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Is Aprepitant Effective in Preventing Postoperative Nausea and Vomiting?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not aprepitant is effective in preventing postoperative nausea and vomiting.

STUDY DESIGN: Review of three English language primary randomized controlled trials from 2012-2014.

DATA SOURCES: Three double-blind, randomized controlled trials comparing oral aprepitant with placebo. All articles were found using PubMed.

OUTCOMES MEASURED: The three studies measured nausea severity using a verbal rating system and number of episodes of nausea and vomiting recorded by a blinded study investigator.

RESULTS: Vallejo et al found that 29.7% of the patients in the placebo group vomited compared to 9.3% of the patients who received aprepitant ($p = 0.003$). They also found that the worst VRS nausea score was a 5 out of 10 in the group of patients who received aprepitant versus 8 out of 10 for the placebo group ($p = 0.014$). Jung et al found that the groups that received aprepitant had a 35% incidence of nausea compared to 63% in the placebo group ($p = 0.0025$). In addition, the aprepitant groups both had 0% incidence of vomiting compared to the placebo group, which had a 20% incidence ($p = 0.005$). Sinha et al found that incidence of vomiting at 72 hours was 3.1% in the experimental group and 15.0% in the placebo group ($p = 0.021$). In all of the studies, mean VRS nausea scores were lower but were not found to be statistically significant.

CONCLUSIONS: Aprepitant is effective in preventing incidence of nausea and vomiting, but is not found to significantly decrease average nausea rating scores.

KEY WORDS: Postoperative nausea and vomiting, aprepitant

INTRODUCTION

Postoperative nausea and vomiting (PONV) is one of the most common complications after undergoing surgery with general anesthesia¹. Symptoms can range from mild nausea to multiple episodes of severe vomiting. This can be distressing to patients and may result in electrolyte imbalances, dehydration, and hypovolemia². Extensive retching and vomiting can also lead to other severe complications such as aspiration, gastric bleeding, and wound hematomas³. In addition, PONV can delay oral intake of drugs, fluids, and food⁴.

Studies have shown that PONV negatively impacts quality of life, and results in delayed recovery after surgery⁴. This can lead to prolonged stay in the post-anesthesia care unit (PACU) or even hospital admission. Prolonged hospital stays only add to the already expensive cost of surgery, as well as being distressing to the patient and increasing morbidity⁵. A single episode of nausea and/or vomiting costs about \$22 in addition to the extra costs associated with a longer hospital stay.

PONV can affect up to 30% of patients undergoing general anesthesia, and this number can reach up to 80% if the patient has risk factors such as female gender, opioid use, or non-smoking status¹. In addition, longer duration of anesthesia also increases risk of PONV⁶.

It is thought that the cause of PONV is multifactorial. Two of the main causes include opioid induced emesis and inhalational anesthesia induced emesis⁴. There are many neurotransmitters involved in this process such as 5-HT, dopamine, and neurokinin-1 (NK1)⁴. These neurotransmitters have receptors in the chemoreceptor

trigger zone in the brain, and imbalances can result in nausea and vomiting in the postoperative period⁴.

Antiemetic medications are used before or during surgery to prevent PONV. The serotonin receptor antagonist ondansetron is most commonly used. Histamine receptor antagonists including dimenhydrinate and promethazine and dopamine receptor antagonists including metoclopramide are also used. Dexamethasone, a corticosteroid, is less commonly used but can also be successful. Non-medical treatment includes acupuncture⁶. While these agents are all effective, there is not one medication that works universally for all patients¹.

A new class of antiemetics, NK1 receptor antagonists, has emerged in recent years and has been used in preventing nausea and vomiting both in postoperative as well as chemotherapy patients. They work by blocking substance P from binding at the NK1 receptors in the dorsal vagal complex and area postrema, which are both central emetic pathways⁷. Aprepitant is currently the only NK1 receptor antagonist on the market and currently it is mostly being used for chemotherapy-induced nausea and vomiting. It has a half life of 9 to 12 hours, which makes it longer acting than the more commonly used serotonin receptor antagonists⁸. Adverse effects are mild and may include fatigue, diarrhea, or dizziness⁹.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not aprepitant is effective in preventing postoperative nausea and vomiting.

