Acetaminophen pharmacokinetics in bariatric patients

NCT02982928

January 20, 2017

NATIONWIDE CHILDREN'S
When your child needs a hospital, everything matters.℠

Department of Anesthesiology & Pain Medicine

Protocol Title: Acetaminophen pharmacokinetics in bariatric patients

Principal Investigator: Ahsan Syed, M.D.

Co-Investigators: Marc Michalsky, MD; Joseph Tobias, M.D.

Support Staff: Heather Dellinger, RN; Julie Rice, RN

Hypothesis:

Current dosing recommendations for acetaminophen including use of a dose of 1000 mg in obese patients will result in inadequate plasma concentrations.

Specific Aims:

1. To determine whether adequate serum concentration of acetaminophen is achieved
2. To determine the acetaminophen loading dose for obese patients
3. To determine duration of therapeutic effect based on serum concentration of acetaminophen

Background and Significance:

Postoperative analgesia remains an integral part of any anesthetic care. Given their potent analgesia effects, the administration of opioids remains an integral component of postoperative analgesic regimens following major surgical procedures. Although generally safe and effective, adverse effects on respiratory function may occur. These effects may be particularly likely in patients with obstructive sleep apnea or those with obesity. As a means of ensuring effective analgesia and limiting the impact of opioids on respiratory function, adjunctive agents (acetaminophen and non-steroidal anti-inflammatory agents) may be administered during the perioperative period. These agents provide analgesia without effects on respiratory function and may decrease opioid requirements by 20-30%. By decreasing opioid requirements, they decrease opioid-related adverse effects. Due to their effects on renal function, non-steroidal anti-inflammatory agents are generally not administered during the initial 24 postoperative hours. Intravenous acetaminophen is a commonly used adjunctive agent, administered to all bariatric patients undergoing major surgical procedures. However, there are limited data to provide information regarding appropriate dosing of such agents in obese patients. In the pediatric population, dosing guidelines recommend the use of 15 mg/kg to a maximum of 1000 mg. It is likely that a dose of 1000 mg (same dose that would be administered to a 70 kg patient) will result in an inadequate plasma concentration in obese patients as pharmacokinetic studies of other medications suggest dosing at somewhere between ideal and actual body weight.

Experimental Design and Methods:

Inclusion Criteria:

- Patients older than 12, but younger than 21 years of age undergoing robotic assisted or laparoscopic bariatric surgery
- ASA status I, II or III
- Parent/guardian willing and able to give consent
- Patient willing to give assent, or consent
- Patients that are otherwise healthy at the discretion of the study staff
- Patients with BMI $\geq 95^{th}$ percentile

Exclusion Criteria:

- Patients with severe right heart failure or severe asthma
- Patients with deficient hepatic function that can affect drug metabolism
- Systemic steroid use within the last 3 months
- Patients who have taken acetaminophen containing medications within 24 hours of surgery date
- Patients younger than 12, but older than 21 years of age undergoing robotic assisted or laparoscopic bariatric surgery
- Patients having other procedures in addition to robotic assisted or laparoscopic bariatric surgery
- ASA status IV and above
- Females testing positive for pregnancy
- Parent/guardian not willing and able to give assent, or consent
- Patient not willing to give assent, or consent
- Patients with BMI < 95th percentile

The study population will consist of 20 patients presenting to the OR for robotic assisted or laparoscopic bariatric surgery. After enrollment of 10 patients, an interim analysis of the primary study hypothesis will be performed to determine whether continuing the study would be futile. This will be a descriptive study carried out by study staff from the anesthesiology department.

Patients meeting our inclusion criteria will be approached with their parents/guardians present on day of surgery in the preoperative holding area for a description of the study. Patients will be screened for purposes of meeting study criteria prior to surgery. The study will be introduced by the PI, co-investigators, or a clinical research nurse.

Pharmacokinetic profiling and determinations will be performed by Dr. Brian Anderson in New Zealand. Volume of distribution and elimination half-life in serum samples are the primary measurements of the study. Dr. Anderson has agreed to calculate the pharmacokinetic data. He is a recognized world authority in this area of pediatric anesthesiology.

Research Design

The patient population will include obese patients scheduled for robot-assisted or laparoscopic bariatric surgery. There will be no change in our usual anesthetic care for these patients which will include our standard protocol as outlined:

1. Premedication with intravenous midazolam (2 mg) at the discretion of the PI or co-investigators
2. Intravenous induction with propofol (2-3 mg/kg) and fentanyl (1-3 μg/kg)
3. Standard monitoring plus arterial cannula and two peripheral intravenous cannulas.
4. Neuromuscular blockade with succinylcholine for endotracheal intubation followed by intermittent doses of rocuronium or cis-atracurium intraoperatively
5. Maintenance with desflurane titrated to maintain the bispectral index at 40-60 and remifentanil (0.05-0.3 μg/kg/min) to maintain the mean arterial pressure at baseline
6. Postoperative analgesia with hydromorphone and local infiltration of port sites
7. After the laparoscopic procedure is completed, intravenous acetaminophen (1 gram) will be infused over 15 minutes
8. The only difference from standard anesthetic care is that 8 acetaminophen levels will be obtained at the following points:

Primary Endpoints:

15-20 minutes
30-40 minutes
50-70 minutes
80-100 minutes
2, 4, 8, 12 hours

Secondary Endpoints:

Based on the volume of distribution, a theoretical loading dose will be determined which results in a therapeutic serum acetaminophen concentration of 10-20 μg/mL.

