# 1) Protocol Title

Multiple Pre-operative Oral Doses Acetaminophen Versus Intravenous Acetaminophen

Protocol Version Date: 11/18/16

# 2) Objectives

Purpose: Acetaminophen is frequently used as an adjunct for pain management in pediatric surgical patients. The drug is available in an over the counter, inexpensive oral form as well as a considerably more expensive intravenous form. This study will compare opioid requirements and acetaminophen plasma levels post operatively for two dosing regimens to compare oral versus intravenous routes given pre operatively.

Hypothesis: Two oral doses of acetaminophen given pre operatively provide superior opioid sparing effects compared to intravenous acetaminophen for pediatric tonsillectomy and adenoidectomy patients.

Specific Aims:

To compare a preoperative acetaminophen oral dosing regimen that is better than a single intravenous dose of acetaminophen given intraoperatively as measured by amount of postoperative opioid rescue pain medication given.

To compare the cost of acetaminophen in the perioperative period for families and the health system.

To evaluate acetaminophen pharmacokinetics by checking a level 1 hour and 4 hours after the 1st IV dose of acetaminophen or placebo.

To evaluate the safety of this protocol.

# 3) Background

The primary purpose of this study is to compare opioid utilization, in post-operative patients undergoing tonsillectomy and adenoidectomy, between IV and PO acetaminophen. Secondarily, it will provide information regarding possible cost savings, pharmacokinetics and safety between these two regimens.

A prior study conducted in cleft palate surgery patients by one of our investigators, Richard L. Applegate II, MD, found that total opioid dose was higher in the PO group initially[1]. The opioid amounts became similar by the third oral dose of acetaminophen. Our study design will further examine whether the effectiveness of oral acetaminophen is enhanced by giving multiple pre-operative oral doses.

Acetaminophen, otherwise known as Tylenol or Ofirmev, has been used by medical providers to help treat moderate to severe surgical pain in children. It is used with various medications including opioids or narcotics to treat pain after surgery.

Opioids can have multiple side effects that are very serious in children after tonsillectomies and adenoidectomies and avoidance of intra-operative and post-operative opiates is strongly encouraged in tonsillectomy and adenoidectomy patients to reduce sedation and apneic events.

Studies evaluating the pharmacokinetics and pharmacodynamics of acetaminophen in children have measured plasma or serum concentrations, with newer studies using plasma levels.

Plasma levels will be drawn twice from each group of patients and measured to assess differences in dosing. If one dosing regimen results in lower concentrations, this may help explain any differences found in pain scores and opioid consumption between groups. If the acetaminophen plasma concentration drawn during the study is less than 10 mg/L, this could help explain differences in post-operative pain control and opioid requirements. An oral regimen of 30 mg/kg x1, followed by 15 mg/kg 4 hours later, could be used to achieve concentrations similar to a 15 mg/kg IV dose.

We think that two oral doses of acetaminophen given before surgery can provide better pain control (as measured by less need for breakthrough pain medicines like morphine or oxycodone) compared to one dose of intravenous acetaminophen for pediatric tonsillectomy and adenoidectomy patients.

## 4) Inclusion and Exclusion Criteria

The clinic schedule for pediatric ENT patients will be screened to identify patients scheduled for obstructive sleep apnea. Faculty surgeon, resident surgeon or the ENT nurse practitioner will recruit patients and complete the informed consent after review of patient eligibility through the inclusion/exclusion criteria:

Inclusion Criteria:

- Patients ages 4 years to 17 years scheduled for tonsillectomy and adenoidectomy for obstructive sleep apnea.

Exclusion Criteria:

- Patients having additional procedures or surgical interventions
- Patients who meet UCDCH criteria for PICU admission: on home oxygen pre-operatively, exhibit airway obstruction when awake (stertor above larynx, stridor at larynx), sleep study with apnea hypoxia index greater than 25 or sleep oxygen saturation nadir <80%, cardiac disease, difficult intubation
- Patients with a known allergy to acetaminophen
- Patients with known hepatic insufficiency or severe hepatic disease
- Patients with known G6PD deficiency
- Patients who are malnourished (ie lower levels of glutathione)
- Patients with severe renal impairment as defined by calculated creatinine clearance <20 ml/min (per modified Schwarz equation)
- Patients who are pregnant

## 5) Study Timelines

Patient recruitment will occur at the Otolaryngology clinic in the days to months prior to surgery date. The start of active participation in the study will commence on the day of surgery and end after 24 hours. The patient will take first oral study drug dose 4 hours prior to scheduled surgery time and remain in study for 24 hours.

