Introduction

Drosophila is a useful, treatment-resistant, developmental epileptic encephalopathy model. In two randomized, patient-controlled, phase 3 clinical trials, fenfluramine administered at doses of 0.2 and 0.7 mg/kg/day substantially and significantly reduced the frequency of convulsive seizures in patients with Drosophila syndrome.[1] Here we report the results of preclinical investigations into the anticonvulsant activity of fenfluramine in three murine models of acute and chronic seizures.

- Acute maximal electroshock (MES) test
- Acute kindled mouse (CKM) model
- Chronic corneal kindled mouse (CCM) model

Methods

- Mice were treated with vehicle or fenfluramine at 3, 10, or 30 mg/kg or 30 mg/kg in the time course assessment. Fenfluramine was administered 0.5 hours after drug administration.
- Fenfluramine demonstrated minimal anticonvulsant activity in the CKM model at the doses tested (3-40 mg/kg).
- No motor impairment was evident at doses tested.
- Maximum protection was 50% at 30 minutes after an ip dose of 30 mg/kg.

Discussion

- The MES model may provide a non-Dravet model to study the antiseizure activity of fenfluramine.
- This study shows that fenfluramine is most effective in inhibiting generalized tonic-clonic seizures in the MES seizure model.
- Fenfluramine was without dose-dependent effect in the CMM.
- Reports of anticonvulsant activity of fenfluramine: Fenfluramine (10 mg/kg ip) was shown to block hindlimb extension in the MES model at a dose that exceeds the median behaviorally-impairing dose, as measured by the rotarod test preceding anticonvulsant testing as described above.

Conclusions

- The three seizure models tested in this study are thought to be associated with different types of seizures, possibly suggesting different underlying neurological circuits that contribute to the seizure phenotype.
- The MES model may provide a non-Dravet model to study the antiseizure mechanisms of fenfluramine.

References

- Edward Weselcouch, PhD, of PharmaWrite, LLC (Princeton, NJ), and was employed, Ownership interest in Zogenix, Inc.
- PM, TR: Employment, University of Washington.
- HSW, MB-H: Employment, Zogenix, Inc.