Review Article

Recent advances in pharmacotherapy of chemotherapy-induced nausea and vomiting

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Abstract

Nausea and vomiting remain among the most feared side effects of chemotherapy for cancer patients. Significant progress has been made in the last 15 years in developing more effective and better-tolerated measures to minimize chemotherapy-induced nausea and vomiting (CINV). During the 1990s, the selective 5-hydroxytryptamine receptor antagonists were first introduced for the treatment of CINV, and resulted in more effective and better tolerated treatment of CINV. Despite recent progress, however, a significant number of patients still develop CINV, particularly during the 2-5-day period (delayed emesis) following chemotherapy. There is evidence that this may be an underappreciated problem on the part of some caregivers. Recently, two new antiemetics, aprepitant, the first member of the neurokinin-1 antagonists, and palonosetron, a second-generation 5-hydroxytryptamine receptor antagonist, received regulatory approval in the U.S. Both represent useful additions to the therapeutic armamentarium for the management of CINV.

Key words: Antiemetics, cancer, chemotherapy, nausea, vomiting

INTRODUCTION

One of the frequently used treatment modalities in the management of cancer is chemotherapy. Although chemotherapy improves survival, its toxicities and side-effects have a negative effect on the quality of life. Severe side-effects can lead to non-compliance, loss of time at work, additional consultations to the care-giver, all of which contribute to annual costs, disability, and death.

Chemotherapy-induced nausea and vomiting (CINV) remains a significant adverse effect of cancer treatment.[1-3] Of all the side-effects of chemotherapy, CINV remains one of the most feared by patients.[4] Patients report a substantial negative effect of CINV on their ability to activities of daily living, obtain adequate rest, participate in social activities and perform work.[5,6] Additionally, CINV can have deleterious physiological effects, including metabolic derangements, malnutrition and esophageal tears, fractures, wound dehiscence among others.[6] Historically, some patients were even reluctant to proceed with potentially curative chemotherapy because of severity of treatment associated CINV.[7] In up to 30% of patients CINV is so distressing that consideration is given to discontinuing treatment which underscores the need of effective control of CINV.[6] Newer insights into the pathophysiology of CINV, a better understanding of the risk factors for these effects and the availability of new antiemetic agents have all contributed to substantial improvements in the emetic control. This article focuses on the current understanding of CINV and the status of the pharmacological interventions for CINV. Search strategy included Pubmed, using terms "Chemotherapy-induced Nausea and Vomiting" citations relevant to the topic were screened.

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TYPES OF CINV

CINV is broadly classified into five categories namely acute, delayed, anticipatory, breakthrough and refractory. Nausea and vomiting can occur at any time after the administration of chemotherapy, but the mechanisms appear different for

CINV occurring during the first 24 hours after chemotherapy, as against that which occurs after chemotherapy.

Acute CINV
Nausea and/or vomiting occurring within 24 hours after chemotherapy for e.g., following cisplatin.

Delayed CINV
Nausea and/or vomiting that develop more than 24 hours after chemotherapy e.g,. following carboplatin, cyclophosphamide and anthracyclines.

Anticipatory CINV
Nausea and/or vomiting triggered by taste, odor, sights, thoughts or anxiety secondary to a history of poor response to antiemetic agents or inadequate prophylaxis in the previous cycle of chemotherapy.

Breakthrough CINV
Occurs despite prophylactic treatment and/or requires antiemetic agents.

Refractory CINV
Occurs during subsequent treatment cycles when antiemetic prophylaxis and/or rescue antiemetic agents have failed in earlier cycles.[8]

RISK FACTORS

The likelihood that nausea and vomiting will develop after chemotherapy depends on several factors; important being sex and age. Higher risk is in younger female patients.[9-12]

Furthermore, patients who have a high pretreatment expectation of severe nausea are more likely to have nausea after chemotherapy.[13]

Conversely, patients with a history of high alcohol intake have a lower risk of CINV.[11,12]

Treatment-related factors such as chemotherapy dose and emetogenicity[14] are also important. Of all the known predictive factors, the intrinsic emetogenicity of a given chemotherapeutic agent is a predominant factor and should serve as a primary consideration in guiding antiemetic treatment.

The American Society of Clinical Oncology has classified the cancer chemotherapeutic agents in four categories of emetogenicity based upon their emetogenic potential [Table 1].[15]

PATHOPHYSIOLOGY OF NAUSEA AND VOMITING

Insight regarding the intricate human emetic pathway has been mainly obtained based upon animal models.[16] The sensation of nausea and the process of vomiting are one protective reflex that dispels the stomach and intestine of toxic substances. The experience of nausea is subjective and nausea could be considered a prodromal phase to the act of vomiting.[17]

It is generally assumed that the emetic pathway is formed by the vomiting center (VC) in the medulla oblongata, the chemoreceptor trigger zone (CTZ) in the area postrema on the caudal margin of the IV ventricle, the visceral afferent neurons and the abdominal vagal afferent neurons. The VC is representing anatomical structures at the level of the nucleus tractus solitarius (NTS) and the visceral and somatic motor nuclei.

