Methadone in Ambulatory Surgery

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Version 1.0
June 25, 2014

Version 2.0 (includes Amendment 1)
January 3, 2015

Version 3.0 (includes Amendent 2)
July 24, 2015

Version 4.0 (includes Amendment 3)
August 27, 2017

Methadone in Ambulatory Surgery

Amendment 1

January 3, 2015

Purpose

1. Add a second study cohort (same-day surgery outpatients) to the original cohort (ambulatory surgery with overnight stay, less than 24 hr total duration)

Changes

A. Additions:

2. Background

Add a second study cohort (same-day surgery outpatients) to the original cohort (ambulatory surgery with overnight stay, less than 24 hr total duration)

9. Statistical Methods
Analysis: Identify that each cohost is analyzed separately

B. Deletions:

4. Eligibility

Delete overnight

C. Changes:

Change from 60 evaluable subjects to 60 evaluable subjects in each cohort (120 total).

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Amendment 2

July 24, 2015

Purpose

Clarify data collection at 30 days to include questions about the subject's remaining pain medications and their disposal.

Changes

Additions:7. Data Collection and Monitoring.

Follow up assessments

A home diary will be used to assess daily drug dosing history upon discharge from the hospital until the patient's postop clinic visit at approximately 30 days. Subjects will also record daily pain self-assessments using a colored-visual analogue scale (at rest, with activity and with coughing). The ORSDS will be completed and recorded on approximately the 7^{th}, 14^{th} and 30^{th} day. We will also ask subjects about remaining number of pain medications and their disposal at the 30 day time point.

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Amendment 3

August 24, 2017

Purpose

Clarify that > 60 evaluable subjects will be enrolled in study cohorts

Changes

Study table clarified to state a minimum of 60 evaluable subjects will be enrolled for each cohort; up to 200 total evaluable.

Protocol para 6 and 9 changed to indicate ≥ 60 evaluable subjects in each cohort may be required for analysis.

Deletions

Protocol p. 12, deleted sentence stating analysis to include total of "120 evaluable"

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 and effectiveness in perioperative pain relief in inpatients is well characterized. There is, however, no information on methadone use in an ambulatory surgery setting and outpatient procedures. This pilot investigation will determine effectiveness of intraoperative methadone in reducing postoperative opioid consumption and providing improved pain relief in patients undergoing moderately painful, ambulatory surgical procedures.

SYNOPSIS

Study Title	Methadone in Ambulatory Surgery
Objective	Two arm randomized controlled pilot study to evaluate the efficacy of a single dose of intraoperative methadone in reducing post-operative pain and opioid consumption in patients undergoing moderately painful, ambulatory (less than 24 hr hospital stay) surgical procedures. Our secondary goal is to assess opioid consumption and pain relief within the first 30 postoperative days
Study Period	Planned enrollment duration: Approximately 12 months. Planned study duration: Approximately 30 days per subject
Number of Patients	200 evaluable subjects
Study Medication Administration	At least 60 evaluable patients in each of two cohorts (ambulatory with less than 24 hr overnight stay, and same-day outpatients) will be randomized into two groups. Group I will receive 0.1- 0.3 mg/kg IV methadone HCl. Group II will be the control group and not receive any methadone.
Study Design	Single-center, randomized, single blinded, positive-controlled dose escalation pilot study. Patients receive standard monitoring for anesthesia and postoperative care. Surgical and anesthesia care (except for intraoperative opioid use) are not altered for study purposes. In each cohort, subjects are randomized 1:2 to either control (standard intraop opioid at anesthesiologists' discretion, not methadone) or methadone HCl (0.1 – 0.3 mg/kg ideal body weight, IBW). Subjects in Group I will receive methadone (IV bolus, at induction of anesthesia) as their primary intraoperative opioid. Dose of methadone may be increased up to 0.3 mg/kg IBW following preliminary analysis and review of initial subjects enrolled to Group I. Subjects in Group II (control) will receive intraoperative opioid administration at the discretion of the anesthesia providers (typically fentanyl or morphine). Postoperative pain management for both groups will be per standard of care.
Inclusion and Exclusion Criteria	Inclusion Criteria 1. Age 18-65 years 2. Undergoing general anesthesia and moderately painful, ambulatory surgical procedures, with anticipated postop stay of < 24 hours 3. Signed, written, informed consent Exclusion Criteria 1. History of liver or kidney disease. 2. Females who are pregnant or nursing. 3. Opioid tolerant patients (e.g. preoperative methadone therapy or use of fentanyl transdermal patches) 4. History of allergy to methadone
Measurements	Total intraoperative and postoperative opioid administration during hospitalization will be recorded from the patient's electronic medical record (EMR). Pain intensity will be assessed using the Numeric Rating Scale (NRS) and colored-visual analogue scale. Pain relief will be assessed using five point scale (0-no relief, 4-complete pain relief). Postoperative sedation will be recorded using Modified Observer`s Assessment of Alertness/Sedation (MOAA/S). Assessment of opioid side effects will be performed using Opioid-Related Symptom Distress Scale (ORSDS). Daily opioid consumption and daily pain self-assessments using a colored-visual analogue scale will be recorded in a home diary for approx 30 days following surgery (from hospital discharge until postop clinic visit). Additional ORSDS assessments will be recorded at various timepoints (approx 7, 14 and 30 days postop) in the home diary. Subjects may have their CYP2B6 genotype determined.

