PCDS
Primary Care Diabetes Society
The latest news and views from the Primary Care Diabetes Society

Recent PCDS activities

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It has been an extremely busy time for the PCDS Committee over the past couple of months.

NICE guidance

We were extremely pleased to see that the type 2 diabetes NICE guidance was reassessed and amended before the final publication in November last year. The letter written to Professor David Haslam, Chair of NICE, encouraged reassessment of the guidelines and after two draft publications and media coverage, the final version of the updated guidance was published. The letter was based on the opinions of PCDS members and is a testament to our influence within the UK diabetes community. Many thanks to all of you who completed the questionnaire.

Diabetic ketoacidosis and sodium–glucose cotransporter 2 (SGLT2) inhibitors

The PCDS Committee has also been busy producing a statement for healthcare professionals in response to a direct communication from the manufacturers of SGLT2 inhibitor agents. Following reported cases of diabetic ketoacidosis during treatment with SGLT2 inhibitors, the direct communication includes updated advice for healthcare professionals. We urge you all to read the statement found immediately below and to pass the message on to colleagues. Particular thanks must go to Jane Diggle and Richard Quigley for the preparation of the statement.

The year ahead

The Committee met at the beginning of January to plan the 12th National Conference, and our regional committees have also been hard at work planning our other events (visit http://www.pcdsociety.org/events for the latest details). We are excited to be continuing to shape the agenda in primary care diabetes and hope to see as many of you as possible later this year at these events. ■

What do you and your patients need to know about SGLT2 inhibitors and diabetic ketoacidosis?

Last month, healthcare professionals were sent a direct communication from the manufacturers of sodium–glucose cotransporter 2 (SGLT2) inhibitor agents, which provided updated advice on the risk of diabetic ketoacidosis (DKA) during treatment. This comes almost a year after the US Food and Drug Administration (FDA) warned that SGLT2 inhibitors may lead to ketoacidosis following reports of rare but serious, sometimes life-threatening, cases of DKA in people on SGLT2 inhibitor treatment. The European Medicines Agency (EMA)'s Pharmacovigilance Risk Assessment Committee (PRAC; 2016) have also recently published recommendations to minimise the risk of SGLT2 inhibitor-associated DKA. The medications

available in the UK that include SGLT2 inhibitor agents are the following:

- Invokana® (canagliflozin) and Vokanamet® (canagliflozin plus metformin).
- Forxiga® (dapagliflozin) and Xigduo® (dapagliflozin plus metformin).
- Jardiance® (empagliflozin) and Synjardy® (empagliflozin plus metformin).

The PCDS Committee has developed a series of answers to common questions on the risk of DKA among people using SGLT2 inhibitors.

What is DKA?

DKA is a potentially life-threatening complication of diabetes caused by insulin deficiency. Glucose is unable to be used as the body's fuel so the body switches to an alternative source breaking down fat to free fatty acids, which are oxidised to produce ketones. Significant ketonaemia produces metabolic acidosis and leads to a rapid deterioration in health and left untreated can lead to coma and death.

Who is most likely to be affected by DKA?

The condition more typically affects those with type 1 diabetes (sometimes at diagnosis), but it occasionally occurs in those with type 2 diabetes. In the small number of SGLT2 inhibitor-associated DKA cases reported in the EMA PRAC alert (2016), up to a third related to the "off-label" use of the agent in people with type 1 diabetes. The remaining individuals were diagnosed with type 2 diabetes, but it remains unclear whether all these individuals were correctly diagnosed. It is possible that a proportion of these could have had atypical diabetes phenotypes, such as latent auto-immune diabetes in adults (LADA) or ketone-prone diabetes (KPD).

What are the typical signs and symptoms of DKA?

Early symptoms

- High blood glucose levels (consistently above 14 mmol/L). However, DKA is not always accompanied by hyperglycaemia. On occasion, DKA can occur when the blood glucose level is below 14 mmol/L (referred to as euglycaemic DKA [euDKA]). This is believed to be the case in some of the individuals diagnosed with SGLT2 inhibitor-associated DKA.
- Frequently passing urine.
- Excessive thirst.
- Ketonuria (high levels of ketones in the urine).

Later symptoms

- Unusual fatigue or sleepiness.
- Abdominal pain, nausea, vomiting.
- Rapid or heavy, laboured breathing.
- Confusion.
- Possible smell of ketones on the breath (likened to the smell of pear drops).

Although these are the typical symptoms of DKA, it is important to remember that these symptoms can be non-specific (i.e. nausea and vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness), so caution is required when someone taking SGLT2 inhibitor therapy presents with such symptoms (EMA, 2016).

