ORIGINAL RESEARCH ARTICLE

Pharmacokinetic and Pharmacodynamic Profiles of Canagliflozin in Japanese Patients with Type 2 Diabetes Mellitus and Moderate Renal Impairment

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Abstract

Background and Objectives This study examined the effects of moderate renal impairment on the pharmacokinetics and pharmacodynamics of canagliflozin in Japanese patients with type 2 diabetes mellitus.

Methods Japanese patients with stable type 2 diabetes (12 with moderate renal impairment and 12 with normal renal function or mild renal impairment) were eligible. This was an open-label, randomized, two-way crossover, two-sequence, single-dose study performed at a single center in Japan. The subjects were hospitalized for the pharmacodynamic/pharmacokinetic evaluations. Twenty-four patients received a single dose each of canagliflozin 100 and 200 mg before breakfast in a crossover manner with a 14-day washout between doses. The main outcome measures were pharmacokinetics of canagliflozin and its main metabolites (M5 and M7) in plasma and urine, and change from baseline in 24-h urinary glucose excretion (ΔUGE24 h).

Results There was no significant effect of moderate renal impairment on the maximum canagliflozin concentration.

The ratios of least square means (90 % confidence intervals [CIs]) of moderate renal impairment relative to normal renal function or mild renal impairment were 0.982 (0.821–1.173) and 0.989 (0.827–1.182) for the 100 and 200 mg doses, respectively. The canagliflozin area under the plasma concentration–time curve was greater in those with moderate renal impairment than in those without, after both canagliflozin doses (ratio of least square means [90 % CI] 1.258 [1.061–1.490] and 1.216 [1.026–1.441]). ΔUGE24 h increased after administration of both doses, but in patients with moderate renal impairment, the increase was approximately 70 % of that in patients with normal renal function or mild renal impairment. The incidence of adverse events was low and no patient developed hypoglycemia.

Conclusion The pharmacokinetics of canagliflozin are affected by renal function, with slight decreases in renal clearance observed. No effect of renal impairment on the

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Key Points

Canagliflozin pharmacokinetics are unknown in Japanese patients with type 2 diabetes mellitus and chronic kidney disease.

Moderate renal impairment increased the canagliflozin area under the plasma concentration–time curve but not the maximum concentration in Japanese patients with type 2 diabetes, and somewhat attenuated the increase in urinary glucose excretion that occurs with canagliflozin treatment in patients with normal renal function or mild renal impairment.

Canagliflozin may be a suitable treatment option for Japanese patients with type 2 diabetes and moderate renal impairment.

maximum concentration was observed. Renal impairment reduced the ability of canagliflozin to promote urinary glucose excretion.

1 Introduction

Chronic kidney disease (CKD) occurs in 20–30 % of patients with type 2 diabetes mellitus globally, according to several reports [1–3]. One US study reported CKD prevalence to be as high as 39.6 % among people with diagnosed diabetes and 41.7 % in those with undiagnosed diabetes [4]. The prevalence of CKD in the general Japanese population is estimated at 13 % [5]. Studies from the USA show that the prevalence of CKD is increasing over time. De Boer et al reported that the prevalence of diabetic kidney disease increased from 2.2 % of the US population in 1988 to 3.3 % in 2008 ($p < 0.001$) in proportion to the reported increase in the prevalence of diabetes [6], while Kramer and Molitch [7] reported a fourfold increase in prevalence of CKD in the last three decades in US Medicare patients with hypertension and diabetes. However, CKD often goes undetected, so the actual prevalence of the disease may be even higher than reported.

Treatment options for patients with type 2 diabetes and CKD are limited. Glucose-lowering agents need to be dose-adjusted and are often contraindicated in patients with stage 3 CKD or higher because of the risk of hypoglycemia [8, 9]. Many, including sulfonylureas, glinides, and thiazolidinediones, also cause weight gain, while the only weight-neutral agent, metformin, is contraindicated or its use is limited in this population [1]. Further treatment options are clearly required.

Canagliflozin is an inhibitor of sodium glucose co-transporter 2 (SGLT2), which is expressed predominantly in the proximal renal tubules, and is responsible for the majority of glucose reabsorption from urine [10]. SGLT2 inhibitors act independently of insulin. The main canagliflozin-metabolizing enzyme is uridine diphosphate (UDP)-glucuronosyltransferase (UGT), and the main metabolites of canagliflozin are the O-glucuronides M5 and M7, both of which are inactive (FDA Endocrinologic and Metabolic Drugs Advisory Committee, NDA 204042, 10 Jan 2013, unpublished data).

By inhibiting SGLT2 expressed in the proximal renal tubules, canagliflozin reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion (UGE) and resulting in a net caloric loss, which may help with weight loss [11–15]. Inagaki et al. [16] found that canagliflozin significantly reduced body weight in Japanese patients with type 2 diabetes. However, because UGE is related to the glomerular filtration rate (GFR), the action of canagliflozin to increase UGE may be affected by decreased renal function [12, 13, 17].

In non-Japanese patients with type 2 diabetes, canagliflozin has shown promising glucose-lowering effects in those with [18] or without [19] kidney disease, and its pharmacokinetics appear to support once-daily dosing [20]. However, the pharmacokinetic profile of canagliflozin has not been assessed in Japanese patients with type 2 diabetes and impaired renal function. Therefore, the primary objective of this study was to compare the pharmacokinetic profiles of canagliflozin and its main metabolites M5 and M7 in Japanese patients with type 2 diabetes with or without moderate renal impairment after a single dose of canagliflozin 100 or 200 mg. Secondary objectives were to assess the pharmacodynamic effects and safety of canagliflozin in the different groups.

