CASE REPORT

Additive Effects of Miglitol and Anagliptin on Insulin-Treated Type 2 Diabetes Mellitus: A Case Study

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Abstract The aim of this case study was to examine the efficacy of a dipeptidyl peptidase-4 inhibitor (anagliptin) and an α-glucosidase inhibitor (miglitol) when added to ongoing insulin treatment in patients with type 2 diabetes mellitus. Continuous glucose monitoring was performed in four Japanese insulin-treated inpatients with type 2 diabetes. Baseline data were collected on day 1. Miglitol was administered on days 2 and 3. On day 4, miglitol and anagliptin were coadministered before breakfast. On days 1, 3, and 5, blood was drawn for plasma glucose, serum C-peptide, plasma glucagon, total and active glucagon-like peptide-1 (GLP-1), and total and active glucose-dependent insulinotropic peptide (GIP) measurements. Coadministration of anagliptin with miglitol resulted in additional improvements in glycemic control over the entire day in three of the four patients. The C-peptide, glucagon, and total and active GLP-1 and GIP responded differently to the medications for each patient, suggesting interindividual differences in hormonal responses, which may be complicated by multifactorial effects.

Key Points
Administration of miglitol to four patients with type 2 diabetes receiving ongoing insulin treatment showed beneficial effects on postprandial hyperglycemia.
Based on the continuous glucose monitoring results, the coadministration of anagliptin with miglitol resulted in additional improvements in glycemic control in three of the patients.
C-peptide, glucagon, and total and active glucagon-like peptide-1 and glucose-dependent insulinotropic peptide responded differently to the study medications for each patient.

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1 Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors, by inhibiting DPP-4 enzymatic activity, increase active glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) levels and improve hyperglycemia in a glucose-dependent manner by increasing serum insulin and decreasing serum glucagon levels in diabetic patients [1–6].

Alpha-glucosidase inhibitors (a-GIs), another type of oral antidiabetic drug, also attenuate postprandial blood glucose fluctuations by delaying the absorption of digested

carbohydrates from the small intestine [7–9]. Considering the different mechanisms of DPP-4 inhibitors and α-GIs, their use in combination therapy is promising for improving glycemic control [10, 11]. The present case study aimed at examining the efficacy, through the use of a continuous glucose monitoring system (CGMS) [12–14] and hormone measurements, of a DPP-4 inhibitor (anagliptin) [15], and an α-GI (miglitol) when added to ongoing insulin treatment in patients with type 2 diabetes mellitus.

2 Case Presentation and Intervention

The baseline characteristics of the four Japanese inpatients with type 2 diabetes in this study are summarized in Table 1. The study protocol was approved by the Ethics Committee of the National Center for Global Health and Medicine (NCGM), and written informed consent was obtained from each subject. The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and Guidelines for Good Pharmacoepidemiology Practice. All patients were admitted to the diabetes ward at the NCGM and equipped with a CGMS device (Medtronic MiniMed, CGMS-GOLD, Minneapolis, MN, USA). Prior to study initiation, oral medications that might affect the results of the study, such as α-GIs or glinides, were discontinued for at least 5 days. A once-daily injection of insulin glargine was continued for all patients throughout the study without changing the dosage and timing of injections (Table 1). The first blood samples, as for baseline data, were collected on day 1. Subsequently, miglitol (50 mg three times a day, just before each meal) was administered on days 2 and 3. On days 4 and 5, anagliptin (100 mg/day) was given before breakfast, in addition to miglitol. Blood samples were collected on the first, third, and fifth days of the study. Measurements of

