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Effect of Glucagon on Plasma Amino Acid and Glucose Levels in a Patient Who Had Undergone Total Pancreatectomy

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Summary The plasma glucose and amino acid levels of a patient who had undergone total gastrectomy and total pancreatectomy 15 years previously were examined under 4 conditions determined by the method of exogenous glucagon injection. Glucagon was not injected in the first period, and 1 mg of glucagon was injected twice a day in the second period. Twice a day 1 mg of zinc glucagon was injected in the third period, and 2 mg/day of glucagon by continuous subcutaneous glucagon infusion (CSGI) was given in the fourth period. The plasma pancreatic glucagon levels were within the normal range during CSGI. The effect of glucagon on plasma amino acid levels was greatest with CSGI. The effect became less in the order of zinc glucagon injection and twice-a-day injection of 1 mg of glucagon. Furthermore, afternoon hyperglycemia and nocturnal hypoglycemia were suppressed with CSGI. Urinary nitrogen excretion was increased with glucagon injection. However, excretion of 3-methylhistidine did not show any significant increase. From these results we consider that exogenous glucagon injection has significant effects on the metabolism of glucose and amino acids after total pancreatectomy. We also conclude that both continuous subcutaneous glucagon infusion and zinc glucagon are useful in the postoperative management of total pancreatectomy.

Key Words: total pancreatectomy, zinc glucagon, continuous subcutaneous glucagon infusion, plasma amino acid levels

Total pancreatectomy is performed in some patients with pancreatic cancer or chronic pancreatitis [1], and thus nutritional management becomes a major

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problem thereafter. Insulin decreases blood glucose levels and glucagon increases them by promoting gluconeogenesis from plasma glycogenic amino acids such as alanine. It is difficult to control the metabolism of glucose and amino acids after total pancreatectomy with insulin alone because pancreatic endocrine functions of both insulin and glucagon are lost. Treatment with exogenous glucagon after total pancreatectomy is used to improve the metabolism of amino acids. However, the biological half-life of conventional exogenous glucagon in plasma is short [2]. Zinc glucagon has a long biological half-life [3]. Continuous subcutaneous glucagon infusion (CSGI) is a new method of glucagon administration, and the half-life should be prolonged by this method.

In the present study, the plasma glucose and amino acid levels of a patient who had undergone total gastrectomy and total pancreatectomy 15 years previously were examined under some conditions determined by these methods of exogenous glucagon injection.

SUBJECT AND METHODS

A 59-year-old man who had undergone total gastrectomy and total pancreatectomy for gastric cancer with pancreatic invasion 15 years previously takes 1,200 cal from regular foods and 900 cal of elementary diet (Elental®, Ajinomoto Co., Ltd., Tokyo) [4] by home enteral elemental hyperalimentation using a naso-jejunal tube. The patient receives 52.8 g/day of amino acid (composition is shown in Table 1) by enteral nutrition every day. Twenty units of lente insulin are injected early in the morning and 5, 8, and 5 units of regular insulin are injected 30 min prior to each meal.

Table 1. Amino acid composition of 100 g of elemental diet (Elental®, Ajinomoto, Tokyo).

L-Isoleucine	803 mg
L-Leusine	1,124 mg
L-Lysine (HCl)	1,110 mg
L-Methionine	810 mg
L-Phenylalanine	1,089 mg
L-Threonine	654 mg
L-Tryptophan	189 mg
L-Valine	876 mg
L-Alanine	1,124 mg
L-Arginine (HCl)	1,406 mg
L-Aspartic acid (Na, H_2O)	1,084 mg
L-Aspartic acid (Mg, K)	1,295 mg
L-Glutamine	2,415 mg
Glycine	631 mg
L-Histidine (HCl, H_2O)	626 mg
L-Proline	788 mg
L-Serine	1,449 mg
L-Tyrosine	138 mg

