The role of neurokinin-1 (substance P) antagonists in the prevention of postoperative nausea and vomiting

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Abstract

Postoperative nausea and vomiting (PONV) can be very debilitating for surgical patients, and effective management reduces potential morbidity, aiding in patient satisfaction, and minimizing the need for unintended hospital stays. Risk factors include female sex, nonsmoker, and having a previous history of motion sickness or PONV. Anesthetic risk factors include receiving opioids, not receiving a total intravenous anesthetic (TIVA), exposure to nitrous oxide, and extended length of anesthetic. Many treatments, including serotonin antagonists, dopamine antagonists, corticosteroids, inhaled isopropyl alcohol, and anticholinergics, as well as techniques such as TIVA, have been utilized over recent decades in an attempt to reduce PONV incidence. However, it remains a problem for a significant number of surgical patients. Aprepitant is a neurokinin-1 (substance P) antagonist, which exerts its effects via a final common pathway of the emetic centers after crossing the blood brain barrier. Aprepitant is commonly used in the cancer population to help prevent cancer chemotherapy-induced nausea and vomiting and has shown great promise in both acute and delayed phase PONV. Published data has shown improved efficacy when compared with ondansetron administered prior to surgery. The use of aprepitant in combination with other antiemetics potentially may help decrease unplanned hospital admissions and potentially, reduce costs associated with PONV.

Key words: Antiemetics, aprepitant, neurokinin-1 (substance P) antagonist, postoperative nausea and vomiting

Introduction

Postoperative nausea and vomiting (PONV) is one of the most common morbidities associated with anesthesiology. The incidence is about 30% on the 1st postoperative day.¹ Nausea occurs at an incidence of about 40-50% and vomiting 25-30% depending on surgical population studied.² Risk factors associated with PONV can be divided into patient factors, surgical factors, and anesthetic factors. Anesthetic causes of PONV in the post anesthesia care unit (PACU) are most commonly due to the use of postoperative opioids, nitrous oxide (N₂O), and volatile anesthetics. From the surgical standpoint, laparoscopic, gynecological surgery, and cholecystectomy are high risk and found to independently increase the risk for PONV.³⁴

Patient-related risk factors include female sex, nonsmokers, and having a previous history of motion sickness or PONV. Anesthetic risk factors include receiving opioids, not receiving a total intravenous anesthetic (TIVA), exposure to N₂O, and extended length of anesthetic. Nausea and vomiting can be very debilitating for some and when combined with pain from their procedure can make for a miserable experience for our patients. PONV is not only uncomfortable for patients but costly and affects patient satisfaction.⁵ Unexpected
hospital admissions due to PONV have decreased but are still estimated to occur approximately 0.5-2% of the time.\textsuperscript{[5,6]} It is, therefore, prudent that as anesthesiologists we identify those at an elevated risk and provide appropriate prophylaxis to all patients.

There are several antiemetic medications, agents, and techniques in use currently. Many treatments, including serotonin antagonists, dopamine antagonists, corticosteroids, inhaled isopropyl alcohol, and anticholinergics, as well as techniques such as TIVA have been utilized successfully over recent decades in an attempt to reduce PONV incidence. These therapies work mainly by interfering with neurotransmitter receptor signaling in the central nervous system (CNS) and gastrointestinal (GI) tract; however, none are universally effective.\textsuperscript{[2]} More options are becoming available. One such option is a relatively new agent aprepitant, which has been used on cancer patients receiving chemotherapy and has shown great effectiveness for PONV.

**Aprepitant and chemotherapy-induced nausea and vomiting**
As in the postoperative phase, nausea and vomiting is a major complication after chemotherapy. It is regarded as the most important complication by cancer patients.\textsuperscript{[7-9]} Chemotherapy-induced nausea and vomiting (CINV), reduces food intake, resulting in malnutrition, weight loss, reduced performance status which increases the incidence of hematoxicity.\textsuperscript{[10]} Without prevention, acute vomiting occurs in close to 100% of patients acutely, and about 70-90% patients in the delayed phase.\textsuperscript{[11,12]} Aprepitant is, therefore, primarily used in the setting of CINV. The most important effect of neurokinin 1 (NK-1)-receptor antagonists is that they are able to markedly prevent both acute and delayed emesis induced by cisplatin and other chemotherapies in humans. It seems to have particular efficacy in the delayed phase, making it advantageous compared to other antiemetics, as they seem to be only efficacious in the acute phase.\textsuperscript{[12,13]} According to guidelines of the American Society of Clinical Oncology, the dose for CINV is 125 mg prior to therapy, and then 80 mg on subsequent days.\textsuperscript{[14]} It is given routinely in combination with 5-HT3 receptor antagonists and dexamethasone.\textsuperscript{[15]}

