

## Drug Interactions of SGLT2 Inhibitors (Gliflozins) Involving UGT Enzymes

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### Abstract

Sodium glucose cotransporter 2 (SGLT2) inhibitors are antidiabetic drugs which are useful in the management of blood sugar of patients with type 2 diabetes, along with diet and exercise. The SGLT2 inhibitors are the substrates of UGT enzymes and SGLT2 inhibitors such as Dapagliflozin, Canagliflozin and Ipragliflozin are metabolised by glucuronidation predominantly by UGT1A9 enzyme. In addition, Canagliflozin and Ipragliflozin are also metabolised by UGT2B4. The drugs inhibiting or inducing UGT1A9 and other UGT enzymes are expected to alter the pharmacokinetics of SGLT2 inhibitors. Although the plasma exposure of Dapagliflozin and Canagliflozin are increased slightly by the concomitant use of Mefenamic acid and Probenecid respectively, these interactions were not considered clinically meaningful. Rifampicin and other UGT inducers such as Phenytoin, Phenobarbital and Ritonavir were observed to decrease the plasma levels of Canagliflozin, insignificantly. Based on the results of this review, SGLT2 inhibitors could be coadministered with any medicines without dosage adjustments except Canagliflozin, which needs higher dosage while using along with UGT enzyme inducers.

**Keywords :** Drug interactions; SGLT2 inhibitors; UGT Enzymes; Canagliflozin; Dapagliflozin; Empagliflozin; Ertugliflozin; Ipragliflozin; Luseogliflozin; Tofogliflozin.

### INTRODUCTION

Sodium glucose cotransporter 2 (SGLT2) inhibitors are antidiabetic drugs which are useful in the management of blood sugar of patients with type 2 diabetes, along with diet and exercise. The members of this class of antidiabetic medications approved by U.S. Food and Drug Administration (FDA) include Canagliflozin, Dapagliflozin, Empagliflozin, and Ertugliflozin. In addition, the other SGLT2 inhibitors such as Ipragliflozin, Luseogliflozin, and Tofogliflozin are approved in Japan [1]. SGLT2 inhibitors prevent the reabsorption of glucose and facilitate its excretion through urine by inhibiting Sodium-glucose cotransporter-2 in the proximal convoluted tubule, which results in decrease in blood sugar [2].

The probability of drug interactions is higher among diabetic patients since they use number of comedications to treat their comorbidities.

Modification of effects of one drug by the administration of other drug(s), supplements, smoking or alcohol is termed drug interaction [3, 4].

Uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase, UGT) enzymes are involved in Phase II metabolism (glucuronidation) of certain drugs. The superfamily of human UGT enzymes consists of UGT1 and UGT2 families that further divided as subfamilies of UGT1A, UGT2A, and UGT2B and the members of these families include UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15 and UGT2B17 [5]. The SGLT2 inhibitors such as Dapagliflozin, Canagliflozin and Ipragliflozin are metabolised by glucuronidation predominantly by UGT1A9 enzyme. In addition, Canagliflozin and Ipragliflozin are also metabolised by UGT2B4. The other SGLT2 inhibitor, Empagliflozin is metabolised by UGT1A3, UGT1A8, UGT1A9 and UGT2B7 [6].

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The drugs inhibiting or inducing UGT1A9 and other UGT enzymes may play a major role in the drug interactions of SGLT2 inhibitors.

### Mefenamic Acid

Mefenamic acid is a Non-steroidal anti-inflammatory drug (NSAID) and it has been identified as a strong inhibitor of UGT1A9 enzyme. The plasma exposure of Dapagliflozin observed to be increased modestly by the concurrent use of Mefenamic acid. However, no dosage adjustments are required while using these drugs concomitantly [7].

### Probenecid

Probenecid is an agent to treat gout and hyperuricemia and it is a known inhibitor of UGT enzymes including UGT1A9. Concomitant administration of Probenecid and Canagliflozin in healthy participants resulted in slight increase in the plasma exposure of Canagliflozin, which is considered clinically irrelevant [8].

### Rifampicin

Rifampicin is an anti-mycobacterial antibiotic and it is used in the treatment of tuberculosis and leprosy [9]. Rifampicin is an inducer of many enzymes including UGT1A9 and the coadministration of Rifampicin with Dapagliflozin lead to slight decrease in plasma exposure of Dapagliflozin. However, the drug interaction between Dapagliflozin and Rifampicin was not considered clinically meaningful and no dosage adjustments are required [7]. Nevertheless, the plasma exposure of Canagliflozin was decreased modestly in healthy participants who took Rifampicin along with Canagliflozin and the monitoring of blood sugar may be required [8].

