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 Nav1.1 sodium channels, resulting in impaired GABAergic inhibitory interneurons and increased seizure activity in Dravet Syndrome.

Methods: An 11/12-year-old patient with Dravet syndrome was administered two different GABA-rewarding drugs, clonazepam and stiripentol, approximately a year apart. qEEG analysis was done before, during and after clonazepam treatment and continues to be assessed during concurrent stiripentol treatment.

Results: Both drugs had a significant effect on theta absolute power, theta coherence and theta phase-lock duration and also resulted in a near of total cessation of seizures. With clonazepam, administration was stopped for ten days, resulting in a return to pre-medicine qEEG characteristics and increased seizure frequency. Clonazepam was then re-administered and the same effects on the qEEG and seizure activity were observed.

Conclusions: Based on this qEEG analysis, both drugs were effective treatments for Dravet Syndrome. These data, along with the cessation of seizures during treatment, support the hypothesis that Dravet syndrome results from an impairment in GABA. Furthermore, the data demonstrates that GABA-enhancing drugs influence qEEG absolute power, coherence and phase reset. These results have implications for future treatment of Dravet Syndrome as well as possible neurofeedback interventions aimed at replicating the pharmacological influence of these medicines.

Case History

The subject of this case study is an 11/12-year-old male. He had a normal birth and development until febrile onset of seizures around 8 months. Several pharmacological attempts to control the seizures failed, including phenobarbitol, carbamazepine, levetiracetam, zonisamide, lamotrigine, phenytoin and felbamate. Seizures continued, lasting 10 min to 2 hours. The subject reached developmental milestones until age 3 at which point he regressed to age 2 development. At age 5, a vagus nerve stimulator was inserted, and it was turned off at age 8 when declared ineffective. Scheduled brain surgery was cancelled after results of genetic testing gave a diagnosis of Dravet Syndrome at age 8.5. Since then, additional pharmacological interventions have been tried including primidone, triple bromide, rufinamide and topiramate. Verapramil was tried in between this study's dosages of clonazepam and stiripentol, but was stopped when stiripentol became an option as an orphan drug in the United States that would be paid for by patient's health insurance.

Current Diagnosis:

- **Axis I:** Pervasive Developmental Disorder, NOS. ADHD, combined type, severe.
- Mixed Receptive/ Expressive Language Disorder. Developmental Coordination Disorder.
- **Axis II:** Severe Mental Retardation
- **Axis III:** Dravet Syndrome

Background

This subject with Dravet Syndrome has a P185S mutation in the SCN1A gene, affecting the sodium channel of his GABAergic interneurons. This impairment of GABAergic interneurons is thought to reduce their inhibitory action and facilitate a condition where seizure activity can occur.

Divalproex sodium is thought to work by increasing concentrations of GABA in the brain (Abbott Laboratories, 2010). Clobozam is a 1,5 benzodiazepine different than other benzodiazepines. The mechanism of action is thought to be biding to the receptor site of the $GABA_A$ receptor (Lundbeck, Inc., 2011). Clonazepam is a 1,4 benzodiazepine thought to work by enhancement of GABA activity (Genentech, Inc., 2010).

Stiripentol is thought to work by increasing the amout of time that the $GABA_A$ receptor channels are open, creating "a barbiturate-like effect ." Stiripentol is also thought to enhance the effects of other antiepileptic drugs through inhibition of liver cytochrome P450 (Quilichini, Chiron, Ben-Ari, and Gozlan , 2006).

Methods

Data was first collected on 04/30/10 with the subject taking dalvaproex sodium sprinkles 1,000 mg and clobozam 10 mg (Table 1). On 07/06/10 clonazepam was administered and data was recorded on 07/07/10. Data was again recorded on 07/16/10, which had given the clonazepam 5 half-lives to exit the body. A second dose of clonazepam was administered on 07/29/10 with EEG data recorded on 07/30/10.

Data was recorded on 07/29/11 with the subject taking dalvaproex sodium sprinkles 1,000 mg and clobozam 10 mg (Table 1). The subject then started stiripentol 500 mg daily on 08/01/11. EEG data was collected on 08/26/11 and 09/02/11 with the patient taking divalproex sodium, clobozam and stiripentol.

