CASE REPORT

Severe Hypernatraemic Dehydration and Unconsciousness in a Care-Dependent Inpatient Treated with Empagliflozin

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Published online: 3 November 2017

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Abstract A 66-year-old Caucasian male became unconscious 2 weeks after initiation of add-on therapy with empagliflozin for poorly controlled type 2 diabetes mellitus. The inpatient had recently suffered focal pontine stroke, rendering him bedridden and requiring increased nursing care, including assistance with drinking. The patient had received empagliflozin 10 mg once daily for glycaemic control. Investigations revealed hypernatraemia (164 mmol/l), a urine glucose level of 3935 mg/dl, and a creatinine level of 2.1 mg/dl. The patient was diagnosed with severe hypernatraemic dehydration due to iatrogenic glucosuria and prerenal kidney failure. Empagliflozin was discontinued and the patient received hypotonic fluids (including 5% dextrose and free water). Over the following 4 days, glucosuria subsided, blood sodium levels and kidney function normalized and the patient regained full consciousness. He was discharged for rehabilitation 40 days after admission. A Naranjo assessment score of 6 was

obtained, indicating a probable relationship between the patient's hypernatraemic dehydration and administration of empagliflozin. In this care-dependent inpatient, who lost the ability to replace water loss autonomously because of a stroke, continuous administration of empagliflozin caused persistent glucosuria and contributed to progressive volume depletion. Excessive dehydration resulted from ignorance of both the populations that are susceptible to dehydration under sodium-glucose cotransporter 2 (SGLT2) inhibitor therapy and the drug's mechanism of action. In patients who depend on support from others in daily tasks, including fluid intake, patients with an impaired sense of thirst and those who have lost the ability to communicate thirst, SGLT2 inhibitor therapy should not be initiated or might be (temporarily) discontinued.

Abbreviations

NIHSS National Institutes of Health Stroke Scale
SGLT2 Sodium-glucose cotransporter 2
TTPG Transtubular potassium gradient

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Key Points

Sustained glucosuria by sodium-glucose cotransporter 2 (SGLT2) inhibition may cause critical dehydration.

Patients depending on others' support in daily tasks, including drinking, may be at particular risk.

Awareness of populations susceptible to dehydration upon SGLT2 inhibitor exposure needs to be increased.

Close monitoring of volume status is vital in SGLT2 inhibitor recipients.

Background

Inhibitors of sodium-glucose cotransporter 2 (SGLT2) are increasingly used in adults with type 2 diabetes mellitus to improve glycaemic control. Inhibition of the SGLT2 in the proximal renal tubules lowers blood glucose levels via a decrease in the renal glucose threshold and an increase in urinary glucose excretion [1]. Furthermore, SGLT2 inhibitors are natriuretic and antihypertensive because SGLT2 reabsorbs filtered glucose together with sodium [1].

Common side effects include glucosuria-associated genital and urinary tract infections. However, glucosuria-induced free water loss may contribute to critical dehydration, particularly in patients who are care dependent and unable to autonomously regulate their fluid intake. Although the use of SGLT2 inhibitors is contraindicated in the presence of apparent dehydration, the risk and clinical significance of volume depletion in susceptible patient groups may not be sufficiently emphasized in recent literature.

Case Presentation

A 66-year-old Caucasian male inpatient was transferred from the neurological ward to the emergency department (critical care unit) of the same hospital because of decreased consciousness. His medical history included poorly controlled type 2 diabetes mellitus, atrial fibrillation and cardiovascular disease.

The patient had been admitted to the department of cardiology 17 days earlier because of a myocardial infarction. He underwent successful percutaneous coronary intervention and felt well during the first days of hospitalisation. The patient developed focal pontine stroke [National Institutes of Health Stroke Scale (NIHSS) 7] 12 days later and was subsequently transferred to the neurology ward for further care. The patient experienced moderate dysarthria, some degree of hemiparesis and limb ataxia but was otherwise alert and responsive. However, reduced general condition with moderately severe disability kept the patient bedridden and necessitated intensified nursing care, including assistance with drinking and personal care, including bodily functions (modified Rankin scale 4). The patient was transferred to the emergency department 5 days later because of progressive loss of consciousness. Figure 1 highlights the medically relevant events that occurred during hospitalisation.

On admission to the emergency department, the patient was stuporous (Glasgow coma scale 10; eye response 3, motor response 4, verbal response 3), had elevated body temperature (38.5 °C) and low blood pressure (95/

50 mmHg) and appeared to be dehydrated. Laboratory findings included severe hypertonic hypernatraemia (164 mmol/l), hyperglycaemia (322 mg/dl), excessive glucosuria (3935 mg/dl) and impaired kidney function (creatinine 2.1 mg/dl). Chest X-ray (posterioranterior) showed patchy consolidations in upper lung fields. Table 1 gives a summary of laboratory test results, the patient's medical history and a list of his medications.

