Treatment with dapagliflozin in pediatric patients with heart failure in four different etiologies: A case series

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INTRODUCTION

Sodium-glucose cotransporter type 2 (SGLT2) inhibitors are an essential part of treatment in adult patients with heart failure (HF). According to the latest European Society of Cardiology HF guidelines, therapy with dapagliflozin or empagliflozin is a category I A recommendation in patients with HF regardless of left ventricular ejection fraction (LVEF) [1, 2]. In addition, it should be noted that SGLT2 inhibitors are well-tolerated, have few side effects, and do not substantially interact with many drugs.

The results of studies regarding the use of SGLT2 inhibitors in other indications, specifically diabetes mellitus type II, metabolic disorders and inherited proteinuric kidney disease, indicate that they can be used safely in pediatric patients [3–6]. Due to the prevalence of the use of SGLT2 inhibitors in the adult HF population, and remarkably good results, we decided to include these drugs in the treatment of HF in selected pediatric patients.

METHODS

We present the cases of 4 patients with HF of different etiologies in whom dapagliflozin was included in the treatment strategy. All parents and patients aged over 16 gave informed consent for the inclusion of off-label treatment.

Patient 1

A 6-year-old boy with Williams syndrome, heart failure with reduced LVEF (HFrEF), dilation of left ventricle (LV), supravalvular aortic stenosis, obstructed left main coronary artery, ventricular arrhythmias in the history and pulmonary hypertension of mixed etiology (pre- and post-capillary), was admitted to the Department of Pediatric Cardiology for modification of HF treatment. At 3 months of age, signs of enlargement of LV with symptoms of HF were observed. In April 2023, echocardiography showed an LVEF of 28%. From May 2023, HF symptoms progression was observed. The boy had become lethargic, and any physical activity was associated with severe fatigue (New York Heart Association III/IV ambulatory class). During several episodes of exacerbation with fluid retention, the boy required the use of albumin parenterally. In July 2023, the patient developed fainting of cardiogenic origin. The boy was treated with sacubitril/valsartan, carvedilol, spironolactone, furosemide and molsidomine. During hospitalization in August 2023, echocardiography showed LVEF of 23%. Laboratory tests indicated elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP), urea, cystatin-C, gamma-glutamyl transferase, bilirubin, international normalized ratio, troponin, hemoglobin A1C and uric acid (Table 1). HF treatment was modified by adding dapagliflozin. No side effects were observed, and the tolerance to the SGLT2 inhibitor drug was good.

Since the modification of HF pharmacotherapy, the parents have noticed an improvement in the boy's general condition. He has been more active, more willing to play, and better tolerated physical exertion. Three weeks later, during a follow-up hospitalization, LV systolic function improved, with LVEF of 29%–31%. NT-proBNP concentration increased despite the improvement in clinical status. This is probably related to the high

Table 1. Baseline characteristics of patients

	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	6	17	13	17
Sex	Male	Male	Male	Male
Type of HF	HFrEF	HFrEF	HFpEF	HFrEF
Cardiovascular disease	Dilated cardiomyopathy, supravalvular aortic stenosis, obstructed left coronary artery trunk, ventricular arrhythmias, pulmonary hypertension	Aortic stenosis after balloon aortic valvuloplasty (2006), bioprosthetic aortic valve replacement (2022), aortic valve prosthesis dislocation and replacement to mechanical valve prosthesis (2022), two mechanical prosthesis repair surgeries (April and May 2023), and third-degree atrioventricular block	Hypertrophic cardiomyopathy	Pulmonary artery atresia with VSD after biventricular repair with xenograft (May 2007), with pulmonary graft stenosis, and occluded left pulmonary artery
Follow-up period, months	1	9	5	1
Symptoms before	Severe fatigue, increased sweating and periodic swelling of lower limbs and face, NYHA III/IV	Severe condition, cachectic, NYHA III/IV	Reduced exercise tolerance and dyspnea on climbing to second floor, NYHA II/III	Increased fatigue, decreased exercise tolerance, dyspnea during climbing to first floor, NYHA II/III
Symptom changes	Improved exercise tolerance, more active, cheerful, willing to play, NYHA II/III	Improved exercise tolerance, NYHA II	No improvement, NYHA II/III	Increased exercise tolerance and decreased fatigue, NYHA II
LVEF before, %	23	29	60	30
LVEF after, %	28–29	50–54	50	46
NT-proBNP before, pg/ml	28 713.4	3084.6	26 328.2	972.0
NT-proBNP after, pg/ml	32 043.0	441.2	23 066.6	647.9

Abbreviations: HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced left ventricular ejection fraction; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; VSD, ventricular septal defect

variability of NT-proBNP levels in the clinical history of this patient.

