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Octreotide administration in the treatment of pancreatic fistulae after pancreas transplantation

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Abstract. Among the surgical complications of pancreas transplantation are pancreatic fistulae, which arise rather frequently. Suppression of exocrine secretion with polymers has succeeded in reducing the rate of this complication. Nevertheless, in some instances, pancreatic fistulas may occur. Thirty pancreas transplantations were performed in 27 diabetic patients. In 5 cases a pancreatic fistula occurred and was drained after the insertion of a catheter for the collection of secretions. A serous liquid was collected with a high concentration of amylases (61604 ± 19562 IU/24 h). Fistula output was 280 ± 87 ml/24 h. Patients were treated with octreotide, administered subcutaneously in a dose of 300–750 μg/day. In all patients a progressive reduction in fistula output was observed after a mean of 16 + 2 days. Fistula flow rate dropped to 24 ± 10 ml/24 h – a reduction of 95% ± 5% and drainage was subsequently stopped. Sonographic follow-up did not show recurrence of peripancreatic collections in these patients. All patients were insulin-independent up to 12–44 months after surgery.

Key words: Pancreas transplantation, fistula – Fistula, pancreas transplantation – Octreotide, fistula, pancreas transplantation

Pancreas transplantation is performed together with kidney transplantation in insulin-dependent diabetic patients affected by end-stage renal failure [4, 15]. A limitation to a wider diffusion of this surgical approach and to the extension of the clinical indications to diabetic patients in a preuremic stage is, among other factors, the relatively high rate of surgical failure: 22% in the period 1984–1988, as reported by the International Registry [18]. Among the sequelae are pancreatic fistulae, a frequent complication of the occlusion method that could eventually lead to local infections and that accounts for 20% of surgical failure [10]. The aim of our study was to evaluate the efficacy of octreotide, a new somatostatin analogue, in the treatment of pancreatic fistulae after pancreas plus kidney transplantation in diabetic uremic patients.

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Materials and methods

Patients

Thirty pancreas transplantations were performed in 27 diabetic patients. Their mean age was 39 ± 2 years. Mean duration of diabetes was 25 ± 1 years and mean duration of dialysis 20 ± 3 months. In 3 cases the pancreas was transplanted after a successful kidney transplant, while in 27 cases the pancreas was transplanted simultaneously with a kidney in uremic patients. All patients were affected by late degenerative complications of diabetes.

Surgical technique

A segmental (body and tail) pancreas graft was anastomosed to the iliac vessels of the recipient. Exocrine secretion was suppressed by the intracanalicolar injection of neoprene, as previously described by Dubernard et al. [5]. A peripancreatic drainage catheter, inserted during surgery, was maintained during the first 3 postoperative days and removed thereafter. In case of a pancreatic fistula, defined as a peripancreatic collection with high concentration of amylases, a drainage catheter was inserted to monitor fistula output and amylase concentration. Treatment with octreotide (Sandostatin, Sandoz, Basel) [1], a somatostatin analogue administered s.c., was then started.

Immunosuppression

Immunosuppression was based on steroids (500 mg before surgery, then 1 mg/kg per day, tapered, in the postsurgical period), azathioprine (2 mg/kg per day, tapered), and antilymphocyte globulin (ALG; during the first 10 days). On the 10th day, ALG was replaced by cyclosporin A (7.5 mg/kg per day, tapered).

Assays

Blood cyclosporin concentration was evaluated via radioimmunoassay, according to two methods: plasma concentration (polyclonal antibodies: PAB [9]) in the first three patients and whole blood concentration (monoclonal antibodies: MAB [14]) in the other two pa-

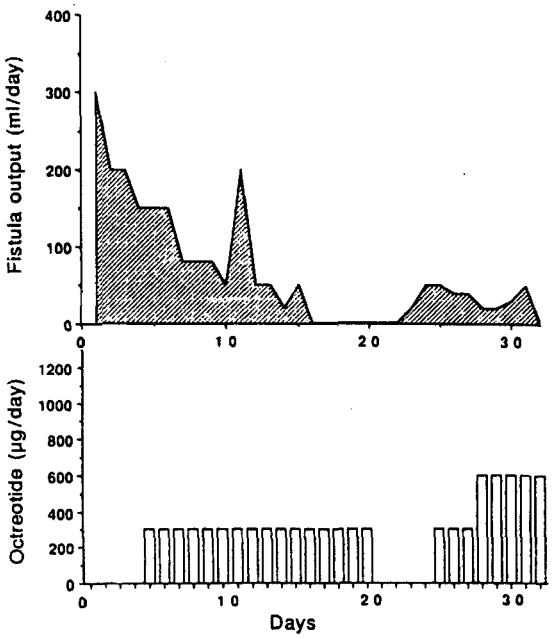

Fig. 1. Pancreatic fistula flow rate (ml/24 h) and drug dosage in patient 1 before and during subcutaneous octreotide administration

