liter	230±294	230±312	0.95
Postoperative maximum serum glucose — mg/dl§	258±70	215±67	<0.001
Time to bowel function — days	4±1	4±2	0.32
Length of stay — days¶	8±4	9±7	0.15
Patients who underwent pancreaticoduodenectomy	9±5	10±8	0.36
Patients who underwent distal pancreatectomy	6±1	7±2	0.02
All 14 doses received — no. (%)	115 (75.7)	128 (86.5)	0.02
Readmission — no. (%)	26 (17.1)	43 (29.1)	0.02

* Plus–minus values are means ±SD.
† Gland texture (either soft or firm) was determined by the surgeon and recorded.
‡ Pancreaticoduodenectomy and distal pancreatectomy were preoperative stratification variables.
§ To convert the values for glucose to millimoles per liter, multiply by 0.5551.
¶ The length of stay was determined among the 220 patients who underwent pancreaticoduodenectomy and the 80 patients who underwent distal pancreatectomy.

(9.2%) met the primary end point, and in the placebo group, 31 patients (20.9%) met the primary end point (relative risk, 0.44; 95% confidence interval [CI], 0.24 to 0.78; P=0.006). This corresponded to an absolute risk reduction of 11.7 percentage points (the number needed to treat to prevent one event was 8) and a relative risk reduction of 56%. Similar findings were observed in the prespecified subgroups of 220 patients who underwent pancreaticoduodenectomy (10% vs. 21%; relative risk, 0.49; 95% CI, 0.25 to 0.95) and 80 patients who underwent distal pancreatectomy (7% vs. 23%; relative risk, 0.32; 95% CI, 0.10 to 0.99), as well as among 136 patients with a dilated pancreatic duct (2% vs. 15%; relative risk, 0.11; 95% CI, 0.02 to 0.60) and 164 patients with a nondilated pancreatic duct (15% vs. 27%; relative risk, 0.55; 95% CI, 0.29 to 1.01) who underwent resection.

The secondary outcome of grade B or grade C postoperative pancreatic fistula occurred in 37 patients (12.3%). In the pasireotide group, 12 patients (7.9%) had grade B fistulas and no patients had a grade C fistula; in the placebo group, 25 patients (16.9%) had grade B fistulas (20 patients) or grade C fistulas (5 patients) (P=0.02 for the comparison between the pasireotide group and the placebo group). Overall, pancreatic complications of any grade occurred in 54 patients (18.0%): 17 patients in the pasireotide group (11.2%) and 37 patients in the placebo group (25.0%) (P=0.002).

Post hoc analysis revealed that the subgroup of patients who had a drain placed at the time of surgery was at increased risk for the primary end point; 20 of 79 patients with a drain reached the end point as compared with 25 of 221 patients without a drain (25% vs. 11%, P=0.003) (Table S3 in the Supplementary Appendix). In the group of 79 patients who underwent surgical place-

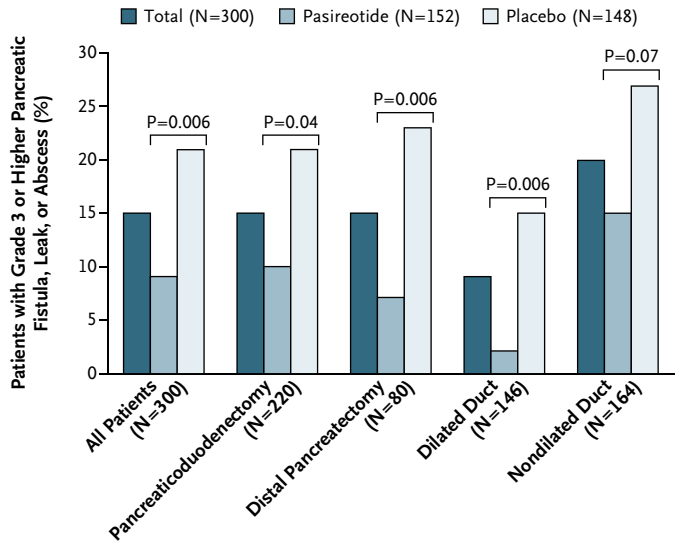

Figure 2. Percentage of Patients with Grade 3 or Higher Pancreatic Fistula, Leak, or Abscess.

ment of a drain, the primary end point was met in 9% of patients who received pasireotide and in 44% of patients who received placebo (P<0.001). In the group of 221 patients who did not undergo placement of a drain, the primary end point was met in 9% of patients who received pasireotide and 13% who received placebo (P=0.32). The interaction between the study group and the subgroup defined according to placement or nonplacement of a drain was not significant (P=0.16 after adjustment for multiplicity; see Table S4 in the Supplementary Appendix).

ADVERSE EVENTS

The overall mortality at 60 days postoperatively was 0.7% (two deaths, one in the pasireotide group and one in the placebo group). The overall rate of grade 3 and grade 4 events (according to CTCAE, version 3.0) at 60 days was 91.0%; 140 patients (92.1%) in the pasireotide group and 133 patients (89.9%) in the placebo group had a grade 3 or grade 4 adverse event. The majority of these adverse events represented expected postoperative abnormalities in the results of serum chemical analyses. Table 3 shows adverse events not related to postoperative pancreatic fistula and adjudicated as possibly or probably related to pasireotide.

