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Cardiovascular Side Effects of Low-dose Fenfluramine Treatment in Dravet Syndrome: A Prospective Echocardiographic Pilot Study

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INTRODUCTION

- Dravet syndrome (DS) is a severe, therapy-resistant epilepsy syndrome that typically presents in the first year of life[1]
- Fenfluramine (FFA) appears to have antiepileptic activity based on a retrospective chart review of 12 DS patients treated under a Belgian Royal Decree[2]
  - In this original cohort of patients, 7 of the 10 patients who were still receiving FFA at the end of 2010 had been seizure-free for periods of 1 to 19 years
- FFA, which was originally approved as an anorectic agent for treatment of obesity, was withdrawn from the market in 1997 because of reports of cardiac valvulopathy and pulmonary hypertension, often while being used at high doses and in combination with phentermine[3]
- In our original cohort of patients, who were treated with FFA for a mean of 11 years and 4 months, only 2 patients exhibited a mild thickening of one or two cardiac valves without clinical significance
- Here we present the results of serial echocardiographic examinations in a new cohort of DS patients treated with low-dose, add-on FFA and followed prospectively using a standardized protocol of assessments

METHODS

- Key inclusion criteria included: patients between 6 months and 50 years of age with a diagnosis of DS
- Key exclusion criteria included: cardiovascular disease including cardiac valvulopathy, hypertension, and glaucoma
- Echocardiography was performed before starting FFA, every 3 months during the first year, every 6 months during the second year, and annually thereafter
  - Standardized valvular scoring systems were used for the evaluation of valvular regurgitation and restrictive function
  - Systolic pulmonary artery pressure was derived from the tricuspid regurgitant jet
  - The presence of pulmonary hypertension was further examined by echocardiography through a quantitative assessment of cardiac hemodynamics, chamber size, and function

RESULTS

- Seven DS patients have enrolled in this cohort since the beginning of 2010, all of whom had confirmed *SCN1A* mutations
- Patient characteristics and FFA dosing history are presented in **Table 1**
- All patients were treated with low-dose FFA (5 to 15 mg/day [0.10 to 0.69 mg/kg/day]) for a median treatment duration of 0.9 years (range 0.2 to 3.9 years)
- During the 90-day run-in period the median frequency of TC seizures was 3.0 per month (range 0.4 to 39.7)
  - Over the entire observation period the median frequency of TC seizures was 0.9 per month, representing an 84% reduction compared to the 3-month run-in period

Table 1. Patient Characteristics and Fenfluramine Dosing History

Parameter	Value
Gender	
Male, n (%)	5 (71%)
Female, n (%)	2 (29%)
Age when starting FFA, years (median (min, max))	11.9 (1.2, 20.3)
Current age, years (median (min, max))	14.5 (5.4, 20.9)
Starting FFA dose, median mg/day (median mg/kg/day)	10 (0.25)
Current FFA dose, median mg/day (median mg/kg/day)	10 (0.27)
Duration of FFA treatment, years (median (min, max))	0.9 (0.2, 3.9)
Cumulative dose of FFA, mg (median (min, max))	3900 (900, 18750)

- The summary of cardiovascular assessments is shown in **Table 2**
- During the observation period all echocardiographic examinations remained normal without signs of valvulopathy, pulmonary hypertension, or other abnormalities

Table 2. Cardiovascular Assessments

Patient #	Gender (M/F)	Current age (yr)	Current weight (kg)	Age at start of FFA (years)	Starting dose FFA (mg/day)	Current dose FFA (mg/day)	Duration of treatment (years)	Number of echocardiography examinations*	Echocardiography findings	Signs suggestive of pulmonary HTN** (Y/N)
1	M	16	37.5	11	10	10	3.9	8	Normal	N
2	F	5	18.1	1	5	12.5	3.6	7	Normal	N
3	M	6	16	5	5	7.5	0.2	2	Normal	N
4	M	13	39.5	11	10	15	0.9	3	Normal	N
5	F	14	52	13	5	10	0.8	4	Normal	N
6	M	20	43.5	19	10	10	1.0	5	Normal	N
7	M	20	59	20	10	10	0.5	2	Normal	N

F, female; FFA, fenfluramine; HTN, hypertension; M, male; M/F, male/female; Y/N, yes/no.
*Echocardiography performed within interval of 3 months before the start of FFA treatment or during the study.
**Assessed by echocardiography according to international expert consensus on the use of echocardiography for assessment of pulmonary hypertension.

CONCLUSIONS

- In this new cohort of DS patients, treatment with low-dose FFA (<20 mg/day) for periods of up to 4 years did not result in echocardiographic or clinical signs of cardiac valve abnormalities or pulmonary hypertension
  - These findings extend the CV safety observations noted in the original cohort published in 2012[2]
- FFA may represent an effective antiepileptic drug for patients with DS
- Randomized, placebo-controlled Phase 3 trials are currently planned to confirm the efficacy and safety observations from both cohorts of Belgian patients

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DISCLOSURE

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