SGLT2 Inhibitor–Associated Euglycemic Diabetic Ketoacidosis: A South Australian Clinical Case Series and Australian Spontaneous Adverse Event Notifications

Emily J. Meyer,[1,2,3] Genevieve Gabb,[2,4] and David Jesudason[1,2,3]

Diabetes Care 2018;41:e47–e49 | https://doi.org/10.2337/dc17-1721

Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been linked with diabetic ketoacidosis (DKA) (1–4). However, characteristics of "at-risk" patients are less well described.

Clinical cases were collected from South Australia between December 2015 and March 2017. The audit was approved by the Royal Adelaide Hospital Human Research Ethics Committee (HREC reference no. HREC/17/RAH/185).

The Therapeutic Goods Administration (TGA) of the Australian Government Department of Health was contacted, and a search of the Database of Adverse Event Notifications (medicines) for all reports of SGLT2 inhibitor–associated DKA was requested up until April 2017 using the search terms ketoacidosis, diabetic ketoacidosis, and generic and brand drug names. Full case line listings for each notification were provided by the TGA.

Autoantibodies against glutamic acid decarboxylase (GAD) and insulinoma-associated antigen 2 (tyrosine phosphatase IA-2) were quantitated using commercial ELISA test kits (Euroimmun AG, Lubeck, Germany). These assays are calibrated in international units (IU) using the first World Health Organization reference reagent for islet cell antibodies (1999, reagent 97/550; National Institute for Biological Standards and Control, Hertfordshire, U.K.), which contains 100 IU of anti-GAD and 100 IU of anti–IA-2 per ampoule by definition.

We identified thirteen cases of SGLT2 inhibitor–associated DKA occurring in South Australia between December 2015 and March 2017 (Table 1). Eight case subjects had type 2 diabetes (T2D) and five had type 1 diabetes (T1D), although two patients were identified as having T1D or latent autoimmune diabetes of adults (LADA) retrospectively after DKA presentation based on positive anti-GAD and anti–IA-2 antibodies. Insulin was coprescribed in half of the patients with T2D (n = 4), was not prescribed in three patients, and was unknown in one patient, raising the possibility of misdiagnosis of T1D or LADA despite antibodies not being detected or indicating advanced T2D. Nine patients required intensive care or high dependency care, and all patients required i.v. insulin and dextrose. Dapagliflozin was implicated in nine and empagliflozin in four cases of DKA. One patient died due to Takotsubo cardiomyopathy. Treating doctors initially overlooked the diagnosis of DKA in two patients and were unaware of the association of SGLT2 inhibitors and DKA in six patients.

Precipitating events were identified in most cases. These included missed insulin (n = 5), undiagnosed T1D (n = 2), infection (n = 5), and surgery (n = 3). Five case subjects had reduced carbohydrate intake precipitating DKA (fasting for surgery, low carbohydrate diet, or anorexia).

Up until April 2017, 82 unique notifications of SGLT2 inhibitor–associated DKA have been reported to the Australian TGA. Reports include twenty-four patients with T2D and nine patients with T1D (two diagnosed retrospectively). Two reports of DKA occurred with off-label drug use for weight loss or insulin resistance, both precipitated by a gastrointestinal illness. Diabetes status was not reported in the majority (n = 47). SGLT2 inhibitors were mostly discontinued; however, they were recommenced in three reports (at lower doses in two). Most reports described treatment with i.v. insulin and dextrose. Eighteen reports of DKA were managed in intensive care, and sixteen were classified as life-threatening.

Precipitants were surgery or perioperative (n = 13), reduction or cessation of insulin (n = 2), low-carbohydrate diet (n = 1), acute coronary events (n = 3), infections (n = 3), and liver and kidney impairment (n = 1). Average duration of SGLT2 inhibitor use prior to DKA presentation was 11.6 weeks (range 1 day to 76 weeks). DKA was generally serious, with mean pH 7.06, bicarbonate 7.35 mmol/L, ketones 6.2 mmol/L, and anion gap

[1]*Endocrine and Metabolic Unit, Royal Adelaide Hospital, Adelaide, Australia*
[2]*Discipline of Medicine, University of Adelaide, Adelaide, Australia*
[3]*Department of Endocrinology and Diabetes, The Queen Elizabeth Hospital, Woodville, Australia*
[4]*Department of General Medicine, Royal Adelaide Hospital, Adelaide, Australia*

Corresponding author: Emily J. Meyer, emily.meyer@sa.gov.au.

Received 21 August 2017 and accepted 2 January 2018.

