MECLIZINE IN COMBINATION WITH ONDANSETRON FOR PREVENTION OF POSTOPERATIVE NAUSEA AND VOMITING IN A HIGH-RISK POPULATION

LT Carrie M. Forrester, CRNA, MS, NC, USN
LT Dennis A. Benfield, Jr, CRNA, MS, NC, USN
Portsmouth, Virginia

LT Christina E. Matern, CRNA, MS, NC, USN
San Diego, California

CDR Joseph A. Kelly, CRNA, MS, NC, USN
Jacksonville, Florida

CAPT Joseph E. Pellegrini, CRNA, DNSc, DNP, NC, USN
Bethesda, Maryland

Postoperative nausea and vomiting (PONV) is prevalent in surgical patients with known risk factors: general anesthesia, female, nonsmoker, motion sickness history, and PONV history. Common treatment involves ondansetron; however, the effects are short-lived, and supplemental medication may be required. Meclizine, a long-acting drug with a low side-effect profile, may be ideal in combination with ondansetron for at-risk patients.

We randomized 77 subjects scheduled for general anesthesia and screened for 4 of 5 PONV risk factors for experimental or control group assignment. Severity of PONV was measured using a 0 to 10 verbal numeric rating scale (VNRS). Other measured variables included time to onset and incidence of PONV and total antiemetic requirements.

No significant differences in demographics (excluding weight), surgical or anesthesia time, analgesic requirements, or nausea incidence in the postanesthesia care unit (PACU) and same-day surgery unit were noted. The meclizine group had lower VNRS scores in the PACU at 15 (P = .013) and 45 (P = .006) minutes following rescue treatment. The incidence of nausea was lower in the meclizine vs placebo group (10% vs 29%) following discharge (P = .038).

Prophylactic meclizine resulted in lower incidence and severity of PONV in a high-risk population, especially after rescue treatment.

Key words: Meclizine, motion sickness, postoperative nausea and vomiting (PONV).

The incidence of PONV in a general anesthesia surgical population ranges from 20% to 30%, resulting in higher overall institutional and patient costs and lower patient satisfaction.1-6 The risk of PONV increases even further when certain risk factors are present. These risk factors include general anesthesia, female gender, nonsmoker, history of PONV, and history of motion sickness.1,2,7-9 In fact, it has been noted that the incidence of PONV increases exponentially from 17% when no risk factors are present to as high as 87% when all 5 risk factors are present.2,8 Therefore, it is imperative that anesthesia providers investigate methods to decrease the overall incidence of PONV, especially when some or all of these risk factors are present.

Postoperative nausea and vomiting has a multifactorial pathogenesis with activation of target receptors in the chemoreceptor trigger zone (CTZ) and afferent impulses relayed to the vestibular center.3 Activation of dopamine, opioid, cholinergic, histamine, and serotonin receptors in the CTZ have traditionally been antagonized with unimodal antiemetic therapy with drugs such as droperidol, scopolamine, metoclopramide, dimenhydrinate, cyclizine, and ondansetron.1,3,5,10-14

Many of these antiemetics, although effective, commonly result in undesirable side effects or increased cost.3,5,6,10,11,15-23 Sensitization of the vestibular system also results in a higher incidence of motion-induced PONV.3,24 Studies suggest that motion during the early postoperative period predisposes patients to PONV, especially patients with a known history of motion sickness.2,25

Current PONV management focuses on combination antiemetic therapy to antagonize different receptors in the CTZ.1,3,10,14 Ondansetron, a 5-HT3 serotonin receptor antagonist, is commonly used in multimodal therapy because it is highly effective with minimal side effects; however, it is expensive.21-23 Histamine H1 receptor antagonists block receptor sites in the CTZ and the vestibular pathways, addressing 2 factors in the pathogenesis of PONV.3,5 To our knowledge, meclizine, a histamine H1 receptor antagonist and anti–motion sickness medication, has never been studied for the prevention of PONV. However, 1 study...
demonstrated that meclizine was significantly effective for the prevention of nausea and vomiting in a high-risk population undergoing an emergency contraceptive regimen.26

Meclizine is inexpensive and has a long duration of action with few side effects.20,23 The over-the-counter availability of meclizine would allow patients at high risk for PONV easy access to medication for the prevention of PONV. The purpose of this study was to compare use of a multimodal approach combining meclizine and ondansetron with a unimodal approach using a placebo and ondansetron for the prevention of PONV in a high-risk population.

