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Novel Off-label Use of Desipramine in Infantile Neuroaxonal Dystrophy: targeting the sphingolipid metabolism pathway to reduce accumulation of Ceramide.

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Study investigators: Yong-hui Jiang and Monica Lemmon

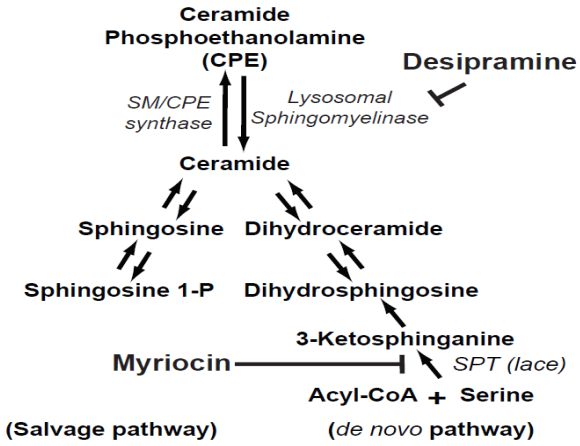
Purpose of the Study:
This study seeks to assess the potential efficacy of Desipramine in a mechanism-based therapy trial for use in Infantile Neuroaxonal Dystrophy (INAD).
Objectives: To determine the safety, efficacy, side effect profile and tolerance of Desipramine use in 3 pediatric patients with INAD.
Hypothesis: Desipramine improves the overall motor and cognitive functions and slow regression in behavioral domains of patients with INAD.

Background & Significance:
Infantile neuroaxonal dystrophy (INAD) is an extremely rare autosomal recessive neurodegenerative disorder that has grave clinical outcome and significant morbidity and mortality. For infantile onset INAD, affected children usually do not survive beyond their first decade. There is no known treatment for this condition.

Clinically, INAD is characterized by severe progressive motor and mental deterioration, which includes hypotonia, motor regression, ataxia and in some cases, seizures. The pathological hallmark of this disorder is the accumulation of axonal swellings or “spheroid” inclusions that are found throughout the central nervous system, accompanied by neuronal loss and gliosis. In some cases iron deposition in the basal ganglia may also occur.

The PLA2G6 gene encodes for iPLA2-VIA, a critical protein in lipid membrane homeostasis. These proteins control the balance between Phosphatidyl and Lysophosphatidyl lipids, which in turn act to remodel the eukaryotic membrane for diversity and symmetry. Mutation in PLA2G6 is believed to result in loss of function of PLA2G6 protein. However, the exact mechanism of how a mutation in PLA2G6 gene causes INAD is still not well understood. A recent study in fly model with PLA2G6 mutation has shown that loss of function of this protein leads to a reduced number of higher order sphingolipids such as Ceramide Phospoethanolamine, (CPE) and an increase in intermediates of the sphingolipid metabolism pathway in aged adult flies. Researchers believe that the accumulation of membranes in these nerve axons lead to axonal swellings that are found in patients with INAD.

Desipramine is a frequent prescribed tricyclic antidepressant (TCA). Desipramine is a potent and relatively selective norepinephrine reuptake inhibitor. It has been shown that Desipramine is an acidic lysosomal acidic sphingomyelinase (SMase) inhibitor that increases CPE and decreases ceramide levels (Lin et al). In the same study, it has been shown that treatment with Desipramine, could effectively correct the biochemical defect and defective neuronal phenotypes in fly PLA2G6 mutant.



Design & Procedures:

The primary objective of this study is to propose a compassion use of Desipramine in 3 patients with clinical diagnosis of INAD and confirmed by mutations in PLA2G6 gene . We will plan to collect clinical data and evaluate the efficacy of Desipramine in these 3 patients. Efficacy will be evaluated on the basis of formal cognitive assessments, physical assessments, including the Gross Motor Function Measure (GMFM) and The Quick Motor Function Test (QMFT).