METHODS

This paper evaluates three double blind randomized control trials comparing efficacy of aprepitant as a medication for improving nausea and vomiting in patients postoperatively. All three studies were chosen using the same criteria. The population included patients that have undergone surgery with general anesthesia and the interventions included 40, 80, or 125 mg of oral aprepitant. All three studies used patients who had at least 2 of the following risk factors for PONV: female gender, nonsmoker, history of motion sickness or previous PONV, and use of postoperative opioids. The treatment group receiving aprepitant was compared an experimental group which received a placebo. The outcomes measured were the effect of aprepitant on the incidence of nausea and vomiting as well as the effect of aprepitant on the severity of nausea. Finally, all three trials were randomized, double blind clinical trials.

All articles were written in English and published in peer reviewed journals. They were selected from Pubmed in 2015 by the author using the keywords “aprepitant” and “postoperative nausea and vomiting.” The articles were chosen based on relevance and that the outcomes of the studies were patient oriented (POEMs). Inclusion criteria included randomized, double blind controlled trials with patients over the age of 18 and exclusion criteria included articles published before 1996 and patients that did not undergo general anesthesia. All articles were published between 2012 and 2014 and have similar demographics and characteristics (Table 1). The statistics reported or used in the studies were control event rate (CER) and experimental event rate (EER), relative risk reduction (RRR), absolute risk reduction (ARR), number needed to treat (NNT), odds ratio (OR), and p-value.

Table 1. Demographics & Characteristics of included studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Vallejo (2012) ¹	Double blind RCT	150	18-65 years	Patients 18-65 years with American Society of Anesthesiology (ASA) 1 to III status who are considered high risk for PONV and were undergoing ambulatory plastic surgery under general anesthesia for at least 1-hour	Patient refusal, received other antiemetics before procedure, history of allergy or sensitivity to study drugs, pregnancy, history of chronic opioid use	1	40 mg of oral aprepitant plus 4 mg of IV ondansetron or oral placebo plus 4 mg of IV ondansetron
Jung (2013) ⁷	Double blind RCT	123	21-60 years	Patients 21-60 years considered high risk for PONV scheduled for elective laparoscopic total hysterectomy with ASA I to II status	Liver, neurologic, and active pulmonary disease, cardiac arrhythmia, allergies to any perioperative medications used in the study	0	Preoperative 80 mg oral aprepitant; pre Operative 125 mg oral aprepitant; or placebo (10 mL saline)
Sinha (2014) ⁸	Double blind RCT	125	18 years or older	Patients over 18 years considered high risk for PONV who are morbidly obese and undergoing elective gastrointestinal surgery with ASA I to III status	Allergy to ondansetron or aprepitant, pregnant or breastfeeding, substance abuse or significant psychiatric disease, history of chronic nausea/vomiting, taking any medication with known antiemetic properties or known interaction with study drugs	1	80 mg oral aprepitant and 4 mg ondansetron or placebo tablet and 4 mg ondansetron

OUTCOMES MEASURED

All three studies measured the severity of nausea as well as the incidence of nausea and vomiting. Severity of nausea was measured by the patient using a verbal rating scale (VRS) where 0 represented no nausea and 10 represented worst possible nausea. Incidence of nausea and vomiting was measured by a blinded study investigator. In the study by Vallejo et al, patients also recorded incidence of nausea and vomiting at home once they were discharged from the hospital¹. All of the studies considered patients to have a complete response if they had no nausea, retching, or vomiting during the postoperative period.

