PROTOCOL AND STATISTICAL ANALYSIS PLAN

Study Title: **Valproic Acid and Dihydroergotamine as Abortive Therapy in Pediatric Migraine**

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	11/27/2018
NCT Number:	NCT03885154
IRB Number	44243
Coversheet created:	8/25/2021

Statistical Analysis Plan

Outcomes measures:

1. The change is pain perception will be reported. The change in pain perception measured by a 10-point visual analogue scale (VAS), where 0 is “no pain” and 10 is “pain as bad as it could be.” Participants will report their pain from baseline to 24 hours. The mean of the change of the reported values with the standard deviation will be calculated to evaluate the change in pain perception for each arm.

2. The presence of photophobia, phonophobia, and nausea will be reported at baseline, 4 hours, 8 hours, 12 hours, and 24 hours as the percentage of participants who experience each symptom. These will be reported per arm.

CONSENT FORM

For ORI Use Only:

Combined Consent and Authorization to Participate in a Research Study

TITLE OF STUDY: IV Valproic Acid v/s Dihydroergotamine as Abortive Therapy for Pediatric/ Adolescent Migraine

WHY ARE YOU BEING INVITED TO TAKE PART IN THIS RESEARCH?

You and your child are being invited to take part in a research study about Acute Management of Migraine headaches in pediatric and adolescent population by comparing two drugs “Valproic Acid and Dihydroergotamine” .You and your child are being invited to take part in this research study because your child is being admitted with diagnosis of acute migraine not responding to initial management. If you and your child volunteer to take part in this study, you will be one of about 120 people to do so *at the University of Kentucky*".

WHO IS DOING THE STUDY?

The person in charge of this study is Dr Kimberly Jones MD of University of Kentucky, Department of Neurology. There may be other people on the research team assisting at different times during the study.

WHAT IS THE PURPOSE OF THIS STUDY?

By doing this study, we hope to learn the best choice of medicine for acute migraines not responding to traditional medicines by comparing two different drugs. The drugs compared are Valproic Acid and Dihydroergotamine. The results of this study will be shared with the Food and

Drug Administration and other federal agencies if required.

ARE THERE REASONS WHY YOU SHOULD NOT TAKE PART IN THIS STUDY?

You should not take part in this study if you are pregnant, have mitochondrial disease, liver failure, heart disease or previous allergy to Valproic acid or Dihydroergotamine.

WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?

The research procedures will be conducted at University of KY Medical Center during your inpatient stay. You will need to come to either emergency department (ED) or inpatient service at Kentucky Children Hospital. The total time you will be asked to volunteer for this study is 24- 48 hours depending upon response to the either of the therapies.

WHAT WILL YOU BE ASKED TO DO?

You will be given either Valproic Acid OR Dihydroergotamine for your headache and you will be assessed closely at 4, 8, 12 and 24 hours (+/- 20 min) after administration of medicine. Both drugs will be given through your veins via IV line. If you are receiving Valproic acid, you will continue to receive the medicine through your vein for entire 24 hour. In case you are getting Dihydroergotamine, you will receive medicine via IV line at admission, then at 8 hour and 24 hour. At the 24 hour mark if headache doesn't resolve those who receive Valproic Acid will be given Dihydroergotamine and vice versa, in that case hospital visit can last up to 48 hours.

We will collect information about your age, gender, weight, Body Mass Index and response to therapy. We will draw labs before starting treatment and may draw more labs to check drug level. The labs will include Cell blood count, Comprehensive metabolic profile, Magnesium, Phosphate, Prothrombin Time /Activated partial thromboplastin time, International Normalization Ratio and Valproic acid levels. All labs will be drawn once except Valproic acid levels, which will be drawn at 4, and 24 hour but may be drawn at 8 and 12 hours interval if needed. Total amount of blood drawn for labs will be ~ 5ml. All females will be checked for pregnancy because we cannot use these medicines if you are pregnant. We will also do an Electro cardiac gram (EKG) before treatment. EKG is done to study your heart waves. Its very easy procedure in which we put stickers over your chest for brief time and record the waves.

Your doctor will assess severity of your headache and symptoms at start of treatment and then at 4 hours, 8 hours, 12 hours and 24 hours.(+/- 20 minutes)

Time	Presentation	4 hour	8 hour	12 hour	24 hour
Headache (Visual Analogue Scale)					
Nausea (YES/NO)					
Sound Bothering You (YES/NO)					
Light Bothering You (YES/NO)					

You and your child will be selected randomly or by chance to assign to one of the treatment groups and both clinician and you will be aware of which group you are assigned to.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

- Nausea and vomiting, leg cramps, limb pain, chest discomfort, abdominal cramps, diarrhea,
- Cardiovascular effects: vasospasms, tachycardia, bradycardia, hypertension
- Coldness of the skin and/or numbness and tingling of the extremities
- Risks related to drawing of blood: Soreness, bruising, pain, infection, possible fainting, bleeding.
- You may have allergic reaction to electrode tape of EKG which may cause redness or swelling of the skin.
-

Possible Risk/Side Effect	How often has it occurred?	How serious is it?	Can it be corrected?
Numbness and Tingling	It may occur after few hours of drug administration	Usually of short duration	Yes, by stopping drug
Nausea / Vomiting/ Abd cramps	Common after the drug Dihydroergotamine	Usually mild	You will be given nausea medicine before treatment
Leg Cramps	Few hours after drug administration	Mild	Improves after stopping treatment
Tachycardia	It may occur after first round of drug Dihydroergotamine	Mild	Resolved after stopping medicine
Chest Pain	Rare	Can be mild to moderate	Corrected by stopping medicine
High Blood Pressure	Can be seen after second or third dose of drug Dihydroergotamine	Mild to moderate	Self-resolving after treatment.
Coldness of Skin	May occur after two rounds of treatment	Mild	Self resolves after treatment
Rash	Rare	It can involve any part of body	It will go away after stopping treatment
Liver damage	It is extremely uncommon	Very serious	The damage is permanent and can affect the rest of your health

There is always a chance that any medical treatment can harm you, and the investigational treatment in this study is no different. In addition to the risks listed above, you may experience a previously unknown risk or side effect.

