The Blood Glucose Level Increased in Parallel with the Heart Rate Following Cilostazol Administration in Three Diabetic Patients

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Abstract

Cilostazol, a phosphodiesterase III inhibitor, is known to increase the heart rate; however, its effects on glucose metabolism remain unclear. We observed that the blood glucose level varied in parallel with the heart rate immediately after starting or stopping cilostazol therapy in three patients with type 2 diabetes. This finding indicates that cilostazol induces hyperglycemia and tachycardia in a portion of diabetic patients, presumably via similar pharmacological effects on different organs. Much more attention should be paid to the possible effects of cilostazol on glycemic control, including taking into consideration the risk-benefit ratio of cilostazol use and individual circumstances.

Key words: cilostazol, phosphodiesterase III inhibitor, diabetes mellitus, hyperglycemia, tachycardia

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Introduction

Cilostazol is an antiplatelet agent that functions as a potent inhibitor of platelet aggregation with vasodilatory effects. The drug is indicated for the reduction of symptoms of intermittent claudication and the secondary prevention of cerebral infarction (excluding cardiogenic cerebral embolism). Cilostazol is a reversible selective inhibitor of phosphodiesterase type III (PDE III) that induces an increase in cyclic adenosine monophosphate (cAMP) in platelets, vascular smooth muscle, endothelial cells, and other PDE III-rich cells (1). The use of cilostazol is known to cause a dose-dependent increase in heart rate (2); however, its effects on glucose metabolism remain unclear (3-8). We herein report three cases of elderly patients with type 2 diabetes in whom we observed an increase in the blood glucose level in parallel with an increase in heart rate following cilostazol administration.

Case Reports

Case 1

In December 2011, an 84-year-old woman was referred and admitted to our hospital for glycemic control. She had been treated for type 2 diabetes and hypertension since 56 years of age. She had suffered from pain in her lower back a few weeks before admission and gradually became inactive and drowsy. On admission, she was 144 cm in height and 46 kg in weight. No diabetic retinopathy was noted. The levels of HbA1c (National Glycohemoglobin Standardization Program (NGSP) equivalent value), plasma glucose, serum albumin, urea nitrogen and creatinine were 10.7%, 405 mg/dL, 3.4 g/dL, 11 mg/dL and 0.58 mg/dL, respectively. Magnetic resonance imaging revealed multiple areas of lacunar infarction in the brain as well as new and old compression fractures of the lumbar spine.

Fig. 1 presents the patient’s clinical course in the hospital, focusing on her blood glucose level and heart rate. She was
started on cilostazol therapy (50 mg twice daily) to prevent cerebral infarction on the 34th hospital day. Due to the persistent elevation of the patient’s heart rate (92 beats/min; blood pressure, 144/85 mmHg) following cilostazol administration, even at a low dose, cilostazol was discontinued and replaced with clopidogrel (75 mg) on the 62nd day. On the next day, as seen in the right panel of Fig. 1, the patient's increased heart rate rapidly returned to the baseline rate (72 beats/min; blood pressure, 155/85 mmHg). In parallel with the significant decrease in heart rate (beats/min) from 93.5 ± 4.8 (mean ± SD) (n=6) to 71.4 ± 0.6 (n=4) (p<0.0001, unpaired t-test), the blood glucose levels (mg/dL), represented as the average of pre-breakfast and pre-supper values, significantly (p<0.0001) decreased from 149.6 ± 6.6 (n=6) to 110.3 ± 5.8 and 71.4±0.6 (n=4), respectively.

