Epilepsia, 53(7):1131–1139, 2012
doi: 10.1111/j.1528-1167.2012.03495.x

FULL-LENGTH ORIGINAL RESEARCH

Successful use of fenfluramine as an add-on treatment for Dravet syndrome

***†Berten Ceulemans, †‡Marc Boel, *Katrien Leyssens, *Carolin Van Rossem, §Pieter Neels, ¶Philippe G. Jorens, and †‡Lieven Lagae**

***Department of Neurology-Pediatric Neurology, Antwerp University Hospital, University of Antwerp, Edegem, Belgium; †Epilepsy Center for Children and Youth, Pulderbos, Belgium; ‡Department of Pediatric Neurology, University Hospitals Leuven, University of Leuven, Leuven, Belgium; §Federal Agency for Medical and Health Products, Brussels, Belgium; and ¶Department of Clinical Pharmacology, Antwerp University Hospital, University of Antwerp, Edegem, Belgium**

Summary

Purpose: Despite the development of new antiepileptic drugs, Dravet syndrome frequently remains therapy resistant and is a catastrophic epilepsy syndrome. Fenfluramine is an amphetamine-like drug that has been used in the past as a part of antiobesity treatments. Because of the possible cardiac adverse effects (valve thickening, pulmonary hypertension) associated with use of fenfluramine, it was withdrawn from the market in 2001. In Belgium, a Royal Decree permitted examination of the potential anticonvulsive effects of fenfluramine in a clinical trial consisting of a small group of patients diagnosed with Dravet syndrome.

Methods: Herein, we report 12 patients, 7 female and 5 male, with a genetically proven (11 of 12) diagnosis of Dravet syndrome who received fenfluramine as add-on therapy.

Key Findings: Their ages at their last evaluation ranged from 3–35 years. The mean dosage of fenfluramine was 0.34 (0.12–0.90) mg/kg/day. Exposure duration to fenfluramine ranged from 1–19 years. Seven of the patients who were still receiving the fenfluramine treatment at the time of the last visit had been seizure-free for at least 1 year. In total, patients had been seizure-free for a mean of 6 (1–19) years. In seven patients, the fenfluramine treatment was interrupted once during the follow-up; seizures reappeared in three of the seizure-free patients. Subsequent reintroduction of fenfluramine controlled the seizures in these three patients again. Only two patients exhibited a mild thickening of one or two cardiac valves without clinical significance.

Significance: Compared with a recent long-term follow-up series in which a maximum of 16% of patients with Dravet syndrome were seizure-free, our result of 70% of patients with Dravet syndrome remaining seizure-free is noteworthy. Given the limitations of this observational study, a larger prospective study should be undertaken to confirm these promising results.

KEY WORDS: Dravet syndrome, Severe myoclonic epilepsy in infancy, *SCN1A*, Fenfluramine, Orphan drugs.

Dravet syndrome (OMIM 607208), or severe myoclonic epilepsy in infancy (SMEI), is a rare and malignant epileptic syndrome that was first described in 1978 (Dravet). Incidence rates among lives births have been reported to range from 1/20,000 to 1/40,000 (Hurst, 1990; Yakoub et al., 1992; Akiyama et al., 2010). More recently, the rate of Dravet syndrome among Spanish children <15 years old with epilepsy was reported to be 1.4% (Dura-Trave et al., 2007). This type of epilepsy typically has an onset during the first year of life in previously healthy children. The duration of the first seizure, most commonly provoked by fever, is variable but is typically longer than classic febrile convulsions (Harkin et al., 2007). Initially, the seizures are generalized or unilateral with a clonic or tonic–clonic component. During the next years, other types of seizures appear that are not always provoked by fever. In the first years of the syndrome, the electroencephalography (EEG) of all patients remains normal; however, later, there is a slowing of the background while generalized and focal epileptic activity becomes visible. Photosensitivity has been observed in up to 42% of patients.

In 2001, a mutation in the neuron-specific voltage-gated sodium channel *SCN1A* was discovered as a cause for Dravet syndrome (Claes et al., 2001). Since this discovery, the relationship between Dravet syndrome and *SCN1A* has been widely recognized.

The overall result of treatment for the seizures is still disappointing (Dravet et al., 2005). Herein, we report a promising clinical outcome in 12 patients with Dravet syndrome after an addition of fenfluramine to their treatment, which was previously used to treat obesity but has since been pulled from the market due to cardiac risks. These data

Accepted March 8, 2012; Early View publication May 3, 2012.
Address correspondence to Berten Ceulemans, MD, PhD, Department of Neurology – Pediatric Neurology, Antwerp University Hospital, University of Antwerp, Wilrijkstraat 10, B 2650 Edegem, Belgium. E-mail: berten.ceulemans@uza.be

illustrate that the positive effects of fenfluramine on this catastrophic epilepsy syndrome may outweigh the known cardiovascular risks.

