Methadone in Pediatric Anesthesia II

PI: Anshuman Sharma MD, MBA
Associate Professor,
Director of Quality Improvement,
Department of Anesthesiology, BO 8054
Tel: 314 454 2190
anshumansharma@wustl.edu

Co-PI: Evan Kharasch, MD PhD
Russell D. and Mary B. Shelden Professor of Anesthesiology
Director, Division of Clinical and Translational Research
Department of Anesthesiology, Box 8054
T 314-362-8796
F 314-362-8571
kharasch@wustl.edu

Co-Investigators: Dr. Chuck Schrock MD
Associate Professor of Anesthesiology
Box 8054,
Tel: 314 454 2190

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Amendment 1: 12/5/13

Amendment 2: 4/16/14

Amendment 3: 09/10/2014

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Amendment 1, 12/5/2013: Administration of PROMIS questionnaire to be administered by the research team to the patient on a tablet device.

Rationale: To help determine patient's preoperative expectations and functional status as impacted by their medical condition requiring this surgical procedure.

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Amendment 2, 4/16/2014: Administration of a questionnaire to the participant's parent or legal guardian

Rationale: To help determine from the primary caregiver the influence of the environment, social and psychological, on post-operative pain.

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Amendment 3, 09/10/2014: Change in dosage range for intraoperative administration of methadone from 0.4-0.5mg/kg Ideal Body Weight to 0.3 – 0.5mg/kg Ideal Body Weight (IBW)

Rationale: Postoperative management of pain for the pediatric spinal surgery population has changed over the course of time since the completion of our last research project (HRPO# 201107357). The previous study had demonstrated that 0.3mg/kg methadone was not effective in reducing postoperative opioid consumption. Currently, patients are prescribed additional drugs such as gabapentin and methocarbamol, with potential for interaction with all opioids. Based on our observations with this current protocol to date, we anticipate that escalation of methadone dosages beyond 0.4mg/kg (ideal body weight) may not be required. We feel that routine postoperative use of gabapentin and methocarbamol require re-evaluation of intraoperative methadone dosing at 0.3mg/kg (IBW) for this population under current standard of care pain management.

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Abstract

The μ-opioid receptor agonist methadone is frequently used in adult anesthesia and adult pain therapy. Methadone has an extremely long half-life, which confers therapeutic advantage by providing more stable plasma concentrations and long-lasting pain relief. Methadone perioperative pharmacokinetics in adults is well characterized. Methadone is also frequently used in children. Previous work by our group demonstrated that pharmacokinetics of methadone in adolescents are very similar to that in adults, but that doses used for major spinal surgery (0.1-0.3 mg/kg) were insufficient to have a significant opioid-sparing effect. This current investigation aims to study opioid sparing effects of higher doses of methadone (0.3 - 0.5 mg/kg) in adolescents undergoing posterior spinal fusion. Additionally, we will determine the pharmacokinetics of the higher doses of IV methadone administered intra-operatively.