Diagnostic work-up primarily focused on the differential diagnosis of hypernatraemia as it was the predominant laboratory finding and considered the cause of impaired consciousness.

Central Diabetes Insipidus

The sensation of thirst is regulated by the hypothalamus, which senses electrolyte concentrations and fluid status and controls the release of vasopressin. Decreased or absent production of vasopressin inhibits the reabsorption of water in the renal collecting ducts, thereby increasing blood sodium levels and blood osmolality, referred to as diabetes insipidus.

Our patient had recently suffered cerebral infarction, and diabetes insipidus following vertebrobasilar ischaemia has been described previously [2]. However, a diagnosis of diabetes insipidus was unlikely. Although ischaemia-associated swelling of the brain theoretically could have caused hypothalamic insufficiency, leading to central diabetes insipidus, this would not have been compatible with non-space occupying pontine stroke. Furthermore, severe hypernatraemia usually does not occur in central diabetes insipidus, as the thirst response is intact except when the thirst sensation is impaired concurrently. Likewise, the high urine osmolality (758 mosmol/kg) observed in our patient was not characteristic of diabetes insipidus, in which urine osmolality is usually low (< 200–300 mosmol/kg).

Mineralocorticoid Excess

Aldosterone plays a major role in electrolyte homeostasis and blood pressure regulation. Aldosterone increases reabsorption through implementation of epithelial sodium channels, whereas potassium is excreted over an aldosterone-sensitive potassium channel, resulting in hypernatraemia and hypokalaemia.

The patient's past medical history included a mass in the adrenal glands, but blood aldosterone and renin levels were not assessed. The urine potassium level was 57 mmol/l, the blood potassium level was 3.3 mmol/l and the transtubular potassium gradient (TTPG) was 8.1. As the blood potassium level was low, TTPG should also have been low

Fig. 1 Timeline of events from hospital admission to discharge. Three days after admission to the hospital (department of cardiology), empagliflozin treatment was initiated to improve glycaemic control. Pontine stroke occurred 9 days later (day 12), and the patient was transferred to the neurology ward. Because of progressive loss of consciousness during the following days, the patient was then transferred to the critical care unit of the hospital's emergency

department (day 17). Severe dehydration, along with excessive glucosuria prompted cessation of empagliflozin treatment and careful administration of hypotonic fluids. With this therapy, free water loss subsided, blood sodium levels decreased to normal and consciousness improved. The patient was discharged for rehabilitation therapy in good clinical condition 56 days after admission to the hospital. ED-CCU emergency department—critical care unit

(< 4). Although an elevated TTPG of 8.1 in the presence of hypokalaemia would have been compatible with a diagnosis of hyperaldosteronism, it is not typically associated with excessive hypernatraemia but rather with slightly elevated blood sodium levels, resistant arterial hypertension, hypokalaemia and metabolic alkalosis.

Sodium Overload

Sodium overload is usually associated with the administration of hypertonic sodium solutions or excessive salt ingestion. Neither had occurred in this case.

On the neurology ward, treatment for suspected pneumonia was started with piperacillin/tazobactam (4.5 g three times daily), which—rarely—can be associated with hypernatraemia [3]. However, one would expect increased urinary sodium excretion (> 100 mmol/l) in sodium overload as the kidneys try to eliminate the excessive sodium. Although urinary sodium levels may be misleading in cases of concomitant dehydration, sodium overload was unlikely to be the main cause of hypernatraemia.

Antidiabetic Therapy and Concomitant Medication

Concomitant medication included antiplatelet drugs (aspirin and ticagrelor), antihypertensive agents (amlodipine, valsartan, hydrochlorothiazide and carvedilol), a

bronchodilator (ipratropium bromide), a cholesterol-lowering agent (rosuvastatin) and a proton pump inhibitor (pantoprazole). None of these is usually associated with severe hypernatraemia.

However, thorough anamnesis revealed that empagliflozin (10 mg once daily) had newly been added to the patient's antidiabetic medications to improve glycaemic control 2 weeks before admission to the emergency department (Fig. 1).

