Non-inferiority prospective randomized trial of acetazolamide vs diazepam in patients with continuous spike and wave in sleep (CSWS)/Landau Kleffner syndrome (LKS)

NCT# 02904265

January 13, 2017

NON-INFERIORITY PROSPECTIVE RANDOMIZED TRIAL OF ACETAZOLAMIDE VS DIAZEPAM IN PATIENTS WITH CONTINUOUS SPIKE AND WAVE IN SLEEP (CSWS)/LANDAU-KLEFFNER SYNDROME (LKS)

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Supported by: N/A

Study Intervention Provided by: N/A

Sponsor of IND (IDE): N/A

Version 5
January 13, 2017

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PRÉCIS

Electrical status epilepticus in sleep is a pattern on electroencephalogram (EEG) in which there is nearly continuous activation of epileptiform discharges in slow-wave sleep. Some children, who have a history of normal development, develop language regression with this pattern and are diagnosed with Landau-Kleffner syndrome (LKS). Other children, typically with a history of developmental delay, seizures, and abnormal neuroimaging, experience global regression of skills and are diagnosed with continuous spike and wave in slow wave sleep (CSWS). Both disorders are associated with poor developmental outcomes if not aggressively treated and represent potentially treatable causes of developmental regression in childhood.

There is no consensus regarding optimal therapy for these disorders and practice is based on small series and expert opinion. One of the agreed upon first line options for these children is high-dose diazepam (0.5 mg/kg/day) which is typically effective in treatment of ESES, but has significant behavioral and cognitive side effects, necessitating brief, pulsatile, treatment periods. Relapse when diazepam is discontinued occurs on over 50% of patients.

Our group has had success in using acetazolamide, a carbonic anhydrase inhibitor FDA approved for the treatment of epilepsy, in children with refractory ESES. We published a case series of 6 children treated with acetazolamide for refractory ESES and at initial follow-up 50% had significant improvement in their spike-wave index (measure of ESES).

Acetazolamide is a well-tolerated medication and has minimal side effects compared to diazepam and other therapies for ESES. Furthermore, acetazolamide can be used as a chronic, rather than intermittent, medication. There have been no studies comparing the efficacy of acetazolamide to diazepam as first line therapy. Our goal is to compare the use of acetazolamide versus diazepam as first line therapy for newly diagnosed ESES in a prospective randomized non-inferiority trial in pediatric patients in the pediatric epilepsy monitoring unit.

Study Title

Non-inferiority prospective randomized trial of acetazolamide (AZM) vs diazepam (DZP) in patients with CSWS/LKS

Objectives

1) To establish non-inferiority of acetazolamide compared to diazepam in children with ESES and clinical CSWS/LKS
2) To demonstrate frequency of ESES relapse in children on long term acetazolamide therapy vs pulse diazepam therapy

Design and Outcomes

This study will be a prospective randomized study to assess the non-inferiority of acetazolamide compared to diazepam as first-line therapy in the treatment of ESES in

pediatric patients aged 3 through 12 years old, inclusive, diagnosed with LKS/CSWS. We will be assessing medication efficacy through measurement of spike-wave index (SWI) and follow-up SWI following intervention, as well as behavioral scales pre- and post-intervention. Additionally, we will assess the frequency of ESES relapse in children on long-term acetazolamide therapy versus pulse diazepam therapy.

Evaluations to be performed include Pediatric Epilepsy Monitoring Unit (PEMU) admission for overnight video EEG monitoring, and baseline behavioral assessments including the Vineland and Vanderbilt forms once a diagnosis of ESES has been made. The subject will then be randomized to either AZM or DZP. The subject will then have repeat overnight EEG and behavioral assessments in 4-5 weeks. If there is SWI response, the primary neurologist will decide whether to continue or wean the study medication. If there is no response or worsening, then the subject may cross-over to the other medication and the EEG and developmental assessments will be repeated after 4-5 weeks.

Interventions and Duration

Interventions to be compared are treatment with acetazolamide versus diazepam. Patients will be randomly selected to receive either diazepam 0.5 mg/kg to a maximum dose of 20 mg by mouth each evening or acetazolamide at an initial dose of 8 to 10 mg/kg/d divided BID to a maximum dose of 375 mg BID to be uptitrated to a maximum dose of 11-16 mg/kg/d divided BID or 750 mg BID. Patients will remain on treatment for 4 to 5 weeks duration at which efficacy will be assessed. If effective, the patient may continue or wean the medication at the discretion of the child's primary neurologist. If the study medication is ineffective, they may opt to cross-over to the other study drug and efficacy will be assessed after an additional 4 to 5 weeks. Subjects will be followed clinically for 6 months following enrollment in the study to assess cognitive and behavioral outcomes and to assess for potential relapse of ESES in the follow-up period.

Sample Size and Population

The target population is pediatric patients aged 3-12 years, inclusive, with a diagnosis of ESES and CSWS/LKS who will be prospectively recruited. Subjects will be recruited from our Pediatric Neurology outpatient clinic at Mayo Clinic in Rochester, MN The goal number of participants will be 100 patients total. There should be approximately 50 patients per treatment group (i.e. 50 in AZM group and 50 in DZP group).