plasma glucose, serum C-peptide, plasma glucagon, total and active GLP-1, and total and active GIP levels were conducted using blood samples that were drawn at five time points (0, 15, 30, 60, and 120 min) after breakfast following a 14-h overnight fast. Active GLP-1 concentrations were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Millipore Corp., Billerica, MA, USA) with solid-phase extraction [16]. Total GLP-1 concentrations were measured using a Total GLP-1 (ver. 2) Assay Kit with an electrochemiluminescence (ECL) method (Meso Scale Discovery, Rockville, MD, USA). Active GIP_{1-42} and inactive GIP_{3-42} were simultaneously measured using nanoflow liquid chromatography tandem mass spectrometry (LC–MS/MS) [17]. Total GIP concentration was calculated as the sum of GIP_{1-42} and GIP_{3-42} concentrations. All sample measurements, except those for total and active GIP, were performed by Mitsubishi Chemical Medience Corporation (Tokyo, Japan). Total and active GIP were measured by Sanwa Kagaku Kenkyusyo Co., Ltd (Aichi, Japan). Serum C-peptide levels were measured using a chemiluminescent immunoassay (CLIA), and plasma glucagon was measured using a double-antibody radioimmunoassay (RIA). The area under the curve (AUC) values for these hormones after meal ingestion were calculated using the trapezoidal rule.

3 Outcomes

Figure 1 shows the representative CGM results of each patient. In case 1, the glucose levels and fluctuations after miglitol administration were not remarkably attenuated but were attenuated when miglitol and anagliptin were coadministered. In case 2, the glucose levels and fluctuations were not remarkably attenuated even after the administration of miglitol alone or coadministration of miglitol and

Table 1 Patient characteristics

Characteristic	Case 1	Case 2	Case 3	Case 4
Age (years)	63	80	77	83
Sex	Male	Male	Male	Female
BMI (kg/m^2)	26.2	26.5	22.1	24.8
Diabetes duration (years)	8	15	22	8
HbA1c (%)	7.1	8.0	7.7	8.7
24-h urinary C-peptide (μg/day)	45.2	36.4	9.7	59.8
OAD use before the study	Metformin	α-GI + glinide	α-GI	None
Insulin use before the study	Ins L + Ins G	Ins G	Ins L + Ins G	Ins G
OAD use during the study	Metformin	None	None	None
Dosage and timing of insulin injection during the study	Ins G (10 units) before bedtime	Ins G (5 units) before breakfast	Ins G (5 units) before lunch	Ins G (5 units) before bedtime