WILL YOU BENEFIT FROM TAKING PART IN THIS STUDY?

There is no guarantee that you will get any benefit from taking part in this study. However, some people have experienced improvement or complete resolution of their acute headache after this treatment .Your willingness to take part, however, may, in the future, help doctors better understand how to treat others who have your condition.

DO YOU HAVE TO TAKE PART IN THE STUDY?

If you decide to take part in the study, it should be because you really want to volunteer. You will not lose any benefits or rights you would normally have if you choose not to volunteer. You can stop at any time during the study and still keep the benefits and rights you had before volunteering. If you decide not to take part in this study, your decision will have no effect on the quality of medical care you receive

IF YOU DON'T WANT TO TAKE PART IN THE STUDY, ARE THERE OTHER CHOICES?

If you do not want to take part in the study, there are other choices such as traditional measures and standard of care to improve your headache.

WHAT WILL IT COST YOU TO PARTICIPATE?

These are costs that are considered medically reasonable and necessary and will be part of the care you receive if you do not take part in this study, The University of Kentucky may not be allowed to bill your insurance company, Medicare or Medicaid for the medical procedures done strictly for research. Therefore, these costs will be your responsibility. You and /or your insurance company, Medicare or Medicaid will be responsible for the costs of all care and treatment you receive during this study that you would normally receive for your condition"

WHO WILL SEE THE INFORMATION THAT YOU GIVE?

We will make every effort to keep confidential all research records that identify you to the extent allowed by law.

Your information will be combined with information from other people taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. You will not be personally identified in these written materials. We may publish the results of this study; however, we will keep your name and other identifying information private. We will make every effort to prevent anyone who is not on the research team from knowing that you gave us information, or what that information is.

You should know, however, that there are some circumstances in which we may have to show your information to other people. For example, the law may require us to show your information to a court or tell authorities if you report information about a child being abused or if you pose a danger to yourself or someone else. Officials of the Food and Drug Administration and the University of Kentucky may look at or copy pertinent portions of records that identify you.

CAN YOUR TAKING PART IN THE STUDY END EARLY?

If you decide to take part in the study you still have the right to decide at any time that you no longer want to continue. You will not be treated differently if you decide to stop taking part in the study. If you choose to withdraw from the study early, the data collected until that point will remain in the study database and may not be removed. The individuals conducting the study may need to withdraw you from the study. This may occur if you are not able to follow the directions

they give you or if they find that your being in the study is more risk than benefit to you, There is no adverse effect if you and your child decide to suddenly withdraw from study

ARE YOU PARTICIPATING OR CAN YOU PARTICIPATE IN ANOTHER RESEARCH STUDY AT THE SAME TIME AS PARTICIPATING IN THIS ONE?

You may take part in this study if you are currently involved in another research study. It is important to let the investigator/your doctor know if you are in another research study. You should also discuss with the investigator before you agree to participate in another research study while you are enrolled in this study.

WHAT HAPPENS IF YOU GET HURT OR SICK DURING THE STUDY?

If you believe you are hurt or if you get sick because of something that is due to the study, you should call Kimberly Jones MD and UK Neurology office. Please contact UKMDs at 859-257-5522 and ask them to connect you with Dr Kimberly Jones.

1. *A dedicated pager number; 859-330-4503*
2. *Other reliable 24-hour contact option at your discretion, and/or UKMDs at 859-257-5522 and ask them to connect you with Dr Sharoon Qaiser*
3. *As deemed necessary, in addition to one or more of the above, referral to 911 for an emergency.*

Dr. Kimberly Jones MD will determine what type of treatment, if any, that is best for you at that time.

It is important for you to understand that the University of Kentucky does not have funds set aside to pay for the cost of any care or treatment that might be necessary because you get hurt or sick while taking part in this study. Also, the University of Kentucky will not pay for any wages you may lose if you are harmed by this study.

The medical costs related to your care and treatment because of research related harm will be your responsibility;

WILL YOU RECEIVE ANY REWARDS FOR TAKING PART IN THIS STUDY?
You will not receive any rewards or payment for taking part in the study.

WHAT IF YOU HAVE QUESTIONS, SUGGESTIONS, CONCERNS, OR COMPLAINTS?

Before you decide whether to accept this invitation to take part in the study, please ask any questions that might come to mind now. Later, if you have questions, suggestions, concerns, or complaints about the study, you can contact, Kimberly Jones MD via UKMD. If you have any questions about your rights as a volunteer in this research, contact the staff in the Office of Research Integrity at the University of Kentucky between the business hours of 8am and 5pm EST, Mon-Fri at 859-257-9428 or toll free at 1-866-400-9428. We will give you a signed copy of this consent form to take with you.

WHAT IF NEW INFORMATION IS LEARNED DURING THE STUDY THAT MIGHT AFFECT YOUR DECISION TO PARTICIPATE?

If the researcher learns of new information in regards to this study, and it might change your willingness to stay in this study, the information will be provided to you. You may be asked to

sign a new informed consent form if the information is provided to you after you have joined the study.

WHAT ELSE DO YOU NEED TO KNOW?

There is a possibility that the data/tissue/specimens/blood collected from you may be shared with other investigators in the future. If that is the case the data/tissue/specimen/blood will not contain information that can identify you unless you give your consent/authorization or the UK Institutional Review Board (IRB) approves the research. The IRB is a committee that reviews ethical issues, according to federal, state and local regulations on research with human subjects, to make sure the study complies with these before approval of a research study is issued.A description of this clinical trial will be available on http://www.ClinicalTrials.gov as required by U.S. Law . This website will not include information that can identify you . At most, the website will include a summary of results. You can search this website at any time.