After identification of patients who meet study inclusion criteria, randomization to either treatment will occur through computer generated randomization. Supervising physician, subjects, and families will not be blinded to treatment.

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1 STUDY OBJECTIVES

1.1 Primary Objective

The primary objective is to evaluate the non-inferiority of acetazolamide versus diazepam as the first-line therapy in children with ESES and the clinical diagnosis of continuous spike and wave in sleep (CSWS) or Landau-Kleffner syndrome (LKS). We hypothesize that there is no difference in the efficacy in acetazolamide compared to diazepam when used as the initial therapy in the treatment of ESES.

The primary objective will be measured using the spike wave index (SWI), a measure of percentage of seconds containing a potentially epileptiform discharge (spikes and/or sharp waves) during slow wave sleep (Galanopoulou 2000). Baseline SWI prior to initiation of therapy will be compared to post-treatment SWI. The SWI will act as an electrographic measure of intervention. Additional measures to assess clinical change will be the Vineland and Vanderbilt behavioral scales which we will use to compare baseline behavior/attention to post-treatment behavior/attention.

1.2 Secondary Objectives

The secondary objectives are to assess the frequency of clinical and electrographic relapse of ESES in children treated with long-term acetazolamide versus pulse diazepam therapy.

2 BACKGROUND AND RATIONALE

2.1 Background on Condition, Disease, or Other Primary Study Focus

The electroclinical syndromes of continuous spike and wave in slow wave sleep (CSWS) and Landau-Kleffner syndrome (LKS) are seen only in the pediatric population. Children affected are typically between the ages of 3 to 12 years of age with a peak onset of 5 to 7 years. It is felt that the continuous activation of epileptiform discharges (ESES) leads to developmental regression and loss of previously acquired skills. In LKS, speech and language can be most severely affected and children will often develop an auditory agnosia. CSWS is associated with global regression of skills and higher seizure burden. In addition to the loss of skills, there are behavioral abnormalities seen, including hyperactivity, inattention, aggressiveness, and autistic-like behaviors. The pattern of ESES is felt to self-resolve by adolescence in the majority of children. However, the developmental milestones lost and behavioral effects will remain. Prior studies have shown that longer duration of ESES and earlier onset of ESES are associated with poorer cognitive outcomes, highlighting the need for early recognition and initiation of therapy (Rossi 1999, Scholtes 2005).

There is no consensus regarding optimal therapy for these disorders and practice is based on small series and expert opinion. Therapies that are trialed in ESES include the antiepileptic medications, immunomodulatory therapies (steroids, IVIG, plasma exchange), dietary therapy (ketogenic diet, modified Atkins diet), and surgery (multiple subpial transections, lesionectomy/lobectomy). Therapy choice varies by institution and

anecdotal evidence.

Acetazolamide is a well-tolerated medication and has minimal side effects compared to benzodiazepines and other therapies for ESES (Fine 2015, Veggiotti 2012). Furthermore, acetazolamide can be used as a chronic, rather than intermittent, medication.

There have been no studies comparing the efficacy of acetazolamide to diazepam as first line therapy. Our goal is to compare the use of acetazolamide versus diazepam as first line therapy for newly diagnosed ESES in a prospective randomized non-inferiority trial in pediatric patients in the pediatric epilepsy monitoring unit.

2.2 Study Rationale

One of the agreed upon first line options for these children is high-dose diazepam (0.5 mg/kg/day) which is typically effective in treatment of ESES, but has significant behavioral and cognitive side effects, necessitating brief, pulsatile, treatment periods (DeNegri 1995, Francois 2014, Sanchez-Fernandez 2013). Relapse when diazepam is discontinued occurs on over 50% of patients (Inustuka 2006).

Our group has had success in using acetazolamide, a carbonic anhydrase inhibitor FDA approved for the treatment of epilepsy, in children with refractory ESES. The use of acetazolamide by our epilepsy group was inspired by a previous publication by Dr. Wirrell on the use of sulthiame, another carbonic anhydrase inhibitor used in the treatment of epilepsy, in the treatment of a child with CSWS (Wirrell 2006). However, sulthiame has been associated with lower cognitive performance at higher doses and this medication is not available in the US (Wirrell 2008).

The antiepileptic properties of carbonic anhydrase inhibitors are felt to be related to pH shifts caused changes in $HCO3^-$ and CO2 in the neuronal environment. There are over 13 known carbonic anhydrase isoforms with 11 found in the brain. Acetazolamide is a membrane permeable sulfonamide carbonic anhydrase inhibitor. The exact mechanism as an anticonvulsant has not been clearly elucidated (Ruusuvuori 2014). In vitro studies suggest that acetazolamide may alter the $GABA_A$ receptor dependent HCO3 efflux in the maintenance of epileptiform events and use of AZM in in vitro studies can reduce epileptiform discharges by reducing neuronal synchronization (Hamidi 2015).