The act of vomiting is triggered when afferent impulses from the CTZ and the vagal afferent fibers of the gastrointestinal tract travel to the VC. Efferent impulses then travel from the VC to the abdominal muscles, salivary center, cranial nerves and respiratory center to produce vomiting. Thus vomiting consists of a pre-ejection phase, retching and ejection. It is also accompanied by shivering and salivation [Figure 1].

Chemotherapeutic agents can cause nausea and vomiting by several ways including the activation of neurotransmitter receptors in the CTZ, VC and GIT [Figure 2].

Conventionally, dopamine D_2 and cannabinoid were the only two neurotransmitter receptors that were the known targets of antiemetic therapy. Significant advances in the management of CINV were seen with the introduction of 5-hydroxytryptamine-3-receptor antagonists ($5HT_3$ RA) including ondansetron and granisetron. These agents, though effective in controlling the acute phase of CINV, were limited in their ability to relieve delayed CINV. Recently, the role of substance P and neurokinin (NK) receptors in the emetic pathway has been investigated resulting in the development of NK receptor antagonists [Figure 3].[18-20]

CONVENTIONAL ANTIEMETIC AGENTS FOR CINV

Prophylactic antiemetic therapy remains the cornerstone in the treatment of CINV. Conventionally dopamine receptor antagonists, corticosteroids, cannabinoids and 5-HT_3 receptor antagonists have been used for these purposes.

Dopamine Receptor Antagonists
Dopamine Receptor Antagonists are present in the CTZ, which are the site of action of these group of drugs. The prototype in this category being metoclopramide, others being domperidone and butyrophenones like droperidol and haloperidol. Chlorpromazine and prochlorperazine have also been used. However, metoclopramide has the

Table 1: Emetogenic levels of Intravenously administered antineoplastic drugs

Level 1	Level 2	Level 3	Level 4
(Minimal Risk, <10%)	(Low Risk, 10-30%)	(Moderate Risk, 31-90%)	(High Risk, >90%)
Bleomycin	Cytarabine	Carboplatin	Carmustine
Busulphan	Docetaxel	Cyclophosphamide	Cisplatin
Fludarabine	Etoposide	Daunorubicin	Dacarbazine
Vincristine	Methotrexate	Doxorubicin	Mechlorethamine
Vinblastine	Mitomycin	Ifosphamide	Streptozocin
	Mitoxantrone	Irinotecan	
	Paclitaxel		

