【 CASE REPORT 】

The Effects of Mitiglinide and Repaglinide on Postprandial Hyperglycemia in Patients Undergoing Methylprednisolone Pulse Therapy

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Abstract:
One adverse effect of methylprednisolone (MP) pulse therapy is an acute dose-dependent increase in the blood glucose level. Five patients with thyroid ophthalmopathy but normal glucose tolerance received MP pulse therapy (3 cycles, 3 days/week) and were assessed by continuous glucose monitoring. Steroid therapy increased the mean sensor glucose level, and all patients developed steroid-induced diabetes. The patients were treated alternately with mitiglinide (30 mg/day) and repaglinide (1.5 mg/day) during the second or third MP pulse therapy. The sensor glucose levels before lunch and dinner were more favorable during treatment with repaglinide than during treatment with mitiglinide. Repaglinide may be more clinically appropriate than mitiglinide.

Key words: steroid-induced diabetes, methylprednisolone pulse therapy, rapid-acting insulin secretagogue, mitiglinide, repaglinide, continuous glucose monitoring

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Introduction

Methylprednisolone (MP) pulse therapy is applied in various diseases, such as active thyroid ophthalmopathy. However, such therapy may have various adverse effects, such as hyperglycemia, acute liver injury, cardiovascular disorders, and cerebrovascular disorders (1). In this regard, acute hyperglycemia is known to increase oxidative stress and endothelial dysfunction through the activation of NADPH oxidase (2); thus, treatment for this condition is necessary. In general, the blood glucose levels begin to increase from 2-3 hours after the administration of steroids, and reach a peak at 5-8 hours after the administration of steroids. Because this hyperglycemic effect of steroid therapy is dose-dependent (3, 4), MP pulse therapy can cause a variable increase in the blood glucose level. However, there is little or no information on the acute and long-term effects of MP pulse therapy on the blood glucose level determined by continuous glucose monitoring (CGM), and thus the variations in the blood glucose levels during MP pulse therapy remain unclear.

Steroid-induced diabetes with casual blood glucose levels of >300 mg/dL are treated with insulin preparations (5). The rapid-acting insulin secretagogue nateglinide has been reported to be effective in patients with lower blood glucose levels (6). However, no studies have closely evaluated the usefulness of other rapid-acting insulin secretagogues - such as mitiglinide and repaglinide - in the treatment of steroid-induced diabetes in patients who were monitored by CGM.

Five patients with thyroid ophthalmopathy and a normal glucose tolerance received MP pulse therapy (3 cycles of 3 days/week) and were retrospectively assessed by CGM. MP pulse therapy increased the mean sensor glucose level and all patients developed steroid-induced diabetes. They were treated alternately with mitiglinide (30 mg/day) and repaglinide (1.5 mg/day) at either the 2nd or 3rd MP pulse treatment. We herein report the effects of mitiglinide and repaglinide on postprandial hyperglycemia in patients undergoing MP pulse therapy.

The study was approved by the Ethics Committee of the University of Occupational and Environmental Health, Japan.

Case Report

Five patients with thyroid ophthalmopathy were admitted to the Hospital of the University of Occupational and Environmental Health, Japan to undergo MP pulse therapy between April 2012 and September 2016. They were originally confirmed to have a normal glucose tolerance through an annual health check-up. The indications for MP pulse therapy for active thyroid ophthalmopathy included a clinical activity score (CAS) of ≥3, CAS 1-2 with the enlargement of the extraocular muscles and high intensity signals on T2-weighted MRI. The diagnostic criterion of steroid-induced diabetes was a non-fasting maximum sensor glucose level of ≥200 mg/dL, as measured by continuous glucose monitoring before the initial course of MP pulse therapy.

The MP pulse therapy protocol was as follows: a weekly cycle of drip infusion of MP (500 mg) starting at 9:00 AM over 1 hour for three consecutive days, repeated for a total of three cycles. In this study, we selected thyroid ophthalmopathy simply because there is a standardized protocol at our hospital for the treatment of such patients, which includes three courses of MP pulse therapy.