Methods

Fenfluramine is an amphetamine-like drug that was part of the popular ''Fen–Phen'' combination antiobesity medication (Spencer et al., 2000). Following the general use of this combination, serious adverse effects were described, especially heart valve disease and pulmonary hypertension (McCann et al., 1997; Dahl et al., 2008; Connolly et al., 2009). These findings led to the withdrawal of the product from the U.S. and European markets in 1997. Based on a small study (Boel & Casaer, 1996) in Belgium, prescription of fenfluramine as an antiepileptic medication for refractory epileptic seizures was allowed by Royal Decree in a clinical trial (KB 2002/22215). Until now, only one such clinical trial has been evaluated and approved by an ethical committee (Antwerp University Hospital: registration number B3002010 8998). As described in the current study, administration of fenfluramine was allowed in this open trial as an add-on treatment for patients with Dravet syndrome and was distributed by the Epilepsy Center for Children and Youth in Pulderbos. Once identified for inclusion in this study, the patients were seen twice a year. The treatment efficacy, based on an individualized seizure diary (filled in by parents or caretakers), antiepileptic drug changes, and side effects were noted. The patients underwent a full clinical examination, a cardiac examination (clinical and ultrasound) at least yearly, a routine blood examination, including evaluation of liver and kidney function, a hemogram and a measurement of the levels of AEDs in the blood if appropriate. In 2010, the files of the included patients were reviewed and summarized. All patients still on fenfluramine underwent a 4-h EEG inclusive intermittent light stimulation (ILS). For this retrospective analysis, seizure freedom was defined as the occurrence of no seizures within the year before the final visit in 2010.

Results

Twelve patients, seven female and five male, were included in this study (Tables 1 and 2). All patients fulfilled the diagnostic criteria for Dravet syndrome as described by the International League Against Epilepsy (ILAE) in 1989 (Commission 1981) and displayed the ''core Dravet syndrome phenotype,'' as described recently by Dravet (Dravet et al., 2011).

Five of the 12 patients (Patients 1–5) were described previously in Boel & Casaer, (1996). These five patients were reported to have self-induced seizures and were treated with fenfluramine. After reviewing their files and performing genetic analysis, they were diagnosed with Dravet syndrome.

The other seven patients who were diagnosed with Dravet syndrome had uncontrolled seizures and were followed up prospectively. Their follow-up period lasted between 1 and 11 years.

In 11 patients, a mutation in *SCN1A* was found: 4 with truncating mutations and 7 with missense mutations. Six of the seven missense mutations were in the important voltage or pore regions S4 – S6 of *SCN1A*. One was in the c-terminal part of the gene. All of the mutations were de novo except two missense mutations, which were inherited. The two patients with these missense mutations were diagnosed with Dravet syndrome in a generalized epilepsy with febrile seizures plus (GEFS+) family. In one patient (Patient 6), sequence analysis could not demonstrate a pathogenic mutation in *SCN1A*. Copy number variations of *SCN1A* and mutation analyses of protocadherin 19 (*PCDH19*) were negative.

The mean age of the patients at the time of evaluation in 2010 was 19 years, but ages ranged widely from 3–35 years. All patients had a typical history of Dravet syndrome, including an initial fever that provoked long-lasting convulsions between the ages of 3 and 12 months. As expected, all patients were unresponsive to treatment and presented multiple seizure types. Inspection of the files and reinterview with the parents from Patients 1, 2, and 3 confirmed, and this especially in the older patients, that most major AEDs were tried, including the channel blockers. The data are shown in Table 1. None of the patients received bromide, ketogenic diet, or vagus nerve stimulation. In the year before the start of fenfluramine treatment, all patients had generalized tonic–clonic seizures, and seven patients also had myoclonic seizures. Four patients had partial seizures, and four patients had atypical absence seizures. Five patients still had frequent status epilepticus episodes in the year before inclusion. Daily seizures were observed in two patients, weekly seizures in five patients, and monthly seizures in three patients. Two patients had only a few seizures per year. At the time of the last evaluation, all patients were mentally retarded: one mild, four moderate, and seven severe.

The mean age at which fenfluramine was started was 8 (1–16) years. Fenfluramine was prescribed in rather small dosages, with a mean of 0.34 (0.12–0.90) mg/kg/day. In all patients, fenfluramine was combined with valproate. Nine patients received at least triple combination therapy. Six patients were treated with topiramate and benzodiazepines (clobazam, lorazepam, or ethyl loflazepate), two patients were treated with lamotrigine, and one patient was treated with levetiracetam and ethosuximide. Once the patients became seizure-free, the medication was no longer changed.

The mean follow-up duration after the introduction of fenfluramine was 11 years and 4 months, with a range of 1–22 years.

Fenfluramine had been stopped in two patients before this last visit. In one of these patients (Patient 7), the medication was discontinued due to a lack of effect on seizure