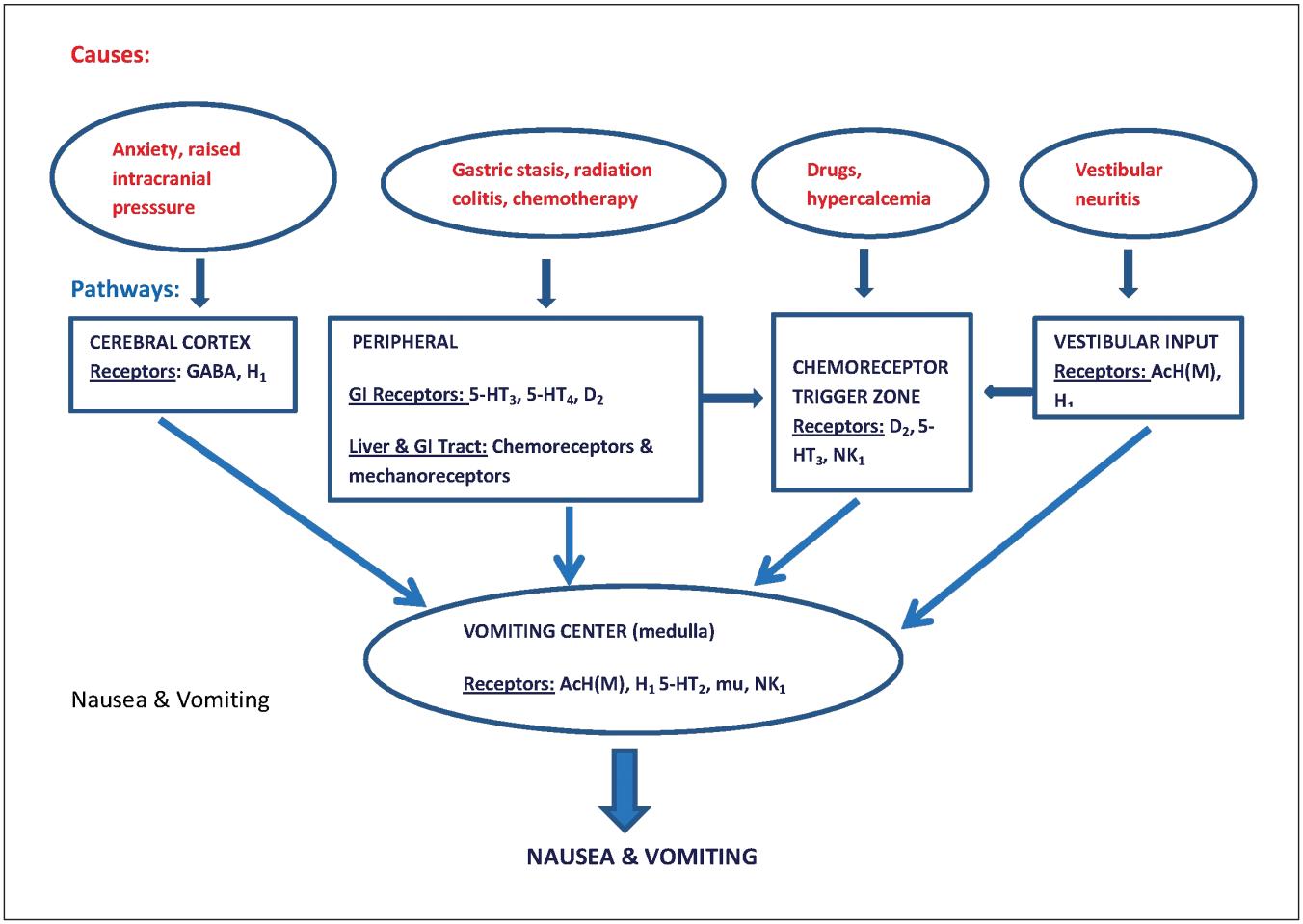

Figure 1: Emetogenic agents

tendency to cause extrapyramidal side-effects including acute dystonic reactions, akathisia and sedation, limiting its use. As domperidone does not cross the blood brain barrier, if at all, causes such side effects.[18,19]

Serotonin (5-Hydroxytryptamine) 3 Receptor Antagonists

Serotonin receptors especially the 5-HT_3 receptor subtype are present in the CNS and gastrointestinal tract. First generation 5-HT_3 receptor antagonists such as ondansetron, granisetron and tropisetron and second generation agents such as palonosetron appear to act through both the CNS and the GIT via the vagus and splanchnic nerves. The introduction of 5 HT_3 receptor antagonists for the prevention of CINV, postoperative nausea vomiting (PONV), and radiotherapy-induced nausea vomiting (RINV) has greatly improved the supportive care in such patients. These agents with or without corticosteroids such as dexamethasone have been recommended in the treatment guidelines for the management of both acute and delayed CINV. They are effective both orally as well as parentally. They have not been associated with any major toxicity; however the most commonly reported adverse events being mild headache, constipation and mild diarrhea.[21-25] Although