2 Methods

2.1 Study Design

The study followed an open-label, randomized, two-way crossover, single-dose design. Patients with moderate renal impairment, mild renal impairment, or normal renal function were randomized to one of two treatment sequences ($n = 6$ per sequence), and each patient received a single dose of canagliflozin 100 or 200 mg 10 min before breakfast. After a washout period of at least 14 days, a second dose (opposite to the first) was administered. Follow-up examinations were performed 14–21 days after the second treatment administration. Randomization was achieved using a list of randomization key codes, and the treatment sequence was allocated on the basis of an ascending order of key codes by a study registration center.

The study protocol and all amendments were approved by the institutional review board of the study site (P-One Clinic, Keikokai Medical Corporation, Tokyo, Japan), and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the Pharmaceutical Affairs Law, and Good Clinical Practice. All patients provided written informed consent.

If a randomized subject was removed from the study before study drug administration in Period I, the subject was to be replaced by another subject. At the time of the subject's discontinuation, the investigator selected a replacement subject who was assigned the smallest subject identification code among those who were assessed as eligible based on the screening examination and not randomized, and were assigned to the treatment group that was originally assigned to the discontinued subject. If there were no eligible subjects at the time of discontinuation, the principal investigator or sub-investigators were to select a

replacement subject with the smallest subject identification code among those who were assessed as eligible based on screening examinations conducted after discontinuation. To facilitate recruitment and replacement, the protocol was amended to allow the prospective enrolment of eligible subjects who could 'stand by' to serve as replacements, as needed, for subjects who withdrew before study drug administration; if the subject was replaced by a standby subject, the standby subject was assigned the same identification number as the discontinued subject. The purpose of this amendment was to facilitate recruitment and subject replacement.

The subjects were hospitalized for the pharmacodynamic/pharmacokinetic evaluations, and their meals (breakfast, lunch, and dinner) were provided by the study site during this time. The intake of other food was prohibited during hospitalization, except for glucose in the event of hypoglycemia. The meal contents were identical in both treatment periods. Breakfast, lunch, and dinner were served at 10 min, 4 h 30 min, and 10 h 30 min after the scheduled study drug administration, and all meals were to be consumed within 20 min of serving.

2.2 Subjects

Twenty-four patients aged 40–79 years with stable type 2 diabetes (12 with moderate renal impairment and 12 with normal renal function or mild renal impairment) were initially enrolled and completed the study. The eligibility criteria are listed in Table 1. Patients using oral drugs entered a 14-day washout after providing informed consent and before the screening visit.

2.3 Plasma Pharmacokinetic Parameters

Blood samples for measurement of total (free and bound) canagliflozin and its metabolites concentrations in plasma were taken a total of 13 times in each dosing period: immediately before the dose, and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 h post-dose. Blood was drawn in K_2EDTA blood collection tubes, cooled in iced water, and centrifuged. The obtained plasma was frozen immediately and stored at −20 °C until analysis. The plasma concentrations of unchanged canagliflozin were measured by high-performance liquid chromatography (HPLC)/tandem mass spectrometry (HPLC–MS/MS; HPLC unit: Alliance® 2795 separations module, Waters, Milford, MA, USA; mass spectrometry unit: API4000™, AB SCIEX, Framingham, MA, USA; L-column ODS, 2.1 × 50 mm, particle size 5 μM, Chemicals Evaluation and Research Institute, Tokyo, Japan) with $^{13}C_6$-canagliflozin as an internal standard. Plasma samples were loaded into an OASIS® HLB (Waters, Milford, MA, USA) and eluted with methanol. The eluate was evaporated to dryness under a stream of nitrogen gas. The residue was dissolved and injected into the LC-MS/MS system. The validated quantification range was 1–2,000 ng/mL. All validation results satisfied the predefined acceptance criteria. The plasma concentrations of metabolites (M5 and M7) were measured using a previously described method [20]. The method used to prepare samples for the determination of metabolites (M5 and M7) involved protein precipitation with acetonitrile followed by HPLC-MS/MS. The validated quantification range for the metabolites (M5 and M7) was 5–10,000 ng/mL [20].

2.4 Urinary Pharmacokinetic Parameters

Seven urine samples were taken in each treatment period: 11–0 h pre-dose on the preceding day, 0–4.5, 4.5–10.5, 10.5–13, and 13–24 h post-dose on administration day, then 24–48 and 48–72 h post-dose. The volume of urine at each timepoint was calculated and described in a case report form. After the volume was calculated, urine was mixed and transferred to two polypropylene tubes (total 5 mL) and immediately stored at −20 °C. Samples were stored at −20 °C until analysis. The urinary canagliflozin concentrations were determined by solid-phase extraction of urine samples followed by HPLC–MS/MS, which was performed as described for the determination of plasma canagliflozin. The validated quantification range was 1–2,000 ng/mL. All validation results satisfied the predefined acceptance criteria.

2.5 Pharmacodynamic Evaluations

Urinary glucose concentrations and excretion rates over a 24-h period were assessed. Ten samples were taken in each treatment period, at 0–4.5, 4.5–10.5, 10.5–13, and 13–24 h after the scheduled dose on the day preceding administration of the study drug, 0–4.5, 4.5–10.5, 10.5–13, and 13–24 h post-dose on administration day, and 24–48 and 48–72 h post-dose.

Plasma glucose concentrations were measured in 33 blood samples obtained in each patient, as follows. Sixteen samples were taken on the day preceding administration: at the time of the scheduled dose (before breakfast), and 0.5, 1, 1.5, 2, 3, 4.5 (immediately before lunch), 5.5, 6, 7, 8, 10.5 (immediately before dinner), 11.5, 12, 13, and 14 h after the scheduled dose. Sixteen samples were taken on the administration day: immediately before the dose, and 0.5, 1, 1.5, 2, 3, 4.5 (immediately before lunch), 5.5, 6, 7, 8, 10.5 (immediately before dinner), 11.5, 12, 13, and 14 h post-dose. Finally, one additional sample was taken the next day (24 h post-dose, before breakfast). Glucose concentrations were also measured in urine samples taken immediately before the dose and at 24 h post-dose (before breakfast).

