Low-dose Granisetron for the Prevention of Postoperative Nausea and Vomiting

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ABSTRACT

Purpose: Post-operative nausea and vomiting (PONV) is commonly experienced by patients after surgical procedures. Among the highest risk group for PONV are women undergoing abdominal procedures. The purpose of this study was to compare the efficacy and safety of serotonin type 3 receptor antagonists (5-HT_3RA) in combination with a ReliefBand (Woodside Biomedical Carlsbad, CA) to prevent PONV in female, adult patients undergoing gynecological and breast surgery.

Methods: One hundred and ninety-four female patients were randomized to receive ondansetron 4 mg, dolasetron 12.5 mg, or granisetron 0.1 mg prior to emergence from anesthesia. All patients received a 5-HT_3RA in combination with a ReliefBand. PONV was assessed during the early (0-6 hours) and late (6-24 hours) time periods after administration of medication. Complete response to medication was defined as no requirement for further anti-emetic medications postoperatively.

Results: The rate of PONV did not differ between study groups. Early and late failure rates were not significantly different between dolasetron (33.0 vs 26.2%), granisetron (22.6 vs 24.2%), and ondansetron (25.4 vs 20.9%). No adverse drug reactions were reported with the exception of dolasetron in which five minor, non-life-threatening

events were reported ($P < 0.05$). Because all patients received non-pharmacologic treatment with a ReliefBand, its effects on drug therapy were not assessed.

Conclusion: Patients administered low-dose granisetron experienced similar rates of PONV compared to ondansetron and dolestron for the prevention of PONV. Low-dose granisetron is a safe and cost-effective regimen to prevent nausea and vomiting in women undergoing gynecologic surgery.

INTRODUCTION

Postoperative nausea and vomiting (PONV) is commonly experienced in patients following surgery. The overall incidence of PONV averages between 25 and 30% of patients, but has been reported to be as high as 75% in earlier studies.[1,2] Patients undergoing major gynecological procedures are especially prone to PONV with incidence rates of 50-60%.[3] Conditions associated with PONV include age, female gender, type of surgical procedure, pre-operative medications, type and duration of anesthetic agents, history of PONV, smoking status, and degree of postoperative pain.[4,5] The occurrence of nausea and vomiting after surgical procedures can result in delayed post-anesthesia care unit (PACU) discharge, unanticipated hospital admissions (for outpatient procedures), and extended length of stay; all of which may impact patient satisfaction and increase health care costs.[6]

Serotonin type 3 receptor antagonists (5-HT_3RA) have been shown to be effective for the prevention of PONV. In 2003, the American Society of Anesthesiologists (ASA) Task Force on Postanesthetic Care issued a set of practice guidelines that included recommendations for prophylaxis and treatment of PONV.[7] The guidelines recommended selective utilization of 5-HT_3RA intraoperatively along with other anti-emetics such as droperidol or dexamethasone for the prevention and treatment of PONV.[7,8] Currently, there are three 5-HT_3RA available in the United States with FDA-approved indications for PONV: dolasetron (Anzemet, Abbott Laboratories, Abbott Park, IL), granisetron (Kytril, Roche Pharmaceuticals, Nutley, NJ), and ondansetron (Zofran, GlaxoSmithKline, Philadelphia, PA). The studies used to gain FDA-approval of granisetron for PONV used dosing recommendations similar to those given to patients for chemotherapy-induced nausea and vomiting (CINV). Lower doses of dolasetron,[9,10] ondansetron,[11,12] and granisetron[13] than is required for CINV have been reported to be effective in PONV. However, in studies evaluating 0.1 mg of granisetron, the 5-HT_3RA was not administered at the optimal time (prior to anesthesia emergence) for efficacy to be evaluated. A comparison of the effectiveness of low-dose granisetron and high-dose dolasetron and ondansetron for the prevention of PONV has not been evaluated concurrently in a randomized, double-blind study.

The purpose of this study was to evaluate low-dose granisetron (0.1 mg) compared to standard doses of ondansetron and dolasetron for the efficacy in the prevention of PONV. A secondary objective to the study was to evaluate the safety profile of granisetron, ondansetron, and dolasetron for the prevention of PONV.

METHODS

This study was conducted at a free-standing 140-bed women's hospital, Baptist Memorial Hospital (BMH)–Women's in Memphis, TN. This facility provides obstetrical, breast, and gynecologic services to more than 9,000 patients per year, with more than 200 hysterectomies and abdominal laparo-

Table 1. Patient Demographics and Type of Surgery

	Dolasetron	Granisetron	Ondansetron	*P*-value
Number of subjects (194)	66	62	66	
Age, years (mean ± SD)	44 ± 14	47 ± 16	44 ± 15	0.38
Adjunct therapy prescribed (n=58)	29%	36%	34%	0.6
Type of surgery (%)				0.94
Breast (n=21)	33%	38%	29%	
Lap (n=37)	30%	38%	32%	
TAH (n=55)	35%	31%	35%	
Other* (n=80)	36%	28%	36%	

*Myomectomy
LAP=laparoscopic abdominal procedure
TAH= total abdominal hysterectomy

scopic surgeries performed here each month. Approximately 10% of the pharmacy's medication budget is for the 5-HT_3RA class. This project was conducted as a cost-containment, hospital-initiated internal-performance improvement project with data collection conducted under a medication use evaluation protocol. Individual patient consent was waived by the hospital's Institutional Review Board. However, because the results may be of interest to other clinicians, the project received expedited Investigational Review Board approval for publication.