Methods
A convenience sample of 84 patients scheduled for elective surgery under general anesthesia were enrolled in this prospective, randomized, double-blind, parallel groups, institutional review board–approved study. Inclusion criteria included patients who consented for surgery under general anesthesia scheduled for 60 minutes or longer, ASA physical classification I or II, age 18 to 65 years, English language proficiency, and the presence of 4 of 5 risk factors for PONV (general anesthesia, female gender, nonsmoker, history of motion sickness, and history of PONV). Exclusion criteria included contraindications to receiving general anesthesia, history of sensitivity to ondansetron or meclizine, antiemetic use within 24 hours of surgery, pregnancy, gastroesophageal reflux disease, and obesity with a body mass index greater than 35%.

During the preanesthesia evaluation, a preoperative questionnaire was given to all adult patients to determine their potential eligibility for the study. This questionnaire specifically identified patients with 4 of 5 risk factors for PONV. During the preoperative interview, an information sheet also was provided to all patients that described the objectives and parameters of the study. Patients who met inclusion criteria were contacted to answer questions and verify their interest in participating in the study.

On the day of surgery, patients meeting inclusion criteria were approached, and formal written informed consent was obtained. The enrolled subjects then were randomly assigned by the pharmacy to 1 of 2 groups using a computer-generated random numbers process. Subjects were assigned to group 1 (meclizine and ondansetron) or group 2 (placebo and ondansetron). The pharmacist placed two 25-mg meclizine tablets (50 mg total) or 2 placebo tablets in an opaque brown plastic bag. The bag labeled “meclizine study drug” was given to one of the investigators. The opaque bag was used to ensure that the investigators were blinded to the study drug because a placebo with an appearance identical to that of meclizine was unavailable. Negative pregnancy test results were verified for all female subjects before study enrollment. Within 15 to 30 minutes before surgery, patients were given the “study drug” with no more than 2 ounces of water by a staff member. When taking the study drug, patients were asked to close their eyes so they would remain blinded to the physical characteristics of the pills. The staff member who administered the study medication preoperatively was not allowed to participate in the care of the patient postoperatively to maintain the integrity of the double-blind study.

In the preoperative holding area, subjects were assessed for a baseline level of nausea using the verbal numeric rating scale (VNRS). The ends of this 11-point horizontal scale are anchored with 0, indicating no nausea, and 10, indicating the worst nausea imaginable. Following informed consent for the general anesthetic, demographic data (age, height, weight, gender, ethnicity, ASA class), number of risk factors identified for PONV, and surgical procedure were recorded on a data collection tool. An intravenous (IV) catheter was inserted, and a lactated Ringer’s infusion was initiated. Preoperative anxiety was treated as needed with midazolam, 0 to 5 mg IV, and/or fentanyl, 0 to 5 µg/kg IV. Preoperative antibiotics were administered if ordered. Preoperative medications, demographics, and time of study drug administration were documented on a preoperative data collection sheet. Anesthesia providers were restricted from giving any other antiemetic medications preoperatively.

On arrival in the operating room, routine monitors were placed and baseline vital signs recorded. General anesthesia was induced with fentanyl, 0 to 5 µg/kg IV; lidocaine, 0 to 1 mg/kg IV; and propofol, 1 to 2 mg/kg IV. Tracheal intubation was facilitated with a muscle relaxant of choice. Providers also were allowed to use a laryngeal mask airway. Maintenance of anesthesia was accomplished with oxygen, 50%; isoflurane, 0.5% to 1.5%; sevoflurane, 1.0% to 3.0%; or desflurane, 3.0% to 8.0%, in combination with air at 50% or nitrous oxide at 50%. No restrictions were placed on intraoperative narcotic or nonopioid analgesic use after induction. Approximately 15 to 30 minutes before the end of the surgical procedure, ondansetron, 4 mg IV, was administered to both groups. Neuromuscular blockade was antagonized, as needed, using neostigmine, 0.05 mg/kg IV, and glycopyrrolate, 0.01 mg/kg IV. After endotracheal extubation or laryngeal...
mask airway removal, subjects were transported to the postanesthesia care unit (PACU). On an intraoperative data collection sheet, anesthesia providers recorded all intraoperative medications, total surgical time, total anesthesia time, and total fluid intake and output. The nature of the surgery (laparoscopic vs open) and the use of orogastric tubes also were recorded.