Table 1. Overview of all included patients with Dravet syndrome

	Age	Sex	Mutation/ copy number variations *SCN1A*/ localization	Seizure type/ frequency 1 year before start of fenfluramine	Previous medication	Mental retardation	Age at start of fenfluramine	Follow-up duration	Doses fenfluramine at last FU	AED combined with fenfluramine	% Reduction of seizures at last FU (years SF)	Four-hour EEG	Weight (kg)/ length (cm) (percentiles)	Side effects	Cardio control within the last year
1	25 y	F	Truncating	TC/w	PB, VPA, PHT, CBZ, NZP, CZP, LEV	Severe	2 y 2 m	22 y	2 × 5 mg 0.12 mg/kg/d	VPA-TPM	75% reduction	BA normal No epileptic activity ILS negative	87.6/173 P 97/P 75	Fatigue	N
2	35 y	F	Missense DII S4-S5	TC/w	PB, VPA, CZP, CBZ, PHT, VGB, Loreclezole, Prominal	Moderate	16 y	19 y	2 × 10 mg 0.26 mg/kg/d	VPA	100% (13 y)	BA normal No epileptic activity ILS negative	75.5/154.5 P 90/P 3		N
3	26 y	M	Missense DII S5–S6	TC-SE-Abs./w	VPA, Prominal, Loreclezole, VGB, CBZ, ETS, CZP, CLB, PHT, PB	Severe	7 y	19 y	2 × 10 mg 0.28 mg/kg/d	VPA	100% (19 y)	BA normal No epileptic activity ILS negative	72/190 P 50/P 90	Excessive sleep	Thickening AV
4	21 y	M	Truncating	M-TC/w	PB, VPA, CBZ, VGB, CLB, PHT, Loreclezole	Severe	4 y	17 y	2 × 10 mg 0.37 mg/kg/d	VPA-LEV-CLB-LTG	0%	BA too slow No epileptic activity ILS negative	54/170 <P 3/P 3–10		N
5	17 y	M	Missense DI S4	M-TC-at. Abs/m	PB, PHT, VPA, LTG, TPM, CLB, CZP, ethylloflazepate	Severe	1 y 4 m	16 y	2 × 5 mg 0.27 mg/kg/d	VPA-TPM- ethyl loflazepate	100% (2 y)	BA normal Sporadic generalized SW ILS negative	36.5/166.8 <P 3/P3–10	<Appetite	N
6	22 y	F	Negative	M-TC-SE/<m	PB, PHT, VPA, CBZ, VGB, LTG,CLB, CZP, ETS	Moderate	13 y	9 y	2 × 10 mg 0.21 mg/kg/d	VPA-LTG	100% (5 y)	BA normal No epileptic activity ILS negative	95/180.5 >P 97/>P 97		N
7	17 y	F	Missense DI S5-S6	M-TC-PS/m	PB, PHT, VPA, CZP, CLB, CBZ, VGB, LTG, NZP, Sulthiame, TPM, OXC, ETS, oxazepam	Severe	5 y	11 y	(2 × 5 mg) STOP	VPA-TPM-CLB	0%	ND	44.4/149 P 50/P 50–75 (at 11 y)		ND

Continued

Epilepsia, 53(7):1131–1139, 2012
doi: 10.1111/j.1528-1167.2012.03495.x

Table 1. Continued

	Age	Sex	Mutation/ copy number variations *SCN1A*/ localization	Seizure type/ frequency 1 year before start of fenfluramine	Previous medication	Mental retardation	Age at start of fenfluramine	Follow-up duration	Doses fenfluramine at last FU	AED combined with fenfluramine	% Reduction of seizures at last FU (years SF)	Four-hour EEG	Weight (kg)/ length (cm) (percentiles)	Side effects	Cardio control within the last year
8	21 y	F	Missense DIV S5-S6	M-TC-at. Abs/<m	VPA, VGB, CZP, CLB, ETS, CBZ, Loreclezole	Moderate	12 y	9 y	(2 × 10 mg) STOP	VPA	100% (9 y)	ND	43/150 P 25/P 10		ND
9	13 y	F	Missense/ GEFS+ C-terminal	M-TC-PS-SE-at.Abs/d	Pb, VPA, ETS, LTG, VitB6, LEV, Sulthiame, CZP, TPM, Ethyl loflazepate	Moderate	7 y	6 y	2 × 10 mg 0.51 mg/kg/d	VPA-CLB-ETS	0%	BA too slow Very frequent generalized epileptic complexes ILS negative	39.1/159 P 10–25/ P 50		N
10	16 y	M	Missense/ GEFS+ DII S5–S6	TC-PS/w	Pb, CBZ, VPA, LTG, PHT, VGB	Severe	11 y	5 y	5–10 mg 0.32 mg/kg/d	VPA-TPM-ethyl loflazepate	100% (5 y)	BA too slow No epileptic activity ILS positive	47.5/172 P3–10/P 25		N
11	15 y	M	Truncating	M-TC-PS-SE/d	Pb, VPA, PRM, LEV, TPM, pirazetam	Severe	13 y	2 y	2 × 5 mg 0.20 mg/kg/d	VPA-TPM	100% (2 y)	BA too slow No epileptic activity ILS negative	44/171.5 P3–10/ P25–50	Fatigue <Appetite	Thickening MV and TV
12	3 y	F	Truncating	TC-SE/m	VPA, CBZ, LRP, LEV, CZP	Mild	1 y 10 m	1 y	2 × 5 mg 0.90 mg/kg/d	VPA-TPM-ethyl loflazepate	100% (1 y)	BA too slow No epileptic activity ILS negative	13/87 P 3/P3–10		N

F, female; M, male; TC, tonic–clonic seizure; M, myoclonia; PS, partial seizure; SE, status epilepticus; at.Abs, atypical absences; y, years; m, monthly; w, weekly; d, daily; <m, less than once a month; CBZ, carbamazepine; CLB, clobazam; CZP, clonazepam; ETS, ethosuximide; LEV, levetiracetam; LTG, lamotrigine; NZP, nitrazepam; OXC, oxcarbazepine; PB, phenobarbital; PHT, phenytoin; TPM, topiramate; VPA, valproate; VGB, vigabatrin; BA, background activity; ILS, intermittent light stimulation; MV, mitral valve; AV, aortic valve; TV, tricuspid valve; SF, seizure-free; N, normal; ND, not done; FU, follow-up.