Patient 2

A 17-year-old boy with HFrEF and aortic stenosis was admitted to the Pediatric Cardiology Department to continue treatment after mechanical valve repair in the Cardiothoracic Surgery Department. Medical history included balloon aortic valvuloplasty (2006), bioprosthetic aortic valve replacement (2022), aortic valve prosthesis dislocation and replacement to mechanical valve prosthesis (2022), 2 mechanical prosthesis repair surgeries (April and May 2023), and third-degree transient atrioventricular block. The patient was treated with acenocoumarol, metoprolol, ivabradine, sacubitril/valsartan and torasemide. In June 2023, after surgery the patient was admitted in severe condition. Tests showed significantly decreased LV contractility with LVEF of 29%, and hypokinesis of the basal segments of the interventricular septum with normal function of the aortic prosthesis. Laboratory tests showed significantly elevated NT-proBNP and anemia (Table 1). During the 30-day hospitalization, HF treatment was intensified. Dapagliflozin was initiated with good tolerance. The patient's general condition gradually improved during hospitalization, and LVEF slightly improved to 33%. During follow-up hospitalization after one month, LVEF was 35% (August 2023), after two months it was 40% (September 2023), after 4 months it was 48% (November 2023), and after nine months it had reached 50%–54% (April 2024). Additionally, exercise tolerance improved.

Patient 3

A 13-year-old boy with heart failure with preserved ejection fraction and hypertrophic cardiomyopathy (HCM), PRKAG2 gene mutation, after implantable cardioverter-defibrillator implantation for primary prevention, sinus node dysfunction, ventricular and supraventricular arrhythmias was admitted for modification of HF treatment. The patient was taking metoprolol and spironolactone. The boy reported chronically reduced exercise tolerance and dyspnea (New York Heart Association II/III). Echocardiography showed massive myocardial hypertrophy of the apical part of the right ventricular (RV) and the LV; interventricular septum was 44 mm (Z-score 8.15), LV posterior wall was 36 mm (Z-score 9.03). LVEF was estimated at 60%. Laboratory tests showed significantly elevated NT-proBNP and cystatin-C levels (Table 1).

During the hospitalization, dapagliflozin and hydrochlorothiazide were included, with good tolerance. Two and five months later respectively, there was no improvement in clinical condition, and the boy was qualified for heart transplantation.

Patient 4

A 17-year-old boy with a congenital heart defect in the form of pulmonary artery atresia with ventricular septal defect, after biventricular repair with xenograft (May 2007), with pulmonary graft stenosis, occluded left pulmonary artery, enlarged RV, and HFrEF *de novo,* was admitted to the cardiology clinic for a planned assessment. The boy also had a history of attention deficit hyperactivity disor-

der, epilepsy, and asthma, and was taking spironolactone and acetylsalicylic acid. Magnetic resonance imaging from September 2023 showed LVEF of 27%, RV hypokinesis and hypertrophy, moderate tricuspid and pulmonary valve regurgitation, pulmonary graft stenosis, and no flow in the left pulmonary artery. In January 2024, the patient had an episode of fainting. He reported increased fatigue, decreased exercise tolerance, and dyspnea. The following month, echocardiography showed LV hypokinesis with LVEF of 30%. Laboratory tests showed elevated NT-proBNP levels (Table 1). Treatment for HF was modified by adding lisinopril, dapagliflozin, and carvedilol, and increasing the dose of spironolactone. During hospitalization, after 9 days LVEF improved to 38%–40%. In addition, right heart catheterization was performed, which confirmed the pulmonary xenograft stenosis. Due to the risk of compression of the right coronary artery, stent implantation was abandoned, and the patient was qualified for a hybrid procedure.

After one month of treatment, echocardiography showed an improvement in LVEF to 46%. In addition, the boy reported increased exercise tolerance and decreased fatigue. A pulmonary artery xenograft replacement procedure was performed. After that procedure and rehabilitation, LVEF was 45%.

RESULTS AND DISCUSSION

The cases reported above show that dapagliflozin is well tolerated in pediatric patients with HF. Some of them could benefit from this treatment, but there is still a lack of trials which would influence the eventual guidelines.

In the pediatric population, SGLT2 inhibitors have been used to treat diabetes mellitus type II, inherited proteinuric kidney disease, glycogen storage disease type Ib, glucose-6-phosphatase catalytic subunit 3 deficiency, and severe congenital neutropenia type 4 [3–6].

In the literature, there is only one study proving the usefulness of dapagliflozin in HF in children [7]. Newland et al. [7] included 26 patients with dilated cardiomyopathy, one patient with restrictive cardiomyopathy, 4 patients with diastolic HF, and 7 single ventricle patients.

In the adult population, there is evidence of the SGLT2 inhibitors' efficiency in treating HF with congenital heart disease, including patients with Fontan circulation [8, 9]. A recent study on diabetic patients with preserved LVEF demonstrated an improvement in LV strain parameters after treatment with SGLT2 inhibitors [10]. It is important to highlight that the etiology and course of HF differ between children and adults. This might impact SGLT2 inhibitors' effectiveness, though the mechanism by which this happens is not yet fully understood.

The effectiveness of SGLT2 inhibitors has not been proven in HCM without reduced ejection fraction [11]. The effect of treatment with SGLT2 inhibitors may depend on the type of mutations causing HCM [12]. In this group of patients, treatment with mavacamten and qualification for heart transplantation should be considered [11].

The results of our research indicate that dapagliflozin may be a promising treatment option for pediatric patients with HF caused by different etiologies. However, due to the study's limitations, particularly the small number of patients, further research is needed to confirm the efficacy of SGLT2 inhibitors in the pediatric HF population.

Article information

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