Empagliflozin belongs to the gliflozin class of oral antidiabetics and inhibits renal SGLT2, which is localised in the proximal tubules of the kidneys and reabsorbs 97% of primarily filtered glucose. SGLT2 inhibitors decrease blood glucose levels by increasing the amount of urinary glucose that is eventually excreted from the kidneys. Glucosuria increases linearly with the tubular glucose load and induces osmotic diuresis [1]. Sustained diuresis due to persisting glucosuria may contribute to volume depletion and subsequent kidney failure, as seen in our patient. Furthermore, SGLT2 inhibitors have a mild natriuretic effect. However, in contrast to glucosuria, the natriuretic effect is balanced over time by declining plasma volume provoking equilibration between sodium excretion and intake [1]. SGLT2 inhibition may also increase urinary potassium excretion through increased distal tubular flow. Yet, in cases of dehydration, urinary potassium levels may be difficult to interpret.

We considered treatment with empagliflozin as a significant contributor to hypernatraemia in this case. Our hypothesis was supported by a Naranjo score of 6.

Table 1 Patient characteristics and laboratory findings at admission to the emergency department (critical care unit)

General condition	Stuporous, dehydrated
Vital signs	Tachycardia (180 bpm), tachypnoea (RR 26/min), oxygen saturation 94% (while receiving 2 litres of oxygen per minute via an oxygen mask), blood pressure 95/50, tympanic temperature 38.5 °C
Medical history	Arterial hypertension, type 2 diabetes mellitus, obesity, hernia of the abdominal wall, coronary artery disease, unknown mass in the adrenal gland
Concomitant medication	Metformin, rapid-acting and long-acting insulin, acetylsalicylic acid, ticagrelor, amlodipine, valsartan, hydrochlorothiazide, carvedilol, rosuvastatin, ipratropium bromide, pantoprazole
Laboratory findings ^a	
Na	164 (136–145) mmol/l
K	3.3 (3.4–4.5) mmol/l
Ca	1.24 (1.15–1.30) mmol/l
Cl	121 (95–106) mmol/l
pH	7.45 (7.35–7.45)
pCO ₂	34 (35–45) mmHg
pO ₂	89 (> 79) mmHg
Glucose	322 (70–120) mg/dl
Lactate	1.5 (< 1.8) mmol/l
Creatinine	2.1 (< 0.9) mg/dl
Base excess	0.0 (0 ± 2)
Osmolality	355 (280–296) mosmol/kg
C-reactive protein	2.34 (< 0.5) mg/dl
WBC	12 (4–10) × 10 ⁹ /l
GFR (MDRD)	34 (> 90) ml/min/1.73 m ²
HbA _{1c}	8.1 (< 6) %
Urinalysis	
Osmolality	758 mosmol/kg
Glucose	3935 mg/dl
Ketone bodies	50 mg/dl
Sodium	20 mmol/l
Potassium	57 mmol/l
Erythrocytes	250 per µl
Protein	75 mg/dl
Nitrite	Positive
pH	5
Leucocytes	Negative
Cranial computed tomography	Subacute ischaemic pontine stroke (paramedian left)
Chest X-ray	Patch consolidations in both lungs, otherwise normal
Transthoracic echocardiogram	Severely reduced left ventricular function, septal akinesia
Electrocardiogram	Left bundle branch block, atrial fibrillation
Urinary dip stick, urinary cultures, blood cultures	No growth

GFR glomerular filtration rate, *HbA_{1c}* glycated haemoglobin, *MDRD* Modification of Diet in Renal Disease, *RR* respiratory rate, *WBC* white blood cell

^aLaboratory data are given with reference range

Treatment

Treatment with empagliflozin was stopped to limit glucosuria and free water loss. The primary goal was careful fluid replacement to reduce sodium levels by 10–12 mmol/

l per day. Intravenous fluid repletion included 5% dextrose (100 ml/h), free water (50 ml/h) and balanced potassium solutions to correct concurrent hypokalaemia. During the first day of treatment, blood sodium levels were measured every 1–2 h to ensure an adequate rate of correction.

Hyperglycaemia was treated with insulin. Atrial fibrillation converted into sinus rhythm with fluid and potassium substitution. Piperacillin/tazobactam was continued. No adverse events occurred.

Outcome

Upon cessation of empagliflozin and administration of hypotonic fluids, free water loss subsided and blood sodium levels decreased to 145 mmol/l over the following 4 days. Fever resolved, kidney function improved and the patient finally regained consciousness. The patient was subsequently transferred back to the neurology ward and began rehabilitative therapy. Antidiabetic therapy was continued with metformin and insulin. About 6 weeks after admission to the emergency department, sodium levels remained in the normal range and the patient was discharged for further rehabilitation in good clinical condition.