Table 2. Overview of temporary withdrawal of fenfluramine

Patient	Age	Sex	Doses fenfluramine at last FU	% reduction of seizures at last FU (years SF)	Trial stop fenfluramine (years ago)	Recurrence of seizures	% reduction of seizures after restart of fenfluramine
1	25 y	F	2 × 5 mg 0.12 mg/kg/day	75% reduction	Yes	Aggravation of seizures	75% reduction
2	35 y	F	2 × 10 mg 0.26 mg/kg/day	100% (13 y)	Yes	Yes	100%
3	26 y	M	2 × 10 mg 0.28 mg/kg/day	100% (19 y)	No	–	–
4	21 y	M	2 × 10 mg 0.37 mg/kg/day	0%	Yes (2 y)	No change	0%
5	17 y	M	2 × 5 mg 0.27 mg/kg/day	100% (2 y)	Yes	Yes	100%
6	22 y	F	2 × 10 mg 0.21 mg/kg/day	100% (5 y)	No	–	–
7	17 y	F	2 × 5 mg STOP	0%	No	–	–
8	21 y	F	2 × 10 mg STOP	100% (9 y)	Yes (2 y)	No	–
9	13 y	F	2 × 10 mg 0.51 mg/kg/day	0%	Yes (4 y)	No change	0%
10	16 y	M	5–10 mg 0.32 mg/kg/day	100% (5 y)	Yes	Yes	100%
11	15 y	M	2 × 5 mg 0.20 mg/kg/day	100% (2 y)	No	–	–
12	3 y	F	2 × 5 mg 0.90 mg/kg/day	100% (1 y)	No	–	–

y, years; F, female; M, male; SF, seizure-free; FU, follow-up.

frequency and severity. The other patient (Patient 8) remained seizure-free while still taking valproate monotherapy after discontinuation of fenfluramine 2 years before.

Seven of the 10 patients who were still taking fenfluramine had been seizure-free for at least 1 year by the time of the last visit. During a recent 4-h EEG registration, six of these patients did not have any epileptic activity, even during ILS. One patient (Patient 5) showed sporadic generalized spike wave activity. The duration of the seizure-free period ranged from 1–19 years with a mean of 6 years and 7 months.

In two patients (Patients 4 and 9), a positive effect on seizure frequency or severity could not be demonstrated, but their parents did not want to stop fenfluramine due to a fear of provoking status epilepticus. In one other patient (Patient 1), tonic–clonic seizures were reduced from approximately once per week to once per month.

In the files of seven patients (Patients 1, 2, 4, 5, 8–10), a temporary withdrawal of the administration of fenfluramine was noted (see Table 2), mainly due to problems with the supply of the drug. One seizure-free patient remained seizure-free after administration of fenfluramine was stopped (Patient 8). Three seizure-free patients (Patients 2, 5, and 10) had a recurrence of seizures after discontinuing fenfluramine. Remarkably, these patients became seizure-free again after restarting the medication. In one non–seizure-free patient, seizure frequency and severity increased but were reversed after restarting fenfluramine (Patient 1). In two patients (Patients 4 and 9), there was no change in seizure frequency or severity; however, once the medication was available again, the parents chose to restart administration due to a fear of provoking status epilepticus.

Remarkably, in six patients (Patients 2, 3, 5, 10–12) seizure freedom was achieved within 3 days after the start or restart of fenfluramine treatment.

Exemplary case descriptions

The last two patients (Patients 11 and 12) were included most recently. Patient 11 was a 13-year-old monozygotic twin boy with a long history of convulsions provoked by fever that had started at the age of 7 months. The convulsions were followed by myoclonic seizures, atypical absences, and at least nine periods of long-lasting status epilepticus. Genetic analysis of *SCN1A* showed a de novo truncating mutation. After treatment with valproate, topiramate, and clobazam, he became free from major convulsive seizures and status epilepticus but still had frequent, short myoclonic seizures that occurred primarily while playing video games. After the add-on treatment of fenfluramine at a dose of 5 mg twice per day (0.20 mg/kg/day), these induced seizures completely disappeared, even on video-EEG registration, and he had been seizure-free for nearly 2 years at the last follow-up.

The last patient (Patient 12) was a young girl starting with typical fever-induced long-lasting convulsive seizures at the age of 5 months. Between the ages of 5 and 22 months, she had been hospitalized 15 times with tonic–clonic seizures or status epilepticus. Twice, she had to be admitted to the intensive care unit for longer periods because of complications of fever-induced status epilepticus. After treatment with valproate, topiramate, and ethyl loflazepate, she was still not seizure-free. At the age of 22 months and after a normal cardiac examination, she was treated with add-on fenfluramine at a dose of 5 mg twice per day (0.90 mg/kg/day). Remarkably, she immediately became seizure-free and remained seizure-free, even through periods of fever, for >12 months.

Side effect profile

Due to the known serious side effects of fenfluramine (pulmonary hypertension and heart valve disease), a yearly cardiac consult with ultrasound was performed during the last 3 years of study in all the patients. Pulmonary hypertension was observed in none of the patients. In two patients, a slight thickening of one or two heart valves was detected. In both patients (Patients 3 and 11), these findings had remained stable for the prior year and were not considered clinically significant by the cardiologist. In both cases, the parents did not wish to stop fenfluramine despite these cardiac side effects.

Because fenfluramine is known as an anorexigen, special attention was given to its effect on appetite and weight evolution. Loss of appetite was reported only in two patients (Patients 5 and 11); both were on a combination therapy with topiramate, a drug also known to reduce appetite.

Weight was below the 50th percentile (P50) for approximately half the patients (7/12). In only two patients (4 and 5), it was below P3, which was discrepant with the height of the patients (between P3 and P10).

None of the patients were less than P3 in height.

Fatigue was reported in two patients (Patients 1 and 11), and excessive somnolence was reported in one patient (Patient 3).

Discussion

Dravet syndrome is a truly catastrophic therapy-resistant epilepsy syndrome, and families faced with this disorder are required to cope with special circumstances (Nolan et al., 2008).