All data was collected using a Cadwell Easy-2 amplifier. A 19-channel Electrocap was placed on the subject using the international 10/20 system of electrode placement. The subject was seated and recording was done in the eyes-open condition for all recordings. The subject was unable to stay still in an eyes-open state during a recording to generate sufficient artifact-free data. Thus all data was recorded with the subject viewing one of three animated movies familiar to the subject.

Data was then analyzed using the Neuroguide™ eyes-open normative database and a linked-ear montage. All selections were at least 60 seconds long. Split-half and test-retest reliability was >0.90 for all recorded sites. Z-scored data was then exported to LORETA (Low Resolution Brain Electromagnetic Tomography). Z-scored source localization was calculated. Neuroguide's Neurostat program was used to compare Z-scores between recording sessions. Neurostat was also used to run a paired t-test on identified maximal sites of change as determined by Z-scored Neurostat analysis.

Table 1. Medications and data collection.

	4/30/10	7/6/10	7/7/10	7/16/10	7/29/10	7/30/10	7/29/11	8/26/11	9/2/11
Dalvaproex sodium sprinkles 1,000 mg									
Clobazam 10 mg									
Clonazepam 10 mg									
Stiripentol 500 mg									
EEG data collected									

Figure 1: Seizure frequency before and after clonazepam.

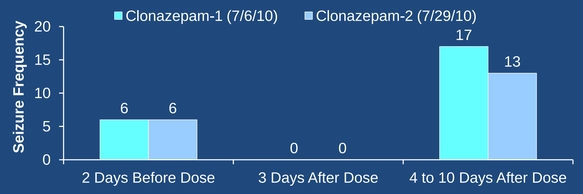


Figure 2: Summary maps of qEEG analysis off-clonazepam 07/16/10 (a) and on clonazepam 07/30/10 (b).

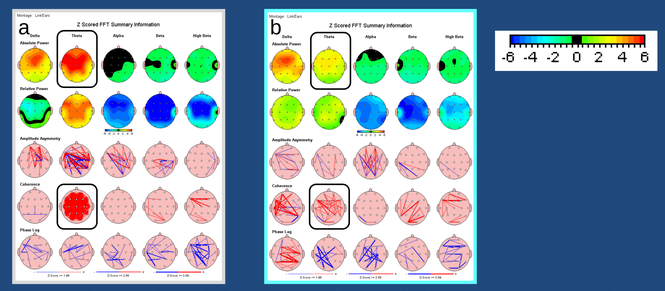


Figure 3: Theta phase lock qEEG analysis off-clonazepam 07/16/10 (a) and on clonazepam 07/30/10 (b).

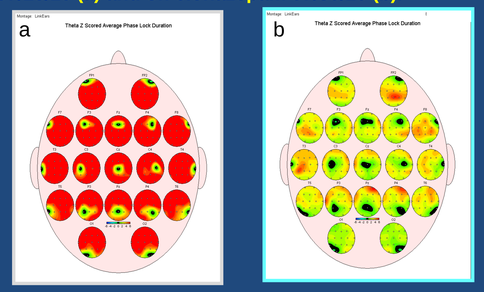
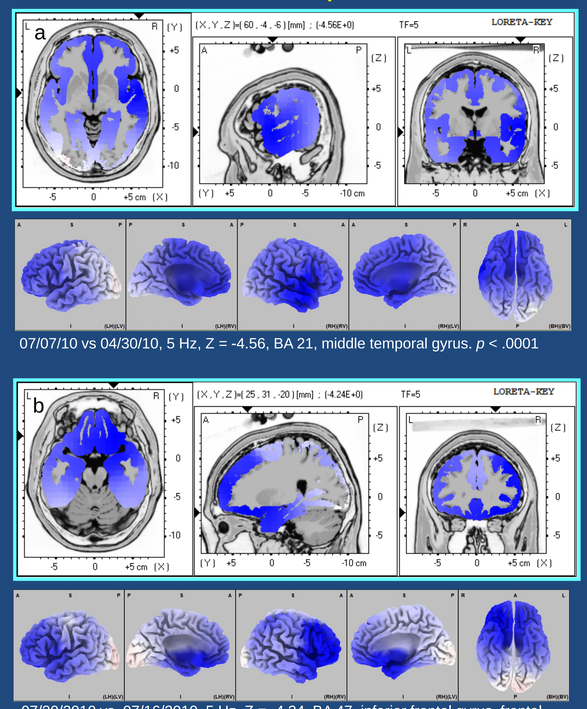


Figure 4: LORETA maps for first (a) and second (b) administrations of clonazepam. Blue color demonstrates a reduction in Z-scored value of amplitude.