AUTHORIZATION TO USE OR DISCLOSE YOUR IDENTIFIABLE HEALTH INFORMATION

The privacy law, HIPAA (Health Insurance Portability and Accountability Act), requires researchers to protect your health information. The following sections of the form describe how researchers may use your health information.

Your health information that may be accessed, used and/or released includes:

Demographic information, headache severity and response, side effects of treatment, associated conditions and exam findings.
The Researchers may use and share your health information with:

- The University of Kentucky's Institutional Review Board/Office of Research Integrity.
- Law enforcement agencies when required by law.
- University of Kentucky representatives.
- FDA
- Institutional Drug Service

The researchers agree to only share your health information with the people listed in this document. Should your health information be released to anyone that is not regulated by the privacy law, your health information may be shared with others without your permission; however, the use of your health information would still be regulated by applicable federal and state laws.

You may not be allowed to participate in the research study if you do not sign this form. If you decide not to sign the form, it will not affect your:

- Current or future healthcare at the University of Kentucky
- Current or future payments to the University of Kentucky
- Ability to enroll in any health plans (if applicable)
- Eligibility for benefits (if applicable)

After signing the form, you can change your mind and NOT let the researcher(s) collect or release your health information (revoke the Authorization). If you revoke the authorization:

- You will send a written letter to Dr. *Kimberly Jones MD 740 S. Limestone, J-445 Lexington, KY 40536* of your decision.
- Researchers may use and release your health information already collected for this research study.
- Your protected health information may still be used and released should you have a bad reaction (adverse event).

You understand that you will not be allowed to review the information collected for this research study until after the study is completed. When the study is over, you will have the right to access the information.]

The use and sharing of your information has no time limit.

If you have not already received a copy of the Privacy Notice, you may request one. If you have any questions about your privacy rights, you should contact the University of Kentucky's Privacy Officer between the business hours of 8am and 5pm EST, Mon-Fri at: (859) 323-1184.

You are the subject or are authorized to act on behalf of the subject. You have read this information, and you will receive a copy of this form after it is signed.

_____ _____

Signature of research subject (*if applicable)* or *research subject's legal representative — Date

_____ _____

Printed name of research subject (*if applicable)* or *research subject's legal representative — Representative's relationship to research subject

*(*If, applicable)* Please explain Representative's relationship to subject and include a description of Representative's authority to act on behalf of subject:

_____

Name of [authorized] person obtaining informed consent/HIPAA authorization

PROTOCOL TYPE

Which IRB

◉ Medical ○ NonMedical

Protocol Process Type

○ Exemption
○ Expedited (Must be risk level 1)
◉ Full

IMPORTANT NOTE: Once you have saved your choices under "Which IRB" and "Protocol Process Type", you will not be able to change your selections. If your application is deemed eligible for a different Protocol Process Type, it may be necessary to create a new application.

Please see below for guidance on which selections to make, and/or download the IRB Introduction Packet for more details [PDF]. If you still have questions about which IRB or Protocol Process Type to choose, please contact the Office of Research Integrity (ORI) at 859-257-9428 prior to saving your selections.

Which IRB

The Medical IRB reviews research emanating from the Colleges of Dentistry; Health Sciences; Medicine; Nursing; Pharmacy and Health Sciences; and Public Health.

The Nonmedical IRBs review research originating from the Colleges of Agriculture; Arts & Sciences; Business & Economics; Communications & Information; Design; Education; Engineering; Fine Arts; Law; and Social Work. The Nonmedical IRB does not review studies that involve administration of drugs or studies that involves invasive medical procedures, regardless of from what college the application originates.

Which Protocol Process Type

Under federal regulations, an investigator's application to conduct a research project involving human subjects can be processed by the IRBs in three ways:
-by full review;
-by exemption certification [see categories];
-by expedited review [see categories];

The preliminary determination that a research project is eligible for exemption certification or expedited review is made by the investigator. For assistance in determining which review process type your IRB application is eligible for, please see the IRB Introduction Packet [PDF].

RISK LEVEL

Indicate which of the categories listed below accurately describes this protocol

- ○ (Risk Level 1) Not greater than minimal risk
- ◉ (Risk Level 2) Greater than minimal risk, but presenting the prospect of direct benefit to individuals subjects
- ○ (Risk Level 3) Greater then minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- ○ (Risk Level 4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of subjects.

*"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests [45 CFR 46.102(i)]

Download UK's guidance document on assessing the research risk for additional information on risk [PDF]

RESEARCH DESCRIPTION

****!!!PLEASE READ!!!** Known Issue: The below text boxes do not allow symbols, web addresses, or special characters (characters on a standard keyboard should be ok). If something is entered that the text boxes don't allow, user will lose unsaved information.**

Workaround(s):

- **Save your work often to avoid losing data.**
- **Use one of the attachment buttons in this section, or under the Additional Information section to include the information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

Background: Provide an introduction and background information. Describe past experimental and/or clinical findings leading to the formulation of your study. For research involving investigational drugs, describe the previously conducted animal and human studies. You may reference grant application/sponsor's relevant protocol pages and attach as an appendix in the E-IRB "Additional Information" section. For research that involves FDA approved drugs or devices, describe the FDA approved uses of this drug/device in relation to your protocol. Attach a copy of the approved labeling as a product package insert or from the Physician's Desk Reference in the applicable E-IRB "Study Drug" or "Study Device" section.

Migraine is disabling headache disorder with wide range of socioeconomic and social impact. According to WHO, its ranked number 19 among all diseases causing morbidity. (1). The mean cost for migraine-related ED visits in US alone is around $700 million (2. Migraine adversely affect quality of life, school attendance, academic performance, family, peer interactions, and socialization in children (3) .There is lack of randomized studies to develop treatment strategies and most of the treatment guidelines are adopted from adult studies. Both Valproic Acid (VPA) and Dihydroergotamine (DHE) are used as abortive therapy in pediatric migraine with variable results .4, 5 There is no study to date to compare these two treatment options in the pediatric age group.