On arrival in the PACU, the data collection tools were delivered to the PACU personnel, who were also blinded to the treatment group. Data collection responsibilities were reviewed with the PACU staff. These responsibilities included obtaining admission and discharge VNRS scores for nausea and recording on a data collection sheet. In addition, PACU personnel were instructed to record any subject complaint of nausea and obtain VNRS scores for nausea immediately before instructed to record any subject complaint of nausea and obtain VNRS scores for nausea immediately before any antiemetic administration and every 15 minutes thereafter on these subjects until complete resolution of the PONV or discharge from the PACU to the same-day surgery unit (SDSU). All subjects had standardized orders written for treatment of PONV in the PACU using the following sequencing order: ondansetron, 4 mg IV, for the first complaint of nausea; metoclopramide, 10 to 20 mg IV, if nausea was unresolved 15 minutes following ondansetron administration, and the dose could be repeated in 30 minutes for persistent nausea; and promethazine, 12.5 to 25 mg IV, if nausea persists 15 to 30 minutes after the first or second administration of metoclopramide. The timing and doses of antiemetics administered to treat PONV were noted and recorded on a data collection sheet. All episodes of emesis in the PACU were noted and recorded on a data collection sheet. Once PACU discharge criteria were met, a discharge Aldrete score was recorded, and all subjects were discharged to the SDSU.

On arrival in the SDSU, an admission VNRS for PONV was obtained by blinded SDSU personnel who were familiar with data collection responsibilities. The VNRS score assessments were the same as used by PACU personnel. On request, antiemetic medications were administered according to the surgeon’s postoperative orders. The VNRS scores were obtained and recorded every 15 minutes after administration of rescue antiemetic medications until resolution of the complaint or discharge. Medications administered for analgesia in the SDSU also were noted and recorded on the data collection sheet. All subjects were discharged from the SDSU to home once discharge criteria were met. Identical data was collected for subjects whose surgery required an overnight admission to the inpatient surgical unit. The reason for overnight admission was noted and recorded.

Approximately 24 hours after discharge, all subjects were contacted by one of the investigators via telephone or personal visit (if on the inpatient surgical ward) to complete data collection. Before discharge, subjects had been given a tool to record their incidence and severity of nausea while at home using the same VNRS method. During the interview, subjects were asked to report the incidence and severity of PONV they may have experienced at home. A tool also was used to assess each subject’s overall satisfaction with the surgical experience, anesthesia experience, and overall control of their nausea and vomiting. Subjects were asked to rate their satisfaction according to the following scale: 0, dissatisfied; 1, somewhat dissatisfied; 2, somewhat satisfied; 3, satisfied; or 4, very satisfied.

Before initiation of this study, a Fisher exact test power analysis was calculated based on the following assumptions: (1) The incidence of nausea is 74% with 4 risk factors present. (2) The incidence is decreased to approximately 35% by using ondansetron. (3) The incidence of nausea can be decreased further to approximately 10% by combining meclizine and ondansetron. By using an \( \alpha \) of .05 and a \( \beta \) of .2 \((1 - \beta = .8)\), it was determined that a sample size of 42 subjects per group was needed, for a total of 84 subjects. This sample size was calculated to allow for a 10% attrition rate. Demographic data and incidence of nausea between the 2 groups was compared using \( \chi^2 \) analysis. A Student \( t \) test was used to analyze the difference between mean VNRS scores. Satisfaction scores were analyzed by using the Mann Whitney \( U \) test. A \( P \) value of less than .05 was considered significant.

**Results**

A total of 84 subjects were enrolled, but 7 were removed from the study because of breaches in protocol or a change in anesthetic management, leaving a total of 77 subjects (group 1, 39; group 2, 38) for the study. With the exception of patient weight, there were no significant differences in relation to demographic variables, including surgical time, anesthesia time, smoking history, or history of motion sickness or PONV between groups (Table). No differences in side effects were noted between groups. Also, there were no significant differences in the amount of any anesthetic agent or narcotic administered between groups.