All inpatient females undergoing gynecological or breast (mastectomy or augmentation) surgery at BMH-Women's were evaluated preoperatively for PONV prophylaxis. Criteria for PONV prophylaxis included having two or more risk factors of developing PONV including female sex, abdominal or gynecological procedure, non-smoker, procedure duration greater than two hours, or previous PONV or motion sickness history. Exclusion criteria included allergy to 5-HT_3RA drugs or previous intolerance, pregnant patients, and age less than 18 years. As an adjunct to PONV prevention, all patients were fitted and educated pre-operatively on the use of a ReliefBand (Woodside Biomedical, Carlsbad, CA) a wrist stimulator of the P6 nerve for prevention of nausea.[14]

The patients were randomly allocated to one of three groups. Each group received either dolasetron 12.5 mg, ondansetron 4 mg, or granisetron 0.1 mg administered at the approximate midpoint to end of the surgical procedure. Anesthesiologists, surgeons, and nurses were blinded to the choice of study medication. Granisetron and dolasetron were diluted to a final volume identical to ondansetron (2 mL) to maintain blinding. All study medications were prepared in the Women's Department of Pharmacy by a pharmacy technician and staff pharmacist who were not involved with the study design, randomization, or data analysis. Type of anesthesia was not controlled in this study but was most commonly induced and maintained with fentanyl, propofol, lidocaine, midazolam, and isoflurane.

The incidence and severity of PONV during the first 24 hours postoperatively was recorded prospectively by a review of the patient medical records, automated dispensing machine records, and pharmacy records. Data collected included patient demographics, medication administration timing, type of procedure preformed, medications administered, PACU time, and nausea and vomiting episodes that required res-

Table 2. Treatment failure for patients given dolasetron, granisetron or ondansetron.

Type of failure (number failed)	Dolasetron	Granisetron	Ondansetron	*P*-value
Total failures % (82)	48%	39%	39%	0.45
Early failure (0-6h postoperatively) (53)	33%	23%	26%	0.37
Late failure (6-24h postoperatively) (46)	26%	24%	28%	0.9

Failures were defined as patients requiring anti-emetic rescue.
17 patients experienced a treatment failure in both the early and late postoperative period.

cue. Incidence of PONV was recorded at 0-6 hours and 6-24 hours postoperatively. PONV was defined as emesis or nausea requiring rescue anti-emetic medication administered postoperatively.

Statistical Analysis

The study was designed so that each group enrolled a minimum of 60 patients to be able to demonstrate a 20% difference between the groups with 90% power assuming a 50% incidence rate of PONV in this patient population. Patient demographics were compared using analysis of variance or chi-square test. The number of patients that experienced PONV in the three groups was compared by chi-square test. A *P*-value <0.05 was considered significant.

RESULTS

One hundred and ninety-four patients were randomized to receive dolasetron 12.5 mg, ondansetron 4 mg, or granisetron 0.1 mg. The baseline demographics and surgical procedure did not differ between study groups (Table 1). All patients were females with a mean age of 44 years (range, 18-78).

Incidence of PONV was similar between all study groups (range, 39-48%; *P*=0.45). PONV was highest (range, 23-33%) in the early postoperative period (0-6 hours) compared to the late postoperative period (range, 24-28%) but did not differ between the groups at the early or late postoperative period (*P*>0.2 for both study periods). In the 0-6 hour time period, 33% of dolasetron, 23% of granisetron, and 26% of ondansetron patients experienced PONV and required rescue therapy. At 6-24 hours postoperatively, 26% of dolasetron, 24% granisetron, and 28% ondansetron experienced PONV (Table 2). For patients who required rescue, the time to therapy did not differ between study groups. Multimodal therapy (5-HT_3 RA administered concomitantly with dexamethasone, promethazine, or droperidol) was administered to 30% of patients in the study but did not differ significantly between the study groups (26% of dolasetron, 34% of granisetron, 30% ondansetron). In patients who received multimodal therapy, the majority of patients received dexamethasone (81%), followed by promethazine (7%), or droperidol (12%).