**Aprepitant and postoperative nausea and vomiting**
Previous studies investigating the use of aprepitant for PONV have demonstrated results which are very promising. In a comparison prophylaxis study, ondansetron 4 mg IV and aprepitant 40 mg PO had similar effectiveness for the first 24 h. However, aprepitant was more effective in the subsequent 24- to 48-h postoperative time period,\textsuperscript{[16]} with an effect on vomiting greater than on nausea.

For those undergoing abdominal surgery under different anesthetic techniques, aprepitant 40 mg or 125 mg was found to be more effective than ondansetron 4 mg IV in reducing nausea and vomiting in first 48 h period.\textsuperscript{[17]} According to a study done by Lim et al., the rate of occurrence of PONV assessed 6 h after surgery was lower for patients who were administered with ondansetron and 125 mg of aprepitant compared to the group that was only administered ondansetron.\textsuperscript{[18]} There were also fewer patients who received rescue treatment in those who had received aprepitant 125 mg. The combination of aprepitant and ondansetron was found to significantly prolong the time to administration of the first rescue antiemetic drug compared with either drug alone, and almost completely prevented the occurrence of emesis.\textsuperscript{[19]} Table 1 outlines various studies comparing aprepitant and other NK-1 inhibitors to ondansetron and/or placebo.\textsuperscript{[20]}

**The neurokinin 1 inhibitor drug group**
In addition to aprepitant only, fosaprepitant and maropitant are in clinical use. Fosaprepitant is a water-soluble prodrug to aprepitant, used both in CINV and PONV. Maropitant is currently in use for motion sickness and vomiting in cats and dogs. According to a study done by Sedlacek et al., maropitant was effective in preventing vomiting caused by stimulation of either central or peripheral emetic pathways whereas the other drugs examined prevented vomiting caused by central (metoclopramide and chlorpromazine) or peripheral (ondansetron) stimulation but not both.\textsuperscript{[21]} Maropitant is still under investigation for use in humans. Other NK-1 receptor inhibitors include GR205171 (vofopitant, GlaxoSmithKline), CP-122721 (Pfizer), CJ-11974 (Pfizer), casopitant (GlaxoSmithKline), netupitant (Helsinn Healthcare), rolapitant or SCH 619734 (Schering-Plough), T 2328 (Mitsubishi Tanabe Pharma), and vestipitant (GlaxoSmithKline); however, they are still under investigation.\textsuperscript{[22]}

**Pharmacological properties**
Substance P, a member of the tachykinin family of bioactive peptides, is a neurotransmitter in the afferent pathway of the emetic reflex.\textsuperscript{[23]} The presence of substance P in regions of the brainstem involved in emesis in humans has been demonstrated.\textsuperscript{[24]} The NK-1 receptor is the preferential site of action of the neuropeptide substance P in regions of the brainstem believed to mediate the emesis reflex.\textsuperscript{[25-27]} Substance P is the natural ligand for the NK-1 receptor found to trigger its signaling and cause nausea and vomiting. NK-1 is widely expressed in the GI vagal afferents and brain areas involved in the vomiting reflex such as the nucleus solitary tract,\textsuperscript{[26-28]} the area postrema of the CNS, as well as in the peripheral nervous system.\textsuperscript{[19]}
### Table 1: Summarized outcomes of neurokinin-1 inhibitors versus Zofran or placebo studies

