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Retrospective Cohort Study of Granisetron Administration for PONV Prophylaxis and Treatment

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Abstract

Postoperative nausea and vomiting (PONV) frequently complicates surgical recovery and is considered to be one of the least desirable surgical side effects. Granisetron *(Kytril)* 1 mg intravenously (IV) was approved by the FDA for the prevention and treatment of PONV in August 2002.

Objective: This cohort study evaluated outcomes and utilization associated with granisetron use for PONV prevention and treatment.

Methods: This was a retrospective cohort study of 400 patient records from 10 US hospitals. Patients included were those greater than or equal to 18 years of age having elective surgery under general anesthesia with granisetron administered IV for prevention or treatment of PONV. Excluded were those with concurrent radiation or chemotherapy, or those observed less than 2 hours in the post anesthesia care unit.

Results: Mean age was 50 y ± 17 with 272 females (68%). The majority was at moderate-high (n = 230; 58%) or mild-moderate risk of PONV (n = 155; 39%). Granisetron was administered predominantly perioperatively, and at 0.1 mg dose (n = 382; 96%) from prefilled syringes extemporaneously prepared from 4 mg/4 mL vials. Total control (absence of nausea and vomiting) was experienced in 330 patients (83%), with 16 (4%) having a vomiting episode. In 167 patients at lower risk of PONV, symptoms were prevented in 148 (less than 90%). Regression analysis indicates that, in addition to absence of key risk factors, combination antiemetic prophylaxis was highly associated with optimal outcome. Granisetron dose did not impact outcome.

Conclusion: The majority of granisetron use for PONV was prophylactic, administered perioperatively at a 0.1 mg dose. Most patients experienced excellent control, even in the highest risk groups, particularly when granisetron was administered in combination with dexamethasone or metoclopramide.

Key Words — PONV; perioperatively; prophylaxis

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Postoperative nausea and vomiting (PONV) are undesirable symptoms experienced by surgical patients undergoing anesthesia or sedation.[1,2] The onset of PONV can produce great physical distress for patients and provoke unanticipated hospitalizations which negates the cost savings of ambulatory treatment.[2] In an era where 60% of surgical procedures are performed on an outpatient basis, the availability of a potent and cost effective antiemetic is necessary to make continuous improvements in the quality of patient care.[3]

Several unrelated risk factors have been shown to provoke PONV in the recovering surgical patient. One study defined four predictive factors for PONV: female gender, history of PONV or motion sickness, nonsmoking, and the use of postoperative opioids. With the presence of none, one, two, three, or all four of these risk factors, the incidence of PONV increased respectively from 10%, 21%, 39%, 61%, and 79%.[4] A study of postoperative surgical patients, performed by Marcio et al, identified vomiting as the most undesirable low morbidity outcome, ahead of gagging on the tracheal tube and incisional pain.[5] The physical consequences of vomiting, in addition to inconveniencing the patient, can cause bleeding, infection, wound dehiscence, and

aspiration pneumonia.[6] Intractable vomiting can also have detrimental metabolic effects such as hypokalemia, hypochloremia, hyponatremic metabolic alkalosis, and dehydration. It has been estimated that 0.18% of all surgery patients experience intractable vomiting.[7] These postanesthesia complications can lead to prolonged recovery room discharge and possible hospital admission.[7]

Antiemetic medication is used commonly for the treatment and prophylaxis of PONV.[7] The target for many antiemetic drugs includes receptors of the area postrema, the nucleus of the solitary tract and the chemoreceptor trigger zone.[7,8] These areas are located in close proximity to the vomiting center of the central nervous system midbrain.[7,8] These receptors receive stimuli from the periphery via afferent vagal and glossopharyngeal nerves and direct stimulation from the central cerebellum resulting in stimulation of the vomiting center.[7,9] This area, also known as the emetic center, ultimately coordinates the complicated act of vomiting. Specific blockage of serotonin subtype 3 (5-HT_3) receptors, predominantly in the area postrema, has been shown to be effective at reducing nausea and vomiting when given either as treatment or prophylaxis of PONV.[7,8] In addition to effectiveness, the low occurrence of adverse side effects has placed (5-HT_3) receptor antagonists at the front line of defense against PONV.[8,10,11]

