Influence of Hepatic Impairment on the Pharmacokinetics and Safety Profile of Dapagliflozin: An Open-Label, Parallel-Group, Single-Dose Study

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ABSTRACT

Background: Dapagliflozin, a selective inhibitor of renal sodium glucose co-transporter 2, is under development for the treatment of type 2 diabetes mellitus. Dapagliflozin elimination is primarily via glucuronidation to an inactive metabolite, dapagliflozin 3-O-glucuronide. Pharmacokinetic studies are recommended in subjects with impaired hepatic function if hepatic metabolism accounts for a substantial portion of the absorbed drug.

Objective: The purpose of our study was to compare the pharmacokinetics of dapagliflozin in patients with mild, moderate, or severe hepatic impairment (HI) with healthy subjects.

Methods: This was an open-label, parallel-group study in male or female patients with mild, moderate, or severe HI (6 per group according to Child-Pugh classification) and in 6 healthy control subjects. The control subjects were matched to the combined HI group for age (±10 years), weight (±20%), sex, and smoking status, with no deviations from normal in medical history, physical examination, ECG, or laboratory determinations. All participants received a single 10-mg oral dose of dapagliflozin, and the pharmacokinetics of dapagliflozin and dapagliflozin 3-O-glucuronide were characterized. Dapagliflozin tolerability was also assessed throughout the study.

Results: Demographic characteristics and baseline physical measurements (weight, height, and body mass index) were similar among the 18 patients in the HI groups (58–126 kg; 151.2–190.0 cm, and 31.5–37.7 kg/m^2, respectively) and the healthy subject group (65.0–102.6 kg; 166.0–184.0 cm, and 23.3–34.3 kg/m^2, respectively). In those with mild, moderate, or severe HI, dapagliflozin mean C_{max} values were 12% lower and 12% and 40% higher than healthy subjects, respectively. Mean dapagliflozin $AUC_{0-\infty}$ values were 3%, 36%, and 67% higher compared with healthy subjects, respectively. Dapagliflozin 3-O-glucuronide mean C_{max} values were 4% and 58% higher and 14% lower in those with mild, moderate, or severe HI compared with healthy subjects, respectively, and mean dapagliflozin 3-O-glucuronide $AUC_{0-\infty}$ values were 6%, 100%, and 30% higher compared with healthy subjects, respectively. These values were highly dependent on the calculated creatinine clearance of each group. All adverse events were mild or moderate, with no imbalance in frequency between groups.

Conclusions: Compared with healthy subjects, systemic exposure to dapagliflozin in subjects with HI was correlated with the degree of HI. Single 10-mg doses of dapagliflozin were generally well tolerated by participants in this study. Due to the higher dapagliflozin exposures in patients with severe HI, the benefit:risk ratio should be individually assessed because the long-term safety profile and efficacy of dapagliflozin have not been specifically studied in this population. (*Clin Ther*. 2011;33:1798–1808)

Key words: dapagliflozin, hepatic impairment, pharmacokinetics, SGLT2 inhibitors, special populations.

INTRODUCTION

The global prevalence of diabetes is projected to rise to 438 million (or ~7.8% of the entire adult population) by 2030.[1] Type 2 diabetes mellitus (T2DM) accounts for the majority (85%–95%) of all cases[2] and is a pro-

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gressive disorder characterized by hyperglycemia, a decrease in insulin secretion, and increased insulin resistance.[3,4] Over time, escalating doses of antidiabetic agents and additional medications are required to meet treatment goals.[5] Despite the availability of several different classes of antidiabetic agents, only a little more than half of patients with T2DM are achieving their glycemic goals.[6]

One strategy under investigation for the management of T2DM is the inhibition of renal glucose reabsorption. Sodium glucose co-transporter type 2 (SGLT2) is the predominant glucose transporter in the proximal tubule, and inhibition of SGLT2 has been shown to improve glycemic control through an increase in urinary glucose excretion.[7] Dapagliflozin is a highly selective inhibitor of the SGLT2 that is currently under development for the treatment of T2DM.[8,9] Improvements in glycemic parameters have been observed with oral dapagliflozin treatment in patients with T2DM when administered as monotherapy, as well as in combination therapy, with a 10-mg dapagliflozin once-daily dose appearing to show the optimal benefit:risk profile.[10–12] The pharmacokinetics (PK) and pharmacodynamics of dapagliflozin have been evaluated in single-ascending-dose and multiple-ascending-dose studies in healthy subjects and patients with T2DM.[13,14] In these studies, dapagliflozin demonstrated linear PK over the dose range of 2.5 to 500 mg and a dose-dependent increase in urinary glucose excretion over 24 hours.

