Colestimide, an Ion-Exchange Resin Agent, May Enhance Glucose Lowering Effect of Voglibose as Their Acute Effect

Naoki Matsumoto, Yuko Takeba, Minoru Watanabe, Yoshie Harimoto, Sachiko Takenoshita-Nakaya, and Shinichi Kobayashi

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Abstract

Hypercholesterolemia frequently accompanies diabetes mellitus in the same patient, and both should be treated together, because these diseases worsen arteriosclerosis. Ion-exchange resin colestimide is used for hypercholesterolemia treatment, but it might absorb concomitantly used agent, such as voglibose, alpha-glucosidase inhibitor for diabetes treatment. We checked the blood glucose level change in 12 healthy subjects (mean age 31.6 ± 6.6 y) for 300 minutes after taking 100 grams of sucrose dissolved in water. Voglibose 0.2 mg, colestimide 1500 mg or voglibose 0.2 mg plus colestimide 1500 mg was administrated 10 minutes before sucrose consumption, and the results from these 3 studies were compared with the result from the control study with water alone. Peak values of blood glucose (at 30 min) from control were the highest with 133.9 ± 6.9 mg/dl, followed by colestimide 131.2 ± 6.8 mg/dl, voglibose 129.2 ± 11.2 mg/dl and their concomitant use was the lowest with 119.6 ± 6.8 mg/dl. We also calculated the area under the curve of blood glucose, revealing the largest value with the control and voglibose, slightly smaller with colestimide and the smallest with their concomitant use. Although these results did not show significant difference statistically, concomitant use of voglibose and colestimide may enhance their blood glucose lowering effect of each other. This effect may be acute, and occurs even in healthy subjects.

Key words

Voglibose, Colestimide, glucose, four-way cross over design

Introduction

Hypercholesterolemia and diabetes mellitus are both well-known risk factors that enhance progression of arteriosclerosis. These abnormalities frequently exist together in one patient, and need to be treated the same time. This means blood glucose lowering agent and cholesterol lowering agent are to be administered concomitantly. An ion-exchange resin agent, that absorbs bile acid and lowers plasma cholesterol level, such as cholestyramine has been long used, but it has adverse effects that can absorb concomitantly used agents. Several studies have shown the possibility of drug interaction when used with adsorbents like colestimide, that we used in this study, resulting in reduced bioavailability of concomitantly used drug in vitro study. Newly developed colestimide actually has a stronger cholesterol lowering effect and smaller possibility of absorbing concomitant agents, but the details of pharmacokinetics and pharmacodynamics in vivo have not been clarified. As we talk about glucose issue, voglibose, alpha-glucosidase inhibitors works on small intestine, delays the digestion and absorption of carbohydrates, thereby inhibiting postprandial hyperglycemia and hyperinsulinemia, and is an aid in the treatment of diabetes. Under these mechanical conditions, we aimed to prove whether the
use of cholesterol lowering agent colestamide together with blood glucose lowering agent voglibose may influence glucose lowering effect.

We evaluated the blood glucose level change in time course after ingesting sucrose on healthy subjects, in order to clarify the effects of voglibose when used with colestamide.

Material and Methods

Drugs

Voglibose and Colestimide were purchased from Takeda Chemical Industries, Ltd. (Osaka, Japan) and Mitsubishi Tanabe Pharma. (Osaka, Japan).

Healthy volunteers

Healthy volunteers were enrolled after obtaining written informed consent. Eight males, 4 females, totally 12 subjects with mean age of 31.6 ± 6.6 years have participated in the present study. The volunteers were all non-smokers, presenting no apparent symptoms and have not been pointed out of any chronic disease by regular health check-up. They were not taking drugs regularly. Baseline health check-up by blood samples were repeated throughout the study, and these check-up revealed that they were all healthy especially on blood glucose metabolism and lipid and cholesterol metabolism.

Study Design

The four-way cross over design study was conducted as examination A, B, C, and D, as shown in Fig 1. All participants started all Exams under a fasting condition in the morning. They took 50 ml of water with/without the study drug(s) according to the study protocols: only water as control for Exam A, 0.2 mg of voglibose for Exam B, 1500 mg of colestimide for Exam C, and 1.5 mg of voglibose and 1500 mg of colestimide together for Exam D. In each of the Exams, 10 minutes after the drug administration, they ingested 100 g of sucrose (Wako Pharm, Osaka, Japan) dissolved in 200 ml of water. Just before the ingestion of sucrose (as 0 min), and 15, 30, 45, 60, 90, 120, 180, 240, and 300 minutes after the ingestion of sucrose, blood samples were taken for blood glucose level evaluation. For basic condition confirmation that the subjects are in fitted conditions, other parameters shown in Table 1 were also investigated. During the Exam, the subjects were prohibited to take anything orally, and each Exam was performed separately at least 5 day intervals. This study was approved by the ethical committee of St. Marianna University School of Medicine on 2001/8/10.

Statistical Analysis

Statistical analysis was performed using JMP (ver. 8.0). Data are expressed as mean ± SD. Multi-Comparison analysis was performed with Dunnett method (Probability values <0.05).

Results

Blood glucose level change in time course is shown in Fig 2. All peaks of blood glucose were found at 30 minutes. Control (Exam A) showed highest result, 133.9 ± 6.9 mg/dl, followed by colestimide (Exam C), 131.2 ± 6.8 mg/dl, voglibose (Exam B), 129.2 ± 11.2 mg/dl, and their concomitant use (Exam D), 119.6 ± 6.8 mg/dl as the lowest.
Interaction of colestimide and voglibose

**Figure 2.** Peak blood glucose decreased when voglibose and colestimide are co-administered. Voglibose showed a slight delay of descending slope. No statistical difference was proven. Error bars: SE.