RESULTS

Vallejo et al enrolled 150 patients between the ages of 18 and 65 with American Society of Anesthesiology (ASA) I to III status who were undergoing plastic surgery with general anesthesia and had 2 or more risk factors for PONV¹. Exclusion criteria included patient refusal, receiving other antiemetics before procedure, history of allergy or sensitivity to study drugs, pregnancy, and history of chronic opioid use. Patients either received 40 mg of oral aprepitant plus 4 mg of intravenous ondansetron or oral placebo plus 4 mg intravenous ondansetron. The aprepitant or placebo was administered within 2 hours before the procedure, and the ondansetron was administered at the start of anesthesia. One patient was lost to follow up after discharge, but their results in the hospital were still included in analysis. Patients rated their nausea severity every 4 hours for the first 24 hours after surgery, and then every 8 hours the second 24 hours. Occurrence of vomiting was recorded hourly until discharge. Intention-to-treat analysis

was performed. They found that 29.7% of the patients in the placebo group vomited compared to 9.3% of the patients who received aprepitant ($p = 0.003$) with a risk reduction of 31.3% (95% CI, 14.3-69.0%) In addition, they found that all of the episodes of vomiting occurred in the first 12 hours after surgery. They also found that the worst VRS nausea score, defined as the highest score reported by the patient in the 48 hours, was a 5 out of 10 in the group of patients who received aprepitant versus 8 out of 10 for the placebo group ($p = 0.014$). The mean VRS nausea scores were also higher in the placebo group, however it was not significant ($p = 0.24$). Complete response occurred in 26 patients in the experimental group and 20 patients in the control group but this was also not significant ($p=0.288$)¹.

Statistical analysis of incidence of vomiting for all three RCTs can be found in table 2. For the study conducted by Vallejo et al, relative risk reduction (RRR) was found to be -69.0%, and absolute risk reduction (ARR) was found to be -20.4%. Number needed to treat (NNT) was calculated to be -4. This means that for every 4 patients treated with aprepitant, one fewer patient vomited than if they had received the placebo.

Jung et al selected patients age 21-65 years with ASA status I or II undergoing elective laparoscopic total hysterectomy⁷. Patients were also considered high risk for PONV, using the same criteria as Vallejo et al. Exclusion criteria included liver, neurologic, and active pulmonary disease, cardiac arrhythmia, and allergies to any perioperative medications used in the study. Patients were randomly divided into three groups of 40 and either received 80 mg aprepitant, 125 mg aprepitant, or 10 mL normal saline as placebo. The aprepitant or placebo was administered 2 hours before anesthesia. Patients were assessed at 2 hours, 24 hours, and 48 hours, and any episodes of nausea and

vomiting were recorded throughout that time period. Both of the groups that received aprepitant had a 35% incidence of nausea compared to 63% in the placebo group ($p = 0.0025$). In addition, the aprepitant groups both had 0% incidence of vomiting compared to the placebo group, which had a 20% incidence ($p = 0.005$). The difference between the 80 mg and 125 mg aprepitant groups was not significant. The peak VRS nausea scores were 6 out of 10 for the placebo group, and 4 out of 10 in both aprepitant groups, but this data is not statistically significant. Complete response during the first 48 hours after surgery was seen in 28% of the control group, 56% of the 80 mg aprepitant group, and 63% of the 125 mg aprepitant group. Both 80 mg and 125 mg aprepitant groups were found to be significantly higher than the control group ($p = 0.007$ and $p = 0.004$ respectively)⁷.

For the study conducted by Jung et al, RRR was found to be -100.0%, and ARR was found to be -20.0%. NNT was calculated to be -5. This means that for every 5 patients treated with aprepitant, one fewer patient vomited than if they had received the placebo.

Jung et al also recorded the incidence of adverse effects. Patients in all three groups reported adverse effects including dizziness, headache, dyspepsia, and abdominal distension. The symptoms were all mild and no patients required additional treatment. There was no statistical significance of incidence of adverse effects between control and experimental groups⁷.