The liver is an important site of drug biotransformation that can also influence PK through factors such as hepatic blood flow, plasma protein binding, and biliary excretion. Altered PK due to changes in these parameters, diseases, or concomitant administration of other drugs may affect the efficacy and safety profile of a drug such that dosage adjustment may be needed. The US Food and Drug Administration recommends a PK study in subjects with impaired hepatic function if hepatic metabolism and/or excretion accounts for a substantial portion (>20%) of the absorbed drug.[15] Metabolism represents the primary pathway for the elimination of dapagliflozin accounting for >75% of the administered drug and is primarily via glucuronidation (hepatic and extra-hepatic) by uridine diphosphate glucuronyl transferase (UGT1A9) to form a major inactive metabolite, dapagliflozin 3-O-glucuronide, which does not inhibit SGLT2 at doses of dapagliflozin shown to reduce glycemia in patients with T2DM.[16] Less than 2% of the administered dapagliflozin dose is recovered in the urine as unchanged drug and radiolabeled dapagliflozin absorption, distribution, metabolism, and excretion studies have shown that dapagliflozin 3-O-glucuronide represents the major clearance pathway in human subjects, and it has similar systemic exposure to parent dapagliflozin.[16] Dapagliflozin 3-O-glucuronide is primarily excreted in the urine and its renal clearance is highly dependent upon creatinine clearance. The dapagliflozin 3-O-glucuronide metabolite is ~2400 times less potent with regard to SGLT2 inhibition compared with parent dapagliflozin.

Because individuals with T2DM have a higher incidence of liver function test abnormalities than those without T2DM, hepatic impairment (HI) is an important consideration in this population.[17,18] Elevated markers of liver dysfunction alanine aminotransferase (ALT) and γ-glutamyl transpeptidase are present in 22.9% and 23.7% of patients with T2DM, respectively.[18] In cases of HI, the use of several antidiabetes drugs is cautioned, limiting the therapeutic options that are available for patients with T2DM who have HI. Prescribing information for metformin states that it should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.[19] Glimepiride dosage should be conservative to avoid hypoglycemic reactions,[20] repaglinide should be used cautiously,[21] and pioglitazone should be initiated with caution.[22] Stringent glycemic control is still necessary in this population of patients with T2DM, and additional effective and safe therapeutic options are needed.

In the study presented here, the PK and safety profile of dapagliflozin and dapagliflozin 3-O-glucuronide following a single oral dose of dapagliflozin (10 mg) in patients with varying degrees of HI were compared with healthy subjects. The influence of HI on the plasma free fraction of dapagliflozin is also assessed.

PATIENTS AND METHODS

Study Population

The study group included a total of 24 participants (16 male, 8 female) aged 31 to 64 years. Six of the participants were healthy, 6 had mild HI, 6 had moderate HI, and 6 had severe HI. The Child-Pugh grading system[23] was used to assess the severity and prognosis of HI (A = mild HI, B = moderate HI, and C = severe HI). HI groups comprised male and female subjects with HI conforming to the Child-Pugh classifications

A, B, or C documented by medical history, physical examination, and one or more of the following tests that were performed by the patients' primary care physicians using standard of care and certified clinical laboratories: liver biopsy, computed tomography, magnetic resonance imaging, ultrasonography, radionuclide liver/spleen scan, abdominal laparoscopy, or appropriate serological markers (eg, albumin, ALT, aspartate aminotransferase [AST], bilirubin, prothrombin time, and international normalized ratio). Control subjects were healthy male or female subjects matched to the combined HI group for age (approximately ±10 years), weight (approximately ±20%), sex, and smoking status. Inclusion criteria for the healthy group consisted of no deviations from normal in medical history, physical examination, ECG, or laboratory determinations.

Women of childbearing potential in all groups were required to have had a negative pregnancy test result approximately 24 hours before the start of study medication.

Key exclusion criteria for all groups were any significant acute medical illness (eg, new conditions or exacerbation of pre-existing conditions) within the past 2 months or major surgery within 4 weeks of study drug administration, active alcoholic hepatitis, current or recent (within 3 months before screening) history of significant gastrointestinal disease other than that secondary to cirrhosis, autoimmune liver disease, previous liver transplantation, abnormal renal function using serum creatinine or Cockroft-Gault formula (serum creatinine >1.5 mg/dL or estimated creatinine clearance <60 mL/min), history of drug allergy, or exposure to study drug or related compounds.