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SYNOPSIS

Study Title	Methadone in Pediatric Anesthesia II
Objective	Multiple arm, randomized controlled trial to evaluate the efficacy of a single dose of intraoperative methadone in reducing post-operative pain and opioid consumption in adolescents undergoing posterior spinal fusion. Our secondary goal is to determine the pharmacokinetics of IV methadone in children (0.3 - 0.5 mg/kg).
Study Period	Planned enrollment duration: Approximately 2 years. Planned study duration: Approximately 6 days per subject
Number of Patients	60 evaluable subjects
Study Medication Administration	60 evaluable patients will be randomized 2:1 to receive intraoperative IV methadone HCL, 0.3 – 0.5mg/kg, or serve as controls and will not receive any methadone. Control subjects will receive standard of care treatment per the attending anesthesiologist.
Study Design	Randomized, controlled, modified, Dixon up and down dose-finding design (1). Patients receive standard monitoring for anesthesia and postoperative care. Surgical and anesthesia (except for opioid use) care are not altered for study purposes. All patients are induced by propofol and muscle relaxants. In the first cohort, subjects are randomized 1:2 to either control (standard intraop opioid at anesthesiologists' discretion) or methadone HCl (0.4 mg/kg ideal body weight, IBW). Based on an interim analysis for the initial treatment dose (0.4mg/kg), the second cohort will be randomized 1:2 to either control (standard intraop opioid) or methadone HCl (0.3 mg/kg ideal body weight, IBW). Subjects in the study groups will receive methadone (IV bolus, after induction of anesthesia) as their primary intraoperative opioid, rather than leaving the choice of intraoperative opioid to the anesthesiologist. Intraoperative breakthrough pain will be treated at the discretion of the anesthesiologist with fentanyl. In the control groups, intraoperative opioid administration will be left at the discretion of the anesthesia providers. Patient controlled analgesia as prescribed by the clinical team, using hydromorphone or morphine, will be used to treat postoperative pain relief.
Inclusion and Exclusion Criteria	Inclusion Criteria 1. Age 11-18 years 2. Undergoing general anesthesia and idiopathic posterior spinal fusion surgery with anticipated postop inpatient stay of> 3 days 3. Signed, written, informed consent from legal guardians and assent from patient Exclusion Criteria 1. History of liver or kidney disease. 2. Females who are pregnant or nursing. 3. Developmental delay and/or neuromuscular scoliosis
Measurements	Total intraoperative and postoperative care unit (PACU) opioid administration will be recorded from the patient's medical record. Daily opioid consumption will be calculated from the PCA utilization and electronic medical records (EMRs) for up to 6 postoperative days. Pain intensity will be assessed using the Wong-Baker FACES scale. Pain relief is also assessed using a Colored-Visual Analog Scale. Blood and urine samples will be collected for 96 hrs after methadone dosing for determination of methadone and metabolite concentrations by HPLC-mass spectrometry. Subjects will be genotyped for major polymorphisms of the methadone metabolizing enzyme CYP2B6.
Statistical Methodology	Demographics data including race, sex, and age will be analyzed. Baseline characteristics of the cohort will be described. Results will be expressed as the mean and standard deviation.
Outcomes	Primary: Intraoperative, postoperative and daily cumulative opioid utilization Secondary: Methadone and metabolite enantiomers plasma AUC, maximum concentration, metabolite /methadone AUC ratios, metabolite formation clearance correlation of methadone enantiomer clearances and metabolite formation clearances, influence of *CYP2B6*6* hetero or homozyge genotype

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	on above primary and secondary outcomes

1. Specific Aims.

1.1. To study the effects of a single dose of methadone on postoperative pain and opioid consumption in pediatric surgical patients.

1.2. Determine the pharmacokinetics of IV methadone (0.3-0.5 mg/kg) in children

1.3. Determine cytochrome P4502B6 (CYP2B6) genotype in patients receiving methadone, and any relationship to methadone clearance.

1.4. Determine from the primary caregiver the influence of the environment, social and psychological, on post-operative pain.

2. Background

Inadequate pain relief has a significant psychological impact upon children, including alterations in their perceptions of future painful experiences and medical procedures (1). The psychological ramifications of pediatric pain include posttraumatic stress disorder, lack of adherence to treatment, poor coping skills, changes in accuracy in the self-report of pain, and lack of trust in health-care providers (2). The degree to which this pain is controlled impacts the ability of patients to cope with the next pain episode. Patients undergoing major spine surgery experience severe pain in the postoperative period, which may increase morbidity and the incidence of complications, as well as prolong postoperative rehabilitation. Postoperative pain itself is a risk factor for development of chronic pain syndromes(3,4).

Methadone is a μ opioid agonist which is highly efficacious in the treatment of acute, chronic, neuropathic, and cancer pain(5). In adults it is increasingly being used as a first-line analgesic. Methadone is highly efficacious in adult anesthesia and postoperative pain(6,7). The typical dose for adult anesthesia is 20 mg (nominally 0.3 mg/kg) at the beginning of anesthesia. Methadone is advantageous because it has slow elimination, resulting in prolonged effect and significantly diminished need for postoperative analgesics. Reducing postop opioid analgesic use also decreases the potential for opioid-related side effects. Methadone has a long half-life, averaging 24-36 hours in healthy adults and adolescent patients (12). It has no active metabolites or pro-drug forms. Methadone is metabolized in the liver by cytochrome P450 CYP2B6 (8–10). Methadone is also widely used in children, particularly in pain treatment(11). In infants and children younger than 10 yrs (mean age 4 yrs), the initial daily dose of methadone did not exceed 0.2–0.4 mg/kg/day, and daily methadone doses rarely exceeded 0.6 mg/kg.

