Bilateral Lower Limb Ischemia and Gangrene with Dapagliflozin: Case Report

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Case Report

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Abstract

Background: Dapagliflozin, sodium- glucose cotransporter 2 inhibitor, is recently introduced in the heart failure treatment plan. Urinary tract infection and Fournier's gangrene are the most known serious adverse events of dapagliflozin.

Case presentation: We came across this case with bilateral lower limb ischemia in a patient with heart failure with reduced ejection fraction. Dapagliflozin was discontinued and new lines of treatment were started.

Conclusions: It is appeared that dapagliflozin could be associated with serious risk of toe ischemia/infection, thus patients received dapagliflozin should be closely monitored.

Introduction

Dapagliflozin is a recently introduced drug in the heart failure treatment plan(1). It belongs to sodium-glucose cotransporter 2 (SGLT2) inhibitor classes which was known previously as a lowering glucose drug. Dap-HF clinical trial proved the value of dapagliflozin in patients with heart failure and a reduced ejection fraction, regardless of the presence of diabetes(2). Safety data about dapagliflozin in heart failure is still building up, however, most known serious adverse events of dapagliflozin are urinary tract infection(3) and Fournier's gangrene(4). We came across this case of lower limb ischemia in patient with heart failure with reduced ejection fraction (HFrEF) who received dapagliflozin. We suggest that this adverse event is induced by dapagliflozin.

Case Presentation

Seventy one year- old male patient presented to the outpatient clinic of Beni-Suef University Hospital, Egypt with shortness of breath and severe bilateral lower limb pitting edema. He had symptoms of NYHA class IV heart failure (HF). Patient has a history of ischemic cardiomyopathy and hypertension. He has no history of diabetes and he is ex-smoker. Five years ago, he had myocardial infarction treated medically (bisoprolol 2.5mg, hydrochlorothiazide 12.5mg, ramipril 2.5mg, aspirin 75mg and atorvastatin 20 mg). On June 2021, recent echocardiographic showed reduced EF (34%) with dilated left ventricular dimensions (6.3 x 5.2 mm) and apical thrombus. New medications were prescribed; Sacubitril- valsartan 50mg twice daily, carvedilol 6.25mg twice daily, toresamide 10mg and warfarin 3mg. During follow up visit 3 weeks later our patient symptomatically improved (NYHA 1-2), Echo showed totally resolved thrombus with nearly same dimensions. Blood pressure was 140/90 mmHg. Toresamide and warfarin were stopped, higher doses of sacubitril valsartan (100mg twice daily) and carvedilol (12.5mg twice daily), and we started dapagliflozin 10mg On November 2021, the patient reached follow up clinic with color changes of both feet in the form of cyanosis (figure 1). There was a fixed color involving the right the second toe with line of demarcation. Concomitant coldness was observed in forefoot. Severe rest pain was experienced by

the patient. However, posterior tibial artery pulsations were well felt bilaterally indicating that level of ischemia at foot and digital vessels.

Arterial duplex revealed mild atherosclerosis at right side infra-popliteal arteries with no significant stenosis. Both lower limb arteries starting from both common femoral artery (CFA) down to popliteal artery are patent, echo free, show tri-phasic flow with average velocities. No evidence of DVT or thrombophlebitis in both lower limb veins Doppler study. Patient’s BP was 110/70mmHg on presentation with 37c temperature and normal HR. His GFR was 33 mL/min/1.73 m2 Laboratory investigations presented at table (1).

Table (1), Laboratory investigation on presentation

Investigation	Result
Sr cr	2.3
BUN	106
Na	137
K	4.59
INR	3.2
FBG	109.3
PP	125.3
HbA1c	5.7
CH	216
TG	132
LDL	191
HDL	25
Vitamin D	17.5

Treatment

We stopped Dapagliflozin and started cilostazol every 12 hr. in addition to pentoxifylline 400mg every 8 hr and aspirin 81 mg. The starting dose of cilostazol was 50 mg bid that was increased to 100 mg bid after one week. Close observation to blood pressure was assured to avoid hypoperfusion status and proper hydration was encouraged. Ten days later (figure2), empirical antibiotics were prescribed; ampicillin sulbactam 1.5 g every 6hr., dalacin 600mg every 6hr, ceftriaxone 1gm every 24hr, levofloxacin 500mg every 24 hr.

