PENNSTATE

HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

Comparisons of Clinical, Pharmacological and Molecular Effects of Intravenous and Oral Acetaminophen in Adults with Sub-Arachnoid Hemorrhage

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1.0 Objectives

1.1 Study Objectives

In individuals diagnosed with subarachnoid hemorrhage (SAH), fevers have been shown to have detrimental micro and macroscopic effects on the brain that can ultimately cause secondary brain injury. The anti-pyretic effects of oral acetaminophen have been studied in critically ill patients but no study has been able to compare these effects to the IV form of acetaminophen also known as OFIRMEV. We wish to explore the notion that IV acetaminophen will be more effective than enteral acetaminophen in reducing the incidence of non-infectious fevers in critically ill patients. In addition, we propose to study the levels of inflammatory cytokines after administration of IV or enteral acetaminophen, as well as, determine the incidence of vasospasm in SAH patients treated with IV acetaminophen. Currently, external ventricular drain (EVD) placement is the “standard of care” in patients who present with SAH and altered mental status/coma. The presence of an EVD allows for continuous sampling and removal of cerebral spinal fluid (CSF) as necessary to alleviate dangerous elevations in intracranial pressure. This clinical scenario allows for a unique, continuous outlet to access the CSF, without placing patients at risk, and without further invasive procedures (i.e. repeated spinal taps). These samples of CSF can be assayed for levels of acetaminophen, as well as inflammatory markers of fever which include interleukin-1beta (IL-1β), interleukin-6 (IL-6), and thromboxane A-2 (TXA-2), in patients selected to be given enteral or IV acetaminophen.

1.2 Primary Study Endpoints

Our primary objective is to determine and compare the bioavailability of acetaminophen given in the enteral and IV formulation. The primary endpoint will be to quantify the amount of acetaminophen in the CSF, in patients with SAH, at eleven time points (0, 5, 15, 30, 45, 60, 90, 120, 180, 240, 360 minutes) beginning directly after administration of either IV or enteral acetaminophen. This will be done by sampling the CSF attained from the EVD (External-Ventricular Drain). Additionally, we will measure the levels of acetaminophen in the blood at these time points. Acetaminophen levels will be continuously monitored in both the blood and CSF with samples collected every 24 hours following first drug administration for 14 days. Patients will also have steady state levels of acetaminophen monitored by taking blood and CSF samples every 35 hours (1 hour before 6th loading dose).

1.3 Secondary Study Endpoints

In addition to acetaminophen, we will measure the levels of IL-1 beta, IL-6, and TXA-2 in the CSF which will be obtained at five time points: 0, 60,120, 240, 360 minutes after administration of either IV or enteral acetaminophen. IL-1β, IL-6, and TXA-2 levels

will be continuously monitored in both the blood and CSF with samples collected every 24 hours following first drug administration for 14 days. We will also obtain temperature readings at these time points making note of the number of febrile events (temperature greater than 38.3 as defined by the Society of Critical Care Medicine) as well as the median and mean temperature for each group) Following the first set of eleven samples, patients will have their temperature and inflammatory cytokines monitored with blood and CSF samples every 24 hours following the time of first drug administration. Age and sex of patients will also be analyzed to determine if they play a significant role in the level of inflammatory cytokines.

Additionally, we will measure the incidence of vasospasm in patients with SAH who receive IV acetaminophen starting on post-bleed day 0 and continuing for 14 consecutive days (typical vasospasm window). Clinical vasospasm will be defined as the presence of new focal neurological deficits (motor or speech deficits) that developed after SAH, a decrease in the Glasgow Coma Score (GCS) of 2 or more points for >6hrs, a new cerebral infarction unrelated to post-treatment (coiling or clipping) complications, re-bleed, progressive hydrocephalus, electrolyte or metabolic disturbance, or infection. The incidence of clinical vasospasm will be identified in the patients EMR after the 14 day period.