Perioperative analgesia remains a major challenge for physicians who care for patients undergoing complex spine surgery. Many patients are controlled by opioid analgesic that can result in postoperative adverse events. We propose to compare the two different doses of methadone in reducing

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the postoperative opioid consumption and reduction in pain scores.

A recent study by our group demonstrated that the pharmacokinetics of methadone enantiomer disposition in adolescents were similar to that of healthy adults (12). Another study by Stemland et al used a three compartmental model to analyze time-concentrations profile of single dose of 0.25mg/kg of methadone. They concluded that the pharmacokinetic profile in adolescents was similar to that of adults. They also observed a rapid redistribution after single bolus of methadone, hence producing inadequate plasma concentrations of the drug for postoperative analgesia. This suggests that in order to improve efficacy of methadone, higher dose than 0.3 mg/kg of methadone or continuous infusion of methadone may be needed (13).

Evaluating the role of methadone in pediatric spinal surgery patients is advantageous because 1) high dose of opioids are routinely used during and after the surgery, 2) methadone is one of the commonly used opioids for this surgery, 3) an arterial catheter or a second IV catheter is needed for the surgery and can be used to draw blood samples, 4) prolonged analgesia from methadone is expected to decrease the need for additional opioids.

Assessment of pain has become standard practice in the treatment of pediatric patients. Several pain scales including the Wong-Baker FACES scale, the Oucher Scale and the Visual Analog Scale (VAS) have been USED in children who were experiencing pain (14,15).

In this study, we propose to evaluate postoperative opioid consumption, pain intensity and pain relief in pediatric patients undergoing posterior spinal fusion who will receive a single dose of methadone during surgery. In addition, we will study dose effect of ing various doses of methadone, between 0.3 – 0.5mg/kg IBW. Secondarily, we will determine the pharmacokinetics of higher doses of IV methadone in children who are undergoing anesthesia and surgery. Lastly, we will determine the role of CYP2B6 genotype on methadone pharmacokinetics.

3. Drug Information

Methadone hydrochloride is a synthetic μ-agonist with multiple actions qualitatively similar to those of morphine. Onset of effect is about 2-10 min for parenteral dosing. Methadone is primarily metabolized by N-demethylation to an inactive metabolite, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). In vitro, cytochrome P450 enzymes, primarily CYP3A4 and CYP2B6 are responsible for conversion of methadone to EDDP and other inactive metabolites. In vivo, CYP2B6 is a major determinant of metabolism to inactive metabolites which are excreted mainly in the urine. The terminal half-life (T½) in healthy children averages 24-36 hrs. Like adults, in teenage children, most common side effect of methadone, like other opioids, is sedation, nausea and vomiting. Respiratory depression is the chief hazard associated with methadone, like all opioids. QT prolongation and serious arrhythmia have been observed during treatment with methadone and have been associated with doses

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>200 mg/day(16).

4. Eligibility

4.1. *Inclusion Criteria.*

4.1.1. Age 11-18 years

4.1.2. Undergoing general anesthesia and idiopathic posterior spinal surgery with anticipated postop inpatient stay of > 3 days

4.1.3. Signed, written, informed consent from legal guardians and assent from patient

4.2. *Exclusion Criteria.*

4.2.1. History of or known liver or kidney disease.

4.2.2. Females who are pregnant or nursing.

4.2.3. Children with developmental delay

4.2.4. Children undergoing surgery for neuromuscular scoliosis

5. Enrollment

5.1. Subjects and parents/guardians will be approached prior to surgery. Patients will be consented for participation and enrolled in the study by study personnel.

6. Methods

6.1. *Preoperative and Intraoperative Period*

Parents and patients will be asked to complete a questionnaire prior to the child's surgery. This will take approximately 5 minutes. Participants can choose to complete the survey and not participate in the randomized part of the study. The questionnaire is to determine if factors such as anxiety and social economic attributes interact with each other prior to surgery. If only participating in the questionnaire information regarding demographic data, pain scores and pain treatment will be collected from the patients' medical record.

