Diabetes, Obesity and Metabolism 18: 702–706, 2016.

Sodium-glucose cotransporter 2 inhibitor luseogliflozin improves glycaemic control, assessed by continuous glucose monitoring, even on a low-carbohydrate diet

This randomized, double-blind, placebo-controlled, crossover study was the first to determine the effects of luseogliflozin in combination with a low-carbohydrate diet (LCD) on 24-h glucose variability, assessed by continuous glucose monitoring (CGM). A total of 18 Japanese patients with type 2 diabetes were randomized into two groups, in which patients first received luseogliflozin 2.5 mg once daily then placebo for 8 days each, or vice versa. Patients took luseogliflozin or placebo with a normal-carbohydrate diet (NCD) on day 7 and with the LCD on day 8. CGM was performed on both days. Luseogliflozin significantly reduced glucose exposure in terms of the area under the curve over the course of 24 h when administered with the NCD (difference vs placebo: −555.6 mg/dl·h [1 mg/dl = 0.0556 mmol/l]; $p < 0.001$) or with the LCD (−660.7 mg/dl·h; $p < 0.001$). No hypoglycaemia was observed over 24 h with either diet. Although glucose levels were lower with the LCD than with the NCD in the placebo treatment period, luseogliflozin with the LCD improved glycaemic control throughout the day to nearly the same extent as luseogliflozin with the NCD, without inducing hypoglycaemia.
Keywords: continuous glucose monitoring (CGM), glycaemic control, SGLT2 inhibitor, type 2 diabetes

Date submitted 14 October 2015; date of first decision 5 November 2015; date of final acceptance 30 November 2015

Introduction

Luseogliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor that was approved and launched in Japan for the treatment of type 2 diabetes (T2D) [1–5]. SGLT2 inhibitors ameliorate hyperglycaemia by increasing urinary glucose excretion (UGE) in a glucose-dependent manner [6]; however, the capacity of SGLT2 inhibitors to enhance UGE becomes limited at glucose concentrations close to or below the renal threshold for glucose [7]. Accordingly, it is important to characterize the effects of SGLT2 inhibitors in patients consuming a low-carbohydrate diet (LCD). We investigated the effects of luseogliflozin on glucose variability assessed by continuous glucose monitoring (CGM) with a LCD and with a normal-carbohydrate diet (NCD).

Methods

Detailed methods are described in the Supporting Information (File S1).

Study Design

In the present randomized, double-blind, placebo-controlled, crossover study, Japanese patients with T2D who agreed to participate in an optional extension to our previous study [8] were randomized into two groups. The patients received luseogliflozin followed by placebo for 8 days each (L/P group), or vice versa (P/L group). Twenty-four-hour CGM and pharmacodynamic tests were conducted on days 7 and 8 while the patients were in hospital (Figure S1). Patients consumed a standardized NCD (536 kcal; ~20% protein, 25% fat and 55% carbohydrate) at dinner on day 6 and at each meal on day 7 and a standardized LCD (553–589 kcal; ~25% protein, 50% fat and 25% carbohydrate) at each meal on day 8. There were no changes to the study methods or outcomes after the study started.

Patients

Patients with T2D, diagnosed according to Japan Diabetes Society guidelines [9], were eligible for this trial if they had adhered to a stable diet therapy for ≥4 weeks before the start of the screening period and if they met the following criteria: age ≥20 years, body mass index ≥18.5 to <35.0 kg/m^2, glycated haemoglobin 7.0–10.0% (53–86 mmol/mol), and fasting plasma glucose ≥126 mg/dl (1 mg/dl = 0.0556 mmol/l). Major exclusion criteria are listed in the Supporting Information (File S1). The use of other antidiabetic drugs, corticosteroids (except for topical use) and intravenous fluids containing saccharides were prohibited during the study period.

Clinical Evaluations

The primary endpoints were indices derived from 24-h CGM measured on days 7 and 8. Other endpoints were pharmacodynamic variables, including serum insulin, plasma glucagon

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Table 1. Patient characteristics at baseline.

