Effect of Colestimide Therapy for Glycemic Control in Type 2 Diabetes Mellitus with Hypercholesterolemia

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Abstract. Colestimide is a new anion-exchange resin used to lower serum cholesterol in Japan. Because of its excellent compliance, colestimide can replace cholestyramine. To clarify the effect of colestimide on glycemic controls, colestimide (3 g/day) or pravastatin (10 mg) was given orally to patients with type 2 diabetes treated with oral hypoglycemic agents or insulin who had low-density lipoprotein (LDL) cholesterol levels exceeding 3.6 mmol/l. In the colestimide groups, fasting plasma glucose concentrations had decreased significantly from 8.5 ± 1.4 to 7.7 ± 1.5 mmol/l at 3 months (P<0.05), as had glycated hemoglobin (HbA1c) from 7.7 ± 0.7% to 6.8 ± 0.5%, for an 8% reduction (P<0.01). Fasting plasma glucose and HbA1c did not change in the pravastatin group. Total cholesterol and LDL-cholesterol decreased significantly (P<0.01) with either medication, with similar reduction rates for both drugs. Doses of oral hypoglycemic agents and insulin did not change during the study, and body weight remained stable. Considering that patients with type 2 diabetes often have hyperlipidemia, colestimide therapy may have a clinically useful dual action in such patients.

Key words: Colestimide, Hemoglobin A1c, Blood glucose, Diabetes mellitus

LOW density lipoprotein cholesterol (LDLc) is the most prominent risk factor for coronary artery disease in patients with type 2 diabetes mellitus [1]. Recent widely use of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) for the treatment of hyperlipidemia has reduced mortality and incidence of cardiovascular disease in patients with type 2 diabetes mellitus [2, 3]. Although bile acid sequestrants are effective in reducing LDLc in patients with various forms of primary hypercholesterolemia [4], they have not been prescribed widely to reduce LDLc in patients with type 2 diabetes mellitus. Obstacle to their use include the predisposition of patients with type 2 diabetes mellitus toward hypertriglyceridemia [5], and poor patient tolerance of the drug.

Colestimide is a new anion exchange resin which has shown strong hypolipidemic effects in rabbits [6]. In addition, because it is associated with patient compliance [7], colestimide has essentially replaced cholestyramine in the treatment of hypercholesterolemia in Japan. Cholestyramine is reported to reduce blood glucose, but the effect of colestimide on glycemic control in diabetic patients has not been reported.

The risk of a major coronary event has been shown to be as high in diabetic subjects without clinically manifest coronary heart disease as in nondiabetic patients who previously have experienced a myocardial infarction. Data from large intervention studies like the Collaborative Atorvastatin Diabetes Study (CARDS) have demonstrated an absolute risk reduction in coronary events resulting from statin treatment in diabetic patients [8]. As a consequence, statin treatment is
being advocated as a first priority in metabolic control for diabetic dyslipidemic patients.

Recently, however, a high dose of atorvastatin was reported to have an adverse effect on glycemic control [9, 10]. In addition, we also showed that a low dose of atorvastatin had an adverse effect on glycemic control in Japanese diabetic patients [11]. On the other hand, the West of Scotland Coronary Prevention Study found that pravastatin therapy reduced the risk of becoming diabetic by 30% [8]. Thus, the effects on glycemic control appear to differ between individual statins. In diabetic patients with dyslipidemia, one needs to select an antilipidemic drug that does not adversely affect glycemic control. In that context, several studies have found that pravastatin did not adversely impact glycemic control [9, 11, 12].

Therefore, the primary objective of this study was to compare the effects of colestimide and pravastatin on glycemic control in patients with type 2 diabetes mellitus.

**Materials and Methods**

Type 2 diabetic patients with hyperlipidemia were recruited for this study, which was approved by the Yokohama City University Medical Center Research Committee. All participants gave their written informed consent. Complete physical examination, electrocardiography, and laboratory evaluation were performed for each patient during screening. Patients were eligible for study if glycated hemoglobin (HbA1c) values were between 6.5 and 9.0% at entry, treatment of type 2 diabetes required oral hypoglycemic agents or insulin, and LDLc concentrations exceeded 3.6 mmol/l. The study included 70 patients, 30 to 75 years old, who had been diagnosed with type 2 diabetes and had been followed up monthly for over 1 year.

Patients with severe diabetic complications such as retinopathy, nephropathy, neuropathy, or ischemic heart disease were excluded. During 3 months of observation, patients who showed unstable glycemic control, and showed more than 10% variation from their initial HbA1c value also were excluded. Patients were randomized pairwise according to the order in which each originally presented to begin with the trial; one was given, oral colestimide (3 g twice daily), and the other, pravastatin (10 mg once daily).