Table 1—Thirteen cases of SGLT2 inhibitor–associated DKA within South Australia from December 2015 to March 2017

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13
Age (years) and sex	67 F	67 F	38 F	82 M	55 F	53 M	64 F	70 M	52 M	45 F	59 F	75 F	67 F
T1D/LADA/T2D	T1D/LADA*	T2D	T1D/LADA*	T2D	T1D	T2D	T1D	T2D	T1D	T2D	T2D	T2D	T2D
T1 antibody titers, IU/mL (normal <10.0)													
Anti-GAD	>2,000	3.8	3.5	UNK	78.2	3.4	UNK	3.1	33.4	3.4	3.4	1.8	1.5
Anti–IA-2	5.8	5.2	36.4		8.4	4.9		4.6	4.9	4.8	5.0	0.5	0.0
Duration of diabetes	>20 years	11 years	6 months	14 years	12 years	UNK	35 years	10 years	15 years	27 years	47 years	UNK	UNK
Insulin	Glargine 8 units d.; NovoRapid 3 units t.d.s.	Humalog Mix25 45 units breakfast, 12 units evening meal	None	None	NovoMix30 30 units breakfast, 12 units evening meal	None	Glargine 14 units mane, 5 units evening; NovoRapid 1–5 units t.d.s.	Glargine 56 units d.	Glargine 20 units d.	Glargine 70 units mane, 50 units evening	None	UNK	Glargine 14 units d.; NovoRapid 3 units t.d.s.
SGLT2 inhibitor	Dapagliflozin 10 mg	Dapagliflozin 10 mg	Dapagliflozin 10 mg	Dapagliflozin 10 mg	Empagliflozin UNK	Dapagliflozin 10 mg	Dapagliflozin 10 mg	Dapagliflozin 10 mg	Empagliflozin 5 mg	Dapagliflozin 10 mg	Empagliflozin UNK	Dapagliflozin 10 mg	Empagliflozin 25 mg
Duration of SGLT2 inhibitor	6 months	6 months	5 months	3 months	1 month	2 weeks	2 weeks	2 months	6 months	6 months	UNK	UNK	3 weeks
OAH	Metformin	Metformin	Metformin, linagliptin	Gliclazide MR, metformin	Metformin	Metformin XR, sitagliptin	Metformin	Metformin	Metformin	Metformin, acarbose	Metformin, sitagliptin	Metformin	Metformin, gliclazide
HbA_{1c}, % (mmol/mol)	8.3 (67)	6.5 (48)	10.1 (87)	9.3 (78)	10.9 (96)	9.6 (81)	9.7 (83)	13.4 (123)	9.8 (84)	10.2 (88)	7.6 (60) (anemic)	UNK	6.8 (51)
Potential contributors	Reduced oral intake, missed insulin, missed T1D	Diarrhea, AKI, UTI	Missed T1D	CABG	Gastroenteritis, missed insulin	No precipitant	Missed insulin	Influenza A, staphylococcal pneumonia and bacteremia	Necrotizing fasciitis	Ceased insulin 2 weeks prior	Chemotherapy for breast cancer, blood dyscrasia, candiduria	Takotsubo cardiomyopathy, LV thrombus, cardiogenic shock, cardiopulmonary arrest	Missed insulin 3 days, acute cholecystitis
Insulin reduction	Yes, glargine by 2 units	Insulin ceased 6 weeks prior	UNK	UNK	Yes	UNK	Yes, glargine by 4 units	No	No	Ceased insulin	UNK	UNK	Missed insulin
BGL, mmol/L (normal 3.2–5.5)	8.6	9.7	13	6.8	20	13.8	11	29	UNK	15	34.6	29.7	18.7
pH (normal 7.38–7.45)	7.0	UNK	UNK	7.3	UNK	7.3	7.1	7.2	UNK	7.1	6.9	6.9	UNK
Ketones, β-hydroxybutyrate, mmol/L (normal <0.30)	3.0 (12 h)	7	13	7	3.5 (24 h)	5.8	6.0	6	UNK	6.2	5.2	7	UNK
Bicarbonate, mmol/L (normal 22–32)	6	13.8	2	14	4	14	5	11	5	7.7	3	7	6
Anion gap, mmol/L (normal 7–17)	24	24	32	26	41	32	32	34	38	26	48	42	40
Admission date	December 2015	December 2015	January 2016	June 2016	June 2016	July 2016	August 2016	September 2016	September 2016	October 2016	October 2016	March 2017	March 2017
Location	ICU	UNK	UNK	ICU	ICU	HDU	ICU	ICU	ICU	Ward	ICU	ICU	ICU
Insulin infusion duration	48 h	UNK	48 h	24 h	24 h	48 h	48 h	24 h	48 h	48 h	UNK	UNK	UNK
Outcome	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Recovered	Deceased	Recovered