BMI body mass index, *HbA1c* glycosylated hemoglobin, *OAD* oral antidiabetic drug, *α-GI* α-glucosidase inhibitor, *Ins L* insulin lispro, *Ins G* insulin glargine
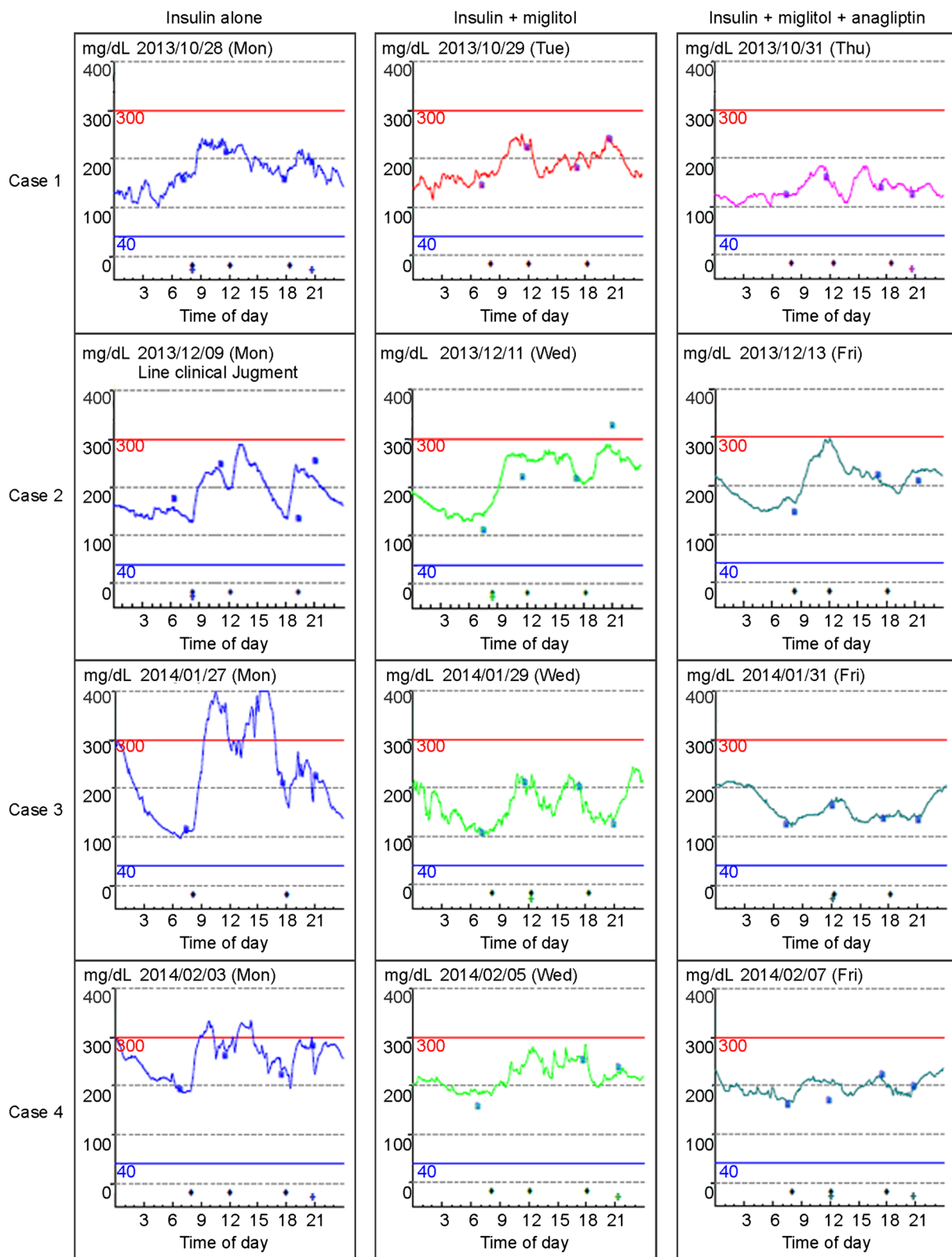
Fig. 1 Continuous glucose monitoring (CGM) results for cases 1–4 under the conditions of insulin administration, coadministration of insulin and miglitol, and coadministration of insulin, miglitol, and anagliptin

Table 2 24-h Glucose levels measured by continuous glucose monitoring (CGM)

Treatment	Glucose level (mg/dL)			
	Case 1	Case 2	Case 3	Case 4
Insulin alone	176 ± 36	189 ± 42	234 ± 91	261 ± 37
Insulin + miglitol	184 ± 30	216 ± 52	165 ± 36	220 ± 26
Insulin + miglitol + anagliptin	137 ± 20	208 ± 37	162 ± 27	198 ± 16

Values are expressed as mean ± SD

anagliptin. In cases 3 and 4, the glucose levels and fluctuations after miglitol administration were attenuated, and this attenuation was even more pronounced with the combination of miglitol and anagliptin. The accuracy of these measurements was reflected in the mean and standard deviation (SD) values of the CGM measurements (Table 2).

The time-course levels of plasma glucose, serum C-peptide, plasma glucagon, total and active GLP-1, and total and active GIP and the AUC values for these hormones for up to 120 min after meal ingestion are summarized in Supplementary Figures 2–5 and Table 3. Under the fixed dosage and timing of the insulin injection, miglitol administration attenuated the postprandial increments in plasma glucose levels in all of the patients. When anagliptin was coadministered with miglitol, further attenuation of postprandial increments in glucose was observed in case 1, but no remarkable changes in postprandial glucose levels were observed in the other patients. Miglitol administration attenuated the postprandial increments in C-peptide levels in all of the patients. When anagliptin was coadministered with miglitol, compared with the sole administration of miglitol, no remarkable changes in postprandial C-peptide levels were observed in cases 1 and 2, but slight increases were observed in cases 3 and 4 although the C-peptide levels in cases 3 and 4 were much lower than in the other patients. Miglitol administration had no observable effect on blood glucagon levels after meal ingestion in all patients except case 1. When anagliptin was administered in addition to miglitol, compared to miglitol alone, no remarkable changes in glucagon levels were observed in cases 2 and 3, but a reduction in glucagon levels was observed in cases 1 and 4.

