Low-dose Fenfluramine Significantly Reduces Seizure Frequency in Dravet Syndrome: Update of the Prospective Study

An-Sofie Schoonjans,1 Fabienne Marchau,2 Bernard Paelinck,3 Boudewijn Gunning,4 Arnold Gammaitoni,5 Brad Galer,6 Lieven Lagae,7 Berten Ceulemans1

1Department of Neurology – Paediatric Neurology, Antwerp University Hospital, University of Antwerp, Antwerp, Belgium; 2Department of Paediatric Cardiology, Antwerp University Hospital, University of Antwerp, Antwerp, Belgium; 3Department of Cardiology, Antwerp University Hospital, University of Antwerp, Belgium; 4Stichting Epilepsie Instellingen Nederland SEIN, Zwolle, The Netherlands; 5Zogenix, Inc., Emeryville, CA, USA; 6Department of Development and Regeneration, Section Paediatric Neurology, University Hospitals Gasthuisberg, Leuven, Belgium

INTRODUCTION

- Dravet syndrome (DS) is a rare, severe, and often drug-resistant epilepsy syndrome
- Typically presents in the first year of life with initial seizures being clonic, generalized, or unilateral
- The incidence is estimated to be 1 in 15,700 to 1 in 40,000 live births
- Mutations in the SCN1A gene, which encodes the alpha subunit of the type 1 voltage-gated sodium channel, have been found in about 80% of DS patients

- Low-dose fenfluramine has been reported to reduce seizure frequency in a group of 10 DS patients who have been treated for 7 to 28 years
- We have recently reported similar findings in a new cohort of 9 DS patients treated with low-dose fenfluramine, a prospectively randomized, double-blind, placebo-controlled study using a standardized protocol of assessments
- Here we present an update on the results of this study

METHODS

- Patients with diagnosis of DS (with or without SCN1A mutation) between the ages of 6 months and 50 years were included
- Patients with cardiovascular disease, including cardiac valvulopathy and drug-treated hypertension, were excluded
- Following a 3-month run-in period, fenfluramine was added to each patient’s current antiepilepsy drug regimen at a dose of 0.5 to 1.0 mg/kg/day (maximum dose, 20 mg/day)
- The incidence of major motor seizures (tonic, tonic-clonic, clonic, atonic, and myoclonic seizures lasting >30 sec) in both the run-in and treatment periods was recorded in a seizure diary
- To assess cardiovascular safety, echocardiographic examinations were performed at baseline, every 3 months during the first year of fenfluramine treatment, every 6 months during the second year of fenfluramine treatment, and annually thereafter

RESULTS

- Demographics
- RESULTS
- Seizure frequency
- Median frequency of major motor seizures was 15.0/month during the run-in period (Table 1, Figure 1)
- All patients demonstrated a decrease in frequency of major motor seizures that was evident as early as 3 months, with sustained benefit noted at 1 year (Table 1, Figure 1)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age at Start of FFA (years)</th>
<th>Height at Start of FFA (cm)</th>
<th>Weight at Start of FFA (kg)</th>
<th>Mutation in SCN1A</th>
<th>Initial FFA Treatment Regimen at Study Entry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>11.9</td>
<td>144</td>
<td>35</td>
<td>De novo nonsense mutation (c.4484A&gt;G)</td>
<td>VPA, CBZ, VNS</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>1.2</td>
<td>78</td>
<td>10</td>
<td>De novo missense mutation (c.897G&gt;A)</td>
<td>VPA, TPM, CBZ</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>5.9</td>
<td>107</td>
<td>17</td>
<td>De novo splice site mutation (c.4287-4289+5del)</td>
<td>CBZ, VPA, VPA, TPM</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>11.9</td>
<td>149</td>
<td>40</td>
<td>De novo duplication (c.3427+4027+4028del)</td>
<td>SB, VPA, TPM</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>13.5</td>
<td>164</td>
<td>30</td>
<td>De novo frameshift mutation (c.657-658insACG)</td>
<td>VPA, TPM, CBZ, VPA, TPM</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>19.8</td>
<td>168</td>
<td>48</td>
<td>De novo splice site mutation (c.5815_5816+del)</td>
<td>VPA, LEV, CBZ, VPA</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>20.3</td>
<td>160</td>
<td>60</td>
<td>De novo splice site mutation (c.2283+3A→G)</td>
<td>VPA, CBZ, CBZ, VPA</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>7.2</td>
<td>124</td>
<td>24</td>
<td>De novo frameshift mutation (c.637-638insACG)</td>
<td>VPA, TPM, CBZ, VPA</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>29.6</td>
<td>162</td>
<td>64</td>
<td>De novo splice site mutation (c.361+8C→T)</td>
<td>VPA, CBZ, TPM, CBZ</td>
</tr>
</tbody>
</table>

- CONCLUSIONS
- The results of this latest analysis of the new cohort suggest that low-dose fenfluramine provides significant improvement in seizure frequency while being generally well tolerated in DS patients
- When looking at month-by-month effectiveness, 7 of 9 patients experienced a ≥50% reduction in seizure frequency for at least 80% of the months they were being treated
- The effectiveness and safety of low-dose fenfluramine as add-on therapy for DS in the new prospective cohort supports previous findings

ACKNOWLEDGEMENTS

This study is supported by Zogenix, Inc. (Emeryville, CA, USA). The authors received professional medical writing and editorial assistance in the preparation of this presentation that was provided by Edward W. Koulos, PhD, of PharmaCore, LLC (Princeton, NJ, USA) and was funded by Zogenix, Inc.

REFERENCES

5. Schoonjans AN, Tomacchiori I, Baxtkoff N, Baxtkoff L. Long-term efficacy and safety of low-dose fenfluramine treatment in Dravet syndrome: Follow-up of the original patient cohort. Presented as part of the 2016 Scientific Exhibit during the 73rd Annual Meeting of the American Epilepsy Society, December 2-6, 2016, Houston, TX.

Presented at the 70th Annual Meeting of the American Epilepsy Society, December 2-6, 2016, Houston, TX.