Pharmacokinetics of Acetaminophen in Pediatric Patients With Congenital Heart Disease

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PROTOCOL TITLE:

Pharmacokinetics of acetaminophen in pediatric patients with congenital heart disease

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	2/24/2021	Adding additional intraoperative and postoperative data to be collected. Changing hospital laboratory to NMS labs.	No
2	3/17/2021	Increasing the amount of blood drawn	Yes
3	11/23/2021	Increasing the sample size to 32 to replace the 2 subjects who had to be withdrawn	Yes

1. Study Summary

Study Title	Pharmacokinetics of acetaminophen in pediatric patients with congenital heart disease
Study Design	Prospective cohort study
Primary Objective	To measure serum acetaminophen concentrations in two groups of patients with congenital heart disease (cyanotic and acyanotic) and to determine pharmacological parameters based on these levels.
Secondary Objective(s)	Not applicable
Research Intervention(s)/ Investigational Agent(s)	Not applicable
IND/IDE #	Not applicable
Study Population	Pediatric patients presenting for repair of congenital heart disease
Sample Size	32
Study Duration for individual participants	6 hours
Study Specific Abbreviations/ Definitions	Not applicable

2. Objectives

This is a prospective study of pediatric patients with congenital heart disease, in which acetaminophen serum concentrations will be measured following a single intraoperative intravenous dose of acetaminophen. These levels will be used to develop a pharmacokinetic model. Serum concentrations will be compared between two groups of patients: (1) cyanotic patients presenting for the Fontan completion operation and (2) patients with acyanotic congenital heart disease presenting for repair via median sternotomy.

3. Background

Pediatric patients presenting for cardiac surgery are at risk for a wide range of perioperative complications, including both acute pain and chronic pain, with associated decrements in postoperative quality of life. The immediate post-operative approach to analgesia for these patients continues to focus on opioid medications as the mainstay of therapy, although the benefits of a multimodal approach are being more clearly recognized. Acetaminophen is routinely used in many institutions for the perioperative management of pediatric patients

undergoing major surgical procedures, including patients presenting for cardiac surgery. The adjunctive use of acetaminophen improves analgesia and decreases opioid requirements thereby limiting opioid-related adverse effects. The pharmacokinetics of acetaminophen have been studied in many surgical populations; however, there are limited data for patients who are undergoing repair of congenital heart defects especially those with cyanotic congenital heart disease. This knowledge deficit is especially important for subsets of this population, who may be at risk for alterations in acetaminophen metabolism and therefore more susceptible to adverse reactions. The predominant pathway of acetaminophen metabolism is via glucuronidation to inactive metabolites; a smaller fraction is oxidized to highly reactive metabolites. Patients with cyanotic congenital heart disease, such as those patients presenting for the Fontan completion operation, may have depleted endogenous antioxidants and higher levels of oxidative stress, which could predispose them to a higher risk of acetaminophen related toxicity in the perioperative period. The objective of this study is to determine acetaminophen concentrations and develop a pharmacokinetic model in pediatric patients undergoing palliation or repair of congenital heart disease, with a comparison between partially and fully palliated cyanotic lesions and acyanotic lesions.

4. Study Endpoints

The primary end point is plasma concentrations at various time points following a single intraoperative intravenous dose of acetaminophen.

5. Study Intervention/Investigational Agent

Not applicable

6. Procedures Involved*

6.1 Describe and explain the study design.

This is a prospective study in which serum levels of acetaminophen will be measured following a single intravenous dose administered intraoperatively. We will enroll patients with cyanotic and acyanotic congenital heart disease who are presenting before surgical palliation (cyanotic patients), or for surgical repair requiring a median sternotomy (acyanotic patients). These patients already routinely receive acetaminophen intravenously in the operating room during sternal closure, as part of a comprehensive pain management strategy. Blood samples will be drawn post-procedure at pre-specified time points and acetaminophen concentrations will be

measured. We have an existing relationship with an expert in pediatric pharmacokinetics, Dr. Brian Anderson, who will perform the pharmacokinetic calculations for this aspect of the study.

6.2 Provide a description of all research procedures being performed and when they are performed, including procedures being performed to monitor subjects for safety or minimize risks.

