

## Review



# Possibility of pharmacokinetic drug interaction between a DPP-4 inhibitor and a SGLT2 inhibitor

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## ABSTRACT

Type 2 diabetes mellitus is a multifactorial condition characterized by high level of sugar in the blood. To control hyperglycemia, combination therapy is recommended if monotherapy fails to achieve glycemic control. The combination of a dipeptidyl peptidase-4 (DPP-4) inhibitor and a sodium-glucose cotransporter type 2 (SGLT2) inhibitor is a promising option of the combination therapies in terms of safety as well as efficacy. Despite of the value of combination therapy of these two agents, the pharmacokinetic drug interactions between these two classes of agents have been evaluated in a few drugs. Thus, we reviewed the potential pharmacokinetic drug interaction based on the *in vitro* metabolism- and transporter-mediated drug interaction information as well as drug interaction studies in human, between a DPP-4 inhibitor and a SGLT2 inhibitor which are marketed in South Korea.

**Keywords:** Dipeptidyl-peptidase IV inhibitors; Sodium-glucose transporter 2 inhibitors; Drug interaction; Pharmacokinetics

## INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a multifactorial condition with a complex etiology and a progressive disease course [1]. To control hyperglycemia, sequential addition of T2DM therapies, from monotherapy to combination therapy is recommended [2,3]. Dual therapy is suggested if monotherapy fails to achieve glycemic control and triple therapy should be considered if the target glycated hemoglobin (HbA1c) is not reached by dual therapy. Various combination approaches have been tried depending on patients' comorbidities and physiologic condition, however, established therapy comprising metformin, sulphonylureas or thiazolidinediones, have some undesirable properties, such as gastrointestinal discomfort, hypoglycaemia risk and weight gain, indicating that the newer agents for combination with more favorable safety profiles is needed. Dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter type 2 (SGLT2) inhibitors which are 2 newest classes of glucose-lowering agents is one of the options [4-6].

**Conflict of interest**

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DPP-4 inhibitors are oral medications that have moderate glucose-lowering effect. They prevent the degradation of endogenously released incretin hormones (glucagon-like peptide [GLP]-1 and glucose-dependent insulinotropic polypeptide [GIP]), which enhance insulin secretion and inhibit glucagon secretion, reducing plasma glucose level [7,8]. DPP-4 inhibitors regulate hyperglycemia with minimizing hypoglycaemia as their mode of action is glucose-dependent and have neutral effect on weight [9].

SGLT2 inhibitors are newest pharmacological class of glucose-lowering agents. They enhance urinary excretion of glucose by inhibiting glucose reabsorption at the proximal tubule of kidney [10]. SGLT2 inhibitors attracted a lot of attention as a remarkable reduction of cardiovascular event was demonstrated in T2DM patients with a history of cardiovascular disease. Moreover, empagliflozin was proved to impede the progression of kidney disease in T2DM patients [11-14]. In spite of high glucose-lowering effect [15] and benefits of cardiovascular and kidney disease, increased risk of urinary tract infection [16] and diabetic ketoacidosis (DKA) [17] associated with SGLT2 inhibitor have been reported. In addition, SGLT2 inhibitor therapy increases plasma glucagon concentrations by enhancing hepatic glucose production [18,19].

DPP-4 inhibitors and SGLT2 inhibitors exert their glucose-lowering effects via complementary mechanisms: DPP-4 inhibitors facilitate insulin secretion and SGLT2 inhibitors promote urinary glucose excretion. Their distinct mechanisms of action make it unlikely for these agents to exhibit deteriorated safety profiles. Most of all, no increased risk of hypoglycemia is expected as both DPP-4 inhibitors and SGLT2 inhibitors regulate hyperglycemia via glucose-dependent manner. In addition, the combination of a DPP-4 inhibitor and a SGLT2 inhibitor is expected to have additional benefits of potential weight loss. Recently, both classes have been reported to exert renoprotective effect [20,21].

Although the value of combination therapy of these two agents is identified, the pharmacokinetic drug interactions between these two classes of agents have been evaluated in a few drugs. Thus, we reviewed the potential pharmacokinetic drug interaction based on the *in vitro* metabolism- and transporter-mediated drug interaction information as well as drug interaction studies in human, between a DPP-4 inhibitor and a SGLT2 inhibitor which are marketed in South Korea.

**PHARMACOKINETICS OF DPP-4 INHIBITORS**

There are nine DPP-4 inhibitors which had been approved for marketing in South Korea till 2019. Although their major pharmacologic mechanisms of antidiabetic action are similar, their pharmacokinetic properties are different. Alogliptin, anagliptin, gemigliptin and sitagliptin are mainly eliminated from the body via urinary excretion, while critical dispositional process of linagliptin is fecal excretion after oral administration. Metabolism is important dispositional mechanism for evogliptin, saxagliptin, teneligliptin and vildagliptin. Anagliptin and vildagliptin are hydrolyzed with cytochrome P450 (CYP)-independent hydrolysis. We summarized the pharmacokinetic characteristics of each DPP-4 inhibitor in terms of possibility of drug interaction. Pharmacokinetic characteristics of each DPP-4 inhibitor are shown in **Table 1**.

