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CASE REPORT ON DAPAGLIFLOZIN TABLET ASSOCIATED ALLERGIC REACTION AND FLUID FILLED LESION ON LIMBS IN A TERTIARY CARE REFERRAL HOSPITAL – KERALA

Shibil. Pk*, Shinu.C, Elizabeth Joseph, Mammen Paul, Dhanya Dharman

Al-Shifa College of Pharmacy, Department of Pharmacy Practice, Kizhattur, Perinthalmanna, Kerala-679325.

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***Correspondence for Author**
Mr.Shibil.PK
Al-Shifa College of Pharmacy, Department of Pharmacy Practice, Kizhattur, Perinthalmanna, Kerala.

ABSTRACT

Dapagliflozin is a drug used to treat type 2 diabetes. Clinical trials are just now starting to include patient with type 1 diabetes. We reported a case on dapagliflozin tablets associated allergic reaction and fluid filled lesion on legs in a diabetic patient. A 36 year old male patient was admitted in dermatology department of the hospital for the treatment of allergic reaction and fluid filled lesion on legs. The causality of the event was analyzed by Naranjo's ADR probability scale and the score was 5, which can be a probable event. The causality of the event was also analyzed by WHO –UMC for standardized case causality assessment criteria which also make it a probable/likely event.

KEYWORDS:- Dapagliflozin, legs in a diabetic patient.

INTRODUCTION

Dapagliflozin, a highly selective inhibitor of the renal sodium-glucose cotransporter-2, increases urinary excretion of glucose and lowers plasma glucose levels in an insulin-independent manner. We evaluated the efficacy and safety of dapagliflozin in treatment-naïve patients with type2 diabetes. Dapagliflozin inhibits subtype 2 of the sodium-glucose transport proteins (SGLT2), which is responsible for at least 90% of the glucose reabsorption in the kidney. Blocking this transporter causes blood glucose to be eliminated through the urine. The efficacy of this medication class has yet to be determined, but in initial clinical trials, dapagliflozin lowers HbA_{1c} by 0.90 percentage points when added to metformin.

Kidney plays an important role in glucose homeostasis, mainly by two mechanisms: gluconeogenesis and reabsorption of filtered glucose in the proximal convoluted tubule.1 About 180 g of glucose is filtered by the kidneys each day and in healthy individuals, virtually all of this is reabsorbed as a function of renal regulation of glucose homeostasis.2 Glucose reabsorption in kidneys occurs via sodium glucose co-transporter (SGLT), of which there are 6 types known to date.3 The two most important glucose co-transporters are SGLT1 and SGLT2. SGLT1 is a high affinity low capacity transporter, responsible mainly for the absorption of glucose in the gastrointestinal tract. It is also expressed in the liver, lungs and kidneys. SGLT2 on the other hand is a low affinity high capacity transporter, found primarily in the S1 segment of proximal convoluted renal tubule, where .90% of renal glucose reabsorption occurs.2 Transport of each glucose molecule is coupled to co transport of one sodium (Na+) ion in the kidneys and once inside the cell, glucose diffuses into blood via facilitated transport. Reabsorption of glucose in proximal tubules of kidneys is an active process requiring energy, which comes from electrochemical gradient generated by reabsorption of Na+ across the brush border and maintained by continuous transport of Na+ across the basolateral membrane intoblood via Na+/K+ ATPase4.

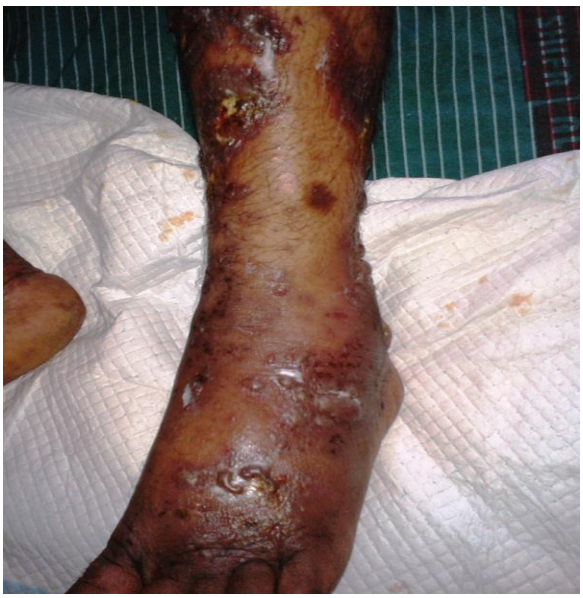
Blocking the reabsorption of glucose in the kidneys as a strategy to treat hyperglycaemia has been the focus of recent ongoing research, though compounds causing renal glycosuria have been known for a long time. Phlorizin, a naturally occurring phenol glycoside, first isolated from the bark of apple tree in 1835, was first discovered to induce glycosuria and diuresis in 1855. In 1933, Chasis, Jolliffe and Smith showed that administering phlorizin intravenously to man increased glucose clearance via kidneys to that of simultaneous xylose and sucrose clearances. William Goldring subsequently gave oral phlorizin to healthy volunteers but found that it was much less efficient in inducing urinary glucose excretion compared with intravenous injection. 5 This relative lack of efficacy of oral phlorizin, a competitive inhibitor of SGLT1 and SGLT2, in inducing complete glycosuria is due to its poor intestinal absorption. When given orally, phlorizin causes galactose malabsorption (via SGLT1 inhibition) and diarrhoea. Phlorizin has also been used in animals to study the mechanism of glucose transport. Lausser et al showed that phlorizin, by correcting glycaemia, significantly increased glucose clearance in alloxan. diabetic dogs.6 Rossetti et al, by using partially pancreatectomized rats, in which fasting insulin levels remained normal but insulin response to hyperglycaemia was markedly impaired, demonstrated that hyperglycaemia per se could lead to the development ofinsulin resistance and that phlorizin normalized insulinsensitivity,