07/07/10 vs 04/30/10, 5 Hz, Z = -4.56, BA 21, middle temporal gyrus. $p < .0001$

07/30/2010 vs. 07/16/2010, 5 Hz, Z = -4.24, BA 47, inferior frontal gyrus, frontal lobe. $p < .0001$

Figure 5: Seizure frequency before and after stiripentol.

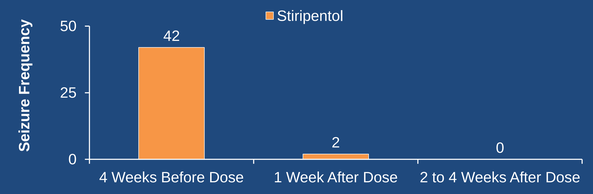


Figure 6: Summary maps of qEEG analysis off-stiripentol 07/19/11 (a) and on clonazepam 08/26/11 (b).

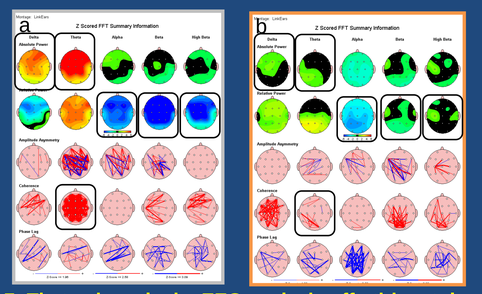


Figure 7: Theta phase lock qEEG analysis off-stiripentol 07/19/11 (a) and on clonazepam 08/26/11 (b).

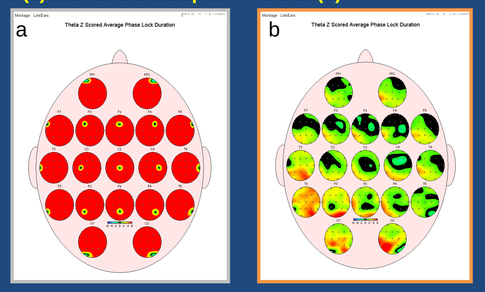
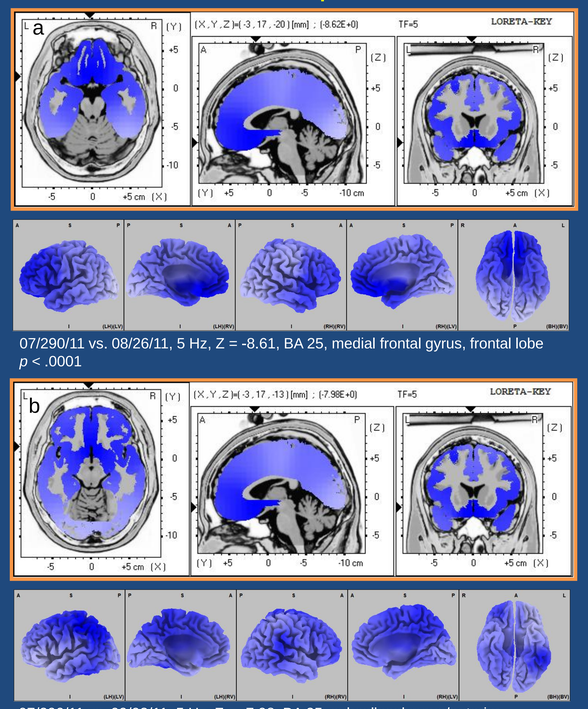


Figure 8: LORETA maps for first (a) and second (b) administrations of stiripentol. Blue color demonstrates a reduction in Z-scored value of amplitude.



07/290/11 vs. 08/26/11, 5 Hz, Z = -8.61, BA 25, medial frontal gyrus, frontal lobe $p < .0001$

07/290/11 vs. 09/02/11, 5 Hz, Z = -7.98, BA 25, subcallosal gyrus/anterior cingulate, frontal lobe, $p < .0001$

Results – Clonazepam Study

Clonazepam was administred 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. Subsequently, there were no seizures noted for 3 days after the administration of clonazepam. However, 4-10 days after both administrations of clonazepam, there were 13-17 seizures observed . See Figure 1.

