

RETHINKING PRESCRIPTIONS: DESIGNING A CLINICAL PROCESS MAP TO MITIGATE DAPAGLIFLOZIN-INDUCED PRESCRIBING CASCADES

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ABSTRACT

A 68-year-old man developed fever, breathlessness, and excessive sweating. He is a known case of type 2 diabetes mellitus; recently, dapagliflozin was prescribed. Dapagliflozin reduces blood glucose by inhibiting selective sodium-glucose cotransporter-2. Sometimes, it induces infection due to an excessive amount of glucosuria. The patient's laboratory report indicates the bacterial infection and prescribes antibiotics. Occasionally, adverse drug reactions (ADRs) are misinterpreted by doctors as new medical conditions or symptoms, adding one more drug to the treatment chart or prescription needlessly, and this process is called the prescribing cascade (PC). This typical case is also the best example for two different types of PCs, such as an intentional, inappropriate, and prophylactic PC, with pantoprazole and ciprofloxacin and tinidazole as an unintentional and appropriate PC. Because of the PC, patients unnecessarily spend money, increasing the treatment cost. A detailed medical and medication history during the consultation and clinical process maps (CPM) will help minimize this advanced stage of ADRs. CPM are one tool generated using different geometric shapes with various colors. Hence, we have designed the CPM, which can play a pivotal role in diminishing the incidence of ADR and PCs by better understanding.

Keywords: Dapagliflozin, Bacterial infection, Adverse drug reactions, Ciprofloxacin, Tinidazole, Prescribing cascade, Drug-related problem, Clinical process maps.

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INTRODUCTION

Every medication that can have the intended therapeutic effects also brings the risk of unintended adverse effects. Healthcare professionals are responsible for ensuring that medications are taken in moderation and being aware of adverse drug reaction (ADR) risks [1,2].

These reactions increase morbidity, mortality, and treatment costs [3-5]. In a few cases, drug-induced signs and symptoms are misinterpreted as new medical conditions by doctors, who recommend new drugs or new laboratory tests and procedures. This process is termed the prescribing cascade (PC) [6].

In 1995, Rochon and Gurwitz introduced a novel term for PC. During this, patients must take unnecessarily extra medications or undergo more medical tests than needed, including taking over-the-counter drugs. It worsens the patient's medical condition and complicates pharmacotherapy [7-9].

Most of the time, the PC is commonly reported with the following drug classes: Antihypertensives, medicines acting on the central nervous system, antibiotics, antidiabetics, anticancer agents, and non-steroidal anti-inflammatory drugs [10].

Often, the management of diabetes mellitus is done with more complex and more than one anti-diabetic medication [11]. One is dapagliflozin, which inhibits selective sodium-glucose cotransporter-2, lowering glucose reabsorption in the kidney's proximal tubule. It is used along with diet and exercise to control blood sugar levels. It was approved in 2014 by the United States Food and Drug Administration [12,13].

It is primarily used to lower the chance of cardiac failure hospitalization in adults, especially those with type 2 diabetes who also have many cardiovascular system risk factors or known cardiovascular-related diseases [12]. It is available in 5 mg and 10 mg tablets and is

contraindicated in type 1 diabetes mellitus due to the risk of diabetic ketoacidosis (DKA) development [13-15]. In a few cases, these dapagliflozin-induced infections are considered or misinterpreted as new infections in the patient, leading to antibiotic prescriptions [16,17].

The main aim of this case report is to explain the PC process and its sequence, as well as the significance of clinical process maps (CPM) in understanding the process of ADR and minimizing the PCs. If any patient expresses fresh complaints after receiving the drug (s), healthcare professionals should consider the possibilities of ADR. Clinical pharmacists can play a vital role in minimizing the PC. Hence, the CPM is designed for this identified, reported, and assessed ADR to mitigate the same reactions in the future in clinical setups.

Clinical description

A 68-year-old man developed fever, breathlessness, excessive sweating, and a known case of type 2 diabetes mellitus, hypertension, and ischemic heart disease. Receiving metformin 500 mg, amlodipine 5 mg, and atorvastatin 10 mg. Recently, he was prescribed dapagliflozin 10 mg by his physician. Family and social history were not significant. He is vegetarian and found that he has no known allergies.

