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DRUG-DRUG INTERACTIONS WITH DAPAGLIFLOZIN: A REVIEW

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Abstract: Diabetes mellitus presents a significant global health issue, necessitating innovative strategies to enhance patient outcomes. Effective glycemic control is crucial for mitigating the risk of complications such as diabetic nephropathy and cardiovascular disease. Traditional oral antidiabetic agents often fall short in long-term glycemic management, underscoring the need for advanced treatments. Sodium-glucose cotransporter-2 (SGLT2) inhibitors offer a novel approach for managing type 2 diabetes mellitus. These agents have demonstrated efficacy in reducing glycated hemoglobin without inducing hypoglycemia, either as monotherapy or in combination with various other glucose-lowering agents. They also provide additional benefits, such as promoting weight loss and lowering arterial blood pressure. Dapagliflozin, a highly potent, reversible, and selective SGLT2 inhibitor, has emerged as a cornerstone in the management of type 2 diabetes mellitus. It represents an attractive therapeutic option for patients whose blood glucose levels are inadequately controlled by metformin and/or other oral antidiabetic drugs (OADs), offering a complementary insulin-independent mechanism of action. Dapagliflozin lowers blood glucose by promoting glycosuria and provides cardiovascular and renal benefits, leading to its widespread use. However, given the polypharmacy typical in diabetic patients, understanding the drug-drug interactions (DDIs) of dapagliflozin is crucial for optimizing patient care. This review explores the pharmacokinetics and pharmacodynamics of dapagliflozin and potential drug-drug interactions (DDIs). Interactions with other glucose-lowering agents and cardiovascular drugs are noted, with potential impacts on efficacy and safety. The review also addresses interactions with UGT modulators, CYP3A4 inducers, and inhibitors, emphasizing the need for careful management to avoid adverse effects and optimize therapy.

Key words **-** Diabetes mellitus, Glycemic control, Sodium-glucose cotransporter-2 (SGLT2) Inhibitors, Type 2 diabetes mellitus, Dapagliflozin, polypharmacy, Drug-drug interactions, Optimizing therapy

INTRODUCTION

Diabetes mellitus is widely recognized as an epidemic, representing a major public health issue in the 21st century [1]. In 2021, it was estimated that 10.5% of individuals aged 20 to 79 years worldwide had diabetes, affecting approximately 536 million people. By 2045, this percentage is expected to rise to 12.2%, encompassing approximately 783.2 million people [1,2]. Normalizing blood glucose levels early on is important to lower the risk of macrovascular and microvascular complications, including diabetic nephropathy and cardiovascular disease and mortality [3]. The existing therapeutic classes of oral antidiabetic agents are not sufficiently effective in sustaining long-term glycemic control in most patients with T2DM, even when used

in combination with other medications [4], and there remains a medical need for advancing pharmacological treatments of T2DM [5].

Since the release of the 2012 position statement, a significant development in treatment options has been the introduction of a new class of hypoglycemic agents: sodium–glucose cotransporter 2 (SGLT2) inhibitors [4,6]. These agents lower HbA1c levels by 0.5–1.0% (5.5–11 mmol/mol) compared to placebo [7,8]. Their mechanism of action involves blocking the SGLT2 in the proximal nephron, which decreases glucose reabsorption and increases urinary glucose excretion by up to 80 grams per day [7,9]. This insulin-independent mechanism can enhance the effectiveness of other oral antidiabetic drugs. Additional potential benefits include modest weight loss of about 2 kg, which tends to stabilize over 6 to 12 months, and a consistent reduction in systolic and diastolic blood pressure of approximately 2–4 mmHg and 1–2 mmHg, respectively [6,7,10]. The use of SGLT-2 inhibitors has beneficial effects on various risk factors associated with chronic kidney disease, including hyperglycemia, blood pressure, body weight, and serum uric acid levels. Dapagliflozin is the first drug in a new class of oral medications, selective sodium-glucose cotransporter 2 (SGLT2) inhibitors, developed for the treatment of type 2 diabetes [11]. Moreover, to lower the risk of cardiovascular complications, a comprehensive global strategy has been recommended for many years, ensuring that most patients with T2DM are also prescribed a range of antihypertensive medications, lipid-lowering drugs, and antiplatelet agents [12]. Relevant pharmacological agents encompass those frequently prescribed to diabetic patients, including lipid-lowering and antihypertensive medications.; those with a narrow efficacy-toxicity ratio, like digoxin and warfarin; and those that either induce (e.g., rifampicin) or inhibit (e.g., fluconazole) the cytochrome P450 (CYP) system [13,14,15].