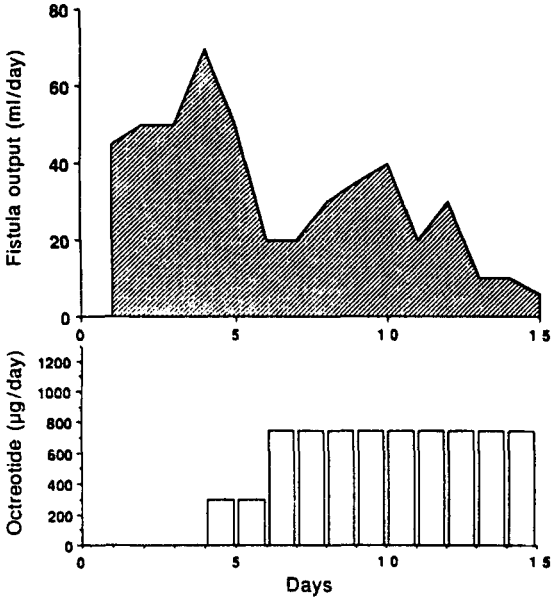

Fig. 2. Pancreatic fistula flow rate (ml/24 h) and drug dosage in patient 2 before and during subcutaneous octreotide administration

tients. Plasma C peptide was determined according to Kaneko et al. [6]. Plasma glucagon was determined according to Mihara et al. [11].

Statistical analysis

Statistical analysis was based on the Mann-Whitney U-test. Data are expressed as mean + SEM.

Results

All patients showed a good renal function, leading to withdrawal of dialysis. Serum creatinine levels 15 days after surgery reached 1.5 ± 0.2 mg/dl. Pancreatic function was

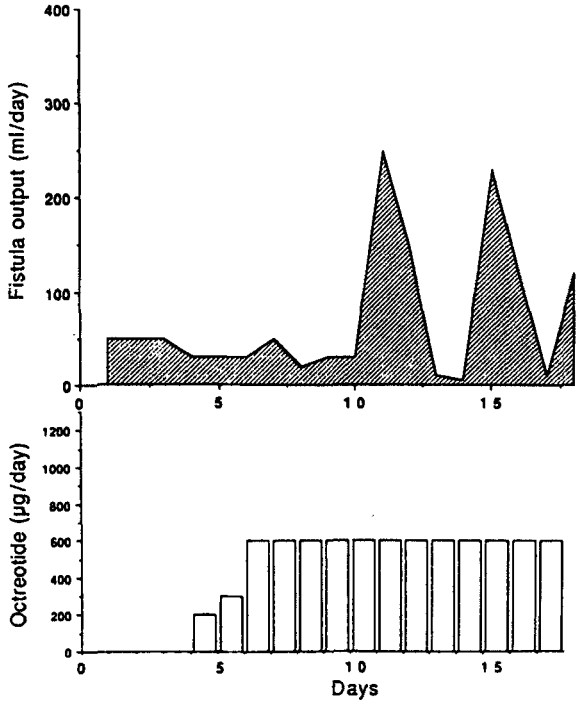

Fig. 3. Pancreatic fistula flow rate (ml/24 h) and drug dosage in patient 3 before and during subcutaneous octreotide administration

good in all patients in the early post-transplantation period, as shown by serum C peptide levels at pancreatic revascularization (14.8 ± 2.0 ng/ml at 60 min). Pancreas failure was observed in nine cases: venous thrombosis ($n = 4$), primary failure ($n = 1$), chronic rejection ($n = 1$), vascular bleeding ($n = 1$), death of the patient with a functioning graft ($n = 1$), and recurrence of diabetes ($n = 1$). Infectious complications were mainly due to CMV infection ($n = 9$), herpes simplex infection ($n = 6$), and herpes zoster infection ($n = 2$). In five cases a pancreatic fistula occurred in the 1st postoperative week. It was drained after the insertion of a catheter for the collection of the secretion. Pancreatic fistulae had a relevant external leakage of a serous liquid (280 ± 87 ml/24 h) with a high concentration of amylases (61604 ± 19562 IU/24 h). In two cases i.v. somatostatin infusion was administered 4 days after the diagnosis of pancreatic fistula and maintained for 6 days at a dose of 3,5 µg/kg per hour, without any effect on fistula output or on amylase concentration. After a 7-day wash-out from i.v. somatostatin, patients were treated with s.c. octreotide in doses of 600–750 µg/day. Three other patients did not receive somatostatin i.v., but were treated with s.c. octreotide (doses 300–750 µg/day) 4 days after the diagnosis of pancreatic fistula.

