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Dear Healthcare Professionals,

SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness

Your attention is drawn to the United Kingdom Medicines and Healthcare products Regulatory Agency's (MHRA) announcement that SGLT2 inhibitor treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses and ketone levels measured, preferably in blood rather than urine.

A detailed European review in 2016 confirmed diabetic ketoacidosis, including euglycaemic diabetic ketoacidosis, as a rare risk for the SGLT2 inhibitor class of medicines. The review recommended healthcare professionals should inform patients on SGLT2 inhibitors of the risks of diabetic ketoacidosis and counsel them on risk factors and actions to take in case of signs and symptoms. Due to the risk of diabetic ketoacidosis, recommendations were added to the product information of these medicines to interrupt SGLT2 inhibitor treatment in patients who are hospitalised for major surgery or acute serious medical illnesses and to not restart treatment until the patient's condition has stabilised.

In 2019 a new European review assessed reports of peri-operative diabetic ketoacidosis in patients taking SGLT2 inhibitors. The review recommended warnings be updated to include routine monitoring of ketones in patients hospitalised for surgery or acute illness. This approach aims to help identify patients who are at risk of developing (or are already in the early stages of) diabetic ketoacidosis, so that prompt corrective measure can be applied.

Testing of ketones in blood is recommended, rather than measuring ketone bodies in urine. The basis for this recommendation is that SGLT2 inhibitors may diminish the excretion of ketone bodies in the urine, thereby making urine measurement of ketone bodies less reliable than blood testing.

The current Joint British Diabetes Society Inpatient Care Group national guideline for the management of diabetic ketoacidosis (2013) already recommends the use of blood ketone tests based on the measurement of β-hydroxybutyrate.

The review of the evidence did not identify a specific type of surgery as being linked to an increased risk of peri-operative diabetic ketoacidosis. In addition, there was insufficient evidence to make specific recommendations concerning peri-operative management such as a specific time-point to stop or restart SGLT2 inhibitor treatment or management of food intake and insulin use.

Diabetic ketoacidosis is a serious complication of diabetes caused by low insulin levels. The 2016 EU review was triggered by rare cases of diabetic ketoacidosis in patients taking SGLT2 inhibitors for type 2 diabetes. In several reports of diabetic ketoacidosis assessed by the review, blood glucose levels were only moderately elevated. Therefore, updates to the product information advised healthcare professionals to test for raised ketones in patients taking SGLT2 inhibitors with signs and symptoms of ketoacidosis, even if plasma glucose levels are near-normal. The review recommended interrupting SGLT2 inhibitor treatment in patients who are hospitalised for major surgery or acute serious illnesses and to not restart treatment until the patient's condition has stabilised. However, the advice did not specifically instruct prescribers to check or monitor ketones. Healthcare professionals were also advised to avoid restarting treatment with a SGLT2 inhibitor in patients who experienced diabetic ketoacidosis during use, unless another cause for the ketoacidosis was identified and resolved.

Healthcare professionals are advised:

- Interrupt sodium-glucose co-transporter 2 (SGLT2) inhibitor treatment in patients who are hospitalised for major surgical procedures or acute serious medical illnesses.
- Monitor ketones during this period – measurement of blood ketone levels is preferred to urine.
- Restart treatment with the SGLT2 inhibitor once ketone values are normal and the patient's condition has stabilised.

Please refer to the following website in MHRA for details:
https://www.gov.uk/drug-safety-update/sglt2-inhibitors-monitor-ketones-in-blood-during-treatment-interruption-for-surgical-procedures-or-acute-serious-medical-illness

In Hong Kong, there are 23 registered pharmaceutical products containing SGLT2 inhibitors, including canagliflozin (4 products), dapagliflozin (5 products), empagliflozin (10 products) and ertugliflozin (4 products) . All products are prescription-only medicines. So far, the Department of Health (DH) has received 3 cases of adverse drug reaction of diabetic ketoacidosis related to SGLT2 inhibitors: dapagliflozin (1 case), canagliflozin (1 case) and empagliflozin (1 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 19 Jul 2018. 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 MHRA's announcement, the matter will be discussed by the Registration Committee of the Pharmacy and Poisons Board. 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 Undesirable Medical Advertisements and Adverse Drug Reaction 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,

(Joseph LEE)
for Assistant Director (Drug)