2.0 Background

2.1 Scientific Background and Gaps

Fever occurs in almost three quarters of acute brain injury patients admitted to the Neuro Surgical Intensive care Unit (1). A recent meta-analysis, which included over 14,000 patients, demonstrated that the presence of fever was associated with worse outcomes (2). Fever is known to cause elevations in intracranial pressure and disruption of blood–brain barrier in the injured brain, as well as releasing excitatory amino acids and free radicals, which can lead to ischemic depolarization. All of these micro and macroscopic effects contribute to secondary brain injury (3-5). SAH accounts for only 5% of all strokes, however, it is responsible for 25% of all stroke-related mortality (6). Of the patients who survive the initial bleed and subsequent surgical/endovascular procedures, up to one-third develop delayed cerebral ischemia (7). The mechanism of delayed cerebral ischemia still remains unclear; however, vasospasm and inflammation are currently the most common targets for novel therapeutic interventions (8,9). Presently, only oral nimodipine has been proven (in one large randomized control trial) to improve outcomes in patients with subarachnoid hemorrhage through an unknown mechanism. Numerous subsequent clinical trials targeting vasospasm have been universally disappointing (10).

The release of modulators of inflammation is a key process in cerebral ischemia and is likely driven by the cytokine interleukin-1 (11). Interleukin-1 up-regulates the expression of interleukin-6, causing local inflammation. Clinical studies have demonstrated elevated interleukin-6 levels in the CSF of patients after SAH. Studies have also shown a correlation between higher concentrations of CSF interleukin-6 and worse clinical outcomes (11,12). There is a proposed link between fever and vasospasm; in 2001, a study demonstrated that SAH patients who were febrile during admission were more likely to experience vasospasm and a poor outcome (13). Paracetamol has been available in Europe in an IV formulation since 2002. Studies have shown that it penetrates rapidly into the cerebrospinal fluid of children and can be

detected in as little as 5 minutes (with the highest CSF concentration detected 57 minutes after administration) (14) (15). Currently, the only study to compare plasma and CSF pharmacokinetics of intravenous, oral, or rectal formulations of acetaminophen consisted of just 6 healthy male volunteers (17). There have been no studies comparing the antipyretic effects of IV and enteral acetaminophen in critically ill adults (16).

2.2 Previous Data

Not applicable. No previous studies have been performed comparing the antipyretic effects of IV and enteral acetaminophen in critically ill adults.

2.3 Study Rationale

Previous studies have demonstrated that the presence of fever in critically ill patients is associated with worse outcomes and secondary brain injury. Controlling fever with the anti-pyretic effects of oral acetaminophen (given either via a feeding tube or if swallowing evaluation has been passed, given by mouth) is the standard of care in patients with SAH. To date there have been no studies that have compared the oral and IV formulations in decreasing the duration of fever. This could potentially lead to overall better outcomes for the patient. Additionally, the IV formulation may have an effect on preventing vasospasms compared to the oral form.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

1. Adults: aged18-100y, inclusive.
2. Diagnosis of subarachnoid hemorrhage. CT, CTA, lumbar puncture, or MRI can confirm this diagnosis.
3. Placement of an external ventricular drain.
4. Cleared by standard of care dysphagia screen and/or speech therapy for ability to swallow. Subjects may also be enrolled with an NG/J tube if they fail the dysphagia screening.

3.2 Exclusion Criteria

1. Anyone under the age of 18 or over the age of 100.
2. Contraindication to acetaminophen such as a known hypersensitivity, hepatic impairment {this will be defined using liver function tests (LFT's) ALT, Alkaline phosphatase, and Total Bilirubin: specifically, transaminase (ALT) greater than twice the normal range} or known/documented severe active liver disease.
3. Known Glucose-6-phosphate dehydrogenase deficiency (G6PD)
4. Severe renal impairment (creatinine clearance ≤ 30 mL/min).

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

1. Removal of EVD
2. Serious adverse reactions to acetaminophen including hepatic injury, serious skin reactions, hypersensitivity, and anaphylaxis.
3. Intolerable side effects of acetaminophen including severe nausea, vomiting, headache, and insomnia.

4. Patients can be withdrawn from the study if ALT, ALK Phosphatase, or T. Bilirubin rise to a level of three times the upper limit of normal or at any point that the treating physician believes that the study protocol unnecessarily places the patient at risk for adverse outcomes.

3.3.2 Follow-up for withdrawn subjects

If the LFTs meet stopping criteria, drug product will be discontinued and LFT monitoring will continue three days and 7 days post initial onset. If LFT's do not decrease to an acceptable level, the PI will continue to monitor past 7 days until labs have reached normal values.