Five adverse events were reported among patients who received dolasetron compared to no reports in the granisetron or ondansetron groups (*P*<0.05). In the dolasetron group, four events were postoperative crying and dysphoria and one event of sustained coughing and possible bronchospasm. None of these patients received droperidol. The events were reviewed by the hospital's Adverse Drug Event Committee and classified as probable and non-life-threatening secondary to dolasetron. No deaths occurred during the study. There were no reported clinically significant alterations in laboratory values secondary to the study medications. Compared to 4 mg ondansetron,

utilizing granisetron 0.1 mg doses which the pharmacy mixed from MDV (multi-dose vials) saved the hospital $10.01 per dose or approximately $45,000 yearly at the time the study. Now, using the new pre-mixed formulation from the manufacturer, the hospital would save $7.23 per dose.

DISCUSSION

The important finding from this study is that low-dose granisetron was as effective in the prevention of PONV when compared to standard doses of dolasetron or ondansetron in female patients undergoing gynecological and breast surgical procedures. Utilizing pharmacy costs of the products, the equivalent efficacy was also at a decreased cost. Treatment was well tolerated in each group. Five of 62 patients (8.1%) in the dolasetron group reported non-life-threatening adverse events compared to no reported events for the granisetron and ondansetron groups.

Complete response rates in this study were similar or slightly lower to previously published studies of the 5-HT_3RA class (~50%).[15-17] In the first trial done with granisetron 0.1 mg, the complete response rate was 45% as compared to 63% with 1 mg granisetron given 5 minutes prior to induction.[17] In a later trial, giving 5 mcg/kg (total dose ~0.3 mg) immediately after induction, improved the success rate to 70%.[13] D'Angelo et al demonstrated a comparable complete response rate using granisetron 0.1 mg, 0.2 mg, and 0.3 mg with efficacy >90%.[15] Rates of PONV in our study were lower than previously reported possibly due to the addition of the ReliefB and, a non-pharmacological method for PONV prevention. Previous studies have shown this therapy to be 10-30% effective at preventing moderate to severe nausea secondary to surgery.[14]

We found a significant increased incidence (7.7%) of adverse drug events in the dolasetron group that was higher than previously reported.[16,18] No other medication-related side effects were reported in the other groups. Although we did not directly measure the Q-Tc interval in the study patients, we do not feel this would affect our results since the prolongation is dose-dependent at doses higher than utilized for the treatment and prevention of PONV.[19] Any cardiac changes would have been detected in the PACU because all patients received full cardiac monitoring for an average of 90-120 minutes.

The study has several limitations. First, the study did not control for the anesthetic agent being administered during surgery. Approximately 80% of the patients received the same anesthetic agents, however there was variation in the selection of reversal agents and inhaled gases that could have increased the risk of PONV. The only statistical difference identified was a higher frequency of patients in the granisetron group received glycopyrrolate than in the other groups. No other significant differences were found between groups with anesthetics, sedatives, or paralytics. Although 5-HT_3RA administration was recommended prior to emergence from anesthesia, considerable variations in time of administration occurred, ranging from the commencement of anesthesia to emergence. Finally, specific conditions that may increase the incidence of PONV (eg, smoking status, menstrual cycle, etc) were not assessed. However, the patients in this study were all at high risk of experiencing nausea and vomiting postoperatively: they were all females having abdominal or breast procedures who received both general anesthesia and opioids postoperatively. In most studies, having three or more risk factors is sufficient to treat patients as high risk. We do not feel that having more information on conditions increas-

ing the likelihood of PONV for these patients would have altered our results.

Other agents (dexamethasone, droperidol, scopolamine patches, prochlorperazine, metoclopramide, and promethazine) have also been utilized for PONV. These agents have demonstrated equal efficacy at less expense than the 5-HT_3RA class in some studies.[20] Multimodal therapy with two or more anti-emetics has shown to be effective in patients with a greater than 30% risk of experiencing PONV.[20-23] Patients at highest risk may benefit from three-drug (droperidol plus dexamethasone plus 5-HT_3RA) prophylaxis as recommended by the ASA Consensus Guidelines.[7]

CONCLUSION

Randomized studies comparing dolasetron and ondansetron have demonstrated equal efficacy.[7] However, recently granisetron has been utilized at a lower-than-approved dosage for PONV prophylaxis in the United States.[15] Our study increases the evidence of the effectiveness of granisetron 0.1 mg as compared to dolasetron 12.5 mg and ondansetron 4 mg in PONV prophylaxis. The effectiveness of granisetron in PONV prophylaxis provides a new cost-efficient agent to our present armament of 5-HT_3RAs. To our knowledge, no other randomized, blinded studies have been published comparing the safety and efficacy of granisetron 0.1 mg, dolasetron 12.5 mg, and ondansetron 4 mg in female patients undergoing gynecological and breast procedures.

All three of the 5-HT_3RAs currently available in the United States are effective and safe for the prevention of PONV. Low-dose granisetron was shown to be equally effective as comparator agents with no toxicity in female patients at high risk for PONV. Low-dose granisetron should be considered as a cost-effective therapy to prevent PONV in high-risk patients.

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