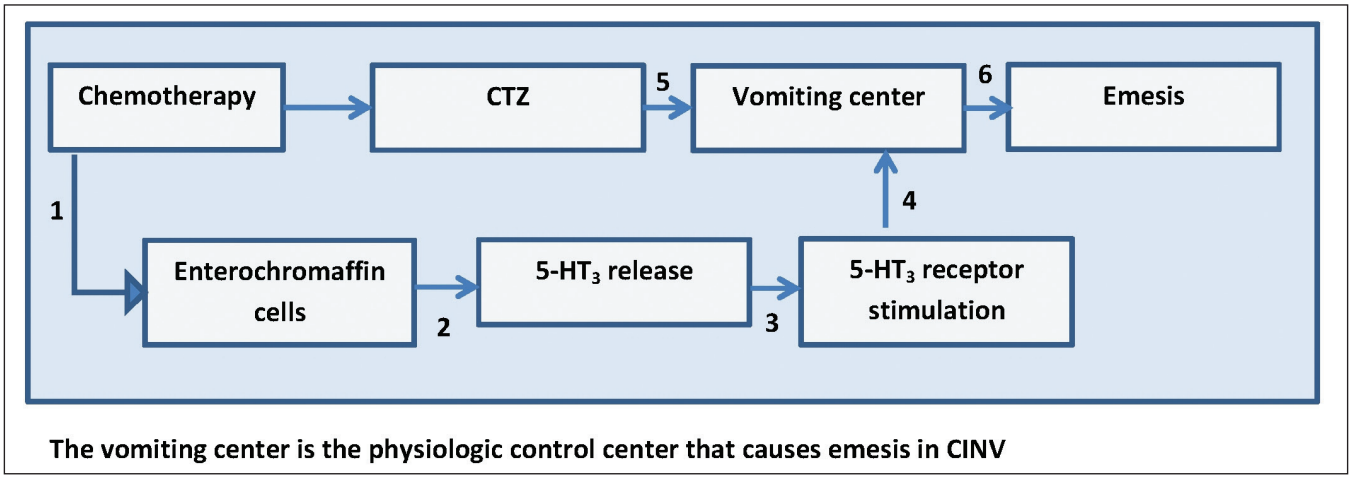

Figure 2: Chemotherapy-induced nausea and vomiting

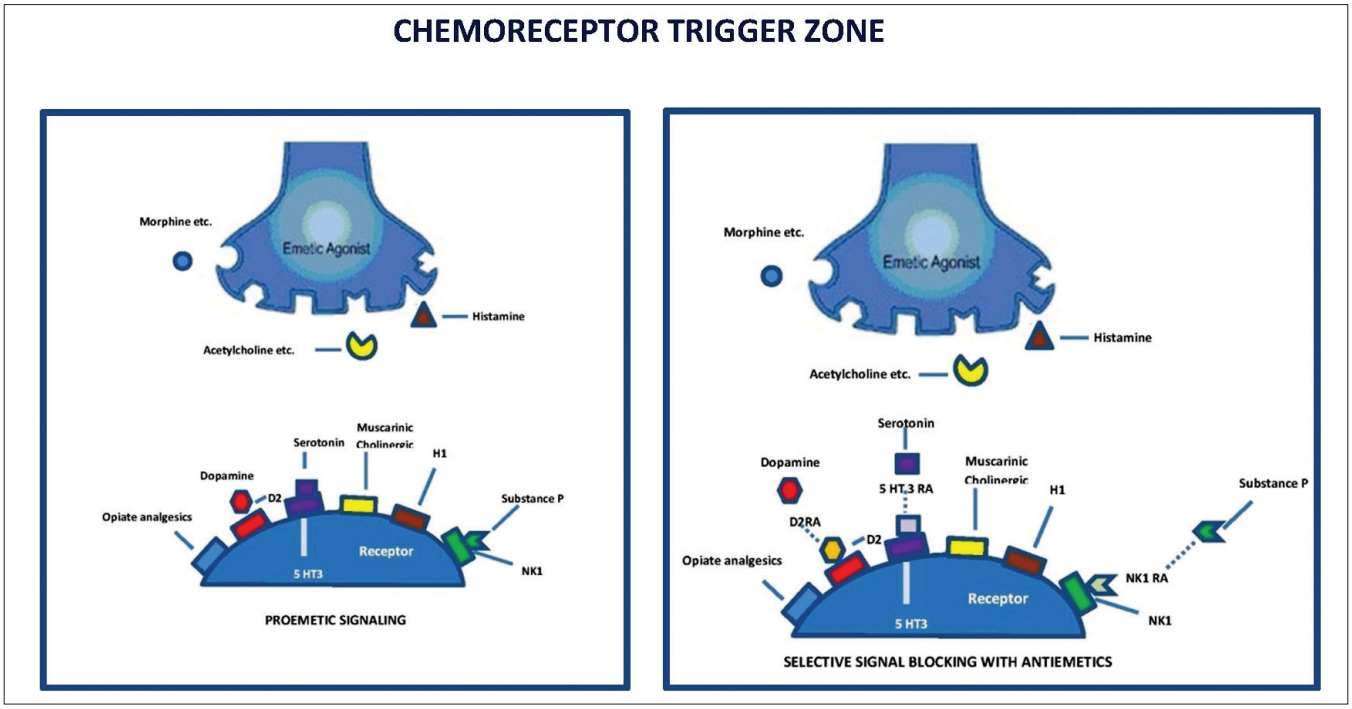

Figure 3: Neurotransmitters and receptors involved in emesis

there have been no reported cardiovascular adverse events, prolongation of cardiac conduction intervals have been reported with dolasteron.[25]

Palonosetron

It is a new antiemetic agent that differs from the currently available $5HT_3$ receptor antagonists because of its long half-life and higher binding affinity to $5HT_3$ receptors.[26] Several studies have shown that palonosetron as a single agent achieves better control of CINV compared with first generation $5HT_3$ receptor antagonists.[27-29] Palonosetron has a single dose advantage. However, conclusive demonstration of its clinical superiority compared to other 5 HT_3 receptor antagonists remains to be elucidated in future.

Cannabinoids

Isolation of cannabinoids (CB) receptors in humans have helped to gain better insight to the mechanisms involved for the use of external cannabinoids. In humans 2 subtypes of CB receptors have been exclusively identified namely CB 1 and CB 2.[30,31] The antiemetic effects of cannabinoids like nabilone appear to be due to the interaction of CB1 receptor and its signaling pathway which are present in high densities in the CNS. The CB1 receptor acts as retrograde synaptic messengers. In a "reverse signaling process" the

neurotransmitters released from the presynaptic neurons activate the post synaptic receptors. These activated post synaptic neurons releases endocannabinoids such as anandamide. Binding of endocannabinoids to the CB1 receptors activates the G-protein reducing the neurotransmitter release, a process called as depolarization-induced suppression of inhibition (DSI).[32,33] CB1 agonists such as nabilone circumvent this multistep process of the endogenous system leading to its antiemetic activity. Additionally, nabilone may also indirectly and partially manipulate $5HT_3$ and D_2 receptors.[34,35]

