

RESEARCH PROTOCOL

Investigation of cerebrospinal fluid (CSF) pharmacokinetics of ondansetron

Simon Haroutounian, PhD

Assistant Professor
Division of Clinical and Translational Research
Department of Anesthesiology
Washington University School of Medicine
660 S. Euclid Ave, Campus Box 8054
Saint Louis, MO, 63110
Tel: 314-286-1715
Fax: 314 286-2948
E-mail: simon.haroutounian@wustl.edu

Co-investigators:

Evan Kharasch, MD, PhD

Russell D. and Mary B. Shelden Professor of Anesthesiology
Director, Division of Clinical and Translational Research
Department of Anesthesiology
Washington University School of Medicine
Tel: 314-362-8796
kharasch@wustl.edu

Carl Nielsen, MD

Professor of Anesthesiology
Department of Anesthesiology
Washington University School of Medicine
E-mail: nielsenc@anest.wustl.edu

Chris C. Lee, MD, PhD

Associate Professor of Anesthesiology
Department of Anesthesiology
Washington University School of Medicine
E-mail: climd@wustl.edu

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1. SYNOPSIS

Study Title	Investigation of cerebrospinal fluid (CSF) pharmacokinetics of ondansetron
Brief Title	CSF PK of ondansetron
Objective	To determine human cerebrospinal fluid (CSF) and plasma pharmacokinetic parameters of 5HT3R antagonist ondansetron after intravenous administration.
Hypothesis	Approaches to enhance CNS penetration of ondansetron might be useful for obtaining analgesic effect with 5HT ₃ antagonists in neuropathic pain.
Study Period	Planned enrollment duration: Approximately 3 months Planned study duration: One (4-hour) study day per subject, on the day of knee/hip arthroplasty surgery.
Number of Subjects	15 evaluable subjects having elective hip or knee arthroplasty with spinal anesthesia from up to 30 consented subjects.
Study Treatment	Single intravenous 15-min infusion of 16mg ondansetron.
Study Design	Prospective, open-label, pharmacokinetic pilot study.
Inclusion and Exclusion Criteria	<p><u>Inclusion criteria:</u></p> <ol style="list-style-type: none"> 1. Age between 18 and 70 years old; 2. Patients planned to undergo hip or knee arthroplasty with spinal anesthesia; 3. Ability to provide informed consent <p><u>Exclusion criteria:</u></p> <ol style="list-style-type: none"> 4. Not giving consent to participate in the study; 5. Patients with history of or current hepatic or renal insufficiency; 6. Patients with BMI \geq 33; 7. Patients with heart failure or active arrhythmias; 8. <u>Patients with severe systemic disease that is a constant threat to life;</u> 9. Contraindication or allergy to ondansetron; 10. Pregnancy or lactation. 11. Prisoners
Measurements	<p><u>Ondansetron CSF and plasma Pharmacokinetics:</u></p> <ol style="list-style-type: none"> 1. A single 4-mL CSF sample per subject. 2. Serial blood sampling at 0 (pre-infusion), 15, 30, 60, 120, and 180 min after ondansetron administration. <p><u>Genotyping:</u> A blood sample will be obtained at baseline for determining the following single nucleotide polymorphisms (SNPs) as confounders of ondansetron PK parameters:</p> <ol style="list-style-type: none"> 1. ABCB1 gene (p-Glycoprotein transporter): C3435T, G2677T, T-129C, G1199A, C1236T.

	2. In SLC22A1 gene (OCT1 transporter): R61C, C88R, G401S, M420del, G456R.
Statistical Methodology	<p>This is a pilot/feasibility study. Individual plasma concentration-time data will be analyzed using non-compartmental methods in Phoenix WinNonlin[®] 6.1, to determine ondansetron PK parameters such as volume of distribution (Vd), clearance (CL), maximum plasma concentration (Cmax), and the time to reach maximum concentration (Tmax).</p> <p>A compartmental population-based PK model will be constructed, to determine the pharmacokinetic variables of ondansetron in CSF, and allow for the estimation of the partition coefficient between the plasma and CSF.</p>

2. STUDY PROTOCOL

2.1 Background and Significance

Neuropathic pain [NeuP] affects 7-8% of the adult population and is particularly challenging to treat. More than 30% of neuropathic pain patients continue to suffer despite treatment; and there is clearly an urgent need for new treatment approaches. However, the translation of findings from current neuropathic pain animal models to clinical trials have been extremely disappointing, with multiple pre-clinically promising agents failing to show robust clinical effectiveness; suggesting that 1) additional pharmacodynamic (PD) and pharmacokinetic (PK) factors responsible for effective animal-to-human translation need to be considered, and 2) because of a large inter-subject variability in pain mechanisms and treatment response, an “all-comers” approach is suboptimal in yielding significant leaps forward in the success of treating neuropathic pain. Therefore, addressing possible PK and PD translational gaps and investigating genotypic and phenotypic predictors of response can improve the translational process and allow more effective drug discovery and individual analgesic tailoring in neuropathic pain.