**Table 1.** Pharmacokinetic characteristics of dipeptidyl peptidase-4 inhibitors

Drug	Metabolism (%)	Excretion unchanged (%)	Protein binding	Metabolic enzymes	Transporters	<i>In vitro</i> assessment of drug interaction	References
Alogliptin	< 7% of alogliptin concentration in urine	60–70% of administered amount	20%	CYP2D6/CYP3A4	Not a substrate of OAT1, OAT3, OCT2	Not inhibit (at clinically relevant concentration): CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP3A4, CYP2D6/OAT1, OAT3, OCT2; not induce (at clinically relevant concentration): CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP3A4	[22-24]
Anagliptin	29.2% of the administered amount	46.6% in urine and 4.1% in feces of administered amount	37.1–48.2%	CYP independent hydrolysis	Substrate of OAT1, OAT3, P-gp, MRP2 (anagliptin), Substrate of OAT3, BCRP, MRP2 and MRP4 (metabolite)	Inhibit: OAT3, OCT2 (in supratherapeutic concentration); not inhibit: CYP1A, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4	[25-27]
Evogliptin	-	< 25% of administered amount (rat study)	-	CYP3A4	Substrate of P-gp, BCRP (weak), not a substrate of OAT1B1, OAT1B3, OAT1, OAT3, OCT2	Not inhibit: CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4/P-gp, BCRP, OAT1B1, OAT1B3, OAT1, OAT3 or OCT2; not induce: CYP1A2, 2B6, 3A4	[28,30-32]
Gemigliptin	30.1–47.6% of plasma radioactivity	67.2–100% of plasma radioactivity	20–50%	CYP3A4	Substrate of P-gp	Inhibit: P-gp (weakly in high concentration); not inhibit: CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4; not induce: CYP1A2, 2C8, 2C9, 2C19, 3A4	[34,35]
Linagliptin	17.4% in feces and 2.2% in urine of administered amount	35.8% in feces and 25.3% in urine of administered amount	75–99%	CYP3A4	Substrate of P-gp, OCT2, not a substrate of OAT1B1/1B3, OAT1/3/4 and OCT1	Inhibit: CYP3A4 (weak to moderate)/P-gp (in supratherapeutic concentration), OCT1/2 (substrate specific); not inhibit: CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 4A11/OCT1/2; not induce: CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 4A11	[36-39]
Saxagliptin	36% of radioactivity in urine	24% of radioactivity in urine	50–75%	CYP3A4/5	Substrate of P-gp	Not inhibit: CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/P-gp; not induce: CYP1A2, 2B6, 2C8, 2C9, 3A4/P-gp	[40,41]
Sitagliptin	16% of administered amount	79% of administered amount	38%	CYP3A4/CYP2C8	Substrate of P-gp, OAT3	Not inhibit: CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6; not induce: CYP3A4	[42-45]
Teneligliptin	66–80% of absorbed teneligliptin	20–34% of absorbed teneligliptin	43–74%	CYP3A4, FMO3	Substrate of P-glycoprotein	Inhibit: CYP2D6, CYP3A4, FMO (weakly)/P-gp and OAT3 (in supratherapeutic concentration); not inhibit: CYP isozyme excluding CYP2D6, 3A4; not induce: CYP3A4, CYP1A2	[46-50]
Vildagliptin	72.4% of total plasma radioactivity exposure	23% of administered amount	85%	CYP independent hydrolysis, UGT2B7, UGT2B17 and UGT2B4	Substrate of P-gp (weak)	Not inhibit: CYP isoforms; not induce: CYP isoforms	[53,55]

CYP, cytochrome P450; OAT, organic anion transporter; OCT, organic cation transporter; P-gp, P-glycoprotein; BCRP, breast cancer resistance protein; FMO3, flavin-containing monooxygenase 3; UGT, UDP-glucuronosyltransferase.

### Alogliptin

Alogliptin is recommended to start at 25 mg once daily. In the clinical dosage range, alogliptin is rapidly absorbed with a time to maximum plasma concentration ( $t_{max}$ ) of approximately 2 hours and is eliminated with a half-life of 21 hours [22]. The absolute bioavailability of alogliptin is reported as approximately 100%. Most of alogliptin in plasma exists freely, with plasma protein binding of 20%, and its distribution in tissue is large with volume of distribution of 417 L after intravenous infusion of 12.5 mg alogliptin in healthy subjects [23].

Two minor metabolites, N-demethylated (M-I) and N-acetylated (M-II), were detected after oral administration of alogliptin with minor portion, < 2% and < 6% of alogliptin concentrations in urine, respectively; M-I was reported to inhibit DPP-4, but M-II was inactive. CYP2D6 and CYP3A4 are suggested to contribute to the metabolism of alogliptin. However, CYP-related metabolism of alogliptin is negligible, and alogliptin is primarily eliminated via renal excretion. It is reported that 60–70% of the administered alogliptin is

excreted as unchanged form in the urine. Its renal clearance is higher than the glomerular filtration rate, suggesting the existence of renal secretion, but it had not been reported which transporters are involved in active renal secretion of alogliptin [22,24].