A continuous glucose monitoring system (CGMS® System Gold™ or iPro2, Medtronic, MiniMed, Northridge, USA) was used before the application of the first cycle and during each cycle of MP pulse therapy. The following parameters were computed from the CGM recording: 1) the mean sensor glucose level; 2) the standard deviation (SD) of the sensor glucose levels; 3) the mean amplitude of glycemic excursions (MAGE); 4) the maximum sensor glucose level and the maximum sensor glucose level after each meal; 5) the minimum sensor glucose level; 6) the pre-meal sensor glucose level (30 minutes before each meal); 7) the area under the curve (AUC) for the sensor glucose level ≥180 mg/dL (AUC ≥180); and 8) the area over the curve (AOC) for the sensor glucose level <70 mg/dL (AOC <70). In this report, the CGM data obtained on day 3 of MP pulse therapy in each week were used for the evaluation. Although the interstitial glucose level determined by the CGM is different from the true blood glucose level, the two values have been reported to show a good correlation in the literature (7). Thus, the sensor glucose levels will be referred to as blood glucose levels hereafter in this report.

All of the patients received optimal meals (25-30 kcal/kg of ideal body weight; 60% carbohydrate, 15% protein and 20% fat), which were kept constant during hospitalization. However, none of the patients performed exercise therapy during MP pulse therapy.

The data were expressed as the mean±SD. The Mann-Whitney U test was used to compare the effects of mitiglinide and repaglinide. Moreover, the Wilcoxon signed-rank test was used to compare the values of various parameters that were measured on the first MP pulse and during the use of each drug. The p values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the Statistical Package for Social Sciences software program (version 21.0; SPSS, Chicago, USA).

The baseline characteristics of the five patients are shown in Table 1. The mean age was 61.4±14.0 years, and the mean body mass index was 21.8±2.2 kg/m^2. Regarding the glucose metabolism, the HbA1c level was 5.5±0.3%, and the FPG level was 89.4±7.8 mg/dL. For the three patients with HbA1c values of ≥5.5%, the 75-g oral glucose tolerance test results confirmed they had normal glucose tolerance. The HOMA-IR index was <2 in all patients. The CGM parameters that were recorded at baseline (before MP pulse therapy) are shown in Figure a and Table 2. The mean sensor glucose level was 98.8±6.3 mg/dL and the MAGE was 63.2±19.1 mg/dL, indicating favorable sensor glucose profiles.

On Day 1 of the first cycle of MP pulse therapy, the sensor glucose levels increased from noon until evening and exceeded 200 mg/dL after dinner in all patients. Their sensor glucose levels gradually decreased from midnight until morning. Similarly, the sensor glucose levels on Days 2 and 3 increased to ≥200 mg/during the period from noon until evening. These patterns allowed for the diagnosis of steroid-induced diabetes. The CGM results on Day 3 of the first cycle of MP pulse therapy are shown in Figure a and Table 2. The mean sensor glucose and MAGE levels were significantly higher at 155.2±11.0 mg/dL and 103.1±20.9 mg/dL, respectively, in comparison to the respective baseline values. In particular, the preprandial sensor glucose levels and the peak postprandial sensor glucose levels at lunch and dinner were significantly higher in comparison to the respective baseline values. Moreover, the sensor glucose level peaked after dinner and then gradually decreased until the following morning. No significant changes (in comparison to baseline) were observed in the sensor glucose levels before breakfast after MP pulse therapy.

The CGM data at the time of glinide administration in the second and third cycles of MP pulse therapy are shown in Figure b and Table 3. Two patients received mitiglinide in the second cycle of MP pulse therapy and repaglinide in the third cycle, while the other three patients received these drugs in the opposite order. There were no differences between the two drugs with regard to the mean sensor glucose level, SD, MAGE, maximum sensor glucose level, or minimum sensor glucose level. However, the sensor glucose levels were significantly lower before lunch and dinner during the use of repaglinide.

Although the CGM data showed episodes of hypoglycemia in three patients during the use of mitiglinide, the fall in the sensor glucose level was asymptomatic in all three. None of the patients developed hypoglycemia during treatment with repaglinide. No other adverse events were observed.