Outcome and Follow up

Rest pain was improved. Coldness became limited to tip of some toes. Color was improved at forefoot (figure 3). However, fixed color was shown to include tip of right big toe, tip of left big toe and tip of left 2nd toe, in addition to the left 2nd toe at time of presentation. Close observation with wound care of the gangrenous parts was assured till separation of gangrenous tissue and stumps healing, (figure 4). Antibiotics continued for 21 days and other drugs for two months. One month later, no further worsening of signs after his first presentation.

Discussion

The risk of limb and toe amputation associated with using SGLT2 inhibitor, as a class effect, has been addressed before(5). FDA released a black box warning regarding the risk of toe amputation with canagliflozin (6) depending on the CANVAS and CANVAS-R Program(7). However, the risk appears to be more among patients ≥ 65 year old with history of cardiovascular disease(8) and peripheral artery disease (PAD) (9). It has been reported a higher risk of amputation associated with canagliflozin use than dapagliflozin and empagliflozin. The risk was attributed to the potent diuresis effect of canagliflozin which can lead to peripheral tissue ischemia. It was also suggested that only canagliflozin, interrupt the mitochondrial electron transport chain which can induce cytotoxicity. Empagliflozin reported to induce upper extremity ulcers or gangrene in patient with type 2 diabetes(10). In DECLARE–TIMI 58 trial, dapagliflozin resulted in higher incidences of limb events in patients with history of PAD (11).

Patient we present has been taking dapagliflozin for 2 month and other new prescribed anti-failure drugs for 5 month. Our suggestion was that dapagliflozin induce this sign of peripheral ischemia which carry the risk of amputation. According to Naranjo causality assessment scale and WHO-UMC algorithm(12) result, we consider that this ischemia is a probable adverse reaction to dapagliflozin use.

Patient was not presented with signs of volume depletion which could precipitate the lower limb ischemia. Toresamide was discontinued since starting dapagliflozin. Also, he was well perfused with high BP. No history of diabetic ketoacidosis (DKA) or hypoglycemia. Patient also did not adapt diet with low carbohydrate which could trigger a state of ketoacidosis(13). Possible drug interaction with dapagliflozin was screened to exclude sudden increase in dapagliflozin blood level.

Dapagliflozin was stopped immediately and drugs indicated for lower limb ischemia started(14). Since we do not know the exact mechanism or reason of LL ischemia in this patient, we had a concern of further ischemia which could lead to gangrene, thus we started empirical antibiotic.

Conclusion

It seems that dapagliflozin could be associated with serious risk of toe ischemia/infection, thus patients received dapagliflozin should be closely monitored.

Abbreviations

SGLT2; sodium- glucose cotransporter 2

HFrEF; Heart failure with reduced ejection fraction

NYHA; New York Heart Association

HF; Heart failure

HR; Heart rate

BP; Blood pressure

GFR; Glomerular filtration rate

FDA; Food and Drug Administration

CANVAS; Canagliflozin Cardio-Vascular Assessment Study

PAD; Peripheral arterial disease

DECLARE–TIMI 58; Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58

CFA; common femoral artery

DKA; Diabetic ketoacidosis

Declarations

Ethics approval: Not applicable

Consent for publication: consent to publish was provided by the patient.

Availability of data and materials: Data are available upon request

Competing interests: All authors have no conflicting interest

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Authors' contributions: H.B & Z.E included the patient, conceptualize the work idea and provide major contribute in writing the manuscript, A.Z performed vascular follow up. All authors read and approved the final manuscript

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Figures

Figure 1

1st day of presentation

Figure 2

10 days after presentation

Figure 3

20 days after presentation

Figure 4

30 days after presentation