Investigation

General physical examinations: S1 and S2 heard, conscious, oriented, normal vesicular breath sound +, blood pressure: 140/790 mmHg, heart rate: 90 bpm, respiratory rate: 28 bpm, temperature: 103°F, SpO₂: 86% at room atmosphere, random blood sugar: 314 mg/dL, increased neutrophil count: 83%, Sodium: 135 mmol/L (136-144), potassium: 4.2 mmol/L (3.7-5.1), chloride: 104 mmol/L (97-105), serum creatinine: 1 mg/dL (0.7-1.3), red blood cells: 4.05 million cells/ μ L (4.7-6.1), white blood cells: 12170/ μ L (4500-11000), Platelet count: 3.9 lakh/cumm (1.5-4.5 lakh/ μ L), and hemoglobin: 12.6 g% (14-18 g/dL). Urine sugar values in this patient during the fever were unavailable as it was not performed.

Management

The physician diagnosed the patient with an upper respiratory tract infection (URTI) due to bacteria, continued the previous medications, and added tablets of aspirin 75 mg, atorvastatin 10 mg, nicorandil 5 mg, ipratropium and levosalbutamol nebulizer, injection pantoprazole 40 mg and a combination of ciprofloxacin 500 mg, and tinidazole 600 mg. The clinical pharmacist discussed the probabilities of bacterial infection with dapagliflozin [10-12]. The physician stopped Dapagliflozin instantly and de-challenged. The patient was discharged after 5 days with the following medications: Tablet ticagrelor 90 mg, tablet nicorandil 5 mg, tablet aspirin 75 mg + rosuvastatin 10 mg, tablet carvedilol 6.25 mg, tablet furosemide 40 mg, tablet pantoprazole 40 mg, tablet ivabradine 5 mg, and tablet metolazone 2.5 mg. After 1 month of follow-up, the patient expressed no fresh complaints.

DISCUSSION

This typical case demonstrates the process of PCs. PC not only adds one or two drugs to the treatment chart. It further worsens the patient's medical and financial condition [18].

More than ten percent of this dapagliflozin induces renal impairment; 1-10% produces URTI, urinary tract infection, back pain, increased urination, nausea, constipation, influenza, and nasopharyngitis. Among these, around 4% of the patients who receive this drug develop a respiratory tract infection. Even though urinary tract infection is common (4-7%), the main reason is excess glucose elimination while urinating, which is the most favorable environment for microbial growth [16,19].

The reasons behind fever and breathlessness in this patient are multifactorial, referable to bacterial URTI, and may be due to DKA. In a few cases, fever and breathlessness in diabetic patients could be complications like DKA. However, such features were not observed in this patient. Furthermore, diabetes patients generally have weaker immune systems and are more prone to developing infections. This patient is a known case of type 2 diabetes mellitus; sometimes, glucose is seen in the urine. These patients have double the risk of developing bacterial infections [14,17-22]. Therefore, monitoring the urine routine and analysis with counseling will help minimize the ADR and PC.

A case report of the source of a "prescribing cascade in an elderly man with Ropinirole-associated orthostatic hypotension" revealed that the PC increases the direct cost by \$64906.22 (approximately ₹ 53,96,273) [19]. In this case, the patient spent approximately 10000 Indian rupees due to the PC. This is a significant amount in a country like India to bear these expenses.

Here, the patient has not had any complaints of gastric irritation. However, during his hospital stay, he was prescribed injections of pantoprazole and tablets after discharge. As per the review article by Dreischulte *et al.*, this can be classified as an intentional, inappropriate, and prophylactic PC [23,24].

This type B ADR is a non-dose-dependent and unpredictable reaction due to excess glucose excretion. This alters the genitourinary environment and acts as a predisposing factor to developing an infection through the pharmacodynamic mechanism [25]. Standard therapy medications, such as paracetamol and bronchodilators can be administered to manage the ADR [26].

Various causality assessment scales assessed the reported ADR, as per the WHO probability scale, which is probable. Naranjo's algorithm 5 is the score, so the reaction was categorized as probable. Severity was evaluated using the modified Hartwig and Siegal scale; it is at a moderate level 4 (b). According to Rawlins and Thomson, the reaction is classified as type A and predictable. It is definitely preventable as per the Modified Shumock and Thronton preventability criteria. Dapagliflozin was de-challenged after the ADR identification in this case. Ponte *et al.*, PC severity assessment

scale was used to assess the severity of this PC as per the scale, and it belongs to moderate [18].

We know that case reports are the hypothesis or signal generators. Regular drug monitoring activities, such as home medication review, patient counseling, and medication history interviews certainly lessen the incidence of ADRs and the PC. Furthermore, the Narwat *et al.* review has revealed that type 2 diabetes mellitus patients have poor medication adherence. ADRs further change the patient's willingness to take medication. Hence, while conducting clinical pharmacy services, emphasis should be placed on the safe and continuous use of antidiabetic medications [27].

