SGLT-2 Inhibitors to Treat Hyponatremia Associated with SIADH: A Novel Indication?

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Enthusiasm is of the greatest value, so long as we are not carried away by it. Johann Wolfgang von Goethe (1749–1832)

Hyponatremia is the most frequent electrolyte disorder encountered in clinical practice; it can be classified according to extracellular volume status into 3 categories: hypovolemic, euvoletic, and hypervolemic [1–3]. Each of these categories has a wide number of etiologies, including but not limited to gastrointestinal losses, diuretic use, low dietary solute intake, endurance exercise, heart failure, and nephrotic syndrome [1–4]. Hyponatremia is associated with increased morbidity, ranging again from bone disorders and increased fracture risk [5] to the most serious complication of acute hyponatremic encephalopathy, a life-threatening condition that can require treatment with hypertonic saline in the emergency setting [6, 7]. Sodium is the most abundant extracellular osmole and changes in serum sodium concentration often reflect abnormal water balance. Serum sodium and serum osmolality are regulated by changing water intake or output through the sense of thirst and secretion of antidiuretic hormone (ADH), which is synthesized in the hypothalamus, is secreted by the posterior pituitary gland, and acts

in the renal collecting duct to increase free-water reabsorption [1–3].

The syndrome of inappropriate antidiuretic hormone excess (SIADH) is the most common cause of euvoletic hyponatremia [8]; it is caused by central nervous system disorders (stroke, trauma, tumors, and others), drugs (antidepressants, anticonvulsants, antipsychotics, anti-cancer agents, and others), malignancies, pulmonary diseases, pain, or stress of various etiologies [1–3]. Other causes of euvoletic hyponatremia include adrenal insufficiency, hypothyroidism, and high water and low solute intake. There are 6 essential and 7 supplemental diagnostic criteria for SIADH [2]; rigorous SIADH diagnosis requires all essential criteria to be met, but in everyday clinical practice the frequency of adequate diagnostic testing is low [8] and many cases are probably falsely labeled. Most importantly, available treatment options for SIADH-induced hyponatremia are few and with limited efficacy. A recent analysis of 1,524 patients with serum sodium ≤ 130 mEq/L diagnosed clinically as SIADH from 146 US and 79 European sites indicated that the most common monotherapy treatments for this condition were fluid restriction (48%) and isotonic saline (27%), but

they failed to increase the serum sodium by ≥ 5 mEq/L in 55% and 64% of episodes, respectively [9]. Other treatments include vasopressin receptor antagonists (e.g., tolvaptan), which are expensive and may overcorrect serum sodium, and urea, which is poorly tolerated [2, 10, 11]. Overall, treatment outcomes are rather poor with serum sodium at discharge < 135 mEq/L in 75% and ≤ 130 mEq/L in 43% of patients, while overly rapid correction occurs in approximately 10% [9].

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors are oral hypoglycemic agents, acting through blockade of the SGLT-2 protein; this is a high-capacity/low-affinity glucose transporter located in the S1 segment of renal proximal tubules and being responsible for 90% of glucose reabsorption. In diabetic patients, an increase up to 3-fold in the expression of SGLT-2 is observed, leading to 20% higher rate of glucose reabsorption at time when the body is already suffering from excess blood glucose. SGLT-2 inhibition results in excretion of 50–60% of the filtered glucose, roughly corresponding to 60–100 g/day [12, 13]. This mode of action is associated with other benefits, including weight loss of around 2–4 kilograms and systolic/diastolic blood pressure reductions of 4–5/2–3 mm Hg, following a mild natriuretic effect [14]. Accumulated evidence from major trials clearly demonstrates that SGLT-2 inhibitors are potent cardioprotective and nephroprotective agents, offering reductions of up to 38% in cardiovascular mortality, 35% in heart failure hospitalization, 45% in progression of renal disease, and 30% in all-cause mortality [13, 15]. They are also generally well tolerated, with the most frequent adverse event being genital mycotic infections and the most serious the rare development of euglycemic ketoacidosis. Following the above findings, SGLT-2 inhibitors are currently recommended after metformin for patients with type 2 diabetes, cardiovascular disease, chronic kidney disease, or heart failure [13, 15].