NEWER ANTIEMETIC AGENTS FOR CINV

Neurokinin 1 Receptors Antagonists

Recently the role of Substance P (SP) and Neurokinin 1 (NK) receptors in the antiemetic pathway has been investigated resulting in the development of NK-1 receptor antagonists. Substance P is a member of a family of small peptides, the tachykinins. NK-1, NK-2, and NK-3 are the 3 receptors for the tachykinins, with substance P being the preferred agonist at the NK-3 receptor.[36] Carpenter *et al.* demonstrated the association of Substance P and emesis in dogs way back in 1984.[37] A wide variety of experiments have confirmed the antiemetic activity of Neurokinin receptor antagonists.[38-41]

Aprepitant being the first clinically available most widely studied of all the neurokinin receptor antagonists.[42] Others being Fosaprepitant and Casopitant.

APREPITANT

It was the first approved oral NK-1 receptor antagonists by the FDA in 2003. Aprepitant has been shown to be efficacious in preventing both acute and delayed CINV induced by highly emetogenic chemotherapeutic agents like cisplatin.

Pharmacokinetics

The pharmacokinetics of aprepitant is nonlinear across the recommended dose range, with clearance and absolute bioavailability decreasing with increasing dose. Oral administration of aprepitant achieved a peak concentration after 4 hours, the bioavailability being 60-65% and plasma protein binding of 95%. The apparent terminal half-life is 9-13 hours. Aprepitant is largely excreted as metabolite in urine and via biliary excretion in the feces. Since aprepitant is metabolized by cytochrome P450 (CYP3A4), coadministration of aprepitant and inducers/inhibitors of this isoenzyme will induce changes in the plasma levels of aprepitant. As a moderate inhibitor of CYP3A4, aprepitant can increase plasma concentrations of coadministered substances that are metabolized through CYP3A4. As a moderate inducer of CYP2A9 and a mild inducer of CYP3A4, aprepitant can decrease plasma concentrations of substances metabolized by these isoenzyme.[43-45]

Therapeutic Efficacy

In phase III clinical studies in patients with solid tumors treated with a single cycle of highly emetogenic chemotherapy (HEC), the aprepitant group (125 mg on Day 1, followed by 80 mg once daily on Days 2 and 3 plus ondansetron and dexamethasone) achieved a significantly higher complete response (no emesis and no rescue therapy) rates than with the control regimen group (only ondansetron and dexamethasone) (63-73% v/s 43-61%; $P<0.01$) during the Day 1-5 phase after HEC administration. The ability of aprepitant group in reducing acute, delayed and overall emesis was significantly higher compared to the control group. The efficacy of the aprepitant in controlling all the phases of emesis was maintained even in multiple cycles of chemotherapy, wherein patients received up to five additional cycles of chemotherapy.

Breast cancer patients treated with moderately emetogenic chemotherapy (MEC) consisting of Cyclophosphamide±anthracycline, the aprepitant regimen resulted in a higher response (51% v/s 42%; $P=0.015$) when compared to the control group consisting of ondansetron plus dexamethasone without aprepitant. Additionally, a single 40 mg dose of aprepitant was superior to ondansetron in preventing PONV (64% v/s 55%).[46]

Dosage Regimen

Aprepitant is administered orally as a single 125 mg dose on Day 1 and then 80 mg once daily on Days 2 and 3. With the 3-day regimen aprepitant regimen, no dosage adjustment is needed in geriatric patients even though they are at a higher risk of dehydration as a result of severe nausea and vomiting.[43,44] In patients with mild hepatic insufficiency, aprepitant was well tolerated without the need for any dosage reduction. However, in patients with severe hepatic insufficiency the data is lacking.[43] No clinically significant differences in the pharmacokinetics of a single 240 mg oral dose of aprepitant was observed between healthy volunteers and patients with end-stage renal disease or patients with severe renal insufficiency undergoing hemodialysis. Hence, no dosage adjustment is required in such patients.[45]

Tolerability

The standard regimen of aprepitant was generally well tolerated when used in the prevention of CINV in cancer patients receiving single or multiple cycle of HEC or MEC. The commonly reported adverse events (≥10% recipients) were asthenia / fatigue, nausea, hiccups, constipation, diarrhea and anorexia. Increases in liver enzymes like ALT, AST, Blood Urea Nitrogen, serum creatinine and proteinuria was observed in ≥3% of recipients. However, the incidence of adverse events in the aprepitant group was similar to that of the control group.

FOSAPREPITANT

A prodrug of aprepitant, fosaprepitant dimeglumine was

developed to provide an intravenous alternative. It is rapidly converted to aprepitant within 30 minutes primarily by CYP3A4.[19] There have been seven metabolites which have been identified in human plasma. However, these metabolites are only mildly active.

The efficacy is the same as that of aprepitant. In the triple antiemetic therapy, fosaprepitant could be administered on Day 1 with other antiemetic's (ondansetron and dexamethasone) before intravenous chemotherapy followed on Day 2 and 3 by oral NK-1 receptor antagonist, aprepitant.