DISCUSSION

This single-center, double-blind, placebo-controlled trial showed that treatment with pasireotide in the perioperative period significantly reduced the risk of clinically relevant postoperative pancreatic fistula, leak, or abscess. In all prespecified subgroups, the rates of grade 3 or higher pancreatic fistula, leak, or abscess were lower with pasireotide than with placebo. These reductions were significant in the subgroup of patients who underwent pancreaticoduodenectomy, those who underwent distal pancreatectomy, and those with a dilated pancreatic duct who underwent resection. The risk of overall pancreatic complications was also reduced with pasireotide.

These results suggest that among patients who received pasireotide, not only were many fistulas and leaks prevented, but when they did occur, they were less clinically relevant. The rate of the secondary end point of grade B or grade C postoperative pancreatic fistula, as defined by the ISGPF, was significantly reduced in the treatment group (7.9% vs. 16.9%, P=0.02). Among patients who received pasireotide, the most common grade of postoperative pancreatic fistula was grade A, and no patient had grade C fistula. In the placebo group, the most common grade was grade B, and five patients had grade C fistula.

The surgical placement of a drain was strongly associated with meeting the primary end point. Since drains are placed selectively at our institution, we propose that this association reflected the surgeon's perception of a high-risk gland and that the drain was not a causative agent. Nevertheless, among patients who underwent surgical placement of a drain, the rate of clinically significant postoperative pancreatic fistula was significantly lower in the group that received pasireotide than in the group that received placebo. This finding is important, since routine drainage during surgery remains common practice, and suggests that the results of this study are applicable to a variety of management approaches.

Previous trials evaluating the somatostatin analogue octreotide have not shown a clear reduction in pancreatic leak.[20] There are at least two possible reasons for the efficacy of pasire-

Table 3. Adverse Events Not Related to Postoperative Pancreatic Fistula.*

Adverse Event	Pasireotide (N=152)			Placebo (N=148)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
	number (percent)					
Hyperglycemia	150 (98.7)	76 (50.0)	2 (1.3)	148 (100.0)	43 (29.1)	1 (0.7)
Nausea	87 (57.2)	3 (2.0)	0	61 (41.2)	5 (3.4)	0
Vomiting	43 (28.3)	1 (0.7)	0	32 (21.6)	2 (1.4)	0
Diarrhea	13 (8.6)	0	0	19 (12.8)	2 (1.4)	0
Abdominal pain	6 (3.9)	2 (1.3)	0	6 (4.1)	1 (0.7)	0
Hypotension	2 (1.3)	0	0	0	0	0
Gastroesophageal reflux disease	0	0	0	1 (0.7)	0	0
Injection-site reaction	1 (0.7)	0	0	0	0	0
Pancreatitis	0	0	0	1 (0.7)	1 (0.7)	0
Acute kidney injury	0	0	0	1 (0.7)	0	0

* All adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. On a scale of grade 1 through grade 5, grade 3 indicates severe adverse events, and grade 4 life-threatening or disabling adverse events. For hyperglycemia, grade 3 is defined as glucose levels from 250 to 500 mg per deciliter (14 to 28 mmol per liter), and grade 4 is defined as glucose levels higher than 500 mg per deciliter or acidosis.

otide in this study. First, the pharmacodynamic and binding profile of pasireotide is very different from that of octreotide. Octreotide has a half-life of less than 2 hours and binds primarily to somatostatin-receptor subtypes 2 and 5.[21] The half-life of pasireotide is approximately 11 hours, and it binds with high affinity to four of five subtypes of somatostatin receptor.[14] This binding affinity is approximately 5 to 40 times as great for somatostatin-receptor subtypes 1, 3, and 5 as the binding affinity of octreotide. Since the primary somatostatin-receptor subtypes in the pancreas are somatostatin receptors 1, 2, 3, and 5, it is possible that pasireotide is more effective at reducing pancreatic exocrine secretions and thus pancreatic leak. Second, the majority of trials evaluating octreotide and postoperative pancreatic fistula were performed before 2005, when there was no consistent definition of postoperative pancreatic fistula. In those trials, there was substantial heterogeneity in reporting postoperative pancreatic fistula, with many investigators reporting clinically insignificant pancreatic drainage according to contemporary grading schemes. Octreotide may have efficacy for the prevention of postoperative pancreatic fistula; however, given the heterogeneity in trial design and the lack of a consistent definition of postoperative pancreatic fistula, this efficacy has not been identified.

In the current study, the two most common adverse events associated with pasireotide were hyperglycemia and dose-limiting nausea (17%). Hyperglycemia is common after pancreatic resection and is known to occur in association with the use of other somatostatin analogues. Dose-limiting nausea has not commonly been reported with pasireotide, and it is unclear why it was observed in this study. However, to our knowledge, this is the first report of pasireotide in the perioperative setting in which patients have undergone general anesthesia and a major operation and have had no oral intake for several days; all these factors may have contributed to the finding of nausea.

In summary, perioperative pasireotide significantly reduced the risk and severity of postoperative fistula, leak, and abscess among patients undergoing pancreatic resection. This reduction was seen among patients undergoing pancreaticoduodenectomy and distal pancreatectomy, as well as among patients with a dilated pancreatic duct and those with a nondilated pancreatic duct who were undergoing resection.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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