Study Design

This study was conducted between March 28, 2008, and October 1, 2008, by 3 clinical sites (Advanced Clinical Research Institute, Anaheim, California, Dennis Riff, MD, FACG; Hospital Austral, Buenos Aires, Argentina, Marcelo Silva, MD; Clinical Research Sp. ZOO, Warsaw, Poland, Katarzyna Jarus-Dziedzic, MD, PhD) and the protocol was approved by institutional review boards or local ethics committees. The study was conducted in accordance with Good Clinical Practice Guidelines. All participants provided written informed consent prior to the study. Participants were recruited and enrolled in the study under the supervision of the principal investigator or his/her qualified designee at each study site. Participants were compensated for their time and expenses associated with their involvement in the study. This study was not registered in a clinical trials registry because the initiation date predates the current guidelines according to the Declaration of Helsinki. This was an open-label, parallel-group, single-dose study in patients with HI and healthy subjects matched to the combined HI groups to the extent possible for age (approximately ±10 years), weight (approximately ±20%), sex, and smoking status. Sample size was chosen based on US Food and Drug Administration recommendations for PK studies in subjects with HI.[15] Six patients with HI were enrolled into each of the 3 Child-Pugh groups (A = mild, B = moderate, or C = severe). Six healthy control subjects, matched to the HI subjects, were enrolled after at least 6 subjects in any HI class group had completed the study. Each participant received a single 10-mg oral tablet dose of dapagliflozin and was required to fast for 6 hours prior until 4 hours post-dosing. Participants remained at the study unit for ≤5 days post-dosing for collection of PK samples and safety monitoring. Participants were also required to fast for 8 hours before laboratory evaluations on day 1 and at study discharge.

Pharmacokinetic Assessments

PK parameters of dapagliflozin and dapagliflozin 3-O-glucuronide were derived from plasma concentration versus time data. The PK profile of dapagliflozin and dapagliflozin 3-O-glucuronide were followed for 96 hours post-dose. Blood samples were taken at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, and 96 hours after dosing. At each collection time point, one 3.0-mL blood sample was collected into a labeled potassium EDTA tube. Immediately after collection, each blood sample was gently inverted 8 to 10 times for complete mixing with the anticoagulant and placed on wet ice. Within 30 minutes of collection, blood samples were centrifuged at 5 degrees for 10 minutes at 1500 × g. Within 15 minutes of centrifugation, plasma was transferred into a screw-capped polypropylene tube and stored at or below −20°C. Samples were shipped on dry ice to the analytical site and were stored at approximately −20°C until analyzed.

Dapagliflozin and dapagliflozin 3-O-glucuronide were assayed at Atlanbio (Saint Nazaire, France) using solid phase extraction and LC-MS/MS by a validated method. The assay used 0.15 mL plasma.[13] C_6-labelled

dapagliflozin and dapagliflozin 3-O-glucuronide were used as internal standards. Following solid phase extraction, chromatographic separation was achieved with gradient elution on a Sunfire C_{18} (50 × 2.1 mm, 5 μm [Water Corp., Milford, Massachusetts]) column. Detection was by negative heated–electrospray ionization mass spectroscopy using a TSQ Quantum Ultra mass spectrometer (Thermo Corp., Philadelphia, Pennsylvania). This assay had a lower limit of quantification of 1.00 ng/mL and an upper limit of quantification of 500 ng/mL for both dapagliflozin and dapagliflozin 3-O-glucuronide. The between-run variability (%CV) was ≤2.5 and ≤3.0 for dapagliflozin and dapagliflozin 3-O-glucuronide, respectively. The within-run variability (%CV) was ≤5.3 for dapagliflozin and ≤10.9 dapagliflozin 3-O-glucuronide. Individual subject PK parameter values were derived by noncompartmental methods,[24] using a validated PK analysis program (Kinetica 4.4.1 within eToolbox 2.6.1 [Thermo Corp.]). C_{max} and T_{max} were obtained from actual observations. The terminal log-linear phase of the concentration–time curve was identified by least-squares linear regression of at least 3 data points. The $t_{½}$ of the terminal log-linear phase was calculated as ln2/Lz, where Lz was the absolute value of the slope of the terminal log-linear phase. The AUC_{0-t} was calculated using the mixed log-linear trapezoidal algorithm in Kinetica. $AUC_{0-\infty}$ was estimated by summing AUC_{0-t} and the extrapolated area, computed by the quotient of the last observable concentration and Lz.

The plasma free fraction of dapagliflozin was evaluated 1.5 hours postadministration by an equilibrium dialysis method.

Safety Profile

Participants were closely monitored throughout the study for adverse events (AEs). AEs were spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. To prevent reporting bias, participants were not questioned regarding the specific occurrence of one or more AEs. AEs and laboratory results were reviewed by a qualified physician who was an investigator or subinvestigator. For each AE, the investigator or subinvestigator also assigned an intensity and relationship to study drug based on his or her clinical judgment. Participants were not to be discharged from the study until the investigator had determined that AEs had either completely resolved or were not of clinical significance.

Statistics

The sample size for this study was not based on statistical power considerations. However, for each of the Child-Pugh classes, data from 6 patients with HI would provide 90% confidence that the estimated impaired:control ratio of C_{max} geometric means were within 17% of the true value and the estimated impaired:control ratio of $AUC_{0-\infty}$ geometric means were within 21% of the true value for each class. Therefore, a total of 24 subjects were enrolled in the study: 6 participants for each of the hepatic function groups (healthy subjects and Child-Pugh classes A, B, and C).