**Case 2**

In July 2011, an 83-year-old man with type 2 diabetes seen in a hospital outpatient department presented with a high HbA1c level (10.3%) and was started on insulin detemir and 2 mg of glimepiride. He had been treated for hypertension since 73 years of age and diabetes since 74 years of age and had undergone total gastrectomy for gastric cancer at 76 years of age. He was 160 cm in height and 52 kg in weight. His blood pressure was 143/63 mmHg, and his heart rate was 49 beats/min. Slight pitting pretibial edema and simple diabetic retinopathy were noted. The levels of serum albumin, urea nitrogen, creatinine and plasma brain natriuretic peptide were 4.3 g/dL, 18 mg/dL, 0.83 mg/dL, and 22.0 pg/mL (normal<18.4 pg/mL), respectively. Electrocardiography and echocardiography showed sinus bradycardia with first-degree atrioventricular block and an ejection fraction of 68%.

**Figure 1.** Clinical course of the patient in Case 1 in the hospital. The upper line, “Blood Glucose,” shows the daily average of the pre-breakfast and pre-supper blood glucose levels. The lower line, “Heart Rate,” shows the daily average heart rate, which was measured three times a day regularly. In January, following the administration of cilostazol, the blood glucose level (mg/dL) increased from 139.7±16.9 (mean±SD) (n=6) to 147.3±29.0 (n=4) without a significant difference (p=0.61, unpaired t-test), while the heart rate (beats/min) significantly (p<0.0005) increased from 75.0±3.8 (n=6) to 96.7±8.1 (n=4). In February, after stopping the administration of cilostazol, the blood glucose level and heart rate significantly (p<0.0001) decreased from 149.6±6.6 and 93.5±4.8 (n=6) to 110.3±5.8 and 71.4±0.6 (n=4), respectively.
such as headache, dizziness and heart palpitations. On his twice daily due to the lack of symptoms of adverse effects, significantly (p=0.015) increased from 47.5 ± 1.9 to 58.3 ± 6.1 on each visit to the Department of Internal Medicine signifi-
cantly (p=0.015) increased from 47.5 ± 1.9 to 58.3 ± 6.1 (n=4 each) after the start of cilostazol therapy. On the other hand, the HbA1c level (%) decreased from 9.6 ± 0.6 to 9.0 ± 0.3 (n=4 each) (p=0.084) after raising the dose of insulin detemir from 13 to 17 U in the morning in January 2012. The fasting plasma glucose and serum C-peptide levels previously measured in 2005 were 104 mg/dL and 0.36 ng/mL, respectively, indicating diminished insulin secre-
tion (10).

**Case 3**

In February 2013, a 90-year-old woman was referred from a nursing home and admitted to our hospital for glycemic control. She had been treated for type 2 diabetes since 68 years of age and diagnosed with dementia at 80 years of age. In October 2012, she suffered from cerebral infarction, and enteral alimentation (400 kcal three times daily) and cilostazol administration (100 mg twice daily) were started at another hospital. After she returned to her nursing home, her HbA1c level increased from 6.6% to 8.7%, and her blood glucose level was elevated above 400 mg/dL despite the administration of 4 mg of glimepiride before admission to our hospital. On admission, the patient was approximately 150 cm in height and 50 kg in weight. Her blood pressure was 104/62 mmHg, and her heart rate was 98 beats/min. The levels of HbA1c, plasma glucose, serum albumin, urea nitrogen and creatinine were 9.3%, 388 mg/dL, 3.1 g/dL, 64 mg/dL, and 0.83 mg/dL, respectively.

Fig. 3 shows the patient’s clinical course in the hospital, focusing on her blood glucose level and heart rate. She was started on insulin therapy (rapid insulin, eight units three times daily) and continued on her previously prescribed drugs, including cilostazol (100 mg twice daily) via gastros-
tomy. The cilostazol was discontinued and replaced with clopidogrel (75 mg) in anticipation of stopping the insulin therapy. On the day of the drug substitution, the patient’s heart rate and blood glucose level began to decrease (Fig. 3A). The blood glucose levels (mg/dL) and heart rate (beats/min) significantly (p<0.005 and p<0.0005) decreased from 184.8 ± 11.9 and 95.4 ± 3.0 to 140.4 ± 21.2 and 84.4 ± 2.9, respectively (n=5 each). In this case, the continuous blood glucose level over the three days before (day 11) and after (days 12 and 13) the drug change was examined using a continuous glucose monitoring system (iPro2⡴), as shown in Fig. 3B. The mean blood glucose level (mg/dL) of the values measured every five minutes from 6 : 00 to 20 : 00 (n=169) significantly (p<0.0001) decreased from 221.4 ± 48.6 to 175.1 ± 34.4 (day 12) and 177.1 ± 33.2 (day 13).