It will take approximately 24 months to enroll 80 patients if surgical volume remains the same as last year. However, the number of ENT surgeons increased by one and the surgical volume is expected to increase proportionately.

It will take an additional 6 months to complete the primary analyses for the study.

## 6) Study Endpoints

The primary endpoint is the total dose of opioid, in morphine equivalents, that the patient receives for breakthrough pain in the 24 hour period following surgery.

A secondary endpoint is the proportion of pain scores in the mild, moderate or severe pain ranges.

A secondary endpoint is the peak acetaminophen level at the end of surgery, just prior to PACU admission.

A secondary endpoint is the plasma acetaminophen level at 4 hours after the first IV dose or second oral dose.

A secondary endpoint is the pharmacokinetics of oral vs intravenous acetaminophen.

A safety endpoint is to identify any patient with an elevated acetaminophen plasma level >39 mg/L. If this threshold is reached, the next dose of acetaminophen will be held and liver function tests will be monitored.

A safety endpoint is to identify any patient that reaches an acetaminophen level >99 mg/L. At this threshold, the next acetaminophen dose will be held, liver function tests will be monitored, and treatment with N-acetylcysteine therapy will be initiated.

## 7) Procedures Involved

Patients will be randomized into two study groups by Investigational Drug Services (IDS). Anesthesiologists, surgeons and nurses will be blinded as to whether the child receives oral or intravenous acetaminophen.

Study drugs will be prepared by IDS. The first oral medication and caregiver instructions will be sent home with parent at the ENT clinic visit. The first dose of oral medication will be given by parent prior to admission on the day of surgery. A member of the research team will give the parent a reminder phone call the day before the scheduled surgery date to ensure understanding of the drug administration and to answer any

possible questions. The ability for the research team to leave the family any voicemail messages is an explicit authorization within the consent form.

Group 1 will receive oral acetaminophen 30mg/kg four hours prior to scheduled surgery time and second oral dose 15 mg/kg just prior to surgery (within 4 to 6 hours after the first dose). Group 1 patients will receive placebo IV infusion just prior to surgery incision.

Group 2 will receive placebo oral medication at four hours prior to scheduled surgery and 2nd dose placebo oral medication just prior to surgery (within 4-6 hours after the first dose). Group 2 patients will receive IV acetaminophen 15 mg/kg just prior to surgery incision.

Anesthesia care will be provided per current practice at UCD Children's Hospital and will include the following intraoperative pain medicines: study drug acetaminophen, IV dexamethasone 0.5 mg/kg to max dose of 10 mg, and fentanyl 1-2 mcg/kg. Surgery will proceed per current practice at UCDCH with coblation surgical technique and will include injection of 0.25% bupivacaine with 1:200K epinephrine to tonsillar beds.

The first acetaminophen level will be drawn while the patient is still under anesthesia (less than 5 ml of blood). In most cases this will be drawn from the existing IV line. If unable to acquire sufficient blood draw from existing IV catheter, a needle will be used to draw blood from a new venous site while the child is still under anesthesia.

The second acetaminophen level will be drawn 4 hours after IV administration of placebo or acetaminophen study drug. If blood cannot be drawn from the IV catheter, the patient and parent will be given the option to have level drawn from a new venous site or decline the test. Patients can remain in the study without the second acetaminophen draw and will be analyzed on an intention to treat basis. If the first acetaminophen level is high and the second level has been declined, then the admitting physicians will address this by holding the next acetaminophen dose and proceeding with standard of care.

Given the evidence established in the literature review, it is highly unlikely that a patient's acetaminophen level will reach the high threshold level of 40mg/L. Though we do not believe the patient is at more than minimal risk, we have established a safety monitoring plan for plasma levels as described in section 10.