Statistical Methodology	Demographic data including race, sex, and age will be analyzed using chi-square and t- test or ANOVA, as appropriate. Baseline characteristics of the cohort will be described. Total daily opioid consumption and pain scores using NRS, will be compared between the groups. Outcome measures will be expressed as the mean and standard deviation. Group outcomes will be compared across the two groups, using t-test and/or analysis of variance, ANOVA and MANCOVA to account for potential cofounders.
Outcomes	Primary: Intraoperative and postoperative opioid utilization Secondary: 1) Opioid consumption and pain relief within first 30 postoperative days 2) Pain scores and pain self-assessments 3) Influence of CYP2B6*6 genotype on methadone clinical effectiveness for pain relief and opioid consumption

1. Specific Aims

1.1. To study the effects of a single dose of methadone on postoperative pain and opioid consumption in patients undergoing moderately painful, ambulatory surgical procedures.
1.2. Determine opioid consumption and pain relief within first 30 postoperative days
1.3. Determine cytochrome P4502B6 (CYP2B6) genotype in patients receiving methadone, and any relationship to postop pain relief and opioid consumption

2. Background

Inadequate pain relief has a significant psychological and physiological impact on patients. The degree to which postoperative pain is controlled impacts the ability of patients to cope with the next pain episode (1, 2). Postoperative pain itself is a risk factor for development of chronic pain syndromes (3).

Methadone is a μ opioid agonist which is highly efficacious in the treatment of acute, chronic, neuropathic and cancer pain. In adults it is increasingly being used as a first-line analgesic. Methadone is highly efficacious in adult anesthesia and postoperative pain (4, 5). The typical dose for adult inpatient 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. It has no active metabolites or pro-drug forms. Methadone is metabolized in the liver primarily by cytochrome P450 CYP2B6 (6, 7).

Perioperative analgesia remains a major challenge for physicians who care for patients undergoing any type of surgery, including ambulatory and 24 hour observation procedures. We propose to compare the standard of care intraoperative opioid administration to intraoperative methadone bolus in reducing postoperative opioid consumption and prescribing.

Evaluating the role of methadone in ambulatory surgery patients is advantageous because 1) prolonged analgesia from methadone is expected to decrease the need for additional opioids in the immediate postoperative period, 2) opioid quantities routinely prescribed upon discharge may be reduced with methadone use, 3) lower overall dose of opioids administered can decrease possible side effects of opioids, and 4) improved immediate postoperative pain relief can decrease occurrence of chronic postoperative pain.

Assessment of pain has become standard practice in the treatment of surgical patients. Several tools are often used, including the Numeric Rating Scale and colored-visual analogue scale (8, 9, 10).

We propose to evaluate intraoperative and postoperative opioid consumption, pain intensity and pain relief in patients undergoing moderately painful, ambulatory surgical procedures (anticipated length of stay <24 hrs) in 2 cohorts, and 2 groups in each cohort. Cohort 1 is ambulatory patients with <24 hr overnight stay, cohort 2 is same-day surgery outpatients). In each cohort, Group I will receive a single dose of methadone during surgery and Group II will receive a non-methadone intraoperative opioid (typically fentanyl or morphine). Secondarily, we will study opioid consumption and pain self-assessments within approximately the first 30 postoperative days, or until the initial postop clinic visit.