After 3 months of administration of colestimide or pravastatin, several clinical indices (fasting plasma glucose [FPG], body weight, serum total cholesterol [TC], triglycerides [TG], LDLc and high density lipoprotein cholesterol [HDLc]) were compared between groups to evaluate the two treatments. All subjects were encouraged to maintain their usual diet and physical activity. Doses of all oral hypoglycemic agents or insulin were not changed during this study. In addition, all medications known to influence hypoglycemic agents or insulin were neither added nor withdrawn during the study.

**Statistical analysis**

We carried out repeated-measure analysis of variance to assess the effect of the order of patients randomization to pravastatin or colestimide and the overall effect of colestimide therapy. 

**Results**

**Baseline characteristics of randomized patients**

We randomized 70 patients to the pravastatin or colestimide treatment group (each n = 35). As shown in Table 1, the groups showed no significant differ-

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pravastatin (n = 35)</th>
<th>Colestimide (n = 35)</th>
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<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Female</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.2 ± 10.7</td>
<td>62.1 ± 13.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.7 ± 2.4</td>
<td>25.1 ± 2.1</td>
</tr>
<tr>
<td>Duration of diabetes (months)</td>
<td>13.5 ± 1.7</td>
<td>11.9 ± 1.5</td>
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| Treatment for diabetes               |                      |                     |
| Diet only                            | 2                    | 2                   |
| Oral monotherapy                     | 9                    | 8                   |
| Oral combination therapy             | 15                   | 19                  |
| Insulin conventional                 | 5                    | 6                   |
| Insulin intensive                    | 4                    | 2                   |
| Other drugs                          |                      |                     |
| ARB                                  | 8                    | 6                   |
| ACEi                                 | 5                    | 5                   |
| Calcium antagonist                   | 9                    | 11                  |

ARB, angiotensin II receptor blocker; ACEi, angiotensin-converting enzyme inhibitor. Variables are expressed as number of patients, or mean ± SD.
ences between one another in demographic and baseline characteristics such as age, gender, body weight, and duration of diabetes. Percentages of patients who were treated at baseline with diet only, a single antihyperglycemic agent, multiple agents, and insulin did not differ significantly between groups. Other medications with potential to affect glucose metabolism, such as antihypertensive drugs, were not significantly different between the two groups.

During 3 months of observation, FPG and HbA$_1c$ did not differ significantly between medication-defined groups (Figs. 1A and 2A). FPG reduction was ob-

Fig. 1. Scatter plots of fasting plasma glucose (FPG) in individual patients at 3 months before, baseline, and 3 month after the initiation of study. (A) colestimide, (B) pravastatin. Panel (C) shows means for the two groups at the two time points; filled circles represent the pravastatin group, and filled triangles represent the colestimide group. Means are given with SD. *$P$<0.05.

Fig. 2. Scatter plots of HbA$_1c$ in individual patients at 3 months before, baseline, and 3 months after the initiation of study. (A) colestimide, (B) pravastatin. Panel (C) shows mean ± SD for the two groups at the two time points; filled circles represent the pravastatin group, and filled triangles represent the colestimide group. **$P$<0.01.
served as early as 1 month after initiating colestimide treatment, persisting for 3 months of observation (0 months, 8.5 ± 1.4 mmol/l; 1 month, 7.94 ± 1.0; 2 months, 7.8 ± 1.3; and 3 months, 7.7 ± 1.5). After 3 months, FPG concentrations still were significantly decreased (by 8%, \( P < 0.01 \)) in the colestimide-treated group, in contrast to no significant change in pravastatin-treated group. FPG still did not differ between groups.

HbA\(_1c\) reduction also was observed as early as 1 month after colestimide treatment, persisting for 3 months of observation (0 months, 7.7 ± 0.7%; 1 month, 7.4 ± 0.7%; 2 months, 7.0 ± 0.6%; and 3 months, 6.8 ± 0.5%). With colestimide treatment, HbA\(_1c\) had decreased significantly at 3 months (by 8% of the baseline value, \( P < 0.01 \); Fig. 1). Given the importance of long-term effect of colestimide on glycemic control, we compared HbA\(_1c\) reduction rate/LDLc reduction rate between colestimide and pravastatin treatments. This ratio was much higher in the colestimide group (0.7) than in the pravastatin group (0.08).

**Discussion**

Studies have found that cholestyramine reduced blood glucose. However, no previous studies had examined the hypoglycemic effect of colestimide, a new anion exchange resin, in type 2 diabetes. In the current study, we examined the effects of colestimide and pravastatin on glycemic control. Colestimide improved glycemic control significantly in diabetic patients, and was effective when given either by itself or in combination with previous medications including multiple antihyperglycemic agents.