4.0 Recruitment Methods

4.1 Identification of subjects

Potential participants of the study will be identified in the neurosurgical intensive care unit by an intensivist or staff physician or resident. The physician will notify a study coordinator

4.2 Recruitment process

An initial screen of their medical record will be performed via a pre-enrollment screening document that will include the study's inclusion criteria. Once patients are identified, the patient will be approached in the hospital and the study will be explained in detail to them or their legally authorized representative. If legally authorized representative (LAR) is required and they are not in the hospital, a member of the research team will telephone the LAR and explain the study in detail to them.

4.3 Recruitment materials

Not applicable

4.4 Eligibility/screening of subjects

Patients' medical records will be reviewed to determine their eligibility. A screening document will be used to assess the eligibility of each potential subject. This document will include the inclusion criteria for this study which can be answered via the EMR.

5.0 Consent Process and Documentation

5.1 Consent Process.

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

After identifying potential study subjects, informed consent will only be obtained by a Research Team Members who are IRB-approved members of the study team as per IRB policies and procedures. The IRB approved study team member will obtain consent, either from the patient directly (If patient is cognitively aware and able to give consent) or through the legal authorized representative (LAR) if the patient is unable to give consent. Indications that a patient may not give consent include sedation and or altered mental status. In such cases, the LAR will be responsible for consenting to the study. Acquiring consent will be done in a quiet and private setting such as the patient's room or

nearby office. If LAR is not in the hospital, a member of the research team will telephone them and ask if they can fax or email the consent to them for review. Once the LAR has received the consent, the research team member will go over the form with them by phone. The team member will ensure that a witness who is not a research team member is present while the team member conducts the consent process with the LAR. If the LAR agrees to allow the patient to be enrolled into the research, the LAR will be instructed to sign at the appropriate signature area in the consent form. The team member and the witness will then sign the phone consent form (see:STUDY00002767 Phone Consent Script). The team member will ask the LAR to send the original, signed consent form back to the team member. Once received, the team member will send a copy of the signed consent form and phone consent form with signatures to the LAR for their records. LAR will be advised that participation in the study may begin when the signed forms are received. Subject participation may begin before receiving the original documents if the LAR is able to send the signed consent form to investigators electronically. However, the LAR still must mail the original consent form to the investigators.

5.1.1.2 Coercion or Undue Influence during Consent

It will be explained that research participation is voluntary. Their decision to participate or not participate will not affect their level of care.

5.1.2 Waiver or alteration of the informed consent requirement

We are requesting a partial waiver to review the patient's medical record to determine their eligibility.

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

Written informed consent for the procedure and participation in the study will be obtained. If consent is obtained by phone, the phone script with signatures will be kept with the signed consent form. An original will be given to the patient or their LAR for their records and another original will be kept by the research team. A copy will be uploaded to their medical record.

5.2.2 Waiver of Documentation of Consent

Not applicable

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

The current IRB approved short consent form and summary (same as the English consent form used for long form of consent documentation) will be obtained.

We will verify that we are using the most current IRB-approved version of the study specific short consent form and summary and that the short consent form is in a language understandable to the subject/representative.

Copies will be given to the subject/representative. Whenever possible we will provide the short consent form and summary to the subject/representative in advance of the consent discussion.

The services of an interpreter fluent in both English and the language understood by the subject/representative will be obtained. Should subject/representative insist upon the use of a friend or family member to provide them with interpreting service, staff shall retain a healthcare interpreter to participate in the exchange to ensure that it represents accurate communication of information between hospital staff and patients (PC-22HAM).

The services of an impartial witness who is fluent in both English and the language spoken by the subject/representative will be obtained to be present during the entire consent discussion to attest that the information in the short consent form, summary, and any other information provided was accurately explained to, and apparently understood by, the subject/representative, and that consent was freely given. The witness and the interpreter may be the same person.

The witness may be a family member or friend. The witness will not be a person involved in the design, conduct, or reporting of the research study.

The interpreter will translate the summary (not the short consent form) to the subject/representative.

Through the interpreter we will explain the details in such a way that the subject/representative understands what it would be like to take part in the research study. When necessary, we will provide a different or simpler explanation to make the information understandable.

We will have the subject/representative read the short consent form or have the interpreter read the short consent form to the subject/representative.