Serotonergic 5HT₃Rs in the central nervous system (CNS) have been identified as a promising pharmacological target in neuropathic pain [1, 2]. After peripheral nerve damage the character of serotonergic descending modulation changes from inhibitory to facilitatory through 5HT₃Rs in the spinal cord [3, 4]. This finding is supported by studies demonstrating that intrathecal (IT) administration of 5HT₃R antagonists such as ondansetron alleviates mechanical and thermal hypersensitivity in animal nerve injury models [1, 5]. In contrast to IT administration, systemic ondansetron does not produce consistent analgesia. However, this is not surprising, considering that CNS concentrations of 5HT₃R antagonists such as ondansetron highly depend on the expression level of P-glycoprotein (Pgp) - an efflux transporter at the capillaries of the blood-brain barrier (BBB) which transports xenobiotics out of the CNS to the systemic circulation [6, 7].

Clinical trials performed with 5-HT₃ antagonists for treating pain have yielded mixed results. Two studies with tropisetron in fibromyalgia have yielded somewhat positive results, but had methodological shortcomings, and a well-designed tropisetron study in 30 patients with low back pain was negative. Two studies with ondansetron in neuropathic pain were overall negative, but in one of the studies, pain reduction 2h after ondansetron administration was larger than with placebo [8, 9]. In both these studies individual data (personal communication with the authors) indicate that certain patients had good analgesic response to intravenous ondansetron, warranting further investigation into the individual response profiles.

We suggest that one of the caveats leading to unsuccessful clinical translation of the promising animal data is related to the essential pharmacokinetic criterion that probably determined the lack of efficacy of systemic ondansetron in rodents - i.e. inability to achieve effective concentration at the site of action. We propose that sufficient exposure of 5HT₃R antagonists at their site of action in the CNS, as well as the choice of appropriate pain condition are of key importance for testing the clinical effectiveness of 5HT₃R antagonists in NeuP. Consequently, the goal of the project is to establish detailed CNS pharmacokinetic (PK) parameters of ondansetron, to provide sound basis for a future study with enhanced CNS penetration of ondansetron in neuropathic pain.

Two genetic factors shown to affect the pharmacokinetics and the antiemetic efficacy ondansetron are 1) polymorphism in the ABCB1 gene expressing P-glycoprotein, a transporter which controls the transport of ondansetron to the CNS via the BBB; and 2) polymorphism in the SLC22A1 gene expressing organic cation transporter-1 (OCT1), a transporter responsible for hepatic uptake of

ondansetron. We will collect the genetic data on these polymorphisms to account for inter-subject variability in pharmacokinetic parameters of ondansetron.

2.2 Preliminary Data

None

2.3 Objective

The primary objective of the study is:

To test the feasibility of:

1. Determining human cerebrospinal fluid (CSF) and plasma pharmacokinetics of 5HT3R antagonist ondansetron, after intravenous administration.
2. Determining single nucleotide polymorphisms in transporters involved in hepatic uptake (organic cation transporter-1 [OCT1]) and CNS disposition (P-glycoprotein) of ondansetron in human subjects.

2.4 Patient Selection

Overall, 15 evaluable subjects planned to undergo hip or knee arthroplasty with spinal anesthesia at Washington University / Barnes Jewish Hospital. We anticipate that we will need to consent approximately 30 subjects to achieve the enrollment goal.