Recruitment and Informed Consent:

Patients and their families that have discussed this elective procedure with their General Surgeon will be given study information at their clinic visit prior to the day of their scheduled surgery. Patients meeting our inclusion criteria will be approached with their parents/guardians present on day of surgery in the preoperative holding area for a description of the study. The study will be presented by the PI, co-investigators, or a clinical research nurse. Risks, benefits, and alternatives will be discussed. If consent and assent are obtained and the patient does not have exclusion criteria, she/he will be enrolled in the study.

Whenever possible the study will be introduced to patients by the general surgeons at their preoperative clinic visit. Information about the study may be given at this time, but formal consent and assent will be obtained on the day of surgery.

Adverse Events:

There are no added risks of additional adverse events related to the study protocol as it involves only obtaining the serum acetaminophen levels.

Patient Safety:

No additional patient safety concerns as intravenous acetaminophen is administered as a routine for such surgical procedures and is approved by the United States FDA for use in this aged patient.

Internal Validity:

Not applicable as the serum acetaminophen levels will be run by the hospital laboratory. The time and number of serum levels obtained are based on previous pharmacokinetic trials performed in the pediatric anesthesiology population.

Statistical Analysis:

Serum acetaminophen levels at 15-20 minutes will be compared to the published lower bound of acceptable concentrations (10μg/mL) using a one sample t-test. Serum acetaminophen levels across all time points in the study will be used to calculate pharmacologic parameters including volume of distribution and elimination half-life. Based on the calculated volume of distribution and the initial serum concentration, the dose required to achieve an effective analgesic level in the serum will be determined.

Within-subject change in serum acetaminophen levels over time will be modeled using mixed effects regression, to identify the influence of dosing on achieving and maintaining an acceptable serum concentration level and to identify the duration for which an acceptable serum concentration of acetaminophen is maintained. Patients will be excluded from analysis if inadequate follow-up prevents sufficient data collection. Once statistical data have been organized the PI and Co-Investigators will develop literature outcomes for use in publications and presentations.

Sample Size Estimation:

The sample size is determined by a power analysis based on previous research on the under-dosing of acetaminophen in pediatric patients. Patients receiving inadequate doses of acetaminophen were found to have serum acetaminophen levels 1.2-4.5μg/mL below the 10μg/mL standard.[5] A two-tailed one-sample t-test would have 80% power to detect a difference in serum acetaminophen concentrations from the 10μg/mL norm as small as 2.5 μg/mL (assuming a standard deviation of 3.5 μg/mL) in a sample of 20 patients at a 95% confidence level. A futility analysis will be performed after the first 10 patients are enrolled, and the study will be discontinued if conditional power to detect a 2.5 μg/mL difference from the standard serum acetaminophen concentration falls below 20%.

Investigative Contributions:

The study Co-Investigators consist of General Surgeons, Anesthesiologists as well as a Biostatistician.

The Generalist Surgeon will contribute to this research by:

1) Identifying the appropriate qualifying patients and approaching these patients and their families for potential participation in the study prior to the date of surgery
2) Participating in discussions leading to when and what type of data should be collected for statistical analysis
3) Involvement in the discussions to determine implications of the study results
4) Providing original intellectual content for publication
5) Participation in data analysis and manuscript preparation

The Anesthesiologists will contribute to this research by:

1) Actively administering the study medications
2) Participating in discussions leading to when and what type of data should be collected for statistical analysis
3) Achieving and maintaining patient hemodynamic parameters within study specifications
4) Involvement in the discussions to determine implications of the study results
5) Providing original intellectual content for publication
6) Participation in data analysis and manuscript preparation

The Biostatistician will contribute to this research by:

1) Participating in discussions leading to when and what type of data should be collected for statistical analysis
2) Involvement in the discussions to determine implications of the study results
3) Providing original intellectual content for publication
4) Participation in data analysis and manuscript preparation

References

1. Ziemann-Gimmel P, Hensel P, Koppman J, Marema R.Multimodal analgesia reduces narcotic requirements and antiemetic rescue medication in laparoscopic Roux-en-Y gastric bypass surgery. Surg Obes Relat Dis 2013;9:975-80.
2. Saurabh S, Smith JK, Pedersen M, Jose P, Nau P, Samuel I. Scheduled intravenous acetaminophen reduces postoperative narcotic analgesic demand and requirement after laparoscopic Roux-en-Y gastric bypass. Surg Obes Relat Dis (in press).
3. Abernethy DR, Divoll M, Greenblatt DJ, Ameer B. Obesity, sex, and acetaminophen disposition. Clin Pharmacol Ther 1982;31:783-90.
4. Lee WH, Kramer WG, Granville GE. The effect of obesity on acetaminophen pharmacokinetics in man. J Clin Pharmacol 1981;21:284-7.
5. Birmingham PK, Tobin MJ, Henthorn TK, Fisher DM, Berkelhamer MC, Smith FA, Fanta KB, Coté CJ. Twenty-four-hour pharmacokinetics of rectal acetaminophen in children: an old drug with new recommendations. Anesthesiology. 1997 Aug;87(2):244-52.