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Blood Glucose-lowering Activity of Colestimide in Patients with Type 2 Diabetes and Hypercholesterolemia: A Case-control Study Comparing Colestimide with Acarbose

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Abstract

Background: An anion exchange resin has been reported to lower blood glucose levels in patients with type 2 diabetes.

Aim: To examine, in comparison with an α-glucosidase inhibitor, the usefulness of colestimide in lowering blood glucose levels in patients with type 2 diabetes and hypercholesterolemia.

Methods: Thirty-three patients with type 2 diabetes and hypercholesterolemia were more or less randomly assigned to receive either colestimide (17 patients) or acarbose (16 patients). At 10 time points before and after administration, plasma glucose levels and serum lipid concentrations were measured in all subjects, and the J-index and M-value were calculated.

Results: Patients receiving colestimide showed significant decreases in glucose levels 2 hours after breakfast (from 216.9 ± 37.2 mg/d*l* before treatment to 191.1 ± 40.9 mg/d*l* after treatment; $p=0.008$), in the J-index (from 42.6 ± 14.5 to 32.6 ± 9.8; $p<0.001$), and in the M-value (from 23.1 ± 12.1 to 14.6 ± 7.1; $p<0.001$).

Conclusion: In patients with type 2 diabetes and hyperlipidemia, colestimide was suggested to have blood glucose-lowering activity as does acarbose.
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Key words: colestimide, glycemic control, acarbose, type 2 diabetes mellitus

Introduction

Colestimide, a new type of anion exchange resin developed in Japan, lowers plasma cholesterol concentrations by absorbing bile acids in the intestinal tract[1]. The blood glucose-lowering activity of cholestyramine, another anion exchange resin, has previously been reported in patients with type 2 diabetes and hypercholesterolemia[2–4]. To date, however, the relationship between glycemic control and the blood glucose-lowering activity of colestimide in patients with type 2 diabetes has not been reported. In addition, the mechanism by which

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cholestyramine decreases blood glucose levels remains unclear. A recent report has described that bile acids decrease obesity and lower blood glucose levels in metabolic syndrome model mice because the acids accelerate energy consumption via thyroid hormones[5]. Therefore, the involvement of an anion exchange resin in this mechanism is also conceivable.

Acarbose is an alpha-glucosidase inhibitor that diminishes carbohydrate digestion, resulting in its delayed absorption from the gut and in reduced postprandial rises in plasma glucose and insulin[6,7].

In the present study, we administered colestimide and acarbose orally to patients with type 2 diabetes and hyperlipidemia to examine and compare their blood glucose-lowering activity.

Materials and Methods

Subjects and Design

From February 2, 2001, to June 30, 2004, the present study was conducted at our hospital in 33 inpatients with type 2 diabetes complicated by hypercholesterolemia (21 men and 12 women) whose postprandial glucose levels were poorly controlled despite a weight-maintaining diet (25～30 kcal/kg of standard body weight [BW]) and treatment with oral hypoglycemic agents. These consecutive patients were more or less randomly assigned to the following two groups: the colestimide administration group (group C) and the acarbose administration group (group A). Group C consisted of 10 men and 7 women (body mass index [BMI]: 25.6 ± 4.0; age: 68.8 ± 12.0 years; HbA_1c: 7.7 ± 1.1%; duration of diabetes mellitus [DM]: 12.0 ± 8.1 years) who were instructed to ingest 1,500 mg of colestimide twice daily, i.e., before breakfast and dinner. Group A consisted of 11 men and 5 women (BMI: 25.0 ± 2.8; age: 67.9 ± 9.9 years; HbA_1c 8.0 ± 1.9%; duration of DM: 12.6 ± 9.5 years) who were instructed to ingest 50 mg of acarbose 3 times daily before each meal. There were no significant differences between groups C and A with respect to treatments (diet therapy only: 10 patients and 8 patients in groups C and A, respectively; and diet therapy plus oral hypoglycemic agents: 7 and 8 patients in groups C and A, respectively) and to background factors. The following oral hypoglycemic agents were administered: in group C, tolbutamide to 1 patient, glibenclamide to 1 patient, glimepiride to 4 patients, gliclazide to 1 patient, and pioglitazone hydrochloride to 1 patient; and in group A, glibenclamide to 5 patients, glimepiride to 2 patients, and gliclazide to 1 patient.