Potential interferences may also occur between glucose-lowering agents and other drugs, and such drug-drug interactions may have important clinical implications. Ideally, combining drugs that have minimal pharmacokinetic interactions and distinct mechanisms of action could be beneficial. Pharmacokinetic interactions impact the absorption, distribution, metabolism, and excretion of drugs. Hence, selecting drugs that have no interactions with each other will improve the management of combined therapy.

This review aims to provide a detailed examination of the interactions between dapagliflozin and commonly co-administered medications.

PHARMACOKINETICS AND PHARMACODYNAMICS OF DAPAGLIFLOZIN

Dapagliflozin, when taken orally, is rapidly absorbed and typically reaches peak plasma concentrations (t_{max}) within 1-2 hours. It has a half-life of approximately 12-13 hours, allowing for once-daily dosing. Its systemic exposure is dose-proportional across a wide range (0.1-500 mg) with an oral bioavailability of 78%. It has a significant extravascular distribution, with an average volume of distribution of 118 L [16,17]. Dapagliflozin is primarily metabolized in the liver and kidneys by uridine diphosphate-glucuronosyltransferase-1A9 (UGT1A9), producing the major metabolite dapagliflozin 3-O-glucuronide, which does not inhibit SGLT2 at clinically relevant exposures. Only a small fraction of dapagliflozin is cleared through renal excretion (less than 2% of the dose is recovered in urine as the parent drug), while its major metabolite is primarily eliminated via renal excretion. Given these PK characteristics, there is potential for significant interactions with inhibitors and inducers of UGT1A9 [16,17,18].

COMMON DRUG-DRUG INTERACTIONS (DDI)

Dapagliflozin, an SGLT-2 has been an effective option in treating diabetes mellitus and is also recommended for the risk of cardiovascular death and hospitalization with reduced ejection fraction. As dapagliflozin is used as add-on therapy in the existing condition, the clinical approach for the use of dapagliflozin should have major concern on drug-drug interaction and their potential interaction effects [19,20].

The databases we used to assess drug-drug interactions between dapagliflozin and some concomitant medications:

- Uptodate (www.uptodate.com/) (https://www.uptodate.com/contents/dapagliflozin-drug-information/print?search=dapagliflozin&source=panel_search_result&selectedTitle=1~33&usage)
- Medscape (www.medscape.com/)
- Drugs.com. (www.drugs.com/drug_interactions.html)

A. Drug-drug interaction with other glucose-lowering agents

Dapagliflozin may enhance the hypoglycemic effect of insulin when used together. It can be managed by a decrease in the dose of insulin when initiating therapy with an SGLT2 inhibitor and monitoring patients for hypoglycemia. It comes under Risk D requiring Consideration of therapy modification [21]. The addition of dapagliflozin in patients insufficiently controlled with glimepiride resulted in a significant reduction in HbA1c with only a slightly increased risk of hypoglycemia [21,22,23,24].it comes under the risk D category requiring to Consider therapy modification. Also, it can be managed by Considering a decrease in the dose of sulfonylurea when initiating therapy with an SGLT2 inhibitor and monitoring patients for hypoglycemia. Dapagliflozin can enhance the hypoglycemic effects of insulin and insulin secretagogues. The management strategy is to educate patients on hypoglycemia symptoms. Regularly monitor blood glucose levels and consider reducing the dose of insulin or insulin secretagogues [22,23,24,26].