Change in seizure frequency was correlated with changes in qEEG. Notably, there were dramatic changes in theta absoulte power, theta coherence and theta phase reset. See Figure 2. Theta phase lock demonstrated high Z-scored values (Z >6) at all locations prior to treatment. After treatment, phase lock Z-scores were substantially reduced by variable amounts depending on location. See Figure 3.

LORETA analysis 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. Z-score changes >1.0 were diffuse. See Figure 4.

Results – Stiripentol Study

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 preceeding administration of stiripentol. There were 2 seizures observed the week of starting stiripentol. There were no seizures observed 2-4 weeks after starting stiripentol. See Figure 5.

Change in seizure frequency was correlated with changes in qEEG. Notably, there were dramatic changes in theta absoulte power, theta coherence and theta phase reset. Unlike with clonazepam, there were also changes in delta absolute power as well as alpha, beta and high beta relative power. See Figure 6. Theta phase lock demonstrated high Z-scored values (Z >6) at all locations 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 were in the same BA 25, differeing slightly in localization and not in amount (Z ≈ -8.0). Z-score changes >1.0 were diffuse. See Figure 8.

Discussion

Both medications showed significant change in areas outside of source localization indicating effects of medication were not limited to one location. Neither medication had maximal source localization in the hippocampal region, the area thought to be a primary site of involvement in the SCN1A mutation of the GABAergic interneurons. However, there were statistically significant changes in theta levels localized to the hippocampal region. This suggests that both clonazepam and stiripentol affect the areas where the SCN1A mutation expresses itself. This further suggests that these drugs compensate for the functional abnormalities because of the genetic mutation and also affect areas not affected by the mutation, serving as a compensatory mechanism for the pathogenesis.

Thatcher, et al (2009) identified a relationship between phase lock, phase reset, GABA and autism. This case demonstrates a relationship between GABA, phase lock, phase reset and Dravet Syndrome, which shares many symptoms of Autism. The Autism study noted phase reset and phase lock issues in the alpha 1 (8-10 Hz) and alpha 2 (10-12 Hz) bandwidths and linked this change in phase to GABA abnormalities. This case showed changes in phase in the theta (4-8 Hz) band suggesting a relationship between GABA and theta phase lock, as well as theta amplitude and coherence.

Conclusion

These data demonstrate the effectivness of GABA enhancing drugs with a single case of Dravet Syndrome with a P185S mutation in the SCN1A gene. Administration of both clonazepam and stiripentol reduced seizure frequency with correspinding statistically significant changes in Z-scored qEEG measures. These results further validate the effectiveness of these drugs in the treatment of Dravet Syndrome. qEEG changes indicate a relationship between GABA and theta amplituide, theta coherence, and theta phase lock, which is in contrast to other studies that show GABA to be related to alpha 1 and alpha 2 phase shift and phase lock only. These results demonstrate the potential for drugs targeting GABA, including the combination of divalproex sodium, clobozam and clonazepam or stiripentol to help other patients with Dravet Syndrome and potentially Autism. Neurofeedback protocols aimed at reinforcing the changes observed in this study may also prove to be an effective, non-medication treatment for Dravet Syndrome. Further study is warranted.

References

Abbott Laboratories. Depakote (dalvaproex) sodium sprinkles [package insert]. North Chicago, IL: 2010.

Genentech, Inc. Klonopin (clonazepam) tablets [package insert]. South San Francisco, CA: 2010.

Lundbeck, Inc. Onfi (clobazam) tablets [package insert]. Deerfield, IL: 2011.

Quilichini, P.P., Chiron, C., Ben-Ari, Y., Gozlan, H. (2006). Steripentol, a putative antiepileptic drug, enchances the duration of opening the GABA-A receptor channels. *Epilepsia 47,(4),* 704-716.

Thatcher, R. W., North, D. W., Neaubrander, J., Biver, D. M., Cutler, S., & DeFina P. (2009). Autism and EEG phase reset: Deficient GABA mediated inhibition in thalamo-cortical circuits. *Developmental Neuropsychology 34(6),* 780–800.