*In vitro* studies have reported that alogliptin is neither a substrate nor an inhibitor of organic anion transporters (OATs) 1 and 3 and organic cation transporter (OCT) 2 and that it does not induce or inhibit CYP isozymes [22,24]. In clinical drug interaction studies, alogliptin slightly increased the area under the curve (AUC) of metformin, which is a substrate of OCT2 and multidrug and toxin extrusion proteins (MATEs) without an increase of maximum plasma concentration ( $C_{max}$ ). Alogliptin increased the AUC and  $C_{max}$  of dextromethorphan, a substrate of CYP2D6, and fexofenadine, a substrate of P-glycoprotein (P-gp), organic anion transporting polypeptide (OATP) 1A2 and OATP2B1, approximately by 1.2–1.4 folds. Alogliptin did not significantly alter the pharmacokinetics of other tested drugs (cimetidine, warfarin, caffeine, pioglitazone, tolbutamide, atorvastatin, ethinylestradiol, norethindrone, midazolam and digoxin). The effect of alogliptin on the pharmacokinetics of metformin, dextromethorphan and fexofenadine is of no clinical significance and dose adjustment is not required [22].

### Anagliptin

Anagliptin is recommended to dose 100 mg twice daily [25]. Anagliptin is well absorbed with bioavailability of > 73% and mean  $t_{max}$  of 0.9–1.8 hours, and its concentration decreases with half-life of 5.8–6.2 hours in patients with T2DM with recommended regimen [26]. The volume of distribution of anagliptin was 2.47 L/kg and plasma protein binding was 37.1–48.2% [27].

About a half of administered anagliptin is eliminated primarily in unchanged form with 46.6% in urine and 4.1% in feces in a clinical trial using [ $^{14}$ C]-radiolabeled anagliptin. Anagliptin is incompletely metabolized via CYP-independent hydrolysis. The main metabolite, carboxylate metabolite (M1), accounts for 29.2% of the administered amount. Renal clearance of anagliptin and M1, which exceed typical glomerular filtration rate of 100 mL/min, implies the involvement of active renal secretion [27].

An *in vitro* study has reported that anagliptin might be a substrate for OAT1, OAT3, P-gp and multi-drug resistance protein (MRP) 2 and that M1 is a substrate for OAT3, breast cancer resistance protein (BCRP), MRP2 and MRP4 [27]. This study also suggests that anagliptin and M1 are potentially good substrates for P-gp and BCRP, respectively. M1 and anagliptin have been reported to have no inhibitory effects on substrates of CYP isozymes at the therapeutic concentration ranges [25]. Although OAT3 and OCT2 were inhibited by anagliptin, the effect of anagliptin on other drugs is not expected in the clinical setting, as the concentration of anagliptin was far above the therapeutic range. In clinical drug interaction studies,  $C_{max}$  of digoxin and glyburide, which are substrates of P-gp (digoxin) and CYP2C9 and OATP 1B1 (glyburide), were increased by coadministration of anagliptin by 1.49 and 1.44 folds, respectively. However, no significant increase in AUC was observed in either drugs. The pharmacokinetics of metformin, miglitol and pioglitazone did not show significant change by coadministration of anagliptin. The effect of anagliptin on the pharmacokinetics of metformin, dextromethorphan and fexofenadine was thought to have no clinical meaning, requiring no dose adjustment [25].

### Evogliptin

Evogliptin is recommended to dose 5 mg once daily [28]. In the recommended dosage range, evogliptin is absorbed with  $t_{\max}$  of 5 hours and its concentration declines with an effective half-life of 33 hours after once daily dosing of 5 mg [29]. The absolute bioavailability of evogliptin is approximately 50% [30].

Evogliptin is metabolized via CYP3A4, but the pharmacological activity of its metabolites has not been reported. The  $K_m$ ,  $V_{\max}$ , and  $Cl_{\text{int}}$  values of formation of metabolite M2, the main metabolite, were 93.4  $\mu\text{M}$ , 91.9 pmol/mg protein/min, and 1.0  $\mu\text{L}/\text{min}/\text{mg}$  protein, respectively. Metabolism seems to be the major elimination route, as a rat study has reported that 15.8%, 4.53%, and 3.92% of intravenously administered evogliptin is excreted as unchanged form in urine, feces, and bile, respectively [31].

Evogliptin does not induce or inhibit any CYP isoforms. In an *in vitro* study, evogliptin was a substrate of P-gp, and a weak substrate of BCRP, but not a substrate of OAT1B1, OAT1B3, OAT1, OAT3 or OCT2. Evogliptin did not inhibit any of these transporters [28,32]. In clinical drug interaction studies, evogliptin did not significantly change the pharmacokinetics of glimepiride, pioglitazone and metformin [28,32].

### Gemigliptin

Gemigliptin is recommended to dose 50 mg once daily. In the recommended dosage range, gemigliptin is absorbed with  $t_{\max}$  of 1.8 hours and its concentration declines with a half-life of 17 hours. Oral bioavailability of gemigliptin is high (> 63%) and plasma protein binding is low (29%) [33,34].

Gemigliptin is primarily eliminated by excretion. In a mass-balance study using [ $^{14}\text{C}$ ]-radiolabeled gemigliptin, unchanged gemigliptin was the most abundant component accounting for 67.2–100% of plasma radioactivity, 45–67% of urinary radioactivity, and 28–52% of fecal radioactivity. At least 23 different metabolites of gemigliptin were identified in plasma, urine and feces after oral administration of gemigliptin in humans, but only one metabolite (LC15-0636) hydroxylated by CYP3A4 accounted for > 10% of systemic drug-related exposure [35].