Table 1 Eligibility criteria

Inclusion criteria

   HbA$_{1c}$ (National Glycohemoglobin Standardization Program values) $\geq$6.5 and $\leq$10.6 %

   No change in dietary or exercise therapy for at least 12 weeks before the study

   Body mass index $\geq$18.5 and $\leq$39.9 kg/m^2

   Fasting plasma glucose $\geq$140 and $\leq$240 mg/dL

   Systolic blood pressure $\geq$90 and $\leq$160 mmHg

   Diastolic blood pressure $\geq$45 and $\leq$100 mmHg

   Pulse $\geq$40 beats/min

   eGFR^a $\geq$30 and <50 mL/min/1.73 m^2 for type 2 diabetes mellitus patients with moderate renal impairment and $\geq$80 mL/min/1.73 m^2 for type 2 diabetes patients with normal renal function or mild renal impairment

   On diet therapy, exercise therapy, and/or oral medications at the time of giving informed consent. Patients using oral drugs entered a 14-day washout after providing informed consent and before the screening visit

Exclusion criteria

   Patients who were not being treated for type 2 diabetes (e.g., diet therapy, exercise therapy, or oral antidiabetic drugs) at the time of giving informed consent

   Type 1 diabetes, diabetes associated with pancreatic disorder, secondary diabetes, severe diabetes complications or their history, or need for insulin therapy

   Inherited glucose–galactose malabsorption or renal diabetes

   Complication of uncontrollable thyroid abnormalities, anorexia, or bulimia

   Complication of urinary tract infection or genital infection

   Complication or history of New York Heart Association Class III or IV heart failure symptoms

   Myocardial infarction or cerebrovascular disorder within the previous 6 months

   Complication of unstable angina or arteriosclerosis obliterans of Class III or IV as categorized by Fontaine Classification

   Complication of serious hepatic disorder, or ALT or AST >2.5 times the upper limit of normal range

   Complication or history of malignancy

   Complication of psychiatric or neurological disease

   Dialysis, nephrectomy, or renal transplantation

   Alcohol or drug addiction

   Complication of shock or anaphylactoid shock to drugs or its history

   Positive test for hepatitis B virus surface antigen, serological test for syphilis, hepatitis C virus antibody, or HIV antibody

   Triglycerides $\geq$600 mg/dL

   Inability to refrain from smoking during hospitalization, e.g., smoking habit of $\geq$10 cigarettes/day

   Surgery known to affect the gastrointestinal absorption of medicinal products (except appendectomy and hernia surgery)

   Use of any over-the-counter or prescription medications (except those that were allowed for concomitant use) within 14 days before the start of study drug administration

   Consumption of fruits or juice containing grapefruit or cranberry within 7 days before the start of study drug administration

   Ingestion of any supplements including St John's wort within 14 days before the start of study drug administration

   Donation or collection of $\geq$400 mL of blood within 12 weeks, $\geq$200 mL within 4 weeks, or $\geq$800 mL within 1 year before the start of study drug administration

   Pregnancy, breastfeeding, or possible pregnancy (including unwillingness to practice contraception)

   Participation in another clinical study and/or receiving another study drug within the previous 12 weeks

   Previous exposure to canagliflozin

   Any other patients who were deemed ineligible for the study in the opinion of the principal investigator or sub-investigators

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *eGFR* estimated glomerular filtration rate, *HbA$_{1c}$* glycosylated hemoglobin

^{a} The eGFR was calculated using the patient's age at the screening examination as follows [25]:

eGFR (mL/min/1.73 m^2) = 194 $\times$ serum creatinine$^{-1.094}$ $\times$ age$^{-0.287}$ ($\times$ 0.739 for females)

2.6 Safety

Adverse events were recorded along with information on their intensity and relationship to the study drug. Adverse events were classified according to system organ class and preferred term [MedDRA® (the Medical Dictionary for Regulatory Activities)/J version 15.0]. Adverse drug reactions were defined as events that were considered

reasonably related to the study drug by the investigator. Other safety assessments included blood and urine laboratory parameters, renal function, vital signs (blood pressure, pulse rate, body temperature), body weight, and 12-lead electrocardiogram.

2.7 Statistical Methods

Statistical methods are described in the online Electronic Supplementary Material.

3 Results

3.1 Patient Characteristics

All 24 patients received at least one dose of canagliflozin and completed the trial (Electronic Supplementary Material Fig. 1). There were some minor protocol violations: ten subjects took longer than 20 min to finish a meal; two subjects did not eat an entire meal; and one subject had a hemolyzed blood sample so some laboratory parameters were classified as missing in this subject (namely, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total protein, potassium, calcium, and inorganic phosphorus). None of these violations prevented any of the patients from being included in the analyses. No subject replacements were necessary. The characteristics of patients are summarized in Table 2.

3.2 Pharmacokinetics of Canagliflozin

The plasma concentrations of unchanged canagliflozin and its metabolites in patients with and without moderate renal impairment are shown in Fig. 1, and key pharmacokinetic parameters for each group are shown in Table 3. Canagliflozin was rapidly absorbed, reaching its maximum concentration (C_{max}) within a median of 1 h. The half-life ($t_{1/2}$) in patients with normal or mild renal impairment was just over 12 h at both doses. The area under the plasma concentration–time curve (AUC) increased in a dose-dependent manner. Renal clearance (CL_R) was low and the amount of canagliflozin excreted into urine from 0 to 72 h was <1 % of the dose for both doses.