Intravenous acetaminophen is routinely administered intraoperatively for patients undergoing cardiac surgery at our institute. A single dose of 15 mg/kg will be administered at the conclusion of the surgical procedure following cardiopulmonary bypass, at the start of sternal closure (first sternal wire/suture). With informed consent obtained pre-operatively, a member of the research team will collect blood samples from each patient at the pre-specified time points (total of 7) following the acetaminophen administration. Each sample will require 1-2 mL of blood. No additional acetaminophen will be administered until after the 6 hour concentration is obtained. These patients, based on the nature of their surgeries, will have existing invasive vascular access in place. The only deviation from the standard perioperative management of these patients will be the collection of blood samples at the following time points:

15-20 minutes
30-40 minutes
50-70 minutes
80-100 minutes
2, 4 and 6 hours

6.3 Describe:

- *Procedures performed to lessen the probability or magnitude of risks.*

  There are minimal risks to subjects in this study, as they already receive intravenous acetaminophen as part of their pain control management plan, and will have existing vascular access that will allow for blood sampling.

- *All drugs and devices used in the research and the purpose of their use, and their regulatory approval status.*

  Not applicable.

- *The source records that will be used to collect data about subjects. (Attach all surveys, scripts, and data collection forms.)*

Not applicable

6.4 What data will be collected during the study and how that data will be obtained.

Demographic data will be collected for each patient from the electronic medical records. This will include age, gender, weight, diagnosis, actual procedure performed, pre-operative medications, and any documented allergies. We will record intraoperative fluid and blood product administration, intraoperative medications, and whether patient was extubated in the OR, as well as duration of cardiopulmonary bypass and cross clamp time (if applicable). The dose of acetaminophen administered in the operating room will be recorded from the intraoperative medical record. Results from the acetaminophen concentration assays, analyzed at NMS labs, will be recorded into the research records. We will also record blood product administration and medications in the ICU up to the 6-hour PK sample collection.

6.5 If there are plans for long-term follow-up (once all research related procedures are complete), what data will be collected during this period.

Not applicable

6.6 For Humanitarian Use Device (HUD) uses provide a description of the device, a summary of how you propose to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures.

Not applicable

7. **Data and Specimen Banking -** Not applicable

8. **Sharing of Results with Subjects -** Not applicable

9. **Study Timelines -** Not applicable

10. Inclusion and Exclusion Criteria*

10.1 Describe how individuals will be screened for eligibility.

Following identification of potential participants (see below; partial waiver of HIPAA authorization requested), they will be approached and informed about the study as part of an informed consent process. This will take place at the pre-admission testing visit or if no PAT visit is scheduled, the day of surgery. After consent, potential participants will be asked a series of questions (data collection form to be attached) in order to verify eligibility for inclusion in the study.

Describe the criteria that define who will be included or excluded in your final study sample.

Inclusion criteria:

Pediatric patients between age 2 and 6 years of age, presenting for Fontan palliation or for surgical repair requiring median sternotomy, will be included in the study. Only patients who receive intravenous acetaminophen in the operating room will have serum levels drawn.

Exclusion criteria:

Patients will be excluded if they have documentation of an allergy to acetaminophen, severe hepatic disease or other contraindications to acetaminophen use, or if they have received acetaminophen within 24 hours of their procedure.

Indicate specifically whether you will include or exclude each of the following special populations: (You may not include members of the above populations as subjects in your research unless you indicate this in your inclusion criteria.)

Children will be included in this study.

11.Vulnerable Populations*

We have reviewed the checklist HRP-416, and have provided sufficient information in this application for completion of the checklist.

12.Local Number of Subjects

12.1 Indicate the total number of subjects to be accrued locally.

We will enroll 32 patients for this study, with 15 patients in each group (2 subjects in the acyanotic group had to be withdrawn, so we will replace those subjects).

12.2 If applicable, distinguish between the number of subjects who are expected to be enrolled and screened, and the number of subjects needed to complete the research procedures (i.e., numbers of subjects excluding screen failures.)

We would anticipate screening 20 patients for each group (for a total of 40 patients screened).

13.Recruitment Methods

We are requesting a partial waiver of HIPAA research authorization in order to identify potential participants, using clinic and operating room schedule. On a weekly basis, the cardiac operating room schedule will be reviewed to identify patients presenting for eligible procedures (Fontan palliation or surgical correction of congenital heart disease with median sternotomy). Patient name, name and date of scheduled procedure, and date of pre-admission testing visit will be noted (data collection form to be attached). If no pre-admission testing visit is scheduled, but a cardiac catheterization is scheduled, the date of the catheterization will be noted. In cases of ambiguity in the operating room or cardiac catheterization schedule or uncertainty as to nature of procedure, the chart will be reviewed to clarify the planned procedure. Only the minimum data necessary will be used to identify participants, who will then be approached and informed about the study as part of the informed consent process. No additional data will be recorded until the informed consent process is complete.

