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SGLT2-I in the Hospital Setting: Diabetic Ketoacidosis and Other Benefits and Concerns

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Abstract
Purpose of Review Sodium-glucose cotransporter 2 (SGLT2) inhibitors are the newest class of antihyperglycemic agents. They are increasingly being prescribed in the outpatient diabetic population. In this review, we examine the risks and benefits of continuation and initiation of SGLT2 inhibitors in the inpatient setting.
Recent Findings There are currently no published data regarding safety and efficacy of SGLT2 inhibitor use in the hospital. Outpatient data suggests that SGLT2 inhibitors have low hypoglycemic risk. They also decrease systolic blood pressure and can prevent cardiovascular death. The EMPA-REG study also showed a decrease in admissions for acute decompensated heart failure. There have been increasing cases of diabetic ketoacidosis, and specifically the euglycemic manifestation, associated with SGLT2 inhibitors use. We present two cases of inpatient SGLT2 inhibitor use, one of continuation of outpatient therapy and one of new initiation of therapy. We then discuss potential risks and methods to mitigate these as well as benefits of these medications in the inpatient setting.
Summary We cautiously suggest the use of SGLT2 inhibitors in the hospital. However, these must be used judiciously and the practitioner must be aware of euglycemic diabetic ketoacidosis and its risk factors in this population.

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Introduction

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a relatively new class of antihyperglycemic drugs, the first of which was initially approved for type 2 diabetes in 2013. These drugs work by blocking the reabsorption of glucose by the kidney, increasing glucose excretion, and lowering blood glucose levels. Two isoforms of sodium glucose cotransporters are present in humans, SGLT1 and SGLT2. SGLT1 is expressed in the intestine, kidney, heart, liver, and skeletal muscle, while SGLT2 is expressed primarily in the kidney [1]. The kidney filters approximately 160–180 g of glucose daily. The maximum glucose reabsorption rate by SGLT2 occurs when plasma glucose levels reach approximately 200 mg/dL [2]. Reabsorption of glucose by SGLT2 is insulin independent and relies solely upon the filtration of glucose. Given its insulin-independent mechanism, inhibition of SGLT2 alone should theoretically not lead to hypoglycemia. Consistent with this, humans with familial renal glycosuria have mutations in the gene encoding for SGLT2, *SLC5A2*. These patients have increased urinary glucose excretion in the presence of normal plasma glucose levels [2]. Thus, inhibition of SGLT2 is an attractive method for the treatment of diabetes. In the 1930s, phlorizin was the first compound shown to inhibit renal glucose reabsorption [3] and was later shown in the 1980s to normalize blood glucose levels in diabetic rats, while improving β-cell function and insulin sensitivity [4, 5]. In the last 10 years, several compounds have been developed to selectively inhibit SGLT2, three of which are now approved for use in the USA and Europe: canagliflozin, dapagliflozin, and empagliflozin [6]. These drugs mostly

differ in their selectivity for SGLT2 over SGLT1, with empagliflozin being the most selective and dapagliflozin being the least selective. However, dapagliflozin is still 160 times more selective for SGLT2 than SGLT1, and all are considered to have negligible effects on SGLT1 action [6]. In outpatient studies, the SGLT2 inhibitors have an effect on HbA1c reduction that ranges from 0.4 to 1.2% and are approved for use alone or in combination with other antihyperglycemic agents [7••, 8••, 9••, 10–15]. Recent data in the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG) study suggesting considerable cardiovascular benefits in patients with diabetes has made these new drugs particularly popular with prescribers in the outpatient setting [16••]. EMPA-REG was a non-inferiority cardiovascular safety trial that examined 7020 participants with T2DM and assigned them in a 1:1:1 ratio of placebo, empagliflozin 10 mg, or empagliflozin 25 mg daily [16••]. Treatment with empagliflozin led to a 38% reduction in cardiovascular death and a 35% reduction in heart failure admissions. There was no reduction in the rate of nonfatal myocardial infarctions or strokes. The FDA has now approved the use of empagliflozin for the prevention of cardiovascular death in patients with cardiovascular disease and type 2 diabetes mellitus (T2DM) [17]. However, currently, there are little data evaluating the effects and safety of these agents in the inpatient settings. In this review, we will examine theoretical risks and benefits of continuing or starting an SGLT2 inhibitor in the inpatient setting utilizing one theoretical and one actual patient case. A summary of the several risks and benefits can be seen in Table 1.

