Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Biomedicine

journal homepage: www.elsevier.com/locate/apjtb

Letter to the Editor https://doi.org/10.1016/j.apjtb.2017.09.025

Sodium glucose cotransporter-2 inhibitors: Are we targeting old devil with new problems?

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Dear editor,

The advent of modern molecular mechanism's approach to disease treatment is highly advancing to mitigate/normalize the symptoms of disease *i.e.* hyperglycemia by targeting at least eight different pathophysiological approaches popularly known as omnious octet [1]. Importantly, type 2 diabetes is a metabolic disorder arises due to disturbances in anabolic and catabolic chemistry of body organs [2]. Till date, only increased blood glucose levels *i.e.* hyperglycemia is used as a common target for the treatment of this metabolic disorder and nonetheless therapy focuses on underlying metabolic abnormalities that causes hyperglycemia [3,4].

Recently, the sodium-glucose cotransporter-2 (SGLT2) inhibitor is emerging as a new therapeutic option in the management of type 2 diabetes by lowering glycaemia, body weight and blood pressure independent of insulin mediated action, which is also useful for the treatment of type 1 diabetes [5]. SGLT2 inhibitors have been reported to decrease the risk of cardiovascular events through reducing the risk of progression or development of heart failure [6]. After taking these advantages into consideration, SGLT2 inhibitors usage has substantially increased in medical fraternity and monitoring their adverse events is quintessential.

In recent past, after analysis by the US Food and Drug Administration adverse (USFDA) event reporting system [5,7], a safety alarm was raised about the adverse event of diabetic ketoacidosis and lower limb amputations in patients with type 2 diabetes taking SGLT2 inhibitors (canagliflozin). Median time required for development of symptoms was 14 days and in most of the cases it was associated with elevated blood or urine ketones [8].

From 2004 to 2016, the USFDA adverse event reporting system data, presented 2 589 cases of diabetic ketoacidosis with reporting list stating SGLT2 inhibitors as suspect or concomitant medication (individual data not presented). Also, it was noted that, median time required for development of symptoms was 14 days and in most of the cases it was associated with elevated blood or urine ketones [8].

In two clinical trials *i.e.* the CANVAS (canagliflozin cardiovascular assessment study) and CANVAS-R (a study of the effects of canagliflozin on renal endpoints in adult participants with type 2 diabetes mellitus) published the risk of lower limb risk amputations were doubled in those who were taking canagliflozin when compared with placebo. Out of every 1 000 patients, 5.9 were treated with canagliflozin and 2.8 out of 1 000 patients were treated with placebo in CANVAS trial, in similar manner 7.5 out of every 1 000 patients were treated with canagliflozin and 4.2 out of every 1 000 patients were treated with placebo in CANVAS-R trial, have reported risk of amputation [9]. Subsequently, USFDA issued a new safety alert in May 2016 and EMA on 12 February 2017 [10].

Tang H *et al.* reported that, due to their specific mechanism of action, SGLT2 inhibitors may cause renal impairment and intravascular volume depletion by osmotic diuresis which finally leads to acute kidney injury [11]. Considering this, on 14 June 2016, USFDA updated a warning about the risk of acute kidney injury associated with dapagliflozin and canagliflozin [12].

SGLT2 inhibitors are reported to have increasing risk of bone fractures with incidence of 9.4% in patients treated with dapagliflozin 10 mg. Moreover, in a pooled analysis of 8 clinical trials of canagliflozin, treated patients experienced nearly 30% increase in bone fractures with longer mean duration of 68 weeks [13]. Based on above findings, in September 2015, USFDA strengthened the fracture warning by including bone fracture risk and decreased mineral density warning to the label [14].

In conclusion, such unexpected safety findings suggest that need of performing large scale and multicentric global trials is

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Peer review under responsibility of Hainan Medical University. The journal implements double-blind peer review practiced by specially invited international editorial board members.