5.3.2 Cognitively Impaired Adults

5.3.2.1 Capability of Providing Consent

The physician will decide if the subject is capable of providing consent. If the patient is deemed incapacitated by the ICU team, we will obtain consent from his/her guardian or legal authorized representative prior to study participation.

5.3.2.2 Adults Unable To Consent

If the subject is unable to provide written consent, authorization will be obtained by the patient's legally authorized representative. Should patient become able to provide consent, we will then obtain written consent from them as well.

5.3.2.3 Assent

If subject is unable to provide written consent, we will try and obtain assent from the subject. Assent will be documented on the consent form that is uploaded to the medical record.

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

Not applicable

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☒ Authorization will be obtained and documented as part of the consent process.
☒ Partial waiver is requested for recruitment purposes only *(Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained)*
☐ Full waiver is requested for entire research study *(e.g., medical record review studies)*
☐ Alteration is requested to waive requirement for written documentation of authorization

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in Section 10 of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

Identifiers will be destroyed once the study is completed.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

The PHI is necessary to access the patient's medical records.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

The information required for screening is only available in the medical record.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

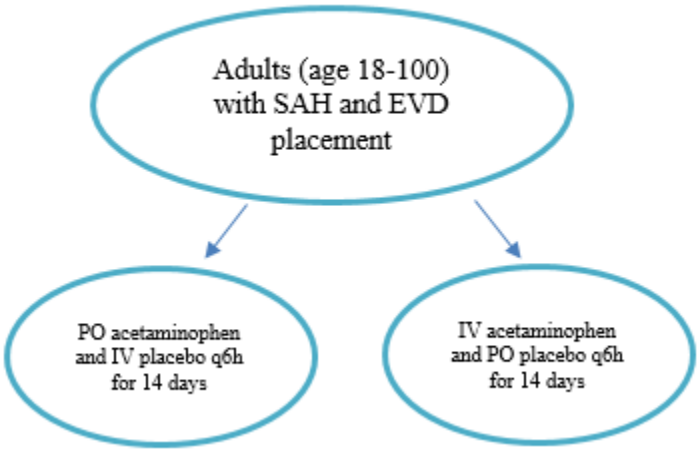
Access to the information will be limited, to the greatest extent possible, within the research team.

All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

This is a randomized double-blind controlled trial. Adults will be randomized to either the enteral or IV acetaminophen group.



7.2 Study Procedures

7.2.1 Day 1 – Consent and Randomization

- Following consent and screening LFT's (exclusion criteria for transaminase, ALT, and T. Bilirubin is listed above), eligible subjects will be randomized to either an enteral or IV acetaminophen group.

7.2.2 Day 1 – Day 14

- Patients will receive two drugs; one enteral drug and one IV drug. The pharmacist will randomize which drug contains acetaminophen and which contains a placebo (based on the patient's randomization code). Patients in the enteral group will receive acetaminophen orally (or per nasogastric tube if necessary), and a saline solution through their IV. Patients in the IV group will receive acetaminophen through their IV and an oral placebo (or per nasogastric tube if necessary).
- Study drugs: patients weighing greater than 50 kg will receive either 1 gram of acetaminophen IV or enteral (as determined by their randomization), this will be administered by the bedside nurse. The IV formulation (OFIRMEV) will be administered via an infusion pump over 15 minutes as prescribed by the manufacturer. In patients that weigh less than 50kg a dose of 15mg/kg every 6 hours will be utilized for both the IV and enteral formulations. The nurse will be blinded to which drug contains acetaminophen.
- Following the first administration of either formulation, a 2ml sample of CSF will be attained from the EVD. The EVD has an initial chamber that is at the level of the trachea which allows for sampling without directly opening the CSF container itself and potentially introducing a source of infection. This chamber is easy to empty between each time point which

ensures that the next sample won't be contaminated with the previous sample of CSF. These samples will be obtained by either a neurointensivist attending/fellow or neurosurgery resident. A blood sample will also be obtained using the in place arterial line following drug administration.