Continuation of an SGLT2 Inhibitor Upon Admission

Case Presentation (Theoretical)

A 60-year-old overweight male with a history of type 2 diabetes, coronary artery disease, and arthritis presents to the hospital for a total knee replacement. His hemoglobin A1c was 6.8% and eGFR of 70 mL/min/1.73 m^2 on canagliflozin 300 mg daily and metformin. The inpatient endocrinology service is consulted for glucose management postoperatively. Specifically, the primary service asks whether canagliflozin should be continued while the patient was in the hospital.

Benefits

Current inpatient guidelines recommend a target blood glucose of less than 180 mg/dL, with recommended pre-meal glucose target of <140 mg/dL [18, 19]. Although a target of 110–140 mg/dL is considered acceptable in selected patients [18], it may be associated with increased risks of hypoglycemia. Currently, most patients who are admitted to the hospital are managed with either intravenous or subcutaneous insulin therapy. While efficacious, these therapies present challenges and can carry risk of hypoglycemia if not given appropriately.

A simpler medication regimen would be ideal for maintaining euglycemia in the hospital. Currently, sitagliptin is the only oral antihyperglycepic medication shown to be safe for use in the management of diabetes in the inpatient setting [20]. However, limited data on inpatient glycemic control has affected its current use and implementation in this setting. SGLT2 inhibitors could potentially be a good candidate for an inpatient regimen as they are orally available, well tolerated, highly selective for SGLT2, theoretically do not cause hypoglycemia, and work well in combination with other antihyperglycemic medications.

Each SGLT2 inhibitor phase III clinical trial examined the rates of hypoglycemia associated with these agents. Because of their insulin-independent mechanism of action, these agents theoretically should not cause hypoglycemia, thus making this new class of medications potentially very suitable for inpatient glycemic control. Data from meta-analyses of canagliflozin, dapagliflozin, and empagliflozin clinical trials showed no risk of hypoglycemia associated with their use unless given in conjunction with insulin or an insulin secretagogue [21–23]. However, there was an increased risk of hypoglycemia when canagliflozin (RR 1.49; 95% CI 1.14–1.95; $p = 0.004$) or dapagliflozin (RR 1.16; 95% CI 1.05–1.29; $p = 0.005$) was used with insulin or a sulfonylurea. In the EMPA-REG trial, which was not included in the above meta-analyses for empagliflozin use, no difference was seen in overall hypoglycemic events or in severe hypoglycemic events with empagliflozin use despite insulin therapy being used in 48% of trial patients with a median totally daily insulin dose of 54 units [16••]. They did not report the percentage decrease in insulin therapy needed to prevent hypoglycemia. Therefore, these data suggest that SGLT2 inhibitors could be potentially advantageous for glycemic control for patients in the hospital who are not also on insulin or sulfonylurea therapy. In the outpatient setting, the risk of hypoglycemia in those patients taking SGLT2 inhibitors with insulin or sulfonylureas was decreased by reducing the dose of insulin or the insulin secretagogue. Thus, the risk of hypoglycemia with SGLT2 inhibitors given with insulin in the inpatient setting could be reduced if insulin doses are appropriately decreased as it is done in the outpatient setting.