B. Drug-drug interactions with cardiovascular agents

Risk of hypotension and renal impairment are the possible interaction effects between dapagliflozin and primarily used antihypertensive agents such as enalapril, lisinopril, atenolol, metoprolol, and amlodipine severity of interaction is found to be moderate. it necessitates monitoring of blood pressure and renal function if co-administration is required.

The effects of administering dapagliflozin concomitant with valsartan, simvastatin, digoxin, or warfarin were assessed in healthy volunteers. valsartan and Simvastatin did not affect the exposure to dapagliflozin. Dapagliflozin 20 mg led to modest increases in exposure to simvastatin and simvastatin acid; however, these changes were deemed not clinically significant. A slight increase in exposure to R-warfarin and S-warfarin was observed when warfarin was taken with dapagliflozin, but there was no change in the International Normalized Ratio (INR). No other significant drug-drug interactions were detected, including any changes in digoxin levels following dapagliflozin administration [27,28].

The study by Schumacher (2024) reports a case of severe hypotension in a patient with heart failure with reduced ejection fraction (HFrEF) who was undergoing combined treatment with a sodium-glucose co-transporter-2 (SGLT-2) inhibitor and an angiotensin receptor-neprilysin inhibitor (ARNI) [28]. The report emphasizes the potential risk of the significant reduction in blood pressure when combining these two drug classes. The findings indicate that careful monitoring is crucial when prescribing this combination to prevent adverse events such as severe hypotension [29].

Inhibition of glucose and sodium co-transport leads to mild diuresis and transient natriuresis, which results in a reduction of intravascular volume. Adverse reactions related to volume depletion, such as hypotension, postural dizziness, orthostatic hypotension, syncope, and dehydration, may occur after starting treatment with SGLT-2 inhibitors. The risk of these reactions can be heightened when SGLT-2 inhibitors are used concurrently with other blood pressure-lowering medications and diuretics [28].

C. Drug-drug interactions with other medications of interest

Since dapagliflozin is primarily metabolized through the UGT1A9 pathway to its main inactive metabolite, dapagliflozin 3-O-glucuronide (D3OG), the potential for drug-drug interactions (DDIs) with two possible UGT1A9 modulators was assessed.: Rifampin, a broad-spectrum drug-metabolizing enzyme inducer, and mefenamic acid, a potent UGT1A9 inhibitor [30]. Mefenamic acid increased dapagliflozin exposure, likely due to the inhibition of UGT enzymes involved in its metabolism. This interaction indicates that dapagliflozin levels may rise when used with UGT inhibitors, potentially leading to increased pharmacological effects or adverse events. Significant changes in dapagliflozin exposure were observed. rifampin caused a substantial decrease in AUC (-22%), and mefenamic acid, led to a notable increase in AUC (+51%). However, only minor changes in urinary glucose excretion (UGE) were detected, none of which were considered clinically relevant [30].

SGLT2 inhibitors may reduce the serum concentration of lithium, which is classified under risk rating C. This interaction can be controlled by routinely monitoring lithium levels and making necessary adjustments to the treatment. A single case report details a 30-year-old patient with schizoaffective disorder who began treatment with empagliflozin following a new diagnosis of type 2 diabetes. Additionally, the prescribing information for dapagliflozin and lithium indicates that concurrent use of dapagliflozin with lithium may lead to reduced serum lithium concentrations [31,32].

D. CYP3A4 Inducers

Drugs such as rifampin, phenytoin, and carbamazepine can decrease the plasma concentration of dapagliflozin by inducing CYP3A4 enzymes. This reduction in dapagliflozin levels may result in diminished efficacy and suboptimal glycemic control. To manage this interaction, blood glucose levels should be monitored closely, and dosage adjustments of dapagliflozin may be necessary to ensure effective treatment [28].