After hospital admission, self-monitoring of blood glucose (SMBG) was performed on consecutive days by all subjects. The coefficient of variance (CV) for SMBG at fasting for 1 week immediately before the first 24-hour measurement of blood glucose levels was calculated. After the CV value was verified to be as low as 2.7%, patients were assigned to group C or group A. Furthermore, the CV values at baseline in both groups C and A were as low as 2.5% and 2.8%, respectively, and no significant difference in CV values was found between the groups. The Multi-Lancet for Forearm & Fingertip Lancet Device (Arkley, Kyoto, Japan) was used to perform a fingertip puncture. Laboratory evaluation before the study indicated coefficient variations of ～4% among strips at plasma glucose levels of ≤ 40, 80, 250, and 400 mg/d*l*.

The above first 24-hour measurement was performed after the SMBG levels had stabilized, and the second measurement was performed 2 weeks thereafter. Plasma glucose levels were measured daily in all subjects at the following 10 time points: 8 : 00 ([fasting plasma glucose (FPG]), 10 : 00 (2-hr postprandial glucose [PPG] level), 12 : 00 (before lunch), 14 : 00, 18 : 00 (before dinner), 20 : 00, and 24 : 00 on the day of administration, as well as 3 : 00, 6 : 00, and 8 : 00 the next morning.

Glycemic control was assessed with the area under the curve (AUC) for blood glucose. The J-index described by Wojcicki[8] and the M-value described by Schlichtkrull[9,10], which are indicators for variations in blood glucose levels, were calculated. The standard euglycemic value of 100 mg/d*l* was chosen to calculate the M-value.

The M-value is calculated using the following formula: $\Sigma\{|10 \times \log_{10}(\text{blood glucose}/100|^3\}/n + \{\text{Max (blood glucose)} - \text{Min (blood glucose)}\}/20$. The J-Index is defined as 0.001 × (mean blood glucose +

Table 1 Baseline characteristics of study patients

	Colestimide	Acarbose	p
n	17	16	
Male/female	10/7	11/5	0.554
Age (years)	68.8 ± 12.0	67.9 ± 9.9	0.806
Body mass index (kg/m^2)	25.6 ± 4.0	25.0 ± 2.8	0.632
Fasting plasma glucose (mg/d*l*)	124.9 ± 21.1	128.7 ± 16.5	0.570
HbA_{1c} (%)	7.7 ± 1.1	8.0 ± 1.9	0.531
Duration of DM (years)	12.0 ± 8.1	12.6 ± 9.5	0.844
Therapy: No concomitant/ combination drug with oral hypoglycemic a gents	10/7*	8/8**	0.611
CV of fasting blood glucose (%)	2.5	2.8	0.494

* Tolbutamide in 1 patient, glibenclamide in 1 patient, glimepiride in 4 patients, gliclazide in 1 patient, pioglitazone hydrochloride in 1 patient

** Glibenclamide in 5 patients, glimepiride in 2 patients, and gliclazide in 1 patient

Table 2 Mean changes in plasma glucose, J-index, and M-value before and after oral administration of colestimide or acarbose

		Before administration	After administration	p
Fasting plasma glucose (mg/d*l*)	C	124.9 ± 21.1	116.2 ± 19.9	0.188
	A	128.7 ± 16.5	120.8 ± 16.9	0.042
Plasma glucose after meal (mg/d*l*)	C	216.9 ± 37.2	191.1 ± 40.9	0.008
	A	219.3 ± 42.4	190.7 ± 35.1	0.021
J-index	C	42.6 ± 14.5	32.6 ± 9.8	<0.001
	A	40.7 ± 10.9	32.6 ± 11.0	<0.001
M-value	C	23.1 ± 12.1	14.6 ± 7.1	<0.001
	A	20.8 ± 9.2	14.1 ± 9.1	0.002

Plasma glucose levels were measured during fasting and after meal at AM 8:00 and AM 10:00, respectively. Letters C and A denote colestimide and acarbose, respectively. Values are expressed as mean ± SD.