In 2001, mutations in the sodium channel gene *SCN1A* were first described to cause this disorder (Claes et al., 2001). It is now generally accepted that 70–80% of Dravet syndrome cases are caused by mutations in *SCN1A* (Marini et al., 2011). Approximately 12.5% of *SCN1A* sequence analysis negative patients have a partial or complete deletion of the gene; in fewer cases duplications are observed (Suls et al., 2006; Marini et al., 2009). Recently it was shown that mutations in protocadherin 19 could also contribute to Dravet syndrome (Marini et al., 2010).

Despite these genetic discoveries, the methods of treatment are still frustrating, and the prognosis remains very poor. Typically, during the second year of life, mental development stagnates and even regresses. As a result, nearly all patients end up with mental retardation, usually moderate or severe (Harkin et al., 2007; Nolan et al., 2008; Ceulemans, 2011). The question as to whether the mental retardation is caused by the mutation itself or is a consequence of the seizures, especially during the first 2 years, is still a matter of discussion. Recently, results have suggested that even with complete seizure control, patients could develop mental retardation (Riva et al., 2009; Ceulemans, 2011). However, controlling seizures and certainly preventing convulsive status epilepticus is still highly recommended (Chiron & Dulac, 2011).

These frequent, unpredictable severe seizures and the risk of a life-threatening status epilepticus are of major concern for parents of children with Dravet syndrome. Such concerns significantly influence the quality of life of these families (Nolan et al., 2008).

In the last 10 years, the treatment for these patients has shifted from a trial-and-error system toward optimal treatment strategies based on a possible consensus (Ceulemans et al., 2004; Chiron & Dulac, 2011). This paradigm is based on three main principles: (1) prevention of seizures by preventing hyperthermia; (2) adequate treatment of severe convulsions by the immediate use of benzodiazepines by parents and caregivers; and (3) an adequate and rational combination AED maintenance therapy with an avoidance of seizure aggravating drugs, such as carbamazepine, lamotrigine, and phenytoin.

There remains an ongoing debate regarding the best maintenance treatment for Dravet syndrome. French, Italian and, recently, Japanese studies have published promising results that have utilized a combination of sodium valproate, stiripentol, and clobazam, in addition to one placebo-controlled trial (Chiron et al., 2000; Thanh et al., 2002; Inoue et al., 2009). Other authors have proposed sodium valproate in combination with topiramate with or without benzodiazepines to be an effective maintenance treatment for Dravet syndrome (Nieto-Barrera et al., 2000; Coppola et al., 2002; Ceulemans et al., 2004; Kroll-Seger et al., 2006). Recently, smaller studies were published that report on levetiracetam (Striano et al., 2007), verapamil (Iannetti et al., 2009), ketogenic diet (Caraballo, 2011), deep brain stimulation (Andrade et al., 2010), and vagus nerve stimulation (Zamponi et al., 2011). However, these therapies did not yield superior results.

The long-term outcome of Dravet syndrome has been considered to be consistently poor, both in regard to developmental outcome and convulsive seizure control (Fujiwara et al., 1992; Oguni et al., 2001; Dravet et al., 2005; Jansen et al., 2006; Akiyama et al., 2010; Genton et al., 2011).

Seizure freedom, even with a long-term follow-up period, is very rare. In a recent publication by a Japanese group, 16.1% of a group of adult patients with Dravet syndrome had been seizure-free for at least 1 year before the last follow-up (Akiyama et al., 2010). Overall, studies have shown that a maximum of 2–16% of patients became seizure-free.

Fenfluramine is a racemic mixture of two enantiomers: dextrofenfluramine and levofenfluramine. Fenfluramine has a half-life of 20 h and a fast urinary excretion rate. A steady state of fenfluramine is reached after 3–4 days of treatment. It is fat-soluble and is able to pass the blood–brain barrier. This drug was introduced onto the U.S. market in 1973. The actions of fenfluramine are explained by inhibition of serotonin reuptake and by release of serotonin (due to a disruption of the vesicular storage). This increase in the levels of serotonin in the brain leads to a loss of appetite (Belohlavkova et al., 2001).

Published data on the use of fenfluramine in neurologic disorders are limited. In 1985 and 1987, Aicardi and Gastaut published four cases of self-induced photosensitive seizures that responded to treatment with fenfluramine (Aicardi & Gastaut, 1985; Aicardi et al., 1988). The first report included three adolescents with absence seizures who responded well to fenfluramine. The second report describes a single case of a girl with induced syncopes and apneas that were elicited by the Valsalva maneuver. She had typical absence seizures that were triggered by her apneic attacks and could also be induced by hyperventilation. Valproate suppressed the absence seizures but had no effect on the self-induced apneas. Using fenfluramine hydrochloride, the authors were able to reduce the number of apneas. In 1987, Gastaut et al. published a summary report on the use of fenfluramine in nonepileptic syncopes due to compulsive respiratory stereotypes in eight patients with autistic features. Four of the five patients, in whom the syncopes were provoked by prolonged Valsalva manoeuvres, became free from these attacks (Gastaut et al., 1987).