Gemigliptin is known as a substrate of CYP3A4 and P-gp. An *in vitro* study has found that gemigliptin does not inhibit or induce CYPs and weakly inhibits P-gp at high therapeutic concentrations [34]. In clinical drug interaction studies with metformin and pioglitazone, gemigliptin decreased the  $C_{\max}$  of metformin, a substrate of OCT2 and MATE, by 13% without a decrease of AUC; and decreased the  $C_{\max}$  and AUC of pioglitazone, a substrate of CYP2C8, by 17% and 15%, respectively. The effect of gemigliptin on the pharmacokinetics of metformin and pioglitazone is considered negligible [34].

### Linagliptin

Linagliptin is recommended to dose 5 mg once daily. In the recommended dosage range, linagliptin is rapidly absorbed with  $t_{\max}$  of 1.5 hours and its concentration declines at least in a biphasic manner with an effective half-life of 12 hours after once-daily dosing of 5 mg [36]. Oral bioavailability of linagliptin is approximately 30%. Linagliptin extensively distributes to the tissues with a large apparent volume of distribution of 1110 L. The fraction of linagliptin which binds to plasma protein ranges from 75% to 99% in a concentration-dependent manner [37].

In a radiolabeled study, intravenously administered linagliptin was excreted via feces (35.8%) or urine (25.3%) as unchanged form. Absorbed linagliptin is only partially metabolized to an inactive metabolites, which only accounts for 19% of the administered linagliptin [38].

Linagliptin is a substrate of CYP3A4 and transporters P-gp and OCT2: the  $K_m$  of P-gp-associated transport was 187  $\mu\text{M}$  and the difference of linagliptin uptake with or without OCT2 inhibitor was over 10  $\mu\text{L}/5 \text{ min}/\text{mg}$ . However, it is not a substrate of OATP1B1/1B3, OAT1/3/4 and OCT1. In an *in vitro* study, linagliptin inhibited CYP3A4 but did not inhibit or induce other CYP isozymes. Linagliptin had an inhibitory effect only on OCT1 and OCT2 and those inhibition potencies were different according to substrates. Linagliptin does not inhibit P-gp at therapeutic concentrations [36,39]. In clinical drug interaction studies, linagliptin did not significantly change the pharmacokinetics of digoxin, glyburide, simvastatin, pioglitazone, warfarin, ethinyl estradiol, norethindrone and metformin, indicating no significant effect of linagliptin on drug transporters including P-gp, OCT2 and MATE and various metabolizing enzymes [36].

### Saxagliptin

Saxagliptin is recommended to dose 2.5–5 mg once daily. In the recommended dosage range, saxagliptin is absorbed with  $t_{\text{max}}$  of 2 hours and its concentration declines with a half-life of 2.5 hours after single oral dose [40]. Oral bioavailability of saxagliptin was 50–75% in the rat, dog and monkey, and the volume of distribution is predicted as high as 2.7 L/kg for humans. Serum protein binding was low ( $\leq 30\%$ ) in an *in vitro* study using human serum [41].

Saxagliptin is primarily metabolized via CYP3A4/5 to BMS-510849, a major metabolite with pharmacological activity. In a radiolabeling study, saxagliptin and BMS-510849 accounted for 24% and 36% of the radioactivity in urine, respectively. In the renal elimination process, saxagliptin is excreted via both glomerular filtration and active renal secretion, while BMS-510849 is excreted only by glomerular filtration [40].

In an *in vitro* studies, saxagliptin is a substrate of CYP3A4/5 and P-gp, but it did not inhibit or induce CYPs or P-gp [40]. In clinical studies, saxagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, pioglitazone, digoxin, simvastatin, diltiazem, ketoconazole ethinyl estradiol and norgestimate, suggesting the absence of significant effect of saxagliptin on important drug transporters and metabolizing enzymes [40].

### Sitagliptin

Sitagliptin is recommended to take 100 mg once daily. In the recommended dosage range, sitagliptin is rapidly absorbed with  $t_{\text{max}}$  of 1–4 hours and its concentration declines with a half-life of 12.4 hours. The oral bioavailability is 87%, and the volume of distribution is 198 L. Thirty-eight percent of the administered sitagliptin reversibly binds to plasma protein [42,43].

Sitagliptin is primarily eliminated via urine and feces, with 79% of the dose actively secreted in urine as unchanged form [43]. Approximately 16% of sitagliptin was found to be excreted as metabolite forms in a radiolabeled study; six metabolites with no DPP-4 inhibitory activity were quantified at trace levels. CYP3A4 is primarily responsible for the limited metabolism of sitagliptin with minor contribution of CYP2C8 [44].

Sitagliptin is known as a substrate of P-gp and OAT3 and these transporters seems to be involved with active tubular secretion in the kidneys. In an *in vitro* studies, the renal secretion

of sitagliptin may be inhibited by P-gp inhibitors (e.g., cyclosporine A) and OAT3 inhibitors (e.g., probenecid, ibuprofen, furosemide, fenofibric acid, quinapril, and indapamide), although sitagliptin was a low-affinity substrate of OAT3 ( $K_m$ : 162  $\mu$ M;  $V_{max}$ : 7.7 pmol/min/ $2 \times 10^5$  cells). *In vitro* studies showed that sitagliptin has no significant inhibitory effects on any CYPs and P-gp, and not induced CYP3A4 [43,45]. In clinical drug interaction studies, sitagliptin did not significantly change the pharmacokinetics of digoxin, glyburide, simvastatin, rosiglitazone, warfarin, ethinyl estradiol, norethindrone and metformin [43].