The ideal approach to prophylaxis and treatment remains a debatable issue. The FDA began approving the use of the current class of serotonin 5-HT_3 receptor antagonists during the 1990s for use in PONV prevention and treatment.[8] This class includes dolasetron mesylate, granisetron hydrochloride, and ondansetron hydrochloride.[12] The contention exists between the incidence of PONV and the relationship between cost and effectiveness of the drugs used for prophylaxis.[10,13] With an increasing national focus on the rising costs of health care, the administration of expensive prophylactic drugs is being scrutinized.[13] The objective of this study was to examine the use of granisetron in actual clinical practice to determine dosing and risk-adjusted outcome.

MATERIALS AND METHODS

This is a retrospective cohort study of 400 randomly selected patients treated in 10 US hospitals with the objective of describing the use of and outcomes associated with patients receiving granisetron for PONV prevention. Sites were selected for participation based on having granisetron on formulary and reporting intravenous (IV) use for PONV prevention. Patients included were 18 years or older, recipients of elective inpatient or outpatient surgery under general anesthesia between November 2002 and March 2004, and were administered granisetron IV for PONV prevention and/or treatment. Patients were excluded if they were undergoing concurrent radiation or chemotherapy, or if they were observed in the hospital/surgery center for less than 2 hours postoperatively prior to discharge from the postanesthesia care unit or hospital surgical center. Institutional Review Board reviews were determined at each site based upon local regulation; two sites obtained full review and eight sites received exemption.

Data was abstracted by trained pharmacists, anesthesiologists, and/ or nurses at each site from randomly selected medical records totaling 40 contributed patients per site. Sample size was determined using the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) standards for the performance of drug use evaluations (DUE) which are: (a) if the average number of cases per quarter is more than 600, at least 5% of cases are reviewed; and (b) if the average number of cases per quarter is less than 600, at least 30 cases are reviewed. Surveys of sites indicated that they performed an average of 800 procedures per quarter, so 40 cases per site were selected.

Common data collection forms and data dictionaries were used at all sites, and data collectors received detailed instruction on record abstraction prior to initiation of data collection. All collected records were examined for collection errors and inconsistencies. Queries were clarified with sites prior to data entry into SPSS v12. Overall, 410 records were randomly selected for inclusion. Of these, 10 were excluded based upon chart review revealing either no general anesthesia administered or documentation of less than 2 hours in the hospital postanesthesia care unit.

Risk of PONV was determined using criteria published by Gan et al[1] (See Figure 1). Each patient was assessed for presence or absence of patient-specific risk factors for PONV (ie, female gender, history of PONV, history of motion sickness, non-smoker, and postoperative opioid use). Surgical factors encompassing type of procedure were also examined for each patient and a risk score was calculated for each individual patient.

Granisetron prophylaxis was defined as planned administration of granisetron given either pre- or perioperatively. Antiemetic rescue

