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SHORT REPORT

Preventive effect of ipragliflozin on nocturnal hypoglycemia in patients with type 2 diabetes treated with basal-bolus insulin therapy: An open-label, single-center, parallel, randomized control study

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Keywords
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ABSTRACT

The efficacy of the administration of sodium-glucose co-transporter 2 inhibitor or the co-administration of sodium-glucose co-transporter 2 inhibitor and dipeptidyl peptidase-4 inhibitor to insulin therapy is not well known. A total of 58 patients with type 2 diabetes, admitted for glycemic control, were randomized to basal–bolus insulin therapy (BBT) alone or BBT plus 50 mg ipragliflozin and/or 20 mg teneligliptin. Insulin doses were adjusted to maintain normal blood glucose levels. Plasma glucose profiles were estimated by continuous glucose monitoring before discharge. Required insulin doses were not significantly different among the treatment groups. The frequency of nocturnal hypoglycemia was significantly lower in the groups treated with ipragliflozin (6.5 ± 10.6%) and ipragliflozin plus teneligliptin (6.9 ± 14.3%) than in the group treated with BBT alone (42 ± 43.6%). The administration of sodium-glucose co-transporter 2 inhibitor with or without dipeptidyl peptidase-4 inhibitor prevented nocturnal hypoglycemia in type 2 diabetes patients with BBT.

INTRODUCTION

Insulin therapy strongly ameliorates hyperglycemia, but has adverse effects, such as hypoglycemia and weight gain, which might increase the incidence of cardiovascular events. These adverse events can be minimized by the initial use of insulin in combination with oral antidiabetic agents[1]. We and other investigators reported the efficacy of the addition of dipeptidyl peptidase-4 inhibitors (DPP-4I) to basal–bolus insulin therapy (BBT)[2,3].

Inhibition of sodium-glucose co-transporter 2 (SGLT2) increases urinary glucose extraction, leads to bodyweight reduction and ameliorates hyperglycemia[4]. The administration of empagliflozin was reported to reduce the incidence of cardiovascular death and hospitalization for heart failure[5]. However, the efficacy of the addition of SGLT2 inhibitor (SGLT2I) to BBT in type 2 diabetes patients was not well-known.

In the present study, we evaluated the efficacy of the administration of SGLT2I and/or DPP-4I to type 2 diabetes patients receiving basal–bolus insulin therapy under short-term hospitalization.

METHODS

Participants

We enrolled 60 patients with type 2 diabetes in an unblinded randomized study. The patients were aged 20–75 years and visited the outpatient clinic of Nippon Medical School Chiba Hokusoh Hospital, Chiba, Japan, from July 2014 to October

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Table 1 | Baseline parameters of glycemic control, complications and medication before admission

	Ins	InsI	InsT	InsIT	*P*-value
n (male)	15 (8)	14 (8)	14 (8)	15 (9)	NS
Age (years)	55 ± 14	57 ± 8	56 ± 11	57 ± 15	NS
Duration of diabetes (years)	6 ± 6	9 ± 11	9 ± 17	7 ± 7	NS
BMI	24.5 ± 3.2	26.0 ± 4.8	23.3 ± 4.1	26.6 ± 4.6	NS
FPG (mg/dL)	217 ± 59	226 ± 63	212 ± 44	220 ± 58	NS
HbA1c, % (NGSP)	12.3 ± 1.9	12.4 ± 2.5	11.4 ± 1.7	12 ± 2	NS
GA (%)	32.3 ± 7.7	30.1 ± 9.6	29.9 ± 7.1	31.1 ± 9.2	NS
U-CPR (μg/day)	75.1 ± 45.7	73 ± 61.7	81.3 ± 50.8	62.9 ± 46	NS
Complication					
Absent ATR (*n*)	5	8	6	8	NS
U-Alb (mg/day)	35.7 ± 91.5	64.3 ± 178.2	52.5 ± 120	76.9 ± 160	NS
DR					
None (*n*)	12	11	12	10	NS
SDR (*n*)	2	3	1	3	
PPDR (*n*)	1	0	1	2	
PDR (*n*)	0	0	0	0	
Medication before admission					
SU (*n*)	0	1	0	1	NS
SU + DPP (*n*)	1	0	2	0	
SU + BG (*n*)	1	0	0	0	
SU + BG + DPP (*n*)	0	0	0	1	
SU + αGI (*n*)	0	2	0	0	
SU + αGI + DPP (*n*)	0	0	0	1	
BG (*n*)	1	0	1	1	

Data are expressed as mean ± SD. *P*-values for ANOVA test or χ^2-test. αGI, alfa glucosidase inhibitor; ATR, Achilles tendon reflex; BG, biguanides; BMI, body mass index; DPP, dipeptidyl peptidase-4 inhibitor; DR, diabetic retinopathy; FPG, fasting plasma glucose; GA, glycated albumin; HbA_{1c}, hemoglobin A_{1c}; Ins, insulin alone; InsI, insulin plus ipragliflozin; InsIT, insulin plus ipragliflozin and teneligliptin; InsT, insulin plus teneligliptin; NS, not significant; SU, sulfonylurea; U-Alb, urinary albumin; U-CPR, urinary C-peptide immunoreactivity.