Table 1. Clinical Characteristics of the Five Patients Recorded at Baseline.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	55	55	45	74	78
Body mass index (kg/m²)	19.5	25.1	22.6	22.0	20.0
Clinical activity score (point)	3	1	2	4	1
Thiamazole (mg/day)	0	5	0	5	5
Thyroid stimulating hormone (μIU/mL)	0.21	3.39	0.34	0.22	1.83
FT3 (pg/mL)	2.36	2.65	3.42	3.26	3.01
FT4 (ng/mL)	1.1	0.97	1.42	1.24	0.99
TSAb (%)	496	290	209	721	120
TRAb (U/mL)	5.6	2.6	3.6	13.1	3.6
HbA1c (%)	5.1	5.4	5.9	5.7	5.6
Fasting plasma glucose (mg/dL)	91	98	88	93	77
75g OGTT					
30 min PG (mg/dL)	-	-	199	165	129
60 min PG (mg/dL)	-	-	154	157	148
120 min PG (mg/dL)	-	-	120	132	94
Fasting plasma insulin (μU/mL)	4.4	7.9	5.5	8.1	2.6
HOMA-IR	1.0	1.9	1.2	1.9	0.5
HOMA-β (%)	57	79	79	97	67
eGFR (mL/min/1.73 m²)	85.6	68.1	85.4	77.1	75.9

FT3: free triiodothyronine, FT4: free thyroxine, TSAb: thyroid stimulating antibody, TRAb: anti-TSH receptor antibody, HbA1c: glycated hemoglobin, HOMA-IR: homeostasis model assessment of insulin resistance, HOMA-β: homeostasis model assessment of β cell function, eGFR: estimated glomerular filtration rate

Discussion

Although MP pulse therapy is an effective treatment for thyroid ophthalmopathy, hyperglycemia is a common adverse effect that is associated with this form of steroid therapy. While the exact mechanism underlying the development of hyperglycemia is not clear, the following mechanisms have been suggested: increased hepatic gluconeogenesis, the reduced uptake of glucose by skeletal muscles, the low secretion of insulin from pancreatic β cells, and the enhanced secretion of glucagon from pancreatic α cells (8, 9). The hyperglycemic effect of steroids is dose-dependent (3, 4) and since MP pulse therapy generally involves a relatively high dose, i.e., 500 to 1,000 mg/day, it is highly likely to induce hyperglycemia. There is general agreement that the blood glucose levels should be monitored during MP pulse therapy in patients with diabetes because this therapy often increases the fasting blood glucose levels. On the other hand, Feldman-Billard et al. stated that blood glucose monitoring is not necessary in patients without diabetes because their blood glucose levels decrease from midnight to morning (10). However, another report warned that blood glucose monitoring is necessary because the fasting blood glucose levels increased in 98% of patients (11). Surprisingly, no previous studies have addressed the detailed effects of MP pulse therapy on blood glucose, e.g., the extent to which the blood glucose levels are affected and the time of day that they are affected - which may explain the controversy.

In this study, the CGM-recorded sensor glucose profiles of five patients during MP pulse therapy showed that not only the mean sensor glucose level but also the SD of the sensor glucose levels and the MAGE were significantly higher in comparison to before MP pulse therapy. It appears that this is due to the preprandial sensor glucose levels and the postprandial maximum sensor levels showing no significant changes at breakfast while being significantly higher at both lunch and dinner. The maximum sensor glucose level after dinner was extremely high (240-293 mg/dL) in all five patients, despite the fact that they did not have diabetes. Thereafter, the sensor glucose levels decreased, and there was a gradual fall in the sensor glucose level from midnight to before breakfast, a period in which the effects of MP pulse therapy seem to be attenuated. This finding suggests that the hyperglycemic effect of MP pulse therapy developed 2 to 3 hours after the administration of MP pulse therapy and that it was then sustained for approximately 12 hours.

