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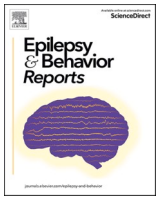

Resolution of Fenfluramine-associated pulmonary arterial hypertension in Lennox-Gastaut syndrome: A case report and literature review

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ABSTRACT

Fenfluramine is a medication originally approved for weight loss before being withdrawn for an association with the development of pulmonary arterial hypertension (PAH) and cardiac valvulopathy. Interest in fenfluramine at lower doses has re-emerged for treatment of drug-resistant epilepsy (DRE). Here, we present a case of a patient with Lennox-Gastaut Syndrome (LGS) treated with fenfluramine with development of PAH and tricuspid regurgitation that resolved upon discontinuation.

A 4-year-old female with LGS refractory to anti-seizure medications and neuromodulation was screened by echocardiogram and started on fenfluramine due to persistent seizures. At 6 months, the patient developed asymptomatic PAH and tricuspid regurgitation. The medication was discontinued, and 2 months post-cessation, an echocardiogram showed PAH and cardiac valvulopathy resolution. The patient was restarted on fenfluramine due to seizures, and follow up exam with echocardiogram 6 months following retrial showed no PAH recurrence.

We present a case of LGS treated with fenfluramine complicated by PAH until cessation, with subsequent retrial tolerated. This is the first pediatric patient to develop cardiac abnormalities during treatment with fenfluramine, which has been demonstrated to be efficacious and safe in DRE at lower doses than those utilized for weight loss. With appropriate screening, fenfluramine should be considered as an adjunct treatment option for DRE in select patients, and PAH as a complication of the medication may be reversible and non-recurrent on retrial.

1. Introduction

Fenfluramine is an orally administered medication with activity as an allosteric sigma-1 modulator and pro-serotonin agent initially approved by the Food and Drug Administration (FDA) in 1984 for use as a weight loss drug to treat obesity [1]. Formulations of fenfluramine combined with phentermine were commonly prescribed together for weight reduction regimes [2]. However, reported cases of valvular heart disease and pulmonary arterial hypertension (PAH) led to reduction of its popularity and eventual withdrawal from the market in 1997. Most of the cardiopulmonary abnormalities improved on subsequent echocardiogram following discontinuation of the drug [3]. The pathophysiology underlying these side effects may be linked to fenfluramine's action as an indirect serotonin agonist which stimulates growth for pulmonary smooth muscle cells [4], although the mechanism of fenfluramine's adverse effects has continued to be debated [5]. Fenfluramine's action on the 5HT2B receptors, specifically, has been hypothesized to produce the hyperplasia responsible for the adverse effect of valvular heart disease [6].

Reports of cardiopulmonary adverse effects were prominent in doses administered for the treatment of obesity, ranging from 40-160 mg/day or 0.5–2.1 mg/kg/day in an adult. In contrast, fenfluramine ranging from 0.2 mg/kg/day-0.7 mg/kg/day has shown safety and efficacy in the treatment of pediatric epilepsy, Dravet Syndrome, and Lennox-

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Gastaut Syndrome (LGS) [1,7–9]. In a review of the literature, fenfluramine in lower doses up to 0.7 mg/kg/day showed a 0 % rate of development of cardiopulmonary complications compared to a rate of 5–18 % in the higher dosing previously utilized for obesity [1,10–12]. Given the safety profile in its use at lower doses, preliminary potential for seizure reduction, and scarcity of effective medication options in certain drug-resistant epileptic syndromes, fenfluramine was approved in 2020 for the adjunct treatment of Dravet Syndrome, and in 2022 for the adjunct treatment of LGS in patients 2 years and older [13,14]. To ensure overall patient safety, annual cardiac screening is still recommended by the FDA while on fenfluramine for the treatment of seizures [14].

The existing literature suggests that cardiopulmonary complications of fenfluramine when used at lower dosages for epileptic patients have not been observed [1,12]. Here, we present a case of a 4-year-old female with LGS refractory to anti-seizure medications and neuromodulation who developed subclinical PAH after receiving adjunct fenfluramine treatment for 6 months, that subsequently resolved on discontinuation of the medication. To our knowledge, this is the first reported case of a pediatric patient developing cardiac abnormalities during treatment with fenfluramine who was rechallenged with fenfluramine after normal echocardiograms were obtained.

2. Case report

2.1. Presentation and diagnosis

A 4-year old female with LGS and intractable epilepsy presented for antiseizure medication (ASM) management. Her past failed medication history included a trial vigabatrin, which was discontinued due to the development of white matter changes. Additionally, valproate was discontinued due to thrombocytopenia, cannabidiol and clobazam were discontinued due to excessive somnolence, lacosamide and perampanel were both deemed ineffective, and felbamate was tapered due to agitation and drowsiness. At the time of presentation, she was being treated with a vagus nerve stimulator implant and the ASMs felbamate, clobazam, and a diazepam rectal kit for seizure termination, and was assessed for trial of adjunctive fenfluramine to treat refractory seizures.

She was screened with a baseline echocardiogram and started on fenfluramine 4.4 mg/day in an effort to control her epilepsy, while continuing her felbamate 1500 mg/day as clobazam was weaned and discontinued. Fenfluramine dose was increased to 7.92 mg/day for 1 week, then held at 14.08 mg/day for 6 months. The increased dosage decreased the frequency of tonic-clonic seizures per the patient's mother's report; however, drop seizures persisted. At 6 months, a screening echocardiogram showed the development of subclinical PAH, with a new tricuspid regurgitation predicting a right ventricular pressure of 40 mmHg increased from her baseline of 14 mmHg. A repeat echocardiogram confirmed the findings.