E. CYP3A4 Inhibitors

Drugs such as ketoconazole and ritonavir can elevate the plasma concentration of dapagliflozin by inhibiting CYP3A4 enzymes. This increase in dapagliflozin levels raises the risk of adverse effects. To manage this interaction, monitor for signs of dapagliflozin-related adverse effects, such as urinary tract infections and volume depletion, and consider dose reduction if clinically necessary [28].

CLINICAL IMPLICATIONS AND MANAGEMENT STRATEGIES

Effective management of DDIs with dapagliflozin involves:

- **Regular Monitoring**: Frequent monitoring of blood glucose levels, renal function, electrolyte balance, and other relevant clinical parameters.
- **Patient Education**: Educating patients about potential side effects, signs of hypoglycemia, dehydration, and the importance of adherence to prescribed therapies.
- **Dose Adjustments**: Adjusting doses of dapagliflozin or co-administered drugs based on clinical response and laboratory findings.
- **Interdisciplinary Approach**: Collaborating with other healthcare professionals, including pharmacists, to identify potential DDIs and optimize therapeutic regimens.

FUTURE PERSPECTIVES

As the use of dapagliflozin expands, ongoing research is needed to fully elucidate the extent of its DDIs and develop more precise management guidelines. Future studies should focus on real-world data to capture the nuances of DDIs in diverse patient populations.

Future research should aim to build detailed profiles of potential drug-drug interactions involving dapagliflozin. This includes evaluating interactions with a broader range of medications used in diabetes management, cardiovascular therapies, and CKD treatments to better understand how dapagliflozin interacts with other commonly prescribed drugs. There is a need for long-term studies to assess how chronic use of dapagliflozin interacts with other medications over extended periods. Understanding long-term effects will be crucial for optimizing treatment regimens and ensuring sustained efficacy and safety.

CONCLUSION

Dapagliflozin is an effective and generally safe option for managing type 2 diabetes. All available studies investigating potential drug-drug interactions (DDIs) between SGLT2 inhibitors and other drugs commonly used in patients with type 2 diabetes provide reassuring results, with no clinically relevant pharmacokinetic (PK) interferences detected when combined with other glucose-lowering agents or cardiovascular agents. However, some case reports indicate potential drug interactions. Large phase 3 clinical trials lasting up to 1-2 years have shown no clinically relevant safety issues when SGLT2 inhibitors are prescribed with other glucose-lowering agents and several cardiovascular agents.

Nevertheless, when agents that selectively act on pathways involved in the metabolism of dapagliflozin (such as UGT inducers and UGT inhibitors) are prescribed, larger changes in exposure to dapagliflozin may occur, which could have clinical consequences. Its interactions with other medications necessitate careful consideration to prevent adverse effects and ensure optimal therapeutic outcomes. Further studies are required to more extensively investigate potential DDIs in patients with type 2 diabetes who are chronically treated with dapagliflozin. By understanding these interactions and implementing appropriate management strategies, healthcare providers can maximize the benefits of dapagliflozin therapy while minimizing risks.

REFERENCES

[1] International Diabetes Federation. IDF Diabetes Atlas, 10th edn. Brussels, Belgium: 2021. Available at: https://www.diabetesatlas.org

[2] American Diabetes Association; 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. Diabetes Care 1 January 2021; 44 (Supplement_1): S15–S33. https://doi.org/10.2337/dc21-S002

[3] Laiteerapong N, Ham SA, Gao Y, Moffet HH, Liu JY, Huang ES, Karter AJ. The legacy effect in type 2 diabetes: impact of early glycemic control on future complications (The Diabetes & Aging Study). Diabetes Care. 2019 Mar;42(3):416-426. doi: 10.2337/dc17-1144. Epub 2018 Aug 13. PMID: 30104301; PMCID: PMC6385699.