Sinha et al enrolled 125 patients aged 18 years or above, were morbidly obese, ASA status I to III, and considered high risk for PONV⁸. Exclusion criteria included allergy to ondansetron or aprepitant, pregnant or breastfeeding, substance abuse or

significant psychiatric disease, history of chronic nausea/vomiting, and taking any medication with known antiemetic properties or known interaction with study drugs. One patient was lost from the placebo group during surgery. Patients either received 80 mg oral aprepitant and 4 mg IV ondansetron or placebo tablet and 4 mg IV ondansetron. The aprepitant tablet or placebo tablet was administered 1 hour before surgery, and IV ondansetron was administered to every patient just before the end of surgery. Nausea severity scores were recorded during the postoperative period at 3 minutes, 1, 2, 6, 24, 48, and 72 hours. Any episode of vomiting was also recorded. Incidence of vomiting at 72 hours was 3.1% in the group that received aprepitant, which was significantly lower than the placebo group which had an incidence of 15.0% ($p = 0.021$, 95% CI, 5.67-24.30%). The odds ratio (OR) of an episode of vomiting in the control group compared to the experimental group was 5.47 times ($p = 0.026$, 95% CI, 1.31-26.46). The results for mean VRS nausea scores were not statistically significant. Complete response was seen in 27 patients (42.18%) in the experimental group and in 22 patients (36.67%) in the control group, but this was also not statistically significant ($p = 0.510$)⁸.

For the study conducted by Sinha et al, RRR was found to be -79.3%, and ARR was found to be -11.9%. NNT was calculated to be -8. This means that for every 8 patients treated with aprepitant, one fewer patient vomited than if they had received the placebo.

Table 2. Statistical Analysis of Oral Aprepitant vs. Placebo Effect on Incidence of Vomiting

Study	Control Event Rate (CER)	Experimental Event Rate (EER)	Relative Risk Reduction (RRR)	Absolute risk reduction (ARR)	Number Needed to Treat (NNT)
Vallejo et al (2012) ¹	29.7%	9.3%	-69.0%	-20.4%	-4
Jung et al (2013) ⁷	20.0%	0.0%	-100%	-20%	-5
Sinha et al (2014)	15.0%	3.1%	-79.3%	-11.9%	-8

DISCUSSION

All three studies showed a significant decrease in the incidence of postoperative vomiting with oral aprepitant compared to placebo. In addition, Jung et al also showed a significant decrease in the incidence of nausea with aprepitant. Peak nausea rating score was significantly higher as reported by Vallejo et al, although the other studies failed to get significant results. Mean VRS nausea scores appeared to decrease with aprepitant, but none of the studies had statistically significant results.

The main limitation of the use of aprepitant is the cost. Since it is a newer drug, it is substantially more expensive than the older, more commonly used agents. Vallejo et al reported that the cost of aprepitant at their institution was \$46.60 compared to \$0.60 for ondansetron¹. While aprepitant is considerably more costly than ondansetron, it must be considered that an extended hospital stay and extra care required for patients with severe nausea and vomiting postoperatively could incur an even higher cost. Patients would likely be willing to pay the extra cost of aprepitant to avoid the potential complications

that can result from extensive episodes of vomiting and extra costs associated with a longer stay at the hospital.

There are also some limitations of the studies themselves. Vallejo et al reports that a limitation of their study was the timing of the administration of ondansetron¹. Previous studies show that ondansetron is most effective when given near the end of surgery¹. In this study, the ondansetron was given at the beginning of surgery to account for the variation in surgery duration between patients¹. Jung et al did not study doses of aprepitant less than 80 mg⁷. In addition, they did not calculate a cost-effectiveness analysis⁷. Finally, Sinha et al reports that they did not compare opioid between the control and experimental groups⁸. Since opioids increase risk of nausea and vomiting, this could have affected the results.

CONCLUSION

Based on this systematic review of three randomized controlled trials, aprepitant is effective in preventing the incidence of nausea and vomiting; however it is not shown to be significantly effective in reducing the severity of nausea if it occurs. Even though the cost may present a problem for some patients, aprepitant has the potential to reduce postoperative complications from excessive vomiting and lead to shorter hospital stays. This not only reduces overall cost, but could also improve quality of life in patients during the postoperative period. Future studies should be focused toward comparing aprepitant to the commonly used antiemetics for PONV such as ondansetron or metoclopramide. In addition, it would be also advantageous to investigate the use of

aprepitant for other causes of nausea and vomiting since it is effective and has mild adverse effects.

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