Potential Risk of DKA Associated With Inpatient Use

There are no published trials examining the risk associated with inpatient use of SGLT2 inhibitors. While not seen in the phase III clinical trials, diabetic ketoacidosis (DKA), and in particular euglycemic DKA, has become a major concern in

Table 1 Details of risks and benefits of SGLT2 inhibitors from selected, comparable phase 3 randomized, double-blind, placebo-controlled RCTs

	Participant (*n*)	Baseline A1c (%) Mean	Change from baseline A1c (%) Mean	Weight loss (kg) Mean	Decrease systolic BP (mmHg)	Hypoglycemia (%)	UTI, *n* (%)	Mycotic infection, *n* (%)	Hypotension, *n* (%)	DKA (%)
Canagliflozin [7••][a] 100 mg	195	8.1	−0.77	−2.5	−3.3	3.6	3 (6.4)	Male, 1 (4.3) Female, 5 (20.8)	0	None reported
Canagliflozin 300 mg	197	8.0	−1.03	−3.4	−5.0	3.0	2 (4.5)	Male, 1 (5.3) Female, 1 (4.0)	2 (1.0)	
Placebo	192	8.0	−0.14	−0.5	0.4	2.6	8 (4.2)	Male, 0 Female, 4 (3.8)	0	
Empagliflozin [9••][b] 10 mg	224	7.87	−0.74	−2.26	−2.9	1	Male, 3 (2) Female, 12 (15)	Male, 4 (3) Female, 3 (4)	Not reported	None reported
Empagliflozin 25 mg	224	7.86	−0.85	−2.48	−3.7	1	Male, 2 (1) Female, 10 (13)	Male, 2 (1) Female, 7 (9)		
Placebo	228	7.91	0.08	−0.33	−0.3	1	Male, 3 (2) Female, 9 (9)	Male, 0 Female, 0		
Dapagliflozin [8••][c] 2.5 mg	65	7.92	−0.58	−3.3	−4.6	1 (1.5)	3 (4.6)	5 (7.7)	0	None reported
Dapagliflozin 5 mg	64	7.86	−0.77	−2.8	−2.3	0	8 (12.5)	5 (7.8)	0	
Dapagliflozin 10 mg	70	8.01	−0.89	−3.2	−3.6	2 (2.9)	4 (5.7)	9 (12.9)	1 (1.4)	
Placebo	75	7.84	−0.23	−2.2	−0.9	2 (2.7)	3 (4.0)	1 (1.3)	1 (1.3)	

[a] Stenlof et al.—efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise $N = 584$; duration 26 weeks; primary outcome: change hemoglobin A1c from baseline

[b] Roden et al.—empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomized, double-blind, placebo-controlled, phase 3 trial $N = 899$; duration 24 weeks; primary outcome: change hemoglobin A1c from baseline

[c] Ferrannini et al.—dapagliflozin monotherapy in type 2 diabetic patients with inadequate glycemic control by diet and exercise: a randomized, double-blind, placebo-controlled, phase 3 trial $N = 485$; duration 24 weeks; primary outcome: change hemoglobin A1c from baseline

post marketing analysis of SGLT2 inhibitor therapy. In the last year, there have been several reports of ketoacidosis occurring with all three US approved SGLT2 inhibitors. Peters et al. described 13 occurrences of euglycemic DKA (as case reports) in the setting of SGLT2 inhibitors use [24•]. Two of the cases occurred in the setting of a surgical procedure. In both cases, canagliflozin was held the morning of surgery. In one case, DKA occurred 5 days postoperatively, and in the second case, it occurred 10 hours after surgery. Erondu et al. analyzed data from 17,596 patients who were enrolled in trials using canagliflozin. In this data set, they found 12 cases of DKA, of which only one occurred in the postoperative setting, following a cholecystectomy [25•]. In 2015, the FDA issued a warning regarding DKA in the setting of SGLT2 inhibitors use. Between March 2013 and May 2015, 73 cases of DKA with SGLT2 inhibitor use were reported to the FDA (canagliflozin, $n = 48$, dapagliflozin, $n = 21$, and empagliflozin, $n = 4$) [26]. Fifteen of the cases were reported in off-label use of SGLT2 inhibitors as an adjunctive therapy in individuals with type 1 diabetes. The median time of onset of ketoacidosis was 43 days from initiation or dose increase of an SGLT2 inhibitor. A concurrent event was associated with 53 of the cases including dehydration, infection, and insulin dose changes. Furthermore, the FDA stated that many cases occurred with a blood glucose of <250 mg/dL. The FDA noted several risk factors for DKA including infection, low-carbohydrate diet, reduced calorie intake, reduction or discontinuation of insulin or insulin secretagogues, and alcohol use. Interestingly, a recent meta-analysis of randomized controlled trials showed no increased risk of DKA in over 13,000 patients (OR 1.71, CI 0.56, 5.20) [27]. However, this analysis did not perform any subgroup analyses for type 1 diabetes mellitus or for inciting factors.