The Wong Baker Faces scale will be used to obtain pain scores in PACU (post anesthesia care unit) and on the ward, and results will be recorded in the EMR. This scale is currently used by nurses in the UC Davis Children's Hospital and available on EMR.

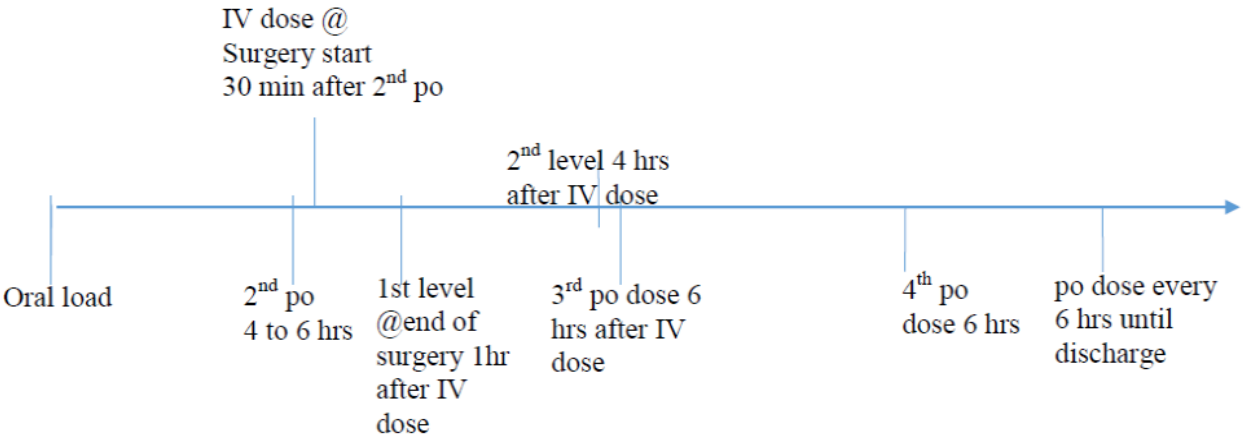
Pain medicines will be given per usual practice at UCDCH with 0.025mg/kg IV morphine for pain scores 4-10 using standardized order sets in the PACU. Oral doses of ibuprofen 10 mg/kg will be given 3 hours after the IV acetaminophen study drug and continued every 6 hours around the clock. Oral acetaminophen 15 mg/kg will be given every 6 hours around the clock following the IV acetaminophen study drug. On the ward,

the usual practice at UCDCH will be used for analgesia for study patients. The ENT in house resident will be called for breakthrough pain not controlled by ibuprofen and acetaminophen scheduled doses (around the clock). If contacted, the in house resident will select the oxycodone pediatric order set as follows: oxycodone 0.05 mg/kg po every 4 hours for pain scores 4-6, oxycodone 0.1 mg/kg po every 4 hours for pain scores 7-10. Breakthrough pain medicine will be recorded in the EMR.

The majority of data will be collected from participants during the first 24 hours. Following discharge, the chart will be accessed to record potential complications related to the study drug and identify length of stay.

Anticipated Timeline for a Surgery Scheduled at 11:30

07:00 30 mg/kg 1st po loading dose or placebo at home
11:00 15 mg/kg 2nd po or placebo
(2nd po dose will be given in pre-op unit 20-30 mins prior to induction and such that it is between 4 and 6 hours after the first dose to allow flexibility of surgery schedule)
11:30 IV dose or placebo as soon as IV started prior to incision
12:30 Draw first acetaminophen level from IV at end of surgery
15:30 Draw second level 4 hours after IV dose
17:30 15mg/kg po all patients per current practice
23:30 15 mg/kg all patients… and every 6 hours until discharge per current practice




Dosing Rationale for Oral and IV Acetaminophen

Oral acetaminophen will be administered in two pre-operative doses: a 30 mg/kg (maximum 1000 mg) loading dose approximately 4-6 hours prior to the start of surgery, and by a 15 mg/kg (maximum 1000 mg) 4-6 hours after the first dose, at the time of general anesthesia. Similar regimens have been shown to achieve therapeutic effect more quickly than standard maintenance dosing of 10-15 mg/kg every 4-6 hours[2-5]. Regimens including oral loading doses of 20-40 mg/kg have not resulted in acetaminophen toxicity.[5-7]

Intravenous acetaminophen will be administered as a single pre-operative dose, 15 mg/kg (maximum 1000 mg) at the time of general anesthesia. This is the most commonly studied and generally accepted pediatric intravenous dose.[7]

The total dose of acetaminophen during the study period will be 90 mg/kg in the oral group and 60 mg/kg in the IV group. Previous publications have recommended maximum daily doses of 75 or 90 mg/kg/day, particularly to allow for single loading doses[4, 9-12].