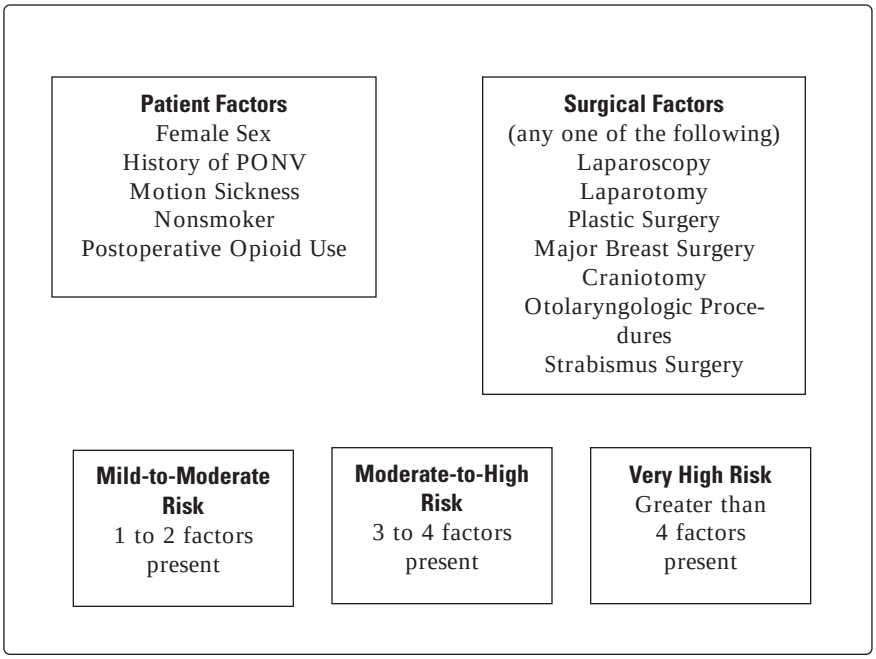

Figure 1. PONV risk stratification[2]

Adapted from Gan et al. *JAMA*. 2002;287:1233–1235

was defined as antiemetic administered in response to PONV following failed prophylaxis. Preoperative antiemetic administration was defined as granisetron administration prior to anesthesia induction; perioperative includes antiemetic administered following anesthesia induction, but prior to reversal of anesthesia; postoperative administration was defined as the time following anesthesia reversal. Successful outcome was determined as the incidence of total antiemetic control. Total control was defined as the absence of nausea and vomiting within the 0 to 6 hour postoperative measurement period.

In addition to clinical data collection on eligible patients, each site participated in a short survey of antiemetic practices. Sites were queried on their use of antiemetic prophylaxis, presence of guidelines for selection, dosing, and administration of antiemetics, preparation of granisetron for administration, and formulary issues surrounding antiemetic use.

Statistical Analysis

Descriptive analysis was performed to examine the risk characteristics and outcomes of these patients. Univariate analyses were utilized based on the preliminary descriptive statistics. The relationship between patient factors such as gender, history of PONV or motion sickness, nonsmoker, postoperative opioid use, as well as several particular surgical procedures and PONV were examined by either Student-t test, χ^2 test, or Fisher exact test based on the nature of variables. Logistic regression analyses were used to identify and quantify the strength of significant predictors of PONV in patients receiving granisetron prophylaxis.

RESULTS

Survey Results

None of the sites included reported having formal clinical guidelines for 5-HT_3 use for PONV prophylaxis. However, five of the 10 sites had embarked on internal DUE-type studies and/or physician education in an effort to begin developing internal guidelines for antiemetic use. Of the 10 sites that were included, nine reported that granisetron, dolasetron, and ondansetron were each available on formulary for PONV prophylactic use, whereas at one site, granisetron was the sole 5-HT_3 agent on formulary. Nine of the 10 sites indicated that the 5-HT_3 class was used for treatment and/or rescue in response to PONV, in addition to prevention. Six of 10 sites reported using granisetron exclusively in combination with other classes of antiemetics, particularly dexamethasone and metoclopramide. The remaining four sites indicated that use of mono vs combination antiemetic therapy was at the discretion of the anesthesiologist. Regarding medication dispensing, the survey results indicated that nine of the 10 sites either utilize the Pyxis system of dispensing or instead operate a satellite pharmacy in the Operating Room area. Since granisetron was not available in unit dose vials of 0.1 mg, the sites utilized the 4 mL multiple dose vial of granisetron that yields 40 doses of the drug when administered at a 0.1 mg dose. The extemporaneous preparation of granisetron prefilled syringes was typically prepared by a pharmacy technician in either the satellite or main pharmacy. The prefilled syringes were prepared by drawing up the contents of the 4 mg/4 mL