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 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 adults averages 24-36 hrs (11, 12).

The 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.

4. Eligibility

Inclusion Criteria

- Age 18-65 years
- Undergoing general anesthesia and moderately painful, ambulatory surgical procedures with anticipated postop hospital stay of < 24 hours
- Signed, written, informed consent

Exclusion Criteria

- History of or known liver or kidney disease.
- Females who are pregnant or nursing.
- Opioid tolerant patients (e.g. preoperative methadone therapy or use of fentanyl transdermal patches)
- History of allergy to methadone

5. Enrollment

Subjects will be approached prior to surgery in the Center for Preoperative Assessment and Planning or preoperative holding area. Patients will be consented for participation and enrolled in the study by trained study personnel.

6. Methods

Preoperative and Intraoperative Period

Enrolled subjects will be asked to complete a questionnaire about their current pain and what they anticipate following surgery. Patients will receive standard physiologic monitoring for anesthesia and postoperative care. Subjects within each cohort ($n \geq 60$ evaluable, depending on the number of dose levels in each cohort) are randomized 1:2 to receive either control (typical intraop opioid, such as fentanyl or morphine) or methadone HCl (0.1 – 0.3 mg/kg ideal body weight, IBW). It is anticipated that the first ten patients will receive 0.1 mg/kg IV methadone. If patients still have significant post-op opioid requirements, subsequent groups may receive 0.2 mg/kg and then 0.3 mg/kg ideal body weight.

Anesthesia and surgical care will not be altered for the purposes of this investigation, except that subjects in methadone group will receive methadone as their intraoperative opioid, rather than leaving the choice of intraoperative opioid to the anesthesiologist. The control group patients will receive intraoperative analgesia with opioids other than methadone left at the discretion of their anesthesiologist (typically fentanyl or morphine).

Administration of Study Medication

Methadone is administered as an IV bolus at induction of anesthesia. Methadone hydrochloride is available commercially for injection (10 mg/ml). Subjects randomized to the control group will receive typical (non-methadone) opioids. Both groups will receive standard of care postoperative analgesia as determined by the treating physician. Postoperative care is not altered for purposes of this study.

Assessments

Pain assessments at rest (when patient awake) will be conducted in the postoperative period by a trained member of the research team. These will occur after handoff in the Postop Anesthesia Care Unit (PACU) and approx every 15 minutes during first PACU hour, then approx every hour for the next 4 hours and at bedtime. The pain assessments will also be performed at approx 24 hrs or prior to discharge from the hospital, whichever occurs first. Pain intensity will be assessed using the 0-10 Numeric Rating Scale and a colored-visual analogue scale. Pain relief will be assessed using five point scale (0-no relief, 4-complete

pain relief). Observed sedation (Modified Observer's Assessment of Alertness/Sedation, MOAA/S) and subject's self-assessment of sedation are recorded at the same intervals as pain assessments. Assessment of opioid side effects is performed at approximately 24 hrs or prior to discharge from the hospital using Opioid-Related Symptom Distress Scale (ORSDS). The total amount of other drugs administered during hospitalization for prophylaxis or treatment of opioid side effects will be recorded from the EMR. Daily home opioid usage and pain self-assessments will be recorded in a home diary. The ORSDS assessments will also be completed at various timepoints (approximately 7, 14 and 30 days postop).

Any adverse events are described, recorded and reported according to GCP and IRB regulations.

7. Data Collection and Monitoring.

Opioid Consumption During Hospitalization

The EMR will be used to calculate the amount of morphine or morphine equivalents administered during surgery and until discharge, as well as other drug administration for treatment and/or prophylaxis of possible opioid side effects.

Follow-up Assessments

A home diary will be used to assess daily drug dosing history upon discharge from the hospital until the patient's postop clinic visit at approximately 30 days. Subjects will also record daily pain self-assessments using a colored-visual analogue scale (at rest, with activity and with coughing). The ORSDS will be completed and recorded on approximately the 7^{th}, 14^{th} and 30^{th} day. We will also ask subjects about remaining number of pain medications and their disposal at the 30 day time point.

