

Lack of Relationship between Blood Glucose-lowering Activity of Colestimide and Serum Cholecystokinin (CCK) Concentrations in Patients with Type 2 Diabetes

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Abstract

Colestimide has been reported to lower blood glucose levels in patients with type 2 diabetes and hypercholesterolemia. We investigated the mechanism of the hypoglycemic activity of colestimide by examining changes in serum cholecystokinin (CCK) and insulin concentrations before and after its 2-week oral administration. A total of seven type 2 diabetes inpatients with hypercholesterolemia received colestimide after their blood glucose levels had stabilized. We daily measured plasma glucose levels and serum lipid concentrations, calculated Body Mass Index (BMI), and determined whole-day changes in serum immunoreactive insulin (IRI) and CCK concentrations in all study subjects. We daily measured plasma glucose levels, as well as serum IRI and CCK concentrations at 10 time points for measurement. Plasma glucose levels, as well as serum IRI and CCK concentrations before and after the 2-week oral administration of colestimide were compared. The means of total cholesterol levels and BMI decreased significantly after administration. At time points for measurement (10 : 00 and 12 : 00), plasma glucose levels decreased significantly after administration ($P=0.026$ and $P=0.009$, respectively). Diurnal changes in serum IRI and CCK concentrations were not observed after administration, except for the IRI concentration at 20: 00. The effect of colestimide on CCK may not explain the mechanism of its blood glucose-lowering activity in patients with type 2 diabetes and hypercholesterolemia.

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Key words: colestimide, cholecystokinin, plasma glucose, type 2 diabetes mellitus

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Introduction

Colestimide is an anion-exchange resin that lowers cholesterol through its binding to bile acids in the intestinal tract. Some studies¹⁻³ including ours have recently reported the blood glucose-lowering activity of colestimide in patients with type 2 diabetes. However, the mechanism by which an anion-exchange resins decrease plasma glucose levels remains unknown. Watanabe et al.⁴ have recently reported that the administration of cholic acid, a type of bile acids, decreases body weight and plasma glucose levels in metabolic syndrome model mice via energy expenditure by promoting intracellular thyroid hormone activation in brown adipose tissue. Colestimide is already known to alter the composition of bile acids in humans⁵. We have reported a modest increase in postprandial glucagon-like peptide-1 (GLP-1) levels accompanied by a decrease in postprandial glucose levels after the 1-week oral administration of colestimide⁶. We consider that the results from this study explain, at least in part, the blood glucose-lowering activity of colestimide because the extent of increase in GLP-1 concentrations was slight. Cholecystokinin (CCK) is also a gastrointestinal hormone capable of stimulating insulin secretion^{7,8}. In the present study, we investigated the relationship between the blood glucose-lowering activity of colestimide and serum CCK concentrations in patients with type 2 diabetes.

Patients and Methods

The present study was conducted at our hospital in patients with type 2 diabetes (2 men and 5 women; mean age: 72.4 ± 12.9 ; BMI: 28.7 ± 3.2 kg/m²; duration of diabetes: 12.9 ± 9.0 years) who were complicated by hypercholesterolemia and whose postprandial glucose levels were poorly controlled despite a weight-maintaining diet (25–30 kcal/kg of standard body weight) and treatment with oral hypoglycemic agents. Three patients were treated by diet alone, and four with oral hypoglycemic agents. The following oral hypoglycemic agents were administered: two subjects were treated with

glimepiride, one with glibenclamide, and one with pioglitazone hydrochloride.

Colestimide (1,500 mg/day) was administered orally twice daily, before breakfast and dinner, for 2 weeks. Plasma glucose levels, as well as serum immunoreactive insulin (IRI) and CCK concentrations were measured before and after the 2-week oral administration of colestimide. No new drugs were added, and the doses of permitted combination drugs were not changed during the study period. Plasma glucose levels, as well as serum IRI and CCK concentrations were measured daily at 10 time points: 08 : 00 (before breakfast), 10 : 00, 12 : 00 (before lunch), 14 : 00, 18 : 00 (before dinner), 20 : 00, 00 : 00, 03 : 00, 06 : 00, and 08 : 00 in the next morning. Before the start of the study, informed consent was obtained from all subjects after a clear explanation had been provided.