What was unusual about the DKA reported in individuals who were taking SGLT2 inhibitors?

An unusual feature of the reported cases of SGLT2 inhibitor-associated DKA was the atypical presentation. In a number of the cases, patients presented with only moderately increased blood glucose levels, often less than 14 mmol/L (euDKA). This could mislead clinicians into believing it is not DKA, resulting in a delay in diagnosis and treatment, so it is important to remain vigilant.

What is the underlying causative mechanism?

The underlying mechanism for SGLT2 inhibitor-associated DKA is not established.

What is the likelihood of DKA occurring during SGLT2 inhibitor use?

Given the number of cases reported to date, DKA during SGLT2 inhibitor treatment is a rare occurrence (affecting up to 1 in 1000 individuals). Information for healthcare professionals in the Summary of Product Characteristics (SPC) and for patients in the patient information leaflet (PIL) will be updated to include DKA as a rare adverse reaction.

Are there any underlying contributory factors or triggers to SGLT2 inhibitor-associated DKA?

Many of the cases reported occurred during the first 2 months of treatment, or just before, or at the same

time as the DKA occurred. Individuals had experienced dehydration, low food intake, weight loss, infection, surgery, vomiting or a decrease in their insulin dose. However, there were also cases of ketoacidosis shortly after discontinuation of the SGLT2 inhibitors. Clinicians should also be aware that treatment with corticosteroids, thiazides and anti-psychotics are associated with increased risk of DKA.

To minimise the risk of DKA, what factors need to be considered before prescribing SGLT2 inhibitor therapy?

There are a number of factors that can increase the risk of DKA and, thus, if an individual presents with one of these factors, SGLT2 inhibitors should be used with caution.

- A low beta-cell function reserve (e.g. latent autoimmune diabetes in adults or a history of pancreatitis).
- Where there is restricted food intake or severe dehydration.
- Sudden reduction in insulin (e.g. if starting SGLT2 inhibitor therapy in individuals established on insulin).
- Increased insulin requirements that remain unmet due to acute medical illness (e.g. sick day or stress).
- Surgery.
- Alcohol abuse.

SGLT2 inhibitor treatment should be paused in individuals who are hospitalised for major surgery or acute serious medical illness and only restarted once the patient's condition is stabilised.

What information should be given to individuals who are prescribed SGLT2 inhibitors?

Individuals need to be advised about the potential risk of DKA when SGLT2 inhibitors are prescribed. They need not only to be made aware of the signs and symptoms of DKA, but also to understand that their blood glucose levels may not become particularly raised. They should be advised to seek immediate medical advice if they develop signs and symptoms of DKA.

Individuals should be advised to stop taking their SGLT2 inhibitor therapy during periods of serious acute illness or infection, if they have a low food or fluid intake, experience nausea and vomiting or become dehydrated.

If DKA is suspected in a person taking an SGLT2 inhibitor, what action needs to be taken?

Where DKA is suspected, a blood or urine test for ketones may be performed to confirm the diagnosis. NICE (2015) now recommends that in an emergency situation, DKA should be diagnosed by blood capillary testing rather than urine testing. A blood ketone value over 3.0 mmol/L indicates a dangerous level of ketones that requires immediate medical care. A value of 1.6–3.0 mmol/L is indicative of high level of ketones and could present a risk of ketoacidosis.

If DKA is confirmed, appropriate measures should be taken to correct the DKA, and identify the underlying precipitating factor or factors. This requires urgent admission to hospital. The SGLT2 inhibitor should be discontinued immediately and should not be restarted unless a clear precipitating factor (other than SGLT2 inhibitor treatment) is identified and resolved.

Should I continue to prescribe SGLT2 inhibitors?

The advice from the regulatory bodies confirms that the benefits of SGLT2 inhibitor agents in the management of type 2 diabetes continue to outweigh the risks. However, healthcare professionals should continue to report suspected adverse reactions associated with these products to the MHRA through the Yellow Card Scheme: www.mhra.gov.uk/yellowcard. ■

EMA PRAC (2016) *EMA confirms recommendations to minimise ketoacidosis risk with SGLT2 inhibitors for diabetes*. European Medicines Agency, London. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/SGLT2_inhibitors__20/Opinion_provided_by_Committee_for_Medicinal_Products_for_Human_Use/WC500202393.pdf (accessed 04.04.16)

NICE (2015) *Type 1 diabetes in adults: diagnosis and management* (NG17). NICE, London. Available at: www.nice.org.uk/ng17 (accessed 04.04.16)