Using Pharmacogenomics (PGx) results to guide post-operative nausea and vomiting (PONV) treatment practices: A pilot study

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Title of the Study: **Using Pharmacogenomics (PGx) results to guide post-operative nausea and vomiting (PONV) treatment practices: A pilot study**

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Background

The incidence of postoperative nausea and vomiting (PONV) in the bariatric surgical population can be between 11-22% despite multiple anti-nausea therapies administered. There is the potential for substantial morbidity associated with any episode of PONV in the bariatric surgical population therefore every attempt must be made to further reduce this adverse anesthetic complication [1].

Pharmacogenomics (PGx) is a new field in individualized medicine generally concerned with genetic polymorphisms in drug-metabolizing enzymes, transporters, receptors, and drug targets that explain inter-individual variation in drug efficacy and toxicity [2].

The continued high failure rates of PONV therapy despite multi-therapy approach makes genetic polymorphisms in the pharmacokinetic and/or pharmacodynamic pathways of the anti-nausea agents a likely contributor to the observed failed therapy. Preemptive PGx testing has the potential to improve clinical outcomes by using an individual's genotype to inform personalization and optimization of drug therapy [3].

Current anti-nausea management includes five drug classes: 5HT3 antagonists, dopamine antagonists, anticholinergics, steroids, and NK-1 receptor antagonists [4,5]. There is a growing body of evidence, including our own preliminary studies, that the efficacy of the commonly used 5HT3 drug ondansetron is influenced by PGx variants in the drug metabolizing enzyme CYP2D6 [6.7]. Any patient with a rapid metabolizer CYP2D6 genotype may have reduced treatment efficacy because of the rapid elimination of ondansetron. Gransietron is an alternative

agent within the same 5HT3 antagonist category which is not dependent on the CYP2D6 genotype that could be selectively used in any patient with a CYP2D6 ultrarapid metabolizer genotype. There are no current studies on selecting a specific anti-nausea drug type based on a patient's genetic status for this high risk population.

Genotype specific drug selection requires advance knowledge of a patient's genotype. Mayo Clinic's Individualized Medicine Clinic (within the Center for Individualized Medicine) has established a Pharmacogenomics Testing Service. Though single gene PGx testing has long been used at Mayo Clinic, panel tests that cover more genes at a lesser cost than previous single gene tests are increasing in availability. This study, to prospectively evaluate the impact of preemptive genome guided pharmacotherapy for PONV in the bariatric surgical population, is one of a limited number of pilots offering clinical PGx testing utilizing these panel tests offered within the Center for Individualized Medicine.

The clinical value of the testing service offered by CIM and integration of genetic data into the clinical decision making process creates the opportunity to improve understanding of the influence of genomics on multimodal anti-nausea therapies in this high risk population as well as the opportunity to assist anesthesiologists and surgeons improve the medication experience of their patients. Patients may also benefit from understanding their own PGx variations and the relevance of their results.

Specific aim

The goal of this study is to examine the current and (potential) future therapeutic relevance of PGx testing for bariatric surgical patients in order to improve patient clinical care at Mayo Clinic with more effective and efficient prescribing of anti-nausea medications.

To help accomplish this we will:

1. Facilitate sample collection and PGx testing;
2. Review returned patient PGx results, identifying PGx variants associated with current anti-nausea therapies;
3. Provide recommendations to anesthesiologist and surgeons for therapeutic adjustments related to the 5HT3 class of anti-nausea medications;
4. Deliver meaningful information to patients for future prescribing events;
5. Create a data repository of bariatric surgical patients' genomic variants and corresponding anti-nausea medication adjustment recommendations;
6. Evaluate pharmacogenomics as a method to reduce PONV rates in the bariatric surgical population;

Patient Selection

To be eligible for this study, the following inclusion and exclusion criteria must be adhered to:

Inclusion Criteria

- A Mayo Clinic patient scheduled to undergo any bariatric surgical procedure, including Roux-en-Y gastric bypass, sleeve gastrectomy, or duodenal switch.
- Patient age 18 or above.

- Patients must understand and provide written informed consent prior to initiation of any study-specific procedures.
- Patient is willing to engage in a medication adjustment as part of their clinical visit (when needed).

Exclusion Criteria

- Patient with uncontrolled concurrent illness including psychiatric illness, or situations that would limit compliance with the study requirements or the ability to willingly give written informed consent.
- Any patient who will be unable to have genetic testing at minimum of 1 week prior to scheduled surgery or with allergies to ondansetron or granisetron.
- Any patient with prior pharmacogenomics testing that is readily available in the medical record will be excluded from this study.
- Any patient that is pregnant

Study Design

We plan to recruit approximately 100 bariatric surgical patients to this study. Patients who have met the inclusion and exclusion criteria and who have signed the informed consent will be asked to provide a one-time buccal scraping. This sample will be sent to OneOme™ Laboratory for use for the CLIA/CAP approved RightMed™ test (PGx gene panel).

Results for the patient will be returned to Mayo Clinic and placed into the patient EHR to be utilized for clinical treatment decisions at minimum of one-week prior to surgery. If necessary, to assist in interpretation of the PGx test results, a PGx-trained pharmacist will review the test report, and document assessment via the e-Consult mechanism. A patient letter based on their results may be recommended by the pharmacist on a case-by-case basis. During this process, we will document PGx variants, identify “actionable” variants potentially impacting current medications and all prescription(s) changes considered. If indicated due to PGx variants or current medication list, the patient may have a face-to-face or virtual visit with a pharmacist to discuss their PGx results. If the patient participates in a face-to-face visit with a pharmacist as part of standard patient care, medication reconciliation would be performed and the data will be collected via interview.

On the day of surgery, the participant will receive either ondansetron or granisetron as the 5HT3 anti-nausea medication based on their CYP2D6 genotype. All other anti-nausea therapies will remain consistent. Medication recommendations and education will be provided to all anesthesiologist and surgeons caring for these patients via the EHR.

All clinical data (demographics as well as predictor, outcome and confounding data) will be collected from the anesthesia exposure database from the Mayo Clinic - Rochester Anesthesiology Department.

Patients will be given information and education materials and references about PGx testing as appropriate, and will also have access to the lab results report and consult notes via the Mayo Clinic Patient Online Services portal. Patients may also request a copy of their results through Mayo Clinic Medical Records.

Consenting Procedures

Study participants will be identified by the bariatric surgeons participating in this pilot study. A member of the research team listed on the IRB will meet with the patient to discuss the study if they are eligible. The informed consent document will be used as a guide for this discussion. If feasible, the consent documents may be sent in advance for review by potential participants and their families. The documents will be accompanied by a letter introducing the study and that patient and his/her family will be invited to meet with a member of the research team during one of their upcoming appointments to learn more about the study and to go over the information provided in the consent documents.

The study team will provide a paper consent form for signature. A photocopy of the signed consent form will be given to the subject for their records.

Data Analysis

The statistical analysis will be largely descriptive. Continuous variables will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum and maximum). Categorical variables will be presented using frequencies and percentages. Time-to-event variables will be described by N, median, range, number censored, and Kaplan-Meier plots.

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