14. **Withdrawal of Subjects -** Not applicable

15. Risks to Subjects*

15.1 List the reasonably foreseeable risks, discomforts, hazards, or inconveniences to the subjects related the subjects' participation in the research. Include as may be useful for the IRB's consideration, a description of the probability, magnitude, duration, and reversibility of the risks. Consider physical, psychological, social, legal, and economic risks.

There are minimal risks to the participants in this study. Intravenous acetaminophen is approved by the US FDA for use in this population. The subjects will receive no medications beyond those routinely incorporated into the post-operative care of this patient population, and the blood samples will be taken from pre-existing vascular access sites. No changes in clinical management will be made for the subjects, who are already receiving numerous medications as well as undergoing repeated blood sampling.

16. Potential Benefits to Subjects

There are no direct benefits to the patients in this study.

17. Data Management* and Confidentiality

Serum acetaminophen concentrations will be obtained and used to calculate pharmacologic parameters; these will include volume of distribution and elimination half-life. Concentrations and pharmacologic parameters will be compared between the two patient groups.

17.1 Describe the steps that will be taken to secure the data (e.g., training, authorization of access, password protection, encryption, physical controls, certificates of confidentiality, and separation of identifiers and data) during storage, use, and transmission.

Research records will be stored in password protected computer files, to which only trained members of the research team will have access.

17.2 Describe any procedures that will be used for quality control of collected data.

NA

17.3 Describe how data or specimens will be handled study-wide:

- *What information will be included in that data or associated with the specimens?* Patient identification will be associated with the specimens.
- *Where and how data or specimens will be stored?*
- *How long the data or specimens will be stored?*

The specimens will be stored until the completion of the study.

- *Who will have access to the data or specimens?*

A member of the research team will be responsible for collecting and transporting the specimens. Only members of the research team who have completed necessary training will have access to the study data, which will be stored in password protected files.

18.Provisions to Monitor the Data to Ensure the Safety of Subjects*

NA

19.Provisions to Protect the Privacy Interests of Subjects

Potential subjects and their families will be identified through review of operating room schedules. To avoid unnecessary or unapproved intrusion into the subjects' medical histories, only the absolute minimum necessary information will be noted from a patient's chart (with requested partial HIPAA waiver) prior to obtaining the consent to participate. No information will be recorded for the patients whose guardians refuse entry into the study. Additionally, all consent procedures will take place in private rooms. Access to the patients' charts for the sake of the study will be strictly limited to study personnel who have completed all necessary training regarding research with human subjects.

20.Compensation for Research-Related Injury

NA

21.Economic Burden to Subjects

There will be no costs for subjects in this study.

22.Consent Process

22.1 Indicate whether you will you be obtaining consent, and if so describe:

A member of the research team will obtain consent from the parents/guardians of the subjects in the study. These patients are seen the preoperative testing clinic in preparation for surgery, and they will be approached at this pre-operative visit regarding this study. Research staff will follow the Informed Consent Process for Research studies. If patients are presenting for cardiac catheterization immediately preceding their operative intervention, without a preoperative testing visit, they will be approached at the time of the cardiac catheterization.

- *Any waiting period available between informing the prospective subject and obtaining the consent.*

There is usually at least one day between the evaluation at the pre-operative clinic or the cardiac catheterization and the actual day of the operation. Potential participants will have this time to consider their desire to participate in the study.

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

The expected patient population for this project will be children between 2 and 6 years of age, who would not be expected to provide assent for inclusion in the study. Their parents/legal guardians will be approached to obtain consent for inclusion in this research.

Parental permission will be obtained from one parent even if the other parent is alive, known, competent, reasonably available, and shares legal responsibility for the care and custody of the child.

If the patient is in the custody of a person other than their parent, consent will be obtained from the person legally able to provide surgical and anesthesia consent for the operation.

Based on the expected age of the participants, assent will not be obtained.

23.Process to Document Consent in Writing

23.1 We will be following "SOP: Written Documentation of Consent (HRP-091)."

23.2 We will attach the appropriate consent form.

24.Setting

24.1 Describe the sites or locations where your research team will conduct the research.

The sample collection will take place in the operating room and in the cardiothoracic intensive care unit at the prespecified time points.

25.Resources Available

Our department has successfully completed a similar study in a population of pediatric patients undergoing bariatric surgery, confirming the availability of the necessary resources for the completion of the current investigation. Based on the surgical case volume at our institute in this patient population, we would not anticipate difficulty in achieving the desired recruitment numbers for the study.