Fosaprepitant 115 mg given intravenously is bioequivalent to aprepitant 125 mg given orally with similar plasma concentrations at 24 hours. It has been tested in single daily doses for up to 4 days. Hence it can be used interchangeably with aprepitant.

In certain circumstances intravenous formulation like fosaprepitant may be more convenient to oral therapy as in patients with severe mucositis, difficulty in swallowing or any gastrointestinal disturbances.

It is very well tolerated with venous irritation being specific to this formulation and headache being most frequent.

Drug Interactions

Being a moderate inhibitor of CYP3A4 both fosaprepitant as well as aprepitant should not be co-administered with drugs such as pimozide, terfenadine, astemizole and cisapride due to the potential of life-threatening ventricular arrhythmias. Similarly caution is advised for patients receiving drugs with narrow therapeutic index that are metabolized by CYP3A4 namely cyclosporine, tacrolimus and sirolimus. Since both fosaprepitant and aprepitant are mild inducers of CYP2C9, concurrent administration of warfarin, phenytoin and tolbutamide may result in lower than desired plasma concentrations. Alternate forms of contraception is recommended in patients on oral contraceptives administered either aprepitant or fosaprepitant.

Cancer chemotherapeutic agents metabolized by CYP3A4 like taxanes, etoposide, irinotecan, ifosfamide, imatinib, vinca alkaloids, had no clinically significant interaction when administered with fosaprepitant or aprepitant.

However, aprepitant increases the AUC of dexamethasone, a substrate of CYP3A4 by 2.2 fold; hence the dose of dexamethasone should be halved.

Strong CYP3A4 inducers like rifampicin reduce its concentration, whereas strong inhibitors like ketoconazole can increase the aprepitant concentration by fivefold.

A clinical trial which assessed the effect of aprepitant on drug-metabolizing enzymes recommend a 50% reduction in oral dose of benzodiazepines metabolized by CYP3A4 including midazolam and alprazolam.[43,47-50]

SUMMARY AND FUTURE DIRECTIONS

The recent development of new antiemetic drugs has provided opportunity to further improve the management of CINV. The decision of choosing should be based not only on the antiemetic drug but also on the possible patient characteristics and etiology of emesis. Preventing rather than treating CINV should be the primary goal. HEC requires triple antiemetic regimens including NK 1 receptor antagonists (aprepitant / fosaprepitant), $5HT_3$ receptor antagonists (ondansetron) and corticosteroid (dexamethasone). Recommended antiemetic regimens for MEC include 5 HT_3 receptor antagonists or corticosteroid.

Selective NK-1 receptor antagonists can be differentiated from the $5HT_3$ receptor antagonists in the preclinical models by virtue of their broad spectrum of clinical activity with a variety of emetic stimuli.

Among the NK-1 receptor antagonist that have been evaluated aprepitant has been most widely studied and has demonstrated significant activity against CINV in patients with cancer.

Despite the availability of more effective $5HT_3$ receptor antagonists and the recent introduction of NK-1 receptor antagonists, hurdles still exists for an effective control of nausea and vomiting. Conventionally antiemetic medications are administered orally or parenterally. Under such circumstances, other delivery routes may be beneficial in certain patients. Second generation 5 HT_3 receptor antagonists like palonosetron could be advantageous in multiday regimens because of its extended delivery. Breakthrough emesis which requires immediate medications could be effectively tackled by acute delivery systems in the form of nasal sprays. External pumps though advantageous in constantly delivering the antiemetic medications, are obstrusive and remind the patients constantly of the illness. Additionally, it involves an invasive procedure, thus potentially becoming a site of infection. Transdermal delivery system provides convenience, hence improves compliance, besides being noninvasive.

Thus all of these strategies may prove beneficial in enhancing antiemetic control and improving patient outcomes.

REFERENCES

1. de Boer-Dennert M, de Wit R, Schmitz PI, Djontono J, Beurden V, Stoter G, *et al.* Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. Br J Cancer 1997;76:1055-61.
2. Herrstedt J, Aapro MS, Smuth JF, Del Favero A. Corticosteroids, dopamine antagonists and other drugs. Support Care Cancer

1998;6:204-14.