Plasma glucose levels were measured by the glucose oxidase method, and serum IRI and CCK concentrations by radioimmunoassay. After admission, self-monitoring of blood glucose (SMBG) was performed by all subjects on consecutive days. The coefficient of variance for SMBG at fasting for 1 week immediately before the initiation of the study was verified to be as low as 3.0%.

Data in the text, tables, and figures are expressed as means \pm SD. Student's and paired t-tests were conducted for between-group comparisons of continuous variables, and χ^2 test for categorical variables. A value of $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of study subjects are shown in **Table 1**. Diurnal changes in plasma glucose levels, as well as serum IRI and CCK concentrations are shown in **Figure 1**. At 10 : 00 and 12 : 00, plasma glucose levels decreased significantly after colestimide administration ($P = 0.026$, $P = 0.009$, respectively). No significant changes were noted in the mean IRI values after administration, except for a significant decrease ($P = 0.006$) at 20 : 00. Furthermore, no significant changes were noted in the mean CCK values, although they tended to

Table 1 Baseline characteristics of study subjects

N	7
Male/female	2/5
Age (years)	72.4 ± 12.9
Plasma fasting glucose level (mg/dL)	123 ± 27
HbA _{1c} (%)	7.8 ± 1.1
Duration of diabetes (years)	12.9 ± 9.0
Body Mass Index (kg/m ²)	28.7 ± 3.2
T-Chol (mg/dL)	224.7 ± 32.4
HDL-C (mg/dL)	43.4 ± 6.2
TG (mg/dL)	218.3 ± 111.5

Therapy: Diet alone or in combination with oral hypoglycemic agents.

Two subjects were treated with glimepiride, one with glibenclamide, and one with pioglitazone hydrochloride.

Values are expressed as mean ± SD.

decrease after administration.

The mean plasma total cholesterol value decreased significantly from 224.7 ± 32.4 to 184.6 ± 28.6 mg/dL ($P=0.001$) after administration. No significant differences were found in changes of serum high-density lipoprotein (HDL) cholesterol and triglyceride concentrations. The mean value of BMI decreased significantly from 28.7 ± 3.2 to 27.4 ± 2.6 after administration ($P=0.044$).

Discussion

In the present study, colestimide decreased plasma glucose levels and body weight in patients with type 2 diabetes. This finding is in line with that of our previous studies¹⁶. However, no significant differences were noted in serum CCK concentrations before and after the 2-week oral administration of colestimide.

CCK, secreted by intestinal endocrine cells that are located mainly in the duodenum, is released into the blood stream during a meal⁹. Many animal studies have reported that cholestyramine, an anion exchange resin, enhances the release of CCK in response to nutrients¹⁰⁻¹². As demonstrated in both *in vitro* and *in vivo* studies^{10,13,14}, furthermore, CCK exerts a potent stimulatory action on insulin secretion. In humans, however, whether CCK has an ability to stimulate insulin secretion is controversial^{8,15-19}. Rushakoff and coworkers¹⁹

reported that the infusion of CCK at rates reproducing postprandial blood levels of the hormone potentiate amino acid-stimulated insulin secretion. In their study, however, the infusion of CCK alone failed to increase plasma IRI concentrations in healthy volunteers. In another study¹⁸ similar in design to the above experiments that was conducted using much lower doses of amino acids than those in the study by Rushakoff et al., i.e., doses probably leading to physiological concentrations thereof, CCK did not enhance insulin secretory response to an amino acid mixture administered intravenously that closely mimicked postprandial increments in circulating amino acid concentrations. Ahren and coworkers¹⁶ showed that a pharmacological dose of CCK given by intravenous bolus injection stimulates the release of basal and meal-related insulin. However, Reimers and coworkers¹⁷ found that a physiological dose of CCK given by exogenous infusion does not enhance insulin release induced by the intravenous infusion of glucose and phenylalanine. Therefore, these studies suggest that CCK is not a physiological incretin hormone in humans.