In all patients a progressive reduction in fistula output was observed after 10, 12, 16, 17, and 24 days, respectively, (mean 16 ± 2 days). Fistula flow rate dropped to 24 ± 10 ml/day, a reduction of 95% ± 5%. Individual data are reported in Figs. 1–5. External drainage was subsequently stopped. Amylase concentration in the fistula fluid the day before catheter removal was 1573 ± 523 IU/24 h. Sonographic follow-up did not show recurrence of peripancreatic collection, thus confirming

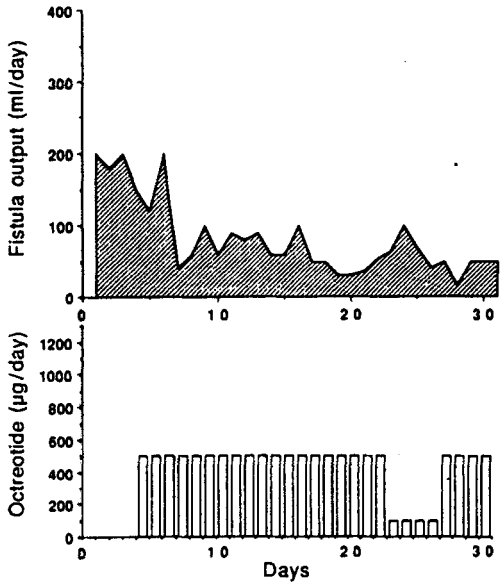

Fig. 4. Pancreatic fistula flow rate (ml/24 h) and drug dosage in patient 4 before and during subcutaneous octreotide administration

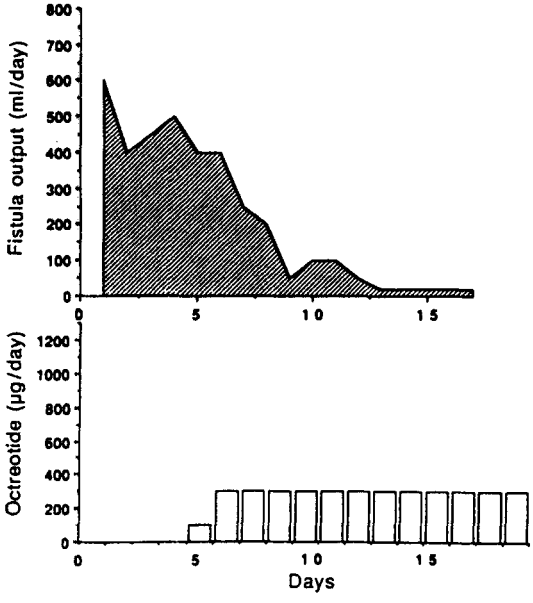

Fig. 5. Pancreatic fistula flow rate (ml/24 h) and drug dosage in patient 5 before and during subcutaneous octreotide administration

the healing of the pancreatic fistulae. In three patients, blood cyclosporin concentration, in the therapeutic range before octreotide administration (530 ± 232 ng/ml, PAB; 296 ± 24 ng/ml, MAB) was not affected by octreotide administration (562 ± 39 ng/ml, PAB; 234 ± 12 ng/ml, MAB). In one patient a reduction in cyclosporin concentration was observed (371 ± 116 ng/ml before administration, 121 ± 22 ng/ml, MAB during administration). No variation of plasma creatinine was observed in these patients. Only in one patient did a reduction in plasma cyclosporin concentration from 842 ± 50 ng/ml before octreotide administration to 143 ± 21 ng/ml during octreotide administration lead to kidney rejection, but this was successfully treated with prednisolone boluses. No side effects were observed during octreotide administration; in one patient a mild nausea was observed, but it did not lead to withdrawal of treatment. The effects of octreotide on endocrine function of the transplanted pancreas were monitored with plasma C peptide levels (Table 1). In two patients, a reduction in fasting C peptide levels was observed (4.8 ± 1.0 and 4.9 ± 0.7 ng/ml before octreotide, 2.0 ± 0.1 and 3.3 ± 0.2 ng/ml after octreotide, respectively) without any effect on metabolic control (mean blood glucose levels 168 ± 9 and 127 ± 6 mg/dl, respectively). In the other three patients, no C peptide variation was observed (6.6 ± 0.4, 8.7 ± 0.3, and 9.8 ± 0.2 ng/ml before octreotide; 5.5 ± 0.6, 7.3 ± 0.4, and 7.6 ± 0.5 ng/ml during octreotide administration, respectively). All patients remained insulin-independent up to 12–44 months after surgery. No substantial effect of octreotide administration on plasma glucagon was observed.