Clemens described a mentally retarded boy with pattern sensitivity-induced seizures that were resistant to conventional anticonvulsive treatment. Fenfluramine successfully terminated these self-induced seizures by blocking the photosensitive triggering mechanism (Clemens, 1988). In 1996, Boel & Casaer reported on the use of add-on fenfluramine for treatment of intractable self-induced seizures in 11 children aged 18 months–15 years. Fenfluramine was administered at a dose of 0.5–1 mg/kg/day. Seven patients became seizure-free, and four exhibited a >75% decrease in seizures. The side effects were mild and transient and mainly included a loss of appetite and somnolence. Hematological and biochemical changes were not observed, and cardiac examinations were not performed. In a 2002 letter to *Epilepsia*, the same authors reported on 22 patients, including the 11 previously reported patients, with self-induced seizures who were treated with fenfluramine as an add-on antiepileptic therapy. Six were seizure-free and another 10 had a 90% improvement. Eleven of the 22 patients had photosensitivity. Side effects were mild; one patient reported a transient loss of appetite, and another reported fatigue after physical exercise (Casaer & Boel, 2002).

At an experimental level, Gentsch et al., (2000) investigated the effect of fenfluramine on epileptiform activity generated in the entorhinal cortex (EC) in an in vitro model of epilepsy. The EC represents the main input structure to the hippocampus and is critically involved in temporal lobe epilepsy. Because the EC receives a strong serotonergic projection from the raphe nuclei and expresses a high density of serotonin receptors, serotonin-releasing drugs (like fenfluramine) could have an effect on the epileptic activity. The authors provoked epileptic activity in brain slides of rats by lowering the extracellular Mg^{2+} concentration. In normal physiologic conditions, Mg^{2+} blocks the *N*-methyl-D-aspartate (NMDA) receptor. Serotonin causes a potent reduction of NMDA receptor–mediated excitation. The addition of fenfluramine prevented low Mg^{2+}-induced epileptiform activity. The authors concluded that fenfluramine may exert a therapeutic value in the treatment of epilepsy.

The limitations of this small, exploratory, retrospective study are recognized. However, the results are remarkable. Seizure freedom for >1 year in 7 of 10 patients with Dravet syndrome is superior to even the most promising results that have been published regarding this disorder. In addition, most of our patients remained seizure-free for many years, with a mean of 6 years 7 months and a range from 1–19 years. As it is known that seizure frequency tends to decline with age in these patients, the mean age of 19 years at the time of the final assessment could be important; however, seizure freedom still remains very rare, even in adults (Dravet, 2011). The results presented here are also substantially better than the recently published report of 16.1% seizure-free adult patients in the large Japanese long-term follow-up study (Akiyama et al., 2010).

Two other factors concerning the efficacy in this study are important to mention. First, in six of the eight seizure-free patients, seizures ceased within days after the start of fenfluramine, which is rare in the treatment of refractory seizures. Second, in three seizure-free patients, withdrawal of fenfluramine led to the recurrence of the seizures, which were again controlled within days after restarting of the treatment.

Although it is known that fenfluramine increases synaptic serotonin concentration, which has potential anticonvulsive effects, it is unclear whether the serotonin effects explain our favorable results (Jobe & Browning, 2005). The first results of fenfluramine were published in patients with photosensitive or self-induced seizures (Aicardi et al., 1988; Boel & Casaer, 1996). It is known that in Dravet syndrome, photosensitive or induced (via light stimulation, bath, or fevers) seizures are frequent. One could therefore hypothesize that fenfluramine reduces only the photosensitive

or self-induced seizures; however, the results of this study showed that all types of seizures were suppressed.

The serious cardiac side effects associated with fenfluramine use that have been described are of a major concern. However, most side effects were described in female patients who were on a combination therapy of fenfluramine with other antiobesity drugs, which may have potentiated the risk of complications. Furthermore, fenfluramine was used at doses between 0.5 and 1 mg/kg/day up to 60 mg/day. In our study, smaller dosages (a mean of 0.34 mg/kg/day and a maximum of 20 mg/day) were used. The possible cardiac side effects were well monitored in our patients. Pulmonary hypertension was never observed, and the thickening of the valves occurred in only two patients and was determined to be mild, nonprogressive and clinically nonrelevant in both patients. Only one of these patients complained of fatigue after exercise, but it remains unclear whether the fatigue was related to the cardiac findings.

A loss of appetite was not a major problem in our study group, and there were no clinically important long-term effects on weight or height evolution in our patients.

Taking into account the devastating prognosis in most children with Dravet syndrome, the authors propose to seriously consider the use of fenfluramine combined with regular clinical and cardiac follow-up for the treatment of this syndrome.

Conclusion

Fenfluramine is an old drug that has been used primarily in the past in combination therapies for controlling obesity in female patients. Because of its severe adverse effects, including cardiac valve thickening and pulmonary hypertension, it has been withdrawn from the market in the United States and the European Union.

In this small exploratory and retrospective study, remarkably good results were reported on the use of fenfluramine as an add-on medication for controlling seizures in patients with Dravet syndrome. The side effects were rare and nonserious and did not result in termination of the treatment.

It is possible that this drug may have anticonvulsive effects for other severe epilepsy syndromes, especially in those characterized by photosensitive or induced seizures.

Further studies are needed to determine whether this drug can be reintroduced as an orphan drug for specific refractory epilepsies and especially for Dravet syndrome.

Acknowledgments

We are thankful to the patients and their parents for their cooperation. We would like to thank Ria Krols, RN, and Imma Uwimana, pharmacist from the epilepsy center in Pulderbos for practical organization of the fenfluramine study. We are grateful to Karin Bellon and Hilde Fleurackers for the technical assistance. We are thankful to our colleagues in pediatric neurology who support us in this work. All authors disclose any commercial, financial, or other associations that could pose a conflict of interest in connection with the submitted article.

Disclosures

None of the authors has any conflict of interest.