Objectives: List your research objectives. You may reference grant application/sponsor's relevant protocol pages and attach as an appendix in the E-IRB "Additional Information" section.

We propose a study to compare clinical efficacy and tolerability of VPA therapy v/s DHE as abortive therapy in pediatric migraine. There is no current study to the date to compare these two agents in pediatric age group. 1) VPA as abortive therapy in Pediatric Migraine: VPA has been an effective migraine abortive treatment in adults but there is lack of data in pediatric population. We conducted a study in 2014 at University of Kentucky in which we did retrospective chart review of all pediatric patients presented with acute migraine between 2009-2012. Children with severe headache were given IV VPA load, followed by continuous infusion (6) . The pain score was collected from nursing flow sheet documentation in electronic health record system. Response was graded according to reduction in pain scoring as Excellent (> than 50 %) Moderate (> than 30 % but < than 50 %) and Poor (< than 30 %). Despite encouraging results, it is important to note that VPA has not been studied in placebo controlled trial for acute migraine in adults or children and randomized studies have efficacy rates notably lower than in open-label series. (7) (8). Hence the role of sodium valproate in the treatment of acute migraine in pediatric age group remains unclear. This is a protocol we have been following at KCH for over 4 years. Dosing and administration: IV VPA load 20mg/kg, followed by continuous infusion of 1 mg/kg/hour for 24 hours. Serum level of VPA levels will be checked at 4, & 24 hours or may be at 8 and 12 hours based on drug levels (+/-20 min). The target serum concentration is 100(+/-10). 2) DHE as abortive therapy in Pediatric Migraine: DHE is an ergot alkaloid or tetracyclic ergolene derivative which is used as an effective abortive agent in adult acute migraine and its role in management of acute pediatric migraine is been studied. (9). One study (10) showed that 74.4% of children were headache free upon discharge. It's important to note that all these patients were treated with dopamine antagonist and IV hydration, which might account for some benefit. Dosing and administration: Weight based dosing. (11) (12) with no single dose > 1mg and total 24 hour dose < 3mg. • 0 hour : 0.5 x (wt in Kg) x (0.014) = X mg • 8 hours: 0.75 x (wt in kg) x (0.014) =X mg • 24 hour :1x (wt in kg) x (0.014) =X mg

Study Design: Describe the study design (e.g., single/double blind, parallel, crossover, etc.). Indicate whether or not the subjects will receive placebo medication at some point in the research procedures. Also, indicate whether or not the subjects will be randomized in this study. You may reference sponsor's protocol pages and attach as an appendix in the E-IRB "Additional Information" section. (Including the study design table from a sponsor's protocol is helpful to IRB members.)

Community-Based Participatory Research: If you are conducting community-based participatory research (CBPR), describe strategies for involvement of community members in the design and implementation of the study, and dissemination of results from the study.

Research Repositories: If the purpose of this submission is to establish a research repository describe the repository design and operating procedures. For relevant information to include, see question 22 of the UK IRB "Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings" [PDF].

It will be open label Random Study we will prospectively enroll pediatric patients with diagnosis of migraine via Emergency Department or inpatient in KCH. We will number subjects as they are enrolled in the study, all odd numbers cases will be assigned to VPA arm and all even numbers will be assigned to DHE arm. All the studies procedure will take place either in ED as they are initially evaluated and then on child neurology inpatient floor. Patients will be admitted either via ED when they fail to response initial acute headache management in ED (as per ED protocol) or as a direct admit to child neurology inpatient service. We will administer either

VPA or DHE and study the response using standard pain scoring (VAS), photophobia, phonophobia, presence or absence of nausea at baseline and then at 4,8,12 and 24 hours. (All these intervals have flexibility of +/- 20 minutes). This pain scale (VAS) is same scale which is been used currently in previous protocol. All patients will have following pre procedure labs. 1. CBC once (0.5ml) 2. CMP once (0.6ml) 3. PT/APTT/INR once (1.8ml) 4. Magnesium and Phosphorous once (0.6ml) 5. Those on VPA will have VPA levels drawn at 4 and 24 hour or may be at 8 and 12 hours based on drug levels (+/- 20 minutes) and each draw will require 0.6ml blood draw. Patients will be assessed by bedside physician or nurse assigned to their care at presentation for headache using standard pain scoring (VAS) , presence or absence of photophobia, phonophobia , presence or absence of nausea at baseline and then at 4, 8 , 12 and 24 hours (+/- 20 minutes) .In If no response at 24 hours then we will change the therapy, those receiving DHE will receive VPA and vice versa. Our patients may stay inpatient for 48 hours or more depending upon response. End point will include significant improvement in headache using pain scale (VAS) and resolution of photophobia, phonophobia and nausea..

Attachments

Back to Top

Study Population: Describe the characteristics of the subject population, such as anticipated number, age range, gender, ethnic background and health status. Identify the criteria for inclusion and exclusion. Explain the rationale for the use of special classes such as fetuses, pregnant women, children, institutionalized, adults with impaired consent capacity, prisoners or others who are likely to be vulnerable. If women or minorities are included, please address how the inclusion of women and members of minority groups and their subpopulations will help you meet your scientific objectives. Exclusion of these groups requires clear and compelling rationale that shows inclusion is inappropriate with respect to the health of the subjects or that inclusion is inappropriate for the purpose of the study. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be excluded routinely from participation in clinical research.

Provide the following information:

• A description of the subject selection criteria and rationale for selection in terms of the scientific objectives and proposed study design;
• A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group;
• The proposed dates of enrollment (beginning and end);
• The proposed sample composition of subjects.

You may reference grant application/sponsor's relevant protocol pages and attach as an appendix using the below attachment button.