2.4.1 Inclusion Criteria

Inclusion criteria:

1. Age between 18 and 70 years old;
2. Patients having elective hip or knee arthroplasty with spinal anesthesia;
3. Ability to provide informed consent

2.4.2 Exclusion Criteria

Subjects will not be enrolled if any of the following criteria exist:

1. Not giving consent to participate in the study;
2. Patients with history of or current hepatic or renal insufficiency;
3. Patients with BMI ≥ 33 ;
4. Patients with heart failure or active arrhythmias;
5. Patients with severe systemic disease that is a constant threat to life;
6. Contraindication or allergy to ondansetron;
7. Pregnancy or lactation.
8. Prisoners

The following ondansetron **contraindications** will disqualify subjects from participating:

1. Congenital QT syndrome
2. QTc interval > 450ms
3. Concomitant therapy with any of the following drugs:

- First generation **antipsychotic** medications Thioridazine, Haloperidol, Chlorpromazine, and Pimozide
- Second generation **antipsychotic** medications Ziprasidone and Quetiapine
- Azole **antifungals** Ketoconazole and Fluconazole
- **Antihistamine** Terfenadine,
- **Antidepressants** Trazodone, Citalopram, and Bupropion,
- **Antiarrhythmics** Propafenone, Flecainide, and Procainamide
- **Fluoroquinolone** antibiotics Norfloxacin, Ofloxacin, and Ciprofloxacin
- **Macrolide** antibiotics Erythromycin and Azithromycin
- **Antiretrovirals** of Protease inhibitor (e.g. Ritonavir, Saquinavir) or Non-nucleoside reverse transcriptase inhibitors (e.g. Efavirenz, Zidovudine) family.
- **Cisapride**
- Other potent **inhibitors** of Cytochromes P450 **2D6** or **3A4**.

2.5 Design and Procedures

2.5.1 Study Design and Methodology

The potential subjects will be recruited from the Washington University / Barnes Jewish Hospital center for perioperative assessment and planning (CPAP) and the Washington University Orthopedics outpatient clinics, before their scheduled visit for elective knee or hip arthroplasty. Subjects may also be recruited from BJH Surgery Registration and the preoperative holding area on the day of surgery. Subjects who are potential candidates for the study will be provided with written and oral description of the study procedures, benefits, and potential risks. They will be given the opportunity to ask questions regarding the study. Informed consent will take place at Washington University/Barnes-Jewish Hospital medical center campus.

If agreeing to participate in the study, each subject will sign the informed consent document. Each subject who qualifies for entry into the study on the basis of inclusion/exclusion criteria and completion of informed consent will be assigned the next available patient number. This indicates enrollment in the study. In subjects with a history of or suspected renal or hepatic disorder, blood tests will be ordered following consent and reviewed prior to study participation for plasma creatinine, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST) and albumin. Subjects with moderate or severe renal or hepatic failure will be excluded from the study at the discretion of the PI. Subjects with any history of cardiac arrhythmias will undergo 12 lead ECG to rule out QTc interval >450ms and will be excluded from the study.

Patients' demographic data will be recorded; height and weight will be measured for calculating BMI. Subjects who drop out of the study prior to completing the study will be replaced by using the next available subject number.

2.5.2 Study Period

Subjects will be studied in the Department of Anesthesiology of Washington University-Barnes Jewish Hospital, prior to and during their scheduled hip or knee arthroplasty surgery.

An intravenous catheter will be inserted in an arm for drug administration and in the opposite arm for obtaining blood samples to evaluate the plasma concentrations of ondansetron. The former will be used also for pre/intraoperative fluids and anesthesia drug administration.

At baseline, a 5ml blood sample will be collected for pharmacokinetics and another 5ml sample for genetic analysis.

Ondansetron will be administered in a 16mg single dose as a 15 min intravenous infusion. Although up to 32mg doses of intravenous ondansetron have been used in clinical trials, 16mg is currently the highest FDA-recommended dose for single administration. Two additional 4mg doses of either IV or oral ondansetron will be allowed for postoperative nausea and vomiting treatment in the study subjects, at the discretion of the treating physicians.

A single CSF sample of 4ml will be collected immediately after spinal needle insertion and before administration of spinal anesthesia. This procedure is routinely performed in the holding area, approximately 30 min before the patient enters the operating room (OR) for planned surgical procedure with spinal anesthesia. As only one sample of CSF is obtained from each subject, the timing of the infusion will be scheduled at approximately 30, 60, or 120 min before planned pre-surgical spinal needle insertion. This will allow 3 time-points of CSF samples from the aggregate study cohort. For determination of the above timing, the patients will be randomized in blocks of 3 for infusion timing (approximately 5 subjects per block), to allow even distribution of CSF PK sample time-points.

Six 5mL serial venous blood samples will be obtained from all subjects at 0 (pre-treatment), 15, 30, 60, 120, and 180 min from the beginning of infusion in each patient, regardless of timing for CSF sampling. The samples will be put on ice, centrifuged for 10 min at 5000 rpm. Plasma will be transferred to two 1.5mL vials and stored at -80°C until analysis by HPLC-MS.