The mechanism by which an anion exchange resin decreases plasma glucose levels without the changing serum concentrations of CCK and IRI remains unknown. Possible mechanisms include reduced or slowed absorption of ingested carbohydrates²⁰. Studies in rat have shown that bile acid compounds, or cholestyramine-supplemented diets decrease ileal glucose uptake²¹. In addition, Watanabe et al. recently reported that administration of bile acids, especially cholic acids, induces energy expenditure by promoting intracellular thyroid hormone activation in brown adipose tissue, preventing obesity and insulin resistance in metabolic syndrome model mice⁴. Colestimide increased fasting plasma cholic acid levels but not to a statistically significant extent⁵. Therefore, the improvement of metabolism with colestimide by increasing energy expenditure in skeletal muscle may partially operate via the same pathway as the supplementation with cholic acid. Farnesoid receptor X (FXR) is an orphan nuclear receptor that is activated by bile acids and has been

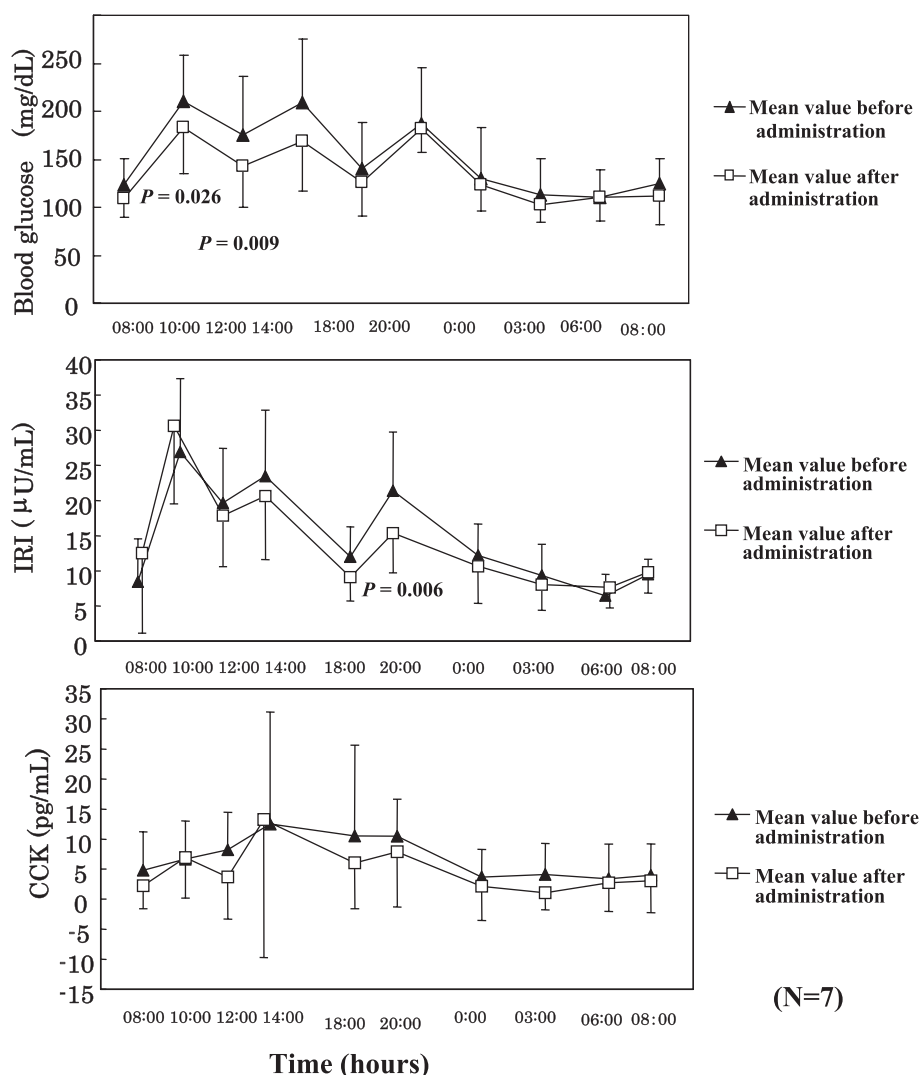


Fig. 1 Diurnal changes in plasma glucose levels, as well as serum IRI and CCK concentrations before and after the 2-week oral administration of colestimide. Data are expressed as means \pm SD.

implicated in glucose metabolism²³. FXR is involved in the regulation of hepatic glucose metabolism. Therefore, colestimide may affect glucose metabolism via FXR.

The present preliminary study may also suggest the lack of a relationship between the blood glucose-lowering activity of colestimide and serum CCK concentrations in patients with type 2 diabetes.

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