Specific mechanisms by which colestimide lowered blood glucose are important to identify. The lipid-lowering effect of colestimide was slightly weaker than that of pravastatin, but not significantly, while pravastatin treatment had no effect on blood glucose. On the other hand, the HbA\(_1c\) reduction rate/LDLc reduction rate was decidedly higher in the colestimide group.

**Table 2.** Changes in TC, TG, HDLc, and LDLc in response to antilipemic medications

<table>
<thead>
<tr>
<th></th>
<th>Pravastatin before</th>
<th>Pravastatin after</th>
<th>Colestimide before</th>
<th>Colestimide after</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>5.9 ± 0.9</td>
<td>5.2 ± 0.7**</td>
<td>5.5 ± 0.9</td>
<td>4.8 ± 0.6**</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>8.2 ± 3.8</td>
<td>7.4 ± 3.7</td>
<td>7.2 ± 3.1</td>
<td>8.2 ± 3.4</td>
</tr>
<tr>
<td>HDL-cholesterol</td>
<td>3.2 ± 0.7</td>
<td>3.0 ± 0.6</td>
<td>3.1 ± 1.4</td>
<td>2.9 ± 1.1</td>
</tr>
<tr>
<td>LDL-cholesterol</td>
<td>3.7 ± 0.8</td>
<td>3.1 ± 0.7**</td>
<td>3.5 ± 0.8</td>
<td>2.7 ± 0.5**</td>
</tr>
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</table>

**\( P < 0.01 \). Variables are expressed as mean ± SD.**
through the intestinal tract, while cholestyramine slightly suppresses postprandial glycemia in normal volunteers without interfering with gastrointestinal transient time or xylose absorption. Furthermore, it has been reported that intestinal sugar transports are increased in diabetic patients [14]. Cholestyramine, therefore, might improve glycemic control in diabetic patients by decreasing abnormally excessive intestinal sugar absorption, although the precise mechanism awaits further investigation.

Recently, the farnesoid X receptor (FXR), a member of the nuclear receptor superfamily, has been reported to take part in regulating carbohydrate metabolism [15]. Stayrook et al. showed that FXR agonists increased PEPCK, a key rate-limiting steps in gluconeogenesis, expression as well as glucose production from primary hepatocytes [15]. Since colestimide, resin acts as an antagonist ligand at the FXR [16, 17], we can hypothesize that colestimide may inhibit gluconeogenesis mediated through the decreased expression of PEPCK via FXR receptor inhibition.

Watanabe et al. recently reported that bile acids induce energy expenditure by promoting intracellular thyroid hormone activation [18]. They demonstrated that administration of bile acids, especially cholic acids, increased energy expenditure in brown adipose tissue, preventing obesity and resistance to insulin. This metabolic effect is critically dependent on induction of a cyclic-AMP-dependent thyroid hormone-activating enzyme, type 2 iodothyronine deiodinase (D2). Colestimide is reported to increase cholic acid content among bile acids [19]. One reasonable hypothesis concerning improvement of glycemic control by colestimide therefore might involve cholic acid-dependent D2 activation.

Colestimide, which has a mechanism of action differing from that of HMG-CoA inhibitors and is not absorbed in the body, is considered to be an important addition to treatment options for hypercholesterolemia. Rhabdomyolysis, severe side effect of statins, precludes their use in renal insufficiency, while colestimide is safe in such circumstances.

Results from the U.K. Prospective Diabetes Study [20–22], have demonstrated that reductions in HbA1c can lower risk of microvascular complications. Unfortunately, glycemic control in type 2 diabetic patients with hypercholesterolemia often is inadequate. In addition, many treatments intended to improve control may not be tolerated by substantial numbers of patients or have undesirable side effects such as weight gain, hypoglycemia, and edema; these can impede the attainment of glycemic control and discourage patient compliance [20–23]. For example, prolonged sulfonyleurea-induced hypoglycemia has occurred in patients with end-stage renal disease [24], and metformin is contraindicated in patients prone to lactic acidosis such as those with hepatic or renal insufficiency. New drugs suitable for use by patients with hepatic or renal insufficiency clearly are needed. As previously described, colestimide is safe in such patients. In addition, cholestyramine has been reported to decrease incidence of coronary heart disease [4, 25]. Colestimide shows potential for improving outcome in patients with both diabetes and hyperlipidemia: two major risk factors for atherosclerotic disease.

In the West of Scotland Coronary Prevention Study, pravastatin therapy reduced the risk of becoming diabetic by 30% [12]. However, pravastatin had no hypoglycemic effect on patients with type 2 diabetes. As patients with type 2 diabetes often also have hyperlipidemia, colestimide may be considered clinically useful for glycemic control in these patients through its dual actions.

In conclusion, colestimide therapy in patients with type 2 diabetes mellitus effectively reduced HbA1c as well as LDL cholesterol during a 3-month period. Long-term efficacy of colestimide therapy requires further evaluation.

Acknowledgements

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References