Spikes in the blood glucose levels are known to lead to increased oxidative stress and endothelial dysfunction via the activation of NADPH oxidase (2). Thus, additional treatment is necessary to regulate these steep increases in the blood glucose levels after meals in patients undergoing MP pulse therapy. In general, steroid-induced diabetes is treated with rapid-acting insulin preparations when the casual blood glucose level exceeds 300 mg/dL. Any increase in the fasting blood glucose level should be corrected with the concomitant use of a sustained release insulin preparation (5). However, it has been reported that nateglinide, a rapid-acting insulin secretagogue, is effective in cases involving mild increases in the blood glucose level (6). Rapid-acting
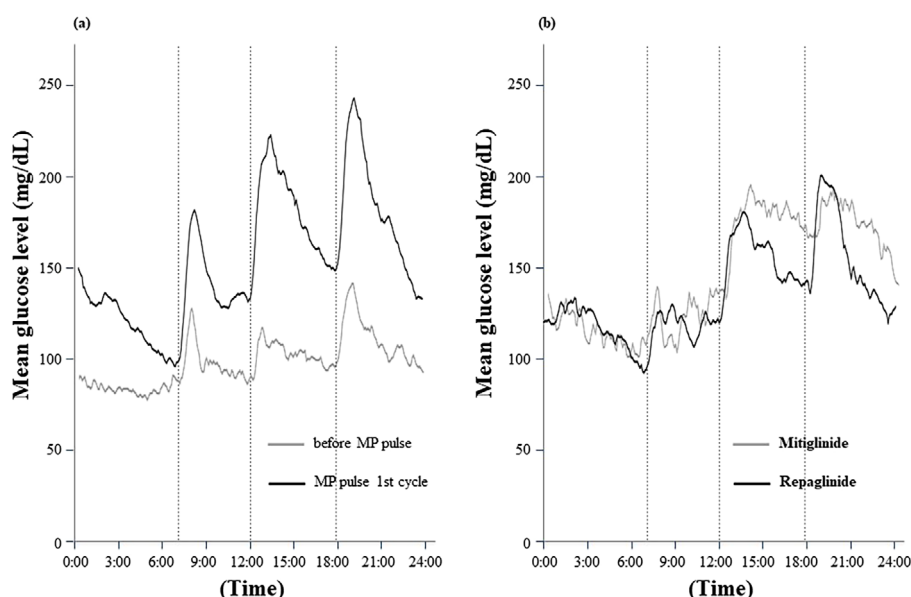
Figure. The mean sensor glucose level measured by continuous glucose monitoring in five patients. The data in both (a) and (b) were recorded on day 3 of MP pulse therapy.

Table 2. Effects of Methylprednisolone Pulse Therapy on Various Parameters Recorded by the Continuous Glucose Monitoring System.

	Baseline	MP pulse first cycle	p value
Mean sensor glucose level (mg/dL)	98.8±6.3	155.2±11.0	0.043
SD (mg/dL)	19.2±5.2	38.5±3.8	0.043
MAGE (mg/dL)	63.2±19.1	103.1±20.9	0.043
Minimum sensor glucose level (mg/dL)	64.8±6.8	93.6±14.0	0.043
Maximum sensor glucose level (mg/dL)	156.6±21.3	255.6±21.3	0.042
Pre-meal sensor glucose level			
Breakfast (mg/dL)	88.8±21.9	97.4±13.6	0.498
Lunch (mg/dL)	88.2±10.5	134.2±10.0	0.043
Dinner (mg/dL)	95.8±10.5	150.0±24.9	0.043
Postprandial peak sensor glucose level			
Breakfast (mg/dL)	135.8±25.7	188.0±24.6	0.068
Lunch (mg/dL)	129.8±13.8	230.8±5.5	0.043
Dinner (mg/dL)	151.6±19.0	255.6±21.3	0.043
AUC ≥180 (mg/dL/day)	0±0	7.8±4.1	0.043
AOC <70 (mg/dL/day)	0±0	0±0	1.000

Data are mean±standard deviation.

p value for baseline vs MP first cycle on day-3, by Wilcoxon signed rank test.

MP: methylprednisolone, SD: standard deviation, MAGE: mean amplitude of glycemic excursions, AUC ≥180: area under the curve for sensor glucose levels ≥180 mg/dL, AOC <70: area over the curve for sensor glucose levels <70 mg/dL

insulin secretagogues stimulate the secretion of insulin by binding to sulfonylurea receptor 1 (SUR1). These agents are characterized by the rapid onset of their hypoglycemia effect (i.e., within 30 min of administration) and the short duration of action (12-15). It has been suggested that MP pulse therapy may interfere with the insulin release mechanisms following an increase in the intracellular Ca^{2+} concentration, resulting in the inhibited secretion of insulin (9). Thus, it is possible that rapid-acting insulin secretagogues, which cause a rapid increase in the blood insulin concentration, are effective in regulating the steep increases in the blood glucose level that are observed during MP pulse therapy. The analysis of the different rapid-acting insulin secretagogues that are used in patients with type 2 diabetes indicates that repaglinide significantly improves the HbAlc and the fasting blood glucose level in comparison to nateglinide (16), while mitiglinide and nateglinide have been shown to have similar HbAlc-improving effects (17). With regard to the differences between repaglinide and mitiglinide, repaglinide is reported to show a slightly longer duration of action (18); however,

Table 3. Comparison of the Effects of Mitiglinide and Repaglinide on Various Parameters Recorded by the Continuous Glucose Monitoring System.