| Study                | Treatment Details | Time (h) | Nausea | Vomiting | Rescue drug | Time to first vomit (h) | Complete response | Author conclusions |
|----------------------|-------------------|----------|--------|----------|-------------|------------------------|-------------------|--------------------|
| Habib, 2011          | (A) 40 mg versus Z 4 mg | 0-24     | 27/51 versus 2/27 (P=0.0026) | 3/51 versus 11/53 (P=0.093) | 20/51 versus 14/51 (P=0.398) | 44.4±11.7 versus 14/51 (P=0.011) | N/A | N/A | 10 mg dexamethasone, (A) 40 mg was more effective than (Z) 4 mg in preventing postoperative vomiting but not the incidence of nausea or need for rescue. |
| Alonso-Damian, 2012  | (A) 80 mg versus (Z) 4 mg | 0-24     | 0/30 versus 0/30 (P=1) | 0/30 versus 1/30 (P=0.313) | N/A | N/A | N/A | (A) 80 mg produced better control in preventing PONV in patients undergoing open cholecystectomy compared with (Z) 4 mg. |
| Diemunsch, 2007      | (A) 125 mg versus (Z) 4 mg | 0-24     | Peak nausea scores were lower in both (A) groups compared with (Z) groups | 16/246 versus 24/246 (P<0.001) | 134/239 versus 113/239 (P=0.001) | 45.7±9.3 versus 43.4±12.2 (P=0.12) | 40 mg and 125 mg (A) were more effective than 4 mg (Z) for preventing vomiting at 24 and 48 h after open abdominal surgery. |
| Gan, 2007            | (A) 125 mg versus (Z) 4 mg | 0-24     | Peak nausea scores showed no difference among the groups | 16/239 versus 36/248 (P<0.001) | 136/248 versus 133/246 (P=0.001) | 43±12 versus 36.3±17.7 (P<0.001) | 40 mg and 125 mg of (A) were superior to 4 mg of (Z) for preventing vomiting in first 24 and 48 h, but not nausea control, the use of rescue drug or complete response. |
| Jung, 2013           | (A) 80 mg versus (A) 125 mg versus P | 0-24     | 14/40 versus 4/40 (P=0.07) | 0/40 versus 0/40 (P=0.05) | 3/40 versus 8/40 (P=0.05) | N/A | N/A | A 80 and 125 mg orally seemed to be promising as prophylactic antiemetics in patients with high susceptibility for PONV when administering opioid based IV PCA. No statistical significant difference in reduction in delayed PONV in 2-48 h except (A) 125 mg, 2-24 h postoperative. |
| Tsutsumi, 2014       | (F) 150 mg versus (O) 4 mg | 0-24     | 8/32 versus 12/32 (P=0.001) | 2/32 versus 8/32 (P<0.001) | 6/32 versus 23/32 (P=0.001) | 44.0±12.1 versus 23/32 (P=0.004) | (F) significantly prevented vomiting in the first 24 and 48 h after craniotomy compared to (O). However, (F) was not more effective in preventing nausea than (O). |
| Altorjay, 2011       | (C) 50 mg versus P | 0-24     | 20/233 versus 38/235 (P=0.013) | 24/233 versus 59/235 (P=0.001) | 60/233 versus 160/233 (P=0.001) | 44.0±12.1 versus 160/233 (P=0.013) | The combination of (C) 50 mg and (Z) 4 mg, superior only in preventing postoperative emesis. |

AP = Aprepitant, Fos = Fosaprepitant, Cos = Casopitant N/A = Not available, PONV = Postoperative nausea and vomiting, PCA = Patient-controlled analgesia
Aprepitant is a NK-1 receptor antagonist which is highly selective and centrally acting, with a half-life of 9.12 h.\textsuperscript{[28,29]} It has a bioavailability of 65%.\textsuperscript{[30]} Aprepitant has the chemical name 5-((2R, 3S)-2-[[1R]-1-[3,5-bis([trifluoromethyl]phenyl)ethoxy]-3-[4-fluorophenyl]-4 morpholinyl)methyl)-1,2-dihydro-3H-1,2,4-triazol-3-one. Aprepitant undergoes oxidation at the morpholine ring and its side chains, and it is metabolized primarily by CYP3A4 with minor metabolism by CYP1A2 and CYP2C19. It is also found to be a weak inhibitor of CYP2C19 and CYP2C9, a moderate inhibitor of CYP3A4 and an inducer of CYP2C9; therefore, there is potential for drug interactions.\textsuperscript{[30]} Aprepitant is eliminated mainly by excretion of metabolites in feces and urine.\textsuperscript{[31]}