- Blood samples (approx. 2ml) will be obtained at the same times in which we sample the CSF. If the arterial line has been removed, subsequent blood draws will be done through a vein in the arm. If a line is absent for a prolonged period of time, the research team will correlate blood sample collection with standard of care routine blood draws between 6-8 am every morning in hopes of minimizing discomfort to the patient.
- Sampling of CSF and blood will be done at eleven time points, including: 0, 5, 15, 30, 45, 60, 90, 120, 180, 240, and 360 minutes after first administration of the drug.
- Measurements of external body temperature will be done at each time point as well.
- Blood and CSF samples once collected will be transported on ice to the Anesthesia Clinical Research laboratory. Whole blood specimens will then be centrifuged for 15 minutes at 1500 RCF. The supernatant will then be aspirated and placed into 1.5ml eppendorf tubes where they will be labeled, cataloged and placed into -70 degree centigrade storage. CSF samples will also be centrifuged and aliquoted (500µl quantities) into 1.5ml eppendorf tubes; labeled and cataloged, and placed into -70 degree C. storage. The levels of acetaminophen, IL-1 beta, IL-6, and TXA-2 will be assayed and quantified for each sample.
- Following the first administration of the drug, patients will continue to receive treatment with an active drug and a placebo every 6 hours through day 14. After the first sequence of measurements (11 CSF and 11 blood samples), patients will have their blood and CSF tested once every 24 hours through day 14, starting from the time of the first drug treatment. Timing of the daily blood samples may vary a few hours if the patient doesn't have an arterial line and requires a venous puncture, in order to collectively get blood samples needed for the day. Daily blood and CSF sampling will allow for analysis of long-term changes in inflammatory cytokine levels. Temperature will also be taken at this time.
- Patients will also have their acetaminophen levels tested at 35 hours (1 hour before 6th loading dose) in separate samples taken from both blood and CSF. This will be used to determine the steady state level of acetaminophen If for any reason (e.g. an emergency or unexpected situation), the flood sample at the 35th hour couldn't be obtained, it will be collected at the earliest stable period and will be noted.
- Liver function tests, ALT, ALK Phosphatase, and T. Bilirubin will be monitored (upon enrollment in the study) and every three days for the duration of the study. The hold/call order for these labs will be written on a paper pharmacy order sheet and/or electronic order page (if available). The paper order sheet will be kept in the patient's bedside chart.
- Upon enrollment, the medical record will be checked daily, for clinical and/or research LFT lab results (including weekends), from day 1 through day 14, or until patient is removed from the study. The PI or a study team physician will be responsible to check Cerner Labs in Powerchart daily

and if LFTs were drawn, determine if they meet criteria to hold the drug. Clinical LFT's -drawn on any day and safety labs obtained every third day will be documented per protocol. The physician will determine if any elevations in ALT, Alk Phos or T. Bili are clinically insignificant or significant based on the reported lab values. ICU nursing HOLD/Call orders are in place with the paper study drug order sheet and/or electronic order to make sure study drug is not given if LFTS are elevated 3X upper limit of normal. Nursing staff will notify research physician if subject meets study drug HOLD/Call order criteria. Lab values will be printed as Lab Safety documents and placed in the Study Binder located in C2813. This will serve as documentation that laboratory values were assessed in a timely manner for to ensure subject safety. If LFTs are determined to be clinically significant but are below stopping criteria, the labs will be followed daily, and the PI will assess if any changes are needed for drug administration or dosing. If the LFTs meet stopping criteria, drug product will be discontinued and LFT monitoring will continue three days and 7 days post initial onset. If LFT's do not decrease to an acceptable level, the PI will continue to monitor past 7 days until labs have reached normal values. All LFT monitoring will be printed off from Powerchart to document continued review and assessment of LFT values.

- Incidence of vasospasm will be reviewed in the patients EMR chart starting on post-bleed day 0 and continuing for 14 consecutive days (typical vasospasm window). Patients who meet the clinical definition of vasospasm defined in section 1.3 will be recorded.

7.3 Duration of Participation

Each individual enrolled in the study will be given either enteral or IV acetaminophen and a corresponding placebo every six hours for a total of 14 days. The primary study end point of quantifying the amount of acetaminophen in the CSF until steady state is reached requires obtaining CSF from the EVD for a duration of six hours. The secondary end point of quantifying the number of vasospasms will occur with chart review after the individual has been hospitalized for 14 days.