The CSF ondansetron pharmacokinetic profile will be constructed using population PK approach, according to the exact time of CSF sampling. Ondansetron concentration in plasma (expected 40-120ng/mL) and CSF (expected 3-12ng/ml) will be determined by HPLC-MS-MS analysis [10].

Ondansetron may cause QT interval prolongation in rare cases; therefore, the subjects' heart rhythm will be monitored throughout the infusion and for approximately 30 min after the end of infusion using standard 4 lead monitors in the holding area. No changes will be made to the routing intraoperative management and hemodynamic physiological monitoring, with the exclusion of the PK blood sampling period.

The DNA isolation and genotyping will include analysis of single nucleotide polymorphisms (SNPs) in OCT1 and P-glycoprotein transporters. We will genotype for the following five P-glycoprotein (ABCB1) SNPs: C3435T, T-129C, G1199A, C1236T, G2677T [11-14], and for five OCT1 (SLC22A1) SNPs: R61C, C88R, G401S, M420del, or G456R that have reported to affect ondansetron pharmacokinetics or clinical antiemetic effect. The genotyping will be performed at Washington University Genome Technology Access Center. The whole blood samples will be extracted using the QiAamp DNA mini Blood kit (QIAGEN). The DNA will be quantified and quality controlled using nanodrop and gel readings. The SNPs will be interrogated using Taqman probes (Applied Biosystems). Each SNP will have its own 20µl reaction well with a final

concentration of 1X Taqman probe mix, 1X Taqman PCR master mix, and 20-40ng of DNA. The samples will be cycled and analyzed on CFX96 Real-time PCR Detection System (Bio-Rad). The collected blood and DNA samples will be de-identified and coded to ensure patient confidentiality and HIPPA compliance.

2.5.3 Minimization of Bias

There will be no specific sex, ethnic or racial background for enrollment. Plasma and CSF ondansetron concentration is not affected by subjects' or investigators' knowledge of study aims and hypothesis.

2.5.4 Observations and Measurements

2.5.4.1 Primary Outcome Measures

Primary outcome:

Plasma and CSF concentrations of ondansetron, and CSF to plasma concentration ratio.

2.5.4.2 Secondary Outcome Measures

Secondary outcomes:

Non-compartmental modeling to determine plasma PK parameters of ondansetron – i.e. volume of distribution (Vd), clearance (CL), maximum CSF and plasma concentration (Cmax), and the time to reach these maximum concentrations (Tmax).

Compartmental modeling using population PK approach to determine CSF pharmacokinetic parameters of ondansetron.

2.5.4.3 Pharmacokinetic data analysis:

Individual plasma concentration-time data will be analyzed using non-compartmental methods. The following PK parameters will be calculated and compared between subjects with different transporter expression level: volume of distribution, systemic clearance, the elimination half-life, and the total area under the concentration-time curve. In addition, a compartmental population-based pharmacokinetic model will be constructed, which will evaluate inter-subject variability in pharmacokinetic parameters. Preliminary assessment of published data indicates that the systemic disposition of ondansetron follows two-compartment model with linear elimination following intravenous administration in humans.

The population model will include a “CSF distribution compartment”, which will allow for the estimation of the partition coefficient between the plasma and CSF. The effect of transporter expression level phenotypes on individual pharmacokinetic parameters will be evaluated using a standard covariate analysis. Utilization of population approach will allow for estimation of population mean and individual patients parameters. This pharmacokinetic methodology is especially useful for analysis of sparse data (i.e., a single CSF sample from each patient).

2.5.5 Sample Size

We plan to recruit 15 subjects to the current study, and propose additional enrollment of 60-80 patients to the subsequent study, upon securing sufficient extramural funding

Typically, 10-15 subjects per study have been used for the assessment of drug pharmacokinetic parameters and is sufficient for a pilot study.

Weekly, more than 30 total hip or knee arthroplasties with spinal anesthesia are performed at our institution. This corresponds to approximately 1000 eligible patients a year that may fulfill the inclusion criteria.

2.5.6 Study design considerations

. A large number of patients undergo total joint arthroplasty at our institution, and spinal anesthesia is standard care; therefore, it will be possible to recruit patients who meet the inclusion criteria without the added risk of spinal needle insertion. Ondansetron is routinely administered in these patients for the prophylaxis or treatment of postoperative nausea and vomiting.