Patients will receive standard physiologic monitoring for anesthesia and postoperative care. Using a modified Dixon up and down dose finding method, subjects in the first cohort are randomized 1:2 to receive either control (standard intraop opioid) or methadone HCl (0.4 mg/kg ideal body weight, IBW). In the second cohort, subjects are randomized 1:2 to receive either control (standard intraop opioid) or methadone HCl (0.3 mg/kg ideal body weight, IBW). Anesthesia and surgical care will not be altered for the purposes of this investigation, except that subjects in groups I and II, will receive methadone as their intraoperative opioid, rather than leaving the choice of intraoperative opioid to the anesthesiologist (patients typically may get methadone or any other opioid). The control group patients will receive intraoperative analgesia with opioids other than methadone left at the discretion of their anesthesiologist. Additional

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randomized cohorts may be included to study IV methadone HCl doses within the range of 0.3 – 0.5mg/kg IBW, based on interim study findings and analysis.

6.2. *Administration of Study Medication.*

Methadone is administered as an IV bolus after induction of anesthesia and after an arterial line is placed. Methadone hydrochloride is available commercially as a solution for injection of 10 mg/ml. Based on our experience, we believe that additional postoperative opioids will still be needed, but that increasing methadone doses will result in lessened postoperative opioid use.

6.3. *Assessments.*

6.3.1. Pain Assessment – Acute postoperative pain will be managed by St. Louis Children's Hospital pain services. Assessments are made in the postoperative period by a trained member of the research team blinded to intraoperative use of methadone. These will be conducted on each post-operative day until discharge or post op day 6, whichever comes first. Pain intensity is assessed using the Wong-Baker FACES scale employed by the inpatient nursing staff and previously validated (9). Pain relief is also assessed using a Colored-Visual Analog Scale. Other questions regarding pain relief and comfort may be given using a tablet. Sedation is assessed using a five-point scale (patient fully alert – not arousable). Itching and nausea are assessed using a five-point verbal scale (none, mild, moderate, severe or excruciating).

6.3.2. Pharmacokinetics – Pharmacokinetics studies will be performed for all patients in methadone treatment groups. Blood samples (approx 3 ml each) will be obtained before methadone and at approx 0.08, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hr after IV methadone administration. Blood samples will be drawn from the arterial line for the first 24 hours and then from the venous lines or collected with routine labs. Total amount of blood drawn will be approx. 48 mls for pharmacokinetic testing for up to four days. Blood will only be collected while the patient is hospitalized; if the patient is discharged from the hospital no further collections will be made.

6.3.3. CYP Genotyping – For all patients, 5 ml of blood will be drawn for CYP2B6 genotyping. Genotyping will be performed at the WUSTL Genome Technology Access Center (GTAC).

6.3.4. Urine samples- For all patients, 24 hour- urine collections will be conducted for up to 96 hours after surgery.

6.4. *Postoperative Period*

Patients receive standard of care analgesia using patient control analgesia method, primarily with hydromorphone or morphine as determined by the treating physician. Postoperative

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care is not altered for purposes of this study.

7. Data Collection and Monitoring.

7.1. *Assessment of Pain Intensity and Pain Relief*- Each pediatric patient enrolled in the study, regardless of type of opioid received, will have pain intensity assessed each post operative hospital day (HD) for up to six days or until discharge, whichever comes first. The Wong-Baker FACES scale and Verbal analogue scale, available as laminated cards, are currently used by the nursing staff to assess pain on the inpatient units. Pain will also be assessed by patients using a colored-visual analogue scale. The study personnel performing the assessment will have a set script to read when administering the scale.

7.2. *Opioid Consumption.* The inpatient medical record will be used to calculate the amount of morphine or morphine equivalents administered for each 24-hour period that subjects are receiving opioid analgesics. Oral opioid administration will be totaled through discharge for each 24-hour period as well.

7.3. *Other Required Studies.* Required baseline measurements that will be obtained from the EMR are vital signs, weight, height, and peripheral oxygen saturation by pulse oximetry and are all collected as standard of care.