Article history:
Received 17 Sep 2017
Received in revised form 22 Sep 2017
Accepted 28 Sep 2017
Available online 6 Oct 2017

quite essential to establish safety regimen of new therapeutic agents. After contemplating these data, more cohort studies are required to ascertain the true risk in clinical practice. To date, there is no specific prescribing guideline in management of this crucial metabolic disorder which is growing at a faster rate and hence care should be taken while prescribing these drugs. Considering these predisposing factors, precise decision should be made while prescribing such regimens in wider population to maximize the benefits and avoid the established safety signals of SGLT2 inhibitors in real world.

Conflict of interest statement

The authors declare that they have no conflict of interest.

References

[1] Inzucchi SE. Is it time to change the type 2 diabetes treatment paradigm? No! Metformin should remain the foundation therapy for type 2 diabetes. *Diabetes Care* 2017; **40**(8): 1128-32.

[2] Piero MN, Nzaro GM, Njagi JM. Diabetes mellitus-a devastating metabolic disorder. *Asian J Biomed Pharm Sci* 2014; **4**(40): 1-7.

[3] Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. Consensus statement of the American Association of Clinical Endocrinology and American College of Endocrinology on the comprehensive type 2 diabetes algorithm-2015 executive summary. *Endocr Pract* 2015; **21**: 1403-14.

[4] International Diabetes Federation Clinical Guidelines Task Force. *Global guideline for type 2 diabetes*. Brussels, Belgium: International Diabetes Federation; 2012, p. 44-465.

[5] Fadini GP, Bonora BM, Avogaro A. SGLT2 inhibitors and diabetic ketoacidosis: data from the FDA adverse event reporting system. *Diabetologia* 2017; **60**(8): 1385-9.

[6] Packer M, Anker SD, Butler J, Filippatos G, Zannad F. Effects of sodium-glucose cotransporter 2 inhibitors for the treatment of patients with heart failure: proposal of a novel mechanism of action. *JAMA Cardiol* 2017. https://doi.org/10.1001/jamacardio.2017.2275.

[7] Fadini GP, Avogaro A. SGTL2 inhibitors and amputations in the US FDA adverse event reporting system. *Lancet Diabetes Endo* 2017. https://doi.org/10.1016/S2213-8587(17)30257-7.

[8] U.S. Food and Drug Administration. FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. Available from: https://www.fda.gov/downloads/drugs/drugsafety/ucm446954.pdf [Accessed on 19th August, 2017].

[9] U.S. Food and Drug Administration. FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet XR). Available from: https://www.fda.gov/downloads/Drugs/DrugSafety/UCM558427.pdf [Accessed on 19th August, 2017].

[10] EMA. Amputation warning with SGLT2 inhibitors must be on label. Available from: http://www.medscape.com/viewarticle/875649 [Accessed on 19th August, 2017].

[11] Tang H, Li D, Zhang J, Li Y, Wang T, Zhai S, et al. Sodium-glucose co-transporter-2 inhibitors and risk of adverse renal outcomes among patients with type 2 diabetes: a network and cumulative meta-analysis of randomized controlled trials. *Diabetes Obes Metab* 2017; **19**(8): 1106-15.

[12] U.S. Food and Drug Administration. FDA drug safety communication: FDA strengthens kidney warnings for diabetes medicines canagliflozin (Invokana, Invokamet) and dapagliflozin (Farxiga, Xigduo XR). Available from: http://www.fda.gov/Drugs/DrugSafety/ucm505860.htm [Accessed on 19th August, 2017].

[13] Taylor SI, Blau JE, Rother KI. SGLT2-inhibitors trigger downstream mechanisms that may exert adverse effects upon bone. *Lancet Diabetes Endocrinol* 2015; **3**(1): 8-10.

[14] U.S. Food and Drug Administration. FDA drug safety communication: FDA revises label of diabetes drug canagliflozin (Invokana, Invokamet) to include updates on bone fracture risk and new information on decreased bone mineral density. Available from: https://www.fda.gov/downloads/Drugs/DrugSafety/UCM461790.pdf [Accessed on 19th August, 2017].