[4] Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012 Jun;55(6):1577-96.

[5] Tahrani AA, Bailey CJ, Del Prato S, et al. Management of type 2 diabetes: new and future developments in treatment. Lancet. 2011 Jul 9;378(9786):182-97.

[6] Vasilakou E, Karagiannis T, Athanasiadou E, et al. Sodium-glucose cotransporter 2 inhibitors for type 2 diabetes: a systematic review and meta-analysis. Ann Intern Med. 2013;159(4):262-274. doi:10.7326/0003-4819-159-4-201308200-00007. Epub 2013 Aug 20.

[7] Bakris GL, Fonseca VA, Sharma K, Wright EM. Renal sodium-glucose transport role in diabetes mellitus and potential clinical implications. Kidney Int. 2009; 75:1272-1277.

[8] Stenlöf K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab. 2013; 15:372-382.

[9] Ferrannini E, Solini A. SGLT2 inhibition in diabetes mellitus: rationale and clinical prospects. Nat Rev Endocrinol. 2012; 8:495-502.

[10] Rosenstock J, Seman LJ, Jelaska A, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes Obes Metab. 2013; 15:1154-1160.

[11] Meng W, Ellsworth BA, Nirschl AA, McCann PJ, Patel M, Girotra RN, et al. Discovery of dapagliflozin: a potent, selective renal sodium-dependent glucose cotransporter 2 (SGLT2) inhibitor for the treatment of type 2 diabetes. J Med Chem. 2008 Mar 13;51(5):1145-9. doi: 10.1021/jm701272q. Epub 2008 Feb 9. PMID: 18260618.

[12] Ryden L, Grant PJ, Anker SD, et al. ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J. 2013 Aug 30;34(39):3035-87.

[13] Scheen AJ. Drug interactions of clinical importance with antihyperglycaemic agents. Drug Saf. 2005;28(7):601-31. doi: 10.2165/00002018-200528070-00004.

[14] Van Gaal L, De Leeuw I. Rationale and options for combination therapy in the treatment of type 2 diabetes. Diabetologia. 2003 Mar;46(Suppl 1):M44-50.

[15] Plosker GL. Dapagliflozin: a review of its use in type 2 diabetes mellitus. Drugs. 2012 Dec 3;72(17):2289-312.

[16] Kasichayanula S, Liu X, Lacreta F, et al. Clinical pharmacokinetics and pharmacodynamics of dapagliflozin, a selective inhibitor of sodium-glucose co-transporter type 2. Clin Pharmacokinet. 2013 Oct 9. Epub 2013/10/10.

[17] Komoroski B, Vachharajani N, Boulton D, Kornhauser D, Geraldes M, Li L, Pfister M. Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. Clin Pharmacol Ther. 2009 May;85(5):520-6. doi: 10.1038/clpt.2008.251. Epub 2009 Jan 7. PMID: 19129748.

[18] Obermeier M, Yao M, Khanna A, Koplowitz B, Zhu M, Li W, Komoroski B, Kasichayanula S, Discenza L, Washburn W, Meng W, Ellsworth BA, Whaley JM, Humphreys WG. In vitro characterization and pharmacokinetics of dapagliflozin (BMS-512148), a potent sodium-glucose cotransporter type II inhibitor, in animals and humans. Drug Metab Dispos. 2010 Mar;38(3):405-14. doi: 10.1124/dmd.109.029165. Epub 2009 Dec 8. PMID: 19996149.

[19] McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med. 2019 Nov 21;381(21):1995-2008. doi: 10.1056/NEJMoa1911303. Epub 2019 Sep 19. PMID: 31535829.