The dose of 16mg ondansetron was chosen, as this is currently the highest recommended dose by FDA for a single administration and was shown safe among patients between ages 18-75. Intravenous 15-minute infusion is chosen over bolus administration to reduce QTc prolongation risks. We did not choose lower doses to be able to reliably measure CSF concentrations, as sampling volume is typically limited to about 4mL, to reduce the risk of post spinal headache. The timing of CSF sampling was based on intravenous ondansetron PK data [17].

2.5.7 Clinical Procedures and Laboratory Tests

Due to the risk of QT interval prolongation with high doses of ondansetron, we exclude patients with QTc > 450ms, and any concomitant administration of drugs that increase the pro-arrhythmic risk with ondansetron. In addition, all subjects will be monitored with ECG for potential arrhythmias.

However, it should be noted that ondansetron administration is standard of care in these patients.

Blood hepatic function and renal tests will be performed and evaluated prior to study treatment for any subjects with suspected or known kidney and or liver disease.

3.0 Management of Intercurrent Events

3.1 Adverse Experiences

The investigators will closely monitor subjects for evidence of ondansetron adverse events. All adverse events will be reported and followed until satisfactory resolution. The description of the adverse experience will include the time of onset, duration, severity, etiology, relationship to the study drug (none, unlikely, possible, probable, highly probable), and any treatment required. The clinicians will manage any postoperative event related to the spinal anesthesia as standard of care.

3.2 Premature Discontinuation

If a subject withdraws from the study, the subject will be replaced in order to provide the required number of evaluable subjects. Subjects will be withdrawn if the investigator decides that discontinuation is in the best interest of the subject, or the subject requests withdrawal from the study.

3.3 Potential Risks

3.3.1 Potential risks from ondansetron

Ondansetron systemic effects associated with high plasma concentration may cause cardiac arrhythmias.

In addition, subjects may experience diarrhea, constipation, headache, dry mouth, malaise, elevation of liver enzymes (incidence of 5% - when administered with chemotherapy to treat nausea and vomiting), and injection site reaction.

Rarely reported adverse effects include:

Hypokalemia, Fever, Anaphylaxis, Seizures, Temporary blindness.

However, this dose is used frequently for postoperative or chemotherapy-induced nausea and vomiting, and is considered safe. In previous studies with 16mg intravenous ondansetron administration, no patient had arrhythmias or other serious side effects; headache and malaise were the main adverse effects [8, 9]. No psychological risks to subjects are envisioned.

3.3.2 Other Potential Risks

Intravenous catheter placement can cause a bruise. The amount of blood drawn is approximately 35cc and will not constitute a risk to subjects since this amount is well below the recommended limits for this population. Spinous catheter placement is a part of the routine perioperative care in this patient group; therefore there is no additional risk as a result of study participation. The collection of a 4mL CSF sample will be performed by an anesthesiologist immediately following spinal needle insertion for standard of care anesthesia. This additional collection of CSF is not expected to increase the risk of post-dural puncture headache, but it may occur, especially in younger patients. No psychological risks to subjects are envisioned. Subjects may experience a loss of confidentiality. Investigators will keep subjects' participation confidential to the extent permitted by law. However, it is possible that others may become aware of subjects' participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies subjects. The results of genotyping will not result in identifiable, clinically diagnostic genetic information that has a known association with a medical condition. The data from the analysis will not be included in the patients' medical records.

3.4 Procedures to Minimize Potential Risks

Studies are conducted in the Washington University Clinical Research Center under the supervision of the PI and Co-investigators. The PI is trained and experienced in performing research in human subjects, and the co-investigators are board-certified anesthesiologists with extensive clinical and research experience in the perioperative setting.

Subjects are also continuously monitored by trained research (RN) nursing personnel throughout the study session and by their clinical team during surgery and recovery in the Past Anesthesia Care Unit (PACU), as a part of routine care. Subjects will be monitored by electrocardiogram for any potential cardiac abnormalities associated with ondansetron administration. Full patient monitoring and resuscitation capabilities are immediately available.

The 16mg dose of ondansetron, when infused over 15 minutes in adults 18-74 years old, was shown not to increase the QTc interval by more than 10ms, even if additional two doses of 8mg are administered later in the day [18]. Based on these data, and the current FDA recommendation, we will administer 16mg dose by 15-min infusion, and apply an upper age limit of 70 years on the study population.

