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【 CASE REPORT 】

Hypoglycemia during the Concomitant Use of Repaglinide and Clopidogrel in an Elderly Patient with Type 2 Diabetes and Severe Renal Insufficiency

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Abstract:
Hypoglycemia should be avoided when treating patients with diabetes. Repaglinide is an insulin secretagogue with a low hypoglycemic risk because of its rapid- and short-acting effects. However, its blood concentration has been reported to increase in combination with clopidogrel, an antiplatelet drug, and in patients with severe renal insufficiency. We herein report an elderly patient with type 2 diabetes mellitus and severe renal insufficiency who received repaglinide and hypoglycemia three days after starting clopidogrel. The concomitant use of repaglinide and clopidogrel can lead to hypoglycemia, especially in patients with severe renal insufficiency.

Key words: hypoglycemia, repaglinide, clopidogrel, cytochrome P450 2C8, diabetes, renal insufficiency

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Introduction

The main goal of diabetes treatment is to ensure these patients have the same quality of life and longevity as healthy people by reducing the risk of micro- and macrovascular complications, such as diabetic nephropathy and cardiovascular disease (CVD). To achieve this goal, the comprehensive control of blood glucose without hypoglycemia as well as that of blood pressure, lipid, and body weight are crucial (1).

In Japan, as of June 2020, seven types of oral hypoglycemic agents (OHA) have been approved for the treatment of type 2 diabetes mellitus (T2DM). Repaglinide, as well as nateglinide and mitiglinide, belongs to the class of medications known as meglitinides, which act on sulfonylurea receptors on pancreatic β-cells to promote postprandial insulin secretion, thus mainly reducing postprandial glucose levels (2). Patients taking repaglinide are at risk of hypoglycemia, similar to that conferred by insulin and sulfonylureas. However, based on its rapid- and short-acting effects, repaglinide has a lower hypoglycemic risk than insulin or sulfonylureas (3). In addition, repaglinide is almost completely metabolized in the liver, and its metabolites are excreted primarily through the bile. Only a very small fraction (less than 8%) of the administered dose is excreted through the urine (4). Therefore, patients taking repaglinide are considered to have a low risk of hypoglycemia even when they have mild or moderate renal insufficiency (5).

Clopidogrel is a second-generation thienopyridine antiplatelet drug that is the mainstay of the treatment and secondary prevention of CVD in patients with T2DM. Recently, the concomitant use of repaglinide and clopidogrel has been shown to result in the elevation of blood concentration of repaglinide (6). In addition, few reports have shown that the concomitant use of repaglinide and clopidogrel causes hypoglycemia in patients with T2DM (7, 8). However, there are no reports on the clinical course of hypoglycemia due to the interaction of these drugs in patients with T2DM and severe renal insufficiency.

We herein report a patient with T2DM with severe renal insufficiency and describe the patient's clinical course, which included hypoglycemia owing to concomitant use of repaglinide and clopidogrel.

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Case Report

Informed consent was obtained from the patient, and all procedures were approved by the appropriate institutional review board (the Ethics Committee of Osaka Police Hospital) and comply with the Declaration of Helsinki and its amendments.

We encountered an 81-year-old Japanese woman with T2DM and severe renal insufficiency who was receiving repaglinide and who developed hypoglycemia 3 days after starting clopidogrel. At 50 years old, she was diagnosed with T2DM and treated with OHAs. She subsequently had hypertension, dyslipidemia, atrial fibrillation, CVD, peripheral artery disease (PAD), and adrenal insufficiency owing to approximately five years of glucocorticoid treatment for autoimmune hepatitis, and her renal function gradually deteriorated. At 81 years old, she was admitted to our hospital for the treatment of acute coronary artery dissection. On admission, she was prescribed the following medications for T 2DM, dyslipidemia, hyperuricemia, hypertension, CVD, PAD, atrial fibrillation, gastroesophageal reflux disease, and secondary adrenal insufficiency: teneligliptin 40 mg, repaglinide 1.5 mg, pravastatin 10 mg, febuxostat 20 mg, carvedilol 1.25 mg, azelnidipine 16 mg, verapamil 80 mg, cilostazol 200 mg, aspirin 100 mg, adoxaban 10 mg, propafenone 300 mg, vonoprazan 20 mg and hydrocortisone 10 mg per day, respectively.