7.4. *Drug and metabolite concentrations and drug effects.* Plasma concentrations of methadone and the mono N-demethylated metabolite EDDP will be determined by HPLC-mass spectrometry.

7.5. *Sources of Research Material*. Background information including demographic data, outpatient medications used, and chronic medical conditions will be obtained from the medical record at the time of enrollment

8. Data and Safety Monitoring Plan.

In general, the PI has developed a specific set of Standard Operating Procedures (SOPs) for clinical research. All individuals working under the PI are required to read and be totally familiar with and compliant with the SOPs. The PI's SOPs are in part developed from and are compliant with the Institutional guidelines, including those for a) Interactions with the Washington University Human Subjects Review Committee, b) Informed Consent Development and Implementation, c) Subject Recruitment and Screening, d) Subject Management While on Study, e) Adverse Event Reporting.

8.1. The specific monitoring plan for this investigation is commensurate with the risks and the size and complexity of the investigations planned. The potential risks are attributable to the use of methadone. Based on these considerations the monitoring plan involves engaging one colleague (a pediatric anesthesiologist, pediatrician or clinical pharmacologist knowledgeable in the pharmacology of opioids) not involved in the study to serve in a monitoring capacity. Based on

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the small size and relatively low risks nature of the protocol, only a third person (the colleague), rather than a full DSMB, is utilized. This individual will review the annual summary of adverse events. In addition, they will review all reports of a Serious Adverse Event, or an Unexpected Adverse Event.

8.2. The specific plan for submitting Adverse Event Reports to the IRB is detailed in the PI's SOP for Adverse Event Reporting.

8.3. *Off-Study Criteria:* Participation will be terminated if requested by the patient or patient's guardian().

8.4. *Stopping Rules*: The study will be temporarily suspended, pending a detailed review, if there is a Serious Adverse Event resulting from methadone.

9. Statistical Methods

9.1. *Primary Assessment*

9.1.1. Overall morphine (equivalents) consumption for each patient during hospitalization

9.1.2. Absolute pain scores and pain relief scores

9.2. *Secondary Assessments*

9.2.1. Methadone clearance

9.2.2. Maximum plasma methadone concentration

9.2.3. Area under the curve (AUC) of plasma EDDP vs time

9.2.4. Maximum plasma EDDP concentration

9.2.5. AUC (plasma EDDP)/AUC (plasma methadone)

9.2.6. Cmax (plasma EDDP)/Cmax (plasma methadone)

9.2.7. Urine concentration of methadone and EDDP

9.2.8. Side effects of opioids

9.3. *Analysis.*

9.3.1. Sample Size- we decided to use our pilot study data which looked into the pharmacokinetics of methadone in pediatric surgical patients attending St. Louis Children Hospital. This is actually the pooling place for the present study and therefore the information provided is a "true" sample of the data to be collected. The pilot study revealed that patients undergoing spinal fusion surgery used an average of 274 mg of morphine equivalents within 72 hours post-surgery with a standard deviation of 82 mg. Based on this information and assuming a 2-sided test of two independent sample means with α 0.05, we were able to estimate that the proposed study will have at least 80% power to detect 30% decrease in the total postoperative consumption of morphine or morphine equivalents among the patients assigned to the two treatment groups combined when compared to the control group

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patients. Specifically, with a total sample of approx. 60 patients assigned equally across study groups (1:2 randomization), we will have adequate statistical power to detect a clinically meaningful reduction of opioid use in patients receiving a single dose of methadone before incision.

To study the effect size between two groups, power calculations were made with alternative mean differences in morphine consumption over 72 hours post-surgery with assumed variation range and a 2-sided test with $\alpha = 0.05$. Based on our conservative assumptions, we found that, with a sample as small as 20 in each group, we will have 80% power to detect a minimum difference between 10 and 20 mg of morphine use, depending on the observed variability between the two groups.

9.3.2. Statistical Analysis- Baseline characteristics of the cohort will be described. Demographics data including race, sex, and age at study entry will be analyzed using chi-square and t- test appropriate. Total daily opioid consumption and pain scores using both Wong-Baker FACES and colored visual analogue scale, will be compared between the groups. Outcome measures will be expressed by the mean and standard deviation. Group outcomes will be compared across the two or three groups, using t-test and/or analysis of variance, ANOVA and MANCOVA to account for potential cofounders.