We published a retrospective case series of 6 children treated with acetazolamide for refractory ESES and at initial follow-up 50% had significant improvement in their spike-wave index (measure of ESES) (Fine 2015). SWI reduction was maintained in 50% of these children. In our unpublished data from that study, 2 additional children who did not meet our inclusion criteria for analysis had initial spike wave improvement when initiated on AZM for ESES recurrence.

3 STUDY DESIGN

This study will be a prospective randomized open-label non-inferiority study comparing

acetazolamide to diazepam when used as the first line therapy in pediatric patients for the treatment of ESES. We hypothesize that there is no difference in the efficacy of acetazolamide compared to diazepam, which is the typical agreed upon first line therapy, in the treatment of the ESES disorders of CSWS/LKS. To determine the efficacy of these medications, we will be evaluating the spike-wave indices (SWI) which is a measure of ESES, as well as developmental assessments with Vanderbilt and Vineland questionnaires. We will additionally be evaluating for the frequency of ESES relapse in children on long-term acetazolamide therapy compared to diazepam therapy.

The study population will be pediatric patients with epilepsy aged 3 to 12 years, inclusive, with a diagnosis on EEG of ESES and a clinical diagnosis of CSWS/LKS. This specific age range has been chosen as this is the typical range of age of onset of ESES (Nickels 2008). Our target sample size will be 100 total patients recruited from Mayo Clinic Rochester We aim to randomize approximately 50 subjects to receive AZM and 50 subjects to receive DZP.

The study location will be the inpatient Pediatric Epilepsy Monitoring Unit (PEMU). This is where the consent process, overnight EEG, randomization, behavioral assessments, and monitoring for side effects will occur. Additional evaluations may occur at visits with the subjects' primary neurologist/epileptologist in the outpatient Pediatric Neurology clinic. The location will be the inpatient PEMU at Mayo Clinic Rochester, St. Marys Campus.

The entire study is expected to last approximately 3 years in duration (subject enrollment, data acquisition, data analysis, and manuscript preparation). For each individual participant, the approximate duration of the study is 6 months, including follow-up period.

The interventions to be performed include the prescription of either acetazolamide or diazepam after randomization (randomization to be performed by computer generated randomization program). There will be no blinding of the prescribing epileptologist, patient, or caregiver. Medication will be dispensed by the inpatient pharmacy while the subject is in the inpatient PEMU and then will be dispensed via the outpatient pharmacy on hospital dismissal. Medications will be given orally (PO).

4 SELECTION AND ENROLLMENT OF PARTICIPANTS

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to participate in this study:

- Child aged 3-12 years of age, inclusive.
- ESES and clinical CSWS/LKS defined by all of the following (confirmed during inpatient PEMU evaluation):
    - SWI ≥50% during first hour of sleep
    - Bilateral synchrony of discharges during sleep
    - Clinical evidence of behavior and/or academic regression

- Daytime SWI ≤20%

4.2 Exclusion Criteria

All candidates for study enrollment meeting any of the following exclusion criteria at baseline evaluation will be excluded from study participation.

- Previous treatment with benzodiazepine or acetazolamide for ESES
- Current treatment with carbamazepine, phenytoin, oxcarbazepine, phenobarbital, vigabatrin
- AED medication changes over the month prior to enrollment
- Epileptic encephalopathy other than CSWS/LKS
- Prior serious adverse reaction to benzodiazepines or acetazolamide
- Sulfa allergy
- Progressive underlying neurologic condition
- Frequent seizures that would prevent the patient from maintaining a stable dose of medications
- Female subjects who have begun menstruation (given risk of pregnancy)

4.3 Study Enrollment Procedures

- Candidates for study recruitment will be identified and informed of the study at the outpatient Pediatric Neurology appointment. At that time, the outpatient neurologist/epileptologist can inform the attending epileptologist on the PEMU service that there is a potential study candidate. Potential subjects will then be monitored in the PEMU, according to standard practice, and if ESES is confirmed on overnight EEG then the study will be further discussed and subjects will be consented.
- Candidates who are ineligible for study enrollment and/or those who chose to not participate in this study will be documented in our "Screening Log."
- Once eligibility for enrollment in this study with confirmation of ESES is performed, then consent of the subject/parent will occur. We have prepared signed informed consent documents which will be discussed with subject/caregivers and signed by parents/caregivers. We additionally will have informed assent for children who are unable to adequately provide informed consent.
- Medication randomization will occur after consent process is performed. Subjects will be entered into a spreadsheet which contains computer generated randomization and assigns the subject to either the AZM or DZP group. No blinding will occur.

5 STUDY INTERVENTIONS

5.1 Interventions, Administration, and Duration

The intervention to be performed in this study is the randomization to receive either diazepam or acetazolamide. Subjects will also undergo behavioral rating scales at baseline, at 4-5 weeks following medication initiation, and potentially at 8-10 weeks if they cross-over to the other medication.