She underwent emergent percutaneous coronary intervention for the dissection site of the left main coronary artery, and aspirin was changed to clopidogrel, while cilostazol was continued. At that time, her diabetes was treated with a 1,440-kcal diabetic diet and two OHAs (teneligliptin 20 mg ×2/day, and repaglinide 0.5 mg×3/day). She did not develop hypoglycemia with these agents. However, her fasting plasma glucose level before breakfast gradually decreased, and hypoglycemia (63 mg/dL) developed 3 days after starting clopidogrel. Her cardiologist then reduced the 40 mg dose of teneligliptin to 20 mg, but her hypoglycemia (50-64 mg/dL) did not disappear. Nine days after starting clopidogrel, she was referred to our department for a detailed examination and treatment of her recurrent hypoglycemia (Figure).

On referral, the patient had no obvious hypoglycemic symptoms despite her pre-breakfast plasma glucose level of 50 mg/dL. Her body weight was 44.1 kg (body mass index: 16.0 kg/m^2), blood pressure 101/60 mmHg, pulse rate 103 bpm, and body temperature 36.8°C. She had no abnormal physical signs. We suspected that her hypoglycemia was caused by the concomitant use of repaglinide and clopidogrel based on her clinical course and therefore discontinued repaglinide from before lunch on the referral day.

Her laboratory examination results the day after referral to our department are shown in Table 1. Her fasting plasma glucose level was 85 mg/dL, indicating no hypoglycemia, probably because repaglinide had been discontinued; her fasting C-peptide was 2.71 ng/mL, and her immunoreactive insulin level was 3.7 μU/mL. In addition, an insulin autoantibody test was negative. Her renal function was impaired, with a plasma urea nitrogen of 25.5 mg/dL, creatinine of 1.3 mg/dL, and estimated glomerular filtration ratio of 30.5 mL/min/1.73 m^2. Endocrinological examinations revealed that the baseline levels of adrenocorticotropic hormone and cortisol were within the normal ranges, and the patient had a postmenopausal status.

After discontinuing repaglinide, her fasting plasma glucose level increased. We evaluated fasting C-peptide levels using her preserved serum 2 days before stopping repaglinide, when hypoglycemia occurred repeatedly. We found that her fasting serum C-peptide level was high (4.73 ng/mL), glucose level was low (64 mg/dL), and C-peptide index (CPI; fasting plasma C-peptide ×100/fasting plasma glucose) was high at 7.4. However, her CPI decreased to 2.3 at 5 days after stopping repaglinide (15 days after admission) (Table 2). Based on these results and her clinical course, we diagnosed her with hypoglycemia due to the concomitant use of repaglinide and clopidogrel. Although we prescribed mitiglinide 10 mg×3/day 8 days after discontinuing repaglinide while continuing clopidogrel, her fasting plasma glucose levels were around 150 mg/dL without hypoglycemia at discharge. Thereafter, her diabetes was treated with teneligliptin 20 mg×2/day and mitiglinide 10 mg×3/day while continuing clopidogrel, and hypoglycemia was not detected 4 months after discharge.

Discussion

We encountered a patient with T2DM and severe renal insufficiency who received repaglinide and developed hypoglycemia three days after starting clopidogrel. To our knowledge, this is the first report to describe the clinical course leading to hypoglycemia due to the concomitant use of repaglinide and clopidogrel in a patient with T2DM and severe renal insufficiency.

Severe hypoglycemia has been shown to be associated with macro- and microvascular events, dementia, fracture, and mortality in patients with diabetes (9, 10). In addition, observational studies have suggested that hypoglycemia is associated with an increased risk of death in patients with diabetes hospitalized for acute coronary syndrome (11, 12). Furthermore, elderly patients with diabetes are more susceptible to hypoglycemic adverse events than younger ones owing to their unspecific and uncharacteristic hypoglycemic symptoms, probably caused by less effective counterregulatory mechanisms, reduced drug elimination caused by renal insufficiency, and motor and cognitive impairment (13). Fortunately, our patient did not experience any hypoglycemic adverse events. However, if she had not been under hospital observation, she might have experienced hypoglycemic adverse events because she did not present with typical hypoglycemic symptoms, and this may have delayed the detection of hypoglycemia. Therefore, various treatment guide-

Table 1. Laboratory Findings on Referral to Our Department.