CYP Genotyping

Approximately 5 ml of blood will be collected from an IV line for CYP2B6 genotyping. Genotyping will be performed at the WUSTL Genome Technology Access Center (GTAC).

Other Measurements

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

8. Data and Safety Monitoring Plan.

In general, the Department of Anesthesiology has developed a specific set of Standard Operating Procedures (SOPs) for clinical research. All individuals working on study are required to read and be totally familiar with and compliant with the SOPs. The 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. The specific plan for submitting Adverse Event Reports to the IRB is detailed in the SOP for Adverse Event Reporting.

The specific monitoring plan for this investigation is commensurate with the risks, size and complexity of the investigations planned. The potential risks are attributable to the use of methadone. Based on the small size and relatively low risks nature of the protocol, only the PI and CoI are involved in monitoring plan, rather than a full DSMB. These individuals 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.

9. Statistical Methods

Primary Assessment

Overall opioid (morphine equivalents) consumption for each patient during hospital stay
Absolute pain and sedation scores

Secondary Assessments
Opioids (morphine equivalence) consumption within approx. first 30 postoperative days
Postoperative pain self assessments
CYP2B6*6 Genotype

Analysis
Sample Size: Our initial plan is to enroll ≥ 60 evaluable subjects in each of two cohorts for this pilot study . More specifically, this pilot plans 20 evaluable subjects in each methadone group within each cohort, with requisite proportional controls. Total number in each of the two cohorts will reflect the number of dose groups in each cohort (per escalation). Anticipated total evaluable is <200.

Statistical Analysis: Each cohort is analyzed separately. Baseline characteristics of each cohort and groups within each cohort will be described. Demographic data including race, sex, and age at study entry will be analyzed using chi-square and t-test or ANOVA, as appropriate. Total daily opioid consumption and pain scores using NRS 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 groups, using t-test and/or analysis of variance, ANOVA and MANCOVA to account for potential cofounders.

10. Risk Assessment
Methadone
The most common side effect of opioids such as methadone is mild sedation. 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. 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 have been used in similar previous studies. Mild respiratory depression is defined as respiratory rate <8/min in adults. 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.

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

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.

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, 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.

Risk/Benefit Assessment
The dose of methadone given will be a standard analgesic dose, and it might provide longer pain relief than other opioids. 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.

11. Human Subjects Research

Protection of Human Subjects
The study will be conducted under appropriate Washington University Institutional Review Board protocols and consent forms approvals. The study will be conducted under the supervision of the PI and Co-Investigator, who is a Board-Certified anesthesiologist with many years of experience in the conduct of human volunteer studies.

Sources of Materials
Information including demographic data, outpatient medications, chronic medical conditions, surgical procedure, length of stay, opioid and other drug administration and physiological monitoring will be obtained from the patient's electronic medical record.

Recruitment and Informed Consent
Patients will be screened based on operating room schedules, and approached prior to surgery at the Barnes-Jewish Hospital Center for Preoperative Planning and Assessment. All study related procedures, risks and benefits will be described to eligible patients, and time will be provided for addressing all questions and concerns.

Potential Benefits of the Proposed Research to the Subjects and Others
1) Prolonged analgesia from methadone is expected to decrease the need for additional opioids in the immediate postoperative period, 2) opioid quantities routinely prescribed upon discharge may be reduced with methadone us, 3) lower overall dose of opioids administered can decrease possible side effects of opioids, and 4) improved immediate postoperative pain relief may decrease the occurrence of chronic postoperative pain

Inclusion of Women
Studies and their advertisements actively encourage the participation of women in the research. Women of childbearing potential are not excluded from our research protocols. Pregnancy testing is performed as standard of care to protect female research subjects, and subjects are instructed when appropriate to use adequate contraceptive measures and avoid breastfeeding.

Inclusion of Minorities
All of our studies actively encourage the participation of minorities in the research. Our minority recruiting typically matches the demographic composition of the Washington University community from which subjects will be recruited (78% white, 21% Black, <1 % Hispanic).

Inclusion of Children
Children <18 yr will <u>not</u> be studied in these investigations.

12. References

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