The effects of two GABA-enhancing drugs on Dravet Syndrome

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Abstract

Background: Dravet Syndrome is a form of intractable epilepsy usually developing during the first year of life. Psychomotor delay and a variety of cognitive impairments typically occur, similar to Autism Spectrum Disorder. Dravet Syndrome is linked to a mutation of the SCN1A gene that alters sodium channels, resulting in impaired GABAergic inhibitory interneurons and increased seizure activity in animals.

Methods: An 11:12-year-old patient with Dravet syndrome was administered two different GABA-enhancing drugs for 7 days during a recording to generate sufficient artifact for analysis of the EEG and seizure activity. Day 1 was the base line of starting stiripentol. There were no seizures observed 2 days after starting stiripentol. There were 42 seizures for the 4 weeks preceding administration of clonazepam. There were 2 seizures during a recording to generate sufficient artifact prior to treatment. After treatment, phase lock Z-scores were substantially reduced by variable amounts depending on location. See Figure 5.

Results: Change in seizure frequency was correlated with changes in EEG. Notably, there were dramatic changes in theta absolute power, theta coherence and theta phase reset. See Figure 6.

Conclusions: Both medications showed significant change in areas outside of source localization because of the genetic mutation and also affect areas not involved in the role of starting stiripentol. There were no seizures observed 42 days after starting clonazepam. See Figure 7.

Clonazepam was administered when there was an acute increase in seizures. For both administrations there were 6 seizures noted 2 days before the dose of clonazepam was given. Seizure frequency decreased to 2 seizures within a day after administration of clonazepam. However, 4-10 days after both administrations of clonazepam, there were 13-17 seizures observed. See Figure 1.

The decision was made for the patient to undergo a trial of stiripentol. qEEG data was recorded on 07/29/11, 3 days before starting stiripentol. There were 42 seizures for the 4 weeks preceding administration of clonazepam. There were 2 seizures during a recording to generate sufficient artifact prior to treatment. After treatment, phase lock Z-scores were substantially reduced by variable amounts depending on location; reductions were greater than those observed after administration of clonazepam. See Figure 7.

As with clonazepam, LORETA analysis after stiripentol administration showed maximum reduction of activity at 5 Hz based on Z-scores. Source localization of maximum change differed between the first and second administrations of clonazepam in the post- and pre-treatment periods. See Figure 8.

Discussion

Both medications showed significant changes in areas outside of source localization indicating effects of medication were not limited to one location. Neither medication had major side effects such as sedation or ataxia, and both were well tolerated. The decision to administer clonazepam is a result of the patient’s increasing seizure frequency. See Figure 7a.

Conclusion

These data demonstrate the effectiveness of GABA-enhancing drugs with a single case of Dravet Syndrome with a 99% reduction in the total number of seizures. Administration of clonazepam and stiripentol reduced seizure frequency with corresponding statistically significant changes in Z-score measures. These results further validate the effectiveness of these drugs in the treatment of Dravet Syndrome. EEG changes indicate a non-epileptiform effect. The change in EEG coherence, reduced beta activity and reduced phase lock Z-scores, which is in contrast to other studies that show GABA to be alpha 1 and alpha 2. This further indicates the potential for two drugs targeting GABA, including the combination of clonazepam, clonazepam and stiripentol, to be effective for other patients with Dravet Syndrome and potentially Autism. Neurofeedback protocols aimed at restoring the changes observed in this study may also prove to be an effective, non-medication treatment for Dravet Syndrome. Further study is warranted.

References