**Figure 3.** Area under the curve of voglibose was identical to the control, while colestimide was lower. Combination of voglibose and colestimide showed the lowest value, though statistically not significant. Error bars: SE.

This order did not differ throughout the study time course, except Exam B and D. Exam B, voglibose showed a small hump like shape in its change around 120 minutes data. Exam D, concomitant use of voglibose and colestimide showed the smallest change of blood glucose level from 120 minutes to 300 minutes. Statistical analysis by ANOVA revealed no significant difference between the drug effects (between the Exam groups from A to D) (F value = 1.7797, p = 0.1502).

We calculated the area under the curve (AUC) of the blood glucose level change from 0 minutes to 300 minutes, and the result is shown in Fig 3. Study A, control (2777.4 ± 841.5 mg · min/dl) and study B (2776.2 ± 1165.0 mg · min/dl), voglibose showed almost identical results, while study C (2770.88 ± 883.5 mg · min/dl), colestimide showed the smaller value. Study D (26508.1 ± 651.4 mg · min/dl), concomitant voglibose and colestimide use showed the smallest value, but statistical analysis by ANOVA revealed no significant difference between the drug effects (between the study groups from A to D) (F value = 0.4525, p = 0.7168).

All statistical analysis by Dunnett method was considered to be useless because of the ANOVA results, but showed no statistical difference.

**Discussion**

Alpha-glucosidase that is found on the mucous surface of small intestine decomposes sucrose into glucose and fructose, and enable them to be absorbed easily and quickly from the small intestine\(^{16}\). An alpha-glucosidase inhibitor inhibits this decomposing process, resulting in sucrose to reach down to the large bowel, because sucrose cannot be absorbed. Once sucrose reaches the large bowel, it is degenerated by fermentation, and finally is absorbed. This process leads to the delay of glucose absorp-
tion and reduction of peak glucose level after meal, which improves the condition of diabetes mellitus patients. Voglibose used in this study has a selective inhibitory effect on alpha-glucosidase, and is barely absorbed into the blood stream, which means almost no additional positive or adverse effects are anticipated.\(^\text{10}\)

Colestimide is an ion-exchange resin agent that reduces plasma cholesterol level. This agent has been also known to reduce the blood glucose level, but details have not been revealed yet.\(^\text{15}\) The reason for the lack of related knowledge is that this agent is not well absorbed, and no additional effects can be anticipated.

As we check the present data of this study, voglibose reduced the peak blood glucose level, while AUC of blood glucose was almost identical to the control. Though the data was not significantly different, this tendency was as expected as an approved drug for diabetes mellitus treatment.

On the other hand, colestimide showed not only a lower peak blood glucose level, but also a reduced AUC of blood glucose, though statistically not significant. The results suggested that colestimide may have blocked glucose absorption, or may have increased blood glucose consumption or may have enhanced some glucose lowering mechanisms. Thinking logically, glucose absorption blockage seems most reasonable, because this agent is not absorbed into blood.

As we compared these data from concomitant use of voglibose and colestimide together, concomitant use seemed to have the largest reductive effect both on the peak blood glucose level and on the AUC. This result suggested that voglibose might enhance the blood glucose lowering effect of colestimide, though our initial concern was that the blood glucose lowering effect of voglibose would be interfered by unwished binding to colestimide. The results at least can be interpreted that voglibose will not be bound to colestimide, and will not reduce its pharmacological effect.

The mechanism of this interaction might be explained within the bowel cavity when thinking simple, because both drugs are known to remain within the bowel content, and not in the blood. However, recent reports have interesting suggestions.

Qualmann et al have suggested that voglibose can increase glucagon-like peptide-1 (GLP-1) that reduces blood glucose level by stimulating insulin secretion.\(^\text{11}\) One more other interesting report suggested that colestimide can increase GLP-1, as well.\(^\text{12, 13}\) If we presume the delay effect of voglibose on sucrase decompose has enhanced the GLP-1 secretion from the ileum, it will well explain our results. Although Qualmann has reported the alpha-glucosidase inhibitor acarbose had a marginal effect on GLP-1 secretion, they also have admitted direct luminal contact of carbohydrate produced by acarbose showed late response from the mucosal endocrine cells in the ileum.\(^\text{11}\) Moritoh et al have reported that voglibose had a favorable effect on GLP-1 secretion than acarbose, which might have suggested Qualmann et al might not be able to show significant difference, because they have used acarbose.\(^\text{14, 15}\) Sugiyama et al have shown in vitro study that sucrase was not effective to increase truncated GLP-1 (tGLP-1) as compared to 5% glucose when these had intraluminal contact to the ileum.\(^\text{16}\) This may suggest that unabsorbed large amount of carbohydrate finally reached the ileum, the terminal portion of the small intestine, becoming glucose and fructose to stimulate GLP-1 secretion. A large amount of glucose may have enhanced the GLP-1 secretion effect of colestimide.

In conclusion, although the mechanism remained as speculation, concomitant use of voglibose and colestimide may enhance their blood glucose lowering effects each other. This effect may be acute, and occurs even with the healthy subjects.

Limitation of the study
We did not measure the GLP-1 itself in this study due to its availability in the study conduct year of 2001, which remained the explanation speculated. We also have to admit that the number of subject, for study was not large enough to show statistical difference.

References