To assess the effects of HI on the PK of dapagliflozin and dapagliflozin 3-O-glucuronide, ANOVAs were performed on log-transformed C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ values for each analyte. The factor in the analyses was hepatic function group. Point estimates and 90% CIs for means and differences between means on the log scale were exponentiated to express the results as geometric means and ratios of geometric means on the original scale. No adjustment was made for multiplicity. Summary statistics were tabulated for each of the PK parameters by hepatic function group for each analyte.

RESULTS

Demographic and Baseline Characteristics

Demographic characteristics and baseline physical measurements were similar among the 24 participants (aged 31–64 years) across the 4 hepatic function groups (**Table I**). All treated subjects completed the study.

Pharmacokinetics

Dapagliflozin

Mean plasma concentration profiles for dapagliflozin in healthy subjects and those with varying degrees of HI are shown in **Figure 1A**. In healthy subjects, following a single oral dose of 10-mg dapagliflozin, plasma concentrations of dapagliflozin rapidly increased to a mean C_{max} of 136 ng/mL, with a T_{max} of 1 hour. The $t_{½}$ for dapagliflozin in these healthy subjects was 12.9 hours. $AUC_{0-\infty}$ and AUC_{0-t} were 465 ng/h/mL and 438 ng/h/mL in healthy subjects. Mild HI resulted in no clinically relevant differences in dapagliflozin exposure (<4% higher) compared with healthy subjects. Increasing severity of HI showed a

Table I. Demographic characteristics and baseline physical measurements by hepatic impairment group.

Characteristic	Impairment Group				Total (N = 24)
	Healthy (n = 6)	Mild (n = 6)	Moderate (n = 6)	Severe (n = 6)	
Age, y					
Mean (SD)	37 (7)	37 (3)	54 (7)	49 (6)	44 (9)
Range	31–49	32–40	46–64	41–56	31–64
Gender, no. (%)					
Male	4 (67)	5 (83)	3 (50)	4 (67)	16 (67)
Female	2 (33)	1 (17)	3 (50)	2 (33)	8 (33)
Race, no. (%)					
White	6 (100)	6 (100)	6 (100)	5 (83)	23 (96)
American Indian/Alaska native	0	0	0	1 (17)	1 (4)
Height, cm					
Mean (SD)	172.5 (6.1)	171.8 (6.6)	166.9 (11.8)	172.7 (11.2)	171.0 (9.0)
Range	166.0–184.0	163.0–181.0	151.2–183.0	161.0–190.0	151.2–190.0
Weight, kg					
Mean (SD)	81.8 (15.4)	80.9 (16.5)	87.5 (20.7)	89.2 (16.2)	84.9 (16.5)
Range	65.0–102.6	58.0–100.8	68.0–126.0	65.3–110.0	58.0–126.0
Body mass index					
Mean (SD)	27.4 (4.6)	27.3 (4.6)	31.3 (5.2)	29.9 (5.1)	29.0 (4.9)
Range	23.3–34.3	21.5–31.3	25.3–37.7	22.5–37.1	21.5–37.7
Estimated creatinine clearance, mL/min					
Mean (SD)	138.3 (30.6)	127.8 (56.0)	158.3 (31.6)	142.8 (42.5)	141.8 (40.3)
Range	91–167	69–232	104–191	91–200	69–232

progressive increase in geometric mean dapagliflozin C_{max} to 190 ng/mL (40% increase) in severely impaired patients, with a corresponding increase in geometric mean dapagliflozin AUC values. $AUC_{0-\infty}$ values increased with decreasing hepatic function and, compared with healthy subjects, were 36% higher in moderately impaired patients and 67% higher in patients with severe HI (**Figure 1B**). AUC_{0-t} also increased with decreasing hepatic function, and compared with healthy subjects was 1% higher in mildly impaired patients, 40% higher in moderately impaired patients, and 74% higher in patients with severe HI.

Median T_{max} and mean $t_{½}$ values were reduced in those with moderate to severe HI (**Table II**). No apparent change in the mean plasma free fraction of dapagliflozin bound to plasma proteins was observed in the HI groups (mild, 8.9% free; moderate, 6.6% free; and severe, 8.4% free) compared with the healthy subject control group (7.9% free).

