Effect of Hepatic or Renal Impairment on the Pharmacokinetics of Canagliflozin, a Sodium Glucose Co-transporter 2 Inhibitor

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ABSTRACT

Purpose: Canagliflozin is a sodium-glucose cotransporter 2 inhibitor approved for the treatment of type 2 diabetes mellitus (T2DM). Because T2DM is often associated with renal or hepatic impairment, understanding the effects of these comorbid conditions on the pharmacokinetics of canagliflozin, and further assessing its safety, in these special populations is essential. Two open-label studies evaluated the pharmacokinetics, pharmacodynamics (renal study only), and safety of canagliflozin in participants with hepatic or renal impairment.

Methods: Participants in the hepatic study (8 in each group) were categorized based on their Child-Pugh score (normal hepatic function, mild impairment [Child-Pugh score of 5 or 6], and moderate impairment [Child-Pugh score of 7–9]) and received a single oral dose of canagliflozin 300 mg. Participants in the renal study (8 in each group) were categorized based on their creatinine clearance (CL_{CR}) (normal renal function [$CL_{CR} \geq 80$ mL/min]; mild [CL_{CR} 50 to <80 mL/min], moderate [CL_{CR} 30 to <50 mL/min], or severe [CL_{CR} <30 mL/min] renal impairment; and end-stage renal disease [ESRD]) and received a single oral dose of canagliflozin 200 mg; the exception was those with ESRD, who received 1 dose postdialysis and 1 dose predialysis (10 days later). Canagliflozin's pharmacokinetics and pharmacodynamics (urinary glucose excretion [UGE] and renal threshold for glucose excretion [RT_G]) were assessed at predetermined time points.

Findings: Mean maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from time zero to infinite $(AUC)_{0-\infty}$ values differed by $<11\%$ between the group with normal hepatic function and those with mild and moderate hepatic impairment. In the renal study, the mean C_{max} values were 13%, 29%, and 29% higher and the mean $AUC_{0-\infty}$ values were 17%, 63%, and 50% higher in participants with mild, moderate, and severe renal impairment, respectively; values were similar in the ESRD group relative to the group with normal function, however. The amount of UGE declined as renal function decreased, whereas RT_G was not suppressed to the same extent in the moderate to severe renal impairment groups (mean RT_G, 93–97 mg/dL) compared with the mild impairment and normal function groups (mean RT_G, 68–77 mg/dL).

Implications: Canagliflozin's pharmacokinetics were not affected by mild or moderate hepatic impairment. Systemic exposure to canagliflozin increased in the renal impairment groups relative to participants with normal renal function. Pharmacodynamic response to canagliflozin, measured by using UGE and RT_G, declined with increasing severity of renal impairment. A single oral dose of canagliflozin was well tolerated by participants in both studies. ClinicalTrials.gov identifiers: NCT01186588 and NCT01759576. (*Clin Ther*. 2015;37:610–628) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: canagliflozin, ESRD, hepatic impairment, pharmacokinetics, renal impairment, T2DM.

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INTRODUCTION

The global prevalence of type 2 diabetes mellitus (T2DM) is increasing rapidly and projected to rise to 552 million by 2030.[1] Canagliflozin,* an active inhibitor of sodium glucose co-transporter 2,[2–7] is a novel oral hypoglycemic agent approved as an adjunct to diet and exercise in several countries to improve glycemic control in adults with T2DM. The recommended dose is 100 or 300 mg once daily.[2,8] Canagliflozin lowers the renal threshold for glucose excretion (RT_G), thereby increasing urinary glucose excretion (UGE) and reducing plasma glucose (PG) concentrations in patients with hyperglycemia.[4,7,9]

The mean absolute oral bioavailability of canagliflozin is ~65%.[10] It is metabolized by *O*-glucuronidation into 2 inactive metabolites (M7 and M5) by uridine diphosphate glucuronosyltransferase (UGT) 1A9 and UGT2B4, respectively. M7 and M5 are each 800-fold less potent sodium glucose co-transporter 2 inhibitors than canagliflozin, and both are thus considered pharmacologically inactive.[11]

When canagliflozin is administered orally as a single dose in healthy participants, ~60% of the administered dose is excreted in the feces as canagliflozin (41.5%) and M7 (3.2%).[11,12] Enterohepatic circulation of canagliflozin is negligible.[10] In vitro data suggest that M7 and M5 are stable in bile but not in feces at 37°C, and the fecal excretion of the unchanged canagliflozin may therefore be due to both incomplete absorption of canagliflozin and the biliary secretion of the *O*-glucuronides, followed by deconjugation or hydrolysis during intestinal transit.[11] The biliary metabolite profile was not characterized in human studies; however, based on the results of the rodent biliary excretion studies, it is anticipated that the biliary excretion is largely composed of glucuronide metabolites (as in rats and mice). In vitro transporter studies showed that canagliflozin is a substrate of all 3 biliary efflux transporters (multidrug resistance protein 2, breast cancer resistance protein, and P-glycoprotein). As described earlier, however, biliary excretion is not considered to be a major route of clearance for unchanged canagliflozin in humans, and hence, the role of efflux transporters in the biliary elimination of unchanged canagliflozin is considered low in humans. Furthermore, this claim is supported by a drug–drug interaction study[13] of cyclosporine (an inhibitor of multidrug resistance protein 2, breast cancer resistance protein, and P-glycoprotein) that found a small effect on canagliflozin, indicating that biliary excretion is not an important route of elimination for unchanged canagliflozin in humans.

Nearly 33% of the administered drug is excreted in urine, mostly as metabolites (M7, 17.2%; M5, 13.3%); ≤1% of the dose is excreted as unchanged canagliflozin in urine.[2,11] The renal clearance of canagliflozin adjusted for protein binding is roughly equal to the estimated glomerular filtration rate (eGFR), suggesting that unbound canagliflozin may be freely filtered and that canagliflozin concentrations in the lumen of the proximal tubule may be approximately equal to the unbound concentrations in the plasma. The available data suggest that despite the relatively low observed renal excretion of canagliflozin (1%), sufficient free concentrations of canagliflozin may be present in the tubular lumen to provide effective inhibition of sodium glucose co-transporter 2-mediated glucose transport.[14]

T2DM is also often associated with renal or hepatic impairment,[15–19] which may affect the pharmacokinetics (PK) of antidiabetic drugs in patients with these conditions.[20–22] The kidney is the target organ for canagliflozin because the expression and inhibition of sodium glucose co-transporter 2 are limited to this organ.[23] Canagliflozin's mechanism of action depends on the amount of glucose filtered in the glomerulus. Because the rate of UGE is proportional to the GFR and PG concentration,[4,7] decreased renal function may reduce the efficacy of canagliflozin. Furthermore, guidance from the US Food and Drug Administration (FDA) and the Committee for Proprietary Medicinal Products on renal studies recommend pharmacodynamic (PD) assessments, in addition to PK analyses in renal impairment studies, whenever appropriate.[20,24]

Understanding the effects of these comorbid conditions on the PK and PD of canagliflozin, and further assessing the safety in these special populations, is essential. Therefore, 2 distinct studies were conducted in nondiabetic participants: the first study evaluated the single-dose PK of canagliflozin in participants with varying degrees of hepatic function (hepatic study), and the second study evaluated the PK and PD of canagliflozin in participants with varying degrees of renal function (renal study) compared with healthy participants.

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