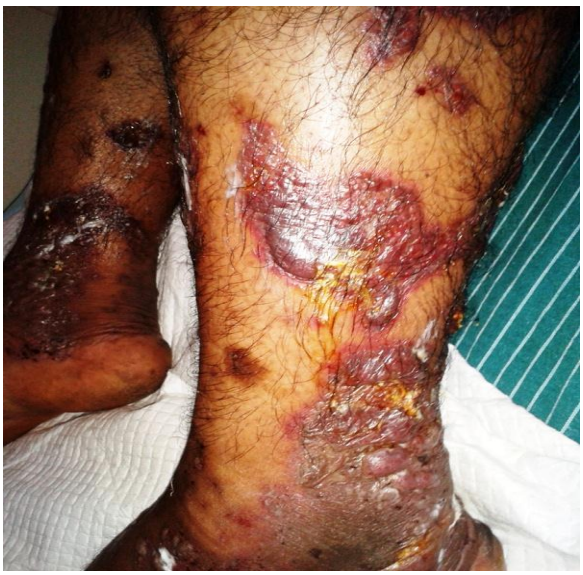
without any change in insulin level, by correcting hyperglycaemia. Despite this, the development of Phlorizin as a potential drug was not pursued due to its poor absorption from the GI tract and its non-selective inhibition of both SGLT1 and SGLT2. Therefore recent emphasis has been on developing a selective SGLT2 inhibitor, of which there are at least seven compounds currently being tested and at various stages of development. Of these, dapagliflozin is the most advanced in its clinical development.

Since dapagliflozin leads to heavy glycosuria (sometimes up to about 70 grams per day) it can lead to rapid weight loss and tiredness. The glucose acts as an osmotic diuretic (this effect is the cause of polyuria in diabetes) which can lead to dehydration. The increased amount of glucose in the urine can also worsen the infections already associated with diabetes, particularly urinary tract infections and thrush (candidiasis).raised red patches on skin. Dapagliflozin is also associated with hypotensive reactions.

Case report

A 36 year old male patient was admitted to dermatology department for presenting with allergic reaction on both lower limbs and reddish fluid filled lesion on the leg. The patient was newly diagnosed as diabetes from UAE and having co morbidities like hypertension and hyperlipidemia. On examination patient was found to be febrile, conscious and oriented. Fever due to bacterial infection on the fluid lesion. The medications he took from UAE were Valsartan 40mg, Atorvastatin 10mg, depagliflozin 10mg, galvusmet 50/1000mg. He is smoker, alcoholic, and non vegetarian. The dermatologist professionally diagnosed the case as necrotizing fasciitis. All vital parameters was normal except first day elevation of temperature and little elevation of blood pressure. The laboratory test reports of blood showed elevation of polymorph 85%, ESR 76mm/hr, CRP 7 4.0mg/dl, $HBA1_c$ 10.5%,D dimer >10000ng/dl. The blood sugar varying all the 7 days was managed by insulin according to sliding scale. Venous Doppler was done, the impression was found to be no DVT in both lower limbs, cellulites of both leg below knee. Skin biopsy was done , microscopic description as skin epidermis showing numerous blood vessels with dense inflammatory infiltrates with mostly neutrophils foci of fibrinoid necrosis seen inflammatory infiltrates seen extending to subcutaneous tissue also. The impression showed leucocytoclastic vasculitis. He was prescribed with linizolid injection 600mg every 12^{th} hourly and cefaperazone sulbactum 1.5g injection 8^{th} hourly, with





Appearance of allergic reaction with reddish fluid filled lesion.

Saline compress followed by fusidic acid cream (fucidin cream), dressed daily and kept lower limbs on a pillow. Tablet prednisolone 5mg was given all the 7 days. The causality of the event assessed as per WHO UMC system for standard case causality assessment criteria can be considered as probable. Analyzed by the Naranjo's ADR probability scale, the score was 5.which also make it a probable adverse drug reaction.

DISCUSSION

There was no ADR reported as allergic reaction with fluid filled lesion on lower limbs with dapagliflozin tablet. Glycosuria, urinary tract infections and thrush (candidiasis), dehydration, vaginal yeast infection, yeast infection of penis, bladder cancer are the common adverse reaction of the drug.

CONCLUSION

Managing diabetes by enhancing glucose excretion is indeed a novel approach. Except in the cases associated with renal impairment, SGLT2 inhibitor should be as effective in controlling T2DM as any other anti-diabetic drug. There are multiple advantages of SGLT2 inhibitors as noted but the serious adverse reactions of dapagliflozin will require larger and long term studies.

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