Clinical assessment prior and post Desipramine dosing:

Clinical assessments will include

1) Detail medical history
2) Family history
3) Basic growth parameters: vital signs, weight, height, head circumference
4) Physical exam including comprehensive neurological and neurobehavioral exams will be conducted by Dr. Monica Lemmon, pediatric neurologist, who has been following one patient for several years and Dr. Yong-hui Jiang, who has also been following one patient over since 2016.
5) Labs: Standard of care Complete Blood Count (CBC) with differential, hepatic function panel (HFP), Basic Metabolic Panel (BMP), blood Desipramine levels, urine analysis (UA), and electrocardiogram (ECG) assessments will be noted in research file.
   Research Ceramide and CPE levels in fibroblast cells will be measured in clinically harvested skin biopsy if permission is provided by participant/parent/guardian.
   Tissue will be stored at Duke in the Rare Diseases Biorepository of Yong-hui Jiang, MD, PhD. (IRB# 100298)

Dosing regimen

Participants will receive clinically prescribed oral Desipramine at an initial dose of 2mg/kg once daily.

Dose may be increased to 4mg/kg after 2-4 weeks if no side effects are noted and an increase in dose is considered by the treating physician to be warranted.

For participants unable to swallow whole tablets the desipramine tablet should be dissolved in 20mL water. After the tablet dissolves completely (3-10mins), it should be immediately administered orally or through g tube.

Desipramine is supplied in 10mg, 25mg, 50mg, 75mg, 100mg, and 150mg tablets. The dose of desipramine in our clinical protocol is 2mg/kg, and the dose may be increased to 4mg/kg if desipramine is well tolerated. If the intended dose of 2mg/kg or 4mg/kg cannot be precisely achieved with the available tablets based on the patient's weight, I propose to round the dose to the nearest dose achievable with available tablet sizes; however, we will

never administer more than 4mg/kg. The actual desipramine amount that each patient receives will be noted in his/her research file and medical record.
Parents will be asked to record information on the child's acceptance of each daily dose by completing a Despipramine Dosing Log to allow us gather information on patient adherence (including information on palatability and swallowability of the desipramine-water mixture)

The follow will occur as clinically warranted but no less frequently than monthly for an additional 3 months.

Study visits will be conducted in conjunction with standard of care appointments.

Baseline visit: confirm inclusion exclusion criteria are met
clinical assessments will be recorded in research file.
1 week: Participant will return for a repeat physical exam and Lab work (CBC & diff, BMP, HFP & UA). This is a standard of care appointment.

If assessments are within normal range, participant will follow up in 2 weeks
If necessary, more frequent follow up will occur (follow up in one week if concern is mild)
If concerns are significant (including, but not limited to, prolonged QT segment, significant liver dysfunction, noticeable deterioration of neurological symptoms) based on clinical judgement of the PI. The possibility of discontinuing study drug dosing will be discussed.
If there are no concerns after two follow up visits, participant will follow up clinically monthly for 3 months
Desiprimine serum concentration will be monitored 1 week after the first dose and then 3 weeks after first dose. If level stable and within normal limits, the level will be rechecked only when dose is adjusted or when clinically indicated.

Discontinuation of study drug:
If no clinical improvement is noted after 6 months, or if the treating physician considers it no longer in the best interests of the child, Desipramine will be discontinued.
After discontinuation of study drug participant will be required to return for safety assessments 3 months after the last dose of Desipramine.

Selection of Subjects:

Inclusion criteria

- 0-17years.
- Able to receive medication either in an intact tablet form, or dissolved in water The ability to receive medication in an intact tablet form will be assessed by asking parents/guardians to report the child's prior experience of taking medications in a tablet form.
- Any gender
- Confirmed homozygotes of pathogenic mutation in PLA2G6
- Documentation of clinical presentation (signs and symptoms of neurodegenerative process) of INAD.

Exclusion criteria

- Patient has sign and symptom suggesting an ongoing acute or chronic illness such as fever of unknown origin or infection.
- Patient has a second genetic condition
- Parents are unable or unwilling to return for continued care for up to 12 months

Subject Recruitment & Compensation:

The study will be introduced to the potential participant and parent/guardian by the patient's provider.

Participant/parents/guardians will not be compensated for participation in this study.