Subject Selection Criteria: Pediatric patients 10 years and above with acute migraine as per ICHD-II criteria will be eligible for inclusion after receiving traditional acute headache management as per AAP /AAN guidelines and still not responding. (11). Contraindications/ Exclusion Criteria: VPA • Pregnancy • Liver Disease (Acute or Chronic) • Urea Cycle Disorder • Mitochondrial Disease Contraindications/ Exclusion Criteria: DHE • Peripheral vascular disease, coronary heart disease. • History of cerebrovascular event. • Severe or poorly controlled hypertension. • Impaired liver or renal function. • Pregnancy. • Triptan given in last 24 hours. • Hemiplegic Migraine Proposed Dates: Enrollment Beginning: 6/1/2017- Enrollment End: 5/1/2022 Proposed Sample Composition: Pediatric age group 10 and above no distinction based upon gender or race.

Attachments

Subject Recruitment Methods & Privacy: Describe plans for the identification and recruitment of subjects, including how the population will be identified, and how initial contact will be made with potential subjects by those having legitimate access to the subjects' identity and the subjects' information. Describe the setting in which an individual will be interacting with an investigator. If applicable, describe proposed outreach programs for recruiting women and minorities as participants in clinical research.

Please note: Based upon both legal and ethical concerns, the UK Medical Institutional Review Board (IRB) will not approve finder's fees for research studies.

We will recruit the patients from University Kentucky Children's hospital ED and / or from inpatient. We expect to recruit 1-3 patients into our study per month for 4 years period. Overall, we expect to recruit 120 patients within this time frame. Patients will be qualified to be included in the study based upon inclusion and exclusion criteria

Back to Top

Advertising: Specify if any advertising will be performed. If yes, please see "IRB Application Instructions - Advertisements" for instructions on attaching copies of the information to be used in flyers or advertisements. Advertisements must be reviewed and approved by the IRB prior to use. For additional details, see topic "Recruitment" on ORI's IRB Survival Handbook web page for the *PI Guide to Identification and Recruitment of Human Subjects for Research* [D7.0000] document [PDF]. If you will be recruiting subjects via advertising at non-UK owned or operated sites, you should include a copy of written permission from that site to place the advertisement in their facilities.

NA

Attachments

Informed Consent Process: Describe the consent/assent procedures to be followed, the circumstances under which consent will be sought and obtained, the timing of obtaining informed consent, whether there is any waiting period between informing the prospective subject and obtaining consent, who will seek consent (Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application), steps taken to minimize the possibility of coercion or undue influence, the method used for documenting consent, and if applicable who is authorized to provide permission or consent on behalf of the subject. Describe, if applicable, use of specific instruments or techniques to assess and confirm potential subjects' understanding of the nature of the elements of informed consent (i.e., research involving adult subjects with impaired consent capacity) and/or a description of other written materials that will be provided to participants or legally authorized representatives. If you have a script, please prepare it using the informed consent template as a guide, and submit it on a separate page. For additional information, see the Informed Consent Standard Operating Procedures (SOPs)" (PDF).

Informed Consent for Research Involving Emancipated Individuals
If you plan to enroll some or all prospective subjects as emancipated, consult with UK legal counsel **when preparing the IRB application and prior to submitting the application to the IRB**. Include legal counsel's recommendations (legal counsel's recommendations may be attached in the E-IRB "Additional Information" section as a separate document, if necessary). For a complete definition of emancipated minors, see the section on *Emancipated Individuals* in the Informed Consent SOP (PDF).

Informed Consent for Research Involving Non-English Speaking Subjects
If you are recruiting non-English speaking subjects, the method by which consent is obtained should be in language in which the subject is proficient. Describe the process for obtaining informed consent from prospective subjects in their respective language (or the legally authorized representative's respective language). In order to ensure that individuals are appropriately informed about the study when English is their second-language, describe a plan for evaluating the level of English comprehension, and the threshold for providing a translation, or explain why an evaluation would not be necessary. For additional information on inclusion of non-English speaking subjects, or subjects from a foreign culture, see IRB Application Instructions for Recruiting Non-English Speaking Participants or Participants from a Foreign Culture.

Research Repositories
If the purpose of this submission is to establish a research repository describe the informed consent process. For guidance regarding consent issues, process approaches, and sample language see the "University of Kentucky Issues to be Addressed and Sample Consent Language for Tissue/Specimen Repositories or Individual Studies Banking Material for Future Use" (PDF).

We will obtain informed consent from the parents or the legal guardian to acquire permission to use the patient's demographic data (Demographic data will include age, gender, weight and BMI) and clinical response for outcome measures. Consent / Assent will be taken after initial assessment by admitting neurology resident/ fellow (in ED or inpatient service) . Parents/ patients will be explained that treatment guidelines remains same whether they are part of the study or not and their decision will not delay the treatment.We will also use assent form explaining our research and procedures. The neurology resident/ fellow admitting the patient will obtain consent and assent . All neurology residents are included in SP list . These therapies and guidelines have been followed at KCH for over 4 years and consenting to research will enable researchers to gather data but will not influence the treatment .

Back to Top

Research Procedures: Describe the research procedures that will be followed. Identify all procedures that will be carried out with each group of subjects. Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project.

We will review the medical record to collect their demographic data such as gender, BMI, weight, headache response, using standard pain scoring (VAS) , presence or absence of photophobia, phonophobia , presence or absence of nausea at baseline and then at 4, 8 , 12 and 24 hours. These intervals are flexible with +/- 20 minutes. These therapies and guidelines have been followed at KCH for over 4 years and consenting to research will enable researchers to gather data but will not influence the treatment .

Attachments

Data Collection: List the data or attach a list of the data to be collected about or from each subject (e.g. interview script, survey tool, data collection form for existing data).

If the research includes survey or interview procedures, the questionnaire, interview questions or assessment scales should be included in the application (use attachment button below).

The data collection instrument(s) can be submitted with your application in draft form with the understanding that the final copy will be submitted to the IRB for approval prior to use (submit final version to the IRB for review as a modification request if initial IRB approval was issued while the data collection instrument was in draft form).