Characteristic	Value
n	18
Males, n (%)	14 (77.8)
Age, years	62.8 ± 7.7
Body weight, kg	64.0 ± 12.7
Body mass index, kg/m^2	23.7 ± 3.3
Duration of diabetes, years	8.0 ± 4.5
Prior treatments for diabetes, yes	4 (22.2%)
HbA1c, %	7.9 ± 0.9
Fasting plasma glucose, mg/dl	166.7 ± 28.3
Glycosylated albumin, %	22.9 ± 4.0
Serum fasting insulin, μU/ml	7.0 ± 4.4
Plasma fasting glucagon, pg/ml	84.6 ± 35.8
eGFR, ml/min/1.73 m^2	87.3 ± 11.5

Data are means ± standard deviation unless otherwise indicated.
eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin.
Glucose: 1 mg/dl = 0.0556 mmol/l.
Insulin: 1 μU/ml = 6.945 pmol/l.
Glucagon: 1 pg/ml = 1 ng/l.

and UGE. The volume of water intake was also recorded during these periods. Major safety variables were adverse events (AEs), adverse drug reactions (ADRs), abnormal or unexpected changes in laboratory test values, vital signs and 12-lead ECG.

Results

Participants and Baseline Characteristics

Of 37 patients who were enrolled and randomized in the original trial [8], 18 patients who agreed, before randomization, to participate in the optional extension to evaluate the effect of luseogliflozin with the LCD were enrolled in the present study. One patient in the L/P group withdrew informed consent on day 8 in treatment period II; therefore, 17 patients completed both treatment periods. The safety analysis set and the pharmacodynamics analysis set were identical, and both included all 18 patients. The demographic and baseline characteristics of the patients are shown in Table 1.

Pharmacodynamics

The 24-h glucose variability, assessed by CGM on days 7 and 8, is shown in Figure 1. The indices derived from CGM are shown in Table S1. Glucose concentrations were consistently lower with luseogliflozin than with placebo, as was the mean 24-h glucose concentration, in patients administered drugs both with the NCD and the LCD (both $p < 0.001$). Likewise, the area under the curve (AUC) for glucose concentrations from 0 to 24 h (AUC_{0-24h}) was significantly smaller with luseogliflozin than with placebo for both diets, as were the AUC and the proportion of time with a glucose concentration ≥181 mg/dl over 24 h (all $p < 0.001$). The area over the curve for daily glucose concentrations and the proportion of time spent over the course of 24 h with a glucose concentration <70 mg/dl were 0% for both luseogliflozin and placebo with each diet (Figure S2). The magnitude of the difference between luseogliflozin and placebo for all indices derived from CGM was not significantly different between administration with the NCD and the LCD (Table S1).

The UGE rate on days 7 and 8 is shown in Figure 1 and Table S2. Luseogliflozin significantly increased the UGE rate compared with placebo in each measurement period with both diets (all $p < 0.05$).

The serum insulin, plasma glucagon and serum ketone body (acetoacetic acid and β-hydroxybutyric acid) concentrations on days 7 and 8 in each treatment period are shown in Figures 1 and S3. The pharmacodynamic variables, serum insulin and plasma glucagon levels are shown in Table S2. Serum insulin concentrations were lower throughout the day with luseogliflozin than with placebo, and the AUCs after each meal, during the sleeping period and over the course of 24 h were significantly smaller with luseogliflozin than with placebo for both diets (all $p < 0.05$).

Plasma glucagon concentrations were higher throughout the day with luseogliflozin than with placebo, as were the AUCs after lunch and during the sleeping period for both diets (all $p < 0.05$). The AUCs after breakfast and dinner were significantly higher only with the LCD ($p < 0.05$).

Although the fasting and preprandial serum ketone body concentrations were higher with luseogliflozin than with placebo for both diets, these higher levels of serum ketone bodies tended to decrease after each meal. The serum ketone body concentrations in both treatment groups were higher when the patients consumed the LCD than when they consumed the NCD, and were higher with luseogliflozin than with placebo. The highest fasting acetoacetic acid and β-hydroxybutyric acid concentrations were 604 μmol/l (normal range: 13.0–69.0 μmol/l) and 3030 μmol/l (normal range: ≤76.0 μmol/l), respectively, in one patient in the morning on day 9, the day after administration of luseogliflozin with the LCD. None of the patients reported any symptoms related to elevated ketone bodies.

Safety

Five AEs occurred in four patients during administration of luseogliflozin, and seven AEs occurred in four patients during administration of placebo (Table S3). Five ADRs occurred in four patients during administration of luseogliflozin and one ADR occurred in one patient during administration of placebo. None of the patients reported any hypoglycaemic symptoms. Table S3 provides a summary of AEs and Table S4 shows urine volume and water intake.