### Teneligliptin

Teneligliptin is recommended to dose 20 mg once daily [46]. In the recommended dosage range, teneligliptin is absorbed with  $t_{max}$  of 1.3 hours after administration and its concentration declines with a half-life of 26.9 hours after single oral dose. Teneligliptin has good oral bioavailability of 43–74% and high tissue distribution (8.9 L/kg). Plasma protein binding was 78–80% [47,48].

In a radiolabeling study, 66–80% of the absorbed teneligliptin was primarily eliminated by metabolism, and 20–34% was eliminated as unchanged form by urinary excretion. CYP3A4 and flavin-containing monooxygenase 3 (FMO3) are primarily responsible for teneligliptin metabolism [47].

Teneligliptin is a substrate of CYP3A4, FMO3 and P-gp. In an *in vitro* studies, teneligliptin weakly inhibits CYP2D6, CYP3A4, and FMO ( $IC_{50} < 500 \mu$ mol/L) without affecting other CYP isoforms. Teneligliptin does not induce CYP3A4 or CYP1A2. At supratherapeutic concentrations, teneligliptin inhibits the transporting activity of P-gp and OAT3 [49,50]. However, no clinically meaningful drug interactions have been reported in clinical studies on the concomitant treatment with metformin, glimepiride and pioglitazone [46]. Moreover, teneligliptin did not alter the exposure of canagliflozin, a SGLT2 inhibitor which is not on sale in South Korea [51].

### Vildagliptin

Vildagliptin is recommended to administer 50 mg or 100 mg once daily. In the recommended dosage range, vildagliptin is rapidly absorbed with the  $t_{max}$  of 1.5 hours and declines shortly with a half-life of approximately 2.0 hours [52-56]. Vildagliptin is minimally bound to plasma proteins of 9.3% and the volume of distribution is 71 L. The oral bioavailability of vildagliptin is 85% [53].

Both metabolism and renal excretion are responsible for the elimination of vildagliptin. Twenty-three percent of vildagliptin is eliminated as unchanged in the urine. In a mass balance study using [ $^{14}$ C]-radiolabeled vildagliptin, vildagliptin and carboxylic acid metabolite resulting from hydrolysis, which is not mediated by CYP enzymes, were the major circulating components in plasma, accounting for 25.7% and 55% of total plasma radioactivity exposure, respectively. In addition to hydrolysis, diverse metabolic pathways including glucuronidation contribute to the elimination of vildagliptin. Another carboxylic metabolite formed from hydrolysis of the amide bond accounts for 8.1% of total radioactivity and glucuronic acid conjugate of vildagliptin formed by UDP-glucuronosyltransferase (UGT) 2B7 accounts for 9.3%. UGT2B17 and UGT2B4 play a minor role in the metabolism of vildagliptin. CYP enzymes have little effect on the metabolism of vildagliptin [53,57].

Vildagliptin does not inhibit or induce CYP enzymes. In the clinical study, there were no clinically significant pharmacokinetic interactions between vildagliptin and the frequently used co-medications (metformin, pioglitazone, glibenclamide, amlodipine, valsartan, simvastatin, ramipril, warfarin and digoxin), suggesting the absence of significant effect of vildagliptin on transporters as well as metabolizing enzymes [56].

## PHARMACOKINETICS OF SGLT2 INHIBITORS

Four SGLT2 inhibitors, namely dapagliflozin, empagliflozin, ertugliflozin and ipragliflozin, are commercially available in South Korea. All of these SGLT2 inhibitors are rapidly absorbed and have high bioavailability. Three of them (dapagliflozin, ertugliflozin and ipragliflozin) are eliminated mainly by metabolism and empagliflozin is eliminated mainly by excretion. In this section we describe the pharmacokinetic characteristics of these SGLT2 inhibitors regarding potential drug interactions. Pharmacokinetic characteristics of each SGLT2 inhibitor are summarized in **Table 2**.

### Dapagliflozin

Dapagliflozin is recommended to start with 5 mg to increase up to 10 mg once daily. In the recommended dosage range, dapagliflozin is rapidly absorbed with a  $t_{max}$  of approximately 1.0 hour and is eliminated with a half-life of 7.2–11.9 hours [58,59]. The oral bioavailability of dapagliflozin is 78%. The volume of distribution of dapagliflozin is 118 L and the protein binding is up to 91%, irrespective of renal or hepatic function [60-62].

Dapagliflozin is eliminated mainly by metabolism through glucuronidation (66% of dose) and oxidation (9% of dose). Metabolism of dapagliflozin is mediated predominantly by UGT1A9, producing inactive glucuronidated metabolites, mostly dapagliflozin 3-O-glucuronide. The metabolism by CYP enzymes is less than 10% of the oral dose [58,63]. Less than 2% of the administered dose is excreted as parent drug via urine, and approximately 15% as parent drug via feces [59]. Hepatic and renal impairment similarly affect the metabolism, increasing the overall exposure by 67% and 87%, respectively,

