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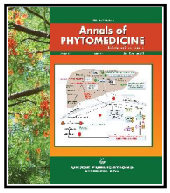

Case report : Open Access

Addressing potential pharmacological adverse reactions of dapagliflozin when taking along with other antidiabetics for the management of type 2 diabetes: A case report

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Abstract

The goal of this clinical report aimed to emphasise the significance of early detection of adverse medication responses for individuals who have taken dapagliflozin during the management of type 2 diabetes. These reactions include loose stools and diarrhoea. On June 1, 2022, a 58-year-old female patient that body weighs 49 kg and has had type 2 diabetes for the past 8 years, presented to the outpatient department of a tertiary care hospital with complaints of uncontrolled diabetes (since 3 years) and lower leg pain. The specialist examined and assessed the patient. On June 2, 2022, the patient experienced 8-10 episodes of diarrhoea and loose stools, following the administration of the drug. The likelihood of experiencing loose stools or diarrhoea when taking dapagliflozin increases with age, drug-drug interactions, genetic polymorphism, and gender. This is one of the first reports pointing to loose stools and diarrhoea as possible adverse medication reactions associated with dapagliflozin. The need for monitoring dapagliflozin medication in clinics and hospitals is highlighted by this case. The requirement for patient self-monitoring as well as the usage of a risk assessment tool to determine a patient's risk.

1. Introduction

Diabetes refers to a group of metabolic illnesses in which hyperglycemia results from deficits in the production of insulin, its action, or both (Duraisami *et al*., 2021; Tiwari *et al*., 2015). The chronic hyperglycemia of diabetes is associated with long-term damage, impairments, and malfunction of many body parts, including the kidneys, heart, eyes, vessels of blood, and nerves (American Diabetes Association, 2014). The projected incidence of diabetes in the global population in 2019 was 9.3% (or roughly 463 million people), and it is predicted to rise to 10.2% (or roughly 578 million people) by 2030 and 10.9% (or approximately 700 million people) by 2045. Accordingly, urban regions (10.8%) and better-income countries (10.4%) have a higher incidence than rural areas (7.2%) and low-income countries (4.0%). 50.1% of diabetics do not know they have the condition (Saeedi *et al.,* 2019).

Other metabolic abnormalities are also usually present in type 2 diabetes mellitus (T2DM) patients: more than 85% of T2DM patients are overweight, and the disorder is characterized by substantial weight gain over the course of a person's lifetime (Avogaro *et al,*. 2018). T2DM is getting more and more prevalent. The health and quality of life of T2DM suffered patients have been impeded by acute complications includes hypertonic coma and ketoacidosis, in addition to chronic complications like neuropathy, retinopathy, nephropathy, and vasculopathy, which now has exacerbated the financial burden on society (Yang *et al.,* 2020). Regardless of the availability of several diabetes treatments, it can be challenging for patients with type 2 diabetes to reduce weight in a healthy way and get their blood glucose levels under control. The significant proportion of oral antihyperglycemic medications, such as thiazolidinediones and sulfonylureas, contribute to weight neutral or weight gain, such like dipeptidyl peptidase-4 (DPP-4) inhibitors, and do not drastically reduce body weight, despite the fact that metformin and glucagon-like peptide-1 (GLP-1) analogues do so (American Diabetes Association 2014, Saeedi *et al.,* 2019). A novel class of antidiabetic medications known as sodium glucose co-transporter 2 (SGLT2) inhibitors improves glycemic control and body weight loss by blocking renal glucose reabsorption. Recent studies on weight loss with SGLT2 inhibitor treatment have really shown reductions in weight of approximately 1 to 4 kg in various trials (Yang *et al.,* 2020; Cai *et al.,* 2018). Although, the dosages and types of SGLT2 inhibitors used during different trials varied (Scheen, 2015). Gliflozins have been proven to substantially enhance the cardiovascular health in T2DM individuals in addition to blood sugar control. Numerous drugs in this class have already got approval or are currently in the process of development (Kaur *et al.,* 2021). Among SGLT2 inhibitors, canagliflozin, empagliflozin and dapagliflozin are the most often utilized. They are recommendable to other antidiabetic medications because they effectively manage glucose levels and HbA1c levels while having minimal side effects, including such hypoglycemia or mass gain (Hsia *et al.,* 2017). Adverse effects of SGLT2 inhibitors are including amputations, diabetic ketoacidosis, kidney injury, and urinary tract infections that result in blood infections. Fractures in the bones, pancreatitis and pancreatic cancer, heart attack, genital mycotic infections in women, perineal necrotizing fasciitis (Fournier's

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Gangrene), hypoglycemia, upper respiratory tract infection, and erythema (Hsia *et al.,* 2017).