We will review the medical record to collect their demographic data such as gender, BMI, weight, headache response, using standard pain scoring (VAS) , presence or absence of photophobia, phonophobia , presence or absence of nausea at baseline and then at 4, 8 , 12 and 24 hours. These intervals are flexible with +/- 20 minutes. The residents will be conducting assessment , collecting and transferring the data to secure computer located in Neurology office at 4th floor in Kentucky Clinic building.

Attachments

Resources: Describe what resources/facilities are available to perform the research (i.e., staff, space, equipment). Such resources may include a) staffing and personnel, in terms of availability, number, expertise, and experience; b) psychological, social, or medical services, including counseling or social support services that may be required because of research participation; c) psychological, social, or medical monitoring, ancillary care, equipment needed to protect subjects; d) resources for subject communication, such as language translation services, and e) computer or other technological resources, mobile or otherwise, required or created during the conduct of the research. Please note: Some mobile apps may be considered mobile medical devices under FDA regulations (see FDA Guidance). Proximity or availability of other resources should also be taken into consideration, for example, the proximity of an emergency facility for care of subject injury, or availability of psychological support after participation.

Research activities conducted at performance sites that are not owned or operated by the University of Kentucky, at sites that are geographically separate from UK, or at sites that do not fall under the UK IRB's authority, are subject to special procedures for coordination of research review. Additional information is required (see IRB Application Instructions - Off-Site Research web page); supportive documentation can be attached in the E-IRB "Additional Information" section. Provide a written description of the role of the non-UK site(s) or non-UK personnel who will be participating in your research. The other site may need to complete its own IRB review, or a cooperative review arrangement may need to be established. Contact the Office of Research Integrity at (859) 257-9428 if you have questions about the participation of non-UK sites/personnel.

If the University of Kentucky is the lead site in a multi-site study, or the UK investigator is the lead investigator, describe the plan for managing the reporting of unanticipated problems, noncompliance and submission of protocol modifications and interim results from the non-UK sites.

Electronic medical record. Research will be conducted at UK and will not require any additional resources other than required in standard patient care.

Potential Risks: Describe any potential risks or likely adverse effects of the drugs, biologics, devices or procedures subjects may encounter while in the study. Please describe any physical, psychological, social, legal or other risks and assess their likelihood and seriousness.

1. Drug related Potential side effects/adverse reactions. • Nausea and vomiting, leg cramps, limb pain, chest discomfort, abdominal cramps, diarrhea, paresthesia • Cardiovascular effects: vasospasms, tachycardia, bradycardia, hypertension • Coldness of the skin and/or numbness and tingling of the extremities may indicate ergotism, which can include gangrene • Somnolence, tremor, dizziness, abdominal pain, diplopia, amblyopia/blurred vision, low platelet counts 2. Breach of Confidentiality: Steps taken to avoid breach of Confidentiality: Files will be stored in the investigators' hospital owned computer that is located in Neurology Office at 4th floor at Kentucky Clinic building. Only investigators will have access to data, which will be further protected by a password on all files.

Back to Top

Safety Precautions: Describe the procedures for protecting against or minimizing any potential risks, *including risks of breach of confidentiality or invasion of privacy*. Where appropriate, discuss provisions for ensuring necessary medical or professional intervention in the event of adverse events, or unanticipated problems involving subjects. Also, where appropriate, describe the provisions for monitoring the data collected to ensure the safety of subjects. If vulnerable populations other than adults with impaired consent capacity are to be recruited, describe additional safeguards for protecting the subjects' rights and welfare.

Measures to reduce side effects before VPA and DHE • EKG • CBC, CMP, Mg, Phosphate , PT , APTT, INR • Urine : Urine Pregnancy Test and UDS • Premedicate with Nausea medicine (Diphenhydramine and /or Metoclopramide) only if they haven't received these medicines already as part of their migraine cocktail in ED.

Benefit vs. Risk: Describe potential benefits to the subject(s); include potential benefits to society and/or general knowledge to be gained. Describe why the risks to subjects are reasonable in relation to the anticipated benefit(s) to subjects and in relation to the importance of the knowledge that may reasonably be expected to result. If you are using vulnerable subjects (e.g., impaired consent capacity, pregnant women, etc…), justify their inclusion by describing the potential benefits of the research in comparison to the subjects' vulnerability and the risks to them. For information about inclusion of certain vulnerable populations, see the IRB/ORI Standard Operating Procedure for Protection of Vulnerable Subjects [C3.0100] (PDF).

As documented in Objective and potential risk section

Available Alternative Treatment(s): Describe alternative treatments and procedures that might be advantageous to the subjects, should they choose not to participate in the study. This should include a discussion of the current standard of care treatment(s).

There are no guidelines for acute migraine abortive therapy for pediatric/ adolescent group and available treatment options are adopted from adult literature. Traditional acute headache management as per AAP /AAN guidelines. (11) will be given to all the patients and only those who do not respond to the treatment will be enrolled .

Back to Top

Research Materials, Records and Privacy: Identify the sources of research material obtained from individually identifiable living human subjects. Indicate what information (specimens, records, data, genetic information, etc.) will be recorded and whether use will be made of existing specimens, records or data. Explain why this information is needed to conduct the study.

Return of Research Results or Incidental Findings (if applicable):
If research has the potential to identify individual results or discover incidental findings that could affect the health of a subject, describe plans to assess, manage, and if applicable disclose findings with individual subjects or provide justification for not disclosing. For IRB expectations, refer to the UK IRB "Frequently Asked Questions (FAQs) on the Return of Research Results or Incidental Research Findings" (PDF).

Electronic Medical Record

Confidentiality: Specify where the data/specimens will be stored and how the researcher will protect both the data and/or specimens with respect to privacy and confidentiality. Address physical security measures (e.g., locked facility, limited access); data security (e.g., password-protection, data encryption); safeguards to protect identifiable research information (e.g., coding, links, certificate of confidentiality); and procedures employed when sharing material or data, (e.g., honest broker (if applicable), written agreement with recipient not to re-identify). If you plan to procure, store, and/or share material (tissue/specimens/data) expressly for use in current or future research, describe measures that you will take to secure and safeguard confidentiality and privacy.