## 8) Data and/or Specimen Management and Confidentiality

Statistical analysis plan

The primary outcome measure is the between group difference in total opioid administration in the first 24 hours after surgery. The groups will be compared for similarity of age, sex, weight, and percentile weight on standard growth charts to ensure adequate randomization. Data will be tested for normal distribution and analyzed by t-test or Wilcoxon rank sum test as appropriate; $p<0.05$ will be considered statistically significant. For this study a difference of 100 mcg/kg morphine equivalents would be considered clinically significant. Sample size was calculated size based on results from a prior study.[1] The assumptions for this calculation are:

- Alpha 0.05
- Power 0.9
- Overall supplemental opioid (morphine equivalents, mcg/kg) found in the prior study; defining clinically significant difference to be 100 mcg/kg of rescue opioid and assuming a normal distribution:
    - IV: 273 ± 110
    - Oral: 377 ± 136
- Sample size to detect difference 63

To allow for early withdrawal, we propose to enroll 80 patients. A planned interim analysis will be conducted after 40 patients have been enrolled to allow us to refine the sample size calculation if needed.

Secondary outcome measures will include between group differences in:

- The proportion of pain scores showing severe or mild pain
- The number of patients requiring no opioid administration after surgery
- The prevalence of side effects such as nausea and vomiting
- The number of patients and total number of episodes of respiratory depression requiring treatment
- Acetaminophen levels determined at surgery end and 4 hours after the first IV dose or second oral dose
- The number of patients with acetaminophen levels above the safety endpoint
- Acetaminophen pharmacokinetics calculated from patients in whom 2 levels are obtained
- Intra-operative opioid dose of fentanyl in mcg/kg/hour

Blood/Data Management and Confidentiality

Blood samples obtained for acetaminophen level determination will be handled following UCDMC policies and procedures. Residual blood from those samples will be stored per Laboratory standard operating procedures until determination that no further testing is needed for individual patients.

Laboratory REDCap will be used as a data collection and management system for the study. As such, there are no plans to physically transfer data from one researcher to the next; ie, data is accessible through logging into REDCap's secured database and not via the handing off a secured flashdrive.

Source documents will be stored in a locked cabinet within the department of Anesthesiology and Pain Medicine when not used by the investigators.

All research staff have completed his/her CITI training, and are knowledgeable surrounding aspects of confidentiality.

Human Research records, including signed and dated consent documents, will be maintained for at least 7 years after the child reaches 18 years of age. Signed and dated HIPAA authorizations will be kept for at least 6 years after completion of the research.

## 9) Provisions to Monitor the Data to Ensure the Safety of Subjects

According to the Rumack-Matthew Nomogram, patients are at risk for hepatic toxicity when the acetaminophen plasma concentration exceeds 100 mcg/mL (100 mg/L) 4-5 hours after an acute ingestion, and treatment with n-acetylcysteine should be initiated.[13] Based on population pharmacokinetics, the dosing regimens used in this study are expected to yield maximum acetaminophen plasma concentrations of 15-20 mcg/mL, well below the levels associated with toxicity.[2,13] Based on this information, the following safety monitoring protocol will be utilized in this study:
Two acetaminophen levels will be obtained during surgery: the first will be drawn 1 hour after administration of the IV dose (or IV placebo), and the second will be drawn 3 hours later (4 hours after the IV dose). These specimens will be delivered to the lab, and results will be reported in the EMR prior to the next dose of acetaminophen. The pediatric pharmacist will monitor the second (4-hour) level and contact the ENT resident on call and the bedside nurse to recommend the appropriate intervention as follows:

- Acetaminophen level $\geq$ 100 mg/L → discontinue acetaminophen, monitor liver function tests (LFTs), initiate N-acetylcysteine therapy
- Acetaminophen level 40 – 99 →hold next acetaminophen dose, monitor LFTs; ENT and pharmacy team to determine when and how to re-dose
- Acetaminophen level 0 – 39 → no intervention needed

Acetaminophen levels will not be blinded and will appear in the EMR.