The dosing of diazepam is 0.5 mg/kg to a maximum dose of 20 mg by mouth (PO) each evening. At hospital discharge, the subject will be given a prescription at their target dose which will be dispensed by the outpatient pharmacy.

Potential side effects of diazepam include agitation, sedation, mood changes. If there is concern for medication toxicity or side effects, the dose of diazepam can be reduced at the attending neurologist/epileptologist's discretion. The side effects experienced and new dose must be clearly documented.

Diazepam is a medication in the benzodiazepine class that is FDA approved for the treatment of epilepsy in children down to 6 months of age. The dosing used in the treatment of ESES is higher than typically used in the treatment of epilepsy. However, this regimen and dose is well-agreed upon in the epilepsy literature and is in line with our standard of care in the treatment of this syndrome (Inutsuka 2006, Kramer 2009, Nickels 2008, Sanchez Fernandez 2014)

The dosing of acetazolamide will be 8-10 mg/kg up to a maximum dose of 375 mg by mouth (PO) divided twice daily X 1 week, then increased to 11-16 mg/kg to a maximum dose of 750 mg by mouth divided twice daily thereafter. At hospital discharge, the subject will be given a prescription and instructions for titration to goal dose, which will be dispensed by the outpatient pharmacy.

Potential side effects of acetazolamide include decreased appetite, nausea, diarrhea, paresthesias (tingling in hands, feet, around mouth), funny taste to carbonated beverages, and risk of kidney stones (in combination with certain medications). If there is concern for medication toxicity or side effects, then the dose of acetazolamide can be reduced at the attending neurologist/epileptologist's discretion. The side effects experienced and new dose must be clearly documented.

Acetazolamide is a sulfonamide carbonic anhydrase inhibitor that is FDA approved in the treatment of epilepsy in patients 12 years and older. It is approved for the treatment of multiple epilepsy types. While it is has not been FDA approved to be used in children, there are multiple reports in the literature regarding its successful and safe use (Irahara 2011, Go 2009, Vradkar 2003, Katayama 2002). Additionally, the use of acetazolamide in the treatment of ESES has been studied previously and is in line with our standard of care in the treatment of this syndrome (Pisani 1995, Fine 2015).

5.2 Handling of Study Interventions

The medication will be provided by the outpatient pharmacy at Mayo Clinic Rochester. Subjects/caregivers may wish to have their outpatient prescription filled at a local pharmacy. The cost of the medications to be used in this study will not be paid for through research funds, since the treatment using either medication is in line with our standard of care in the treatment of this syndrome. Medication will be dispensed to the subject and payment will be the subject/caregiver responsibility.

5.3 Concomitant Interventions

5.3.1 Allowed Interventions

- Subjects may receive their prescribed seizure rescue medications as needed (i.e. diazepam rectal gel, diazepam buccal solution, lorazepam buccal solution, midazolam intranasal solution, clonazepam tablets, etc.)
- Subjects may take their previously prescribed antiepileptic therapy, provided that the there are no dose adjustments made prior to, during, or after the enrollment period.

5.3.2 Required Interventions

- Baseline overnight EEG in the PEMU
- Baseline Vineland scale
- Baseline Vanderbilt Parent scale
- Follow-up PEMU stay or ambulatory 24-hour EEG at 4-5 weeks post medication initiation (and at 8-10 weeks if cross-over)
- Follow-up Vineland scale at 4-5 weeks post medication initiation (and at 8-10 weeks if cross-over)
- Follow-up Vanderbilt Parent scale at 4-5 weeks post medication initiation (and at 8-10 weeks if cross-over)

5.3.3 Prohibited Interventions

- The use of the following antiepileptic agents is prohibited during this study, due to known exacerbation of ESES associated with these medications:
    - oxcarbazepine,
    - carbamazepine,
    - phenytoin,
    - phenobarbital,
    - vigabatrin,

5.4 Adherence Assessment

Adherence to the study regimen will be defined as those study participants who complete both baseline EEG and behavioral scales and post-intervention EEG and behavioral scales. As medication will be dispensed to subjects, we cannot ensure medication compliance. If participants do not complete the follow-up testing, then they will be considered withdrawn from this study and their information will not be analyzed. Adherence will need to be 100% to all required study interventions in order for subjects to count towards data analysis.

6 STUDY PROCEDURES

6.1 Schedule of Evaluations

1) Part 1
    a. Patients with suspected CSWS/LKS will have education regarding syndrome, treatment, and possible enrollment into study discussed prior to PEMU admission
    b. Patient will be admitted to Pediatric Epilepsy Monitoring Unit (PEMU) for overnight admission to confirm presence of ESES, consistent with standard practice of care
    c. After confirmation of ESES on EEG, parental consent and child assent will be completed (day 2 of admission) by the supervising consultant on the PEMU service to provide clinical care
    d. Patients meeting above inclusion/exclusion criteria with be randomly selected to receive either:
        i. Diazepam 0.5 mg/kg to a maximum dose of 20 mg by mouth each evening, or
        ii. Acetazolamide 8-10 mg/kg to a maximum dose of 375 mg by mouth divided twice daily X 1 week, then increase to 11-16 mg/kg to a maximum dose of 750 mg by mouth divided twice daily thereafter
    e. Randomization will be completed through computer program. Patient/family and consenting provider will not be blinded to treatment.
    f. Vanderbilt and Vineland assessments will be completed at the time of enrollment to assess focus, attention, and behavior (day 2 of PEMU admission, prior to discharge)
        i. Should the scoring on Vanderbilt Parent scales rate positive then a Vanderbilt Teacher scale will be sent home with the family
        ii. Vanderbilt Teacher scale will be mailed back to study staff for scoring
        iii. If both Parent and Teacher scales are positive then a referral to Child Psychiatry will be offered to family

