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Editorial Board Member of *World Journal of Meta-Analysis*, Matthew L Bechtold, MD, Assistant Professor, Director of Endoscopy and Ambulatory Services, Division of Gastroenterology and Hepatology, Department of Internal Medicine, University Hospital and Clinics, Columbia, MO 65212, United States

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MINIREVIEWS

# Drug interactions of dipeptidyl peptidase 4 inhibitors involving CYP enzymes and P-gp efflux pump

Naina Mohamed Pakkir Maideen

**ORCID number:** Naina Mohamed Pakkir Maideen (0000-0002-6950-9783).

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**Naina Mohamed Pakkir Maideen,** Department of Pharmacy, Dubai Health Authority, Dubai 4545, United Arab Emirates

**Corresponding author:** Naina Mohamed Pakkir Maideen, PhD, Doctor, Pharmacist, Pharmacologist, Department of Pharmacy, Dubai Health Authority, Al Maktoum Bridge Street, Dubai 4545, United Arab Emirates. nmmaideen@dha.gov.ae
**Telephone:** +971-42-164952
**Fax:** +971-42-244302

## Abstract

Dipeptidyl peptidase 4 (DPP4) inhibitors are oral antidiabetic drugs approved to manage type 2 diabetes mellitus. Saxagliptin is a substrate of CYP3A4/5 enzymes while other DPP4 inhibitors such as sitagliptin, linagliptin, gemigliptin and teneligliptin are weak substrates of CYP3A4. DPP4 inhibitors have also been identified as substrates of P-gp. Hence, the drugs inhibiting or inducing CYP3A4/5 enzymes and/or P-gp can alter the pharmacokinetics of DPP4 inhibitors. This review is aimed to identify the drugs interacting with DPP4 inhibitors. The plasma concentrations of saxagliptin have been reported to be increased significantly by the concomitant administration of ketoconazole or diltiazem while no significant interactions between various DPP4 inhibitors and drugs like warfarin, digoxin or cyclosporine have been identified.

**Key words:** Drug interactions; Sitagliptin; Saxagliptin; Linagliptin; Gemigliptin; Teneligliptin; Vildagliptin; Anagliptin; CYP3A4; P-gp efflux pump



**Core tip:** The probability of adverse drug interactions is higher among diabetic patients due to the concomitant administration of antidiabetic drugs with multiple medications to treat comorbidities such as hypertension, dyslipidemia, other cardiovascular problems, infections, depression, and others. Dipeptidyl peptidase 4 (DPP4) inhibitors are oral antidiabetic drugs approved to manage type 2 diabetes mellitus. Some of the DPP4 inhibitors have been identified as substrates of CYP3A4/5 enzymes and P-gp efflux pump. The drugs inhibiting or inducing CYP3A4/5 enzymes and/or P-gp can alter the pharmacokinetics of DPP4 inhibitors. The prescribers and the pharmacists are required to be aware of the drugs altering the pharmacokinetics of DPP4 inhibitors significantly to prevent adverse drug interactions.

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## INTRODUCTION

Dipeptidyl peptidase 4 (DPP4) inhibitors are oral antidiabetic drugs approved to manage type 2 diabetes mellitus. The members of this class include sitagliptin, vildagliptin, saxagliptin, linagliptin, gemigliptin, anagliptin, teneligliptin and alogliptin. DPP4 enzyme is involved in the biodegradation of incretins such as glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide. DPP4 inhibitors help to increase the postprandial insulin secretion and inhibit glucagon secretion through the inhibition of inactivation of glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide[1].

Diabetes is a group of metabolic disorders occurring due to the defects in insulin secretion and insulin action. It has been estimated that more than 500 million people around the globe were living with diabetes in 2018 and the numbers are increasing daily[2].

Inappropriate use of multiple medications or polypharmacy is more common among diabetic patients as they may receive many medications to manage comorbid conditions such as hypertension, dyslipidemia, other cardiovascular problems, infections, depression, and others along with their antidiabetic medications. The risk of drug interactions increases with the number of comedications. Drug interaction is defined as the interference of effects of a drug by the concomitantly administered other drug(s), herbs, minerals, vitamins, food, fruit juices, tobacco smoke or alcohol, and the drug interaction resulting in increased unintended effects or decreased intended effects is termed adverse drug interaction[3,4].