Hematology		ALP	128 U/L
WBC	8,400 /μL	γ-GTP	20 U/L
RBC	284×10,000 /μL	CRP	3.62 mg/dL
Hb	8.7 g/dL	Glucose	85 mg/dL
Ht	25.3 %	HbA1c	6.4 %
Plt	24.9×10,000 /μL	IRI	3.7 μU/mL
		C-peptide	2.71 ng/mL
Biochemistry		Insulin antibody	<0.4 %
TP	6.1 g/dL		
Alb	2.8 g/dL	Endocrine examination	
BUN	25.5 mg/dL	ACTH	15.7 pg/mL
Cr	1.3 mg/dL	Cortisol	10.3 μg/dL
eGFR	30.5 mL/min/1.73 m^2	TSH	2.43 μU/mL
Na	133 mEq/L	Free T4	1.09 ng/mL
K	3.9 mEq/L	GH	0.76 ng/mL
Cl	101 mEq/L	IGF-1	76 ng/mL
Ca	9.1 mg/dL	LH	16.61 mIU/mL
P	2.7 mg/dL	FSH	48.7 mIU/mL
TB	0.5 mg/dL	Estoradiol	22 pg/mL
AST	16 U/L	Prolactin	16.52 ng/mL
ALT	10 U/L		

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, HT: hematocrit, Plt: platelet, TP: total protein, Alb: albumin, BUN: urea nitrogen, Cr: creatinine, eGFR: estimated glomerular filtration ratio, Na: sodium, K: potassium, Cl: chloride, Ca: calcium, P: phosphate, TB: total bilirubin, AST: aspartate aminotransaminase, ALT: alanine aminotransaminase, ALP: alkaline phosphatase, γ-GTP: gamma glutamyl transpeptidase, CRP: C-reactive protein, HbA1c: glycated hemoglobin A1c, IRI: immunoreactive insulin, ACTH: adrenocorticotropic hormone, TSH: thyroid stimulating hormone, Free T4: free thyroxine, GH: growth hormone, IGF-1: insulin-like growth factor-1, LH: luteinizing hormone, FSH: follicle stimulating hormone

Table 2. Changes in CPI with and without Repaglinide and Clopidogrel.

	repaglinide	clopidogrel	FPG (mg/dL)	CPR (ng/mL)	CPI	eGFR (mL/min/1.73 m^2)
Day 8	+	+	64	4.73	7.4	34.2
Day 10	-	+	85	2.71	3.2	30.5
Day 15	-	+	135	3.04	2.3	35.9

Day: Days after admission, FPG: fasting plasma glucose, CPI: C-peptide index (fasting plasma C-peptide×100/fasting plasma glucose), eGFR: estimated glomerular filtration ratio

lines for diabetes generally recommend not only avoiding hypoglycemia but also enacting less stringent glycemic control in elderly patients (14, 15). The Japan Diabetes Society recommends setting a lower limit for the target HbA1c value in elderly patients receiving insulin, sulfonylureas, or meglitinide, who are at risk of hypoglycemia (1). According to this recommendation, the target HbA1c value in our patient was 7.0-8.0%. Considering that the patient had mild anemia, probably because of severe renal insufficiency, and her actual HbA1c value was assumed to be slightly higher than the measured value (6.4%), we believe that our patient's condition was adequately controlled.

It has recently been reported that the concomitant use of repaglinide and clopidogrel causes hypoglycemia in patients with T2DM (7, 8). Wei et al. reported that the concomitant use of repaglinide and clopidogrel was associated with an increased risk of hypoglycemia compared with repaglinide alone in a population-based study using real-world data in Taiwan (adjusted odds ratio: 2.42; 95% confidence interval: 1.75, 3.35). In addition, no significant associations of hypoglycemia were found with the concomitant use of repaglinide with aspirin or with that of nateglinide and clopidogrel (7). Akagi et al. also reported a risk of hypoglycemia associated with the combined use of repaglinide and clopidogrel in a retrospective cohort study using hospitalized patients who started repaglinide and whose preprandial plasma glucose level was measured. In that study, hypoglycemia was observed in 6 of 15 patients in the repaglinide and clopidogrel group, while it was observed only in 1 of 15 patients in the mitiglinide and clopidogrel group; no patients in the repaglinide alone group developed hypoglycemia. All patients who developed hypoglycemia had a plasma glucose level of <150 mg/dL measured 5 days before starting glinide (8). Based on this finding, our patient likely had