g. The first hour of overnight sleep EEG will be independently reviewed by 2 pediatric epileptologists, blinded to history and treatment for confirmation for research.
    i. They will determine SWI (calculated as percent of time containing spike wave discharge during the first hour of sleep)
    ii. They will document presence of bilateral synchronous discharges

2) Part 2
    a. All other medications will be held at steady doses from 1 month prior to enrollment and continue at steady doses until return admission to PEMU for overnight EEG.
    b. Rescue medication can be given as needed for breakthrough seizures
    c. Study medications (diazepam or acetazolamide) can be reduced by the attending epileptologist if the child is experiencing unacceptable side effects.

3) Part 3
    a. Patient will return to PEMU for overnight EEG 4-5 weeks after initial assessment, consistent with current standard of care. An alternative option will be to undergo 24-hour ambulatory EEG with outpatient follow-up visit following EEG.
    b. On the day of admission/return visit:
        i. Vanderbilt and Vineland assessments will be completed at the time of admission to assess focus, attention, and behavior
            1. Should the scoring on Vanderbilt Parent scales rate positive then a Vanderbilt Teacher scale will be sent home with the family
            2. Vanderbilt Teacher scale will be mailed back to study staff for scoring
            3. If both Parent and Teacher scales are positive then a referral to Child Psychiatry will be offered to family
        ii. Parents will be questioned on whether they perceive the child's regression as improved, worse, or no change
        iii. Presence of side effects will be determined based: medication reduced, medication stopped, full medication course completed
    c. The first hour of the overnight sleep EEG will be reviewed by the supervising consultant on the PEMU service to provide clinical care
        i. Improvement will be defined as
            1. Mild improvement: decrease in SWI by 20-49%
            2. Significant improvement: decrease in SWI by ≥50%
        ii. If no improvement in EEG seen, the patient will be crossed over to the other medication
        iii. If improvement in EEG is seen, continuation or weaning of benzodiazepine or acetazolamide will be completed at the primary neurologist's discretion

iv. The patient will be monitored clinically for signs or relapse and, if they occur, readmitted to PEMU for confirmation of recurrence of ESES.

d. The first hour of the overnight sleep EEG will be reviewed by 2 pediatric epileptologists, blinded to history and treatment for confirmation for research

4) Part 4
   a. For those who crossover to the other medication, the patient will return to PEMU for overnight EEG 4-5 weeks after previous assessment or undergo 24-hour outpatient ambulatory EEG followed by outpatient return visit, consistent with the current practice of care
   b. On the day of admission to the PEMU/or return visit:
      i. Vanderbilt and Vineland assessments will be completed at the time of admission to assess focus, attention, and behavior
         1. Should the scoring on Vanderbilt Parent scales rate positive then a Vanderbilt Teacher scale will be sent home with the family
         2. Vanderbilt Teacher scale will be mailed back to study staff for scoring
         3. If both Parent and Teacher scales are positive then a referral to Child Psychiatry will be offered to family
      ii. Parents will be questioned on whether they perceive the child's regression as improved, worse, or no change
      iii. Presence of side effects will be determined based: medication reduced, medication stopped, full medication course completed
   c. The first hour of the EEG will be reviewed by the supervising consultant on the PEMU service to provide clinical care
      i. Improvement will be defined as
         1. Mild improvement: decrease in SWI by 20-49%
         2. Significant improvement: decrease in SWI by ≥50%
      ii. Additional medication management will be completed at the primary neurologist's discretion
   d. The first hour of the overnight sleep EEG will be reviewed by 2 pediatric epileptologists, blinded to history and treatment for confirmation for research

6.2 Description of Evaluations

6.2.1 Screening Evaluation

Screening

Potential candidates will be identified in the outpatient Child Neurology clinic. At that time, this study may be discussed with subjects and their families as an introduction; however, screening will not take place until admission to the PEMU occurs.

Once potential candidates are admitted to the PEMU, they will undergo overnight EEG as part of their evaluation for ESES (routine standard of care for children with suspected ESES). If an ESES pattern is identified and other inclusion criteria are met, then the study will be discussed and consenting will occur.

Overnight EEG must be performed at the time of study enrollment for a subject to participate in this study.