Discussion

This study was conducted to investigate the effects of luseogliflozin on glucose variability and pharmacodynamic variables throughout the day in patients administered it with the LCD and NCD.

Consistent with our earlier report [8], the administration of luseogliflozin with the NCD reduced glucose concentrations throughout the day. Although the glucose concentrations were lower with the LCD than with the NCD during the placebo period, luseogliflozin further reduced the glucose concentrations throughout the day with the LCD relative to placebo.

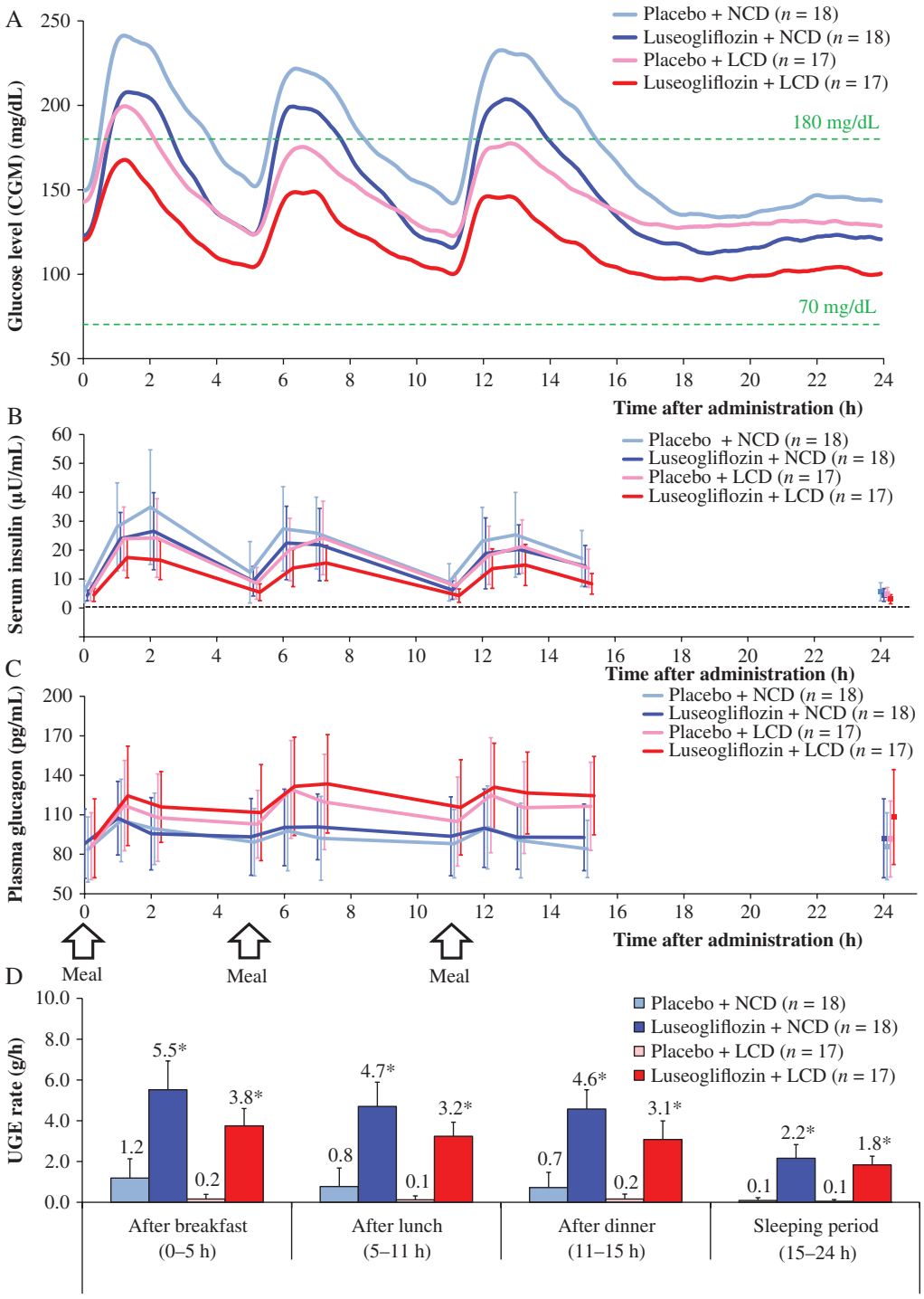

Figure 1. (A) Twenty-four-hour glucose concentrations assessed by continuous glucose monitoring (1 mg/dl = 0.0556 mmol/l). (B) Twenty-four-hour serum insulin concentrations (1 μU/ml = 6.945 pmol/l). (C) Twenty-four-hour plasma glucagon concentrations (1 pg/ml = 1 ng/l). (D) Urinary glucose excretion rate. Values are presented as mean (A) (error bars were omitted for clarity) or mean ± standard deviation (B–D). *$p < 0.05$ for luseogliflozin versus placebo.

