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(來函請敍明此檔案號碼) DH DO DIMC/7-30/1
(IN REPLY PLEASE QUOTE THIS FILE REF.)

27 Sep 2024

Dear Healthcare Professionals,

Summary Safety Review - Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors (canagliflozin, dapagliflozin, empagliflozin) - Assessing the potential risks of prolonged or incident diabetic ketoacidosis despite stopping treatment in adult patients with type 2 diabetes

Your attention is drawn to the Health Canada's announcement that diabetic ketoacidosis (DKA) is a serious and potentially life-threatening complication of diabetes that develops when the body breaks down fat for energy, which causes a buildup of ketones in the blood. Increased blood levels of ketones can lead to symptoms such as difficulties in breathing, stomach pain, nausea and vomiting, confusion, tiredness, loss of appetite, and excessive thirst. Severe cases of DKA can lead to coma. DKA can happen to anyone with diabetes but it is not common in people with type 2 diabetes.

In 2016, Health Canada reviewed the potential risk of DKA in patients using SGLT2 inhibitors and concluded that this class of drugs may increase the risk of DKA. At that time, the Canadian product monograph (CPM) for all products in the drug class were updated to include this risk, as well as the symptoms associated with DKA and recommendations on what to do if patients experienced these symptoms. DKA generally resolves within 48 hours with standard management, including discontinuing the medication.

In 2023, following a manufacturer requested labelling update for canagliflozin-containing products [Invokana (canagliflozin) and Invokamet (canagliflozin / metformin)] to include the risk of prolonged DKA despite stopping treatment as part of standard DKA management, Health Canada reviewed this potential risk to determine the need for labelling changes across the SGLT2 inhibitor drug class. Health Canada also reviewed the potential risk of incident DKA after temporary treatment cessation prior to surgical procedures for SGLT2 inhibitors to determine the optimal time to stop these medications before scheduled surgery.

In this review, DKA was considered prolonged if it started during treatment with SGLT2 inhibitors and lasted 3 or more days after treatment was stopped as part of standard management. Incident DKA occurred after treatment with SGLT2 inhibitors was stopped before a planned surgery, and while the patient was recovering from the surgery. Patients often need to fast before surgery or other invasive procedures, which may also increase the risk of DKA in patients with type 2 diabetes.

Health Canada reviewed information from searches of the Canada Vigilance database and the scientific literature.

Prolonged DKA after stopping SGLT2 inhibitor treatment as part of standard DKA management:

- Health Canada reviewed 167 cases (144 Canadian and 23 international) of DKA in adult patients with type 2 diabetes taking SGLT2 inhibitors where treatment was stopped when DKA was suspected or confirmed (67 in patients taking empagliflozin, 31 in patients taking dapagliflozin and 69 in patients taking canagliflozin). Twenty-six of the 167 cases (3 Canadian) were from the published literature.
- DKA was prolonged in over half of the Canadian cases despite stopping SGLT2 inhibitor treatment.
- DKA lasted 18 days in 1 Canadian patient taking dapagliflozin. There were 6 Canadian cases of DKA lasting longer than 10 days in patients taking canagliflozin, which included 1 case where DKA lasted 21 days. There were no cases of DKA lasting longer than 10 days in patients taking empagliflozin.
- Health Canada's review could not confirm a definitive link between the use of SGLT2 inhibitors and prolonged DKA despite stopping treatment because other factors, such as pre-existing liver or kidney disease, restricted food intake, stress of surgery, dehydration and other medications, may have been involved in the prolongation of DKA. However, a possible link could not be ruled out.