7.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

7.4.1 Description

The study will be performed using acetaminophen in both the enteral and IV form. The enteral formulation will be acetaminophen oral suspension at a concentration of 160mg/5mL. . In cases where the patient is unable to swallow, the oral suspension will be given through the nasogastric tube. The IV formulation will be the FDA approved OFIRMEV which comes in a single glass bottle at a concentration of 1000mg/100ml (10mg/ml) containing a total of 1 gram of acetaminophen.

The pharmacy will provide the appropriate placeboes for this study. Placebo for the IV formulation will be 0.9%NaCl. Placebo for enteral/oral doses will be an oral suspension consisting of Ora-Plus (suspending vehicle), Ora-Sweet (sugar-free flavored syrup vehicle), and flavored syrup (syrup vehicle for oral solution).

7.4.2 Treatment Regimen

The total dose of acetaminophen regardless of route of administration will be 1 gram every 6 hours in subjects weighing greater than or equal to 50kg or 15mg/kg every 6 hours in subjects weighing less than 50 kg. Treatment should begin within 24-48 hrs subject meeting the inclusion criteria. At the time of active drug administration, a corresponding placebo dose (IV saline or placebo oral suspension) will be administered. Medications will be given for a total of 14 days as to encompass the typical window for vasospasm. If for any reason a dose needs to be skipped (eg. Emergency situation (alteration in consciousness, CPR, need for intubation, and surgical intervention)), it can be given as a coupled treatment in each alternative scenario.

7.4.3 Method for Assigning Subject to Treatment Groups

The department of Public health Sciences will supply the Investigational pharmacy with the randomization table assigning patients into the enteral or IV acetaminophen treatment group.

7.4.4 Subject Compliance Monitoring

Not Applicable as study drug will be administered by study personnel.

7.4.5 Blinding of the Test Article

Pharmacy will assign patients to either an IV or an enteral form of acetaminophen based on the patient's randomization code. Pharmacy will provide the study team with the blinded test articles. Patients in the enteral group will receive acetaminophen orally, and a saline solution through their IV. Patients in the IV group will receive acetaminophen through their IV and an oral placebo suspension. Nursing staff, who will administer the drugs, will not be aware of which form of drug (IV or PO) contains acetaminophen. Data that identifies a patient's group will not be released until after the entire study is completed.

7.4.6 Receiving, Storage, Dispensing and Return

As this is a randomized, blinded study we will be obtaining the medications from the investigational pharmacy. The pharmacy will prepare and store the drugs as per package insert until the time that patient specific doses are drawn up. Once drawn up the IV medications may be stored for up to 6 hours at room temperature.

8.0 Data and Specimen Banking For Future Undetermined Research

Not applicable

9.0 Statistical Plan

9.1 Sample size determination

A parallel design will be used to make comparisons between two treatment groups: oral acetaminophen or IV acetaminophen. The primary outcome variable will be the maximum concentration of acetaminophen in plasma (C_{max}). Subjects will be randomized to treatment groups in blocks to attempt to maintain balance in the sample size between the groups.

From a previous study, we found a pooled standard deviation for the difference between oral and IV acetaminophen in C_{max} to be 4.864. The basic method at the core of ANCOVA that we can use to determine the total sample size needed for each group is a Two-sample t-test. Given these parameters, a sample size of 25 subjects for each group for a total sample size of 50 subjects will provide 80% power to detect a difference of at least 4.0 µg/mL (an effect size of 0.822) between treatment groups using a two-sided Two-sample t-test and Type I error rate of 0.05.

9.2 Statistical methods

To make comparisons between the treatment groups, an Analysis of covariance (ANCOVA) model will be used (Neter J, Kutner MH, Nachtsheim CJ, Wasserman W. Applied Linear Statistical Models. The McGraw-Hill Companies, Inc., 1996.) The ANCOVA model is an extension of the Analysis of variance and the Two-sample t-test that allows us to adjust for potentially confounding covariates if deemed necessary such as age or sex. Diagnostics will be assessed to determine the fit of the model and the adherence to modeling assumptions, and, if necessary, transformations of the outcome variable will be used to meet modeling assumptions. The effect size will be quantified using the difference in means between the groups with their associated 95% confidence intervals. Post-hoc hypothesis tests will be corrected as needed for multiple testing using appropriate techniques such as Bonferroni's method or Tukey's procedure.