3. Hesketh PJ, Grunberg SM, Gralla RJ, Warr DG, Roila F, de Wit R, *et al*. Aprepitant Protocol 052 Study Group The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: A multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin-the Aprepitant Protocol 052 Study. J Clin Oncol 2003;21:4112-9.
4. Sun CC, Bodurka DC, Weaver CB, Rasu R, Wolf JK, Bevers MW, *et al*. Rankings and symptom assessments of side effects from chemotherapy: insights from experienced patients with ovarian cancer. Support Care Cancer 2005;13:219-27.
5. Lee J, Dibble SL, Pickett M, Luce J. Chemotherapy-induced nausea/vomiting and functional status in women treated for breast cancer. Cancer Nurs 2005;28:249-55.
6. Wiser W, Berger A. Practical management of chemotherapy-induced nausea and vomiting. Oncology 2005;19:637-45.
7. Schwartzberg LS Chemotherapy-induced nausea and vomiting: which antiemetic for which therapy? Oncology 2007;21:946–53.
8. Hesketh PJ, Kris MG, Grunberg SM. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-9.
9. Pollera CF, Giannarelli D. Prognostic factors influencing cisplatin-induced emesis: definition and validation of a predictive logistic model. Cancer 1989;64:1117-22.
10. du Bois A, Meerpohl HG, Vach W, Kommoss FG, Fenzl E, Pfleiderer A. Course, patterns, and risk-factors for chemotherapy-induced emesis in cisplatin-pretreated patients: A study with ondansetron. Eur J Cancer 1992;28:450-7.
11. Hesketh P, Navari R, Grote T, Gralla R, Hainsworth J, Kris M, *et al*. Double-blind, randomized comparison of the antiemetic efficacy of intravenous dolasetron mesylate and intravenous ondansetron in the prevention of acute cisplatin-induced emesis in patients with cancer. J Clin Oncol 1996;14:2242-9.
12. Osoba D, Zee B, Pater J, Warr D, Latreille J, Kaizer L. Determinants of postchemotherapy nausea and vomiting in patients with cancer. Quality of Life and Symptom Control Committees of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1997;15:116-23.
13. Roscoe JA, Bushunnow P, Morrow GR, Hickok JT, Kuebler PJ, Jacobs A, *et al*. Patient experience is a strong predictor of severe nausea after chemotherapy: A University of rochester community clinical oncology program study of patients with breast carcinoma. Cancer 2004;101:2701-8.
14. Hesketh PJ. Defining the emetogenicity of cancer chemotherapy regimens: Relevance to clinical practice. Oncologist 1999;4:191-6.
15. Hesketh PJ. Chemotherapy-induced nausea and vomiting. N Engl J Med 2008;358:2482-94.
16. Peroutka SJ, Snyder SH. Antiemetics: Neurotransmitter receptor binding predicts therapeutic actions. Lancet 1982;1:658-9.
17. Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Julie Ma G, Eldridge K, Hipple A, *et al*. Addition of the Neurokinin 1 receptor antagonist aprepitant to standard antiemetic therapy improves control of chemotherapy-induced nausea and vomiting. Results from a randomized, double-blind, placebo-controlled trial in Latin America. Cancer 2003;97:3090-8.
18. Dewan P, Singhal S, Harit D. Management of chemotherapy-induced nausea and vomiting. Indian Pediatr 2010;47:149-55.
19. Navari RM. Pharmacological management of chemotherapy-induced nausea and vomiting: Focus on recent developments. Drugs 2009;69:515-33.
20. Ruhlmann C, Herrstedt J. Casopitant: A novel NK(1)-receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting Ther Clin Risk Manag 2009;5:375-84.
21. Hesketh PJ, Navari RM, Grote T, Gralla R, Hainsworth J, Kris M, *et al*. Double blind randomized comparison of the antiemetic efficacy of intravenous dolasetron and intravenous ondansetron in the prevention of acute cisplatin-induced emesis in patients with cancer. Dolasetron Comparative Chemotherapy-induced Emesis Prevention Group. J Clin Oncol 1996;14:2242-9.
22. Navari R, Gandara D, Hesketh P, Hall S, Mailliard J, Ritter H, *et al*. Comparative clinical trial of granisetron and ondansetron in the prophylaxis of cisplatin-induced emesis. J Clin Oncol 1995;13:1242-8.
23. Mantovani G, Macciò A, Bianchi A, Curreli L, Ghiani M, Proto E, *et al*. Comparison of granisetron versus ondansetron versus tropisetron in the prophylaxis of acute nausea and vomiting induced by cisplatin for the treatment of head and neck cancer; A randomized controlled trial. Cancer 1996;77:941-8.
24. Perez EA, Navari RM, Kaplan HG, Gralla RJ, Grunberg SM, Palmer RH, *et al*. Efficacy and safety of different doses of granisetron for the prophylaxis of cisplatin-induced emesis. Support Care Cancer 1997;5:31-7.
25. Navari RM, Koeller JM. Electrocardiographic and cardiovascular effects of the 5-hydroxytryptamine3 receptor antagonists. Ann Pharmacother 2003;37:1276-86.
26. Oo TH, Hesketh PJ. Drug insight: new antiemetics in the management of chemotherapy-induced nausea and vomiting. Nat Clin Pract Oncol 2005;2:196-201.
27. Eisenberg P, MacKintosh FR, Ritch P, Cornett PA, Macciocchi A. Efficacy, safety and pharmacokinetics of palonosetron in patients receiving highly emetogenic cisplatin-based chemotherapy: A dose-ranging clinical study. Ann Oncol 2004;15:330-7.
28. Eisenberg P, Figueroa-Vadillo J, Zamora R, Charu V, Hajdenberg J, Cartmell A, *et al*. Improved prevention of moderate emetogenic chemotherapy-induced nausea and vomiting with palonosetron, a pharmacologically novel 5-HT3 receptor antagonist: Results of a phase III, single-dose trial versus dolasetron. Cancer 2003;98:2473-82.
29. Gralla R, Lichinitser M, Van Der Vegt S, Sleeboom H, Mezger J, Peschel C, *et al*. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy: Results of a double-blind randomized phase III trial comparing single doses of palonosetron with ondansetron. Ann Oncol 2003;14:1570-7.
30. Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, *et al*. International union of pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev 2002;54:161-202.
31. Martin BR, Wiley JL. Mechanism of action of cannabinoids: How it may lead to treatment of cachexia, emesis, and pain. J Support Oncol 2004;2:305-14.
32. Freund TF, Katona I, Piomelli D. Role of endogenous cannabinoids in synaptic signaling. Physiol Rev 2003;83:1017-66.
33. Diana MA, Mart A. Endocannabinoid-mediated short-term synaptic plasticity: Depolarization-induced suppression of inhibition (DSI) and depolarization-induced suppression of excitation (DSE). Br J Pharmacol 2004;142:9-19.
34. Ward A, Holmes B. Nabilone: A preliminary review of its pharmacological properties and therapeutic use. Drugs 1985;30:127-44.
35. Nahas G, Harvey DJ, Sutin K, Turndorf H, Cancro R. A molecular basis of the therapeutic and psychoactive properties of cannabis (delta9-tetrahydrocannabinol). Prog Neuropsychopharmacol Biol Psychiatry 2002;26:721-30.
36. Maggi CA. The mammalian tackykinin receptors. Gen Pharmac 1995;26:911-44.
37. Carpenter DO, Briggs DB, Strominger N. Peptide-induced emesis in dogs. Behav Brain Res 1984;11:277-81.
38. Bountra C, Bunce K, Dale T. Anti-emetic profile of a non-peptide neurokinin NK1 receptor antagonist, CP-99,994, in ferrets. Eur J Pharmacol 1993;249:R3-4.