Intriguingly, the differences in CGM-derived variables between luseogliflozin and placebo were consistently observed with both diets. In addition, luseogliflozin did not induce hypoglycaemia and the proportion of time with plasma glucose concentrations <70 mg/dl was 0% for both diets. These findings suggest that the effects of luseogliflozin on glycaemic control are not attenuated and hypoglycaemia is not induced by administration of luseogliflozin with consumption of the LCD for at least 1 day.

Although the LCD contained approximately only half the carbohydrate content of the NCD, luseogliflozin + LCD

increased UGE by >80% compared with UGE in luseogliflozin + NCD; however, further studies are needed to clarify why luseogliflozin with the LCD improved glycaemic control to the same extent as did luseogliflozin with the NCD. Luseogliflozin also decreased insulin concentrations and significantly decreased the AUC of insulin with both diets. It is likely that the reduction in circulating glucose reduced the amount of insulin required, even when the amount of carbohydrate consumed was decreased by half. Interestingly, some of the AUCs for insulin were smaller with the LCD than with the NCD, which implies that the combination of luseogliflozin and an LCD could reduce insulin requirements, and could be a useful treatment option that does not place an excessive burden on pancreatic β-cells.

The increases in ketone bodies tended to be smaller after food intake. However, in one patient treated with luseogliflozin and the LCD, the ketone bodies were markedly increased the next morning. Luseogliflozin is likely to increase ketone bodies by inducing mild starvation or by enhancing glycogenolysis through an increase in glucagon concentrations [10,11]. Because the increases in ketone bodies with the LCD in luseogliflozin-treated patients with T2D were quite large, clinicians should be aware of the risk of hyperketonaemia.

The present results should be interpreted cautiously, considering the study's possible limitations. Luseogliflozin and placebo were administered for only 8 days, while each diet was administered for a single day, which may have been insufficient to observe improvements in some variables.

In summary, although clinicians should be aware of the risk of hyperketonaemia, even when the increase in postprandial glucose concentrations was suppressed by the LCD, luseogliflozin with the LCD ameliorated hyperglycaemia throughout the day to nearly the same extent as luseogliflozin with the NCD, without inducing hypoglycaemia.

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Acknowledgements

This study was supported by Taisho Pharmaceutical Co., Ltd, Tokyo, Japan. The authors wish to thank Nicholas D. Smith, PhD, of Edanz Group Ltd., for providing editorial support, which was funded by Taisho Pharmaceutical Co., Ltd.

Conflict of Interest

R.N. has received consultancy fees or lecture fees from Abbott Diabetes Care, Inc., Astellas Pharma US, Inc., AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Inc., Eli Lilly Japan K.K., Kissei Pharmaceutical Co., Ltd., Novartis Corporation, Novo Nordisk Pharma Ltd., Sanofi K.K., Taisho Pharmaceutical Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Company Limited. H.O., K.S., M.U., S.S. and Y.S. are employees of Taisho Pharmaceutical Co., Ltd, which is developing luseogliflozin.

All authors helped design the study, interpreted the results, helped write the manuscript, and read and approved the final version of the manuscript. S.S. and Y.S. secured the research funding. Y.S. is the guarantor for this report.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

File S1. Supplentary methods and exclusion criteria.

Figure S1. Study design.

Figure S2. Proportion of time over 24 h with glucose concentrations of ≥181 mg/dl, ≥70 to ≤180 mg/dl, or <70 mg/dl, as measured by continuous glucose monitoring.

Figure S3. (A) Twenty-four-hour serum acetoacetic acid concentrations. (B) Twenty-four-hour serum β-hydroxybutyric acid concentrations.

Table S1. Twenty-four-hour glucose variables.

Table S2. Pharmacodynamic variables.

Table S3. Summary of adverse events.

Table S4. Urine volume and water intake.

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Appendix

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