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SGLT2 inhibitors and Ketoacidosis: Epidemiology and Pathophysiology

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Abstract

SGLT 2 inhibitors are a recent addition to the armamentarium of agents approved for treatment of hyperglycemia in management of type 2 diabetes. Unfortunately, the agents are fairly expensive with a modest efficacy rendering them to be probably the least cost effective drugs in management of hyperglycemia in subjects with type 2 diabetics. The cost efficacy falls even more because of additional expenses required for management of several short term and long term adverse outcomes causing a decline in quality of life. Ketosis and ketoacidosis are two of the several cautions issued by regulatory agencies and have gained prominence because of their serious nature with an occasional fatality. In this review, epidemiology and pathophysiology of onset of ketoacidosis in subjects administered SGLT2 inhibitors is discussed in order to improve recognition in early stage of the disorder and implement a prompt management strategy to prevent further morbidity, morbidity as well as recurrent events.

Introduction

Ketosis and ketoacidosis are well established metabolic complications of diabetes mellitus of both types, 1 and 2. Fortunately, most subjects recover completely without a specific sequele following appropriate management although occasionally with a lethal outcome or a morbidity especially among children and adolescents [1-5]. Onset of ketosis and ketoacidosis is frequently attributed to a precipitant such as acute illness including sepsis, dehydration, myocardial infarction, pregnancy or certain drugs, e.g. Antipsychotics [1-6]. However, never in the history of the disorder, ketosis and ketoacidosis have been attributed to any drug used in treatment of the disorder itself. In contrast, SGLT 2 inhibitors are the first class of drugs approved in management of diabetes being directly implicated in onset of ketosis and ketoacidosis [6-27]. Acute illness especially genito urinary sepsis and dehydration are apparently the frequent contributors to ketosis and ketoacidosis in subjects treated with these drugs [6,8,10,13,17-19,21-24,26]. Unfortunately, both these well established precipitants of these metabolic complications are also the most frequent adverse outcomes of treatment with SGLT 2 inhibitors [6,13,14,18-20,28-35]. Moreover, in elderly subjects, these adverse outcomes are reported to be even more frequent and more serious in nature; men due to concurrent presence of prostatism and post menopausal women because of frequent manifestation of urinary incontinence [36,37]. In fact, this observation was the major determinant of the cautions by both the U.S Food and Drug Administration (FDA) and European Medicine Agency (EMA)[38,39]. However, manufacturers of these drugs refuted the significance of these reports by FDA and EMA based on the retrospective analysis of their pre marketing clinical trials [40,41]. However, the initial caution by FDA is recently confirmed by a further analysis of larger FDA data base over a long duration as well as the persistent continuing rise in incidence of ketoacidosis following approval and increase in usage of these drugs worldwide as evident by several case series and individual case reports[6-27].

Therefore, lack of significant occurrence of Ketoacidosis in these trials as compared to the extensive postmarketing data examined by FDA and EMA may be explained by the fact that the participating subjects in these premarketing clinical trials were healthier and younger because of their selection bias based on several inclusion and exclusion criteria when compared with the population of subjects with type 2 Diabetes, more frequently the elderly with several comorbidities in clinical practice. Furthermore, occurrence of ketosis and/or ketoacidosis may have been missed because of lack of anticipation due to lack of knowledge and therefore lack of laboratory assessment for ketonuria, ketonemia, serum electrolytes and especially arterial blood gases despite onset of marked polyuria, polydipsia, nocturia and dehydration all being well established side effects of drugs themselves as well as occurrence of characteristic manifestations of ketonemia, e.g. nausea, vomiting, abdominal pain, lethargy etc. (1-6,13,14,18-20,28-35). It is also apparent that plasma glucose concentrations were variable ranging from hypoglycemia, euglycemia and hyperglycemia in individual subjects with ketoacidoses administered these drugs(6-27). Presence of ketosis or ketoacidosis was probably not considered in subjects with euglycemia or hypoglycemia despite presenting aforementioned manifestations and therefore was probably overlooked.