Discussion

Irrespective of the surgical technique used, pancreatitis remains a major risk after pancreas transplantation, leading to local complications (infections, thrombosis, fistulae) or generalized complications (sepsis, disseminated intra vascular coagulation). Investigations in animals have shown the efficacy of a new, potent somatostatin analogue – octreotide – in the outcome of pancreas transplantation [8], although other studies have not confirmed these results [16]. Nicholson et al. have recently reported that the same somatostatin analogue has no negative effects on the exocrine secretion of bladder-drained pancreas transplantations performed in pigs. In contrast to this, the authors suggest a negative effect of octreotide on the transplanted pancreas as a consequence of a decrease in blood flow [12]. A preliminary investigation has shown the efficacy of this drug in reducing fistula output in patients receiving pancreatic transplants, although the occurrence of purulent pancreatitis led to transplantectomy [13]. Cooper and Stratta report the successful treatment of high-output fistula or pancreatitis with octreotide following bladder-drained pancreas transplantation [3, 17].

Our investigations have shown that the administration of octreotide helps to reduce fistula output after pancreas transplantation, leading to the healing of fistulae that are unresponsive to i.v. infusion of somatostatin. Only minor side effects were observed, mainly related to the reduction in plasma cyclosporin concentration, as previously described [7]. The result was a successfully treated kidney rejection. Strict control of blood cyclosporin levels is necessary during octreotide administration. In our experience octreotide administration leads to mild interference with the endocrine function of the transplanted pancreas, as shown by C peptide levels. It did not worsen metabolic control, as shown by the complete insulin independence that was maintained up to 12–44 months after surgery. We therefore suggest that octreotide be administered to all patients affected by pancreatic fistulae or pancreatitis, regardless of the surgical technique used (polymer injection, intestinal diversion, or bladder diversion). Furthermore, octreotide administration could be useful when chronic

Table 1. Fasting C peptide, mean blood glucose, and mean plasma glucagon levels in patients affected by pancreatic fistulae before and during s. c. administration of octreotide. ND, not determined; *(n)* the total number of determinations: 1 per day for fasting C peptide and plasma glucagon, 3–5 per day for blood glucose

Patient no.	Fasting C peptide (ng/ml)		Mean blood glucose (mg/dl)		Mean plasma glucagon (pg/ml)	
	Before *(n)*	During *(n)*	Before *(n)*	During *(n)*	Before *(n)*	During *(n)*
1	4.8 ± 1.0 (9)	2.0 ± 0.1 (16)	173 ± 10 (33)	168 ± 9 (38)	99 ± 14 (3)	70 ± 6 (10)
2	6.6 ± 0.4 (6)	5.5 ± 0.6 (8)	204 ± 11 (39)	200 ± 9 (38)	364 ± 30 (5)	316 ± 45 (7)
3	4.9 ± 0.7 (6)	3.3 ± 0.2 (5)	116 ± 7 (36)	127 ± 6 (49)	ND	
4	8.7 ± 0.3 (5)	7.3 ± 0.4 (17)	166 ± 6 (42)	169 ± 6 (75)	260 ± 57 (5)	287 ± 88 (16)
5	9.8 ± 0.2 (5)	7.6 ± 0.5 (8)	178 ± 7 (38)	175 ± 5 (72)	ND	

aseptic cystitis or severe bicarbonate loss occurs after the bladder diversion technique. In this case, surgical conversion to intestinal diversion is suggested [2]: the reduction of exocrine secretion with octreotide administration may make surgery avoidable. Among the advantages of this treatment is the possibiliy of administering the drug s.c., rather than as a continuous i.v. infusion. Finally, octreotide administration could lead to outpatient management of pancreatic complications, with a reduction in costs due to hospitalization.

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