Incident DKA after stopping treatment before scheduled surgery:

- Health Canada reviewed 44 cases (10 Canadian and 34 international) from the published literature of DKA following surgery in adult patients with type 2 diabetes taking SGLT2 inhibitors where treatment was temporarily stopped before surgery (22 in patients taking empagliflozin, 7 in patients taking dapagliflozin, and 15 in patients taking canagliflozin). Forty-one of the 44 cases reviewed were in patients who stopped treatment with SGLT2 inhibitors 2 days or less before surgery (20 of the 22 patients taking empagliflozin, 6 of the 7 patients taking dapagliflozin, and all patients taking canagliflozin).
- No relationship was found between the number of days before surgery the treatment with SGLT2 inhibitor was stopped and the onset of DKA.
- Health Canada also reviewed 5 epidemiologic studies, which indicated that temporarily stopping treatment with SGLT2 inhibitors for a longer period of time before surgery may lower the risk of incident DKA after surgery by 30-50%. However, none of these studies investigated the optimal time for temporary treatment cessation of SGLT2 inhibitors before surgery and there were study limitations.

- Based on the pharmacology of SGLT2 inhibitors, stopping treatment at least 3 days before surgery or other invasive procedure requiring prolonged fasting is reasonable to ensure that the drug has enough time to be eliminated from the body.

While a definitive link could not be confirmed, Health Canada's review of the available information could not rule out a possible drug class effect for the risk of prolonged DKA despite stopping SGLT2 inhibitor treatment as part of standard management in adult patients with type 2 diabetes. Health Canada's review of the available information also identified a number of cases of incident DKA following surgery in adult patients with type 2 diabetes taking SGLT2 inhibitors where treatment was temporarily stopped 2 days or less before surgery.

To reduce the potential risk of incident DKA, Health Canada recommends stopping treatment with SGLT2 inhibitors at least 3 days before surgery or other invasive procedures requiring prolonged fasting, which is consistent with recommendations from Canadian and international diabetes associations and the U.S. Food and Drug Administration. Health Canada also recommends monitoring for DKA following the surgery or procedure, with the decision to reinitiate treatment with SGLT2 inhibitors to be made by the healthcare professional.

Health Canada is working with the manufacturers to update and align the CPM for SGLT2 inhibitors to include a warning about the risk of prolonged DKA despite stopping treatment as part of standard DKA management in adult patients with type 2 diabetes, and a recommendation for temporary treatment cessation before a surgical procedure. Health Canada will also inform healthcare professionals about these updates through a Health Product InfoWatch communication.

Please refer to the following website in Health Canada for details:
https://dhpp.hpfb-dgpsa.ca/review-documents/resource/SSR1724175682293#wb-auto-4

In Hong Kong, there are 20 registered pharmaceutical products containing SGLT2 inhibitors, including canagliflozin (4 products), dapagliflozin (5 products), empagliflozin (10 products) and ertugliflozin (1 product). All products are prescription-only medicines. So far, the Department of Health (DH) has received 4 cases of adverse drug reaction of diabetic ketoacidosis related to SGLT2 inhibitors: canagliflozin (1 case), dapagliflozin (1 case) and empagliflozin (2 case).

Related news on the risk of diabetic ketoacidosis of SGLT2 inhibitors was previously issued by various overseas drug regulatory authorities, and was posted on the Drug Office website since 16 May 2015, with the latest update posted on 15 Feb 2022. In Feb 2017, the Registration Committee of the Pharmacy and Poisons Board discussed the matter, and decided that the package insert of products containing SGLT2 inhibitors should include safety information on the risk of diabetic ketoacidosis.

In light of the above Health Canada's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board.

Please note that this letter serves as a means for the DH to communicate important new safety information about registered pharmaceutical products with healthcare professionals in Hong Kong and is not intended to serve as guidelines or to replace professional clinical judgement. Healthcare professionals are advised to balance the risk of possible adverse effects against the benefit of treatment.

Please report any adverse events caused by drugs to the Clinical Trials and Pharmacovigilance Unit of the DH (tel. no.: 2319 2920, fax: 2319 6319 or email: adr@dh.gov.hk). For details, please refer to the website at Drug Office under "ADR Reporting": http://www.drugoffice.gov.hk/adr.html. You may wish to visit the Drug Office's website for subscription and browsing of "Drug News" which is a monthly digest of drug safety news and information issued by Drug Office.

Yours faithfully,

P.P. (Terence MAN)
for Assistant Director (Drug)