[20] Anitha AP, Balasubramanian S, Ramalingam AG, Samuel Kennady SR, Ganamurali N, Dhanasekaran D, Sabarathinam S. An exploration of the experience of dapagliflozin in clinical practice. Future Sci OA. 2022 Nov 1;8(8): FSO816. doi: 10.2144/fsoa-2022-0038. PMID: 36457541; PMCID: PMC9704035.

[21] Wilding JP, Norwood P, T'joen C, Bastien A, List JF, Fiedorek FT. A study of dapagliflozin in patients with type 2 diabetes receiving high doses of insulin plus insulin sensitizers: applicability of a novel insulin-independent treatment. Diabetes Care. 2009 Sep;32(9):1656-62. doi: 10.2337/dc09-0517. Epub 2009 Jun 15. PMID: 19528367; PMCID: PMC2732143.

[22] Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K, Parikh S; Dapagliflozin 006 Study Group. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial. Ann Intern Med. 2012 Mar 20;156(6):405-15. doi: 10.7326/0003-4819-156-6-201203200-00003. PMID: 22431673.

[23] Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metab. 2011 Oct;13(10):928-38. doi: 10.1111/j.1463-1326.2011.01434. x. PMID: 21672123.

[24] Matthaei S, Bowering K, Rohwedder K, Grohl A, Parikh S. Dapagliflozin improves glycemic control and reduces body weight as add-on therapy to metformin plus sulfonylurea: a 24-week randomized, double-blind clinical trial. Diabetes Care. 2015 Mar;38(3):365-72. doi: 10.2337/dc14-0666.

[25] Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. Lancet. 2010 Jun 26;375(9733):2223-33. doi: 10.1016/S0140-6736(10)60407-2. PMID: 20609968.

[26] Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. BMC Med. 2013 Feb 20; 11:43. doi: 10.1186/1741-7015-11-43. Erratum in: BMC Med. 2013; 11:193. PMID: 23425012; PMCID: PMC3606470.

[27] Kasichayanula S, Chang M, Liu X, et al. Lack of pharmacokinetic interactions between dapagliflozin and simvastatin, valsartan, warfarin, or digoxin. Adv Ther 2012 Feb; 29 (2):163-77.

[28] Gomez-Peralta F, Abreu C, Lecube A, Bellido D, Soto A, Morales C, Brito-Sanfiel M, Umpierrez G. Practical approach to initiating SGLT2 inhibitors in type 2 diabetes. Diabetes Ther. 2017 Oct;8(5):953-62. doi: 10.1007/s13300-017-0277-0. Epub 2017 Jul 18. Erratum in: Diabetes Ther. 2017 Oct;8(5):963-5. doi: 10.1007/s13300-017-0290-3. PMID: 28721687; PMCID: PMC5630545.

[29] Schumacher C. Severe hypotension with concomitant sodium-glucose co-transporter-2 inhibitor and angiotensin receptor-neprilysin inhibitor therapy in a patient with heart failure reduced ejection fraction: a case report. J Pharm Pract. 2024 Apr;37(2):495-499. doi: 10.1177/08971900221142686. Epub 2022 Nov 28. PMID: 36441976

[30] Kasichayanula S, Liu X, Griffen SC, Lacreta FP, Boulton DW. Effects of rifampin and mefenamic acid on the pharmacokinetics and pharmacodynamics of dapagliflozin. Diabetes Obes Metab. 2013 Mar;15(3):280-3. doi: 10.1111/dom.12024. Epub 2012 Nov 19. PMID: 23061428.

[31] Lytvyn Y, Kimura K, Peter N, Lai V, Tse J, Cham L, Perkins BA, Soleymanlou N, Cherney DZ. Renal and vascular effects of combined SGLT2 and angiotensin-converting enzyme inhibition. circulation. 2022;146(6):450-462. doi:10.1161/CIRCULATIONAHA.122.059150.

[32] Armstrong GP. Empagliflozin-mediated lithium excretion: A case study and clinical applications. Am J Case Rep. 2020;21: e923311. doi: 10.12659/AJCR.923311.