10.0 Confidentiality, Privacy and Data Management

See Research Data Plan Review Form

11.0 Data and Safety Monitoring Plan

11.1 Periodic evaluation of data

The PI and research coordinator will review cumulative adverse events, early termination of study participation, and accrual every six months and report any issues requiring modification of the study or alteration of the risk: benefit ratio to the IRB immediately. A summary of adverse events, study progress and protocol modifications will be included for IRB review in the continuing review.

11.2 Data that are reviewed

The data to be reviewed will be:

- Safety data
- Untoward events
- Efficacy data

11.3 Method of collection of safety information

Safety information will be collected by the research staff as described in Section 7.2.

11.4 Frequency of data collection

Samples of CSF and blood will be collected for analysis at time points 0, 5, 15, 30, 45, 60, 90, 120, 180, 240, 360 minutes after administration of either IV or enteral acetaminophen. Starting from the point of first drug administration, additional data will be collected from both CSF and blood every 24 hours to determine changes in temperature, IL-1, IL-6, TXA-2, and acetaminophen. Samples will also be collected every 35 hours (one hour prior to the 6th loading dose) to determine acetaminophen

concentration. Additionally, data will be collected to determine confirmed instances of vasospasm throughout the 14 day study period. This data will be obtained from the patient's chart.

11.5 Individual's reviewing the data

Oversight for the conduct of the study will be provided by the PI and the research coordinator will monitor the data. They will ensure that all eligibility criteria and consent requirements are met prior to a subject's participation in the study and that the procedures and adverse event reporting occur according to the IRB approved protocol.

11.6 Frequency of review of cumulative data

The PI and research coordinator will review cumulative adverse events, early termination of study participation, and accrual every six months and report any issues requiring modification of the study or alteration of the risk: benefit ratio to the IRB immediately. A summary of adverse events, study progress and protocol modifications will be included for IRB review in the continuing review.

11.7 Statistical tests

Not applicable

11.8 Suspension of research

Not applicable

12.0 Risks

The possible risks for this study include:

Oral Solution:
Dermatologic: Skin rash
Endocrine & metabolic: Decreased serum bicarbonate, decreased serum calcium, decreased serum sodium, hyperchloremia, hyperuricemia, increased serum glucose
Genitourinary: Nephrotoxicity (with chronic overdose)
Hematologic & oncologic: Anemia, leukopenia, neutropenia, pancytopenia
Hepatic: Increased serum alkaline phosphatase, increased serum bilirubin
Hypersensitivity: Hypersensitivity reaction (rare)
Renal: Hyperammonemia, renal disease (analgesic)

IV Solution:
>10%: Gastrointestinal: Nausea (adults 34%; children ≥5%), vomiting (adults 15%; children ≥5%)
1% to 10%: Cardiovascular: Hypertension, hypotension, peripheral edema, tachycardia
Central nervous system: Headache (adults 10%; children ≥1%), insomnia (adults 7%; children ≥1%), agitation (children ≥5%), anxiety, fatigue, trismus
Dermatologic: Pruritus (children ≥5%), skin rash
Endocrine & metabolic: Hypervolemia, hypoalbuminemia, hypokalemia, hypomagnesemia, hypophosphatemia
Gastrointestinal: Constipation (children ≥5%), abdominal pain, diarrhea
Genitourinary: Oliguria (children ≥1%)
Hematologic & oncologic: Anemia
Hepatic: Increased serum transaminases
Local: Infusion site reaction (pain)

Neuromuscular & skeletal: Limb pain, muscle spasm
Ophthalmic: Periorbital edema
Respiratory: Atelectasis (children ≥5%), abnormal breath sounds, dyspnea, hypoxia, pleural effusion, pulmonary edema, stridor, wheezing
Miscellaneous: Fever (children ≥1%)

- Both IV and Oral formulations: <1%, postmarketing, and/or case reports: Anaphylaxis, hepatic injury (dose-related), hypersensitivity reaction, severe dermatological reaction (acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis)
- Treatment of Suspected overdose: If an acetaminophen overdose is suspected, we will obtain a serum acetaminophen assay as soon as possible followed by liver function studies initially and repeat at 24-hour intervals. We will administer the antidote N-acetylcysteine (NAC) as early as possible.
- Patients who have their arterial line removed prior to the conclusion of the study may have their blood drawn from a vein. Risks include a slight pinch or pinprick when the sterile needle enters the skin. The risks also include mild discomfort and/or a black and blue mark at the site of puncture. Less common risks include a small blood clot, infection or bleeding at the puncture site, and on rare occasions fainting during the procedure
- The risk of randomization. The route of the acetaminophen will be assigned randomly; there is a 50/50 chance of how the drug will be administered. Either the IV or oral form of acetaminophen may carry a greater risk of side effects.
- Risk of loss of confidentiality if your medical information or your identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening.