Many have postulated possible mechanisms for SGLT2 inhibitor-associated DKA. DKA occurs generally from insulin deficiency, relative (such as in the setting of illness or infection) or absolute (such as in type 1 diabetes and advanced type 2 diabetes requiring insulin), which leads to reduced glucose utilization and increased lipolysis. This results in increased free fatty acid transport to the liver. Simultaneously, glucagon levels are increased which leads to free fatty acid oxidation and the production of ketone bodies [28]. Traditionally, ketoacidosis was thought to only occur with hyperglycemia. However, euglycemic DKA has been reported as well and is likely the more frequent type of DKA with SGLT2 inhibitors use. When patients are on maximum dose SGLT2 inhibitors, there is an increase in urinary glucose extraction of 50–100 g/day [29]. This leads to decreased plasma glucose levels and decreased dose requirements of insulin or insulin secretagogues. As a result, patients have both decreased amounts of glucose for energy expenditure while also being insulin deficient. This combination can lead to euglycemic DKA. The risk of euglycemic DKA increases in various settings that exacerbate precipitating factors, such as fasting, decreased carbohydrate intake, and decreased insulin doses. Infection was also cited by the FDA as a risk factor for DKA in these patients, likely due to the increase glucose demand which is dampened by the use of SGLT2 inhibitors. Thus, DKA is likely a legitimate, although small, risk associated with SGLT2 inhibitor use.

Patients who are admitted to the hospital have similar profiles to those that are at increased risk of SGLT2 inhibitor-associated DKA. Patients often present with infections and have decreased oral intake due to illness or for procedures. Timing of procedures in the hospital is often unpredictable leading to the need to stop oral intake at any time in these patients. Because many of the DKA cases reported presented with euglycemia rather than the typical hyperglycemia, it makes the ketoacidosis recognition and diagnosis even more challenging for the treating physician. Thus, DKA is a real possibility in the inpatient setting and the benefit of SGLT2 inhibitor use in the hospital needs to be weighed carefully.

In euglycemic DKA, the triad of classic DKA diagnosis (hyperglycemia >250 mg/dL, serum bicarbonate ≤18 mEq/L, and pH <7.3) [30] is altered due to the lack of hyperglycemia, thus posing a unique set of challenges as well as the need for alternative laboratory testing to achieve accurate and timely diagnosis of ketoacidosis in the setting of normoglycemia.

This is a critical factor, as diagnosis can be easily missed or delayed in the absence of hyperglycemia, if no further studies are performed in patients taking SGLT2 inhibitors presenting to the emergency department or admitted to the hospital.

Although generally ketonuria is sufficient for confirmation of DKA diagnosis in addition to hyperglycemia, low serum bicarbonate, and pH, it measures only acetoacetate and small amounts of acetone. However, the major ketoacid in DKA is beta-hydroxy-butyric acid (b-OHB), which appears in the blood at the onset of DKA. Whole blood levels above 3 mmol/L together with hyperglycemia over 250 mg/dL suggest the presence of DKA [31]. Relying only on measurements of urine ketones may not accurately reflect the severity of ketonemia. Therefore, measurement of whole blood b-OHB, if rapid turnaround time is possible such as with a bedside meter, may be more helpful in allowing "real-time" diagnosis of DKA and initiate therapy [32].