Discussion

This report describes a care-dependent patient with diabetes unable to manage his fluid intake after suffering pontine stroke who was treated with an SGLT2 inhibitor and subsequently developed severe dehydration manifesting as unconsciousness.

SGLT2 inhibitors have an emerging role in the management of type 2 diabetes mellitus. These agents reduce blood glucose levels independent of insulin by inhibiting renal SGLT2, a novel and unique mechanism of action [4]. Despite glycaemic-lowering effects, they are considered to beneficially affect metabolics and cardiovascular risk [5]. Blood pressure reduction through natriuresis and plasma volume contraction with subsequent improvement of arterial wall stiffness is a potential mechanism underlying the drug's cardio-protective effect [6]. In this context, empagliflozin has recently been demonstrated to reduce both the risk of cardiovascular death and overall mortality in high-risk diabetic patients [7].

SGLT2 inhibitors have already been intensively studied and shown to be safe and well tolerated. Common side effects are related to increased renal glucose excretion and include mostly mycotic genital infections [8]. However, in susceptible patients, glucosuria may potentially result in severe dehydration [8, 9]. Yet, in our opinion, patient populations at risk of volume depletion upon exposure to SGLT2 inhibitor therapy are poorly emphasized by recent literature.

The risk of critical dehydration is admittedly negligible in individuals who are not dependent on care and have a

normal daily fluid intake. As in diabetes insipidus, thirst response is preserved with SGLT2 inhibitor therapy, triggering appropriate fluid intake. Likewise, the initial plasma volume contraction by natriuresis stabilizes over time. In contrast, osmotic diuresis through glucosuria persists [1]. Volume depletion and dyselectrolytaemia may develop, particularly in patients who are unable to replace water loss by themselves, as highlighted in this report.

In our patient, progression of volume depletion resulted from the interplay of several factors, including the patient's inability to drink autonomously because of dysarthria and bedriddenness following pontine stroke, the care provider's failure to continuously monitor the patient's clinical volume status and the ignorance of both at-risk populations susceptible to dehydration upon SGLT2 inhibitor exposure and the drug's mechanism of action. Moreover, hypernatraemia—indicating dehydration—remained unnoticed. However, the continuous administration of empagliflozin resulting in sustained glucosuria, osmotic diuresis and free water loss was likely a further factor contributing to excessive volume depletion. Whether dehydration in turn contributed to the development of stroke in this patient can only be speculated. Yet, recent data suggest that patients with atrial fibrillation may have a significant risk of stroke in cases of concomitant dehydration [10]. On the other hand, the EMPA-REG OUTCOME trial, which assigned more than 7000 patients with diabetes to receive empagliflozin or placebo once daily over more than 3 years, found no difference between the groups in the rate of stroke across all patients (3 vs. 3.5%; $p = 0.26$) [7].

The patient presented here is admittedly not representative of the majority of patients with diabetes receiving therapy with an SGLT2 inhibitor. However, it should be kept in mind that inadequate thirst response to osmotic stimuli is not necessarily associated with a specific disease (such as stroke) but may also occur in elderly, otherwise healthy patients [11]. Individuals with inadequate thirst response, those who do not adequately communicate thirst, and those who depend on support of others for daily tasks, including fluid intake, may be at particular risk of dehydration under SGLT2 inhibitor therapy and need continuous monitoring by the prescribing physician and other care providers. Post-marketing surveillance studies may further characterize conditions in which initiation or continuation of SGLT2 inhibitor therapy should be avoided.

Conclusions

This report highlights that SGLT2 inhibition can contribute to critical dehydration in a susceptible patient. Populations that may (temporarily) not be suitable for initiation of antidiabetic treatment with an SGLT2 inhibitor need to be

better emphasised. Sufficient hydration and close monitoring of clinical volume status is vital in SGLT2 inhibitor recipients.

Acknowledgements This case has been presented at the 5th European conference on clinical and medical case reports.

Author Contributions Authors certify that they have participated sufficiently in the work to take public responsibility for the entire content of the manuscript. GG, NB and CS collected data, conducted the chart review and performed the literature search. MS and MR cared for the study patient. MS obtained informed consent from the patient. MR served as scientific advisor. GG, NB and CS wrote the first draft of the report. MS and MR critically revised the report. All authors reviewed and approved the final submitted manuscript.

Compliance with Ethical Standards

Consent for publication Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available, upon request, from the corresponding author.

Ethics approval and consent to participate At the Medical University of Vienna, the publication of case reports does not require ethics approval.

Conflict of interest Georg Gelbenegger, Nina Buchtele, Christian Schoergenhofer, Martin Roeggla and Michael Schwameis have no conflicts of interest.

Funding No sources of funding were used for this work.

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