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13.0 Potential Benefits to Subjects and Others

13.1 Potential Benefits to Subjects

Previous studies have demonstrated that the presence of fever is associated with worse outcomes, secondary injury to the brain, and prolonged hospitalizations. If the antipyretic effects of IV acetaminophen are greater than those from oral administration, the duration of fever could potentially be lessened leading to better overall outcomes for the patient. Additionally, this route of administration may have an effect on preventing vasospasms compared to the oral form.

13.2 Potential Benefits to Others

If the study concludes that the IV formulation has a higher bioavailability, decreased duration of fever, decreased incidence of vasospasm, and/or produces a better overall patient outcomes, this formulation could potentially become the standard of care compared to the enteral formulation.

14.0 Sharing Results with Subjects

We will not be sharing the results with subjects.

15.0 Economic Burden to Subjects

15.1 Costs

There are no additional costs to the subjects to participate in this study. We are obtaining funding from sponsor to provide study drugs.

15.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Number of Subjects

We plan to accumulate a total of 50 patients with 25 to be assigned to the enteral formulation and another 25 to be assigned to the IV formulation.

17.0 Resources Available

17.1 Facilities and locations

The research will be conducted at the Hershey Medical Center.

17.2 Feasibility of recruiting the required number of subjects

A preliminary search in the EMR for “subarachnoid hemorrhage” yielded 350 patients. A majority of subarachnoid hemorrhage is caused by trauma and not aneurysm rupture however. Looking back at the NSICU census for patients admitted for aneurysmal subarachnoid hemorrhage over the past 1year yielded as few as 0 and as many as 9 patients per month. Obviously not all of these patients will meet inclusion criteria; however, it seems feasible that 50 patients could be enrolled in as little as one year as more ‘telestroke” centers join Penn State Hershey Medical Center.

17.3 PI Time devoted to conducting the research

Currently I am employed as a 0.9 FTE in the department of Anesthesia leaving one academic day per week that I devote to research. In addition I spend one week per month as the intensivist in the NSICU.

17.4 Availability of medical or psychological resources

Not applicable

17.5 Process for informing Study Team

Meetings will be held periodically as needed to ensure all research team members are informed about the protocol and their duties. Team emails will also be used to keep team members updated.

18.0 Other Approvals

Registered with clinicaltrials.gov
Bio-safety
Departmental review
Sponsor approval

19.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Not applicable

20.0 Multi-Site Research

Not applicable

21.0 Adverse Event Reporting

21.1 Adverse Event Definitions

For drug studies, incorporate the following definitions into the below responses, as written:	
Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

21.2 Recording of Adverse Events

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  Note: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.
- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study
- The test finding is considered an adverse event by the investigator.

21.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

21.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

Not applicable

21.5 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

21.6 Unblinding Procedures

The Investigational Pharmacist will provide pertinent information to attending physician should unblinding become necessary.

21.7 Stopping Rules

Patients can be withdrawn from the study if LFT's, ALT, ALK phosphatase, or T. Bilirubin rise to a level of three times the upper limit of normalor at any point that the

treating physician believes that the study protocol unnecessarily places the patient at risk for adverse outcomes.

22.0 Study Monitoring, Auditing and Inspecting

22.1 Study Monitoring Plan

22.1.1 Quality Assurance and Quality Control

This is a low risk therapeutic study with agents with a known safety profile. The PI will ensure that this study is conducted, and that the data are generated, documented (recorded), and reported, in compliance with this protocol, with institutional and IRB policies, with Good Clinical Practice guidelines and any other applicable regulatory requirements.

22.1.2 Safety Monitoring

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The **research coordinator** will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA, and/or DSMB of all Unanticipated Problems/SAE's.

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24.0 Appendix