9.3.3. Methadone Calculations -Methadone and EDDP plasma concentration-time data will be analyzed by linear and nonlinear regression analysis using noncompartmental or compartment models to determine total area-under-the-curve (AUC), and systemic clearance. Results will also be analyzed using population methods, with age and dose as covariates, to determine linearity of pharmacokinetic parameters and effects of age.

10. Risk Assessment

10.1. *Methadone* The most common clinical effect of opioids such as methadone is mild sedation. Based on prior experience with this opioid and doses, and prior published experience, some subjects might experience mild sedation for about 0.5-1 hr after methadone administration, were they awake. Since patients will be anesthetized during this period, clinical methadone effects are expected to be no different from those of anesthesia and any other opioid administered during anesthesia. We have further attempted to minimize the risk to the patients by following a conservative approach of two step randomization. The most common adverse effect of methadone is nausea and/or vomiting. Patients will have only clear liquids 6 hours before anesthesia, per standard of care. If nausea and/or vomiting occur, they will be treated using the standard of care for all post-anesthesia nausea and vomiting. Respiratory depression is a potential concern with all opioids, but has not been problematic at the doses of methadone that

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have been used in similar previous studies. Mild respiratory depression is defined as respiratory rate <8/min in adults and children older than 10, <12–16 in children age 3-10, and <20 in children younger than two. Severe depression will be defined as the administration of naloxone to a patient with respiratory rate < 6/min. If treatment is required, naloxone will be used. Patients in the hospital are routinely periodically monitored by blood pressure and/or pulse oximetry, and receive supplemental oxygen if dictated, according to good clinical practice.

10.2. Genotyping – With regard to the determination of CYP2B genotype: 1) CYP2B genes are not associates with any disorder(s), syndrome(s), or adverse condition. 2) Samples will be kept confidentially. They will be coded, with a key to the code linking code numbers to names kept at a separate location, under lock and key. 3) The link to identifiers will be destroyed at the end of the study. 4) We have no evidence to suggest that testing will provide evidence of previously undiagnosed or unrecognized illness, or susceptibility to illness. 5) We will not use samples for any purpose other than to study genes related to the disposition and response to study drugs. 6) Blood samples will not be used to establish permanent cell lines. 7) Data will be stored under lock and key (office, file cabinet) and only the investigators will have access. If data are published, there will be no link to identifiers. Study data will not be revealed to any organization, individuals other than the subjects, or the subjects themselves. 8) We will not enter any genetic study data in subjects' medical records. 9) Studies are not likely to result in findings that meet the National Bioethics Advisory Commission criteria for disclosure. 10) We will not have genetics counseling available to subjects, as they will not be informed of results and there are no know implications with respect to disease. 11) DNA samples will stripped of identifiers and given a separate code numbers unrelated to the subjects' study identification numbers. The code key will be kept by the PI under lock and key.

10.3. *Special Precautions***.** Standard of care for all surgical patients includes placement of an IV, pulse oximetry, ECG and blood pressure monitoring.

10.4. *Procedures to Maintain Confidentiality.* Any information that is obtained in connection with research that can be identified with a subject will remain confidential. The consent form, medical information, flow-sheets, and pharmacokinetic and genetic data will be stored under lock and key (office, file cabinet) and only the PI, physician investigators, and research team will have access.. Statisticians involved in the project will have access to de-identified data for the purposes of analysis.

10.5. *Risk/Benefit Assessment.* The dose of methadone given will be a standard analgesic dose, and it might provide longer pain relief. In addition, this study will result in increased awareness of standard of care and appropriate pain assessment in the nursing staff and treating physicians

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that will benefit patients not enrolled on study. The risk of respiratory depression is no more than that expected from standard morphine therapy as the patients will only receive one dose of methadone and it will be at doses less than treatment doses. Understanding the pharmacokinetics of methadone in children will allow more appropriate dosing of methadone thereby increasing clinical pain relief and decreasing the risk of these toxicities.

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