SD)[2] for blood glucose measurements in milligrams per deciliter.

New drugs were not added, and the doses of permitted combination drugs were not changed during the 2-week administration period of colestimide and acarbose. The BMI was calculated as BW (kg)/height (m^2).

Before the start of the study, informed consent was obtained from all subjects after a sufficient explanation had been provided.

Statistical Analysis

Values are expressed as mean ± SD. The J-index and the M-value before and after oral administration of colestimide and acarbose at 10 time points for measurement were compared according to paired Student's t-test. Data monitored over time were compared according to the AUC value in order to reduce the number of tests, and repeated measures ANOVA was made to examine the AUC of blood glucose before and after oral administration of colestimide and acarbose.

A value of $p<0.05$ was considered statistically significant. Statistical analyses were made using a SPSS software (version 12.0; SPSS Inc., Chicago, IL, USA).

Results

No significant differences were found between groups C and A with respect to background factors (**Table 1**). The following changes were observed

Table 3 Mean changes in serum total cholesterol, HDL-cholesterol, triglyceride, body weight (BW), and Body Mass Index (BMI) before and after oral administration of colestimide or acarbose

		Before administration	After administration	p
Total cholesterol (mg/dl)	C	223 ± 32	184 ± 29	<0.001
	A	211 ± 18	181 ± 24	0.002
HDL-cholesterol (mg/dl)	C	46 ± 12	43 ± 13	0.084
	A	46 ± 13	42 ± 10	0.077
Triglyceride (mg/dl)	C	203 ± 123	175 ± 92	0.290
	A	154 ± 88	118 ± 43	0.089
Body Weight (kg)	C	62.6 ± 12.8	59.3 ± 12.6	0.005
	A	63.1 ± 8.7	61.1 ± 8.7	0.036
Body Mass Index (kg/m^2)	C	25.6 ± 4.0	24.7 ± 4.4	0.008
	A	25.0 ± 2.8	24.7 ± 2.7	0.053

Letters C and A denote colestimide and acarbose, respectively. Values are expressed as mean ± SD

before and after treatment, respectively, in regard to the FPG value and 2-hr PPG value (**Table 2**): in group C, a tendency for decrease in FPG value from 124.9 ± 21.1 mg/dl to 116.2 ± 19.9 mg/dl and a significant decrease (p=0.008) in 2-hr PPG value after breakfast from 216.9 ± 37.2 mg/dl to 191.1 ± 40.9 mg/dl; and in group A, a significant decrease (p=0.042) in FPG value from 128.7 ± 16.5 mg/dl to 120.8 ± 16.9 mg/dl and a significant decrease (p=0.021) in 2-hr PPG value after breakfast from 219.3 ± 42.4 mg/dl to 190.7 ± 35.1 mg/dl. Furthermore, the following changes were observed before and after treatment, respectively, in regard to the J-index and M-value: in group C, a significant decrease (p<0.001) in J-index from 42.6 ± 14.5 to 32.6 ± 9.8 and a significant decrease (p<0.001) in M-value from 23.1 ± 12.1 to 14.6 ± 7.1; and in group A, a significant decrease (p<0.001) in J-index from 40.7 ± 10.9 to 32.6 ± 11.0 and a significant decrease (p<0.001) in M-value from 20.8 ± 9.2 to 14.1 ± 9.1.

Table 3 shows the mean changes in serum total cholesterol (TC) concentrations, high density lipoprotein (HDL)-cholesterol concentrations, and triglyceride (TG) concentrations at baseline, about which no significant differences were found between group C and group A. Both groups showed a significant decrease in serum TC concentrations after administration (from 223 ± 32 mg/dl to 184 ± 29 mg/dl [p<0.001] in group C and from 211 ± 18 mg/dl to 181 ± 24 mg/dl [p<0.002] in group A) but exhibited no significant changes in HDL-C and TG before and after administration. Furthermore, no significant difference was found in BW or BMI at baseline between the groups. Group C showed significant decreases after administration (from 62.6 ± 12.8 kg to 59.3 ± 12.6 kg [p<0.005] in BW and from 25.6 ± 4.0 kg/m^2 to 24.5 ± 4.7 kg/m^2 [p<0.008] in BMI). Group A showed a significant decrease in BW (from 63.1 ± 8.7 kg to 61.1 ± 8.7 kg [p<0.036]) and a trend to decrease in BMI (from 25.0 ± 2.8 kg/m^2 to 24.7 ± 2.7 kg/m^2 [p<0.053]). Furthermore, no significant difference was found in BMI between the groups.