Consent Process:

Parent/guardian will be approached for consent by the PI or designated key personnel upon presentation to Dr Jiang with a documented pathogenic variant in PLA2G6.
Parent/guardian may take as much time as they need to consider participation

Subject's Capacity to Give Legally Effective Consent:

All participants in this study will be minors and consent will be provided by parents or legal guardian. If developmentally appropriate signed assent will be provided by children 12 years and older and verbal assent will be provided by children 6 -11 years.
If participants reach the age of 18 whilst on the study they will be reconsented.

Study intervention:

Participants will receive oral desipramine at an initial dose of 2mg/kg once daily.
Dose may be increased to 4mg/kg after 2-4 weeks if no side effects are noted, and an increase in dose is considered by the PI to be warranted.

Risk/Benefit Assessment:

Participants may or may not experience an improvement in their disease symptoms and a slowing of the progression of disease. Improvements cannot be guaranteed.

The following are known side effects of desipramine. The frequency for these side effects are not known but expected to quite infrequent

- Low/high blood pressure, palpitations, heart block, heart attack, stroke, abnormal heart rhythm, and sudden death.
- Confusion, hallucinations, disorientation, delusions, anxiety, restlessness, agitation, sleeplessness and abnormal dreams.
- Numbness, tingling, incoordination, tremors, nerve disease, seizures and alterations in EEG patterns.
- Dry mouth, blurred vision, visual disturbances, dilatation of pupil and increased eye pressure.
- Skin rash, hives, itching, photosensitivity, swelling in the face and tongue or general and fever. Bone marrow depression.
- Loss of appetite, nausea, vomiting, peculiar taste, abdominal cramps, diarrhea, mouth ulcer, jaundice, liver inflammation, constipation, intestinal obstruction. Breast enlargement in male, milk secretion in the female, increased or decreased sexual drive, impotence, painful ejaculation, testicular swelling, urinary retention, delayed urination and dilation of urinary tract. Weight gain or loss, flushing, urinary frequency, drowsiness, dizziness, weakness, fatigue, headache, fever and hair loss.

Known risks related to Desipramine described above will be discussed with parents

Potential for loss of Confidentiality: There is a risk of loss of confidentiality. Every effort will be made to minimize this risk; participants will be assigned a unique study identifier. All samples and study data will be identified only with a unique identifier. The key to the identification code will be stored securely with access limited to designated research personnel. All study personnel will act in accordance with HIPAA guidelines, the study database will be password protected, and medical records and paper files associated with the study will be kept in a locked file cabinet.

Costs to the Subject:

There will be no additional costs to the participant or parent for participation in this study.

Costs for standard of care will be billed to the participant or their insurance company.

Data Analysis & Statistical Considerations:

We anticipate enrolling 3 participants within 12 months of IRB approval. Given that INAD is a very rare disease, this will be a small exploratory study to examine the safety and efficacy in three participants.

Efficacy will be evaluated on the basis of formal cognitive assessments and physical assessments, including the Gross Motor Function Measure (GMFM) and The Quick Motor Function Test (QMFT).

Data & Safety Monitoring:

Primary safety concerns are ECG changes, specifically prolonged Q-T interval, lowering of seizure threshold, neutropenia, changes in hepatic function, and suicidal ideation. Monitoring of potential adverse events will be addressed through frequent clinical assessment. Monitoring of safety parameters will occur no less frequently than every 3 months. Safety and data monitoring will be overseen by the PI and the co-investigators. Any adverse events will be reported promptly to the PI or his designee and reported to the IRB and FDA in accordance with DUMC IRB policies and 21CRF312.32. No data monitoring committee will be used.

Privacy, Data Storage & Confidentiality

All information gathered for the purposes of the research projects will be treated confidentially, in compliance with the Duke University Institutional Review Board policies and consistent with the rights of all participants to privacy. All research personnel have passed Duke's required training on regulations for protecting participants' privacy. A list of participant numbers, names, and other demographic information will be kept on a server that is compliant with Duke School of Medicine data security policies. Network access will be restricted to approved users and physical access will be restricted to Duke IT staff. Details of server information will be described in RDSP and RDSP will be updated when there are any changes.