The cytochrome P450 (CYP) enzymes are involved in the phase 1 metabolism of drugs and they consist of 57 different CYP forms. Almost 90% of drugs are metabolized by seven CYP enzymes including CYP3A4 and others[5]. Saxagliptin is a substrate of CYP enzymes, and it is primarily metabolized by CYP3A4/5 to form the active metabolite, 5-hydroxy saxagliptin through hydroxylation[6]. Moreover, other DPP4 inhibitors such as sitagliptin[7], linagliptin[8], gemigliptin[9] and teneligliptin[10] are weak substrates of the CYP3A4 enzyme. They are metabolized incompletely by CYP3A4, and major parts of the drugs are excreted as unchanged drug through urine except linagliptin, which is excreted through feces. Vildagliptin[11] and anagliptin[12] are metabolized by cyano group hydrolysis and about 50% of the administered dose is excreted as unchanged drug. The drugs inhibiting or inducing the CYP3A4 enzyme may interact with DPP4 inhibitors as some of them are substrates of the CYP3A4 enzyme.

P-glycoprotein (P-gp) is an efflux transporter and it is also known as multidrug resistance protein 1 as it is overexpressed in tumor cells causing resistance to different anticancer drugs. P-gp is involved in the absorption and excretion of drugs as it is also found in various tissues like small intestine, liver and kidney. P-gp pumps the orally administered drugs back in to lumen and limit their bioavailability[13]. DPP4 inhibitors have been identified as substrates of P-gp[14] and the drugs inducing or inhibiting P-gp transporters may also affect the pharmacokinetics of DPP4 inhibitors.

## LITERATURE REVIEW

As the DPP4 inhibitors are the substrates of both CYP3A4 enzymes and the P-gp transporter, the present review is focused on the possible drug-drug interactions of them. The literature review was done in databases such as MEDLINE/PubMed/PMC, ScienceDirect, Google scholar, Cochrane Library and reference lists using the keywords such as drug interactions, sitagliptin, saxagliptin, linagliptin, gemigliptin, teneligliptin, vildagliptin, anagliptin, CYP3A4 and P-gp efflux pump.

## LITERATURE REVIEW RESULTS

Most of the drug-drug interactions of DPP4 inhibitors involve mainly saxagliptin as it

is metabolized extensively by the CYP3A4 enzyme. The plasma concentrations of saxagliptin increased by the concomitant administration of CYP3A4 and P-gp inhibitors such as ketoconazole and diltiazem and future studies are required to confirm the possibility of drug-drug interactions with other CYP3A4 inhibitors. In addition, other DPP4 inhibitors such as sitagliptin, linagliptin, gemigliptin and teneligliptin interact with CYP3A4 inhibitors insignificantly as they are weak substrates of CYP3A4 enzyme. The prescribers and the pharmacists are required to be aware of the drug-drug interactions of saxagliptin to prevent adverse complications.

### Ketoconazole

Ketoconazole is an antifungal agent and it is a known potent inhibitor of CYP3A4 enzyme and P-gp transporter[15]. It has been observed that the plasma exposure of saxagliptin was increased by the concurrent administration of ketoconazole due to the inhibition of CYP3A4 enzyme-mediated metabolism of saxagliptin and a weak inhibition of P-gp mediated transport. Hence, it has been suggested to use the lowest therapeutic dose (2.5 mg) of saxagliptin when concomitant use of ketoconazole and saxagliptin is necessary[16]. Significant elevation of plasma concentrations of gemigliptin was observed in healthy male Korean volunteers who took ketoconazole along with gemigliptin[17] while there was no significant interaction reported with the concomitant use of ketoconazole and teneligliptin[18].

### Diltiazem

Diltiazem is a calcium channel blocker and it is indicated in the management of hypertension, angina and certain cardiac arrhythmias. Diltiazem is a moderate inhibitor of CYP3A4 enzyme and P-gp transporter[19] and its coadministration with saxagliptin resulted in a significant increase in plasma exposure of saxagliptin[16].