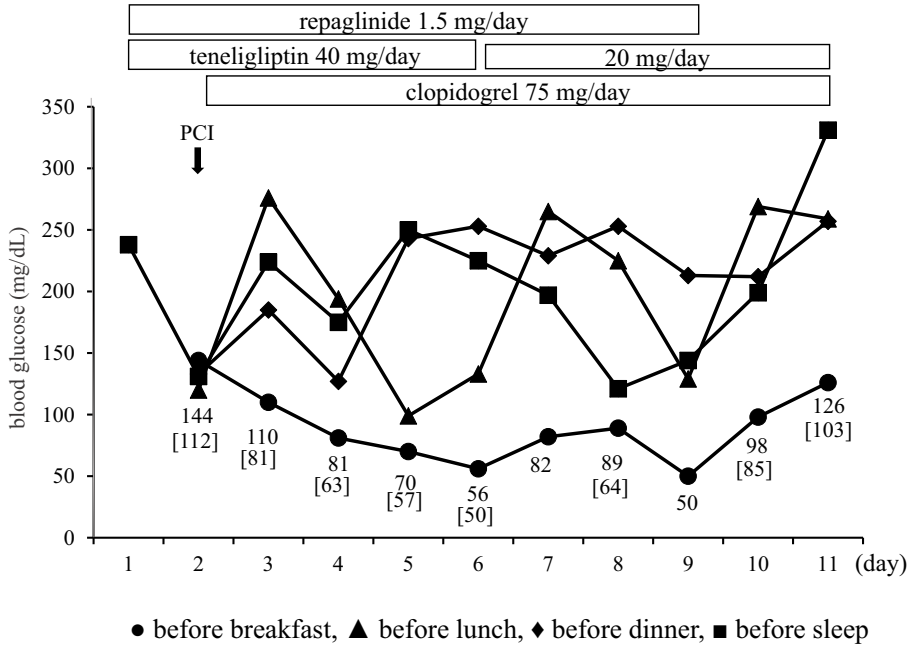

Figure. Clinical course of the daily profile of blood glucose and medications. Blood glucose was measured with a glucometer. [ ] indicates the plasma glucose levels measured in the laboratory. PCI: percutaneous coronary intervention

hypoglycemia, since the preprandial plasma glucose level before starting clopidogrel was 112 mg/dL.

The mechanism underlying hypoglycemia development caused by the concomitant use of repaglinide and clopidogrel is assumed to be as follows: repaglinide is primarily metabolized by cytochrome P450 (CYP) 2C8 (16). However, clopidogrel is metabolized by multiple CYP enzymes, mainly CYP2C19, and its metabolite, clopidogrel acyl-β-D-glucuronide, has been shown to inhibit CYP2C8 potently in a time-dependent manner *in vitro* (6). A physiologically based pharmacokinetic model has also indicated that inactivation of CYP2C8 by clopidogrel acyl-β-D-glucuronide leads to uninterrupted 60-85% inhibition of CYP2C8 during daily clopidogrel treatment (6). These results suggest that clopidogrel causes drug interactions with other medications metabolized by CYP2C8, such as repaglinide. In actuality, a placebo-controlled crossover study in 9 healthy volunteers who received clopidogrel for 3 days (300 mg on day 1 followed by 75 mg daily) and repaglinide (0.25 mg at 9 AM, 1 hour after clopidogrel intake on day 1 and 3) showed that the geometric mean area under the concentration-time curve ($AUC_{0-\infty}$) of repaglinide was increased by 5.1- and 3.9-fold on days 1 and 3 of clopidogrel treatment, respectively. In addition, that study showed that the maximum plasma concentration (C_{max}) was increased 2.0- and 2.5-fold, the elimination half-life ($t_{1/2}$) was prolonged by 42% and 22%, and the CYP2C8-dependent metabolite (M)4 to repaglinide AUC_{0-9h} ratio was reduced to 19% and 27%, respectively. Furthermore, the lowest mean blood glucose for the study participants was 59.5 mg/dL despite an adequate food intake (6). These results strengthen the possibility that clopidogrel substantially increases the hypoglycemic risk in patients with T2DM who receive repaglinide. In fact, a retrospective survey in our hospital revealed that two of four patients who underwent concomitant use of repaglinide and clopidogrel, except for the patient in the present case, developed hypoglycemia (unpublished data). Based on these results and the fact that the concomitant use of repaglinide and clopidogrel has been contraindicated since 2015 in Canada (17) and cautioned against on the drug package insert since 2016 in Japan (18), the concomitant use of repaglinide and clopidogrel is now (as of 2020) contraindicated under the approval of our pharmaceutical affairs committee in our hospital. However, meglitinides other than repaglinide, such as nateglinide and mitiglinide, are presumed to not cause hypoglycemia when used concomitantly with clopidogrel, although this presumption needs to be confirmed. This is because nateglinide is metabolized by CYP2C9 (70%) and CYP3A4 (30%), on which clopidogrel has little inhibitory effect, and because mitiglinide is eliminated through gluconidation by uridine 5'-diphospho-glucuronosyltransferases 1A 3 and 2B7 (19, 20). Therefore, if patients receiving clopidogrel need meglitinides, nateglinide or mitiglinide may be suitable for avoiding hypoglycemia.