Dapagliflozin 3-O-glucuronide

Mean plasma concentration profiles for dapagliflozin 3-O-glucuronide in patients with varying degrees of HI are shown in **Figure 2A**. Following a single oral dosing of 10-mg dapagliflozin, dapagliflozin 3-O-glucoronide geometric mean C_{max} was 196 ng/mL at a T_{max} of 1.25 hours post-dose in healthy subjects. Dapagliflozin 3-O-glucuronide geometric mean $AUC_{0-\infty}$ and AUC_{0-t} values were 837 ng/h/mL and 803 ng/h/mL, respectively, in healthy subjects, and the $t_{½}$ for dapagliflozin 3-O-glucuronide was 16.4 hours. Patients with mild HI showed no relevant difference to healthy subjects in dapagliflozin 3-O-glucuronide

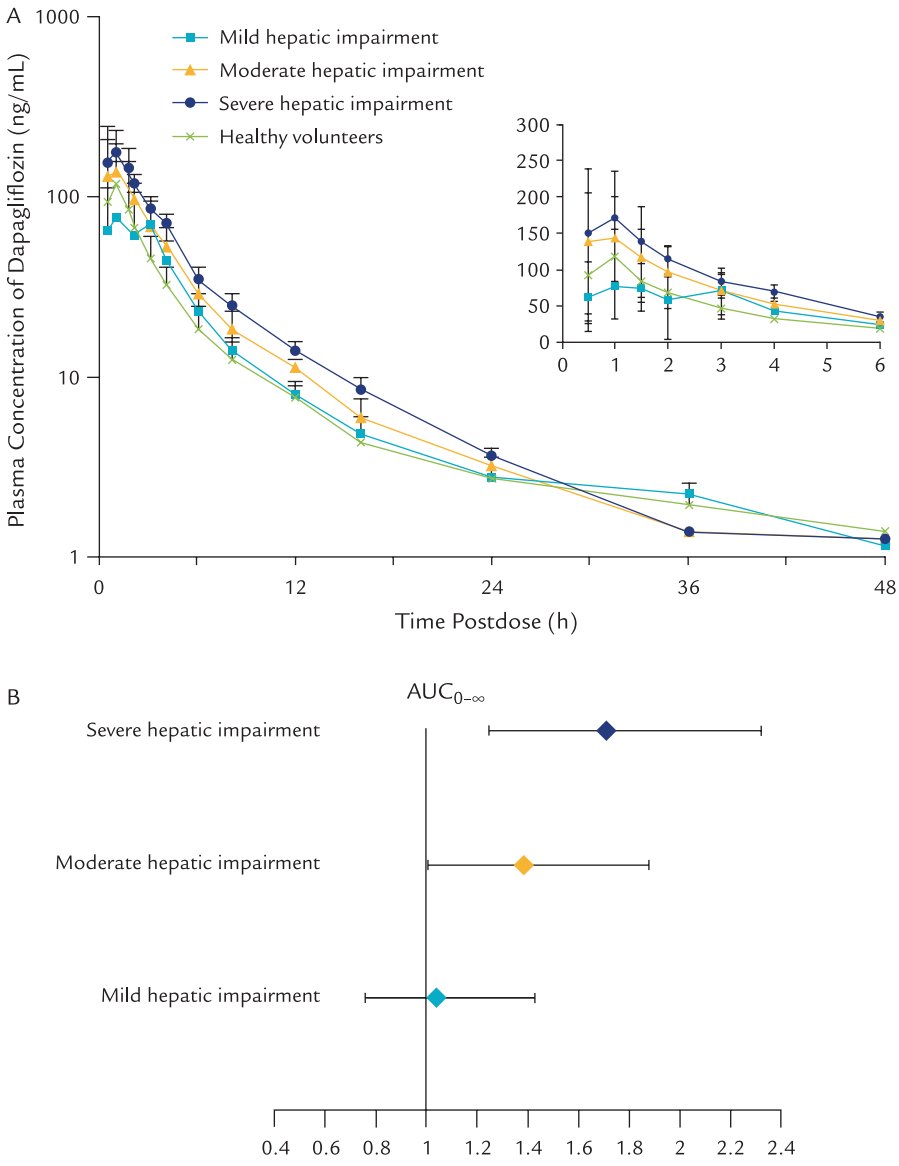

Figure 1. Dapagliflozin plasma concentration–time profiles (A) and ratio of geometric means for dapagliflozin $AUC_{0-\infty}$ (B) in subjects with varying degrees of hepatic impairment compared with healthy subjects.

geometric mean C_{max} or $AUC_{0-\infty}$ values (3.5% and 6.2% higher, respectively). Compared with the healthy group, dapagliflozin 3-O-glucuronide geometric mean C_{max} was 58.2% higher in the moderate HI group and 14.3% lower in the severe HI group (**Table II**). Geometric mean dapagliflozin 3-O-glucuronide $AUC_{0-\infty}$ values were 100% higher in those with moderate HI and 29.3% higher in the severe HI group compared with healthy subjects (**Figure 2B**).