## 10) Withdrawal of Subjects

Subjects who refuse to swallow the oral medication will be withdrawn from research.

## 11) Risks to Subjects

Parents will be asked to give a pain medicine at home prior to surgery. The blood draws will be done from the existing IV for most patients and will be no more than 5 ml per draw. If the IV cannot be drawn back from then a new venipuncture will be performed while the child is under anesthesia. For the level on the ward, the patient will be given the option to decline a blood draw if the IV does not draw back for the sample and remain in the study.

## 12) Potential Benefits to Subjects

The patient may have better pain control if enrolled in the study.

## 13) Provisions to Protect the Privacy Interests of Subjects

The faculty surgeon, faculty ENT attendings, ENT residents, nurse practitioner and/or ENT clinical research coordinator will identify potential participants via the use of the requested IRB HIPAA Waiver for Authorization for participant identification and recruitment. From the list of ENT patients scheduled for clinic visits for obstructive sleep apnea, they will access EMR to screen for eligible participants.

They will discuss the study and allow for pertinent questions and concerns to be addressed and answered before obtaining assent of the patient and consent from the appropriate family member to minimize the number of outside interactions for conducting the study.

## 14) Drugs or Devices

☒ I confirm that all investigational drugs will be received by the Investigational Drug Service (IDS). The IDS will store, handle, and administer those drugs so that they will be used only on subjects and be used only by authorized investigators.

☐ I confirm that all investigational devices will be labelled in accordance with FDA regulations and stored and dispensed in such a manner that they will be used only on subjects and be used only by authorized investigators.

References

1. Nour C, Ratsiu J, Singh N, et al.Analgesic effectiveness of acetaminophen for primary cleft palate repair in young children: a randomized placebo controlled trial.Paediatr Anaesth2014;24:574–81
2. de Martino M, Chiarugi A. Recent Advances in Pediatric Use of Oral Paracetamol in Fever and Pain Management. Pain and Therapy 2015;4:149-68.
3. Gibb IA, Anderson BJ. Paracetamol (acetaminophen) pharmacodynamics: interpreting the plasma concentration. Arch Dis Child. England2008:241-7.

4. Shann F. Paracetamol: when, why and how much. J Paediatr Child Health 1993;29:84-5.
5. Treluyer JM, Tonnelier S, d'Athis P, Leclerc B, Jolivet-Landreau I, Pons G. Antipyretic efficacy of an initial 30-mg/kg loading dose of acetaminophen versus a 15-mg/kg maintenance dose. Pediatrics 2001;108:E73.
6. Romsing J, Ostergaard D, Senderovitz T, Drozdziewicz D, Sonne J, Ravn G. Pharmacokinetics of oral diclofenac and acetaminophen in children after surgery. Paediatr Anaesth. France2001:205-13.
7. Anderson BJ, Holford NH, Woollard GA, Kanagasundaram S, Mahadevan M. Perioperative pharmacodynamics of acetaminophen analgesia in children. Anesthesiology 1999;90:411-21.
8. Jahr JS, Lee VK. Intravenous acetaminophen. Anesthesiol Clin. United States: 2010 Elsevier Inc; 2010:619-45.
9. Anderson BJ. What we don't know about paracetamol in children. Paediatr Anaesth 1998;8:451-60.
10. Temple AR. Pediatric dosing of acetaminophen. Pediatric pharmacology (New York, NY) 1983;3:321-7.
11. Kleiber C. Acetaminophen dosing for neonates, infants, and children. J Spec Pediatr Nurs. United States2008:48-9.
12. van der Marel CD, van Lingen RA, Pluim MA, et al. Analgesic efficacy of rectal versus oral acetaminophen in children after major craniofacial surgery. Clin Pharmacol Ther. United States2001:82-90.
13. Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. Pediatrics 1975;55:871-6.