Plasma glucose levels, which were measured daily before and after oral administration of colestimide and acarbose, are shown in **Figure 1**. At 10 : 00, 12 : 00, and 14 : 00, group C showed significant decreases in plasma glucose levels after administration (p=0.008, p=0.003, p=0.010, respectively). However, plasma glucose levels remained unchanged after18 : 00. At 8 : 00, 10 : 00, and 20 : 00, group A showed significant decreases in blood glucose levels (p=0.042, p=0.025, and p<0.0001, respectively).

The AUC values of blood glucose before and after oral administration of colestimide and acarbose are shown in **Figure 2**. Group C showed significant decreases (p<0.001) in the mean AUC values of blood glucose from 3,764 ± 685.1 mg・h/dl to 3,364.4 ±

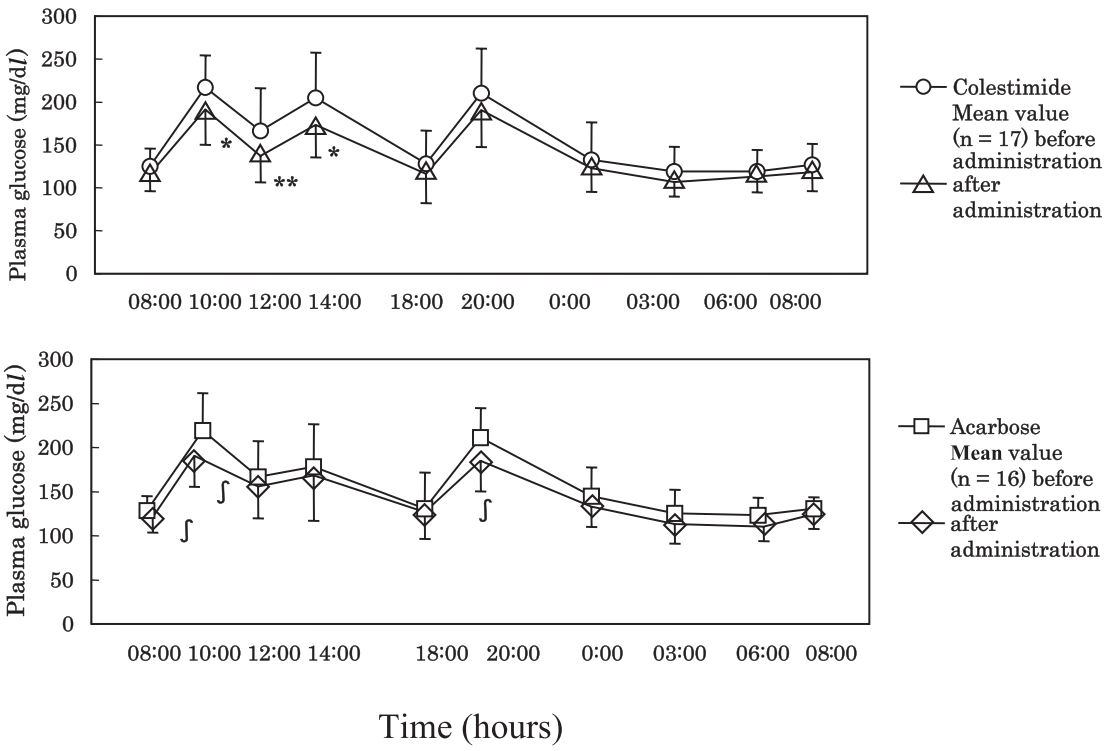

Fig. 1 Diurnal changes in plasma glucose levels before and after oral administration of colestimide (upper panel) and acarbose (lower panel)
Values are expressed as mean ± SD. * : P<0.05, ** : P<0.01, before vs. after administration of colestimide (paired t-test) ∫ : P<0.05, before vs. after administration of acarbose (paired t-test)

