**INTRODUCTION**

Prevention of premature mortality due to sudden unexpected death in epilepsy (SUDEP) is a major unmet need in neurology. Most of the witnessed clinical cases of SUDEP involved generalized seizures that led to respiratory and then cardiac failure during post-ictal behavioral depression (PIDD). Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter released during PIDD that affects respiration (Fisher and Schachter, 2000). Dravet Syndrome is an intractable form of epilepsy that shows an elevated incidence of SUDEP. A recent report indicated that patients with Dravet Syndrome have improved clinical course when treated with fenfluramine (Ceulemans et al., 2016), a drug that enhances 5-HT release. In the DBA/1 mouse model of SUDEP, the incidence of SUDEP is higher than in other strains. Therefore, the present study was designed to evaluate whether fenfluramine could prevent SUDEP in the DBA/1 mouse model.

**METHODS**

1. **DBA1** mice were subjected AGSz priming involving 3-4 daily tests by presenting 122 dB SPL (re: 0.0002 dyne/cm²) broadband acoustic stimulus for 21 min.

2. The ordinal AGSz severity scoring used as: no seizure=0; wild running=1; clonic seizure=2; tonic seizure=3; death/S-IRA=4 (De Sarro et al., 2017).

3. Mice that showed S-IRA were resuscitated by placing the inhalation tube of a rodent respirator (200 strokes/min) over the nose.

4. At least 24 h after the final priming seizure the consistent S-IRA susceptible mice were given fenfluramine (5-40 mg/kg) or vehicle (saline) intraperitoneally.

5. The experimental paradigms used to determine the dose and time course of fenfluramine's effect on AGSz, post-ictal depression (represented by righting reflex latency) and S-IRA incidence were:(A)30 min, 12 h and 24 h following fenfluramine (10-40 mg/kg) or saline (effect dose-response relationship). (B) 8 h intervals for 24 h (selective S-IRA blocking effect).

6. The drug and active metabolite (nor-Fen) AUC was determined using trapezoidal rule from the concentrations determined by liquid chromatography–mass spectrometry (Algorithmie Pharma Inc.) using the samples obtained terminally (Euthasol) at 8 h intervals as in paradigm (A).

7. Behaviors were recorded on videotape, quantified and analyzed offline using SPSS software.

8. The effective dose 50 (ED50) of fenfluramine against AGSz in DBA1 mice was calculated linear regression analysis with Sigma Plot and Microsoft Excel.

**REFERENCES**

De Sarro et al., Epilepsy Behav. 71(Pt B):165-173, 2017.

Ceulemans et al., Epilepsia 57(7):e129-34, 2016.

Faingold et al., Epilepsy Behav. 22(2):186-190, 2011.

Faingold et al., Epilepsy Behav. 37:198-203, 2014.


**SUPPORT**

Zegenix International Limited
Southern Illinois University School of Medicine

**ABBREVIATIONS / DRUGS**

- **ABBBREVIATIONS**
  - **5-HT**: 5-hydroxytryptamine
  - **AGSz**: Audiogenic seizures
  - **AUC**: Area under the curve
  - **ED50**: Effective dose 50
  - **FA**: Fluoxetine Selective 5-HT reuptake inhibitor
  - **Fen**: Fenfluramine
  - **n**: Number of animals
  - **PIDD**: Post-ictal depression
  - **PND**: Post-Natal Day
  - **SUDEP**: Sudden Unexpected Death in Epilepsy
  - **S-IRA**: Seizure-induced respiratory arrest

- **DRUGS**
  - **nor-Fen**: Active metabolite of Fen.
  - **SUDEP**: Sudden Unexpected Death in Epilepsy
  - **S-IRA**: Seizure-induced respiratory arrest
  - **AUC**: Area under the curve
  - **n**: Number of animals

**SUMMARY & CONCLUSIONS**

1. Fenfluramine, a drug that enhances the release of 5-HT, reduces incidence and severity of AGSz and S-IRA in DBA1 mice.

2. Fenfluramine displayed long-lasting dose- and time-dependent anticonvulsant and S-IRA blocking effect.

3. The present study suggests a novel application of fenfluramine to prevent respiratory failure after seizure, which may further improve clinical outcomes in Dravet syndrome (Ceulemans et al., 2016).

4. These findings suggest that fenfluramine may be useful to better control seizures and is a potential therapeutic agent that deserves investigation for preventing SUDEP in epilepsy patients.