Several methods of available blood b-OHB measurements have been reported, ranging from use in the laboratory (e.g., Sigma or Cobos, Roche) to home monitoring (Precision Xtra meter, Abbott Diabetes Care) to bedside measurement by a handheld device as accurate as reference laboratory methods (Precision Xceed Pro System, Abbott Diabetes Care) [33–35].

Therefore, blood measurements of b-HOB could potentially become a very useful tool for laboratory or even bedside analysis in patients treated with SGLT2 inhibitors who present with possible DKA in the absence of hyperglycemia.

A separate cohort of patients are generally admitted to the hospital for elective inpatient or outpatient surgical procedures. As the risk associated with DKA is felt to be increased with NPO status, these patients are likely at increased risk for DKA. These patients are not monitored as closely as those being admitted to the hospital, and euglycemic DKA is difficult to diagnose because capillary blood glucose values are normal and typically laboratory tests are not routinely performed in the outpatient setting. Research is needed to determine whether these patients should discontinue their SLGT2 inhibitors prior to elective outpatient procedures and if so for how long in order to minimize the risk of DKA.

Initiation of SGLT2 Inhibitors in the Hospital

Case Presentation (Actual)

A 67-year-old male with a past medical history significant for heart failure with preserved ejection fraction, coronary artery disease, and insulin requiring type 2 diabetes mellitus presented to Northwestern Memorial Hospital with acute decompensated heart failure. His diabetes was managed with 120 units of U-300 glargine daily, 25 units of lispro insulin with meals, liraglutide 1.2 mg daily, and lispro supplemental scale prior to admission, with a HbA1c of 7.6%. He has never been prescribed an SGLT2 inhibitor. In the hospital, a continuous intravenous bumetanide infusion was started to treat the heart failure exacerbation. He was hyperglycemic on subcutaneous insulin while in the hospital with glucose levels ranging between 119 and 205 mg/dL on 120 units of glargine daily and 60 units of lispro insulin with meals. The endocrine service was consulted and was asked if an SGLT2 inhibitor agent could be initiated while the patient was hospitalized to address glycemic control as well as his decompensated heart failure.

Benefits

As discussed previously in this article, SLGT2 inhibitors would be potentially advantageous for inpatient glucose control due to their low risk of hypoglycemia. Independent of their glucose-lowering effects, SGLT2 inhibitors potentially have a role in the treatment of blood pressure and heart failure. As discussed above, in the EMPA-REG study, empagliflozin was shown to lead to a reduction in cardiovascular mortality specifically in patients with heart failure with reduced ejection fraction (HFrEF). There also was a decrease in admissions for acute decompensated heart failure. This landmark trial suggests that empagliflozin, and possibly all SGLT2 inhibitors, can improve outcomes in patients with systolic heart failure. Unfortunately, these data did not examine the effects of empagliflozin on acute decompensated heart failure, but it could be postulated that it would be efficacious in such setting. In support of this theory, Sha et al. demonstrated that urine output increased by 300 mL daily within 24 h of starting canagliflozin, but an association with heart failure was not assessed [36]. Fitchett et al. analyzed the data from EMPA-REG and reported that in all patients enrolled in the trial, there was a decreased need for loop diuretics in patients treated with empagliflozin [37]. While EMPA-REG examined patients in the outpatient setting, these additional data are compelling to consider initiating SGLT2 inhibitors for patients with type 2 diabetes admitted to the hospital with acute decompensated heart failure.

The SGLT2 inhibitors presently available have been shown to decrease systolic blood pressure by 5 mmHg and diastolic blood pressure by about 2 mmHg irrespective of a previous diagnosis of congestive heart failure. Interestingly, there is no relationship between the degree of glucose lowering and the decrease in blood pressure seen with these medications [38]. As with other blood pressure medications, SGLT2 inhibitors tend to have a synergistic effect with other medications. For example, addition of a beta-blocker or calcium channel blocker with dapagliflozin led to increased blood pressure reductions than would be expected with either drug alone [39]. This effect was also seen with renin-angiotensin system blockers [40]. Interestingly, and for unclear reasons, there was no synergistic effect when canagliflozin was added to a thiazide diuretic [41]. Because of these effects, it may be potentially advantageous to prescribe an SGLT2 inhibitor in the hospital to patients who are hypertensive and hyperglycemic to achieve dual benefit of glycemic and blood pressure control.