There were no significant differences in VNRS scores for nausea at any time except following rescue treatment. The VNRS scores were significantly lower in group 1 following rescue treatment in the PACU, achieving statistical significance at 15 minutes \((P = .013)\) and 45 minutes \((P = .015)\) following treatment (Figure 1).
No significant differences were noted in time from placebo or meclizine administration to first complaint of nausea between groups in the PACU or SDSU, but a significant difference was noted following discharge to home. The mean ± SD time from placebo or meclizine administration to first reported nausea event at home was 428 ± 107 minutes in group 2 compared with 737.2 ± 303 minutes in group 1 (\(P = .008\)) (Figure 2).

When the overall incidence of nausea was analyzed, no differences were noted between the groups in the PACU and SDSU. However, a difference was noted following discharge to home. Of group 1 subjects, 4 (10%) reported at least 1 nausea event following dis-
charge, compared with 11 (29%) of group 2 subjects ($P = .038$) (Figure 3). The incidence of vomiting was similar between groups at all interval measurements in the hospital and following discharge to home.

**Discussion**

In this study, the combination of preoperative oral meclizine with intraoperative ondansetron significantly improved the subject’s response to rescue antiemetics, allowed for a longer nausea-free period postoperatively, and decreased the incidence of nausea postdischarge compared with placebo and ondansetron. No significant differences in side effects were noted between groups.

To our knowledge, this study is the first to evaluate meclizine’s effectiveness in preventing nausea and vomiting in a perioperative setting. Previous studies have demonstrated the success of meclizine in the management of motion sickness and vertigo. A review of the literature revealed 1 study that used meclizine in the prevention of nausea and vomiting unrelated to a perioperative scenario. Raymond et al compared oral meclizine with placebo for the prevention of nausea and vomiting in females receiving the Yuzpe emergency contraceptive regimen. This regimen, composed of 100 µg of ethinyl estradiol and 500 µg of levonorgestrel, is known to produce an incidence of nausea and vomiting at rates as high as 42% and 16%, respectively. In this high-risk population, pretreatment with meclizine significantly decreased the incidence of nausea by 17%.

A comparable high-risk population was obtained for our study based on preoperative screening for 4 of 5 risk factors known to contribute to PONV. Current research has identified that female gender, nonsmoking status, history of PONV, history of motion sickness, and general anesthesia are true risk factors for PONV. In this study, all subjects had 4 of 5 of these risk factors; therefore, all subjects had a 74% to 87% chance of experiencing a postoperative nausea event. Based on our inclusion criteria, subjects in our study had a baseline risk for nausea nearly double that of subjects in the Yuzpe study.

With the exception of subject weight, no significant differences were noted in relation to demographic and independent variables (see Table). Although group 2 averaged approximately 8.4 kg more in weight than group 1, we do not believe that this small difference in weight contributed significantly to our results because body mass index has failed to independently predict PONV.

Histamine $H_1$ receptor antagonists, such as meclizine, cyclizine, and dimenhydrinate, block histamine receptor sites in the CTZ and cholinergic receptor sites in vestibular pathways, addressing 2 factors in the pathogenesis of PONV. These drugs have minimal side effects, including drowsiness and dry mouth. Recent studies investigating dimenhydrinate have shown approximately 40% effectiveness for preventing PONV and even compare favorably with the efficacy of ondansetron. Cyclizine, an antihistamine that is not available in the United States, was equally as effective as ondansetron in reducing PONV by approximately 50% compared with placebo.

Although there are medications that can antagonize each individual receptor in the CTZ, there is no single drug available that can block all receptors, and research has focused on the use of combination antiemetic therapy to reduce the incidence of PONV. Ahmed et al studied the effects of the antihistamine cyclizine in combination with ondansetron and found that the incidence of vomiting was less than 5% compared with approximately 50% in the group receiving placebo. In our study, we determined that the administration of meclizine in combination with ondansetron for the prevention of PONV in a high-risk population had significant benefit during the postoperative period in the hospital and in the home environment. A statistically significant decrease in VNRS scores in group 1 was noted at 15 and 45 minutes after the initial complaint of nausea and subsequent rescue antiemetic therapy in the PACU, with a decrease in the VNRS score to zero at the 45-minute interval (see Figure 1). This finding could be attributed to the action of meclizine in conjunction with the subsequent administration and action of rescue
antiemetics at the CTZ and vestibular apparatus. Group 2 did not benefit from the meclizine drug effect at the CTZ and vestibular apparatus.