2. Case description

A 58-year-old female patient with a body mass index of 49 kg who has had type 2 diabetes for the past 8 years. She visited the tertiary care hospital in an outpatient department on 1st June 2022 with the complaints of uncontrolled type-2 diabetes (since 3 years) along with pain in her lower limbs. Patient was evaluated and investigated by the consultant and her vitals were recorded as follows: HR-78, RR-18, BP-140/85 mmHg and Temp 98.8°F. Her laboratory investigation reports showed increase in the following values before starting the medication like blood sugar fasting 188 mg/dl, postprandial blood sugar fasting-340 mg/dl, HbA1c-13.5, SGOT, 60 U/L, SGPT, 56 U/L, LDL, 170 mg/dl. Consultant prescribed the following medications: tablet Zoryl M1 1/500 mg OD, tablet Teniva M 20/500 mg OD, tablet Dapavel 10 mg OD, tablet Atorvas 10 mg, tablet Pragabalin M 75 mg OD, tablet Telma 40 mg OD and tablet Supradyn OD. The patient was taking Telmisartan, Pregabalin, Atorvastatin, Teneligliptin, Glimepiride, and Metformin without any history of diarrhea. However, after initiating dapagliflozin therapy, the patient reported diarrhea. After taking of Tablet Dapavel patient started loose motion/diarrhoea (8-10 episode) on next day, patient attainder informed to the consultant, consultant advised to withhold tablet Dapavel 10 mg , and treated the loose motion by the Tablet Rasecadotril and add pre and probiotics. After the loose motion stopped, before reintroduction of tablet Dapavel consultant do the laboratory investigation. A stool culture and CBC was performed on the patient, but the results came back negative. But, it is possible that it was done to rule out an infectious cause of diarrhea. Consultant again started tablet Dapavel 10 mg after that loose motion started again and after that consultant discontinued the tablet Dapavel 10 mg. On the basis of rechallenge, consultant decided that tablet Dapavel 10 mg was suspected drug.

3. Discussion

In this case, the individual had no co-morbidities or problems, and the adverse event was not recurrent or life-threatening in nature. The WHO-UMC causality categories evaluation result for ADR of dapagliflozin therapy demonstrates that the medication has certainly caused (definite cause) of ADR (Table 1) (Meyboom *et al*., 1997). A score of 9 was obtained on the Naranjo Causality Assessment Scale (Table 2, Table 3). Any score of ≥9 indicates that the medication had certainly produced ADR (Naranjo *et al*., 1981). Dapagliflozin has been linked to a number of characteristics, including older age, drug-drug interactions, genetic variability and gender. In this situation, there is a chance of an inherited polymorphism. Dapagliflozin's gastrointestinal side effects include.

3.1 Constipation

Constipation was observed in 2.2% and 1.9% of the individuals treated with Dapagliflozin and Propanediol 5 mg (n=1145) and 10 mg (n=1193), as well as, in 12 research studies, that include four research studies as monotherapy and eight research studies as an add-on to experience antidiabetic therapy or as a combination treatment with metformin, of between twelve and twenty-four weeks duration, as opposed to 1.5% of individuals who received a placebo (n=1393) (Sigler, 2014; Compton *et al*., 2023).