Potential Risks

Initiation of SGLT2 inhibitors in the hospital poses similar risks as continuing therapy prescribed by an outpatient provider. As described, DKA can occur both at initiation and after several months of SGLT2 inhibitor therapy. Patients with acute decompensated heart failure are often prescribed increased or additional doses of diuretics which can lead to acute kidney injury due to cardiorenal effects. SGLT2 inhibitors are renally dosed and, thus, worsening kidney function without changing the dose of the SGLT2 inhibitor could potentially lead to an increased risk of DKA. SGLT2 inhibitors themselves have also been associated with impaired renal function which may increase the risk of worsening renal function when used in combination with diuretics. During the process of diuresis, many patients have increasing bicarbonate levels, often described as contraction alkalosis. For this reason, the decrease in bicarbonate expected in DKA may be less profound in the setting of therapy with SGLT2 inhibitors. This in combination with the euglycemia seen in DKA associated with SGLT2 inhibitors may result in delayed recognition and diagnosis of DKA.

An additional risk to consider is the increased rates of urinary tract infection and genital mycotic infections, particularly in women, which are seen in patients treated with SGLT2 inhibitors (reference 7••, 8••, 9••). This may be of particular relevance in the inpatient setting in patients who have Foley catheters placed and are already at increased risk of urinary tract infections. This should be considered when making decisions regarding the appropriate patient for inpatient treatment with these agents. Due to the naturiesis caused by SGLT2 inhibitors, they are also associated with postural hypotension. When these medications are started in the outpatient setting, patients are often encouraged to increase fluid intake particularly in the beginning. The ability for inpatients to increase oral intake due to illness, lack of mobility, or fluid restrictions placed in the hospital may increase the risk of postural hypotension.

The EMPA-REG study also investigated the effect of empagliflozin on renal function [42•]. They noticed a sharp initial decrease in estimated glomerular filtration rate (eGFR) in the first 4 weeks of treatment. However, this decrease plateaued and was favorable over time compared to placebo. Patients being treated with emapagliflozin had a risk reduction of 44% in creatinine doubling, 55% in initiation of renal replacement therapy, and a 38% reduction in progression to microalbuminuria. While the inpatient health care providers might be discouraged by an acute worsening of renal function after initiation of empagliflozin, they should be aware that they should consider continuing therapy long term, as empagliflozin has been shown to prevent worsening of renal function.

Conclusions

SLGT2 inhibitors are an important new category of antidiabetic agents. They have potential benefits for the inpatient setting including a decreased risk of hypoglycemia and secondary treatment of heart failure and hypertension. However, as discussed above, there is growing evidence to suggest that SGLT2 inhibitors can lead to euglycemic DKA. Furthermore, several characteristics of the hospitalized patient including infection and fasting increase the risk of SGLT2 inhibitor-associated DKA. Despite the risks, we believe that the benefits of SGLT2 inhibitors are greater than the risks. Euglycemic DKA is difficult to recognize, especially by the general practitioner who might not be aware of this risk. Therefore, we would only recommend the use of SGLT2 inhibitors if an automated system existed alerting the provider of the possibility of euglycemic DKA. This alert would occur if patients are prescribed an SGLT2 inhibitor, have a bicarbonate <18 mEq/L, and have an anion gap >12. Furthermore, we would suggest that this alert be in place regardless of whether SGLT2 inhibitors are continued in the hospital for those taking them as outpatients as it is unclear how long the risk exists after stopping the medication upon admission. Further data are needed to fully answer the questions posed in our discussion but we are encouraged about the possibility of using SGLT2 inhibitors in the inpatient population.

Compliance with Ethical Standards

Conflict of Interest Joshua A. Levine and Susan L. Karam declare that they have no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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