39. Tattersall FD, Rycroft W, Hargreaves RJ, Hill RG. The tachykinin NK1 receptor antagonist CP-99,994 attenuates cisplatin induced emesis in the ferret. Eur J Pharmacol 1993;250:R5-6.
40. Gardner CJ, Twissell DJ, Dale TJ, Gale JD, Jordan CC, Kilpatrick GJ, *et al*. The broad-spectrum anti-emetic activity of the novel non-peptide tachykinin NK1 receptor antagonist GR203040. Br J Pharmacol 1995;116:3158-63.
41. Minami M, Endo T, Yokota H, Ogawa T, Nemoto M, Hamaue N, *et al*. Effects of CP-99,994, a tachykinin NK(1) receptor antagonist, on abdominal afferent vagal activity in ferrets: Evidence for involvement of NK(1) and 5-HT(3) receptors. Eur J Pharmacol 2001;428:215-20.
42. Antonarakis ES, Hain RD. Nausea and vomiting associated with cancer chemotherapy: Drug management in theory and practice. Arch Dis Child 2004;89:877-80.
43. Product information. Emend (Aprepitant). Whitehouse station: Merck NJ; May 2003.
44. Aapro MS, Macciocchi A, Gridelli C. Palonosetron improves prevention of chemotherapy-induced nausea and vomiting in elderly patients. J Support Oncol 2005;3:369-74.
45. Bergman AJ, Marbury T, Fosbinder T, Swan S, Hickey L, Bradstreet TE, *et al*. Effect of impaired renal function and haemodialysis on the pharmacokinetics of aprepitant. Clin Pharmacokinet 2005;44:637-47.
46. Curran MP, Robinson DM. Aprepitant: A review of its use in the prevention of nausea and vomiting. Drugs 2009;69:1853-78.
47. Massaro AM, Lenz KL. Aprepitant: A novel antiemetic for chemotherapy-induced nausea and vomiting. Ann Pharmacother 2005;39:77-85.
48. McCrea JB, Majumdar AK, Goldberg MR, Iwamoto M, Gargano C, Panebianco DL, *et al*. Effect of the neurokinin1 receptor antagonist aprepitant on the pharmacokinetics of dexamethasone and methylprednisolone. Clin Pharmacol Ther 2003;74:17-24.
49. Majumdar AK, McCrea JB, Panebianco DL, Hesney M, Dru J, Constanzer M, *et al*. Effects of aprepitant on cytochrome P450 3A4 activity using midazolam as a probe. Clin Pharmacol Ther 2003;74:150-6.
50. Miners JO, Birkett DJ. Cytochrome P4502C9: An enzyme of major importance in human drug metabolism. Br J Clin Pharmacol 1998;45:525-38.

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