

DIABETIC KETOACIDOSIS ASSOCIATED WITH SGLT2 INHIBITORS: A REVIEWNeethu J.*², Alinta S. B. Muth¹, Christy Surendran¹, Anisha D. S.¹ and Arya Rajan¹²Student of Sree Krishna College of Pharmacy and Research Centre, Thiruvananthapuram.¹Assistant Professor, Dept. of Pharmacy Practice, Sree Krishna College of Pharmacy and Research Centre, TVM.***Corresponding Author: Neethu J.**

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ABSTRACT

Sodium glucose co-transporter (SGLT) 2inhibitors, called as ‘gliflozins’ are a relatively new class of oral hypoglycemic agents(OHA) approved by FDA in 2013 for use in type2 diabetes mellitus. These special class of OHAs induce glycosuria by reducing renal glucose reabsorption and thereby improve glycemic control. Apart from glucose lowering effect, other metabolic benefits are affirmed and safety concerns including 3 FDA drug safety communications issued in 2015.One of it was, Diabetic ketoacidosis,which occur in presence of low insulin levels, prolonged fasting or during stressful conditions. On May2015,USFDA declared the safety announcement that SGLT2 inhibitors such as Canagliflozin, Dapagliflozin, and Empagliflozin may cause ketoacidosis which may require emergency treatment. Investigations are continuing in this safety issue.These agents are still undergoing clinical studies concerning their safety and efficacy. This review is an effort to assess diabetic ketoacidosis as a safety concern associated with SGLT2 inhibition by going through past research studies, case reports and series.

KEYWORDS: SGLT2 inhibitors, diabetic ketoacidosis, Canagliflozin, Dapagliflozin, Empagliflozi.**INTRODUCTION**

Diabetes mellitus is a progressive metabolic disorder which require strict glycemic control with adequate lifestyle modifications and use of hypoglycemic agents.Several agents are in use to treat hyperglycemia. Among them, Sodium-Glucose Co-transporter 2 inhibitor is a relatively new class of drugs which do not have direct effect on insulin secretion or action. FDA approved use of SGLT2 inhibitors in Type 2 diabetes mellitus, but the safety and efficacy regarding their use in type 1 diabetes patients is not still established and FDA has not approved use in these patients. But, SGLT2 inhibitors are being used in clinical practice (off-label) in patients with type 1 diabetes. Unlike other classes of OHAs they act on renal SGLT2 receptors to reduce glucose reabsorption which leads to glucose excretion through urine. Most of these compounds show affinity towards SGLT2 receptors. Canagliflozin, Dapagliflozin, Empagliflozin are the drugs currently approved for clinical use while others are on clinical trials. The combination of these agents are also in use.

FDA Adverse Event Reporting System (FDAAERS) has identified 20 cases of acidosis reported as DKA, ketoacidosis, or ketosis in patients treated with SGLT2 Inhibitors and issued a safety announcement.^[1] Diabetic ketoacidosis is an acute, serious condition, frequently seen in Type1 diabetes mellitus, and is a potentially fatal complication of diabetes. It occurs when insulin

deficiency results in excessive lipolysis and protein catabolism at tissue level, with increased hepatic beta oxidation of fatty acids to ketone bodies, which may cause ketonemia, and metabolic acidosis, and is characterized by the triad of hyperglycemia(250mg/dl or 13.9 mmol/l), anion gap acidosis, and increase in plasma ketones.^[2] Euglycemic diabetic ketoacidosis (euDKA), a rare condition, is defined as ketoacidosis without markedly elevated blood sugar levels.^[2] Mainly, reduced insulin concentrations and increased concentrations of counter regulatory hormones such as catecholamines, cortisol, glucagon and growth hormone can lead to hyperglycemia and ketosis which is worsened in presence of insulin resistance and elevated free fatty acid concentrations. Free fatty acids are metabolized to ketone bodies leading to ketonaemia and metabolic acidosis.^[2] Infections, food restrictions or starvation, alcohol consumption and inhibited gluconeogenesis are precipitating factors in DKA. In a study with incidently identified cases,13 episodes of euglycemic DKA or ketosis was identified in nine individuals, among which seven with type 1 diabetes and two with type 2.In this study, all the patients were treated with Canagliflozin either 100 or 300 mg/day.^[3] Concomitant mild infection, increased activity, and/or reduced food intake together with sudden reduction in insulin dose or omission were identified to be the contributing factors in developing ketoacidosis in patients with type 1 diabetes mellitus while on Canagliflozin and in patients with type 2

diabetes mellitus, euDKA was found to be a SGLT2 inhibition associated complication, particularly in those with a history of DKA or who are in the postoperative period.^[3] Not only Canagliflozin, but all other gliflozins that have similar actions are expected to pose the similar risk. This study concluded euDKA as a troublesome and life threatening adverse event associated with the use of SGLT2 inhibitors in both type 1 and 2 diabetes mellitus.^[3]