In all HI groups, compared with the healthy group, median T_{max} values were 0.5 to 0.75 hours longer and mean $t_{½}$ values were 36% to 63% shorter for dapagliflozin 3-O-glucuronide. The ratio of dapagliflozin 3-O-glucuronide to dapagliflozin (metabolite ratio [MR]) was calculated by dividing the $AUC_{0-\infty}$ of dapagliflozin 3-O-glucuronide by the $AUC_{0-\infty}$ of dapagliflozin and correcting for their difference in molecular mass. The mean MR was 1.32 (0.50) in the healthy group. This

Table II. Summary of dapagliflozin and dapagliflozin 3-O-glucuronide pharmacokinetics by hepatic function group

	Hepatic Function Group			
Pharmacokinetics	Healthy	Mild	Moderate	Severe
Dapagliflozin				
C_{max}, geometric mean (%CV), ng/mL	136 (31)	120 (28)	153 (51)	190 (40)
T_{max}, median, h (min, max)	1.00 (0.50,2.00)	1.25 (0.50,3.17)	0.75 (0.50,3.00)	0.75 (0.50,4.00)
AUC_{0-t}, mean (%CV), ng/h/mL	438 (34)	443 (25)	614 (40)	762 (22)
$AUC_{0-\infty}$, geometric mean (%CV), ng/h/mL	465 (34)	480 (26)	632 (40)	776 (22)
$t_{1/2}$, mean (SD), h	12.9 (5.5)	15.0 (16.3)*	8.1 (2.9)	6.1 (1.4)
Dapagliflozin 3-O-Glucuronide				
C_{max}, geometric mean (%CV), ng/mL	196 (41)	203 (60)	310 (53)	168 (43)
T_{max}, median, h (min, max)	1.25 (1.00,3.00)	2.00 (1.00,4.17)	1.75 (1.50,3.00)	2.00 (1.50,6.00)
AUC_{0-t}, mean (%CV), ng/h/mL	803 (38)	853 (46)	1650 (49)	1049 (34)
$AUC_{0-\infty}$, geometric mean (%CV), ng/h/mL	837 (38)	889 (44)	1670 (49)	1082 (32)
$t_{1/2}$, mean (SD), h	16.4 (15.2)	10.5 (5.1)	9.3 (7.2)	6.0 (1.7)

*The mean (SD) $t_{1/2}$ for dapagliflozin in the mild impairment group is 8.5 (3.52) if the one outlier with a value of 47.6 hours is excluded.

ratio was slightly higher in the mild and moderate HI groups (1.42 [0.71] and 2.02 [0.94], respectively) and lower in the severe HI group (0.99 [0.17]) compared with the healthy group.

Safety Profile and Tolerability

Dapagliflozin was well tolerated by all participants. There were no deaths during the course of the study and no discontinuations due to AEs following the administration of dapagliflozin. The degree of HI had no apparent effect on the incidence of AEs in this study (**Table III**). Overall, 4 participants (1 healthy, 2 moderate, 1 severe) experienced 5 AEs during the study, including abdominal discomfort, back pain, dizziness, rash, and phlebitis. All AEs resolved before study discharge.

Thirteen subjects (healthy, n = 3; Child-Pugh A, n = 1; Child-Pugh B, n = 3; Child-Pugh C, n = 6) had 25 laboratory marked abnormalities after receiving dapagliflozin. The majority of the marked abnormalities occurred in the Child-Pugh C group (n = 18), as would be expected with their advanced disease state. No marked abnormalities were reported as AEs and none were considered to be clinically important by the investigators, given the subjects' liver disease status. No participants in the study had ALT and/or AST elevations to 3 times the upper limit of normal or had liver function test elevations associated with elevated total bilirubin.

There were no changes in vital sign measurements or ECG findings in the healthy or HI groups.

DISCUSSION

This study assessed the effects of varying degrees of HI on the exposure to dapagliflozin, as well as the safety profile of dapagliflozin in patients with reduced liver function compared with healthy subjects. The PK profile for dapagliflozin in healthy subjects in this study is