Consenting Procedure

Informed consent will take place after identification of eligible candidates via screening EEG. All study staff will be able to consent participants into the study. The informed consent will be signed by the parents/guardians after the consent procedure. An assent form is also available for children who can participate in the assent process. Once consent is obtained, this document will be scanned into the electronic medical record (EMR) and a copy of the signed consent will be kept in a locked cabinet with other confidential study materials.

6.2.2 Enrollment, Baseline, and/or Randomization

Enrollment

Enrollment date in this study will be considered when the candidate/proxy has signed informed consent after meeting inclusion criteria.

Baseline Assessments

Following enrollment in this study, participants and parents will complete baseline behavioral assessments (on Day 2 of PEMU admission). These assessments include the Vanderbilt Assessment Scales (National Institute for Children's Health Quality), a measure of childhood behavior, primarily used to rate the symptoms of ADHD (attention deficit hyperactivity disorder), but also measures symptoms of oppositional defiant disorder, conduct disorder, depression, and anxiety. An additional assessment is the Vineland Adaptive Behavioral Scale (Pearson), which measures communication, social skills, motor skills, daily living skills, and adaptive living skills.

If scores on the Vanderbilt Parent Informant scales rate positive then Teacher scales will be sent home with families to be mailed back to study staff. If both scales rate positive, then a referral to Child Psychiatry will be offered.

Randomization

Following enrollment, the subjects will be assigned a study number. This number will then be entered into a computer program which will then randomize them to receive either of the 2 study medications (AZM or DZP).

Randomization must occur following enrollment in this study at the time of initial EEG.

6.2.3 Follow-up Visits

- Visit 2 (4-5 weeks after enrollment/initial assessment):
    - Return to PEMU for overnight EEG or 24-hour outpatient ambulatory EEG followed by outpatient return visit, according to standard practice of care
    - On the day of admission/or outpatient return visit:
        - Vanderbilt and Vineland assessments will be completed
        - Should the scoring on Vanderbilt Parent scales rate positive then a Vanderbilt Teacher scale will be sent home with the family
        - Vanderbilt Teacher scale will be mailed back to study staff for scoring
        - If both Parent and Teacher scales are positive then a referral to Child Psychiatry will be offered to family
        - Parents will be questioned on whether they perceive the child's regression as improved, worse, or no change
        - Evaluation of side-effects
    - The first hour of the overnight sleep EEG will be reviewed by the supervising consultant on the PEMU service to provide clinical care
        - Improvement will be defined as
            - Mild improvement: decrease in SWI by 20-49%
            - Significant improvement: decrease in SWI by ≥50%
        - If no improvement in EEG seen, the patient will be crossed over to the other medication
        - If improvement in EEG is seen, continuation or weaning of benzodiazepine or acetazolamide will be completed at the primary neurologist's discretion
        - The patient will be monitored clinically for signs of relapse and, if they occur, readmitted to PEMU for confirmation of recurrence of ESES, according to standard practice of care.
    - The first hour of the overnight sleep EEG will be reviewed by 2 pediatric epileptologists, blinded to history and treatment for confirmation for research
- Visit 3 (8-10 weeks after enrollment)
    - For those who crossover to the other medication, the patient will return to PEMU for overnight EEG or undergo 24-hour outpatient ambulatory EEG followed by an outpatient return visit, according to standard practice of care.
    - On the day of admission/or outpatient return visit:
        - Vanderbilt and Vineland assessments will be completed

        - Should the scoring on Vanderbilt Parent scales rate positive then a Vanderbilt Teacher scale will be sent home with the family
        - Vanderbilt Teacher scale will be mailed back to study staff for scoring
        - If both Parent and Teacher scales are positive then a referral to Child Psychiatry will be offered to family
        - Parents will be questioned on whether they perceive the child's regression as improved, worse, or no change
        - Evaluation of side-effects
    - The first hour of the EEG will be reviewed by the supervising consultant on the PEMU service to provide clinical care
        - Improvement will be defined as
            - Mild improvement: decrease in SWI by 20-49%
            - Significant improvement: decrease in SWI by ≥50%
        - Additional medication management will be completed at the primary neurologist's discretion
    - The first hour of the overnight sleep EEG will be reviewed by 2 pediatric epileptologists, blinded to history and treatment for confirmation for research

6.2.4 Completion/Final Evaluation

Participants will have completed the study investigations following either visit 2 or 3. They will have regular follow-up with their primary neurologist/epileptologist for continued medication management following study completion at the discretion of their primary neurologist.

Should a participant choose to withdraw from this study, then no additional evaluations or interventions are required for research. They should continue to be seen by their primary neurologist regarding further management.

Following study termination, continued care and management, including evaluation for concerns of possible relapse of ESES, will be provided by the primary neurologist/epileptologist.