**Table 2.** Pharmacokinetic characteristics of SGLT2 inhibitors

Drug	Metabolism (%)	Excretion unchanged (%)	Protein binding	Metabolic enzymes	Transporters	<i>In vitro</i> assessment of drug interaction	References
Dapagliflozin	75% of dose	< 2% and 15% of dose via urine and feces, respectively	91%	UGT1A9 (major)/CYP (minor)	Substrate of P-gp (dapagliflozin), OAT3 (metabolite)	Not inhibit: CYP 1A2, 2C9, 2C19, 2D6, or 3A4/P-gp, OCT2, OAT1, or OAT3; not induce: CYP1A2, 2B6, or 3A4	[58-63]
Empagliflozin	7.8–13.2% of dose in urine and 1.9% of dose in feces	75.5–77.4% of plasma radioactivity	86.2%	UGT2B7, UGT1A3, UGT1A8, UGT1A9	Substrate of P-gp, BCRP, OAT3, OATP1B1, OATPB3/ not substrate of OAT1 and OCT2	Not inhibit: CYP isoforms/UGT1A1, UGT1A3, UGT1A8, UGT1A9, or UGT2B7/P-gp, BCRP, OAT3, OATP1B1, OATPB3; not induce: CYP isoforms	[67,68,70]
Ertugliflozin	< 45.9% of administered dose	35.3% of administered dose	Protein binding: 95%	UGT1A9 and UGT2B7, CYP (minor)	Substrate of P-gp, BCRP/ not substrate of OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3	Weakly inhibit: UGT1A1, UGT1A4; not inhibit: CYP1A2, CYP2C9, CYP2C19, CYP2C8, CYP2B6, CYP2D6, CYP3A4/ UGT1A6, UGT1A9, UGT2B7/P-gp, OCT2, OAT1, OAT3, OATP1B1, OATP1B3 (at clinically relevant concentration); not induce: CYP1A2, 2B6, or 3A4	[71-73]
Ipragliflozin	> 66.9% of administered dose	< 33.7% of administered dose	94.6–96.5%	UGT2B7 (major), UGT2B4, UGT1A9 (minor)	Substrate of P-gp	Not inhibit or weakly inhibit: CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, 4A11/UGT1A1, 1A4, 1A6, 1A9, 2B7; not induce: CYP1A2, CYP3A4	[74-76]

UGT, UDP-glucuronosyltransferase; P-gp, P-glycoprotein; CYP, cytochrome P450; OCT, organic cation transporter; OAT, organic anion transporter; BCRP, breast cancer resistance protein.



suggesting that enzymes both in the liver and kidney are involved in the metabolism of dapagliflozin [61,62].

*In vitro* studies have demonstrated that dapagliflozin is a weak substrate of P-gp and not a substrate of OAT1 or OCT [59,63]. The extent of dependence on P-gp transporters are not reported. It has also been shown that dapagliflozin and dapagliflozin 3-O-glucuronide does not inhibit or induce CYP isozymes and does not inhibit P-gp, OCT2, OAT1 or OAT3 [59]. In clinical drug interaction studies, dapagliflozin increased AUC of glimepiride, a substrate of CYP2C9, by 13% without increasing  $C_{max}$ . Dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, hydrochlorothiazide, bumetanide, valsartan, simvastatin, digoxin and warfarin. The effect of dapagliflozin on the pharmacokinetics of glimepiride is clinically insignificant, requiring no dose adjustment [59].

### Empagliflozin

Empagliflozin is recommended to start with 10 mg and can be increased up to 25 mg once daily. In the recommended dosage range, empagliflozin is rapidly absorbed with a  $t_{max}$  of 1.0–2.0 hours and eliminated with a half-life of 10.7–14.3 hours [64–66]. Based on a mass-balance study, the oral bioavailability of empagliflozin is assumed to be over 60% [67]. The protein binding of empagliflozin is 86.2% and the volume of distribution is 73.8 L [68].

Empagliflozin is eliminated primarily in unchanged form. In a study using [14C]-radiolabeled empagliflozin, the unchanged form of empagliflozin accounted for 75.5–77.4% of plasma radioactivity, with 34.1% and 23.7% of the administered dose excreted in urine and feces, respectively [67]. Both glomerular filtration and active tubular secretion are equally responsible for urinary excretion of empagliflozin [69]. Metabolism plays a minor role in the elimination of empagliflozin. The most abundant metabolites in urine are two glucuronide conjugates (7.8–13.2% of dose), and the most abundant metabolite in feces is a tetrahydrofuran ring-opened carboxylic acid metabolite (1.9% of dose) [67]. The production of glucuronide conjugates are mediated by UGT2B7, UGT1A3, UGT1A8 and UGT1A9. Empagliflozin is a substrate of several transporters of OAT3, OATP1B1, OATP1B3, P-gp and BCRP. However, it is not a substrate of OAT1 or OCT2 [68,70]. The extent of dependence on those transporters has not been reported.

In an *in vitro* study, empagliflozin did not inhibit or induce CYP isoforms. Empagliflozin did not inhibit UGT enzymes including UGT1A1, UGT1A3, UGT1A8, UGT1A9 and UGT2B7 and transporters including OAT3, OATP1B1, OATP1B3, P-gp or BCRP [68]. The UGT induction by empagliflozin exposure has not been reported. In clinical drug interaction studies, empagliflozin decreased the exposure of pioglitazone, a substrate of CYP2C8; and increased digoxin, a substrate of P-gp. However, empagliflozin did not alter the pharmacokinetics of other drugs (metformin, glimepiride, sitagliptin, linagliptin, ethinyl estradiol, simvastatin, warfarin, Ramipril and hydrochlorothiazide). The effect of empagliflozin on the pharmacokinetics of pioglitazone and digoxin is considered to have no clinical significance, requiring no dose adjustment [68].