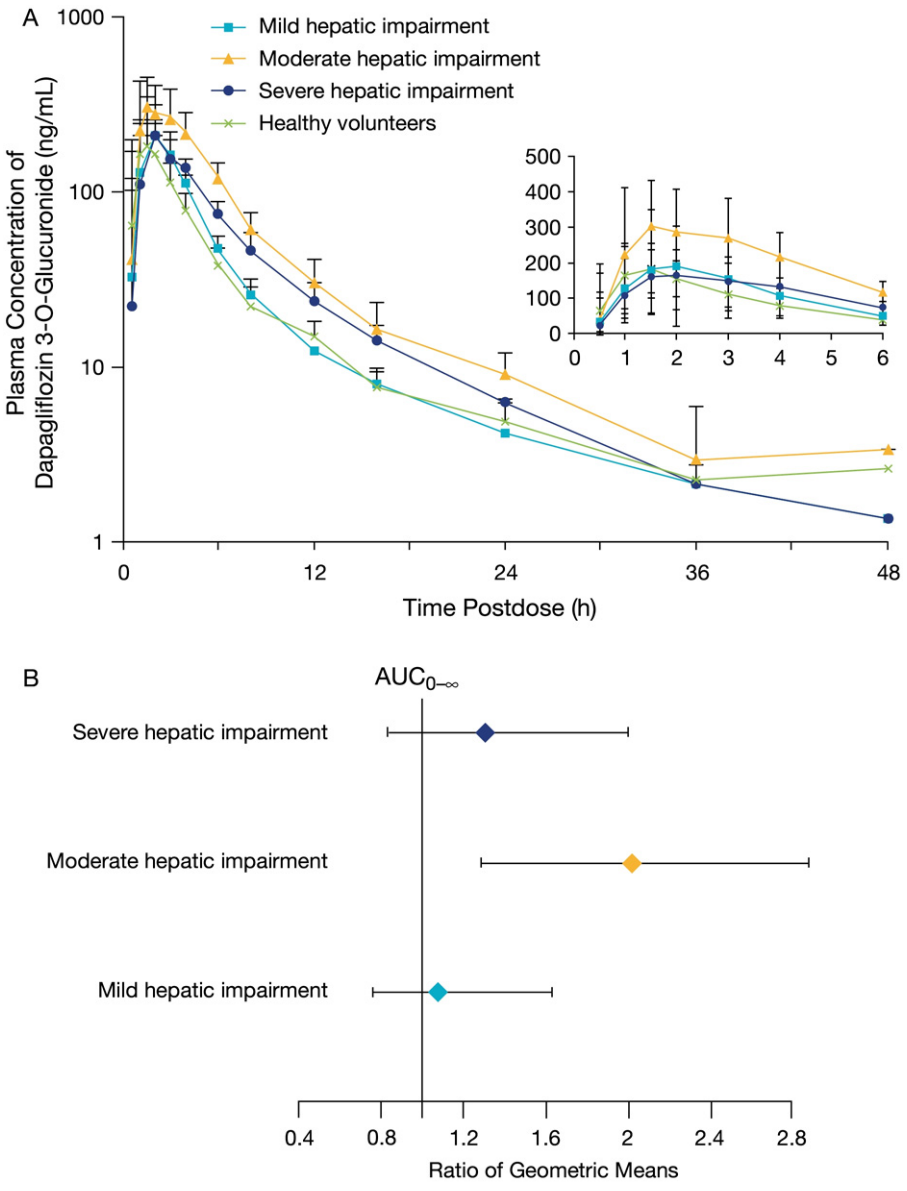

Figure 2. Dapagliflozin 3-O-glucuronide plasma concentration–time profiles (A) and ratio of geometric means for dapagliflozin 3-O-glucuronide plasma $AUC_{0-\infty}$ (B) in subjects with varying degrees of hepatic impairment compared with healthy subjects.

consistent with results previously reported for dapagliflozin.[13] Mild HI had no effect on overall exposure to either dapagliflozin or its major metabolite dapagliflozin 3-O-glucuronide. However, consistent with a possible reduction in hepatic UGT1A9 enzyme activity, higher systemic exposures to dapagliflozin were observed in the patients with moderate and severe HI compared with healthy subjects. Although a body weight–adjusted analysis of PK parameters was not performed, which is a potential limitation of this study, the matching of healthy subjects to within a mean to the combined HI groups' weight (approximately ±20%) and other important demographic characteristics allows for a minimally confounded evaluation of the effect of HI on dapagliflozin PK at the proposed usual dose of 10 mg.

Table III. Adverse events (AEs) by hepatic function group.

AE	No. (%) of Subjects with AEs			
	Healthy Subjects	Mild Impairment	Moderate Impairment	Severe Impairment
Abdominal discomfort	0	0	1 (16.7)	0
Back pain	0	0	1 (16.7)	0
Dizziness	0	0	0	1 (16.7)
Rash	0	0	1 (16.7)	0
Phlebitis	1 (16.7)	0	0	0
Total subjects with AEs	1 (16.7)	0	2 (33.3)	1 (16.7)
Total AEs	1	0	3	1