No difference in C_{max} was seen between those with moderate renal impairment and those with normal renal function or mild renal impairment. The ratio of least square means (90 % confidence interval [CI]) of moderate renal impairment relative to normal renal function or mild renal impairment was estimated to be 0.982 (0.821–1.173) and 0.989 (0.827–1.182) for the 100 and 200 mg doses, respectively. However, AUC was greater in those with moderate renal impairment than in those with normal renal function or mild renal impairment following both doses of canagliflozin. The ratio of least square means (90 % CI) of moderate renal impairment relative to normal renal function or mild renal impairment was estimated at 1.258 (1.061–1.490) for the 100 mg dose and 1.216 (1.026–1.441) for the 200 mg dose. Analysis of variance showed significant differences between doses for C_{max} and AUC ($p < 0.001$). There was no significant difference between patients with moderate renal impairment and those with normal renal function or mild renal impairment for C_{max}, whereas the difference was significant for AUC ($p = 0.039$). The $t_{1/2}$ was slightly prolonged. CL_R was slightly lower in patients with moderate renal impairment, but the amount of canagliflozin excreted into urine was unchanged relative to those in patients with normal renal function or mild renal impairment.

3.3 Pharmacokinetics of M5 and M7

The C_{max} of both M5 and M7 occurred 2 h post-exposure at both doses, indicating that both metabolites were rapidly produced after administration of canagliflozin. Like canagliflozin, exposure in terms of AUC was dose dependent. Their $t_{1/2}$ values were also similar to that of canagliflozin. No difference in the C_{max} of M5 was seen between patients

Table 2 Patient characteristics	Variable	Moderate renal impairment ($n = 12$)	Normal renal function or mild renal impairment ($n = 12$)
	Sex (male)	12	12
All data are presented as means ± standard deviation, except for sex (n) and eGFR [mean ± standard deviation (range)]	Age (years)	63.7 ± 10.2	57.8 ± 9.7
	Height (cm)	168.59 ± 6.28	171.11 ± 8.32
	Bodyweight (kg)	74.85 ± 7.01	75.33 ± 10.38
	BMI (kg/m^2)	26.33 ± 1.98	25.75 ± 3.32
BMI body mass index, *eGFR* estimated glomerular filtration rate, *HbA$_{1c}$* glycosylated hemoglobin, *NGSP* National Glycohemoglobin Standardization Program	Duration of diabetes mellitus (years)	5.74 ± 2.24	4.20 ± 2.34
	Fasting plasma glucose (mg/dL)	167.5 ± 21.5	183.1 ± 21.8
	HbA$_{1c}$ (NGSP) (%)	7.97 ± 1.27	8.68 ± 1.34
	eGFR (mL/min/1.73 m^2)	39.7 ± 6.6 (30–49)	92.7 ± 10.7 (80–108)

Fig. 1 Mean plasma
concentration–time profiles for
a canagliflozin, b M5, and
c M7. Error bars show standard
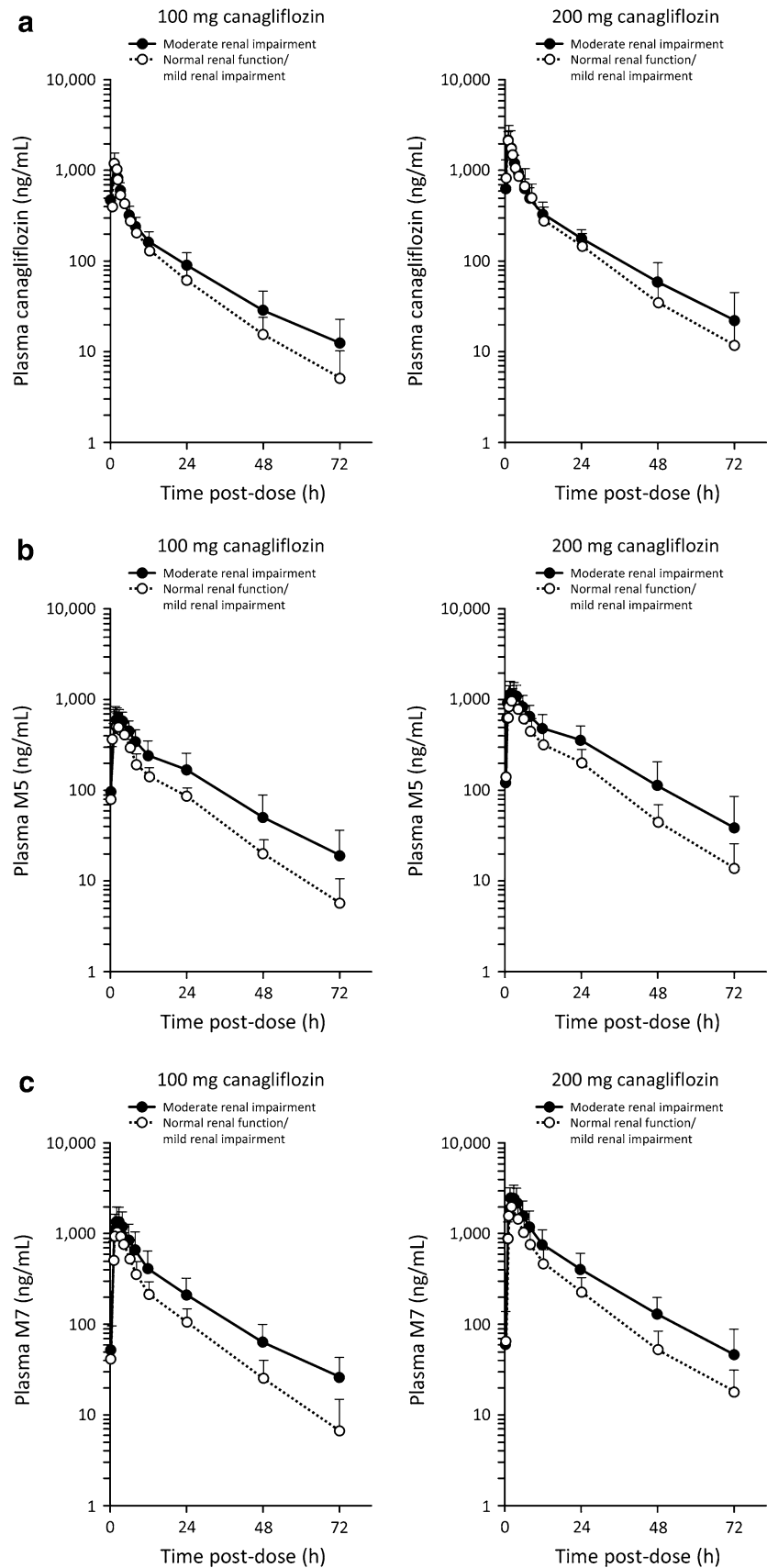deviation. For clarity, only the
upper error bars are shown