Note blood glucose level (BGL) and laboratory results are taken from time of hospital admission. AKI, acute kidney injury; CABG, coronary artery bypass grafting; d., once daily; HDU, high dependency unit; ICU, intensive care unit; LV, left ventricular; OAH, oral antihyperglycemic agent; t.d.s., three times a day; UNK, unknown; UTI, urinary tract infection. *Diagnosis of T1D made after reevaluation post–DKA presentation.

23.7 mmol/L. The mean glucose was 14.1 mmol/L (range 4.8 to 35 mmol/L), and four patients had glucose ≤8.0 mmol/L.

We suggest temporary cessation of these drugs during acute illness and surgery. The SGLT2 inhibitor–associated DKA illness prodrome was similar to that of DKA in T1D; however, DKA often occurs in the absence of marked hyperglycemia. Thus, early detection of the ketotic state while symptomatic with malaise, nausea, and/or vomiting, particularly in the context of precipitants, could prompt temporary cessation of SGLT2 inhibitor, hydration, frequent carbohydrate consumption, and administration of full-dose insulin to prevent progression to DKA (2). Consider excluding a diagnosis of T1D before prescribing these medications or reevaluating diabetes diagnosis upon DKA presentation.

The TGA reports are unlikely to have captured all cases of SGLT2 inhibitor–associated DKA as adverse drug events are generally underreported (5). Further limitations include variable and incomplete case information, with reporting bias subject to media influence.

Within South Australia between December 2015 and March 2017, 20,548 empagliflozin and 65,303 dapagliflozin scripts were dispensed. This equates to 85,851 SGLT2 inhibitor scripts dispensed over the 16-month duration in which our case series was conducted. This equates to 7,154.25 patient-years of SGLT2 inhibitor treatment in which 13 SGLT2 inhibitor–associated DKA cases occurred, resulting in an adverse event rate of 1.8 cases of SGLT2 inhibitor–associated DKA per 1,000 patient-years. While this estimate is higher than all but one previous, it must be treated with caution (1–4). Limitations include uncertainty around case detection and medication compliance. SGLT2 inhibitor–associated DKA incidence requires further validation.

Key issues identified were that *1*) most patients did not recognize DKA, *2*) treating physicians often did not initially recognize DKA due to relative euglycemia, and *3*) effective treatment was delayed. Most cases were severe, with one associated death, the second within the literature (4). Identifiable precipitants were often present, suggesting the potential for risk mitigation.

Acknowledgments. The authors thank Kylies Moore (pharmacist, South Australia Pharmacy Medicines Information Service) for providing South Australian SGLT2 inhibitor prescription data, Sonya J. Conrad (Women's Information Service, South Australia) for analysis of TGA reports, and the TGA for providing nationally reported notifications of adverse events of SGLT2 inhibitor–associated DKA.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. E.J.M. researched data, performed the audit, and wrote the manuscript. G.G. contributed to the discussion and reviewed the manuscript. D.J. contributed to the audit and reviewed the manuscript. E.J.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this study were presented at the Australian Diabetes Society and Australian Diabetes Educators Association Annual Scientific Meeting, Perth, Australia, 30 August to 1 September 2017.

References

1. Fralick M, Schneeweiss S, Patorno E. Risk of diabetic ketoacidosis after initiation of an SGLT2 inhibitor. N Engl J Med 2017;376:2300–2302

2. Rosenstock J, Ferrannini E. Euglycemic diabetic ketoacidosis: a predictable, detectable, and preventable safety concern with SGLT2 inhibitors. Diabetes Care 2015;38:1638–1642

3. Handelsman Y, Henry RR, Bloomgarden ZT, et al. American Association of Clinical Endocrinologists and American College of Endocrinology position statement on the association of SGLT-2 inhibitors and diabetic ketoacidosis. Endocr Pract 2016;22:753–762

4. Isaacs M, Tonks KT, Greenfield JR. Euglycaemic diabetic ketoacidosis in patients using sodium-glucose co-transporter 2 inhibitors. Intern Med J 2017;47:701–704

5. Hazell L, Shakir SA. Under-reporting of adverse drug reactions: a systematic review. Drug Saf 2006;29:385–396