26.Multi-Site Research*

NA

27.0 Protected Health Information Recording

1.0 Indicate which subject identifiers will be recorded for this research.

☒ Name
☐ Complete Address
☐ Telephone or Fax Number
☐ Social Security Number (do not check if only used for ClinCard)
☒ Dates (treatment dates, birth date, date of death)
☐ Email address , IP address or url
☒ Medical Record Number or other account number
☐ Health Plan Beneficiary Identification Number
☐ Full face photographic images and/or any comparable images (x-rays)
☐ Account Numbers
☐ Certificate/License Numbers
☐ Vehicle Identifiers and Serial Numbers (e.g. VINs, License Plate Numbers)
☐ Device Identifiers and Serial Numbers
☐ Biometric identifiers, including finger and voice prints
☐ Other number, characteristic or code that could be used to identify an individual
☐ None (Complete De-identification Certification Form)

2.0 Check the appropriate category and attach the required form* on the Local Site Documents, #3. Other Documents, page of the application. (Choose one.)

☒ Patient Authorization will be obtained. (Include the appropriate HIPAA language (see Section 14 of consent template) in the consent form OR attach the HRP-900, HIPAA AUTHORIZATION form.)
☐ Protocol meets the criteria for waiver of authorization. (Attach the HRP-901, WAIVER OF HIPAA AUTHORIZATION REQUEST form.)
☐ Protocol is using de-identified information. (Attach the HRP-902, DE-IDENTIFICATION CERTIFICATION form.) (Checked "None" in 1.0 above)
☐ Protocol involves research on decedents. (Attach the HRP-903, RESEARCH ON DECEDENTS REQUEST form.)
☐ Protocol is using a limited data set and data use agreement. (Contact the Office of Technology Commercialization to initiate a Limited Data Use Agreement.

***Find the HIPAA forms in the IRB Website Library, Templates.**

Attach the appropriate HIPAA form on the "Local Site Documents, #3. Other Documents", page of the application.

3.0 How long will identifying information on each participant be maintained?
Identifying information will be kept until study completion.

4.0 Describe any plans to code identifiable information collected about each participant.
NA

5.0 Check each box that describes steps that will be taken to safeguard the confidentiality of information collected for this research:
☒ **Research records will be stored in a locked cabinet in a secure location**
☒ **Research records will be stored in a password-protected computer file**
☒ **Only certified research personnel will be given access to identifiable subject information**

6.0 Describe the provisions included in the protocol to protect the privacy interests of subjects, where "privacy interests" refer to the interest of individuals in being left alone, limiting access to them, and limiting access to their information. (This is not the same provision to maintain the confidentiality of data.)

Please see above in section 18.

Confidential Health Information

1.0 Please mark all categories that reflect the nature of health information to be accessed and used as part of this research.

☒ Demographics (age, gender, educational level)

☒ Diagnosis
☒ Laboratory reports
☐ Radiology reports
☐ Discharge summaries
☐ Procedures/Treatments received
☐ Dates related to course of treatment (admission, surgery, discharge)
☐ Billing information
☒ Names of drugs and/or devices used as part of treatment
☐ Location of treatment
☐ Name of treatment provider
☐ Surgical reports
☒ Other information related to course of treatment
☐ None

2.0 Please discuss why it is necessary to access and review the health information noted in your response above.
The above information is necessary for us to describe our patient population, ensure that they meet the enrollment specifications, and evaluate the outcomes of the study.

3.0 **Is the health information to be accessed and reviewed the minimal necessary to achieve the goals of this research?** ☒ Yes ☐ No

4.0 **Will it be necessary to record information of a sensitive nature**? ☐ Yes ☒ No

5.0 **Do you plan to obtain a federally-issued Certificate of Confidentiality as a means of protecting the confidentiality of the information collected**? ☐ Yes ☒ No

References

1. Lauridsen, M.H., et al., *Chronic pain in children after cardiac surgery via sternotomy.* Cardiology in the Young, 2014. **24**(5): p. 893-899.
2. Matsuda, M., et al., *Post-surgical chronic pain and quality of life in children operated for congenital heart disease.* Acta Anaesthesiologica Scandinavica, 2019. **63**(6): p. 745-750.
3. Bigeleisen, P.E. and N. Goehner, *Novel approaches in pain management in cardiac surgery.* Current Opinion in Anesthesiology, 2015. **28**(1): p. 89-94.
4. Zeilmaker-Roest, G.A., et al., *An international survey of management of pain and sedation after paediatric cardiac surgery.* BMJ paediatrics open, 2017. **1**(1).

5. Morita, K., *Surgical reoxygenation injury of the myocardium in cyanotic patients: clinical relevance and therapeutic strategies by normoxic management during cardiopulmonary bypass.* General thoracic and cardiovascular surgery, 2012. **60**(9): p. 549-556.