7 SAFETY ASSESSMENTS

Intervention	**Potential adverse experience**	**Criteria for modification of intervention**
Electroencephalogram	• Scalp irritation	• Evidence of skin irritation
Acetazolamide	• Gastrointestinal upset	• Frequent diarrhea,

		concern for dehydration
	• Decreased appetite	• Weight loss
	• Rash, Stevens-Johnson syndrome	• New rash not felt to be due to other causes (such as atopic dermatitis)
Diazepam	• Behavior/mood change	• Violent/aggressive behaviors
	• Sleep disturbance	• Insomnia/excessive sedation

7.1 Specification of Safety Parameters

Subject safety will be monitored at inpatient PEMU visits. Additionally, subjects/families will be instructed on potential side effects of medication and if concern for medication side effects or toxicity will be instructed to inform study staff immediately.

For example, if a new rash is noted, the patient will be advised to see his/her primary care physician and the primary neurologist/epileptologist will be notified if the rash is not felt to be due to atopic dermatitis.

7.2 Methods and Timing for Assessing, Recording, and Analyzing Safety Parameters

Subject safety will be monitored at inpatient PEMU visits. Additionally, subjects/families will be instructed on potential side effects of medication and if concern for medication side effects or toxicity will be instructed to inform study staff immediately.

7.3 Adverse Events and Serious Adverse Events

Potential adverse events that can occur in this study are medication side effects, worsening of clinical seizures, and worsening of ESES. These are potential events that can occur in the routine treatment of a child with ESES regardless of being included in this study.

Potential side effects of diazepam include sedation, mood changes, and agitation. Potential side effects of acetazolamide include decreased appetite, nausea, diarrhea, paresthesias (tingling in hands, feet, around mouth), funny taste to carbonated beverages, and risk of kidney stones (in combination with certain medications), rash, and Stevens Johnson syndrome. If there is concern for medication toxicity or side effects, then the doses of diazepam or acetazolamide can be reduced or discontinued at the attending epileptologist's discretion.

Adverse events will be logged in our event log that will be maintained as part of our data collection. Adverse events that are deemed serious will be immediately reported to the Principal Investigator who will determine the appropriate steps and with forward the event on to our IRB for documentation.

There should be no potential serious adverse events (SAE) directly related to participating in this study as the interventions to be performed are the same as those performed in a routine PEMU visit including the use of overnight EEG, administration of benzodiazepines, and administration of antiepileptic medications. The only intervention that is not routinely performed in the PEMU are the administration of behavioral rating scales.

7.4 Reporting Procedures

All serious adverse events or events that are felt to be outside the expected potential adverse experiences that a subject may encounter by taking part in this study will be reported to the PI by study staff within 24 hours (Sunday-Thursday) or 48 hours (Friday-Saturday). The PI will then investigate the event and log the event with the IRB of record.

7.5 Follow-up for Adverse Events

All AE/SAEs will be followed through to resolution or until the investigators attribute the AE/SAEs to a cause other than the study drugs or assesses them as chronic or stable. This period may go beyond the proposed study/follow-up period for an individual subject.

7.6 Safety Monitoring

Safety monitoring will be performed per our DSMP plan. The PI will oversee subject safety and reporting any unexpected AE to the IRB. All AEs will be documented in our collection logs.

8 INTERVENTION DISCONTINUATION

Potential reasons for individual study discontinuation include:

- Voluntary subject withdrawal
- Adverse medication effects necessitating withdrawal
- Worsening of ESES requiring deviation from study protocol
- Worsening of ESES requiring use of alternative therapy
- Worsening of seizures requiring change in other anti-seizure medications
- No follow up EEG
- No follow up behavioral scales

Following discontinuation, if for reasons of medication toxicity or worsening of ESES then the subjects will continue to be followed (with permission) and be seen by their attending Pediatric Neurologist for continued management of their ESES. If the subject agrees, then information may be collected such as interventions performed at that time and in the future (i.e. future EEGs, medication interventions, etc.). Additional information to be collected on subjects who withdraw from this study include cognitive/behavioral outcomes on those not treated with diazepam or acetazolamide and those treated with brief courses of either/both medications.

9 STATISTICAL CONSIDERATIONS

9.1 General Design Issues

Our statistical hypothesis is that there is no difference in the efficacy of acetazolamide compared to diazepam in the treatment of CSWS/LKS.

We have chosen a non-inferiority study as our study design. The reason being that we believe that acetazolamide is "not inferior" to diazepam, "our standard," in the treatment of ESES. Acetazolamide may have benefits over diazepam in that the side effect profile is better tolerated in children. Additionally, it is a medication that can be used for long-term rather than short cycles.

