

# The Medical Letter<sup>®</sup>

## on Drugs and Therapeutics

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Objective Drug Reviews Since 1959

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### IN THIS ISSUE

**In Brief: Ketoacidosis with SGLT2 Inhibitors** ..... p 94

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### IN BRIEF

#### Ketoacidosis with SGLT2 Inhibitors

The FDA has warned that use of an SGLT2 (sodium-glucose co-transporter 2) inhibitor for treatment of type 2 diabetes may lead to ketoacidosis.<sup>1</sup> Three SGLT2 inhibitors, canagliflozin (*Invokana, Invokamet*), dapagliflozin (*Farxiga, Xigduo XR*), and empagliflozin (*Jardiance, Glyxambi*), are approved for treatment of type 2 diabetes in the US. Between March 2013 and June 2014, 20 cases of ketoacidosis requiring emergency room visits or hospitalization were reported in patients who had recently started taking an SGLT2 inhibitor; the median time to onset of symptoms after initiation of therapy was 2 weeks (range 1-175 days). SGLT2 inhibitors decrease renal glucose reabsorption and increase urinary glucose excretion, resulting in a reduction in blood glucose levels. The mechanism by which these drugs could cause ketoacidosis has not been established.

Diabetic ketoacidosis (DKA) occurs primarily in patients with type 1 diabetes; it is characterized by elevated blood glucose levels (usually  $\geq 250$  mg/dL), a high anion gap, glucosuria, and ketonuria.<sup>2</sup> Unlike typical cases of DKA, most ketoacidosis cases associated with SGLT2 inhibitors have occurred in patients with type 2 diabetes, and in some patients glucose levels were  $< 200$  mg/dL. Only half of the 20 cases were associated with a recognizable DKA-precipitating factor, such as infection, reduced caloric intake, or reduced insulin dose. Other factors that may contribute to the development of high anion gap metabolic acidosis, such as hypovolemia, hypoxemia, reduced oral intake, acute renal impairment, and a history of alcohol use, were identified in some patients.<sup>1</sup> ■

View our detailed online table: [SGLT-2 Inhibitors](#)

1. FDA drug safety communication: FDA warns that SGLT2 inhibitors for diabetes may result in a serious condition of too much acid in the blood. Available at: [www.fda.gov/Drugs/DrugSafety/ucm446845.htm](http://www.fda.gov/Drugs/DrugSafety/ucm446845.htm). Accessed June 11, 2015.
2. AE Kitabchi et al. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care* 2009; 32:1335.

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