Although smaller fractions of the dapagliflozin dose would be expected to be metabolized to dapagliflozin 3-O-glucuronide with increasing severity of HI, differences in systemic exposure (both C_{max} and AUC) to dapagliflozin 3-O-glucuronide between the HI and healthy subject groups did not correlate directly with the severity of HI. In the moderate HI group, a near doubling was seen in exposure to dapagliflozin 3-O-glucuronide, whereas in the severe HI group, the overall exposure was closer to that observed in the healthy group. One possible explanation for these findings is that dapagliflozin 3-O-glucuronide is cleared mainly via renal excretion and the estimated creatinine clearance values were not balanced between the groups in this study. **Figure 3** shows the relationship between dapagliflozin 3-O-glucuronide $AUC_{0-\infty}$ and estimated creatinine clearance for the various groups in this study. Even with the differences in parent dapagliflozin, a relationship between renal function and dapagliflozin 3-O-glucuronide is evident. The moderate HI group had the widest range of estimated creatinine clearance (69 mL/min–232 mL/min) of any group (**Table I**), but this group also had several patients clustered at the lower end of the estimated creatinine clearance range in this study. These factors are likely to have contributed to the large variability and the relatively higher metabolite-to-parent $AUC_{0-\infty}$ ratio in this group. Similar to dapagliflozin 3-O-glucuronide AUC, the mean dapagliflozin 3-O-glucuronide C_{max} was highest in the moderate HI group (58% higher than healthy subjects), whereas the mean dapagliflozin 3-O-glucuronide C_{max} values were similar in the healthy subjects and the mild and severe HI groups. The reasons for these findings may also be related to the differences in renal function between the groups.

Aside from the effect of decreasing hepatic glucuronidation with loss of liver function, other factors may influence the exposure to dapagliflozin and dapagliflozin 3-O-glucuronide, including free fraction in plasma. The free fraction of dapagliflozin is relatively low in healthy subjects (<10% free) and it was considered that HI could potentially lead to a reduction in plasma protein levels, resulting in higher free fractions of dapagliflozin. However, the results from this study

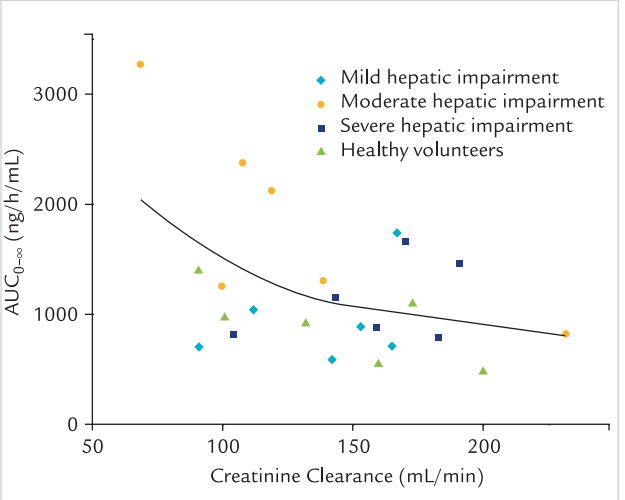

Figure 3. Exposure of dapagliflozin 3-O-glucuronide after single dose of dapagliflozin versus estimated creatinine clearance in patients with varying degrees of hepatic impairment.

indicated that decreasing liver function had no effect on the free dapagliflozin plasma concentration.

Glucuronidation is generally considered to be less affected by HI compared with oxidative metabolic pathways through cytochrome P450 enzymes,[25,26] and total dapagliflozin exposure may, in part, be related to the distribution and expression of UGT1A9. Although the liver is the major site of glucuronidation, a number of extrahepatic tissues exhibit UGT1A9 activity, including the kidney.[26–28] In patients with various degrees of HI, somewhat similar differences in exposure to those observed in this study for dapagliflozin have been observed with the immunosuppressant mycophenolic acid, which is also glucuronidated by UGT1A9.[29] Those authors also speculated that there may be upregulation of UGT1A9 in the kidney as a compensatory mechanism for reduced hepatic metabolic capacity. Extra-hepatic UGT1A9 metabolism, particularly in the kidney, whether upregulated or not, may also result in relatively modest effects of HI on dapagliflozin PK.

Dapagliflozin was well tolerated across the HI groups with no deaths, serious AEs, or discontinuations due to AEs. Dapagliflozin was well tolerated in previously published clinical trials at exposure levels many times greater than those produced in this study,[13,14,30] and no evidence for a direct effect of dapagliflozin on liver function has been previously noted.[10,11]

The results of this single-dose study suggest that the PK of a single 10-mg dose of dapagliflozin in participants with varying degrees of HI is correlated with the degree of HI, probably as a result of decreased metabolic capacity with increasingly severe hepatic disease. The US Food and Drug Administration recommends dosage adjustments in labeling if there is a ≥2-fold increase in AUC with hepatic impairment. However, even in the most severe cases of HI (Child-Pugh C), the mean differences in exposure to dapagliflozin were <2-fold higher compared with healthy subjects. In this study, dapagliflozin was well tolerated in patients with liver disease who had various additional underlying diseases and who were taking a number of other medications.

CONCLUSIONS

Dapagliflozin was well tolerated in this population of hepatically impaired patients. Due to higher dapagliflozin systemic exposures in patients with severe HI, however, the benefit:risk ratio should be individually assessed, because the long-term safety and efficacy of dapagliflozin was not specifically studied in this population.

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