Table 3 Pharmacokinetic parameters of canagliflozin, M5, and M7 following single-dose administration of canagliflozin

Parameter	Canagliflozin 100 mg			Canagliflozin 200 mg		
	Normal renal function or mild renal impairment ($n = 12$)	Moderate renal impairment ($n = 12$)	Ratio (90 % CI)	Normal renal function or mild renal impairment ($n = 12$)	Moderate renal impairment ($n = 12$)	Ratio (90 % CI)
Canagliflozin						
C_{max} (ng/mL)	1,213.66 (337.87)	1,197.13 (310.56)	0.982 (0.821–1.173)	2,415.61 (739.88)	2,333.36 (414.90)	0.989 (0.827–1.182)
AUC_∞ (ng·h/mL)	6,929 (1734)	8,766 (2551)	1.258 (1.061–1.490)	14,815 (4162)	17,835 (4434)	1.216 (1.026–1.441)
t_{max} (h)	1.0 (1.0–3.0)	1.0 (1.0–3.0)		1.0 (1.0–6.0)	1.0 (1.0–2.0)	
$t_{1/2}$ (h)	12.58 (3.14)	15.50 (4.35)		12.10 (2.66)	15.15 (6.68)	
CL/F (L/h)	15.24 (3.65)	12.15 (2.87)		14.43 (3.73)	11.73 (2.36)	
V_d/F (L)	269 (66)	264 (81)		244 (53)	242 (67)	
CL_R (L/h)	0.085 (0.037)	0.064 (0.021)		0.080 (0.029)	0.058 (0.022)	
Ae_{0-72h}%	0.541 (0.168)	0.538 (0.229)		0.559 (0.182)	0.480 (0.143)	
M5						
C_{max} (ng/mL)	546.50 (153.46)	630.42 (180.80)	1.148 (0.945–1.395)	1,032.92 (247.63)	1,267.33 (365.18)	1.218 (1.002–1.479)
AUC_∞ (ng·h/mL)	6,454 (2047)	11,132 (4798)	1.655 (1.312–2.087)	13,487 (4124)	22,729 (8912)	1.639 (1.299–2.067)
t_{max} (h)	2.0 (1.5–4.0)	2.0 (1.5–4.0)		2.0 (1.5–6.0)	2.0 (1.5–4.0)	
$t_{1/2}$ (h)	12.28 (2.42)	14.79 (4.44)		12.33 (2.32)	14.63 (5.45)	
M7						
C_{max} (ng/mL)	1,092.08 (333.58)	1,461.67 (565.50)	1.306 (1.064–1.603)	2,040.00 (780.85)	2,715.83 (898.30)	1.342 (1.093–1.646)
AUC_∞ (ng·h/mL)	10,152 (3659)	18,205 (9025)	1.709 (1.375–2.124)	20,307 (8333)	33,927 (13,214)	1.669 (1.343–2.074)
t_{max} (h)	2.0 (2.0–4.0)	2.0 (2.0–4.0)		2.0 (1.5–6.0)	2.0 (2.0–4.0)	
$t_{1/2}$ (h)	12.13 (2.74)	15.62 (4.35)		12.07 (2.21)	15.26 (6.57)	

All results are presented as means (standard deviation) except t_{max}, which is presented as the median (range). Ratio (90 % CI) represents the ratio of least square means of moderate renal impairment relative to normal renal function or mild renal impairment

Ae_{0-72h} % cumulative urinary excretion rate from time zero to 72 h, AUC_∞ area under the concentration–time curve from time zero to infinity, *CI* confidence interval, *CL/F* apparent total clearance, CL_R renal clearance, C_{max} maximum concentration, $t_{1/2}$ half-life, t_{max} time to maximum concentration, V_d/F apparent distribution volume at elimination phase

with moderate renal impairment and those with normal renal function or mild renal impairment, but AUC was greater in those with renal impairment than in those without. The ratios of least square means (90 % CI) of moderate renal impairment relative to normal renal function or mild renal impairment for the C_{max} and AUC of M5 were estimated to be 1.148 (0.945–1.395) and 1.655 (1.312–2.087), respectively, for 100 mg, and 1.218 (1.002–1.479) and 1.639 (1.299–2.067), respectively, for 200 mg. There were significant differences between doses for C_{max} and AUC ($p < 0.001$). There was no significant difference between patients with moderate renal impairment and those with normal renal function or mild renal impairment for C_{max}, whereas the difference between patient groups was significant for AUC ($p = 0.001$). The M5 $t_{1/2}$ was slightly prolonged in patients with impaired renal function compared with those with normal renal function or mild renal impairment, after both doses.