Table 2 | Required insulin dose before discharge

	Ins	InsI	InsT	InsIT	*P*-value
Insulin glulisine					
Before breakfast (units)	9 ± 6	8 ± 5	7 ± 4	7 ± 4	NS
Before lunch (units)	3 ± 2	3 ± 2	3 ± 1	3 ± 3	NS
Before dinner (units)	7 ± 3	8 ± 3	6 ± 3	6 ± 3	NS
Insulin glargine					
Bed time (units)	12 ± 8	10 ± 6	12 ± 8	9 ± 9	NS

Data are expressed as mean ± SD. *P*-values for ANOVA test. InsI, insulin plus ipragliflozin; InsIT, insulin plus ipragliflozin and teneligliptin; InsT, insulin plus teneligliptin; NS, not significant.

2015, with a hemoglobin A_{1c} level of ≥10% at the first visit, and who agreed to hospitalization for diabetes control. Participants were excluded if they were treated with insulin or SGLT2I, were positive for antiglutamic acid decarboxylase antibody, or had a history or evidence of recent myocardial infarction, heart failure, cerebral vascular disease, endocrine disease or any carcinoma.

Study protocol and treatment

The protocol of the present study was approved by the ethics committee of Nippon Medical School Chiba Hokusoh Hospital (no. 526004), and was registered at UMIN Clinical Trials Registry (UMIN000020742). On admission, all participants stopped taking oral antidiabetic agents, received diet therapy and were randomly assigned to receive either insulin alone (Ins group; $n = 15$), insulin plus ipragliflozin (InsI group; $n = 15$), insulin plus teneligliptin (InsT group; $n = 15$) or insulin plus ipragliflozin and teneligliptin (InsIT group; $n = 15$).

The Ins group received basal–bolus insulin therapy (BBT) with insulin glulisine and insulin glargine. Patients received BBT plus ipragliflozin 50 mg s.i.d. in the InsI group, BBT plus teneligliptin 50 mg s.i.d. in the InsT group, and BBT plus ipragliflozin 50 mg and teneligliptin 20 mg s.i.d. in the InsIT group. In all groups, the dose of insulin injection was adjusted to maintain the blood glucose levels before each meal within 90–120 mg/dL by the attending physicians. The ophthalmologist checked diabetic retinopathy within 3 days after admission, and if required, fluorescent fundus angiography and retinal laser photocoagulation were immediately carried out.

Table 3 | Continuous glucose monitoring parameters before discharge

	Ins	InsI	InsT	InsIT	*P*-value
Mean (mg/dL)	110 ± 19	120 ± 14	114 ± 18	114 ± 12	NS
SD (mg/dL)	30 ± 12	30 ± 8	28 ± 12	26 ± 8	NS
MAGE (mg/dL)	69 ± 28	73 ± 26	65 ± 26	63 ± 15	NS
Frequency of glucose sensor ≤70 mg/dL from 0.00 to 8.00 h (%)	42 ± 43.6	6.5 ± 10.6†	19 ± 33	6.9 ± 14.3†	0.0093

Data are expressed as mean ± SD. *P*-values for ANOVA test. †Bonferroni *post-hoc* analysis <0.05 vs insulin alone (Ins) group. InsI, insulin plus ipragliflozin; InsIT, insulin plus ipragliflozin and teneligliptin; InsT, insulin plus teneligliptin; MAGE, mean amplitude of glycemic excursions; NS, not significant; SD, standard deviation.

Daily blood glucose profiles were also assessed using a continuous glucose monitoring (CGM) system (iPro™2; Medtronic, Minneapolis, Minnesota, USA) for the last 2 days before discharge. To assess daily glycemic variability, the mean glucose, SD of the daily glucose and mean amplitude of glycemic excursion[6] were calculated using CGM data. When the glucose sensor of CGM showed <70 mg/dL, we considered the patients have hypoglycemia.

Statistical analysis

All analyses were carried out using the Jmp 12.2 software (SAS Institute, Cary, North Carolina, USA). Values are presented as mean ± SD. Statistical analyses of sex differences and complication of diabetes at baseline were carried out using the χ^2-test. The significance of differences in the baseline characteristics and parameters of glycemic control before discharge among the four treatment groups was tested by analysis of variance (ANOVA), with the least significant difference test as a *post-hoc* test and Bonferroni correction for multiple comparisons. A *P*-value of <0.05 was considered significant.

RESULTS

A total of 68 patients were assessed for eligibility, and 60 patients (56.9% men, mean age 56 ± 12 years, body mass index 25.2 ± 4.4 kg/m^2, diabetes duration 7 ± 11 years, hemoglobin A_{1c} 12 ± 2%, glycated albumin 30.9 ± 8.5% and urinary C-peptide immunoreactivity 72.9 ± 50.3 μg/day) were selected. One patient dropped out because of the detection of malignancy in the InsI, and another patient in the InsT group dropped out because antiglutamic acid decarboxylase antibody was detected. There were no significant differences in the baseline characteristics among treatment groups (Table 1).