Table 1. Demographics, Patient, and Surgery-Specific PONV Risk Factors

	Total Population n = 400
Mean age (range)	50 (18 to 96)
Female – n (%)	272 (68)
Male – n (%)	128 (32)
Mean weight – kg (range)	81.9 (40.5 to 181.8)
Inpatient – n (%)	223 (55.8)
Outpatient – n (%)	177 (44.3)
Received granisetron prophylaxis - n (%)	399 (greater than 99)
Received granisetron treatment without prophylaxis – n (%)	1 (less than 1)
Patient-specific risk factors - n (%)	
Non-smoker	308 (77)
History of PONV	23 (5.8)
History of motion sickness	6 (1.5)
Postoperative opioids	291 (72.8)
Surgical risk factors - n (%)	
Laparotomy	91 (22.8)
Laparoscopy	64 (16)
Otolaryngologic procedure	17 (4.3)
Major breast surgery	11 (2.8)
Plastic surgery	4 (1)
Strabismus	2 (0.5)
Craniotomy	2 (0.5)

multidose vial. The entire contents of the vial were drawn up taking into account any potential overfill. A sufficient quantity of normal saline was added to yield a final volume of 80 mL. The mixture was divided into 40 doses of 0.1 mg/2 mL using a 5 mL syringe. Alternatively, granisetron prefilled syringes were created by adding the entire contents of a 4 mg/4 mL multidose vial to a sufficient quantity of normal saline to yield a final volume of 40 mL. This mixture was divided into 40 doses of 0.1 mg/mL using a 3 mL syringe. All prefilled syringes were prepared, labeled, stored, distributed and dated, as per individual state law and the individual Pharmacy Department's policies and procedures which included procedures and requirements for compounding sterile preparations as outlined in USP-NF <797> pharmaceutical compounding of sterile preparations.[14] The medication was administered IVP by the anesthesiologist in the operating suite. The expiration dates ranged from 14 to 30 days. Seven of 10 sites reported full utilization of the prefilled syringes with minimal waste due to expiration reported in three sites.

Clinical Outcomes

The mean age of patients was 50 ± 17 with 272 females (68%) and 128 males (32%). Of the total, 223 (56%) were inpatients, and the remaining 177 (44%) were outpatients. The most frequently identified patient-specific risk factors for PONV were female gender, non-smoker, followed by postoperative opioid use. Surgical-specific risk factors included 191 (48%) procedures with documented increased risk of PONV with the majority of 155 (39%) represented by laparotomy/laparoscopy (see Table 1). Of the total, 307 (77%) had propofol induction and 119 (30%) received nitrous oxide. Most patients (n = 318; 80%) received intraoperative opioids and 82 (21%) underwent neuromuscular blockade. The majority (n = 233; 58%) was at moderate-high, or mild-to-moderate risk of PONV (n = 157; 39%). Five patients (1%) were at very high risk, and the remainder had no documented patient or surgical-specific risk factors.

Granisetron was administered predominantly during the perioperative period (n = 372; 93%). One patient was administered granisetron only as rescue after failing his non-granisetron prophylaxis regime. Thus, he was excluded from analysis with the outcomes related to granisetron prophylaxis. Granisetron was administered at a dose of 0.1 mg, nearly exclusively (n = 382; 96%). The remaining 17 (4%) patients received either 0.2 or 0.3 mg. There were differences in incidence of PONV risk factors among the dose groups. The patients administered greater than 0.1 mg appeared more likely to have a past history of PONV with five of 17 (30%) reporting prior episodes, compared with 18 of 382 (5%) ($P < 0.05$) in the lower dose group. Higher dose patients were more likely to be female (n = 15; 88%) than lower dose (n = 256; 67%) ($P < 0.05$). The patients that received 0.2 or 0.3 mg tended to be heavier patients with a mean weight of 93.3 vs 81.4 kg in the lower dose group and also received postoperative opioids more frequently 17 of 17 (100%) compared to 273 of 382 (71%) ($P <$