Provide a time table for destroying the data/specimens and identify how they will be destroyed, or provide rationale for perpetual maintenance [Note: The investigator is responsible for retaining the signed consent and assent documents and IRB research records for at least six years after study closure as outlined in the Study Closure SOP (PDF). If the research falls under the authority of FDA or other regulatory agency, the investigator is responsible for retaining the signed documents and IRB records for the period specified if longer than six years after completion of the study]. For multi-site studies, the PI consults the study sponsor regarding retention requirements, but must maintain records for a minimum of six years after study closure. Also, specify who will access the identified data/specimens, and why they need access. If applicable, describe what measures will be taken to ensure that subject identifiers are not given to the investigator. If applicable, describe procedures for sharing data/specimens with entities not affiliated with UK.

> *NIH-funded genomic research*: The National Institutes of Health (NIH) Genomic Data Sharing (GDS) Policy sets forth expectations that ensure the broad and responsible sharing of genomic research data consistent with the informed consent of study participants from which the data was obtained. If you are submitting genomic data to an NIH data repository, describe your NIH data sharing plan.

Please note: The IRB expects researchers to access the minimal amount of identifiers to conduct the study and comply with applicable HIPAA and Family Educational Rights and Privacy Act (FERPA) requirements. If data are going to be collected, transmitted, and/or stored electronically, for appropriate procedures please refer to the guidance document "Confidentiality and Data Security Guidelines for Electronic Data" (PDF).

Also please note that storage of data on cloud services may not be appropriate and is subject to applicable university policies regarding the use of cloud services. If deemed too sensitive or inappropriate to be stored or collected using cloud services, the IRB may require an alternate method of data storage in accordance with applicable university policies and the electronic data security guidance document referenced above.

If a research protocol involves the creation and/or use of a computer program or application, mobile or otherwise, please specify whether the program/application is being developed by a commercial software developer or the research team and provide any relevant information regarding the security and encryption standards used, how data is stored and/or transmitted to the research team, what information about the subjects the program/application will collect, etc. The IRB may require software programs created or used for research purposes be examined by a consultant with appropriate Internet technology expertise to ensure subject privacy and data are appropriate protected.

Back to Top

Files will be stored on the investigators' hospital owned computer(s) that is located in a locked office in Neurology 4th floor at Kentucky Clinic building. Only investigators will have access to data, which will be further protected by a password on all files. All the data will be deleted after 10 years of completion of research

Back to Top

Payment: Describe the incentives (e.g., inducements) being offered to subjects for their time during participation in the research study. If monetary compensation is offered, indicate how much the subjects will be paid and describe the terms and schedule of payment. (It is IRB policy that provision should be made for providing partial payment to subjects who withdraw before the completion of the research. Monetary payments should be prorated or paid in full.)

NA

Costs to Subjects: Describe any costs for care associated with research (including a breakdown of standard of care procedures versus research procedures), costs of test drugs or devices, and research procedure costs that are the subject's responsibility as a consequence of participating in the research. Describe any offer for reimbursement of costs by the sponsor for research related injury care.

NA

Data and Safety Monitoring: The IRB requires review and approval of data and safety monitoring plans for greater than minimal risk

research, clinical research, or NIH-funded/FDA-regulated clinical investigations.

If you are conducting greater than minimal risk research, clinical research, or your clinical investigation is NIH-funded/FDA-regulated, describe your Data and Safety Monitoring Plan (DSMP). Click here for additional guidance on developing a Data and Safety Monitoring Plan.

If this is a *non-sponsored investigator-initiated* protocol considered greater than minimal risk research, clinical research, or your clinical investigation is FDA-regulated, *and* if you are planning on using a Data and Safety Monitoring Board (DSMB) as part of your DSMP, click here for additional guidance for information to include with your IRB application.

If relying on an independent agent or committee for DSMB services, it is the PI's responsibility to establish the services with the agent or committee. Please be reminded that the PI must submit DSMB reports to the IRB via modification or continuing review.

Advisory to Principal Investigator for DSM is Dr Larry B Goldstein 1. Monitoring the progress of clinical investigations and the safety of participants: All participants will have pre procedural labs as indicated in section 10 . All patients will be monitored at bedside by resident and bedside nurse as per KCH protocol and evaluated at intervals 4 ,8,12 and 24 hours (+/- 20 min) for any acute clinical change and adverse effects as explained in section 9. VPA levels will be drawn at 4 hour and 24 hour and may be repeated at 8 and 12 hours based upon the drug levels. In case of any adverse effect resident will contact Child neurology faculty and if appropriate may change the therapy . 2. .Assuring compliance with the requirements regarding the reporting of unanticipated problems or adverse experiences: The primary investigator (Dr Jones) will review the adverse effects reported and documented by residents after each case. PI will review the events every three months and report to advisory to PI (Dr Larry B Goldstein) and IRB any unanticipated events. 3. .Assuring that any action resulting in a temporary or permanent suspension of the study is reported to the appropriate entities (i.e., funding agency): NA 4. Assuring data accuracy and protocol compliance Quality Control Measures: We will use standardized VAS pain scale which is already part of electronic medical record charting by both nurses and resident physicians . All patients will be assessed at interval 4,8,12 and 24 hour (+/- 20 minutes) in addition to any other regular assessment as part of standard care.

Back to Top

Subject Complaints: Describe procedures (other than information provided in consent document) for handling subject complaints or requests for information about the research. The procedures should offer a safe, confidential, and reliable channel for current, prospective, or past research subjects (or their designated representative) permitting them to discuss problems, concerns and questions, or obtain information.

NA

Does your research involve **Non-English Speaking Subjects or Subjects from a Foreign Culture**?