Ketoacidosis may be attributed to Diabetes alone though only in subjects with plasma glucose >250 mg/dl as defined by diagnostic criteria established by all Diabetes organizations including American Diabetes Association(1-5,42). Alternatively, ketosis or ketoacidosis in subjects with euglycemia or hypoglycemia must be accounted for by concurrent presence of other disorders. Starvation may be one contributing factor whereas alcoholic ketoacidosis following ethanol intake may be another cause (1-5,9,43-46).Finally, ketoacidosis with hypoglycemia or euglycemia described in some of these subjects may be in fact “Kabadi Syndrome of Pancreatic Ketoacidosis” induced by markedly elevated circulating lipase concentration in acute pancreatitis (47-52) since acute pancreatitis has been described in several reports in the literature(53-55).

Thus, It is apparent that occurrence of ketoacidosis secondary to acute pancreatitis was overlooked as well due to lack of determination of serum lipase and amylase concentrations in spite of the presence of classical clinical manifestations, e.g. nausea, vomiting and abdominal pain.

Therefore, it is likely that several known aforementioned pathophysiologic factors may have induced ketosis or ketoacidosis in many subjects receiving SGLT2 inhibitors. However, lack of presence of these pathophysiologic factors or the established precipitants facilitating ketosis or ketoacidosis in many of the subjects in these reports [1-27005D may indicate direct pathophysiologic role of the drugs themselves in onset of ketogenesis warranting further examination.

Elevated plasma glucagon level is well documented in subjects with type 2 diabetes and is attributed to lack of glucose entry into pancreatic alpha cells secondary to insulin resistance as well as decline in circulating incretins [56-60]. It is apparent that rise in plasma glucagon is further exacerbated in response to a modest decline in circulating glucose due to glycosuria induced by SGLT2 inhibitors [61-65]. Thus, hyperglucagonemia is deemed to be a compensatory mechanism required to promote hepatic glucose production to compensate for glycosuria [61-70]. However, rise in plasma glucagon is also well established to facilitate lipolysis and ketogenesis with onset of ketonemia and consequential ketonuria(68-70). Moreover, onset of ketoacidosis may also be directly attributed to increased lipolysis and consequential ketogenesis induced by glucagon rise secondary to persistent glycosuria induced by these agents (71-73). Alternatively, dehydration caused by glycosuria on administration of SGLT2 inhibitors is well established to induce prompt stimulation of gluco- counter regulatory hormones, e.g. catecholamines, cortisol. human growth hormone and glucagon and all these hormones are well documented to play a major pathophysiologic role in promoting unrestrained lipolysis and ketogenesis resulting in occurrence of Ketoacidosis (73-75). Finally, several other pathophysiologic mechanisms are being recently implicated in onset of ketosis and ketoacidosis irrespective of the degree of glycemia in subjects administered SGLT 2 inhibitors (77-80).

Unfortunately, ketosis and ketoacidosis are just two of many unacceptable hazards and untoward adverse effects associated with use of SGLT2 inhibitors rendering them relatively unsafe based on risk benefit analysis(28-35). Moreover, additional costs incurred in management of these adverse effects in conjunction with modest efficacy further plummets their cost efficacy. Alternatively, adverse effects and burdensome costs is likely to cause marked decline in quality of life. Fortunately, prompt initiation of well established protocols for management of ketoacidosis assists in reducing morbidity and prevents fatality in most subjects. A prompt cessation of drugs may help prevent recurrent events.

In the final analysis, safety of newly approved drugs is often better established in post marketing surveillance in comparison to premarketing data (81-82). This observation may be attributed to sponsorship and funding of the clinical trials by manufacturers Moreover, their direct involvement rather than the independent organizations in performance of these trials may also contribute this fact.Alternatively, the discrepancy regarding safety of the drugs between postmarketing surveillance and real world data on one hand and premarketing clinical trials on the other may be attributed to the role of manufacturers in the design of the protocols, their biases as well as their main focus on obtaining a timely approval by the regulatory agencies. In fact, these factors probably contribute to withdrawal of drugs after initial approval by the regulatory agencies. Therefore, both the manufacturers and regulatory agencies must be held accountable and responsible for lack of establishing acceptable degree of safety and premature approval.

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