As glucosuria leads to osmotic diuresis and consequently increased excretion of free-water, investigators hypothesized that SGLT-2 inhibitors could help SIADH patients without major adverse effects. In a pilot crossover study in 14 healthy volunteers with desmopressin-induced SIADH, a single tablet of empagliflozin 25 mg increased total urine output (579.3 vs. 367.3 mL, $p = 0.017$) due to glucosuria (74.18 vs. 0.12 mmol, $p < 0.001$) 2–8 h after drug administration compared to placebo [16]. In a recently reported trial, the same authors randomized 88 hospitalized patients with SIADH-induced hyponatremia to empagliflozin 25 mg or matching placebo once daily for 4 days in addition to standard fluid

restriction of 1,000 mL/day [17]. The authors rigorously defined SIADH-induced hyponatremia as clinically assessed euvoolemia, plasma osmolality < 275 mmol/kg, urine osmolality > 100 mmol/kg, and urine sodium > 30 mmol/L, with exclusion of hypothyroidism and hypocortisolism. Among exclusion criteria, hyponatremia with severe symptoms in need of treatment with 3% sodium chloride solution, renal impairment, hepatic impairment, and systolic blood pressure < 90 mm Hg were listed. At study end, a significantly higher median increase in plasma sodium concentration of 10 mmol/L (IQR, 5–12) with empagliflozin versus 7 mmol/L (IQR, 3–11) with placebo was noted ($p < 0.04$). The proportion of patients with plasma sodium ≥ 130 mmol/L was 87 and 68% in empagliflozin and placebo arms, and the relevant proportions of normal plasma sodium at discharge were 48 and 36%, respectively. Interestingly, at day 2 the mean serum sodium was already above 130 mmol/L, without differences between groups.

These results are relatively promising, especially as they come from a double-blind, placebo-controlled trial. However, some limitations need to be mentioned. First, the study involved hospitalized patients who had hyponatremia; however, the reason for admission (i.e., hyponatremia vs. others) is not specified. Second, the treatment period was only 4 days; thus, the mid- or long-term efficacy of this intervention cannot be established. Third, at discharge only 48% of empagliflozin-treated patients were normonatremic. Whether a difference of 3 mmol/L between treatments with $> 50\%$ of actively treated patients being hyponatremic is clinically important is debatable. Fourth, free-water clearance was not assessed; that is, the authors could rather not conclusively support their main hypothesis. Thus, current knowledge from major trials that empagliflozin is a generally mild diuretic not substantially altering free-water clearance and $[\text{Na}^+]$ in the long term [15] is not disproven. Finally, the investigators did not further define “clinical euvoolemia,” “renal impairment,” or “hepatic impairment”. Throughout the manuscript, serum creatinine/estimated glomerular filtration rate, liver enzymes, or other measures of renal or hepatic function are not provided. Furthermore, there is no assessment and exclusion of heart failure, a major cause of hyponatremia associated with decreased free-water clearance. The mean age of the population was 75 years, and almost 75% of patients had cardiovascular disease. Weight loss on empagliflozin (estimated from median weights) was around 3.2 kg in 4 days versus an increase of 1.1 kg in placebo patients. While no hypotensive events were observed on empagliflozin, 2 placebo patients had an or-

thostatic collapse. The good tolerance of such weight loss in the active group argues against baseline euvoolemia. With such characteristics and with poor population description, one can assume that other common causes of hyponatremia, such as undiagnosed heart failure, could be present in the population.

There are multiple instances of drug repurposing that have happened largely by chance. For example, sildenafil became an established treatment for erectile dysfunction after erections were identified as a side effect in phase 1 cardiovascular trials [18]. Another example is the antihypertensive minoxidil reformulated into a topical cream after patients treated with this drug reported hair regrowth. Such repurposing successes have driven more targeted approaches to find new indications for existing or failed drugs. These include detailed knowledge of the mode of action. As such, the SGLT-2 inhibitors could po-

tentially become a novel treatment for SIADH. However, as our critique of the emerging literature demonstrates, there is still a considerable way to go before these agents are routinely used for this indication. To paraphrase Goethe, let us not get carried away just yet.

Conflict of Interest Statement

P.S. is an advisor/speaker to Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Elpen Pharmaceuticals, Genesis Pharma, Menarini, Innovis Pharma, and Winmedica and has received research support for an investigator-initiated study from AstraZeneca. A.O. is a consultant for Sanofi Genzyme and had received speaker fees from Shire, Amicus, Amgen, Otsuka, Mundipharma, Fresenius Medical Care, Kyowa-Kirin, AstraZeneca, and Menarini. C.J.F. is an advisor/speaker to Amgen and Vifor.

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