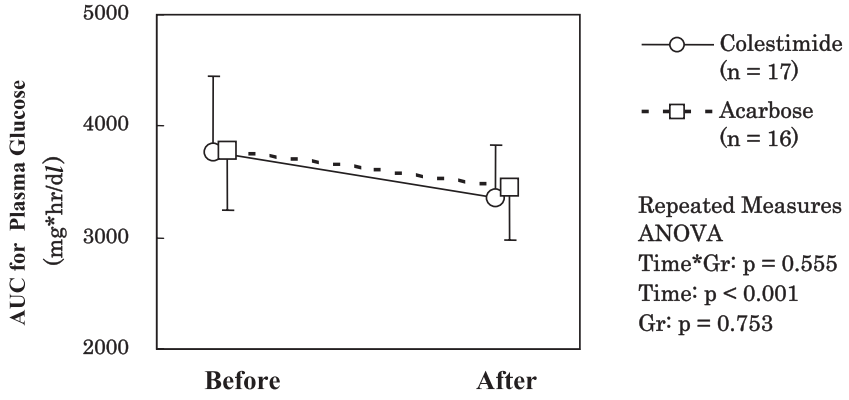

Fig. 2 Comparison of diurnal changes in AUC for plasma glucose levels before and after oral administration of colestimide and acarbose
A significant difference (p<0.001) was noted in the time-course for AUCs of plasma glucose levels. No significant difference was found (p=0.753) between groups C and A. The interaction was not significant (p=0.555).
Values are expressed as mean ± SD.

461.7 mg・h/dl. Furthermore, group A also showed similar decreases in the mean AUC values of blood glucose from 3,782 ± 532.9 mg・h/dl to 3,460.4 ± 478.2 mg・h/dl (p<0.001). The AUC values of blood glucose 24 hours before and after administration in groups C and A showed no interaction (p=0.555) and no intergroup difference (p=0.753).

During the study period, colestimide and acarbose were not discontinued due to adverse reactions in any patient.

Discussion

The results of the present study indicate that colestimide has not only a cholesterol-lowering effect but also a blood glucose-lowering effect in patients with type 2 diabetes and hypercholesterolemia.

Hanefeld et al. have reported that patients receiving acarbose at a dosage of 300 mg daily for 24 weeks showed a decrease in the 1-hr postprandial PG value from 14.4 mmol/*l* to 11.6 mmol/*l* 4 weeks after the start of treatment; patients receiving placebo showed a strong tendency for decrease in the 1-hr postprandial PG value from 14.8 mmol/*l* to 13.6 mmol/*l* 24 weeks after the start of treatment; furthermore, patients receiving acarbose showed a significant decrease in HbA_{1c} as compared with the placebo group[11]. Garg et al. have examined the effects of an anion exchange resin on glycemic control[2]. They found in a randomized, double-blind, cross-over study that cholestyramine, another anion exchange resin, improved glycemic control in patients with type 2 diabetes. They studied 21 patients with type 2 diabetes whose plasma glucose levels were well controlled either with glyburide or by insulin therapy and reported that the blood glucose-lowering activity of colestimide is comparable to that of cholestyramine. Patients received cholestyramine or placebo for 6 weeks, and plasma glucose levels were measured at 3 : 00, 7 : 00, 11 : 00, 16 : 00, and 20 : 00 (on days 0, 28, and 38). Compared with those in the placebo group, the mean plasma glucose levels in the cholestyramine group decreased by 13%. The present study, which compared colestimide with a postprandial antihyperglycemic agent acarbose and used twice as many time points for measurement as did the study of Garg et al., revealed a significant decrease in plasma glucose levels after oral administration of colestimide at 10 : 00, 12 : 00, and 14 : 00 but not after 18 : 00.

