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