**Aprepitant dosing, side effects, and cost**

Aprepitant, which is made in capsular form, is administered orally, 1-2 h preoperatively, for PONV prophylaxis.\textsuperscript{[2]} A typical dose is 40 mg, although doses up to 125 mg for PONV have been studied. Fosaprepitant, a pro-drug is available for intravenous administration, with a typical dose of 115 mg.\textsuperscript{[30]} Fosaprepitant, is only Food and Drug Administration approved for use in CINV although it has been shown to be more effective than ondansetron in reducing vomiting in gynecologic, neurological, and lower limb surgeries.\textsuperscript{[32-34]} Aprepitant is relatively safe; however, common side effects include dizziness, constipation, and hypotension, especially when used in the setting of PONV prophylaxis. In the setting of CINV prophylaxis, common side effects are fatigue, diarrhea, weakness, indigestion, abdominal pain, hiccups, leukopenia, dehydration and altered liver function tests, cough, and hiccups.\textsuperscript{[35]}

The cost of a 80 mg capsule is approximately US$100 and a 125 mg capsule is about US$110.\textsuperscript{[36]} There is no generic form available; so it is considerably costly compared to other antiemetics, such as ondansetron, which became generic in 2007.\textsuperscript{[31]}

**Conclusion**

Aprepitant, a NK-1 receptor antagonist, exerts its effects via a common pathway of the emetic centers after crossing the blood brain barrier. Aprepitant is a drug with limited side effect profile and works very efficiently for PONV. Dosed alone or in combination with other antiemetics, this medication has shown tremendous relief of symptoms and for a prolonged period of time. The novel drug has addressed both acute and delayed onset of nausea and vomiting, which is very useful in the postoperative population because it decreases the need for rescue doses later in the postoperative period. It should be noted that aprepitant has been found to be more effective than ondansetron at preventing PONV in the perioperative period.\textsuperscript{[37]}

The major drawback and limitation of aprepitant for its use is that it is expensive, making it difficult to justify its use outside of very severe symptoms or potential risk factors for nausea and vomiting. Hopefully, prices will become more competitive in the future and allow for the integration of this effective medication for everyday use of prophylaxis for PONV.

All classes of antiemetics, including aprepitant, have demonstrated efficacy for the treatment of nausea and vomiting. However, much of the data is contradictory given the complex multifactorial nature of PONV, and thus, no one agent is likely to prevent PONV in all patients. Ongoing and future large studies are warranted to best sort out the role for aprepitant vis-à-vis individual variables and best practice strategies in high-risk patients, which ultimately increase patient comfort, satisfaction, and minimize morbidity associated with extended PACU times and unplanned hospital stays.