### Other UGT Enzyme Inducers

The UGT-mediated metabolism of Canagliflozin is enhanced by the coadministration of UGT inducers such as Phenytoin, Phenobarbital or Ritonavir resulting in decreased plasma concentrations of Canagliflozin [10]. Hence, the patients taking Canagliflozin along with UGT enzyme inducers are recommended to increase the dose of Canagliflozin from 100mg to 300mg, if needed [11].

### Acetaminophen (Paracetamol)

Acetaminophen is an antipyretic and analgesic medication and it is metabolised primarily by UGT1A6 enzyme and by UGT1A9 enzyme with lesser extent.

Concomitant use of Canagliflozin and Acetaminophen did not result in any alteration in the clearance of Acetaminophen [12].

### Warfarin

Warfarin is an oral anticoagulant drug and it is used mainly to manage conditions such as Deep vein thrombosis (DVT) and Pulmonary embolism (PE) and to prevent stroke in patients with atrial fibrillation [13]. The pharmacokinetics parameters of Warfarin was not affected by the concurrent use of Dapagliflozin [14] or Canagliflozin [15].

### Digoxin

Digoxin is a cardiac glycoside and its coadministration with Dapagliflozin [14] or Canagliflozin [15], did not result in clinically meaningful interaction, in healthy participants.

### Simvastatin

Simvastatin is an agent useful to treat dyslipidemia and its concomitant use with Dapagliflozin [14] or Canagliflozin [16] resulted in slight increase in the plasma exposure of Simvastatin and Simvastatin acid, in healthy participants. However, these interactions were not considered clinically significant.

### Valsartan

Valsartan is an angiotensin receptor blocker (ARB) and it is used to treat hypertension, heart failure and others. Coadministration of Dapagliflozin and Valsartan in healthy participants, lead to slight increase in the plasma exposure of Valsartan, which is not clinically important [14].

### Oral contraceptives

The plasma exposure of Oral contraceptives containing Ethinyl estradiol and Levonorgestrel was increased slightly by Canagliflozin [15] while Empagliflozin [17] did not affect the pharmacokinetics of Oral contraceptives.

### Thiazide Diuretics

Thiazide diuretics help to manage the patients with hypertension and edema. Coadministration of Canagliflozin and Hydrochlorothiazide in healthy participants did not produce any clinically significant changes in pharmacokinetics of either drugs [18].

### Other Oral antidiabetic drugs

The plasma exposure of Glyburide and Metformin did not get altered by their co-administration with Canagliflozin [16] while the pharmacokinetics parameters of Pioglitazone, Metformin, Glimepiride and Sitagliptin were not altered by the addition of Dapagliflozin, in healthy subjects [19]. Moreover, there was no significant interaction observed in study participants taking Ipragliflozin and other oral antidiabetic drugs such as Metformin, Sitagliptin, Pioglitazone, Glimepiride, Miglitol or Mitiglinide [20] and in Japanese patients with type 2 diabetes who took Dapagliflozin and Voglibose concomitantly [21].

### CONCLUSION

The SGLT2 inhibitors are the substrates of UGT enzymes and SGLT2 inhibitors such as Dapagliflozin, Canagliflozin and Ipragliflozin are metabolised by glucuronidation predominantly by UGT1A9 enzyme. The drugs inhibiting UGT1A9 such as Mefenamic acid and Probenecid slightly increased the plasma exposure of Dapagliflozin and Canagliflozin respectively. Rifampicin and other UGT inducers such as Phenytoin, Phenobarbital and Ritonavir were observed to decrease the plasma levels of Canagliflozin, insignificantly.

The pharmacokinetics parameters of Warfarin, Digoxin, Simvastatin, Valsartan, Oral contraceptives containing Ethinyl estradiol and Levonorgestrel and Thiazide diuretics (Hydrochlorothiazide) were not altered significantly by the concomitant administration of Canagliflozin or Dapagliflozin. Moreover, coadministration of SGLT2 inhibitors such as Canagliflozin, Dapagliflozin and Ipragliflozin with other oral antidiabetic drugs did not result in any clinically significant interactions.

Based on the results of this review, SGLT2 inhibitors could be coadministered with any medicines without dosage adjustments except Canagliflozin which needs higher dosage while using along with UGT enzyme inducers.

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