9.2 Sample Size and Randomization

Sample size calculations

-Sample size, n, based on formula:

$n = f(\alpha, \beta) \times [\pi_s \times (100 - \pi_s) + \pi_e \times (100 - \pi_e)] / (\pi_s - \pi_e - d)^2$

Test Significance level , alpha (one-sided): 0.05

Power (1-beta): 80% (0.8)

Non-inferiority limit, d: 0.15 (15%)

Percentage 'success' in control group (diazepam): 30%-50% (based on literature)

Percentage 'success' in experimental group (acetazolamide): 50% (based on our prior review)

n= **48-276** (based on 30-50% success rate in diazepam "control" group)

(i.e. 24 – 138 per group)

-Two test group of equivalence in proportions (large equal n's)

Test Significance level , alpha (one-sided): 0.05

Standard proportion, π_s: 0.5 (50% expected response rate to diazepam)

Equivalence limit difference, $\pi_T - \pi_s$, Δ_0: 0.2 (20% difference limit)

Test expected proportion, π_T : 0.5 (50% expected response rate to acetazolamide)

Expected difference, $\pi_T - \pi_s$, Δ_1 : 0.0

Power (1-beta): 80% (0.8)

n per group : **78 subjects**

Numbers needed to treat (NNT) analysis:

Percentage of patients who experienced side effect on diazepam in literature: 25%

Percentage of patients who experienced side effects on acetazolamide in our review: 0%

Absolute risk reduction: 33.33%

NNT: 3

95%CI (2.3-4.4)

9.2.1 Treatment Assignment Procedures

Subjects will be randomized to either AZM or DZP therapy after study enrollment. Randomization will occur via computer generated program which will assign the study medication. Neither the participants nor the study investigator will be blinded to the study medication being administered. There will be no stratification.

9.3 Interim analyses and Stopping Rules

No interim analyses are planned.

Potential reasons for stopping this study include:

- Slow subject accrual
- Loss of subject follow up
- High attrition rate
- Significant number of adverse events

9.4 Outcomes

9.4.1 Primary outcome

The primary outcome measure is the non-inferiority of acetazolamide compared to diazepam as first-line therapy in ESES.

This will be measured using EEG data (SWI measurement) recorded at baseline and compared to the EEG data recorded at PEMU visit 2 (and if applicable visit 3).

This will also be measured clinically using the behavioral scales (Vineland and Vanderbilt) recorded at baseline and compared to the subsequent scales completed at PEMU visit 2 (and if applicable visit 3).

9.4.2 Secondary outcomes

The secondary outcome is the frequency of relapse of ESES that occurs in children on long-term acetazolamide therapy compared to short-cycle diazepam. This information will be obtained from the EEG data and the behavioral data and will be obtained from information seen from baseline, visit 2, visit 3, and in the follow-up period.

9.5 Data Analyses

Data analyses will be performed with the assistance of a Health Sciences Research Statistician at Mayo Clinic in Rochester.

10 DATA COLLECTION AND QUALITY ASSURANCE

10.1 Data Collection Forms

Data will be collected and entered into one standardized form. Subjects will be assigned a study ID and demographic information will be entered into a data collection form (i.e. RedCap). For confirmation of ESES and SWI, 2 pediatric epileptologists who will be blinded to subjects' diagnosis and intervention will be asked to review EEG with only the Study ID as the identifier. Epileptologists will be able to enter the interpretation of EEG into the collection sheet by using subject study ID but will not be able to enter or see other identifying information. The remainder of data collection will be entered by other study staff who do not need to be blinded to therapy.

Confidentiality of the data will be maintained as this data collection tool will be password protected and only study staff will have access. All study information will be kept in a folder on a secure, password protected server as well.

10.2 Data Management

Mayo Clinic Rochester investigators will be involved in data collection.

Data collection will occur in a centralized form where all study investigators can access. One such possibility is RedCap where users can log-in securely and enter data.

10.3 Quality Assurance

10.3.1 Training

All study staff have undergone Human Subjects Protection training.

10.3.2 Protocol Deviations

Protocol deviations will be documented and submitted to the IRB of record for review.

10.3.3 Monitoring

Protocol compliance will be monitored by the PI. The PI will receive monthly updates from investigators regarding protocol compliance and any data quality concerns.

11 PARTICIPANT RIGHTS AND CONFIDENTIALITY

11.1 Institutional Review Board (IRB) Review

This protocol and the informed consent document (uploaded separately) and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. The consent form should be separate from the protocol document.

11.2 Informed Consent Forms

A signed consent form will be obtained from each participant. For participants who cannot consent for themselves, such as those with a legal guardian (e.g. person with power of attorney), this individual must sign the consent form. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy will be given to each participant or legal guardian and this fact will be documented in the participant's record.

11.3 Participant Confidentiality

Any data, forms, reports, video recordings, and other records will be identified only by a participant identification number to maintain confidentiality. All records will be kept in a password protected server. All computer entry and networking programs will be done using participant IDs only.

11.4 Study Discontinuation

The study may be discontinued at any time by the IRB, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research participants are protected.

12 ETHICAL CONSIDERATIONS

This study is being conducted under the guiding ethical principles of respect for persons, beneficence, and justice as set forth in the report of The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research titled "Ethical Principles and Guidelines for the Protection of Human Subjects of Research," also known as "The Belmont Report."

13 PUBLICATION OF RESEARCH FINDINGS

Information regarding this study will be available publically on Clinicaltrials.gov. Study information will be updated regarding subject enrollment and preliminary information as available on this website. The data obtained from this study will be published for the scientific community.

14 REFERENCES

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15 SUPPLEMENTS/APPENDICES