Table 2. Symptom Outcomes per PONV Risk Studies

	No Risk Factors (n = 7) n (%)	*Mild-Moderate Risk (n = 157) n (%)*	*Moderate-High Risk (n = 230) n (%)*	*Very High Risk (n = 5) n (%)*	*All Patients (n = 399)* n (%)*
Total control	6 (85.7)	142 (90.4)	179 (77.8)	3 (60)	330 (82.7)
Nausea	1 (14.3)	15 (9.6)	51 (22.2)	2 (40)	69 (17.3)
Emesis	0	4 (2.5)	11 (4.8)	1 (20)	16 (4)
Nausea onset 0 to 2 hours	1 (14.3)	14 (8.9)	45 (19.6)	0	62 (15.5)
Emesis onset 0 to 2 hours	0	4 (2.5)	8 (3.4)	2 (40)	12 (3)
Nausea onset 2 to 6 hours	0	1 (0.1)	6 (2.6)	0	7 (1.8)
Emesis onset 2 to 6 hours	0	0	3 (1.3)	1 (20)	4 (1)
Rescue administered	1 (14.3)	15 (9.6)	49 (21.3)	2 (40)	67 (16.8)

*Excludes one patient who received granisetron as rescue therapy only

0.05).

When granisetron was administered perioperatively, it was given 45 minutes (range 0 to 240 minutes) prior to anesthesia reversal. In the patients administered granisetron during the preoperative period, the dose was administered 19 minutes (range 2 to 75 minutes) prior to anesthesia induction. Granisetron was administered on average 38 (±42) minutes prior to the end of anesthesia. The mean time under anesthesia was 116 minutes (range 15 to 450 minutes). Granisetron was administered as monotherapy in 155 patients (40%) or in combination with either dexamethasone (n = 115; 29%) or metoclopramide (n = 135; 33%), most commonly. Selection of mono vs combination therapy was independent of patient or surgical-specific risk factors. Specifically, mono patients were 70% female (n = 108) compared to 67% (n = 163) of combination patients. Also, mono patients were non-smokers 73% (n = 113) vs 79% (n = 194) of combination patients. Mono patients received postoperative opioids 71% of the time (n = 110) compared with 74% (n = 180) of combination patients, and 59% (n = 92) were at moderate-high to very high-risk of PONV compared with 75% (n = 146) of combination patients, respectively. None of these differences were statistically significant.

Total control of PONV symptoms occurred in 330 (83%) of all granisetron prophylaxis patients. This ranged from a low of 60% in very high-risk patients to a high of 90% in mild-to-moderate risk patients (see Table 2). Most nausea, when it occurred, had an onset within 2 hours after the surgical procedure and each affected patient experienced 1.4 nausea episodes on average (range 1 to 4 episodes). Only 16 people (4%) had a vomiting episode postoperatively and emesis, when it occurred, was documented primarily in the highest risk groups. Each patient that vomited experienced an average of 1.6 emetic episodes (range 1 to 4 episodes). Only 2.5% of patients in the lowest two risk groups experienced emetic events. In the 164 prophylaxis patients at lowest risk for PONV, all symptoms were absent in 148 patients representing greater than 90% of the patient population. In the highest two risk groups, total control of emetic symptoms was demonstrated in 182 of 235 (77%) patients (see Table 2). Total control was higher in the patients receiving the lower (0.1 mg) dose of granisetron with 319 of 382 (84%) having total control, vs 11 of 17 (65%) in the 0.2 to 0.3 mg group. Total control was also documented more frequently in patients receiving combination therapy with 217 of 244 (89%) of combination patients experiencing no symptoms, compared with 113 of 155 (73%) of monotherapy patients. Rescue antiemetic was administered in 67 (17%) patients with incidence increasing with increase PONV risk (see Table 2). Administering granisetron 0 to 15 minutes prior to the end of anesthesia had no significant impact on PONV symptoms compared to those administered earlier (17% vs 18%, respectively). Only 13 patients (3%) had discharge delayed due to PONV symptoms and there were no unplanned hospital admissions of outpatient surgery patients due to PONV symptoms.