Plasma glucagon levels, glucose levels, and amino acids levels were examined under 4 conditions determined by the method of exogenous glucagon injection. Glucagon was not injected in the first period, and 1 mg of glucagon was injected twice a day (9:00, 21:00) in the second period. Twice a day (9:00, 21:00) 1 mg of zinc glucagon was injected in the third period, and 2 mg/day of continuous subcutaneous glucagon infusion (CSGI) delivered by a micro infusion pump (Nipro SP-3HQ, Tokyo) was given in the fourth period. Each method of injection of glucagon was continued for 4 days, and the method was changed after a 6-day glucagon-free interval. Blood and urine samples were collected from the first to fourth days of each period. Blood glucose level was measured by an enzyme method (Glu-DH)[5]; and plasma pancreatic glucagon, by a radioimmunoassay using the OAL-123 antibody [6]. Amino acids levels were determined by high-performance liquid chromatography (HPLC) [7]. Urinary nitrogen and 3-methylhistidine excretion were measured with an AutoAnalyzer [8] and by HPLC [7].

The results are presented as the mean of the values of 4 days. Statistical significance was evaluated by Student's paired *t*-test.

RESULTS

Afternoon hyperglycemia and nocturnal hypoglycemia were prominent in the absence of exogenous glucagon. Blood glucose levels showed abnormal fluctuations over the day with glucagon injection twice a day. These changes in blood glucose levels became less pronounced with zinc glucagon injection, and the afternoon hyperglycemia and the nocturnal hypoglycemia were completely suppressed by CSGI (Table 2). The plasma amino acids levels, especially, those of glycogenic amino acids, were high without exogenous glucagon injection. These levels were decreased by twice a day injection of 1 mg of glucagon. The decrease in plasma amino acids levels became more pronounced with zinc glucagon injection and was greatest with CSGI (Table 3). The mean level of plasma glucagon that bound with the specific antibody for pancreatic glucagon was 46.0 ± 17.8 pg/ml at 12 h after injection of 1 mg of zinc glucagon. The level of plasma pancreatic glucagon rose to 100.0 ± 12.5 pg/ml by 21:00 with CSGI (Table 4).

Table 2. Blood glucose levels (mg/dl) under various conditions of glucagon administration.

Time	Glucagon(−)	Intermittent	Zinc glucagon	CSGI
6:00	57±20	79±17	75±16	96±7*
12:00	239±50	222±20	179±11	127±8*
18:00	263±40	88±8*	141±20*	168±21*
24:00	64±16	267±42*	99±20	130±26*

Values are means±SD ($n=4$). Glucagon(−), glucagon was not injected; intermittent, 1 mg of glucagon was injected twice a day (9:00, 21:00); zinc glucagon, twice a day (9:00, 21:00) 1 mg of zinc glucagon was injected; CSGI, 2 mg/day of continuous subcutaneous glucagon infusion (CSGI) was given. *$p<0.05$ vs. glucagon(−).

Table 3. Plasma amino acid levels (nmol/ml) under various conditions of glucagon administration.

Amino acid	Standard level	Glucagon(−)	Intermittent	Zinc glucagon	CSGI
Glutamin	658.5～478.3	938.4±133.8	678.9±81.4*	740.7±73.1	544.6±70.1*
Alanine	479.9～321.9	1,219.5±2,441.4	726.7±91.6*	672.0±86.8*	344.9±61.2*
Valine	276.3～224.1	458.8±49.7	504.0±91.3	415.7±36.1	237.8±19.5*
Glycine	268.9～181.1	616.8±109.9	512.9±93.5	344.3±50.3*	258.8±27.7*
Proline	243.6～165.6	466.9±116.0	401.9±70.8	243.0±48.8*	285.2±34.5*
Lysine	208.3～142.5	500.8±100.6	467.6±64.8	194.4±21.0*	162.5±19.4*
Threonine	181.1～122.5	388.7±96.4	314.0±70.3	214.0±35.8*	131.0±35.0*
Leucine	144.1～107.3	135.1±18.7	159.1±14.7	160.6±25.2	139.1±25.6
Serine	142.4～98.0	460.6±99.5	420.0±68.7	152.0±22.9*	109.1±25.2*
Histidine	98.6～67.4	107.7±17.3	108.5±16.4	108.5±16.5	89.0±18.4
Arginine	97.8～64.6	311.4±49.5	265.5±78.0	112.9±26.0*	77.4±20.1*
Isoleucine	88.0～63.4	95.7±22.0	90.5±31.1	80.0±25.8	74.1±14.2
Tyrosine	75.2～54.6	108.2±24.9	105.3±33.9	83.0±21.8	53.8±14.5*
Phenylalanine	68.7～57.1	156.1±83.9	159.4±30.4	108.1±15.2	68.4±10.6*
Ornithine	72.5～47.1	132.8±26.7	142.2±30.2	92.6±23.8	50.1±11.6*
Tryptophan	67.2～43.0	87.4±19.4	98.1±30.5	93.2±22.2	48.4±25.0
Taurine	57.1～43.9	86.9±25.7	88.5±21.0	74.5±43.4	49.6±13.0
Glutamic acid	22.8～45.4	104.9±19.2	80.7±36.0	95.3±44.1	53.1±18.1*
Methionine	36.0～26.4	50.6±13.1	50.1±20.7	42.0±22.1	26.4±20.5