The duration of hospitalization was 14 ± 3, 14 ± 4, 14 ± 2, and 14 ± 4 in the Ins, InsI, InsT and InsIT groups, respectively. The required insulin doses were not significantly different among treatment groups before discharge (Table 2). No

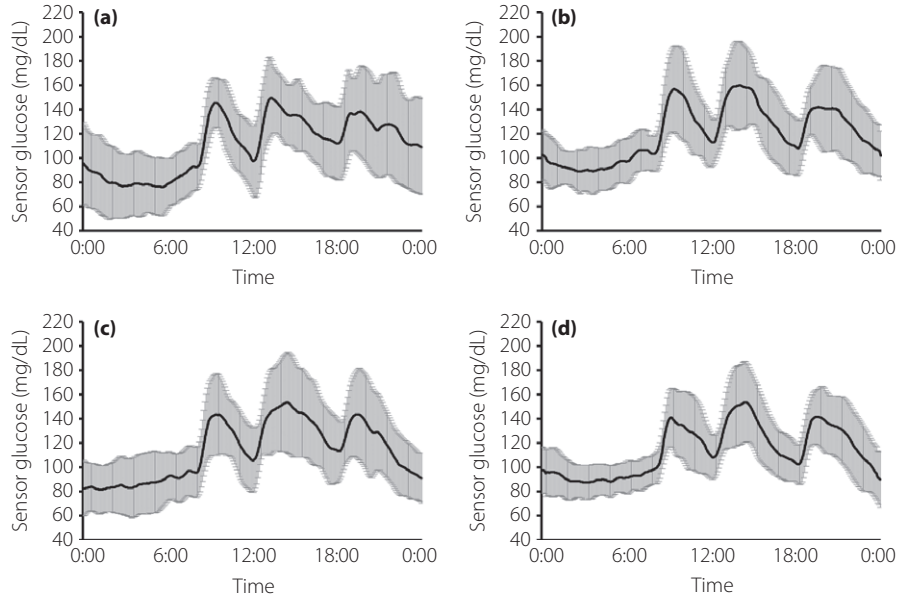

Figure 1 | Mean ± SD continuous glucose monitoring values before discharge. Mean values (solid black line) and the range of SD (gray area) in continuous glucose monitoring data before discharge in the (a) insulin alone group, (b) insulin plus ipragliflozin group, (c) insulin plus teneligliptin group and (d) insulin plus ipragliflozin and teneligliptin group.

significant difference was found in the mean glucose, SD and mean amplitude of glycemic excursion levels among treatment groups (Table 3; Figure 1). The incidence of nocturnal hypoglycemia was significantly reduced in the InsI and InsIT groups compared with that in the Ins group (Table 3; Figure 1).

DISCUSSION

This was the first study to show that SGLT2I with and without DPP-4I significantly prevents nocturnal hypoglycemia in patients with type 2 diabetes treated with BBT.

In the present study, the nocturnal glucose levels estimated by CGM in the Ins group were low, in the hypoglycemic range at a high frequency, and long term. However, administering SGLT2I with and without DPP-4I prevented glucose level depression during the nocturnal phase. These data suggested that SGLT2I increased the serum insulin counter-regulatory hormone (which mainly acts on the liver to increase hepatic gluconeogenesis[7]) concentrations, including glucagon, cortisol, growth hormone and/or catecholamine.

SGLT2I is known to increase hepatic glucose production by the increase of serum glucagon in type 2 diabetes patients[8]. SGLT2 is expressed in pancreatic α-cells, and inhibiting SGLT2 induces glucagon secretion under normo- to hypoglycemic conditions *in vitro*[9]. DPP-4I increases the concentration of plasma incretins, including glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide[10,11]. Glucagon-like peptide-1 decreases and glucose-dependent insulinotropic polypeptide increases the serum glucagon level[12,13]. Furthermore, DPP-4I attenuates glucagon secretion under high- to normoglycemic conditions, but not under hypoglycemic conditions[14]. Therefore, the modulation of glucagon secretion by the administration of SGLT2I with and without DPP-4I seems to be one of the mechanisms that caused the preventive effect toward hypoglycemia as shown in the current study.

Furthermore, the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) study showed that SGLT2I reduced the incidence of cardiovascular mortality and hospitalization for heart failure in patients with type 2 diabetes[5]. Hypoglycemia activates sympathetic nerves to ameliorate hypoglycemia[15], but might worsen heart failure[16]. In some clinical trials, hypoglycemia significantly increased mortality in patients with type 2 diabetes[17,18]. However, the impact of nocturnal hypoglycemia on cardiovascular mortality and hospitalization of heart failure remains unclear.

In conclusion, SGLT2I might have a preventive effect on nocturnal hypoglycemia. Further investigations on the effect of SGLT2I on serum insulin counter-regulatory hormone concentration in the nocturnal phase, and the association between nocturnal hypoglycemia and complications are required.

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DISCLOSURE

The authors declare no conflict of interest.

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