To further examine the rela-

Table 3. Effect of Risk Factors and Granisetron Use on the Development of PONV: Logistic Regression Model*

	Odds Ratio	*P-value*	*95% CI*	
			Lower	*Upper*
Postoperative opioids	2.8	< 0.05	1.2	6.3
Anesthesia duration greater than 90 minutes	2.7	< 0.01	1.5	5
Female gender	2.1	< 0.05	0.4	5.5
High risk surgery	1.9	< 0.05	1.1	3.4
Granisetron 0.1 mg dose	1.7	NS	0.5	5.8
Weight greater than 75 kg	1.3	NS	0.7	2.4
History PONV or motion sickness	1.2	NS	0.4	3.5
Non-smoker	0.6	NS	0.3	1
Combination antiemetic prophylaxis	0.3	< 0.001	0.2	0.5

*Includes constant

tionship between granisetron use, particularly dose and mono vs combination therapy, and risk factors, a logistic regression model was utilized. Parameters likely to increase PONV risk including female gender, high-risk procedures, postoperative opioid use, history of PONV or motion sickness, anesthesia time, weight, and smoking status were entered into a model with granisetron dose and mono vs combination therapy. The model was used to predict incidence of any PONV in the postoperative period. Results are contained in Table 3. Use of postoperative opioids, anesthesia time of greater than 90 minutes, female gender, and surgical-specific factors were each highly associated with increased risk of PONV in our patient sample. Use of granisetron in combination with other antiemetic agents demonstrated a significant protective effect. Lower dose of granisetron, history of PONV, smoking status, and weight had no significant effect on the development of PONV symptoms when controlling for other potential predictors. The model was also run with the addition of age; however, age did not have a significant impact on the model.

DISCUSSION AND CONCLUSIONS

This study documents the first multicenter drug use evaluation of granisetron for management of PONV. Perhaps the most significant finding of this study is that granisetron at lower than FDA-approved dosage appeared to prevent the incidence and onset of PONV. Our findings suggest that granisetron hydrochloride is effective at lower doses. Our data suggests that granisetron, used in conjunction with a prudent assessment of a patient's risk factors, may provide hospitals with a direct, low-dose, low-cost alternative for the prophylaxis of PONV. However, prospective studies would be needed to confirm this finding.

Although limited by its retrospective study design, our results are consistent with prospective work that identifies patient and surgical-specific risk factors important to the development of PONV.[4,15–17] Overall, our incidence of reported PONV is lower than the reported 20% to 30% range in recent literature.[9] Our data supports recent studies indicating the multifactorial origin of PONV, with aggravating factors associated with the type of surgery and the nature of the underlying disease.[9] Consistent with the literature, females in our data set, particularly in the presence of a high-risk surgical procedure, were more than twice as likely to develop PONV.[6,18] There was insufficient prevalence of PONV history or history of motion sickness to determine the impact on outcome, if any. Other surgical procedures noted to increase the risk of PONV include gynecologic, ophthalmologic, and otolaryngologic. Duration of anesthesia independent of surgical procedure and use of postoperative opioids were also significantly associated with PONV in our patients consistent with previous studies.[19,20]

Noteworthy among our patient group is that receiving granisetron in combination with another antiemetic agent had a significant protective effect indepen-

dent of risk and patient-specific factors.[21] As the onset of PONV originates from several different receptors, this observation likely represents the attenuation of parallel stimuli. In a recent randomized double-blinded study of high-risk female gynecological surgery patients, researchers demonstrated the increased effectiveness of granisetron and dexamethasone combination therapy for PONV prophylaxis. At doses of granisetron (40 mcg/kg) and dexamethasone (8 mg), this combination achieved the highest incidence of total control (96%).[22] It appears from our data that the addition of dexamethasone or metoclopramide to granisetron improved patient outcomes significantly. However, this study was not designed to examine combination therapy. In particular, we were limited by sample size in determining if addition of one agent vs another further enhanced patient outcome. This is a topic for future investigation.

Our study concludes that granisetron at low doses is effective in preventing PONV in patients at risk due to patient and surgical-specific factors; however, further study is recommended. Nausea and emesis were prevented in three of four patients in even the highest risk groups indicating that patients with high-risk surgical procedures combined with many risk factors can benefit from granisetron administration. Results were even more impressive when granisetron was combined with either dexamethasone or metoclopramide.

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