Mathematical indices describing the time-course of glycemia have been considered to be useful variables for the short-term monitoring of glucose control in patients with diabetes. The universal indices related to both mean glucose level and glucose variation, which are now used in clinical practice, are the J-index described by Wojcicki[8] and the M-value described by Schlichtkrull[9,10]. Patients with diabetes in whom blood glucose levels are well-controlled have lower values of these two variables than do patients with poorly-controlled blood glucose levels. In the present study, the J-index and the M-value decreased significantly after oral administration of colestimide. These results indicate that colestimide lowers blood glucose levels on a whole-day basis and more extensively than does diet therapy alone or in combination with sulfonylureas. Furthermore, the patients receiving colestimide showed significant decreases in both the J-index and M-value after treatment, as was observed in patients receiving acarbose.

It is admittedly possible that diet therapy after hospital admission reduced BW and lowered plasma glucose levels. However, these variables were measured near discharge. Therefore, we believe that plasma glucose levels were relatively stable. Group A showed decreases in both BW and plasma glucose levels, thus providing almost equivalent blood glucose-lowering effects. Furthermore, group C showed decreases in serum TG concentrations. However, this variable showed a wide range (203 ± 123 mg/d*l*), and the number of patients in the present study was small. Similarly, group C showed a trend for decreased FPG levels before and after treatment. Therefore, we are willing to increase the number of patients to be examined in the future.

The mechanism by which an anion exchange resin decreases plasma glucose levels remains unclear. However, bile salts play a physiological role in the negative feedback regulation of cholecystokinin (CCK) release in response to luminal nutrients. As demonstrated in both *in vitro* and in *in vivo* studies[12–14], CCK exerts a potent stimulatory action on insulin secretion. In the future, therefore, it may be necessary to investigate these hormone levels in an assay.

Furthermore, Watanabe et al. have recently reported that the administration of cholic acid, a kind of bile acid, to metabolic syndrome model mice alters the composition of bile acids, increases energy consumption, suppresses BW increase, and lowers

blood glucose levels, thus improving metabolic control[5]. The administration of colestimide has already been reported to alter the composition of bile acids[15], leading us to consider that these changes might be involved in the mechanism of blood glucose decrease. To elucidate these mechanisms, however, further research on colestimide-induced changes in bile acid composition are needed.

Anion exchange resins might cause fat malabsorption[18], which may provoke a weight reduction and lead to an improvement in glycemic control. The present study revealed a significant decrease in the mean BMI from 25.6 ± 4.0 to 24.5 ± 4.7 kg/m^2 after oral administration of colestimide. However, BW was not affected by cholestyramine therapy in the study conducted by Garg et al.[2] Diet restriction after hospital admission significantly reduced BW in both group C and group A.

Furthermore, group C showed greater BW reductions and higher BMI values, thus suggesting possible effects on changes in plasma glucose levels. In fact, Watanabe et al. have reported greater reductions in BW and greater decreases in plasma glucose levels in patients treated with a high-fat diet and bile acids[5].

This finding leads us to speculate that factors other than diet restriction may underlie the blood glucose-lowering effect of colestimide.

Further research is needed to elucidate the mechanism by which colestimide lowers blood glucose levels. Since only 17 patients with type 2 diabetes and hypercholesterolemia received colestimide in the present study, larger numbers of patients should be enrolled in future studies.

The present study, although the duration of drug administration was as short as 2 weeks, provided informative results, i.e., patients receiving colestimide showed significantly greater decreases in the 2-hr PPG levels than did patients receiving acarbose and exhibited similar time-course changes in the J-index and M-value.

Acarbose is a promising agent for diabetes mellitus which lowers postprandial blood glucose levels[19,20]. Our study provides for the first time the evidence that colestimide has efficacy nearly equivalent to that of α-glucosidase inhibitors, drugs with such blood glucose-lowering activity. A limitation of this study is the practical difficulty of conducting a placebo-controlled study in Japan. Therefore, we believe that further research according to the prospective randomized open blinded endpoint (PROBE) method[21,22] or by an randomized controlled trial will be required to verify the actions of colestimide.

The present study suggests that colestimide not only has lipid-lowering activity but also possesses blood glucose-lowering activity as does acarbose. Colestimide may be considered clinically useful for glycemic control through its dual actions in patients with type 2 diabetes complicated by hyperlipidemia. Further research is needed to clarify the mechanism by which colestimide improves glycemic control.

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