For M7, both C_{max} and AUC were greater in patients with moderate renal impairment than in patients with normal renal function or mild renal impairment. The ratios of least square means (90 % CI) of moderate renal impairment relative to normal renal function or mild renal impairment for the C_{max} and AUC of M7 were estimated to be 1.306 (1.064–1.603) and 1.709 (1.375–2.124) for 100 mg, and 1.342 (1.093–1.646) and 1.669 (1.343–2.074) for 200 mg. There were significant differences between doses for C_{max} and AUC ($p < 0.001$), and the difference between the two patient groups was also significant for C_{max} and AUC ($p = 0.023$ and $p < 0.001$, respectively). The $t_{1/2}$ of M7 was slightly prolonged in patients with moderate renal impairment.

3.4 Pharmacodynamics of Canagliflozin

The mean change from baseline in 24 h UGE (ΔUGE24 h) in patients with and without moderate renal impairment is shown in Fig. 2. ΔUGE24 h increased after administration of both doses of canagliflozin in both patient groups. However, ΔUGE24 h in patients with moderate renal impairment was approximately 70 % of that observed in patients with normal renal function or mild renal impairment.

The 24-h mean percent inhibition of renal glucose reabsorption after administration of canagliflozin was slightly higher in patients with moderate renal impairment

than in those with normal renal function or mild renal impairment (Fig. 3).

The plasma glucose concentrations after administration of canagliflozin decreased at almost all measurement timepoints in both patients with normal renal function or mild renal impairment and those with moderate renal impairment. In addition, the decrease in plasma glucose concentrations was smaller in patients with moderate renal impairment than in those with normal renal function or mild renal impairment.

The 24-h mean plasma glucose concentrations after administration of canagliflozin decreased in both patients with normal renal function or mild renal impairment and in patients with moderate renal impairment (Fig. 4). As for plasma glucose, the decrease in 24-h mean plasma glucose concentrations was smaller in patients with moderate renal impairment than in patients with normal renal function or mild renal impairment.

3.5 Safety

Table 4 presents a summary of adverse events by preferred term in patients with and without moderate renal impairment following single doses of canagliflozin 100 and

Fig. 2 Mean changes in cumulative 24-h urinary glucose excretion. *Error bars* show standard deviation. *UGE* urinary glucose excretion
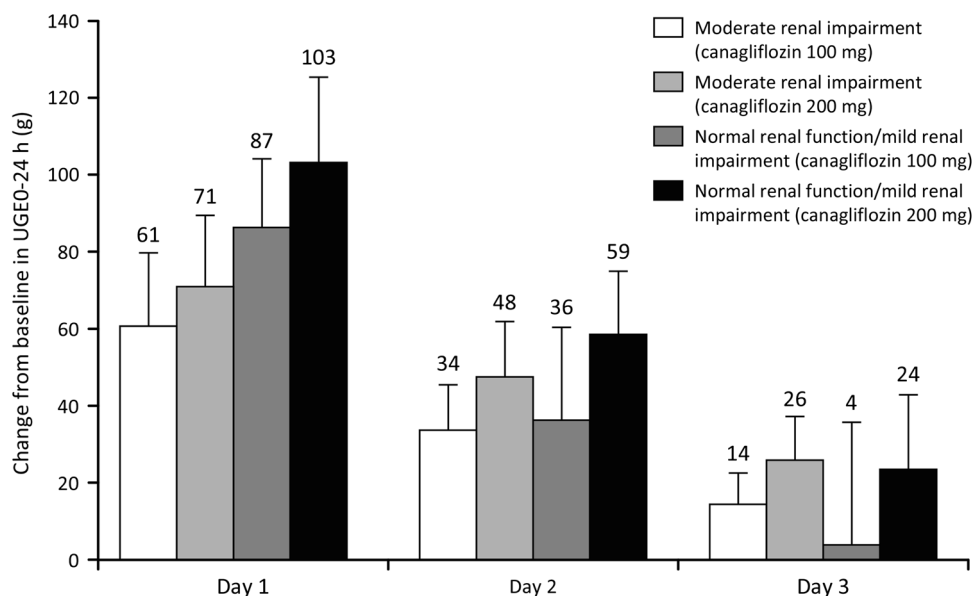
Fig. 3 Mean percent inhibition of renal glucose reabsorption over 24 h. *Error bars* show standard deviation
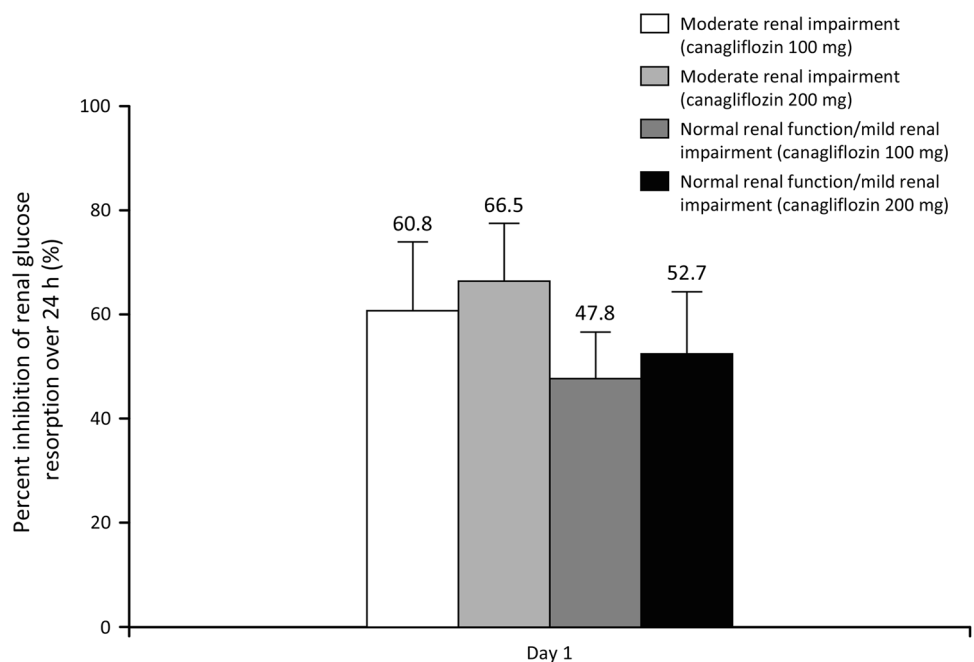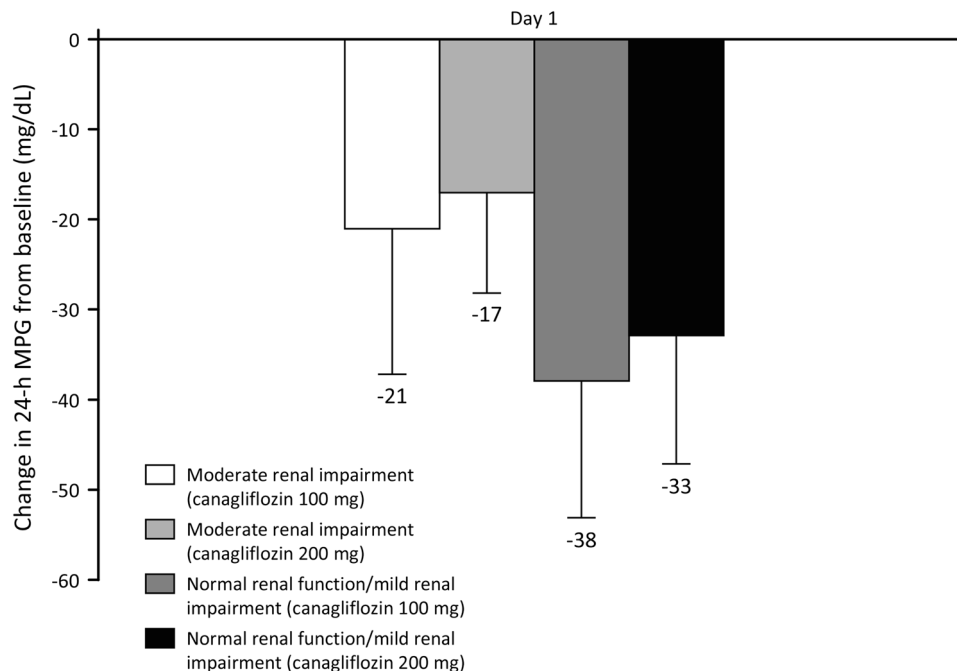
Fig. 4 Changes in 24-h mean plasma glucose concentrations. *Error bars* show standard deviation. *MPG* mean plasma glucose