○ Yes ◉ No

Non-English Speaking Subjects or Subjects from a Foreign Culture

Describe how information about the study will be communicated to potential subjects appropriate for their culture, and if necessary, how new information about the research may be relayed to subjects during the study.

Include contact information for someone who can act as a cultural consultant for your study. The person should be familiar with the culture of the subject population and/or be able to verify that translated documents are the equivalent of the English version of documents submitted. The consultant should not have any direct involvement with the study. If you do not know someone who would be willing to act as your cultural consultant, the Office of Research Integrity will try to find someone to fill this role (this may delay the approval process for your protocol). Please include the name, address, telephone number, and email of the person who will act as the cultural consultant for your study. For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

For recruitment of Non-English speaking subjects, the consent document needs to be in the subject's native language. Download the informed consent template available in the E-IRB "Informed Consent/Assent Process" section and use it as a guide for developing the consent document. (Note: Your translated consent document can be attached to your application in the "Informed Consent" section; **be sure to save your responses in this section first**.)

If research is to be conducted at an international location, identify local regulations, laws, or ethics review requirements for human subject protection. If the project has been or will be reviewed by a local Ethics Committee, attach a copy of the review to the UK IRB using the attachment button below. You may also consult the current edition of the International Compilation of Human Research Standards

Does your study involve **HIV/AIDS research and/or screening for other reportable diseases (e.g., Hepatitis C, etc…)**?

○ Yes ◉ No

HIV/AIDS Research

If you have questions about what constitutes a reportable disease and/or condition in the state of Kentucky, see ORI's summary sheet: "Reporting Requirements for Diseases and Conditions in Kentucky" (PDF).

HIV/AIDS Research: There are additional IRB requirements for designing and implementing the research and for obtaining informed consent. Describe additional safeguards to minimize risk to subjects in the space provided below.

For additional information, visit the online IRB Survival Handbook to download a copy of the Medical IRB's requirements for Protection of Human Subjects in Research Involving HIV Testing [D65.0000] (PDF), and visit the Office for Human Research Protections web site for statements on AIDS research, or contact the Office of Research Integrity at 859-257-9428.

PI-Sponsored FDA-Regulated Research

Is this an investigator-initiated study that:

Back to Top

1) involves testing a Nonsignificant Risk (NSR) Device, or
2) is being conducted under an investigator-held Investigational New Drug (IND) or Investigational Device Exemption (IDE)?

○ Yes ◉ No

PI-Sponsored FDA-Regulated Research

If the answer above is yes, then the PI assumes the regulatory responsibilities of both the investigator and sponsor. The Office of Research Integrity provides a summary list of sponsor IND regulatory requirements for drug trials (PDF), IDE regulatory requirements for SR device trials (PDF), and abbreviated regulatory requirements for NSR device trials. For detailed descriptions see FDA Responsibilities for Device Study Sponsors or FDA Responsibilities for IND Drug Study Sponsor-Investigators.

- Describe your (the PI's) experience/knowledge/training (if any) in serving as a sponsor (e.g., previously held an IND/IDE); and
- Indicate if you have transferred any sponsor obligations to a commercial sponsor, contract research organization (CRO), contract monitor, or other entity (provide details or attach FDA 1571).

IRB policy requires mandatory training for all investigators who are also FDA-regulated sponsors (see Sponsor-Investigator FAQs). A sponsor-investigator must complete the applicable Office of Research Integrity web based training, (drug or device) before final IRB approval is granted.

Has the PI completed the mandatory PI-sponsor training prior to this submission?

○ Yes ○ No

If you (the PI) have completed equivalent sponsor-investigator training, you may submit documentation of the content for the IRB's consideration.

Attachments

FUNDING/SUPPORT

If the research is being submitted to, supported by, or conducted in cooperation with an external or internal agency or funding program, indicate below all the categories that apply.

☑ Not applicable

Check All That Apply

- ☐ Grant application pending
- ☐ (HHS) Dept. of Health & Human Services
  - ☐ (NIH) National Institutes of Health
  - ☐ (CDC) Centers for Disease Control & Prevention
  - ☐ (HRSA) Health Resources and Services Administration
  - ☐ (SAMHSA) Substance Abuse and Mental Health Services Administration
- ☐ (DoJ) Department of Justice or Bureau of Prisons
- ☐ (DoE) Department of Energy
- ☐ (EPA) Environmental Protection Agency
- ☐ Federal Agencies Other Than Those Listed Here
- ☐ Industry (Other than Pharmaceutical Companies)
- ☐ Internal Grant Program w/ proposal
- ☐ Internal Grant Program w/o proposal
- ☐ National Science Foundation
- ☐ Other Institutions of Higher Education
- ☐ Pharmaceutical Company
- ☐ Private Foundation/Association
- ☐ U.S. Department of Education
- ☐ State

Other:

Click applicable listing(s) for additional requirements and/or information:

- (HHS) Dept. of Health & Human Services
- (NIH) National Institutes of Health
- (CDC) Centers for Disease Control & Prevention
- (HRSA) Health Resources & Services Administration
- (SAMHSA) Substance Abuse & Mental Health Services Administration
- Industry (Other than Pharmaceutical Companies) [IRB Fee Info]
- National Science Foundation
- (DoEd) U.S. Department of Education
- (DoJ) Department of Justice or Bureau of Prisons
- (DoE) Department of Energy Summary and Department of Energy Identifiable Information Compliance Checklist
- (EPA) Environmental Protection Agency

Specify the funding source and/or cooperating organization(s) (e.g., National Cancer Institute, Ford Foundation, Eli Lilly & Company, South Western Oncology Group, Bureau of Prisons, etc.):

Add Related Grants

If applicable, please search for and select the OSPA Account number or Electronic Internal Approval Form (eIAF) # (notif #) associated with this IRB application:

Add Related Grants

Grant/Contract Attachments

The research involves use of Department of Defense (DoD) funding, military personnel, DoD facilities, or other DoD resources. (See DoD SOP [PDF] and DoD Summary [PDF] for details)

○ Yes ◉ No