We confirm that we have read the Journal's position on issues involved in ethical publications and affirm that this report is consistent with those guidelines.

References

Aicardi J, Gastaut H. (1985) Treatment of self-induced photosensitive epilepsy with fenfluramine. *N Engl J Med* 313:1419.

Aicardi J, Gastaut H, Mises J. (1988) Syncopal attacks compulsively self-induced by Valsalva's maneuver associated with typical absence seizures. A case report. *Arch Neurol* 45:923–925.

Akiyama M, Kobayashi K, Yoshinaga H, Ohtsuka Y. (2010) A long-term follow-up study of Dravet syndrome up to adulthood. *Epilepsia* 51:1043–1052.

Andrade DM, Hamani C, Lozano AM, Wennberg RA. (2010) Dravet syndrome and deep brain stimulation: seizure control after 10 years of treatment. *Epilepsia* 51:1314–1316.

Belohlavkova S, Simak J, Kokesova A, Hnilickova O, Hampl V. (2001) Fenfluramine-induced pulmonary vasoconstriction: role of serotonin receptors and potassium channels. *J Appl Physiol* 91:755–761.

Boel M, Casaer P. (1996) Add-on therapy of fenfluramine in intractable self-induced epilepsy. *Neuropediatrics* 27:171–173.

Caraballo RH. (2011) Nonpharmacologic treatments of Dravet syndrome: focus on the ketogenic diet. *Epilepsia* 52 (Suppl. 2):79–82.

Casaer P, Boel M. (2002) Fenfluramine as a potential antiepileptic drug. *Epilepsia* 43:205–206.

Ceulemans B. (2011) Overall management of patients with Dravet syndrome. *Dev Med Child Neurol* 53(Suppl. 2):19–23.

Ceulemans B, Boel M, Claes L, Dom L, Willekens H, Thiry P, Lagae L. (2004) Severe myoclonic epilepsy in infancy: toward an optimal treatment. *J Child Neurol* 19:516–521.

Chiron C, Dulac O. (2011) The pharmacologic treatment of Dravet syndrome. *Epilepsia* 52(Suppl. 2):72–75.

Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, Dulac O, Pons G. (2000) Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. *Lancet* 356:1638–1642.

Claes L, Del-Favero J, Ceulemans B, Lagae L, Van Broeckhoven C, De Jonghe P. (2001) De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. *Am J Hum Genet* 68:1327–1332.

Clemens B. (1988) Dopamine agonist treatment of self-induced pattern-sensitive epilepsy. A case report. *Epilepsy Res* 2:340–343.

Commission. (1981) Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* 22:489–501.

Connolly JM, Bakay MA, Fulmer JT, Gorman RC, Gorman JH 3rd, Oyama MA, Levy RJ. (2009) Fenfluramine disrupts the mitral valve interstitial cell response to serotonin. *Am J Pathol* 175:988–997.

Coppola G, Capovilla G, Montagnini A, Romeo A, Spano M, Tortorella G, Veggiotti P, Viri M, Pascotto A. (2002) Topiramate as add-on drug in severe myoclonic epilepsy in infancy: an Italian multicenter open trial. *Epilepsy Res* 49:45–48.

Dahl CF, Allen MR, Urie PM, Hopkins PN. (2008) Valvular regurgitation and surgery associated with fenfluramine use: an analysis of 5743 individuals. *BMC Med* 6:34.

Dravet C. (1978) Les épilepsies graves de l'enfant. *Vie Méd* 8:543–548.

Dravet C. (2011) The core Dravet syndrome phenotype. *Epilepsia* 52(Suppl. 2):3–9.

Dravet C, Bureau M, Oguni H, Fukuyama Y, Cokar O. (2005) Severe myoclonic epilepsy in infancy (Dravet syndrome). In Roger CW, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf F (Eds) *Epileptic syndromes in*

infancy, childhood and adolescence. John Libbey Eurotext Ltd, Paris, pp. 89–103.

Dravet C, Bureau M, Dalla Bernardina B, Guerrini R. (2011) Severe myoclonic epilepsy in infancy (Dravet syndrome) 30 years later. *Epilepsia* 52(Suppl. 2):1–2.

Dura-Trave T, Yoldi-Petri ME, Gallinas-Victoriano F. (2007) Epilepsy in children in Navarre, Spain: epileptic seizure types and epileptic syndromes. *J Child Neurol* 22:823–828.

Fujiwara T, Watanabe M, Takahashi Y, Higashi T, Yagi K, Seino M. (1992) Long-term course of childhood epilepsy with intractable grand mal seizures. *Jpn J Psychiatry Neurol* 46:297–302.

Gastaut H, Zifkin B, Rufo M. (1987) Compulsive respiratory stereotypies in children with autistic features: polygraphic recording and treatment with fenfluramine. *J Autism Dev Disord* 17:391–406.

Genton P, Velizarova R, Dravet C. (2011) Dravet syndrome: the long-term outcome. *Epilepsia* 52(Suppl. 2):44–49.

Gentsch K, Heinemann U, Schmitz B, Behr J. (2000) Fenfluramine blocks low-Mg2 + -induced epileptiform activity in rat entorhinal cortex. *Epilepsia* 41:925–928.

Harkin LA, McMahon JM, Iona X, Dibbens L, Pelekanos JT, Zuberi SM, Sadleir LG, Andermann E, Gill D, Farrell K, Connolly M, Stanley T, Harbord M, Andermann F, Wang J, Batish SD, Jones JG, Seltzer WK, Gardner A, Sutherland G, Berkovic SF, Mulley JC, Scheffer IE. (2007) The spectrum of SCN1A-related infantile epileptic encephalopathies. *Brain* 130:843–852.