Inclusion and exclusion criteria, monitoring, and the clinical protocol are designed to ensure that risks are absolutely minimal. Subjects are informed that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty. A pregnancy test will be performed on women of childbearing potential and subjects excluded if pregnant. Subjects will be told that in the event of a physical injury as the direct result of study procedures, they will be cared for by a member of the investigating team at no cost, within the limits of the Washington University compensation plan.

With regard to confidentiality; 1) all subjects will be assigned a study ID number, 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) Data will be stored under lock and key (office, file cabinet) and only the investigators and research team 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. 5) Study data will not be entered in subjects' medical records.

3.5 Data and Safety Monitoring Plan

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 ondansetron infusion. Based on these considerations, the monitoring plan involves engaging a colleague from the Department of Anesthesiology not involved in the study to serve in a monitoring capacity. Based on the relatively low risks nature of the protocol, only a third person (the colleague), rather than a full Data Safety Monitoring Board will be used. The colleague will be an anesthesiologist knowledgeable in the risks associated with 5HT3 antagonist administration. This individual will review the annual summary of adverse events. In addition, this colleague will review all reports of a Serious Adverse Event, or an Unexpected Adverse Event.

4. HUMAN SUBJECTS RESEARCH

4.1 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, a licensed pharmacist with several years of experience in the conduct of human studies, and the co-PIs, board-certified anesthesiologists with many years of experience in spinal and regional anesthesia for surgeries.

4.2 Sources of Materials

Subjects will be recruited from Washington University Orthopedics and the Center for Perioperative Assessment and Planning (CPAP), as well as from BJH Surgery registration and the preoperative holding area.

Data on comorbidities and concomitant medication use are provided by subjects. Specimens include blood obtained for transporter genotyping and for determining ondansetron plasma concentration. CSF samples are obtained for determining ondansetron CSF concentration.

4.3 Recruitment and Informed Consent

Participants will be recruited primarily through Washington University Orthopedics and the Center for Perioperative Assessment and Planning (CPAP).

Two primary recruitment mechanisms will be utilized:

1. Participants will be referred from Washington University Orthopedics by the corresponding physicians. Interested subjects will contact the investigators.
2. A weekly list of patients scheduled for CPAP visit before knee or hip arthroplasty will be generated from SIS system. The potential subjects will be approached by the study coordinator for inclusion consideration.

Subjects may also be consented in the surgery registration area and the preoperative holding area. Subjects will be given verbal (initially) and then written descriptions of the study aims, procedures, risks, and benefits, and will be required to give written informed consent. A member of the investigative team provides all study descriptions, informed consent, and answers all questions. Subjects are informed verbally and in writing that participation is voluntary and they may refuse to participate and may withdraw from the study at any time without penalty. Subjects that participate, but do not complete all study procedures because their surgery is cancelled or rescheduled by their treating physician may re-consent to participate and be re-enrolled as long as there has been a minimum of 48 hours between the last study procedure and the re-consent event.

4.4 Potential Benefits of the Proposed Research to the Subjects and Others

We do not know if the patients will benefit from the intervention. Perioperative ondansetron administration may decrease postoperative nausea and vomiting, and is used as standard of care in this setting.

Potential understanding of which patients are more likely to have higher CSF concentration of ondansetron may lead to introducing a potential analgesic treatment, from which patients with neuropathic pain may benefit in the future.

The society may benefit from a new approach of treating neuropathic pain with CNS-penetrating 5HT₃R antagonists.

4.5 Inclusion of Women

Studies actively encourage the participation of women in the research. As a matter of operational policy, our studies routinely and deliberately attempt to include equivalent numbers of women and men. However, the nature of the current study precludes enrollment of a set number of female or male patients since the main criteria for inclusion is hip or knee replacement surgery. Women of childbearing potential are not excluded from our research protocols.

4.6 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).

4.7 Inclusion of Children

Children <18 yr will not be studied in this investigation. Children rarely undergo hip or knee replacement procedures. Including children may expose them to an unnecessary risk without the benefit of generalizability of the results.

Additional Collaborators:

Chris Sawyer, PhD

Washington University Genome Technology Access Center (GTAC)

St Louis, MO

Role: SNP genotyping

Leonid Kagan, PhD

Department of Pharmaceutics, Ernest Mario School of Pharmacy

Rutgers, The State University of New Jersey

Piscataway, NJ

Role: Assistance with Pharmacokinetic modeling

Only the PI, the co-PIs, and the research coordinators will have access to patient identifiers or PHI. The external collaborators will be blinded to any patient identifying information.

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