### Ertugliflozin

Ertugliflozin is recommended to start with 5 mg to increase to 15 mg once daily. In the recommended dosage range, ertugliflozin is rapidly absorbed with  $t_{max}$  of 1.0 hour and its concentration declines with a half-life of 16.6 hours. The oral bioavailability is 100%, the volume of distribution is 1.8 L/kg and the protein binding is up to 94% [71,72].

In a mass balance study using [<sup>14</sup>C]-radiolabeled ertugliflozin, 50.2% and 40.9% of total administered radioactivity excreted in urine and feces, respectively [73]. Of the total radioactivity excreted in urine and feces, unchanged ertugliflozin accounted for 1.5% of the administered dose in urine and 33.8% of the administered dose in feces, respectively. These findings suggest a moderate degree of metabolic elimination of ertugliflozin. The metabolites accounted 43.9% of the administered dose in urine. The metabolites in feces represented < 2.0% of the administered dose [72,73]. The main metabolic pathway involves glucuronidation by UGT1A9 and UGT2B7 to yield two inactive O-glucuronides. The involvement of CYP enzymes is minimal in the metabolism of ertugliflozin [71,73].

In an *in vitro* study, ertugliflozin and its glucuronide metabolites did not inhibit CYP450 isozymes including CYP1A2, 2C9, 2C19, 2C8, 2B6, 2D6 and 3A4; and did not induce CYP1A2, 2B6 or 3A4. Ertugliflozin did not inhibit UGT1A6, 1A9 or 2B7 but weakly inhibited UGT1A1 and 1A4. Ertugliflozin glucuronides did not inhibit UGT1A1, 1A4, 1A6, 1A9 or 2B7. The transport of ertugliflozin is mediated by P-gp or BCRP, but ertugliflozin is not a substrate of OATs (OAT1, OAT3), OCTs (OCT1, OCT2), or organic anion transporting polypeptides (OATP1B1, OATP1B3). Ertugliflozin or ertugliflozin glucuronides do not meaningfully inhibit transporters (P-gp, OCT2, OAT1, OAT3, OATP1B1 and OATP1B3) at clinically relevant concentrations [71]. In clinical drug interaction studies, ertugliflozin decreased the exposure of simvastatin, a substrate of CYP3A4/5 and OATP1B1. However, ertugliflozin did not alter the pharmacokinetics of metformin, glimepiride and sitagliptin. The effect of ertugliflozin on the pharmacokinetics of simvastatin is minimal and does not require no dose adjustment [71].

### Ipragliflozin

Ipragliflozin is recommended to use 50 mg once daily. After administration of 50 mg of ipragliflozin in healthy volunteers, ipragliflozin reaches peak concentrations rapidly with a  $t_{max}$  of 1.3 hours and the concentration declines with a half-life of 11.2 hours [74]. The oral bioavailability of ipragliflozin is 90.2% and the protein binding is 94.6 to 96.5% [75].

Ipragliflozin is extensively metabolized, with < 1% of the dose excreted as unchanged form. In a mass balance study using [<sup>14</sup>C]-radiolabeled ipragliflozin, 67.9% and 32.7% of administered dose was excreted in urine and feces, respectively. Less than 1% of the amount eliminated in urine were unchanged form, whereas in feces unchanged form was the main component [76]. Ipragliflozin is metabolized mainly by UGT2B7, and UGT2B4, UGT1A8 and UGT1A9 play minor roles, producing several inactive metabolites [74].

In an *in vitro* study, ipragliflozin did not inhibit or slightly inhibited CYP isozymes (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 and CYP4A11) or UGT isozymes (UGT1A1, UGT1A4, UGT1A6, UGT1A9 and UGT2B7), and did not induce CYP1A2 or CYP3A4 [75]. Ipragliflozin is a substrate of P-gp. In clinical drug interaction studies, ipragliflozin decreased the exposure of miglitol and mitiglinide. However, empagliflozin did not alter the pharmacokinetics of other drug (metformin, glimepiride, pioglitazone and sitagliptin). The effect of ipragliflozin on the pharmacokinetics of pioglitazone and digoxin is considered to have no clinical significance, requiring no dose adjustment [75].

## DRUG INTERACTION BETWEEN DPP-4 INHIBITORS AND SGLT2 INHIBITORS

Six studies have been reported pharmacokinetic drug interactions between DPP-4 inhibitors and SGLT2 inhibitors commercially available in South Korea, namely sitagliptin-dapagliflozin, sitagliptin-empagliflozin, sitagliptin-ertugliflozin, sitagliptin-ipragliflozin, saxagliptin-dapagliflozin, and linagliptin-empagliflozin [77-82]. In the study on drug interaction between linagliptin and empagliflozin,  $C_{max}$  of empagliflozin decreased by 12% (geometric mean ratio [GMR], 0.88; 90% confidence interval [CI], 0.79–0.99) although AUC was comparable (GMR, 1.02; 90% CI, 0.97–1.07). The authors of this study argued that the decrease of  $C_{max}$  was not clinically significant, as the efficacy of empagliflozin would be affected by its total exposure not by its peak level [82]. Other five drug interaction studies did not show any statistically significant changes in  $C_{max}$  and AUC of either DPP-4 inhibitors or SGLT2 inhibitors.