In another phase 2 study on safety and efficacy of Canagliflozin in patients with type 1 diabetes, the incidence of serious adverse events of DKA was illustrated at 18th week as 4.3% with Canagliflozin 100 mg and 6.0% with Canagliflozin 300 mg. The incidence of ketone related adverse events, defined as any of the events such as acidosis, present or increased blood ketone bodies, DKA, diabetic ketoacidotic hyperglycemic coma, ketoacidosis, ketonuria, ketosis, metabolic acidosis, ketone bodies in urine was found to be 5.1% and 9.4% respectively with Canagliflozin 100 and 300mg^[4]. In this study, all patients with DKA had been found to have precipitating factors like infection, reduced carbohydrate intake, withdrawal from or reduction of insulin therapy, but gender differences and difference in baseline characteristics were not reported.^[4] Some serious adverse events that occurred with minimal elevations in blood glucose had lead to misdiagnosis and thus delayed proper treatment in this study.^[4]

In a randomized trial on incidence of serious adverse events of DKA with Canagliflozin among patients with type 2 diabetes mellitus, a low frequency of DKA and related events (0.07%) have been observed.^[5] This study concluded that, patients with type 2 diabetes or misdiagnosed as type 2 diabetes, (but originally having Late Autoimmune Diabetes of Adulthood(LADA) or Type 1 diabetes mellitus) and those who having a low b-cell reserve together with SGLT2 inhibition associated glucagon increase are unable to produce adequate amount of insulin, particularly in the presence of an acute illness can develop DKA.^[5]

Two case reports demonstrated the development of ketoacidosis with the use of SGLT2 inhibitors, in which one patient have been initiated on Empagliflozin together with Metformin and Alogliptin, and the other with Dapagliflozin who have been changed recently from insulin. Both events were characterized by euglycemic or mild hyperglycemic ketoacidosis, minimal dehydration, an elevated anion gap with normal albumin levels, ketonuria and rapid recovery also.^[6] In a randomized, double blind, placebo-controlled study, exploring the potential of Dapagliflozin (given in the dose range 1-10mg) in 70 patients with type 1 diabetes, there was no evidence of volume depletion or ketoacidosis.^[7] In another randomized, placebo –controlled trial on Cardiovascular outcomes and mortality with Empagliflozin in patients with type 2 diabetes, diabetic ketoacidosis had occurred as an adverse event in 0.1%

and <0.1% of patients who were on Empagliflozin 10 and 25 mg respectively, which is almost similar in placebo group.^[8]

A case report of a 32 year old woman with Prader-Willi syndrome, who had diagnosed with diabetes at the age of 10 years and was on treatment with Glimepride, Mtformin, Linagliptin, then switched to a SGLT2 inhibitor, Ipragliflozin 50mg/day had demonstrated an incidence of ketoacidosis.^[9] The conditions of the patient had met the most widely used diagnostic criteria for diabetic ketoacidosis including blood glucose>250 mg/dl, arterial pH<7.3, serum bicarbonate <15mEq/L and a moderate degree of ketonemia and/or ketonuria.^[9] In a meta analysis of randomized controlled trials to assess the risk of DKA with use of SGLT2 inhibitors in patients with type 2 diabetes, the event rates were < 0.1 % and this study did not support risk of DKA among type2 diabetes patients.^[10] Consistent with this, a study on safety concern with SGLT2 inhibitors had also reported occurrence of DKA in <0.1% of patients with type 2 diabetes.^[11] But, in patients with prolonged type 2 diabetes with marked β cell insufficiency or LADA with rapid progression towards type1 diabetes and during prolonged starvation, after surgery, or during inter current illness the risk of DKA was found to be increased.^[11] In patients with type 1 diabetes, euglycemic DKA occurs primarily due to reduced availability of carbohydrate, in conjunction with reduced insulin dose while in type 2 diabetes, increased glucose excretion through urine, daily carbohydrate availability and significantly increased glucagon concentrations are the major factors leading to euglycemic DKA.^[11]

Diabetic ketoacidosis occur as an integrated response to some imbalances and abnormalities. Mainly, in the absence of insulin, glucose utilization is reduced and enhanced lipolysis occurs in adipocytes to release free fatty acids into circulation which are taken up by liver to convert into triglyceride and for synthesis of ketone bodies.^[11] Abnormalities caused by lack of insulin activity explain hyperglycemia, tissue wasting etc. Not only this, but a relative increase in glucagon, epinephrine, cortisol and growth hormone, particularly an elevated glucagon: insulin ratio, caused by stressful events characterizes DKA.^[12]

CONCLUSION

Diabetic ketoacidosis, mainly euglycemic ketoacidosis have been reported as a major safety concern with the use of SGLT2 inhibitors, especially after the safety announcement by FDA regarding this issue. The off-label use of SGLT2 inhibitors in type1 diabetes leads to reduced insulin dose requirements, in which ketoacidosis is a concern and are already prone to develop ketosis.^[10] Patients with type 2 diabetes were found to be lesser prone to ketoacidosis, but a low b-cell reserve in conjunction with enhanced glucagon secretion associated with SGLT2 inhibition and presence of an acute illness increases the risk. DKA associated with the use of

SGLT2 inhibitors appears to be a preventable event, if proper attention is given to the patients on these agents.

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