	Mitiglinide	Repaglinide	p
Mean sensor glucose level (mg/dL)	147.2±15.5	137.1±11.8	0.080
SD (mg/dL)	36.0±9.5	29.8±8.2	0.138
MAGE (mg/dL)	80.0±8.7	87.1±22.4	0.345
Minimum sensor glucose level (mg/dL)	94.4±25.1	88.6±3.4	0.176
Maximum sensor glucose level (mg/dL)	224.0±29.4	217.2±37.9	0.686
Pre-meal sensor glucose level			
Breakfast (mg/dL)	108.2±8.2	94.0±3.2	0.068
Lunch (mg/dL)	138.2±14.6	121.6±18.2	0.043
Dinner (mg/dL)	166.6±23.9	142.8±23.0	0.043
Postprandial peak sensor glucose level			
Breakfast (mg/dL)	154.8±19.2	148.0±28.4	0.345
Lunch (mg/dL)	222.2±32.8	193.4±6.6	0.078
Dinner (mg/dL)	207.4±26.5	209.2±45.4	0.686
AUC ≥180 (mg/dL/day)	5.4±5.0	2.1±2.8	0.080
AOC <70 (mg/dL/day)	0.0±0.1	0.0±0.0	0.317

Data are mean ± standard deviation.

p value for mitiglinide on day-3 vs repaglinide on day-3, by Wilcoxon signed rank test.

MP: methylprednisolone, SD: standard deviation, MAGE: mean amplitude of glycemic excursions, AUC ≥180: area under the curve for sensor glucose levels ≥180 mg/dL, AOC <70: area over the curve for sensor glucose levels <70 mg/dL

there no studies have directly compared the HbAlc, fasting blood glucose, and postprandial blood glucose levels.

In this study, CGM allowed for the confirmation of the different effects of mitiglinide and repaglinide on MP pulse therapy-associated hyperglycemia. The sensor glucose levels before lunch and dinner were lower during the use of repaglinide than they were during the use of mitiglinide. Repaglinide has a slightly longer duration of action than mitiglinide (18), and this may explain how repaglinide achieved the longer inhibition of the steroid-induced increase in blood glucose that was observed before lunch and dinner. The mean sensor glucose level and the AUC value (≥180) also tended to be lower during treatment with repaglinide than with mitiglinide (p=0.080). Because there was no difference between these two drugs with regard to the maximum sensor glucose level, it is possible that the difference in their effects is due - at least in part - to differences in the duration of action.

In this study of five patients without diabetes who underwent MP pulse therapy, the CGM recorded data showed a marked increase in the preprandial and postprandial sensor glucose levels, especially during the evening. Based on this finding, we recommend evaluation of the blood glucose level in patients before and during MP pulse therapy - in both patients with and without diabetes using the CGM for this purpose. Steroid-induced diabetes cannot be diagnosed based solely on the blood glucose level measured before breakfast. Thus, when CGM is not feasible, it is important not to overlook hyperglycemia by ensuring that blood glucose levels are measured after dinner, the time when blood glucose levels are at their highest. In our patients,

repaglinide significantly improved the pre-meal glucose level, especially before lunch and dinner, suggesting that treatment with repaglinide is clinically feasible in steroid-induced diabetes.

The present study is associated with certain limitations. First, the sample size was relatively small, and thus the results obtained need to be confirmed in a larger study population. Second, since the present study was conducted to investigate patients with steroid-induced diabetes, the extrapolation of the results to patients with type 2 diabetes mellitus should be avoided until similar studies are conducted in such patients.

All of the procedures followed in this study were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions.

The authors state that they have no Conflict of Interest (COI).

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