Miglitol administration decreased active GLP-1 levels in cases 1 and 2, but not in cases 3 and 4. However, when anagliptin was administered in addition to miglitol, all of the patients showed increased active GLP-1 levels compared to when miglitol alone was added. The AUC values for active GLP-1 with the coadministration of miglitol and anagliptin tended to be larger than the AUC values for active GLP-1 when miglitol alone was added ($p = 0.07$; Wilcoxon signed-rank test). Miglitol administration showed remarkable reductions in active GIP levels in all patients. Compared to when miglitol alone was added, coadministration of miglitol and anagliptin showed higher

active GIP levels in all patients, with varying patterns. The active:total GLP-1 ratio and active:total GIP ratio in each patient are shown in Supplementary Figures 6 and 7, respectively. Miglitol administration showed lower or at least similar active:total GLP-1 ratios and active:total GIP ratios in all patients, whereas coadministration of miglitol and anagliptin showed remarkably higher active:total GLP-1 ratios and active:total GIP ratios in all patients.

4 Discussion

In the present study, administration of miglitol to four patients with type 2 diabetes receiving ongoing insulin treatment showed beneficial effects on postprandial hyperglycemia. Based on the CGM results, the coadministration of anagliptin with miglitol resulted in additional improvements in glycemic control over the entire day in three of the patients, including lower glucose levels and attenuated glucose fluctuations. In addition, administration of only miglitol or in combination with anagliptin reduced postprandial C-peptide levels in all patients we studied, which might be explained by the associated decrease in blood glucose levels. The reason underlying the lack of a further effect on glycemic control with anagliptin co-administration in case 2 is not clear. A previous study conducted in Japanese patients with type 2 diabetes indicated that treatment with a different DPP-4 inhibitor, sitagliptin, lowered glycosylated hemoglobin (HbA1c) levels, especially in those with higher baseline HbA1c levels, lower body mass indices (BMIs), and shorter durations of diabetes [18]. Therefore, the combination of a high HbA1c level, relatively high BMI, and long history of diabetes in case 2 may have affected the efficacy of anagliptin in this patient to some extent.

Regarding glucagon levels, the effect of miglitol-only administration was varied; however, when anagliptin was coadministered with miglitol, all of the patients, except case 2, showed a tendency for suppressed glucagon secretion. Theoretically, DPP-4 inhibitors, including anagliptin, increase GLP-1 levels, and GLP-1 lowers glucose levels not only by its potent insulinotropic action but also by its ability to suppress glucagon secretion [19–21]. It remains uncertain and controversial whether GLP-1 directly suppresses glucagon release by binding to GLP-1

Table 3 Area under the curve (AUC) values during the 120-min meal test

Parameter	Case 1	Case 2	Case 3	Case 4
Glucose AUC ($10^3 \times$ mg/dL·120 min)				
Insulin	22.2	31.6	23.8	33.9
Insulin + miglitol	18.9	24.4	14.7	22.2
Insulin + miglitol + anagliptin	15.3	24.0	14.6	25.8
C-peptide AUC (nmol/L·120 min)				
Insulin	132.4	109.5	35.5	67.3
Insulin + miglitol	93.6	86.1	16.9	42.5
Insulin + miglitol + anagliptin	92.1	88.6	24.6	61.3
Glucagon AUC ($10^3 \times$ ng/L·120 min)				
Insulin	17.5	17.3	12.4	11.9
Insulin + miglitol	15.4	16.8	13.0	12.3
Insulin + miglitol + anagliptin	13.7	18.4	11.8	10.8
Total GLP-1 ($10^2 \times$ pmol/L·120 min)				
Insulin	26.8	29.9	7.3	14.4
Insulin + miglitol	21.4	19.8	11.6	16.9
Insulin + miglitol + anagliptin	22.1	29.3	9.9	17.0
Active GLP-1 ($10^2 \times$ pmol/L·120 min)				
Insulin	5.1	3.5	1.4	3.2
Insulin + miglitol	3.1	1.9	1.4	3.6
Insulin + miglitol + anagliptin	8.7	10.7	2.5	6.8
Total GIP ($10^2 \times$ pmoL/L·120 min)				
Insulin	278.6	318.2	131.7	73.0
Insulin + miglitol	92.0	120.5	58.6	61.6
Insulin + miglitol + anagliptin	150.7	73.6	28.6	37.7
Active GIP ($10^2 \times$ pmol/L·120 min)				
Insulin	109.6	60.0	31.9	31.0
Insulin + miglitol	19.2	24.2	8.4	8.1
Insulin + miglitol + anagliptin	97.5	44.0	9.8	18.1