### The possibility of drug interaction by metabolism

Evogliptin, saxagliptin, teneligliptin and vildagliptin are mainly eliminated by metabolism. All of them except vildagliptin are metabolized by CYP3A4 or CYP3A5 and vildagliptin goes through CYP-independent hydrolysis and minorly glucuronidation by UGT2B7. For alogliptin, anagliptin, linagliptin, gemigliptin and sitagliptin, more than half of the administered dose is excreted via urine or feces as unchanged; and except for anagliptin, the rest of the dose is eliminated by metabolism through CYP enzymes including CYP3A4, CYP2D6 or CYP2C8. Whether DPP-4 inhibitors induce or inhibit UGT enzymes has not been reported.

All four SGLT2 inhibitors undergo variable degrees of metabolism and renal excretion. For dapagliflozin, ertugliflozin, and ipragliflozin, glucuronidation by UGT is the main route of elimination, whereas more than half of the administered dose of empagliflozin is excreted as unchanged via urine or feces. All these SGLT2 inhibitors do not inhibit or induce CYP450 enzymes.

Taken together, 8 DPP-4 inhibitors and 4 SGLT2 inhibitors do not share major metabolic pathways for their elimination. Although vildagliptin and 3 SGLT2 inhibitors (empagliflozin, ertugliflozin and ipragliflozin) share UGT2B7, the proportion of vildagliptin metabolized by UGT2B7 is less than 10%. Besides, SGLT2 inhibitors do not affect CYP450 enzymes which is responsible for the metabolism of DPP-4 inhibitors. Although the possibility of inhibition or induction of UGT enzymes by DPP-4 inhibitors cannot be excluded, none of the existing studies involving a DPP-4 inhibitor and a SGLT2 inhibitor have not shown significant pharmacokinetic drug interactions. Therefore, we conclude that a significant drug interaction between a DPP-4 inhibitor and a SGLT2 inhibitor in terms of drug metabolism is highly unlikely.

### Possibility of drug interaction by drug transporters

Except for alogliptin, all the DPP-4 inhibitors we reviewed here are the substrates of P-gp. Also, anagliptin and its metabolite are substrates of OAT1/3, MRP2, MRP4 or BCRP; and evogliptin, linagliptin and sitagliptin are a substrate of BCRP, OCT2 and OAT3, respectively. Anagliptin has been reported to inhibit OAT3 and OCT2; and linagliptin, gemigliptin and teneligliptin are reported to inhibit P-gp. Teneligliptin can also inhibit OAT3. However, these inhibitions occur at supratherapeutic concentrations. To our knowledge, the effect of vildagliptin on drug transporters has not been reported.

Several drug transporters are involved in the disposition of SGLT2 inhibitors. Dapagliflozin is a substrate of OAT3, empagliflozin a substrate of OAT3, BCRP, OATP1B1 and OATP1B3, and ertugliflozin a substrate of BCRP. Moreover, all 4 SGLT2 inhibitors are substrates of P-gp. SGLT2 inhibitors have not been reported to inhibit or induce drug transporters, although evidence is limited.

Based on *in vitro* studies on transporters, drug interactions mediated by transporters may exist theoretically: drug interactions between sitagliptin and dapagliflozin or empagliflozin by sharing OAT3; between evogliptin and empagliflozin or ertugliflozin by sharing BCRP; between anagliptin and empagliflozin by sharing OAT3 or BCRP; or between anagliptin and ertugliflozin by sharing BCRP. However, prior studies involving co-administration of linagliptin-empagliflozin, saxagliptin-dapagliflozin, sitagliptin-ertugliflozin or sitagliptin-ipragliflozin sharing P-gp and co-administration of sitagliptin-dapagliflozin or sitagliptin-empagliflozin sharing OAT3 and P-gp have demonstrated no significant pharmacokinetic changes [77-82]. In addition, clinically significant pharmacokinetic interactions requiring dose adjustment were not found for any of DPP-4 inhibitors or SGLT2 inhibitors when one of these agents was concomitantly administered with metformin or digoxin, substrate of OCT2 and MATEs and of P-gp, respectively [22,25,28,34,36,40,43,46,56,59,68,71,75]. This suggests that an interaction via OCT2, MATEs and P-gp is unlikely, although there were some pharmacokinetic alterations in some drugs.

In summary, a possible interaction between a DPP-4 inhibitor and SGLT2 inhibitor by sharing transporters can theoretically exist. However, existing interaction studies have shown no significant pharmacokinetic alterations. Considering the existing interaction studies and the safety margins of DPP-4 inhibitors and SGLT2 inhibitors, a clinically significant interaction between these drugs is very unlikely.

### Possibility of drug interaction by plasma protein binding displacement

All SGLT2 inhibitors reviewed here exhibit a high degree of binding to plasma proteins, whereas DPP-4 inhibitors do not. Given the information on the protein binding rate of each drug, the competition between these two classes of drugs for plasma proteins is not expected, suggesting a very low chance of drug interaction between DPP-4 inhibitors and SGLT2 inhibitors by the mechanism of protein binding displacement.

## CONCLUSION

Co-administration of a DPP-4 inhibitor and a SGLT2 inhibitor is a desirable treatment option for T2DM because of their complementary mechanisms of action and no effect on safety profile of each agent. Our review of current evidence does not account for all the metabolic enzymes, transporters, pharmacologic agents, and combinations thereof. However, based on the existing *in vitro* data, drug interaction studies in humans, and the safety margins of DPP-4 inhibitors and SGLT2 inhibitors, we conclude that a clinically significant drug interaction between these two classes of drugs is unlikely, although we cannot exclude all the possible pharmacokinetic interactions. Additional future studies in humans may shed more light on a possible interaction between these two agents.

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