### Other CYP3A4 inhibitors

The plasma concentrations of saxagliptin might be elevated by its coadministration with strong CYP3A4 inhibitors including macrolide antibiotics like clarithromycin and antiretroviral drugs (protease inhibitors) such as ritonavir, atazanavir, and others[20]. Future studies are required to confirm the interaction of macrolide antibiotics, antiretroviral drugs and other potent CYP3A4 inhibitors with saxagliptin and other DPP4 inhibitors.

### 3-Hydroxy-3-Methyl-Glutaryl-CoA reductase inhibitors (statins)

3-Hydroxy-3-Methyl-Glutaryl-CoA reductase inhibitors or statins are used to lower the risk of acute cardiovascular events by controlling dyslipidemia[21]. Statins include lovastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, pravastatin, rosuvastatin and pitavastatin[22]. The statins such as lovastatin, simvastatin, atorvastatin and cerivastatin are reported to be substrates of CYP3A4 enzyme and P-gp transporter[23].

The exposure of saxagliptin was slightly increased by the concomitant use of simvastatin[16], and no clinically significant changes in pharmacokinetics of simvastatin and sitagliptin[24] or vildagliptin[25] was observed when they were used concomitantly.

Although the initiation of sitagliptin in a patient with chronic renal insufficiency and receiving simvastatin resulted in developing the symptoms of rhabdomyolysis such as leg pain, weakness and tenderness[26] the efficacy and safety of the fixed dose combination of sitagliptin and simvastatin was found to be acceptable[7]. However, the pharmacokinetics of either gemigliptin or rosuvastatin was not altered during their concurrent use[27].

Furthermore, it has been reported that a patient taking sitagliptin and lovastatin[28] and the patients taking sitagliptin and atorvastatin[29,30] developed rhabdomyolysis. The patients taking sitagliptin along with statins like atorvastatin and lovastatin are required to be monitored for the symptoms of muscle toxicity.

### Warfarin

Warfarin is an oral anticoagulant agent, and R-warfarin is a substrate of CYP1A2 and CYP3A4 enzymes[31]. The pharmacokinetics of warfarin and sitagliptin[32], linagliptin[33], or vildagliptin[34] did not significantly *get al*tered during their concomitant use, and it has been reported that no dosage adjustments of either drugs are required.

### Digoxin

Digoxin is a cardio tonic agent, and it is approved to treat patients with heart failure and arrhythmias including atrial fibrillation[35]. Digoxin is a substrate of P-gp and its co-administration with linagliptin[36] or vildagliptin[37] did not lead to significant alterations in pharmacokinetic parameters of digoxin. Moreover, no dosage

adjustment of either drugs are required when digoxin and linagliptin or vildagliptin are used concomitantly.

### *Cyclosporine*

Cyclosporine is an immunosuppressant, and it is an inhibitor of CYP3A4 enzymes[38] and P-gp transporter[39]. The Pgp-mediated transport of sitagliptin was reported to be inhibited significantly by the coadministration of cyclosporine[40]. The magnitude of this interaction is considered low as sitagliptin has a high safety margin[41].

### *Rifampicin*

Rifampicin is an antitubercular antibiotic, and it is a potent inducer of CYP3A4 enzymes and P-gp transporter[42]. Clinically insignificant reduction of systemic exposure of saxagliptin was observed when it was coadministered with rifampicin and no dosage adjustment of saxagliptin is required[43]. However, the concomitant use of gemigliptin and rifampicin in Korean volunteers resulted in significant reduction of systemic exposure of gemigliptin. The dose of gemigliptin may need to be adjusted when concurrent use is necessary[17].

## CONCLUSION

Saxagliptin is a substrate of CYP3A4/5 enzymes and other DPP4 inhibitors such as sitagliptin, linagliptin, gemigliptin and teneligliptin are metabolized incompletely by CYP3A4 enzymes as they are weak substrates of CYP3A4. The plasma concentrations of saxagliptin have been reported to be increased significantly by the concomitant administration of ketoconazole or diltiazem while no significant interactions between various DPP4 inhibitors and drugs like warfarin, digoxin or cyclosporine have been identified.

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