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EC DIABETES AND METABOLIC RESEARCH

Opinion

Dapagliflozin and Euglycaemic Diabetic Ketoacidosis - "But Doctor My Sugars were Normal!"

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Background

A "Dear Doctor Letter" was issued by the manufacturer of Forxiga® (Dapagliflozin) in November 2021, this followed reviews by the European Medicines Agency and the UK MHRA [1]. The letter stated that "The removal of the indication is not due to any safety concern for dapagliflozin in any indication, including T1DM" but must be discontinued in patients with T1DM by or in consultation with a physician specialised in diabetes care and be conducted as soon as clinically practical." Dapagliflozin was previously approved in the treatment of diabetes for combination with insulin therapy in Type 1 diabetes and with oral medications and insulin in Type 2 patients.

Euglycaemic Ketoacidosis (EuDKA) pathogenesis and dapagliflozin

The pathogenesis of EuDKA occurs as a consequence of absolute insulin deficiency leading to reduced glucose utilization and enhanced lipolysis; increased delivery of free fatty acids (FFAs) to the liver coupled with raised glucagon levels promoting FFA oxidation, and subsequent production of ketone bodies [2]. The authors also reported that following a US FDA safety communication, and the majority of reports of EuDKA between 2014 and 2015 in the USA were in patients with Type 2 diabetes. The UK Yellow Card report did not specify the type of diabetes.

Safety review of dapagliflozin and EuDKA

A review of the UK MHRA Yellow Card reporting system on dapagliflozin in March 2022 [3] showed the following results table 1.

Total number of Adverse Drug Reactions (ADR) reports: 2013; Serious ADR reports: 1304 - Fatal ADR reports: 25 (Cut-off 31-Mar-2022). Details of ADR's which could be related to EuDKA are shown in the table 1 below.

Metabolism and nutrition disorders	Single Active Constituent		Multiple active constituents		Total reactions	
	All	Fatal	All	Fatal	All	Fatal
Diabetic ketoacidosis	316	5	105	1	420	6
Euglycaemic ketoacidosis	71	0	4	0	75	0
Hypoglycaemic conditions	6	0	4	0	10	0

Table 1

The number of reports submitted had raised following the letter from the manufacturer. It is expected that a large number of these reports could be related to the concomitant use of dapagliflozin and insulin therapy in patients with Type 2 diabetes. Appropriate monitoring and awareness of health care professionals and patients are necessary to prevent potentially harmful and fatal consequences.

What to do?

The advice from both, the manufacturer and the medicines regulatory agencies, surrounding the actions required in patients with Type 1 diabetes is clear and we may prevent problems by close monitoring of patients in diabetes specialist units. Such task is facilitated by the use of electronic medical records and access to the list of all medications used by these patients.

Following the research findings on the occurrence of EuDKA in patients with Type 2 diabetes, we may argue that these patients should also be included in a review for EuDKA. From personal and documented reports, patients with type 2 diabetes often react negatively to the introduction of insulin therapy to their medications [4]. Part of the rationale to include insulin therapy usually includes improved glycaemic control. Following a period of improvement in their self-monitored blood sugars, some patients might react by stopping or reducing their use of insulin. The resulting ketonaemia in patients with insulin deficiency taking SGLT2 inhibitors is initially asymptomatic or clinically undetectable and could gradually lead to severe ketoacidosis.

Most patients with Type 2 diabetes are managed in primary care and initiating a community wide alert would take time to complete and require significant human resource, increased budget and likely lead to increased patient anxiety. Blood tests to detect low endogenous insulin secretion would also take time and increased resources. A more rapid and simple approach is required.

One option could be to request that all patient with longstanding Type 2 diabetes who are treated with insulin in combination with dapagliflozin or any other SGLT2 inhibitors should be advised to use blood or urine ketone testing to detect EuDKA, particularly when insulin doses are being reduced or withdrawn. Awareness of these such parameters would help health professionals to quickly identify and treat patients at risk. The Association of British Clinical Diabetologists and Diabetes UK produced joint guidance on communication and education requirements to be provided to patients who were prescribed an SGLT2 for the first time [5]. This provides useful and practical suggestions for minimising adverse reaction to the use of these medicines.

Acknowledgements

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