3.2 Nausea

In twelve research studies, nausea was observed in 2.8% and 2.5% of the individuals receiving Dapagliflozin Propanediol 5 mg (n=1145) and 10 mg (n=1193), accordingly, in contrast with 2.4% of individuals who received a placebo (n=1393). These studies included four research studies as monotherapy and eight research studies as an addition to current hypoglycemic therapy or as mixed therapy with additional medications (Sigler, 2014; Compton *et al*., 2023). It is indeed possible that the diarrhea observed in the patient could be associated with the effects of SGLT1 inhibition and subsequent impairment of intestinal glucose absorption. But, still not listed type of adverse drug events of Dapagliflozin. Since SGLT1 is the primary transporter responsible for absorbing glucose in the gut, Dapagliflozin is a powerful and reversible SGLT2 antagonist that is > 1400 times more specific for SGLT2 than SGLT1 (Dhillon, 2019). The elevated HbA1C level of 13.5 in the patient suggested inadequate control of diabetes. There were no gastrointestinal (GI) complications observed. Even bowel habits not affected before treating with Dapagliflozin. Hence, there was no significant past medical history regarding diarrhea associated with other drugs (Telmisartan, Pregabalin, Atorvastatin, Teneligliptin, Glimepiride and Metformin). Based on the patient's medication history and interview, it appears that the patient was adherent to the prescribed medication regimen and was following a diabetic diet on a regular basis. This information suggests that the diarrhea observed in the patient may not be attributed to non-adherence to medication therapy or dietary recommendations.

Table 1: WHO-UMC causality categories

Causality term	Assessment criteria
Certain	Event or laboratory test abnormality, with plausible time relationship to drug intake. Cannot be explained by disease or other drugs. Response to withdrawal plausible (pharmacologically, pathologically). Event definitive pharmacologically or phenomenologically (ce. an objective and specific medical disorder or a recognized pharmacological phenomenon) re-challenge satisfactory, if necessary.
Probable/Likely	Event or laboratory test abnormality, with reasonable time relationship to drug intake. Unlikely to be attributed to disease or other drugs. Response to withdrawal clinically reasonable. Re-challenge not required.
Possible	Event or laboratory test abnormality, with reasonable time relationship to drug intake. Could also be explained by disease or other drugs. Information on drug withdrawal may be lacking or unclear.

Unlikely	Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations.
Conditional/Unclassified	Event or laboratory test abnormality. More data for proper assessment needed, or additional data under examination.
Unassessable/Unclassifiable	Report suggesting an adverse reaction. Cannot be judged because information is insufficient or contradictory. Data cannot be supplemented or verified.

Table 2: Naranjo adverse drug reaction probability scale

Naranjo adverse drug reaction probability scale			
Question	**Yes**	**No**	**Do not know**
Are there previous conclusive reports on this reaction?	+1	0	0
Did the adverse event appear after the suspected drug was administered?	+2	−1	0
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
Did the adverse event reappear when the drug was readministered?	+2	−1	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	−1	+2	0
Did the reaction reappear when a placebo was given?	−1	+1	0
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0
Was there action more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0

Table 3: Naranjo algorithm ADR probability scale

Score	**Interpretation of scores**
Total scoree ≥ 9	**Definite:** The reaction (i) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (ii) followed a recognized response to the suspected drug, and (iii) was confirmed by improvement on withdrawing the drug and reappeared on re-exposure.
Total score 5 to 8	**Probable:** The reaction (i) followed a reasonable temporal sequence after a drug, (ii) followed a recognized response to the suspected drug, (iii) was confirmed by withdrawal but not by exposure to the drug, and (iv) could not be reasonably explained by the known characteristics of the patient's clinical state.
Total score 1 to 4	**Possible:** The reaction (i) followed a temporal sequence after a drug, (ii) possibly followed a recognized pattern to the suspected drug, and (iii) could be explained by characteristics of the patient's disease.
Total scored ≤ 0	**Doubtful:** The reaction was likely related to factors other than a drug.

4. Conclusion

The recent case as presented above showed the development of diarrhea on Dapagliflozin therapy. It is obvious that close monitoring of patients at risk of developing complications (loose motion and diarrhea) is crucial. Above case also highlighted the need for continuous monitoring of patients receiving Dapagliflozin treatment, both in the clinic and in the hospital. It is essential to recognize that adverse reactions to medication can occur at any time during treatment and may not be immediately evident. Healthcare providers must work collaboratively with patients to develop a monitoring plan that considers the patient's unique needs and circumstances. This will help to identify adverse reactions early, intervene promptly, and prevent further complications. Additionally, patient education and counseling regarding potential adverse reactions and the importance of promptly reporting any changes in their condition can help improve outcomes and reduce the risk of adverse events.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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