2.2. Management

The patient's fenfluramine dose of 14.08 mg/day was tapered off over 1 week before complete cessation due to the new onset PAH. The patient was started on zonisamide 50 mg/day and cannabidiol 240 mg/day, and was instructed to continue felbamate 600mg/5mL at 4mL TID = 1440 mg/day.

While repeat echocardiography at 2 months after fenfluramine cessation revealed a return of right ventricular pressure to a near baseline of 20 mmHg, the patient continued to have intractable seizures. The number of tonic-clonic seizures increased to pre-fenfluramine conditions per the patient's mother's report. Cannabidiol dosing was increased to 360 mg/day with the continuation of zonisamide and felbamate.

After 1 month of persistent seizure frequency, discussion with the patient's caregivers and medical team led to an agreement to retrial fenfluramine 3 months post-cessation. The patient was restarted on fenfluramine at 4.4 mg/day for 2 weeks before an increase to 8.8 mg/day. Repeat imaging 6 months later showed no evidence of recurrence of PAH with the retrial of fenfluramine.

The patient presented for a follow-up visit two months after her last echocardiogram, with an ASM regimen of felbamate 600mg/5mL at 7mL BID = 1680 mg/day, zonisamide 100 mg/day, cannabidiol 100 mg/day, and fenfluramine 14.08 mg/day, the maximum dosage for the patient's weight. Given the lack of reduction in drop seizures with her previous varied ASM regimens, corpus callosotomy was discussed as the next step in management, and agreement was reached between the caregivers and the medical team. In the months leading up to her scheduled surgery, the patient was weaned off of cannabidiol, while her other ASMs were maintained.

3. Discussion

The management of LGS is often complex due to the presence of frequent seizures of various semiologies that are often refractory to multiple anti-seizure medications [15]. While valproate is the current first-line option, the choice of adjunct and optimal therapy varies [16,17]. Fenfluramine has shown effectiveness as adjunct treatment in reducing seizure frequency compared to placebo in a randomized controlled trial in patients with LGS and two trials in patients with Dravet syndrome [11,18]. Because of the history of fenfluramine contributing to PAH and cardiac valvulopathy [1], there is concern regarding its usage for LGS despite the results of trials where it was proven to be efficacious. We present here a case of LGS with DRE treated with fenfluramine that was complicated by PAH until cessation of fenfluramine, which is to our knowledge the first reported case of cardiopulmonary abnormalities developing in a pediatric patient treated with fenfluramine for epilepsy and resolving and not recurring when rechallenged with fenfluramine. In light of the challenge of treating patients with drug-refractory epilepsy, here we highlight a possible path towards incorporation of fenfluramine in ASM regimens for patients. Close clinical and cardiac monitoring, with cessation and re-trial of fenfluramine, proved tolerable to our patient without recurrence of her PAH, and may be an option for others with few other options for therapy.

Historically, fenfluramine's drug safety and tolerability has been complicated by indirect serotonin agonism on the cardiopulmonary system [4]. While this impacted its safety in the higher doses utilized as an anorectic drug, fenfluramine has been shown to be well tolerated with minimal side effects in the lower doses utilized in patients treated for seizures, with no known cases of PAH or valvulopathy [18,19]. Moreover, regular imaging with echocardiography has shown to vastly reduce the attributable risk for valvulopathy from 20 % to 6 % of cases for patients using fenfluramine as an anorectic [108], and is currently required before, during, and after treatment when utilized in epilepsy [14]. In previous cases of PAH and valvulopathy attributable to fenfluramine, discontinuation was associated with significant improvement of electrocardiographic measures over time [3], and PAH was similarly noted to resolve in our patient upon discontinuation of fenfluramine, with no recurrence upon re-trial of the medication. Given fenfluramine's efficacy in significantly reducing the frequency of drop seizures in patients with LGS [18], fenfluramine is an attractive adjunct to the ASM regimen for patients with LGS and uncontrolled seizures, when paired with appropriate counseling and monitoring.

4. Conclusion

Fenfluramine can be a safe addition to ASM regimens in patients with LGS when coupled with close cardiopulmonary monitoring protocols. When adverse cardiopulmonary side effects do occur, cessation of the medication can provide significant improvement, and re-trial of the medication may not necessarily cause recurrence of the same adverse effects.

Ethical Statement

This case report adhered to the ethical principles set forth by the Declaration of Helsinki. The patient's legal guardians provided written informed consent for the publication of this case report and any accompanying images. The study was conducted in accordance with institutional guidelines for the protection of human subjects.

CRediT authorship contribution statement

Rebecca Strafella: Writing – review & editing, Writing – original draft, Investigation. **Richard Wang:** Writing – review & editing, Writing – original draft, Investigation. **Marissa Petchpradub:** Writing – review & editing, Conceptualization. **Ariel Sacknovitz:** Writing – review & editing. **Patricia E. McGoldrick:** Writing – review & editing, Supervision, Project administration, Investigation, Conceptualization. **Steven M. Wolf:** Writing – review & editing, Supervision, Project administration, Investigation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: SW and PM report honoraria from LivaNova, Eisai, UCB, Sunovion, Greenwich Pharmaceuticals, JAZZ, Marinus, Zogenix and participation as an investigator in clinical trials for Zogenix, GW Pharma, NeuroPace, Neurelis, UCB, Eisai.

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