200 mg. There were no adverse events leading to study discontinuation, deaths, other serious adverse events or other significant adverse events. Two adverse events were assessed as moderate in intensity (one event of constipation after canagliflozin 100 mg and one of nasopharyngitis after 200 mg, both in patients with normal renal function or mild renal impairment). The remaining nine events were assessed as mild. Only one case of pollakiuria and one of diarrhea were considered to be related to the study drug. Both events were mild and resolved. The incidence of adverse events was not affected by renal function or canagliflozin dose. None of the patients developed hypoglycemia.

4 Discussion

This study assessed the pharmacokinetics of two doses of canagliflozin in Japanese patients with type 2 diabetes and moderate renal impairment or normal renal function/mild renal impairment. Canagliflozin was rapidly absorbed, with a relatively long $t_{1/2}$. Importantly, UGE continued to increase from day 2 onward, suggesting that a once-daily dosing regimen may be possible. The metabolites M5 and M7 were formed rapidly after administration, and their $t_{1/2}$ values were similar to the $t_{1/2}$ of unchanged canagliflozin.

The pharmacokinetics of canagliflozin in Japanese patients with type 2 diabetes and normal renal function or mild renal impairment were similar to that reported in Western patients. Devineni et al. [20] administered canagliflozin 50, 100, or 300 mg to patients with type 2

diabetes with normal or mildly decreased renal function for 7 days, and evaluated the pharmacokinetics after single and multiple doses. After a single dose of 100 mg, the C_{max} was 1,096 ng/mL in the Western population [20] compared with 1,214 ng/mL in the Japanese population with mild or no renal impairment in the current study. The corresponding values for the canagliflozin AUC from time zero to 24 h were 6,357 and 5,645 ng·h/mL. The canagliflozin AUC and C_{max} increased dose dependently in the present study and in the study by Devineni et al. [20].

Although decreased clearance of canagliflozin was observed in patients with renal impairment, the urinary excretion ratio of unchanged drug was <1 % in our study. This difference in canagliflozin clearance is not likely to be due to altered protein binding in patients with renal impairment, because total protein and albumin levels were similar between those with moderate renal impairment and those with normal renal function/mild renal impairment (data not shown). In non-Japanese patients with normal renal function or mild renal impairment, the mean 24-h urinary excretion ratios for M5 and M7 following a single dose of canagliflozin 100 mg were 8.11 and 25.1 %, respectively, both of which are higher than the ratio for unchanged canagliflozin (0.55 %) [20]. Accordingly, the observed increases in the plasma concentrations of M5 and M7 in our study can be partly explained by lowered CL_R of the metabolites resulting from reduced renal function.