This PC case report is the first of its kind in India. It discusses the advanced stage of ADRs and the sequence mentioned in Fig. 1. Search indexes, such as Google Scholar and PubMed revealed a few research activities in India. Even many healthcare professionals, including doctors, nurses, and pharmacists, are not aware of this sequence of PCs. In this case, the PC leads to increased length of stay and treatment costs in the hospital.

A clinical process could be a speedy and easy series of steps carried out by one person that comes naturally to them, like taking a scanning or any medical procedures and tests. It can also be a complicated series of tasks or activities over time involving many

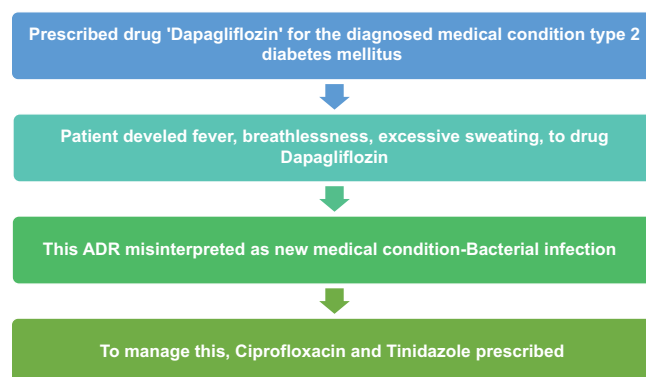


Fig. 1: Sequence of prescribing cascade in this patient

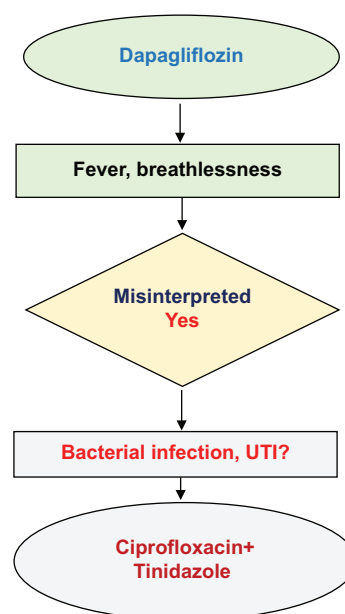


Fig. 2: Designed clinical process map of dapagliflozin-induced fever and breathlessness leading to prescribing cascade

people, like caring for cancer patients and cardiovascular disease-suffering patients [24].

CPMs help improve communication and offer robust documentation. Nowadays, these are some of the most widely used tools for solving problems in healthcare facilities [28]. CPMs are occasionally called flowcharts because of their depiction through diagrams. Different types of symbols are used between the input and output processes. The starting point of the process is represented by an oval shape, actions by rectangles, waiting by an inverted triangle, and decisions by a diamond shape. All these shapes are connected through lines and arrows to show interactions and process directions [29].

In this case, for the design of the CPM (Fig. 2), the below geometric shapes are used.

1. Light green shade of oval shape with blue font to show the beginning of the PC
2. A light green shade of rectangle with a light green color and black font is used for ADR
3. Cream color shade diamond shape with dark blue and red fonts were used for the decision
4. A light blue color shaded rectangle shape with the red color font used for misinterpreted diagnosis
5. A light blue oval shape with red font was used to represent the second drug prescribed to manage the ADR.

CONCLUSION

Due to pharmacokinetic and pharmacodynamic modification in the elderly population, the incidence of ADRs is higher; this unique population suffers from multiple diseases or disorders and is prescribed polypharmacy. As they are complaining of many symptoms and signs, the difficulty for doctors may be due to drugs, leading to the development of new medicines and PCs. These cascades will further make the treatment complex and increase morbidity and mortality. This case shows that PC also increases treatment costs and the length of hospital stays. Designed CPMs, Patient counseling, and proper medication history by pharmacists will play a significant role in reducing PCs.

PATIENT CONSENT AND ETHICAL APPROVAL

This study was performed according to the Declaration of Helsinki; written informed consent was received from each study participant. The Institutional Ethical Committee approved the study with Ref No: SSCPT/SHRC/PPD/2021-2022.

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AUTHOR'S CONTRIBUTION

Mr. Ravinandan A P identified, documented, and assessed this ADR. Dr. E. Maheswari conceived the idea of generating a CPM and evaluated the data collected. Mr. Vishwas H N edited the manuscript. All authors have carefully read and approved this manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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