Our patient had severe renal insufficiency due to diabetic kidney disease. Repaglinide is theoretically considered to confer a low risk of hypoglycemia even in patients with renal insufficiency, because repaglinide is metabolized mainly in the liver, and most of its metabolites are excreted through the bile. However, the $AUC_{0-\infty}$, C_{max} and $t_{1/2}$ of repaglinide in patients with severe renal insufficiency (creatinine clearance: 20-39 mL/min) as in our case, have been reported to be increased 1.7- and 1.3-fold and prolonged 130%, respectively, although these parameters in patients with mild-to-moderate

renal insufficiency are comparable to those with a normal renal function (5). In addition, renal insufficiency impairs not only renal glucogenesis but also insulin clearance, leading to an increased risk of hypoglycemia (21). Therefore, based on these findings, severe renal insufficiency as in our case is assumed to enhance the risk of hypoglycemia owing to the concomitant use of repaglinide and clopidogrel.

Several limitations associated with the present study warrant mention. First, it is possible that hypoglycemia was caused by the direct effect of repaglinide, via the induction of glucose toxicity, rather than to the concomitant use of repaglinide and clopidogrel. Unfortunately, we were unable to evaluate the clinical course and CPI levels with repaglinide and without clopidogrel after hypoglycemia. However, considering the patient's HbA1c values with anemia 3 months before and after admission (6.7% and 6.4%, respectively) and the daily profile of blood glucose after hospitalization, we believe that the patient's diabetes was controlled without remarkable glucose toxicity. In addition, considering that the patient had no detected hypoglycemia during the treatment with repaglinide and without clopidogrel, before and after admission, and that hypoglycemia occurred after initiating clopidogrel, we considered the hypoglycemia to be due to the concomitant use of repaglinide and clopidogrel. Second, it is possible that adrenal insufficiency influenced the hypoglycemia. However, we speculate that adrenal insufficiency had little effect on the hypoglycemia in this patient, as the hypoglycemia did not occur before starting clopidogrel, and the discontinuation of repaglinide improved the hypoglycemia without changing the dose of hydrocortisone. In addition, insulin secretion was not suppressed during hypoglycemia. Third, the patient's blood concentration of repaglinide was not investigated. Fourth, CYP2C8 gene polymorphisms may have affected the blood concentration of repaglinide and were also not investigated (22). However, we believe that our report provides information on safe diabetes treatment that aims to prevent incidental hypoglycemia in patients with macrovascular complications requiring repaglinide and/or clopidogrel.

In conclusion, we encountered an elderly patient with T2DM and severe renal insufficiency who developed hypoglycemia due to the concomitant use of repaglinide and clopidogrel. The risk of developing hypoglycemia is considered to vary from patient to patient, but we should recognize that a patient's concomitant use of repaglinide and clopidogrel puts them at high risk of developing hypoglycemia, especially those with T2DM and severe renal insufficiency.

Author's disclosure of potential Conflicts of Interest (COI).
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