Hurst DL. (1990) Epidemiology of severe myoclonic epilepsy of infancy. *Epilepsia* 31:397–400.

Iannetti P, Parisi P, Spalice A, Ruggieri M, Zara F. (2009) Addition of verapamil in the treatment of severe myoclonic epilepsy in infancy. *Epilepsy Res* 85:89–95.

Inoue Y, Ohtsuka Y, Oguni H, Tohyama J, Baba H, Fukushima K, Ohtani H, Takahashi Y, Ikeda S. (2009) Stiripentol open study in Japanese patients with Dravet syndrome. *Epilepsia* 50:2362–2368.

Jansen FE, Sadleir LG, Harkin LA, Vadlamudi L, McMahon JM, Mulley JC, Scheffer IE, Berkovic SF. (2006) Severe myoclonic epilepsy of infancy (Dravet syndrome): recognition and diagnosis in adults. *Neurology* 67:2224–2226.

Jobe PC, Browning RA. (2005) The serotonergic and noradrenergic effects of antidepressant drugs are anticonvulsant, not proconvulsant. *Epilepsy Behav* 7:602–619.

Kroll-Seger J, Portilla P, Dulac O, Chiron C. (2006) Topiramate in the treatment of highly refractory patients with Dravet syndrome. *Neuropediatrics* 37:325–329.

Marini C, Scheffer IE, Nabbout R, Mei D, Cox K, Dibbens LM, McMahon JM, Iona X, Carpintero RS, Elia M, Cilio MR, Specchio N, Giordano L, Striano P, Gennaro E, Cross JH, Kivity S, Neufeld MY, Afawi Z, Andermann E, Keene D, Dulac O, Zara F, Berkovic SF, Guerrini R, Mulley JC. (2009) SCN1A duplications and deletions detected in Dravet syndrome: implications for molecular diagnosis. *Epilepsia* 50:1670–1678.

Marini C, Mei D, Parmeggiani L, Norci V, Calado E, Ferrari A, Moreira A, Pisano T, Specchio N, Vigevano F, Battaglia D, Guerrini R. (2010) Protocadherin 19 mutations in girls with infantile-onset epilepsy. *Neurology* 75:646–653.

Marini C, Scheffer IE, Nabbout R, Suls A, De Jonghe P, Zara F, Guerrini R. (2011) The genetics of Dravet syndrome. *Epilepsia* 52(Suppl. 2):24–29.

McCann UD, Seiden LS, Rubin LJ, Ricaurte GA. (1997) Brain serotonin neurotoxicity and primary pulmonary hypertension from fenfluramine and dexfenfluramine. A systematic review of the evidence. *JAMA* 278:666–672.

Nieto-Barrera M, Candau R, Nieto-Jimenez M, Correa A, del Portal LR. (2000) Topiramate in the treatment of severe myoclonic epilepsy in infancy. *Seizure* 9:590–594.

Nolan K, Camfield CS, Camfield PR. (2008) Coping with a child with Dravet syndrome: insights from families. *J Child Neurol* 23:690–694.

Oguni H, Hayashi K, Awaya Y, Fukuyama Y, Osawa M. (2001) Severe myoclonic epilepsy in infants – a review based on the Tokyo Women's Medical University series of 84 cases. *Brain Dev* 23:736–748.

Riva D, Vago C, Pantaleoni C, Bulgheroni S, Mantegazza M, Franceschetti S. (2009) Progressive neurocognitive decline in two children with Dravet syndrome, de novo SCN1A truncations and different epileptic phenotypes. *Am J Med Genet A* 149A:2339–2345.

Spencer DC, Hwang J, Morrell MJ. (2000) Fenfluramine–phentermine (Fen–Phen) and seizures: evidence for an association. *Epilepsy Behav* 1:448–452.

Striano P, Coppola A, Pezzella M, Ciampa C, Specchio N, Ragona F, Mancardi MM, Gennaro E, Beccaria F, Capovilla G, Rasmini P, Besana D, Coppola GG, Elia M, Granata T, Vecchi M, Vigevano F, Viri M, Gaggero R, Striano S, Zara F. (2007) An open-label trial of levetiracetam in severe myoclonic epilepsy of infancy. *Neurology* 69:250–254.

Suls A, Claeys KG, Goossens D, Harding B, Van Luijk R, Scheers S, Deprez L, Audenaert D, Van Dyck T, Beeckmans S, Smouts I, Ceulemans B, Lagae L, Buyse G, Barisic N, Misson JP, Wauters J, Del-Favero J, De Jonghe P, Claes LR. (2006) Microdeletions involving the SCN1A gene may be common in SCN1A-mutation-negative SMEI patients. *Hum Mutat* 27:914–920.

Thanh TN, Chiron C, Dellatolas G, Rey E, Pons G, Vincent J, Dulac O. (2002) [Long-term efficacy and tolerance of stiripentaol in severe myoclonic epilepsy of infancy (Dravet's syndrome)]. *Arch Pediatr* 9:1120–1127.

Yakoub M, Dulac O, Jambaque I, Chiron C, Plouin P. (1992) Early diagnosis of severe myoclonic epilepsy in infancy. *Brain Dev* 14:299–303.

Zamponi N, Passamonti C, Cappanera S, Petrelli C. (2011) Clinical course of young patients with Dravet syndrome after vagal nerve stimulation. *Eur J Paediatr Neurol* 15:8–14.