A statistically significant difference also was noted between the groups in the time to first nausea event after discharge from the hospital. The time from administration of the placebo or meclizine preoperatively until the first reported nausea event after discharge from the hospital was significantly shorter in group 2 compared with group 1 (see Figure 2). This longer nausea-free period in group 1 could be related to the short half-life of ondansetron, 3.5 hours, whereas the half-life of meclizine is 6 hours. Meclizine also has a duration of action extending up to 24 hours. As the antiemetic effect of the ondansetron subsided, group 1 subjects may have benefited from the continued action of meclizine, whereas group 2 subjects did not receive this advantage. The continued action of meclizine into the home environment may, therefore, be responsible for the prolonged nausea-free period at home.

A statistically significant difference also was noted between groups in the incidence of nausea events occurring in the home environment. Subjects in group 1 experienced a 19% lower incidence of nausea episodes in the home environment than group 2 (see Figure 3). The postdischarge period inherently involves increased motion such as ambulation, wheelchair transport, and motor vehicle transport. The lower incidence of nausea episodes in the home environment for group 1 also may be attributed to its anti–motion sickness properties at the vestibular center and its prolonged duration of action. Patients in group 2, who did not benefit from the anti–motion sickness properties of meclizine, were more prone to nausea episodes at home.

Limitations of this study include a relatively small sample and possible variance of bioavailability of meclizine between patients. Our convenience sample of 77 subjects obtained from 1 institution may limit the ability to extrapolate the study results to a larger population. Also, because meclizine is available only in an oral preparation, bioavailability could vary greatly between patients, and some practitioners may find it inconvenient to administer an oral medication in the immediate preoperative setting. However, a recently published study also has corroborated that an oral preoperative antihistamine can be successfully used in multimodal prophylaxis for PONV. Turner et al found that a single dose of oral dimenhydrinate in combination with droperidol significantly reduced the treatment failure for vomiting in comparison with droperidol alone in outpatient gynecological laparoscopy. Further study is needed to evaluate the effectiveness of meclizine for the prevention of PONV in a larger sample. It also may be practical to conduct further studies on meclizine in a standardized surgical population (eg, gynecological laparoscopy). The onset of action of meclizine is 60 minutes, with peak plasma concentrations achieved in approximately 3 hours. In this study, meclizine was administered a mean ± SD of 47.8 ± 21.5 minutes before induction of general anesthesia and 155.4 ± 54.8 minutes before arrival in the PACU postoperatively. However, despite the administration of meclizine within the noted 60-minute onset of action time frame before arrival in PACU, VNRS scores at the first complaint of nausea in the PACU were similar between groups. With possible variance of oral drug bioavailability between patients, it may be beneficial to administer meclizine 3 hours before induction of anesthesia to ensure that peak plasma levels have been achieved before any nausea-stimulating medications or procedures are initiated. The prolonged duration of action of meclizine ensures that earlier preoperative administration of the medication will not significantly impact length of nausea relief postoperatively. Additional studies are needed to elucidate the optimal timing of preoperative meclizine administration.

Conclusion

In this study, we determined that the administration of meclizine in combination with ondansetron for the prevention of PONV in a high-risk population had significant effects during the postoperative period in the hospital and home environment. Postoperative nausea and vomiting persists as the most common complaint following general anesthesia, in part because of the remarkable growth in outpatient surgery and emphasis on early mobilization and discharge. Because managing PONV can be challenging and costly, it is imperative that patients who may be at high risk for PONV be identified preoperatively. For patients at high risk for PONV, multimodal therapy is the mainstay of treatment using double and even triple antiemetic combinations. The antihistamine meclizine may give providers a long-acting alternative for the prevention of PONV in high-risk patients. Based on the results of our study, we conclude that the low cost, minimal side-effect profile, and efficacy in PONV prevention may make meclizine an ideal agent to administer in combination with ondansetron to prevent PONV.

REFERENCES