Under conditions involving the same number of ingested calories and same doses of insulin and hypoglycemic agents, the patient’s daily blood glucose level gradually decreased. The insulin administration was stopped before the patient returned to her nursing home, which the nursing home had re-
quested. The doses of sitagliptin and glimepiride were also decreased from 100 mg and 4 mg per day to 50 mg and 2 mg per day, respectively. The urinary C-peptide level (10)
The authors state that they have no Conflict of Interest (COI).

Discussion

Compared with nonspecific PDE inhibitors, such as theophylline and caffeine, PDE isozyme subclass-specific inhibitors are expected to have a better risk-benefit ratio. The use of cilostazol, a PDE III-specific inhibitor, is associated with increases in heart rate, conductivity in the atrioventricular node, ventricular premature beats and nonsustained ventricular tachycardia (2, 11, 12). Cilostazol is contraindicated in patients with any severity of congestive heart failure, as increased mortality has been documented following the long-term use of oral milrinone, another PDE III inhibitor, despite its beneficial hemodynamic actions in these patients (13). Cilostazol has a lower cardiotonic effect than milrinone (14), and its safety and efficacy have been demonstrated in long-term clinical studies (15-17). In this study, the heart rates of three patients increased after cilostazol use. Treatment with cilostazol was continued in Case 2 in anticipation of favorable chronotropic effects in patients with sinus bradycardia (18).

As for an association between cilostazol and glucose metabolism, studies using animal models of type 2 diabetes have suggested that cilostazol improves insulin sensitivitity (4, 5), and the possibility was recently raised that impaired β-cell viability and insulin-secretory responses to glucose in patients with type 2 diabetes are ameliorated by cilostazol (6). It has been demonstrated that selective PDE III inhibitors stimulate both glycogenolysis and gluconeogenesis in hepatocytes isolated from fasted rats (7). In a clinical study of the secondary prevention of cerebral infarction (8), diabetes mellitus occurred or was exacerbated in a greater number of patients in the cilostazol group (11/520 patients) than in the placebo group (1/523 patients). Clinical studies evaluating the effects of cilostazol on glycemic control are scarce. Randomized controlled studies of cilostazol therapy in diabetic patients (19-21) demonstrated no significant changes in the HbA1c and glucose levels; however, the anti-diabetic therapy used in these studies did not necessarily remain unchanged because the studies did not aim to evaluate glycemic control.

The blood glucose levels of the three patients presented in this report varied in parallel with the heart rates soon after the patients started or stopped treatment with cilostazol. It can be inferred that such changes in the blood glucose level are compensated for or masked by common medication adjustments, as suggested in Case 2. Despite the results of a few experimental studies, cilostazol clinically appears to have the potential to elevate the blood glucose level, presumably via the overproduction of glucose in the liver beyond the insulin-secretory capacity (7, 9, 10). Regarding individual circumstances, as indicated in Case 3, the use of cilostazol may have an influence on determining whether insulin therapy can be discontinued.

The pharmacological effects of cilostazol on physiological functions, as exemplified by inhibited platelet aggregation, vasodilatation and increases in heart rate, are convincing. The three cases presented in this report suggest that cilostazol induces hyperglycemia and tachycardia in a portion of diabetic patients, through the same pharmacological effects on different organs. More attention should be paid to the possible effects of cilostazol on glycemic control, including taking into consideration the risk-benefit ratio and individual circumstances.
References