Values are means±SD ($n=4$). Blood was obtained at 12:00. Standard level: healthy control given by SRL Co. (Tokyo). See legend of Table 2 for types of administration. *$p<0.05$ vs. glucagon(−).

Table 4. Plasma pancreatic glucagon levels (pg/ml) under various conditions of glucagon administration.

Time	Glucagon(−)	Intermittent	Zinc glucagon	CSGI
6:00 ($n=3$)	13.3±6.1	7.3±2.5	10.3±5.5	89.7±13.5*
12:00 ($n=4$)	14.3±7.4	255.2±52.5*	145.8±29.3*	98.8±18.7*
21:00 ($n=4$)	9.2±7.1	18.8±10.3	46.0±17.8*	100.0±12.5*

Values are means±SD. See legend of Table 2 for types of administration. *$p<0.05$ vs. glucagon(−).

Table 5. Urinary nitrogen and 3-methylhistidine excretion under various conditions of glucagon administration.

	Glucagon(−)	Intermittent	Zinc glucagon	CSGI
BUN (g/dl)	7.2±1.1	11.5±2.8*	11.8±2.9*	13.4±3.6*
3-Methylhistidine (μmol/day)	282±67	303±75 NS	318±90 NS	340±92 NS

Values are means±SD ($n=4$). See legend of Table 2 for types of administration. *$p<0.05$ vs. glucagon(−). NS, not significant vs. glucagon(−).

The urinary nitrogen excretion was 7.2±1.1 g/day without exogenous glucagon injection. It increased to 11.5±2.8 g/day by the twice a day injection of 1 mg of glucagon. The level increased further (13.4±3.6 g/day) with CSGI, but no

significant increase in the urinary 3-methylhistidine excretion was found with any type of administration (Table 5).

DISCUSSION

Boden *et al.* [9] reported significant hyperaminoacidemia after total pancreatectomy. We also found very high plasma amino acid levels, especially those of glycogenic amino acids, after total pancreatectomy without exogenous glucagon injection. Hyperaminoacidemia is recognized because gluconeogenesis from glycogenic amino acids is suppressed due to the absence of glucagon, which hormone promotes gluconeogenesis from plasma glycogenic amino acids. As the biological half-life of conventional exogenous glucagon in plasma is short, we used zinc glucagon and CSGI to lower the level of glucogenic amino acids.

The pancreatic glucagon level was within the normal range during CSGI. The effect of glucagon on plasma amino acid levels was greatest with CSGI. Zinc glucagon injection was also effective in controlling the levels of plasma glucose and amino acids. Furthermore, afternoon hyperglycemia and nocturnal hypoglycemia were suppressed with CSGI. Urinary nitrogen excretion was increased with glucagon injection because glucagon is one of the catabolic hormones. However, excretion of 3-methylhistidine did not show any significant increase. Thus the data suggest that the origin of the greater part of the urinary nitrogen is not muscle protein but plasma amino acids.

From these results we conclude that exogenous glucagon injection after total pancreatectomy exerts a significant effect on glucose and amino acid metabolism and that both continuous subcutaneous glucagon infusion and zinc glucagon are useful for postoperative management of total pancreatectomy.

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