Other SGLT2 inhibitors have yielded similar results in patients with renal impairment. Macha et al. [21] reported decreased CL_R and moderately increased systemic exposure to empagliflozin in patients with moderate renal

Table 4 Summary of adverse events by preferred term

Adverse event	Moderate renal impairment						Normal renal function or mild renal impairment					
	Canagliflozin 100 mg ($n = 12$)			Canagliflozin 200 mg ($n = 12$)			Canagliflozin 100 mg ($n = 12$)			Canagliflozin 200 mg ($n = 12$)		
	No. of events	No. of subjects	Incidence (%)	No. of events	No. of subjects	Incidence (%)	No. of events	No. of subjects	Incidence (%)	No. of events	No. of subjects	Incidence (%)
Total	3	3	25.0	1	1	8.3	3	2	16.7	4	3	25.0
Constipation	0	0	0.0	0	0	0.0	1	1	8.3	0	0	0.0
Diarrhea	0	0	0.0	0	0	0.0	1	1	8.3	0	0	0.0
Nasopharyngitis	1	1	8.3	1	1	8.3	0	0	0.0	1	1	8.3
Blood CPK increased	0	0	0.0	0	0	0.0	0	0	0.0	1	1	8.3
Blood creatinine increased	0	0	0.0	0	0	0.0	0	0	0.0	1	1	8.3
Blood glucose increased	0	0	0.0	0	0	0.0	0	0	0.0	1	1	8.3
Protein urine present	1	1	8.3	0	0	0.0	0	0	0.0	0	0	0.0
Back pain	0	0	0.0	0	0	0.0	1	1	8.3	0	0	0.0
Pollakiuria	1	1	8.3	0	0	0.0	0	0	0.0	0	0	0.0

CPK creatine phosphokinase

impairment, while Kasichayanula et al. [22] found that the C_{max} and AUC for dapagliflozin increased incrementally with declining renal function.

Although canagliflozin exposure was slightly increased as a result of decreased renal function, ΔUGE24 h was lower in patients with moderate renal impairment than in those with normal renal function or mild renal impairment. Despite the reduction in ΔUGE24 h as a result of decreased renal function, the percent inhibition of renal glucose reabsorption was slightly higher in patients with impaired renal function than in those with normal renal function or mild renal impairment. This may have resulted from a difference in SGLT2 expression in patients with reduced renal function. Reduced expression of SGLT2 has been observed in the remnant kidney of five of six nephrectomized rats, a model of chronic renal failure [23], and it is therefore possible that SGLT2 expression may also be slightly decreased in patients with moderate renal impairment. Another possibility is that there was a difference in canagliflozin exposure in the active site in these patients. However, because there was no difference in the cumulative urinary excretion of canagliflozin among the three groups of patients with different levels of renal function, it is unlikely that there was a difference in canagliflozin exposure in the renal tubules. The exact reason for the discrepancy therefore remains unclear.

Other SGLT2 inhibitors have also been shown to increase UGE in patients with impaired renal function.

Ipragliflozin significantly increased UGE in each estimated GFR (eGFR) class in a study by Ferrannini et al. [24]. In this same study, absolute glycosuria decreased with declining GFR, while fractional glucose excretion (excretion/filtration; a measure of the efficiency of SGLT2 inhibitors) was unaffected by renal impairment. Because UGE is affected by the rate of glomerular filtration of glucose, the decrease in ΔUGE24 h may result from decreased renal function.

In type 2 diabetes patients with moderate renal impairment, the blood glucose-lowering effect is likely to be attenuated associated with decreased ΔUGE24 h. However, in these patients, the 24-h UGE was approximately 70 % of that in type 2 diabetes patients with normal renal function or mild renal impairment (60–70 g), and a decrease in 24-h mean plasma glucose was also observed. Based on this observation, we expect canagliflozin to reduce blood glucose levels in Japanese patients with moderate renal impairment. In addition, a phase III study in non-Japanese type 2 diabetes patients with moderate renal impairment (eGFR ≥30 and <50 mL/min/1.73 m^2) demonstrated a significant blood glucose-lowering effect of canagliflozin in these patients compared with placebo [18].

Both doses of canagliflozin appeared to be well-tolerated: only one case of pollakiuria and one of diarrhea were considered related to the study drug. Both were mild and resolved. There were no cases of hypoglycemia. However, as this was a pharmacokinetic study in which only one dose

was administered, the safety of canagliflozin in patients with renal impairment should be examined in larger, longer-term studies.

The results of this study should be considered in light of its limitations, including its small sample size and enrolment of Japanese patients. Therefore, the results may not be generalizable to other populations. However, our findings were consistent with those in Western patients reported by Devineni et al. [20]. In addition, we only studied patients with moderate renal impairment, so the findings may be different in patients with more severe kidney disease. Finally, we only administered single doses so we cannot infer whether the pharmacokinetics of canagliflozin and its metabolites would be affected during longer-term administration. Longer-term studies in a larger number of patients are needed to clarify this issue.

5 Conclusion

The pharmacokinetics of canagliflozin and its metabolites (M5 and M7) in Japanese patients are affected by renal function, with slight decreases in CL_R found. No difference in the C_{max} of canagliflozin was observed, but the C_{max} of M5 and M7 was greater in patients with normal renal function or mild renal impairment than in patients with moderate renal impairment. In patients with moderately decreased renal function, the exposure to canagliflozin is greater than in those with normal renal function or mild renal impairment, although the increases in exposure were minimal. The ability of canagliflozin to promote UGE was reduced as a function of decreasing GFR. In Japanese type 2 diabetes patients with and without moderate renal impairment, canagliflozin administered as a single dose was well-tolerated, raising no safety concerns. The small increase in exposure to canagliflozin in patients with moderately decreased renal function is unlikely to be clinically relevant; thus, dose reductions may not be necessary and canagliflozin may be a suitable treatment option for Japanese patients with type 2 diabetes and moderate renal impairment.

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