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**Conflicts of interest**

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**References**

1. Green MS, Green P, Malayaman SN, Hepler M, Neubert LJ, Horrow JC. Randomized, double-blind comparison of oral aprepitant alone compared with aprepitant and transdermal scopolamine for prevention of postoperative nausea and vomiting. Br J Anaesth 2012;109:716-22.
2. Kovac AL. Update on the management of postoperative nausea and vomiting. Drugs 2013;73:1525-47.
3. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, et al. Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2014;118:85-113.
4. Hill RP, Lubarsky DA, Phillips-Bute B, Fortney JT, Creed MR, Glass PS, et al. Cost-effectiveness of prophylactic antiemetic therapy with ondansetron, droperidol, or placebo. Anesthesiology 2000;92: 958-67.
5. Gold BS, Kitz DS, Lecky JH, Neuhaus JM. Unanticipated admission to the hospital following ambulatory surgery. JAMA 1989;262:3008-10.
6. Blacoe DA, Cunning E, Bell G. Paediatric day-case surgery: An audit of unplanned hospital admission royal hospital for sick children, Glasgow. Anaesthesia 2008;63:610-5.
7. Hesketh PJ. Treatment of chemotherapy-induced emesis in the 1990s: Impact of the 5-HT3 receptor antagonists. Support Care Cancer 1994;2:286-92.
8. de Boer-Dennert M, de Wit R, Schmitz PI, Djontono J, Beurden VV, Stoter G, et al. Patient perceptions of the side-effects of chemotherapy: The influence of SHT3 antagonists. Br J Cancer 1997;76:1055-61.
9. Griffin AM, Butow PN, Coates AS, Childs AM, Ellis PM, Dunn SM, et al. On the receiving end. V: Patient perceptions of the side effects of cancer chemotherapy in 1993. Ann Oncol 1996;7:189-95.
10. Ando Y, Hayashi T, Ito K, Suzuki E, Mine N, Miyamoto A, et al. Comparison between 5-day aprepitant and single-dose fosaprepitant meglumine for preventing nausea and vomiting induced by cisplatin-based chemotherapy. Support Care Cancer 2016;24:871-8.
11. Hesketh PJ, Kris MG, Grunberg SM, Beck T, Hainsworth JD, Harker G, et al. Proposal for classifying the acute emeticity of cancer chemotherapy. J Clin Oncol 1997;15:103-9.
12. Tavolaro R, Hesketh PJ. Drug treatment of chemotherapy-induced delayed emesis. Drugs 1996;52:639-48.
13. Gralla RJ, Osoba D, Kris MG, Kirkbride P, Hesketh PJ, Chinnery LW, et al. Recommendations for the use of antiemetics: Evidence-based, clinical practice guidelines. American Society of Clinical Oncology. J Clin Oncol 1999;17:2971-94.
14. Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2011;29:4189-98.
15. Rozzi A, Lanzetta G. Editorial Comment to Palonosetron with aprepitant plus dexamethasone to prevent chemotherapy-induced nausea and vomiting during gemcitabine/cisplatin in urothelial cancer patients. Int J Urol 2015;22:915.
16. Wallenborn J, Kranke P. Palonosetron hydrochloride in the prevention and treatment of postoperative nausea and vomiting. Clin Med Insights Ther 2010;2:387-99.
17. Jung WS, Kim YB, Park HY, Choi WJ, Yang HS. Oral administration of aprepitant to prevent postoperative nausea in highly susceptible patients after gynecological laparoscopy. J Anesth 2013;27:396-401.
18. Lim CS, Ko YK, Kim YH, Park SI, Kim JK, Kim MJ, et al. Efficacy of the oral neurokinin-1 receptor antagonist aprepitant administered with ondansetron for the prevention of postoperative nausea and vomiting. Korean J Anesthesiol 2013;64:202-11.
19. DeMunsch P, Gan TJ, Philip BK, Girao MJ, Eberhart L, Irwin MG, et al. Single-dose aprepitant vs ondansetron for the prevention of postoperative nausea and vomiting: A randomized, double-blind phase III trial in patients undergoing open abdominal surgery. Br J Anaesth 2007;99:202-11.
20. Aapro MS, Walko CM. Aprepitant: Drug-drug interactions in perspective. Ann Oncol 2010;21:2316-23.
21. Emend® [Product Information], Whitehouse Station, New Jersey: Merck & Co., Inc.; August, 2014. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022023s011lbl.pdf. [Last Accessed on 2015 Oct 22].
22. Nakata N, Kume K, Hamaguchi E, Tsutsumi R, Mita N, Tanaka K, et al. The effects of intravenous fosaprepitant and ondansetron in the prevention of postoperative nausea and vomiting in patients who underwent lower limb surgery: A prospective, randomized, double-blind study. J Anesth 2015;29:836-41.
23. Soga T, Kume K, Nakata N, Hamaguchi E, Tsutsumi R, Kawanishi R, et al. Fosaprepitant versus ondansetron for the prevention of postoperative nausea and vomiting in patients who undergo gynecologic abdominal surgery with patient-controlled epidural analgesia: A prospective, randomized, double-blind study. J Anesth 2015;29:696-701.
24. Tsutsumi YM, Nakata N, Soga T, Kume K, Hamaguchi E, Tsutsumi R, et al. The effects of intravenous fosaprepitant and ondansetron for the prevention of postoperative nausea and vomiting in neurosurgery patients: A prospective, randomized, double-blind study. Biomed Res Int 2014;2014:307025.
25. Emend® [Patient Information], Whitehouse Station, New Jersey: Merck & Co., Inc.; December, 2015. Available from: http://www.merck.com/product/usa/pi_circulars/e/emend/emend_ppi.pdf. [Last Accessed on 2016 Jan 11].
26. Messori A. Treatment of postoperative nausea and vomiting. BMJ 2003;327:762-3.
27. DeMunsch P, Apfel C, Gan TJ, Candioti K, Philip BK, Chelly J, et al. Preventing postoperative nausea and vomiting: Post hoc analysis of pooled data from two randomized active-controlled trials of aprepitant. Curr Med Res Opin 2007;23:2559-65.