GLP-1 glucagon-like peptide-1, *GIP* glucose-dependent insulinotropic polypeptide

receptors expressed on the alpha cell [19, 22]. Indirectly, other intraislet paracrine factors, including insulin [23, 24], somatostatin [19, 25, 26], γ-aminobutyric acid (GABA) [27], and zinc ions (Zn) [28], are considered to modulate glucagon secretion. In addition, a recent report suggested that increased portal GLP-1 levels activate brain-derived neurotrophic factor (BDNF) and BDNF modulates glucagon secretion from pancreatic α cells via the central and peripheral nervous systems [29].

In patients with diabetes, miglitol is also reported to induce enhanced and prolonged GLP-1 release after meal ingestion [30–37]. A possible mechanism may be increased exposure of nutrients to the distal small intestine, where L-cells are located [32, 34–36]. To confirm these results, we previously studied postprandial active GLP-1 levels in patients with type 2 diabetes treated with or without insulin and found that miglitol administration increased active GLP-1 levels in some, but not all, patients [10, 11]. The effect of miglitol administration in the present study resulted in varying total or active GLP-1 levels in each patient, but no typical pattern was observed. As we

expected, coadministration of miglitol and anagliptin showed increased postprandial active GLP-1 levels in all patients of various magnitudes, reflecting the pharmacologic effect of anagliptin as a DPP-4 inhibitor. Despite increased active GLP-1 levels, an increase in total GLP-1 levels was not observed in all patients.

Miglitol administration is reported to decrease GIP levels, possibly via inhibited glucose absorption in the proximal small intestine [34]. Our results are consistent with this theory. Compared to miglitol administration alone, the coadministration of miglitol and anagliptin showed increased active GIP levels in all of our patients, reflecting the pharmacologic effect of anagliptin as a DPP-4 inhibitor; however, there was a decrease in total GIP levels in all patients, except case 1. As previously suggested, this phenomenon may be explained by a feedback inhibitory mechanism; the elevated concentrations of endogenous biologic active (intact) forms of the incretins may themselves restrict further secretion from the K- and L-cells [5, 37].

In cases 1 and 2, both total and active GIP levels were higher than in the other patients, even before anagliptin administration. The BMIs of these patients were also higher than the other patients. It is well known that GIP promotes the efficient storage of ingested fat and directly links overnutrition to obesity [38–40]. Furthermore, recent research suggests that GIP receptor antagonists may offer a new therapeutic option for obesity in diabetes [41]. As we only examined four patients, our results do not necessarily generalize to the majority of the patients with type 2 diabetes. Therefore, further studies with larger samples are needed.

5 Conclusion

Through the use of CGMS, we determined that a combination of α-GI, miglitol, and a DPP-4 inhibitor, anagliptin, was effective in reducing glucose fluctuations and stabilizing postprandial blood glucose levels in three of the four patients. Furthermore, C-peptide, glucagon, and total and active GLP-1 and GIP responded differently to the study medications for each patient, suggesting that hormonal responses to these drugs differ among individuals and may be complicated by multifactorial effects. Another larger study is needed to confirm the associations observed in our patients.

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